CRYSTALLOGRAPHIC INVESTIGATIONS

OF

HETEROCYCLIC COMPOUNDS

OF

PHARMACOLOGICAL INTEREST

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SUMMARY

Single-crystal X-ray structure determinations are reported for the following heterocyclic compounds: (1) 3,4-dihydro-4-phenylimino- 1,2,3-benzotriazine (DIPB) (2) 4,7-dihydro-6,7-diphenyl-7-ethoxy [1,2,4] triazolo [5,1-c] triazine (DETT) (3) 4,6-diamino-p-chlorophenyl-1,2-dihydro-s-triazine (cycloguanil) hydrochloride (CGT) (4) 2,4-diaminoquinazoline (DAQ) and (5) 3-hydroxy-4-oxy-1,2,3-benzotriazine. The refinement of hydrogen atom parameters for CGT from neutron data was also undertaken. The medicinal interest in each of the above compounds is surveyed. CGT and DAQ are inhibitors of dihydrofolate reductase (DHFR). The biochemistry of DHFR inhibition is reviewed, along with a detailed comparison of geometrical parameters for DHFR inhibitors which have been investigated crystallographically. Clinical investigations of the antimalarial activity of CGT have been reviewed. The position of protonation in CGT was unambiguously identified in a neutron Fourier synthesis and found to conform to the pattern observed in all other known DHFR inhibitors. With the object of investigating possible cis-trans isomerism, CNDO/2 molecular orbital calculations have been carried out for DIPB and two other crystallographically investigated 4-anilino substituted 1,2,3-benzotriazines. The calculated energies indicated that it is steric rather than electronic considerations which govern the isomeric form adopted.

A survey of the crystallographic software available at the University of Aston and the University of Manchester Regional Computer Centres is reported along with the development of programs for four-circle diffractometer data reduction, display of unit cell contents for structures of monoclinic and higher symmetry, molecular geometry calculations and the contouring and peak searching of Fourier syntheses.

Key Words:

FOLATE CYCLOGUANIL
TRIAZINE QUINAZOLINE

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Table of Contents

Tables and Illustrations

Note: Page-number refers to previous numbered page.

Chemical Formulae

Note: Page-number refers to previous numbered page.

ABBREVIATIONS

ABS FOM	Absolute Figure of Merit -- see Sec 2.3
A.E.R.E.	Atomic Energy Research Establishment
AFIX	see Sec 2.5.2(a)
AMNB	see Sec 9.1
Ar	Aryl substituent
a.u.	Atomic units
Bz	Benzil
CGT	Cycloguanil Triazine (see Chapter 6)
DAQ	Diaminoquinazoline (see Chapter 7)
DETT	see Chapter 5
df	Degrees of freedom
DFIX	see Sec 2.5.2(b)
DHFR	Dihydrofolate Reductase
D.I.B.P.	Double Inversion Base Pairing
DIPB	see Chapter 4
DMBH	see Table 10-1
DNA	Deoxyribonucleic acid
DTT	see Sec 5.1
DVD	Diaveridine
e.s.d.	Estimated standard deviation
FA	Folic Acid
FAH_2	Dihydrofolate
FAH_4	Tetrahydrofolate
fv	Free variable
HOB	see Chapter 8
IBAF	"Insoluble Baker's antifol"

LCAO	Linear Combination of Atomic Orbitals
Lp	Lorentz-polarisation factor
Me	Methyl substituent
MTX	Methotrexate
NADP	Nicotinamide Adenine Dinucleotide
p	Probability (<u>but</u> in a chemical expression p='para')
PAB	see Sec 9.1
PABA	para-Aminobenzoic acid
Ph	Phenyl substituent
PMA	Pyrimethamine
QSAR	Quantitative Structure-Activity Relationships
R	Unweighted R-factor -- see Table 2.5.2-2
RESID	Karle R-factor -- see Sec 2.3
Rg	Weighted R-factor -- see Table 2.5.2-2
Rw	Weighted R-factor -- see Table 2.5.2-2
S.G.	Space group
S.I.B.P.	Single Inversion Base Pairing
TCQ	Triaminochloroquinazoline
TMP	Thymidine Monophosphate (Chapter 1)
TMP	Trimethoprim (Chapter 10)
TMP-A	see Table 10-1
TMP-HBR	see Table 10-1
TMP-O	see Table 10-1
TZT	Triazinate
UMP	Uridine Monophosphate
U.M.R.C.C.	University of Manchester Regional Computer Centre
VSEPR	Valence Shell Electron Pair Repulsion

CONVENTIONS

(1) Refinement

The term 'isotropic refinement' of a structure refers to the refinement of non-hydrogen atoms only with the refinement of all temperature factors isotropically.

The term 'anisotropic refinement' of a structure refers to the refinement of all atoms, with the temperature factors for non-hydrogen atoms refined anisotropically and hydrogen atom temperature factors refined isotropically.

(2) Units

For convenience, units have sometimes been omitted from figures and tables. In this case, the following units are understood:

Distance	Angstrom units
Angle	Degrees
Charge	Electronic charge
Energy	Atomic units

(3) Standard Deviations

Numbers appearing in brackets following the value of the parameter refer to the standard deviation. The number of decimal places in the value of the parameter determines the sense of the standard deviation. Thus 1.328(6) refers to a standard deviation of 0.006.

Chapter 1: Introduction

1.1 Crystallography as an Aid to the Study of Materials of Pharmacological Interest

X-ray crystallography provides a method of unambiguously determining the connectivity of organic molecules, hence of confirming or refuting molecular formulae proposed on the basis of synthetic pathway, infrared, ultraviolet and mass spectroscopy, and nuclear magnetic resonance. In addition, the isomeric form will be revealed in a crystallographic investigation -- an example being the "Stilbene-cis" and "Stilbene-trans" isomeric forms in the 1,2,3-benzotriazines (see Chapter 9) -- information not easily obtainable by other means. The process of Fourier reconstruction of the molecular image provides reasonably accurate information about bond distances, bond angles and torsion angles. Thus particular adaptive features of the molecule may be seen.

Apart from the very large investment in both human and material resources, X-ray crystallography suffers from weaknesses which limit its effectiveness in the investigation of small-molecule structures from the point of view of pharmacological interest. The first of these is that nitrogen atoms may not be unambiguously distinguishable from carbon atoms -- an important feature in the study of heterocyclic systems where the position of nitrogen atoms is essential to the activity of the molecule. Here bond lengths may be of considerable aid in interpreting results with the order of atom-atom distances being $C\overset{\cdots}{-}C>C\overset{\cdots}{-}N>N\overset{\cdots}{-}N$. This inequality depends on an approximately equal π-bonding contribution in all three cases. In heterocyclic systems conjugation is unlikely to be uniform and bond lengths may be taken only as a guide to the identification of nitrogen positions. During refinement, insertion of all heterocyclic atoms as carbons should result in unusually low temperature factors at the nitrogen positions. Unfortunately this effect is masked by the variation in thermal oscillation at different points in the heterocycle -- with bridgehead atoms normally having the lowest temperature factors. Nevertheless, comparison of isotropic temperature factors (Uiso) for atoms at similar positions should show differences of approximately $0.05\ \text{Å}^2$ between nitrogen and carbon atoms. The combination of these methods, consideration of synthetic pathway and conventional spectroscopy usually gives a clear indication of the positions of the nitrogen atoms. A second weakness in X-ray structure analysis is the question of hydrogen positions. Given high-quality intensity data, hydrogen positions can be expected, in difference Fourier syntheses, to appear with intensities in the range $0.3\ e\text{Å}^{-3}$ to $0.4\ e\text{Å}^{-3}$

(Stout and Jensen, 1968 - p381) but may well be either above or below these limits. Poor quality data or large thermal parameters or a combination of the two may make hydrogen positions unobservable altogether. This problem is particularly important where the position of protonation is essential to understanding the biochemical activity of the molecule. The best solution to this problem -- provided a satisfactory crystal can be grown and provided the beam facilities can be made available -- is the collection of neutron diffraction intensity data, where -- because hydrogen has a scattering length approximately one-half in magnitude to that of carbon -- hydrogen atomic positions should be easily visible in a Fourier synthesis. The protonation of heterocyclic nitrogens is of particular interest pharmacologically and this subject is discussed in a separate section below. The third weakness of X-ray structure analysis of compounds of biological importance is that it relates to the material in the crystalline state. The conformation -- or even the isomeric form -- may not be the one the material may exhibit in its biologically active state. Some idea of the conformations available may, however, be obtained by varying the torsion about single bonds and eliminating those conformations that give impossible contact distances. Particularly in the case of the protonated species hydrogen bonding plays an important role in the biological activity. Hydrogen bonding between molecules in the crystalline state may give some clue as to the arrangement of hydrogen bonds to the molecule when it is in its active site. Small molecule crystallographic investigations thus complement those of the enzyme-inhibitor complex. Work done on the enzyme dihydrofolate reductase and its inhibitors is discussed in Section 1.5.3.

1.2 Protonation of Ring Nitrogens

A question of very great interest in heterocyclic systems is that of the protonation of the ring nitrogens. For example, the protonation of N(1) of the 2,4-diaminopteridines is an essential element in current models of the binding of these compounds to dihydrofolate reductase (see Sec 1.5.3). Because of the difficulty of imaging hydrogen atoms from X-ray data and the scarcity of neutron facilities, the crystallographer must often rely on other evidence for the presence or absence of protonation.

In the case of the unprotonated heterocyclic nitrogen atom, the fully-occupied sp^2 hybridised lone-pair orbital leaves a single $2p_z$ electron to be contributed to the π-system of the heterocycle, whereas the protonated nitrogen receives one electron from the hydrogen and contributes one electron to each of the sp^2 orbitals. The remaining two electrons occupy $2p_z$ and are non-bonding (see Fig 1.2-1). The bonds to the protonated nitrogen atoms are, therefore, formally single whereas the unprotonated species forms one double bond. Allowing for delocalisation, it can therefore be expected that the bonds to the protonated nitrogen atom will be longer than the corresponding bonds to the unprotonated one. Moreover, the lone-pair electrons can be

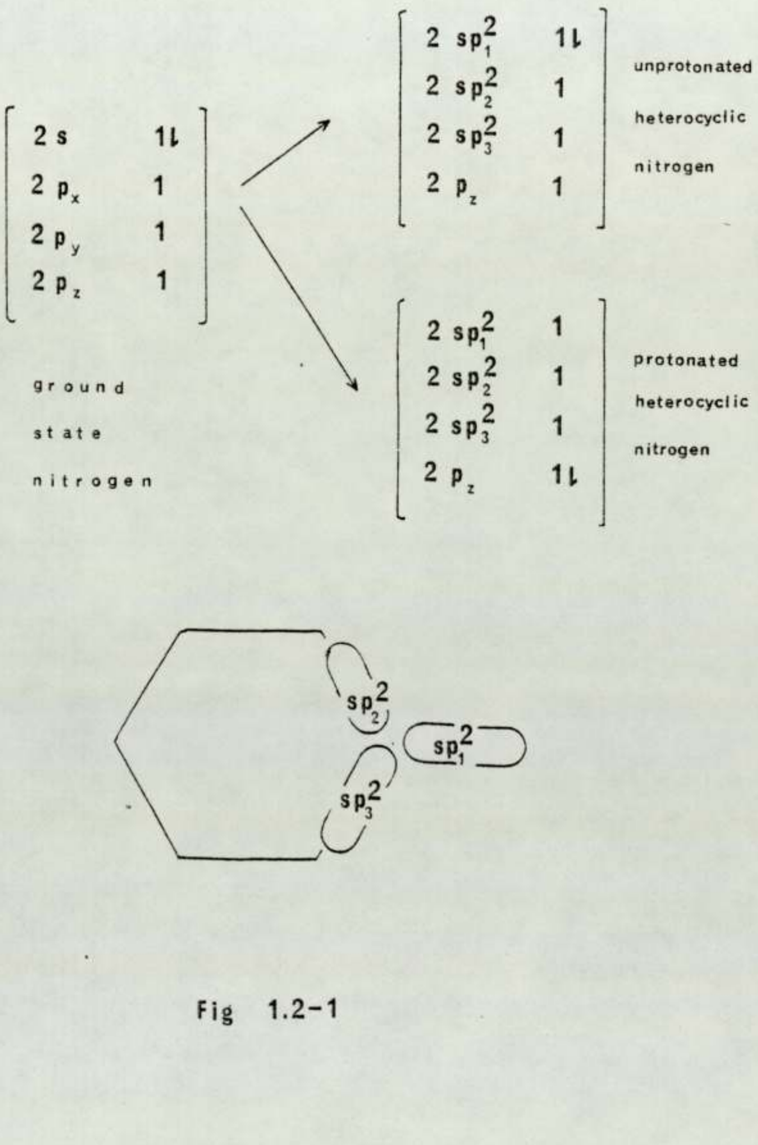

2 s 1↓
2 p_x 1
2 p_y 1
2 p_z 1
ground state nitrogen
2 sp_1^2 1↓
2 sp_2^2 1
2 sp_3^2 1
2 p_z 1
unprotonated heterocyclic nitrogen
2 sp_1^2 1
2 sp_2^2 1
2 sp_3^2 1
2 p_z 1↓
protonated heterocyclic nitrogen
sp_2^2
sp_1^2
sp_3^2

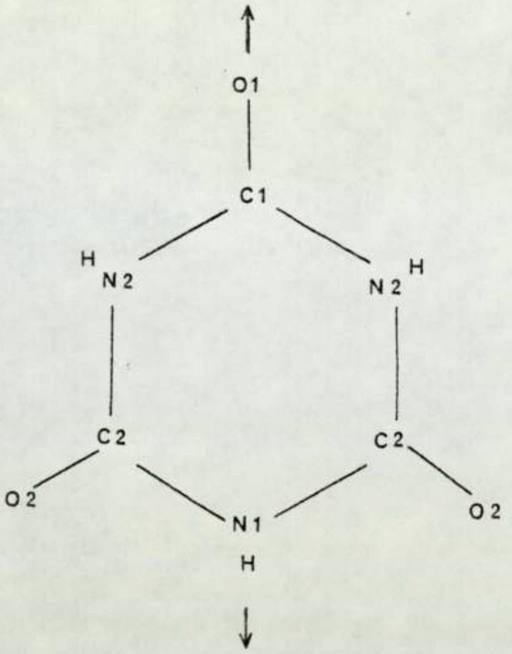
Fig 1.2-1

expected to be more spread out than the corresponding bonding orbital and repulsion effects between the lone pair and the heterocylic bonding orbitals can be expected to reduce the bond angle from 120° (Gillespie,1960). The crystallographic literature was searched by Chatar Singh (1965) for heterocyclic structures containing protonated and unprotonated nitrogen atoms. From his survey, the range of values $125\pm3^\circ$ (for C-NH-C) and $116\pm3^\circ$ (for C=N-C) emerged.

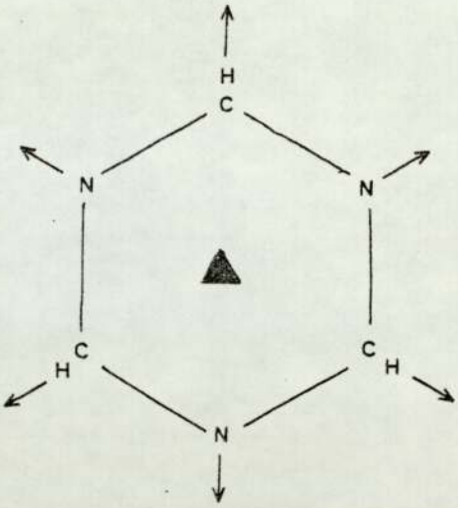
The above valence state electron pair repulsion theory has been investigated in detail crystallographically for simple systems. With use of low-temperature X-ray and neutron data on the unprotonated s-triazine and the protonated cyanuric acid, X-N syntheses of these structures have been undertaken (Coppens,1967; Coppens and Vos,1971). X-N synthesis is a variation of Fourier difference synthesis of the form (for a centrosymmetric structure)

$$\rho(\underline{r}) = \frac{1}{V}\sum_{\underline{h}} \left\{ (F_o)_{\underline{h}} - (F_c)_{\underline{h}} \right\} \cos 2\pi\, \underline{h}\cdot\underline{r}$$

where the terms $(F_o)_{\underline{h}}$ refer to the X-ray data and the terms $(F_c)_{\underline{h}}$ refer to structure factors calculated using X-ray scattering factors and neutron refinement positions. Since the neutron atomic positions are not influenced by the electron distribution, X-N synthesis reveals deviations from spherical symmetry of the electron cloud about the nuclei -- hence the bonding and lone-pair orbitals. Both the lone-pair orbitals of s-triazine and the bonding orbitals at the protonation sites of cyanuric acid were



I cyanuric acid



II s-triazine

	I	II
C(1) - N(2)	1.372	1.317
N(2) - C(2)	1.369	---
C(2) - N(1)	1.369	---
C(1) - N(2) - C(2)	124.6	114.8
C(2) - N(1) - C(2)	126.6	---

Table 1.2-2

imaged and the slight additional spreading of the lone-pair orbitals observed. In addition, the expected differences in bond distances and bond angles were observed (see Table 1.2-2).

1.3 Pharmacological Interest in the 1,2,3-Benzotriazines

Pharmacological interest in the 1,2,3-benzotriazines arose through the belief that the positively-charged N(2) of the 2-n-alkyl substituted 1,2,3-benzotriazines could imitate the quaternary nitrogen of acetylcholine. Subsequent in vitro experiments on frog rectus abdominus and chicken biventer cervicis muscle showed that the contractile activity of the 1,2,3-benzotriazine series persisted even in the presence of large quantities of tubocurarine (Cull and Scott,1973). It was therefore concluded that the compounds were not active at the acetylcholine receptor site. A similar effect was observed with the drugs quinine and quinidine (Lammars and Ritchie,1955). More recent research has suggested that the compounds may be active at the intracellular calcium binding sites (Muir and Scott,1977). Concentrations required to produce the contractile effect are at least an order of magnitude greater for the 1,2,3-benzotriazines than for acetylcholine and the response time is much longer. There appears to be antagonism between acetylcholine and the 4-benzylamino and 4-phenylamino series but not the 4-anilino and 4-p-tolylamino series (Cull and Scott,1973).

1.4 Pharmacological Interest in the 1,2,4-Triazolo-1,2,4-Triazines

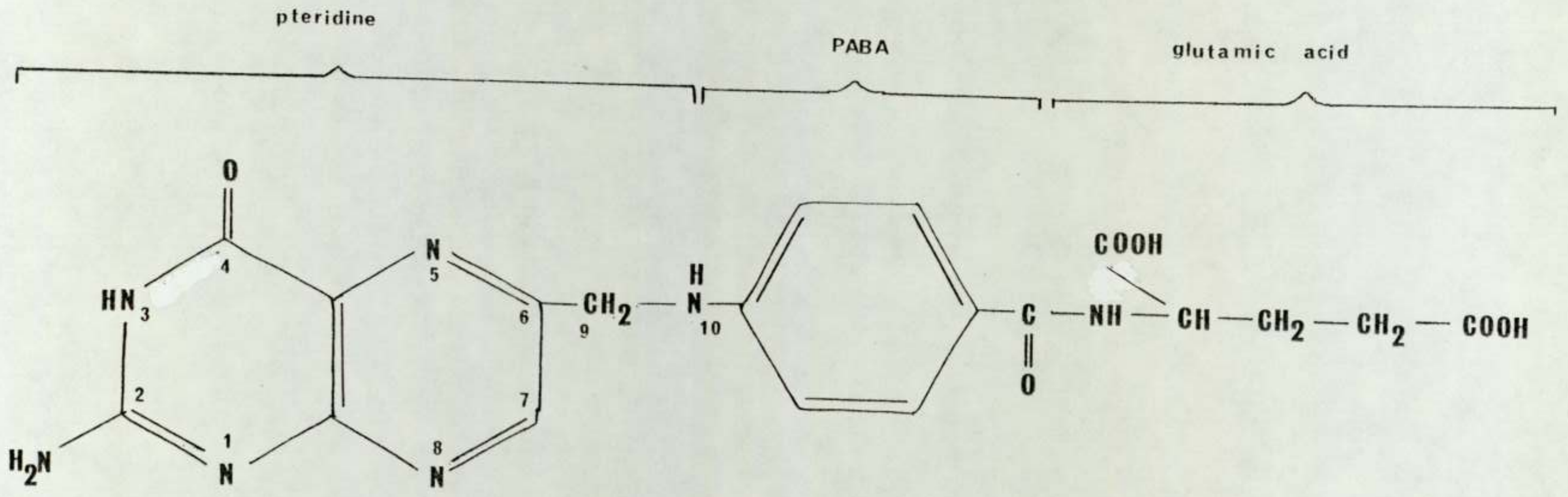
It is possible that the 1,2,4-triazolo-1,2,4-triazines act as purine analogues and inhibit the replication of DNA. 6-Methyl-1,2,4-triazolo -[5,1-c]-1,2,4-triazine or 7-methyl-1,2,4-triazolo-[5,1-c]-1,2,4- triazine may be the active metabolite of the anti-leukaemic agent methylglyoxal bis(guanilhydrazone) (Gray,1976). This series is, therefore, worthy of investigation as possible anticancer agents, although the only patent taken out on any member has been for herbicidal activity (Gray,1976).

Only two members of the series have been investigated crystallographically: 6,7-diphenyl-1,2,4-triazolo-[5,1-c]-1,2,4-triazine (Schwalbe, et al,1978) and its 7-ethoxy adduct (see Chapter 5). The structural determinations are of theoretical chemical interest since the 1,2,4-triazolo-1,2,4-triazines undergo Dimroth rearrangement (Daunis,et al,1969) and structure analysis confirms that the arrangement found in the crystalline state is the one with the lower CNDO-calculated energy (Guerret,et al,1971).

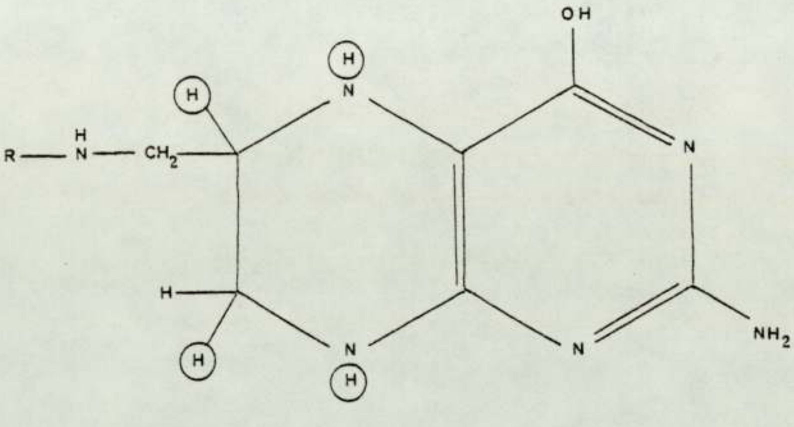
1.5 2,4-Diamino Compounds as Inhibitors of Dihydrofolate Reductase

1.5.1 The Biological Importance of Folic Acid

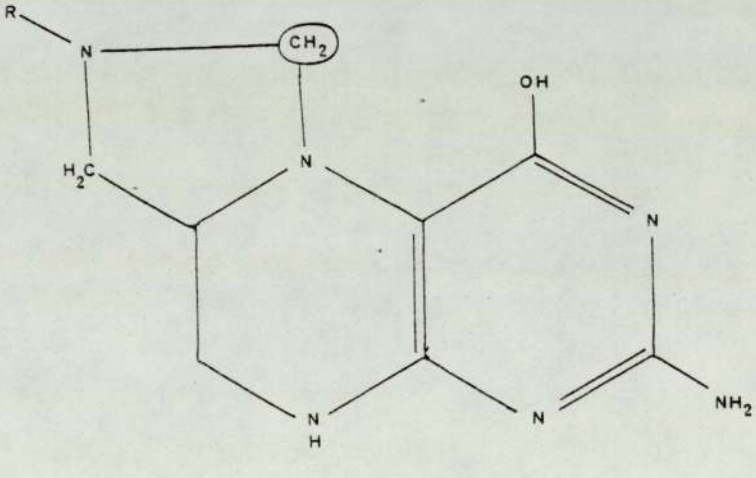
Folic acid (FA, 1.5.1-I) is an essential factor in the human diet, the minimum quantity required being of the order of 50 μg daily. The first symptoms of deficiency are


pteridine
PABA
glutamic acid
O
4
HN
3
N
5
2
1
N
8
N
6
7
H_2N
CH_2
9
H
N
10
C
O
NH
COOH
CH
CH_2
CH_2
COOH

1.5-I



1.5 -II



1.5 -III

anaemia with megaloblastic changes in the bone marrow. When it is ingested, folic acid must first undergo reduction to the dihydrofolate (FAH_2) and then the tetrahydrofolate (FAH_4, 1.5.1-II). Both these reactions may be catalysed by the same enzyme (Zakrzewski and Nichol,1960), the reaction being driven by the conversion of NADPH to $NADP^+$ (Futterman,1957):

$$FA + NADPH + H^+ \longrightarrow FAH_2 + NADP^+$$

$$FAH_2 + NADPH + H^+ \longrightarrow FAH_4 + NADP^+$$

FAH_4 undergoes further conversion to a number of one-carbon unit carrying cofactors which are then involved in amino acid interconversions and purine synthesis. (In the diagram of FA the 4(3H)-one form has been shown, while in the diagrams of FAH_4 and the cofactor 1.5.1-III the 4-hydroxy form has been shown; R=remainder of the molecule as in FA.)

There are important differences between host and parasite in the above description.

(1) Plasmodia and some pathogenic bacteria synthesise folate-containing cofactors _de novo_, i.e. from the folic acid constituents pteridine, p-aminobenzoic acid and glutamic acid (Ferone and Hitchings,1966).

(2) The above parasites use preformed folic acid extremely inefficiently -- probably after prior degradation of FA into its subunits (Ferone and Hitchings,1966). They therefore require no active

transport system for FA and presumably lack one (Baker and Ho, 1964).

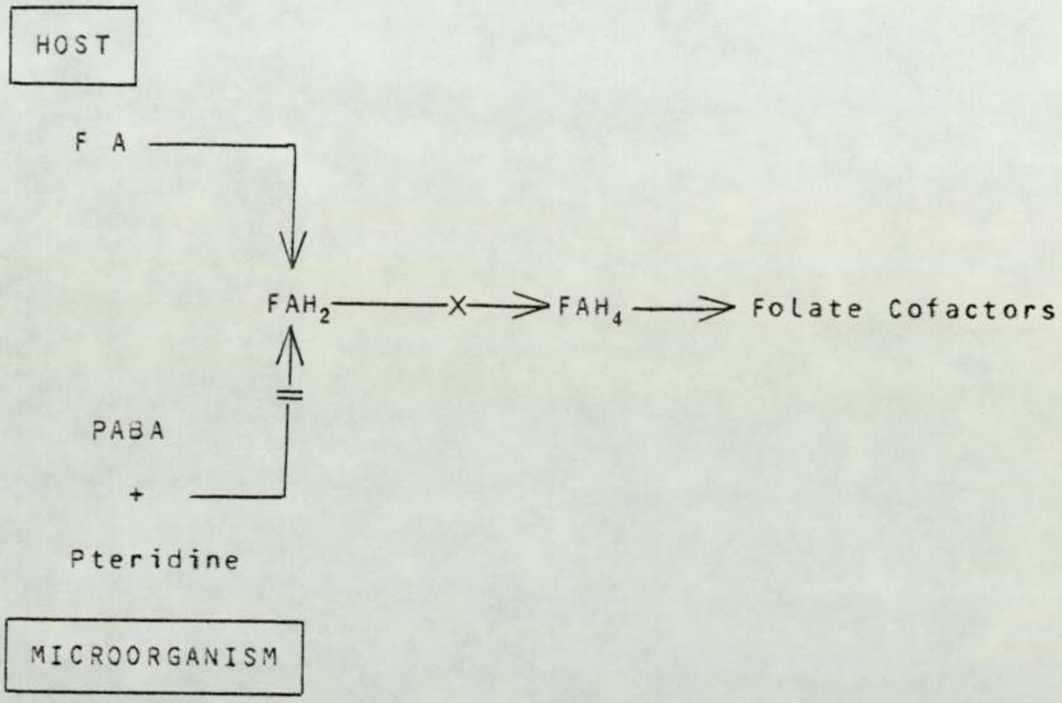
(3) There appear to be important host-parasite differences in the geometry of the active site of the dihydrofolate reductase (DHFR) enzyme (Hitchings and Burchall,1965)

The above considerations are important in the design of antibacterial and antimalarial agents. Fig 1.5.1-1 illustrates a strategy for the inhibition of folate cofactor synthesis in microorganisms. Host cells are partially protected against DHFR inhibitors by their active transport system for folic acid (Baker and Ho,1964). The sulphonamides are analogues of PABA and inhibit the synthesis of folic acid from its subunits. Sulphonamides and DHFR inhibitors act synergistically and are sometimes given in combination.

The activity of folate cofactors as carriers of one-carbon units has been reviewed elsewhere (Rader and Huennekens,1973). The 5,10-methylene-FAH coenzyme (1.5.1-III) appears to play a particularly important role mediating the interconversion of glycine and serine:

$$5,10\text{-methylene-FAH}_4 + \text{Gly} + H_2O \underset{\text{SHMT}}{\rightleftharpoons} \text{L-serine} + \text{FAH}_4$$

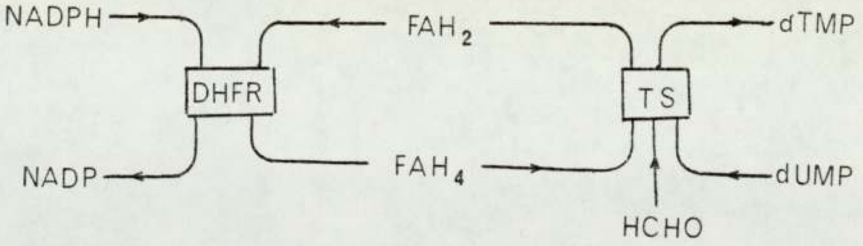
where SHMT=serine hydroxymethyltransferase (Blakley,1954), and the incorporation of one carbon atom from formaldehyde into thmidylate where use of tritiated FAH_4 has definitely confirmed the transfer of hydrogen from the folate to the



Inhibition of folate metabolism in microoganisms (after Ferone and Hitchings,1966). Sulfonamides act at the site marked =. DHFR inhibitors act at the site marked X.

Fig 1.5.1-1

thymine methyl group (Pastore and Friedkin,1962):



where TS=thymidylate synthetase. In this cycle the need for continuous regeneration of FAH_4 can be seen and the 'thymine-less death' of cells where DHFR has been irreversibly inhibited has been documented. The FAH_4-dependent incorporation of C^{14} from formaldehyde into methionine has also been observed (Nakao and Greenberg,1958). The conversion of FAH_4 to the one-carbon carrying cofactors probably occurs non-enzymically (Blakley,1960).

1.5.2 The Classical Inhibitors

For some time it has been known that the substitution of an amino group for the 4-(3H)-one group of FA greatly increases binding to the enzyme DHFR, preventing the reduction of FAH_2 to FAH_4, thus blocking the incorporation of one-carbon units into thymine, a requirement for DNA synthesis. Simple substitution at the 4-position yields a compound (aminopterin) which binds to the enzyme more strongly by a factor of the order of 10^5 (Werkheiser,1961). Methylation of N_{10} yields amethopterin (Methotrexate,BP -- MTX). These compounds are potent inhibitors of DHFR, whatever the source, and attack all rapidly-dividing cells.

Methotrexate has been used in the treatment of acute leukaemia (Li,et al,1958). In combination with other agents it may be useful in the treatment of carcinoma of the breast, ovary and colon (Goth,1972). Undesirable effects listed by the British Pharmaceutical Codex (1973) include: nausea, vomiting, ulceration and haemorrhage of mouth and bowel, kidney damage, bone-marrow depression, fall in white blood cell and platelet counts and hair loss. The non-specificity of these compounds and the failure to develop others which preferentially inhibit DHFR from malignant cells represents a very great disappointment in the advance in cancer chemotherapy in this decade.

1.5.3 The Mechanisms of DHFR Binding

The mechanism of binding of folates to DHFR has been the subject of intense research since the mid-sixties. Early theories sought to explain the enhanced binding of aminopterin in terms of the difference in hydrogen-bonding potential between the 4-hydroxy and the 4-amino group. Zakrzewski (1963) observed that the energy involved in promoting FA from the stable keto form (4-one,protonated at N(3)) to the 4-hydroxy form could explain some, but not all, of the difference in binding constants between FA and aminopterin. In the hydrogen-bonding scheme published (see Fig 1.5.3-1) N(1) acted as a site of hydrogen bond acceptance, although there was no thermodynamic evidence indicating the direction of the hydrogen bonding. More recently the focus has shifted to some of the less direct effects of the replacement of 4-OH by 4-NH_2. Perault and Pullman (1961) showed on the basis of LCAO molecular orbital calculations that the change of substituent shifted the site of greatest basicity from N(8) to N(1). All crystallographic studies of DHFR inhibitors (see Chapter 10) have shown that when the molecule is protonated, the hydrogen is attached at N(1) (or its equivalent, N(3), in the case of s-triazine systems). The effect of the change of substituent may, therefore, be indirect: the 4-amino substituted pteridines have N(1) as a site for hydrogen-bond donation -- which the folates do not. Recent ultraviolet spectroscopic evidence (Erickson and Mathews,1972; Poe,et al,1974) has indicated that the degree of protonation of methotrexate is enhanced upon binding to DHFR -- strongly supporting the hypothesis that there is a nearby hydrogen bond acceptor site on the enzyme. That an equivalent change in the ultraviolet spectrum is not observed in FA,FAH_2 or dihydroaminopterin is further evidence that protonation may be an essential feature for greatly-enhanced binding.

Recently Matthews and co-workers have succeeded in solving the crystal structure of two DHFR-MTX complexes. In the first (Matthews,et al,1977) the source of the enzyme was MTX-resistant E.coli. The list of interactions between the drug and the amino acid side-groups in the neighbourhood of the active site is given in Table 1.5.3-2. Of particular interest is the existence of a negatively

charged carboxylate group from Asp-27 which is in a position to stabilise the protonation of N(1). Moreover, the backbone amide of Gly-95 is only 3.2 Å from the 4-amino group and is positioned in such a way as to be able to donate a hydrogen-bond to the 4-keto group. Thus it may be possible for the 4-radical of the DHFR substrates to be either a hydrogen bond recipient or a donor.
Crystallographic investigations of known DHFR inhibitors (see Chapter 10) have shown that with one exception the amino nitrogens are sp^2 hybridised. The one exception -- 2,4,6-triamino-5-chloroquinazoline (Rogan and Williams,1979) -- may be of very great importance. Here the amino group attached to C(2) is partially sp^3 hybridised, probably under the influence of hydrogen-bond acceptance from the C(6) amino group. Such simultaneous hydrogen bond donation and acceptance by an amino group has been reported only once previously (Andreetti,et al,1970), but does open the possibility that the C(4) amino group on the inhibitors may be in a position to use both the hydrogen-bond acceptance and donation capacity of the enzyme (Schwalbe,et al,1979).

In the second crystal structure of DHFR (Matthews, et al,1978) the enzyme was obtained from MTX-resistant L.casei and was in the form of the DHFR-MTX-NADPH complex. The differences between the two structures will reflect not only minor differences between the amino acid sequence of the enzyme from the two species, but also differences caused by the NADPH molecule, which is attached very near to the active site.

Zakrzewski's hydrogen bonding scheme for aminopterin (A) and folic acid (C) is shown in Fig 1.5.3-1. The scheme requires that folic acid (B) be converted to the 4-hydroxy form before binding. The illustration is taken from Zakrzewski's 1963 paper. The chemical structure of the coenzyme NADPH is shown in Fig 1.5.3-3. The position of the MTX molecule is illustrated in relation to the amino-acid backbone of DHFR in Fig 1.5.3-4. Stereo views of the E.coli DHFR-MTX complex (Fig 1.5.3-5) and the L.casei DHFR-MTX-NADPH complex (Fig 1.5.3-6) have been included. Fig 1.5.3-4 was taken from the paper of Matthews,et al(1977) while Fig 1.5.3-5 and Fig 1.5.3-6 were taken from the paper of Matthews,et al(1978).

1.5.4 The Non-classical Inhibitors of DHFR

Attention since the mid-sixties has shifted away from 'classical antifolates' which are minor modifications of folic acid to ring systems other than pteridine, usually with aryl substituents.

Other heterocylic ring systems which have been found to be DHFR inhibitors comprise (a) the 2,4-diamino-pyrido[2,3-d] pyrimidines (Hurlbert,et al,1968;Hurlbert and Valenti,1968) with the N(5) of pteridine replaced by a carbon atom, (b) the 2,4-diaminoquinazolines (Ashton,et al,1973), (c) the 2,4-diaminopyrimidines (Baker,et al,1965,1970) -- this series includes the antibacterial

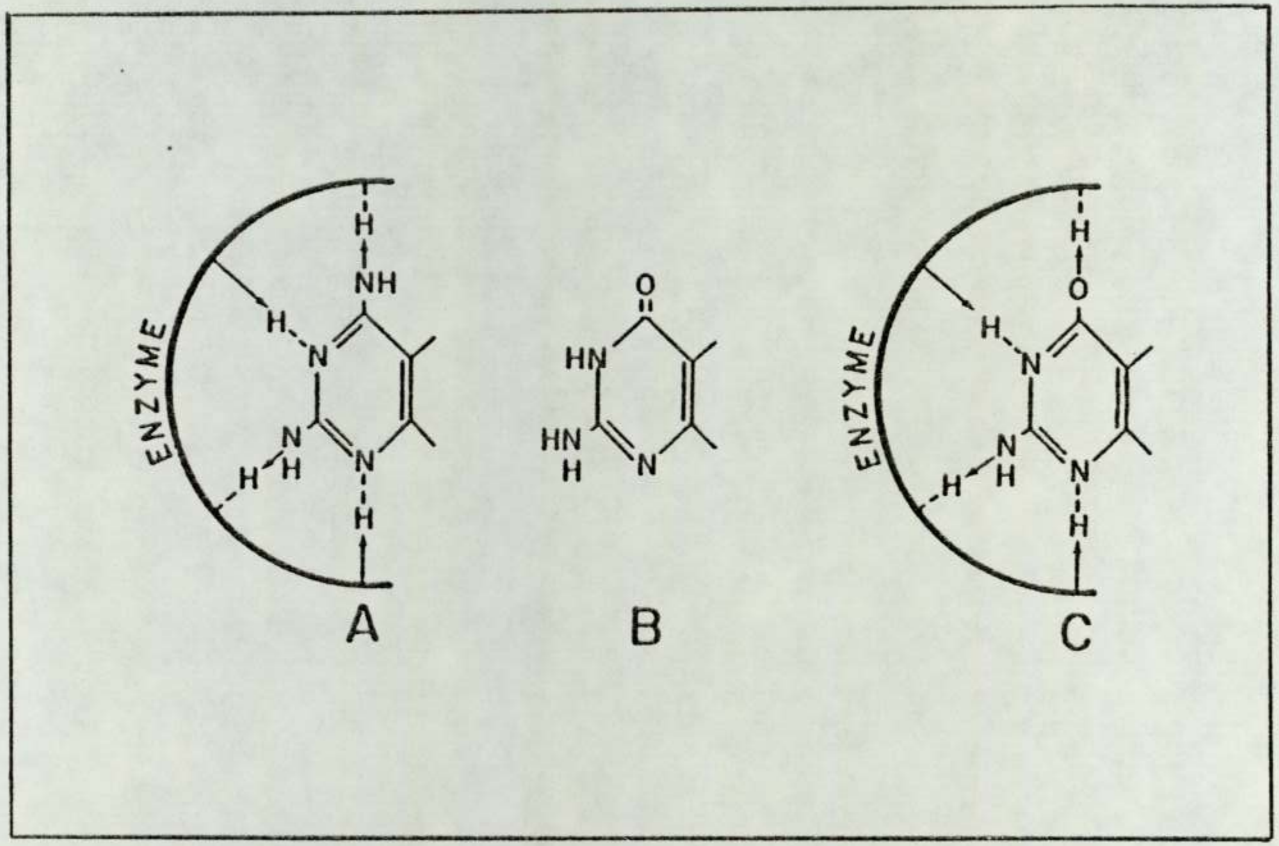


Fig 1.5.3-1

INTERACTIONS INVOLVED IN BINDING MTX TO DHFR*

(1) Primary Hydrophobic Pocket

- (a) Van der Waals contacts between the pteridine ring and the side chains of Ile-5, Ala-7, Leu-28,Phe-31 and Ile-94.
- (b) π - π interaction between the fragment N(1)-C(2)-N(2)H_2-N(3) of the pteridine ring and the Ala-6 to Ala-7 peptide bond (separation distance = 3.5A).
- (c) Hydrogen-bond donation from N(2) to the side-chain hydroxyl of Threonine - 113.
- (d) Hydrogen - bond donation from N(4) to the carboxyl oxygen of Ile-5.
- (e) Hydrogen-bond donation from N(1) to the carboxyl group of Asp-27.

(2) Secondary Hydrophobic Pocket

- (a) Van der Waals contact between the aromatic ring of the p-aminobenzoyl moiety and the side chains of Leu-28 Ile-50, Leu-54 and Ile-94.
- (b) Van der Waals contact between the β-carbon of Ser-49 and the methyl group at N(10).
- (c) Hydrogen-bond acceptance by α-carboxyl group from Arg-57.

*Matthews *et al*, 1977

Table 1.5.3-2

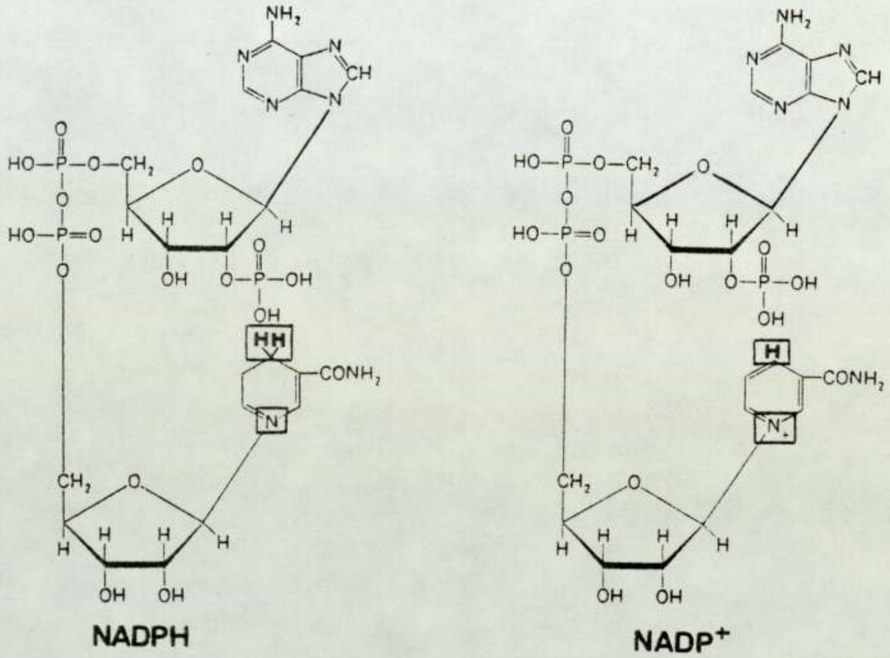


Fig 1.5.3 - 3

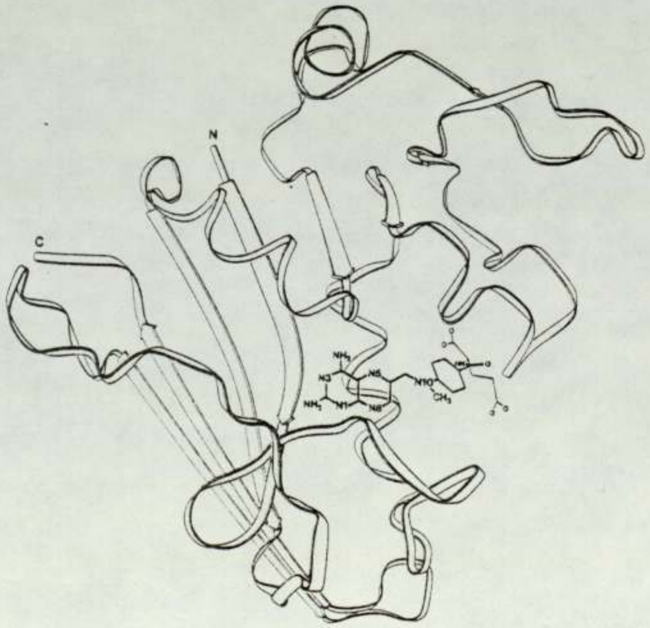


Fig 1.5.3 - 4

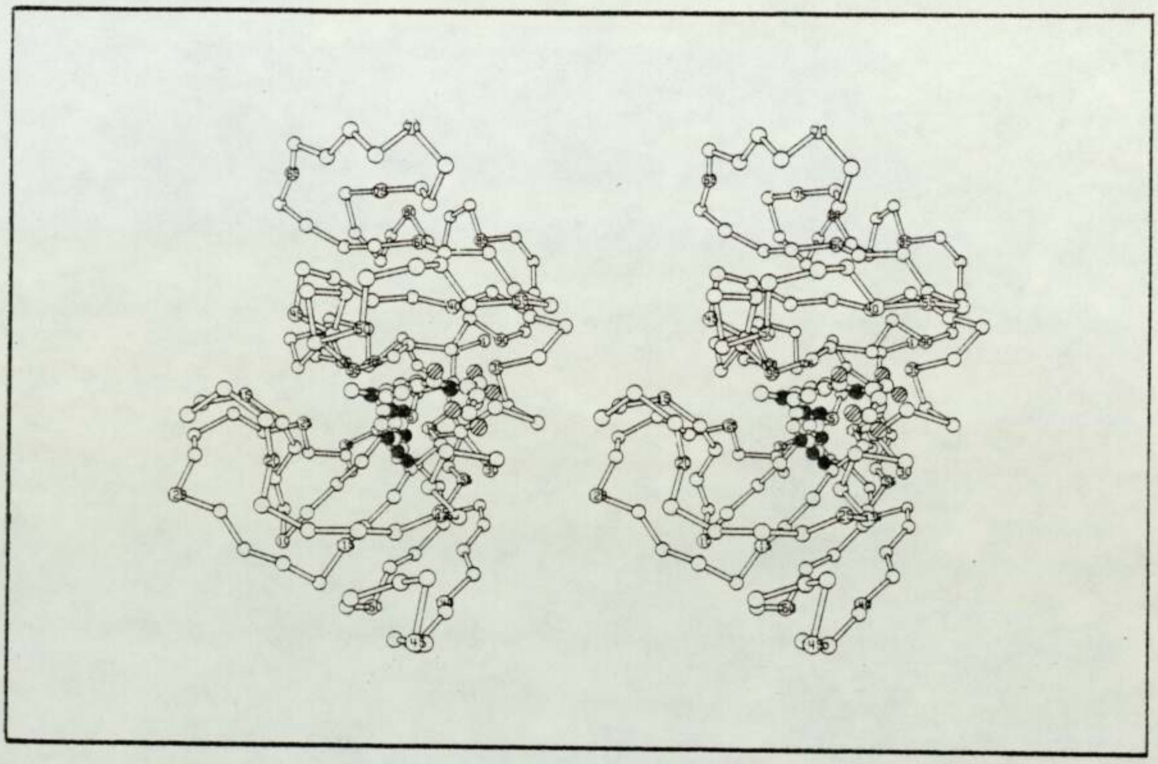


Fig 1.5.3-5

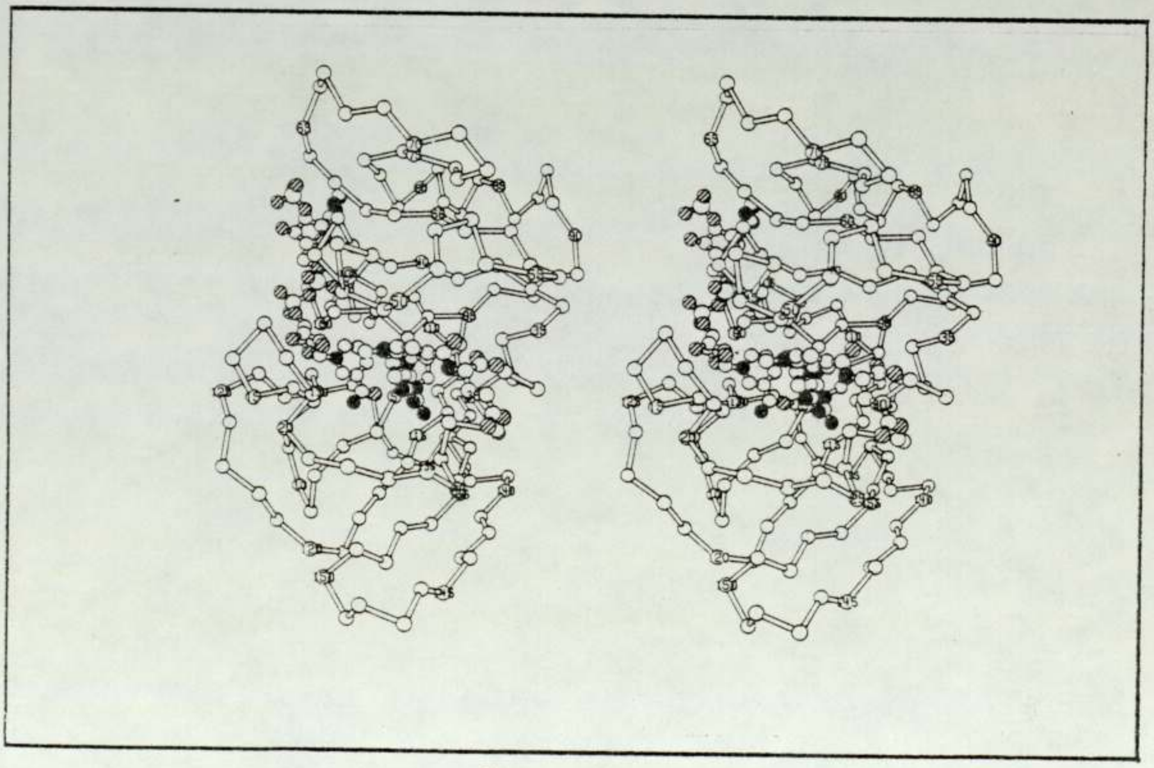


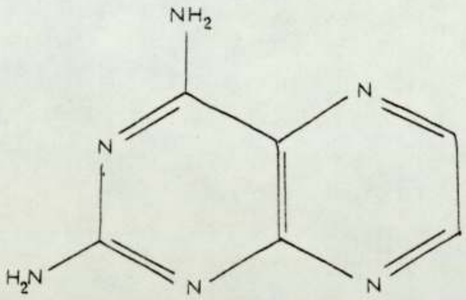
Fig 1.5.3-6

drug Trimethoprim and the antimalarial Pyrimethamine-- and (d) the 4,6-diamino - 1,2-dihydro-s-triazines (Baker and Ho,1966), a series which includes the antimalarial Cycloguanil and the experimental anticancer agent Triazinate (Skeel,et al,1974).

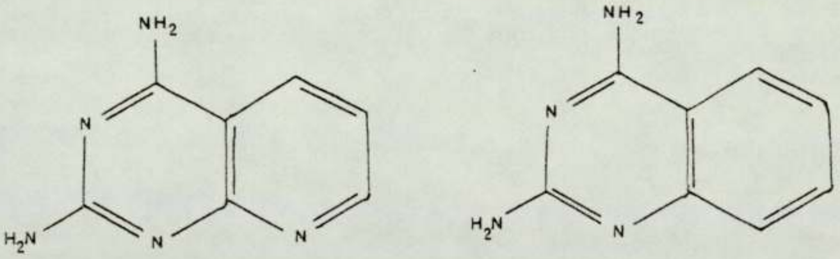
Members of all these series have been investigated crystallographically. Two examples are reported in Chapters 6 and 7 and a survey of the crystallographic studies is given in Chapter 10. The development of the non-classical DHFR inhibitors has been motivated by the possibility of exploiting host-parasite differences with respect to the enzyme active site and active transport system (see Sec 1.5.1). B.R.Baker and his colleagues have examined a variety of non-classical inhibitors for differences in activity depending on the source of the enzyme (Baker,1967). A survey of these results has elucidated some of the geometrical requirements for inhibitory activity (Hitchings and Burchall,1965). These are illustrated in Fig 1.5.4-2.

Hansch and co-workers have characterised the observed activity of the enzyme inhibitors in terms of a number of independent variables (Hansch,et al,1973b) with empirically-determined values for each functional group (Hansch,et al,1973a). The technique -- called quantitative structure-activity relationships (QSAR) -- has been applied to the inhibition of DHFR by substituted pyrimidines (Yoshimoto and Hansch,1976), p-substituted phenyl-2,2-dimethyl - 4,6-diamino-s-triazines (Silipo and

Heterocylic Ring Systems of Known DHFR Inhibitors

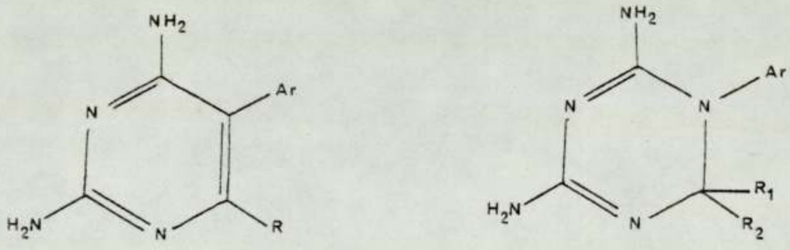


2,4-diaminopteridine



a) 2,4-diamino-pyrimido-[2,3-d]pyridine

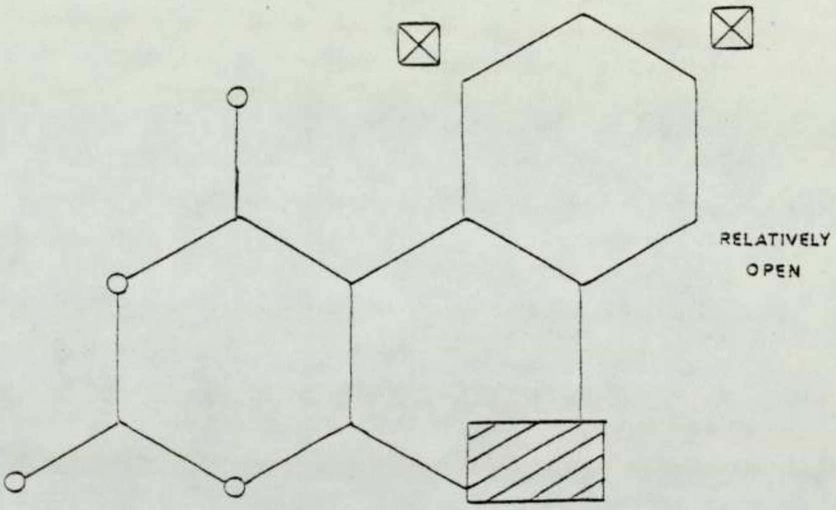
b) 2,4-diaminoquinazoline



d) 2,4-diaminopyrimidine

e) 4,6-diamino-1,2-dihydro-s-triazine

Fig 1.5.4-1



Geometrical considerations in DHFR inhibition
(Hitchings and Burchall,1965)

○ Binding Sites (all species)

☒ Binding Sites (species differences)

▨ Geometrical Limitations (species differences)

Fig 1.5.4-2

Hansch,1976) and quinazolines (Fukunaga,et al,1976).

QSAR analyses of 4,6-diamino-2,2-dimethyl-1-aryl-s-triazines has indicated that there are important differences in the hydrophobic pocket between the mammalian and bacterial enzymes with the mammalian pocket being the smaller of the two (Hansch,et al,1979).

1.5.5 Crystallographic Investigation of a Folate Cofactor

A very recent advance in the study of the stereochemistry of folic acid has been the crystal structure analysis of two diastereomers of 5,10-methylene-FAH_4 (Fontecilla-Camps, et al,1979). The two structures differ only at the asymmetric carbon C(6) on the pteridine ring, and in the crystalline state the structures are approximate mirror images of each other, with the exception of the L-glutamate portion of the molecule, which exhibits a considerably different conformation in the two structures. The cell dimensions of the two structures are given in Table 1.5.5-1. No coordinates were published in this preliminary report. The structure (+)5,10-methylene-FAH_4 appears to be the natural diastereomer. The structure appears to be highly conjugated with the imidazoline ring formed by the 5-10 bridging, the pteridine rings and the phenyl substituent all coplanar to within ±0.35 Å. This is quite a different situation to the near-perpendicularity observed for the crystalline DHFR inhibitors (see Chapter 10) and Methotrexate in the DHFR-MTX complex. It must be

Unit Cell Dimensions

of

Two Diastereomers

of

5,10-Methylene-FAH_4

	(+)	(-)
Space Group	$P2_1$	$P2_1$
a	12.696	12.459
b	14.487	14.528
c	6.990	7.006
β	100.80	96.06

a) both diastereomers exist in the crystalline form $(5,10\text{-methylene-}FAH_4)^+ \cdot 2Br^- \cdot 2H_2O$

Table 1.5.5-1

remembered, however, that because the conversion of FAH_4 to 5,10-methylene-FAH_4 is non-enzymic these compounds are not DHFR substrates.

1.6 Fused Six-membered Rings

The π-bond orders of fused ring systems are not equally distributed in fused ring systems even in the absence of nitrogen substitution. In the three possible resonance structures for naphthalene (see Fig 1.6-1) some bonds are double in two cases whereas others are double in only one. Unequal bond lengths have been observed in the crystal structure of naphthalene.

Naphthalene crystallises in space group $P2_1/a$ (equivalent to $P2_1/c$) with a=8.235 Å, b=6.003 Å, c=8.658 Å and β=122.9°. The structure was solved originally by Abrahams,et al (1949) and later refined by Cruikshank (1957). The point group symmetry of the molecule in the crystalline state is $\bar{1}$, a subgroup of <u>mmm</u> expected on the basis of purely chemical considerations. Differences in the crystal structure between chemically equivalent bonds are not significant statistically. The bond lengths shown in Fig 1.6-1 are parameters from Cruikshank's refinement with equivalent bonds averaged and corrections applied for rotational motion of the molecule.

In some cases the characteristic differences in bond length persist when nitrogen atoms are substituted into the ring system. Significant differences have been found between the lengths of bonds C(5)-C(6) and C(7)-C(8) and

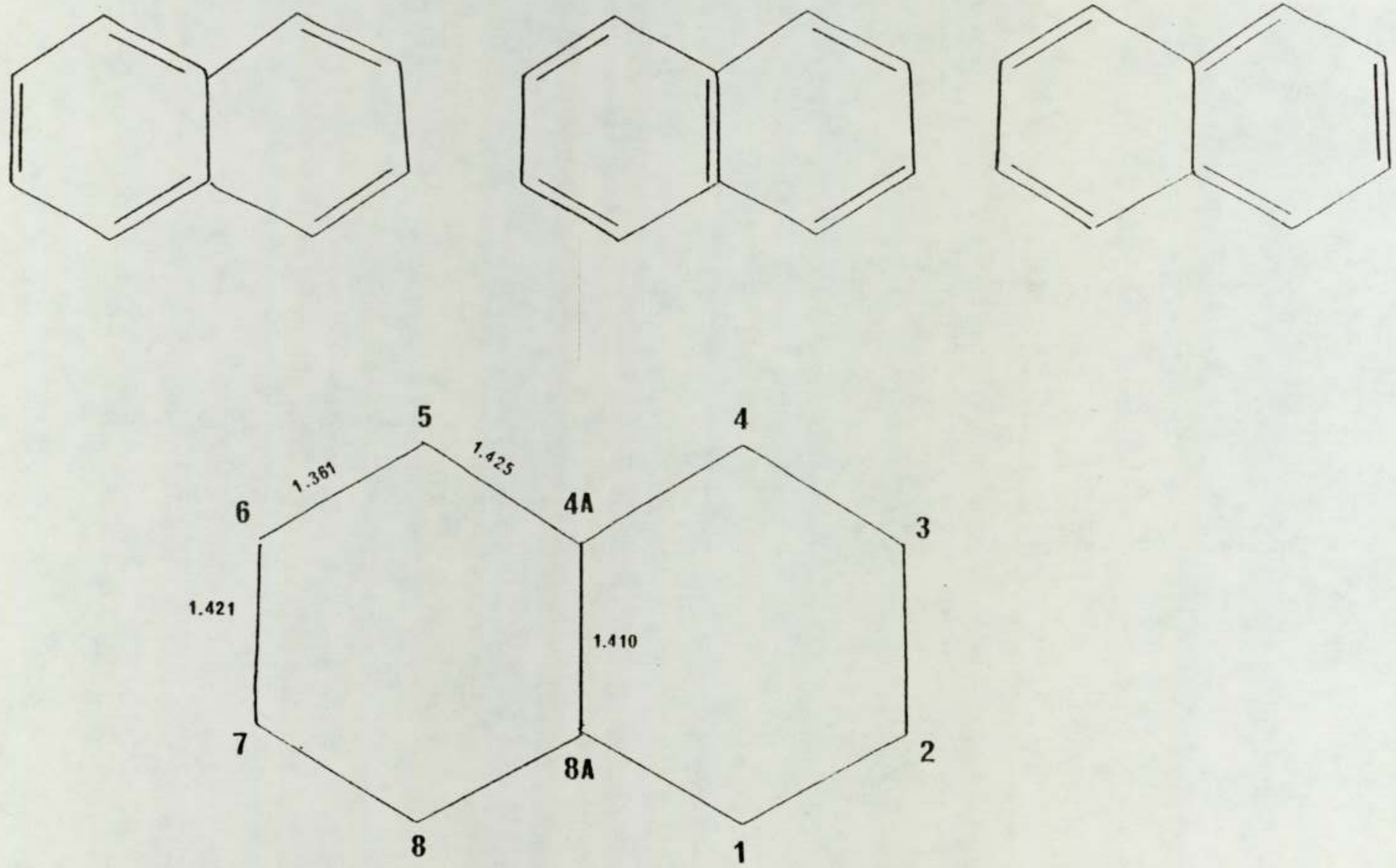


Fig 1.6-1

the lengths of the bonds C(4A)-C(5) and C(8)-C(8A) in the fused six-membered ring structures included in this study.

Chapter 2: Implemented Crystallographic Software

2.1 Introduction

The Medicinal Chemistry section of the Aston University Pharmacy Department has access to the following computers:

(a) CDC 7600 at U.M.R.C.C

(b) ICL 1904S at Aston

(c) HP2000 at Aston

The usual strategy has been to solve the structure and carry out early isotropic refinement on the 1904S, then proceed to final anisotropic refinement on the CDC7600. The situation, however, is changing rapidly. Initially (1975) the CDC7600 suffered from difficulties with the link to the local computer with the result of extremely long turnaround times and frequently lost jobs. In addition, the only supported crystallographic package was XRAY72. The implementation of the SWAN system greatly improved the reliablity of the link and cut turnaround times by an order of magnitude, while at the same time increased undergraduate use of the 1904S has meant a steady increase

	ICL 1904S	CDC7600[a]
Wilson Plot	NORMAL	NORMAL
MULTAN	MULTAN	MULTAN78
Centrosymmetric Direct Methods	-----	EEES (SHELX)
Least-squares Refinement	ORFLS XRAY72	L.S. (SHELX)
Least-squares Planes	Gottingen Program GEOM78	XRAY72
Bond Distances, Angles and Torsion Angles	MOLJOM GEOM78	XRAY72
Unit-cell Contents	CELPIC	PLUTO[b]
Ball-and-Spoke/ Space-filling Models	-----	PLUTO
Thermal Ellipsoid Models	-----	ORTEP
Fourier Synthesis	PHUSIS/FURSUM	XRAY72 FMAP (SHELX)
Fourier Peak Search	PEAKS	XRAY72 FMAP (SHELX)
Data Reduction	BAKSUB[c] BHAMDR[d]	XRAY72 AXIS (SHELX)
Crystallographic Literature Search	-----	RETRIEV
Structure Connectivity Search	-----	CONNSER

a) The Crystals package was mounted at UMRCC but never used in this department.
b) The author twice unsuccessfully attempted to implement PLUTO on the 1904S before it became available at UMRCC.
c) for four-circle data only.
d) Birmingham University data reduction program for Stoe two-circle data -- supplied by Dr. T.A.Hamor of the Chemistry Department.

Table 2.1-1

in the times taken for jobs to be run at Aston. At the time of writing (1979) turnaround on the CDC7600 is about equal for medium-sized jobs (say 60 sec. with 40K core on the 1904S) while for larger jobs the turnaround is actually better. In addition a number of new crystallographic packages have been mounted on the CDC7600. It is probable that in the future structures will be solved ab initio at U.M.R.C.C. Table 2.1-1 shows a survey of crystallographic software now available on the two computers. In 1976 the HP2000 was installed at Aston University. This computer with its interactive BASIC programming facility provides a useful service where immediate answers are required for comparatively simple problems.

2.2 Normalised Structure Factors

Direct methods programs require that the structure factors be placed on an absolute scale -- i.e. that the numerical value of the structure factor be independent of its position in reciprocal space. The principal method of achieving this is the Wilson Plot Method (Wilson,1942) which has been described in textbooks (see, for example, Woolfson,1970 - p332). Where the Lp-corrected intensities have been averaged over a particular range in θ (mean value $\langle I_\theta \rangle$) then

$$\langle I_\theta \rangle = K \sum\nolimits_\theta \exp(-2B \sin^2\theta/\lambda^2)$$

where K is a scale factor and $\sum_\theta$ is the structure factor for a randomly-distributed set of atoms calculated with the atomic scattering factors evaluated at the appropriate $\sin\theta/\lambda$. $\underline{B}$ is an overall isotropic temperature factor. Since

$$\log_e\left\{\frac{\langle I_\theta\rangle}{\Sigma_\theta}\right\} = \log_e K - 2B\sin^2\theta/\lambda^2$$

a plot of the logarithm of the ratio on the left vs. $\sin^2\theta/\lambda^2$ will have an intercept log $\underline{K}$ and gradient $-2\underline{B}$. It is essential that the averaging involved in the calculation of $\langle I_\theta\rangle$ be carried out over all points in the reciprocal lattice, including those corresponding to systematic absences. The above procedure enables the scaling of the observed structure factors:

$$I_{hkl} = K|F_{hkl}|^2$$

i.e.

$$|F_{hkl}| = k\, I_{hkl}^{1/2}$$

where $k=1/\sqrt{K}$, and the placement of the structure factors on an absolute scale:

$$E_{hkl} = \frac{|F'_{hkl}|}{\varepsilon\Sigma_\theta}$$

where ε is a factor correcting for systematic absences and the structure factors have been corrected for thermal vibration:

$$|F_{hkl}| = |F'_{hkl}|\exp(-B\sin^2\theta/\lambda^2)$$

The factor ε accounts for the systematic absences for the particular space group and class of reflexion: e.g. in $P2_1/c$ $\varepsilon=2$ for reflexions of the h0l and 0k0 classes and $\varepsilon=1$ for all others.

The above features have been incorporated into the Fortran program NORMAL (Main,1972). An additional feature of this program is that the calculation of $\sum_\theta$ can also be done on the basis of randomly-oriented molecular fragments. This procedure eliminates some of the irregularity resulting from the non-random nature of the structure. Calculations on the basis of randomly-distributed atoms (Wilson calculation) and on the basis of these atoms being incorporated into rigid fragments (Debye calculation) appear on the final output. The quantities $\underline{k}$ and $\underline{B}$ are calculated from a least-squares fit to the Debye curve. NORMAL was implemented on the 1904S at Aston University by Dr. C.H.Schwalbe during the period 1972-73. A version has also recently been made available on the CDC7600.

SHELX (Sheldrick,1976) has its own normalised structure factor calculation procedure called using the MERG instruction. The method used is that of Karle,et al (1958).

2.3 MULTAN

MULTAN (Main,et al,1971) is a computer program for the largely automatic solution of crystal structures of moderate complexity. It is applicable to centrosymmetric and non-centrosymmetric structures; however, since all structures described in the present study are centrosymmetric, discussion here will be limited to phase determination where the only allowed angles are 0 and 180°.

The program is divided into three sections (1)SIGMA2, (2) CONVERGE and (3) FASTAN.

The SIGMA2 section records triplets of the type $\underline{h}\underline{k}\underline{l}$, $\underline{h}'\underline{k}'\underline{l}'$ and $\underline{h}-\underline{h}'$ $\underline{k}-\underline{k}'$ $\underline{l}-\underline{l}'$. The expected phase of the reflexion E(hkl) is given by

$$s\left\{E\left(hkl\right)\right\} \approx s\left\{E\left(h'k'l'\right)\right\} \bullet s\left\{E\left(h-h'\,k-k'\,l-l'\right)\right\}$$

where the notation $s\{\}$ indicates the sign of the quantity indicated within the curly brackets. The probability that the phase assignment is correct depends on the product of the magnitudes of the three E-values. The program calculates from the N_1 strongest E-values the indices for the N_2 triplets for which the probability of correct phase assignment is best. The quantities N_1 and N_2 are input by the user and are subject to dimensioning within the program. The triplets are weighted on the basis of the product of the E-values for later phase refinement.

In the centrosymmetric space group the phases of reflexions with all indices even are independent of the choice of origin. The probable phase of these reflexions is given by the Σ_1 formula of Hauptman and Karle(1953):

$$s\left\{E\left(2h\,2k\,2l\right)\right\} \approx s\left\{\left|E\left(hkl\right)\right|^2 - 1\right\}$$

Starting Set of Reflexions

Type	Number	Restrictions
Σ_1	depends on PROB input	parity group ggg only
origin-determining	3	no two from same parity group none from parity group ggg
permuted	N input	2^N phase permutations computed, i.e. phase refinemnt computing time is doubled for each additional reflexion.

Table 2.3-1

These reflexions are used in the starting set for refinement if the probability exceeds a value PROB specified by the user. The CONVERGE procedure then determines the best three reflexions of appropriate parity group to be used for origin definition. This procedure is the equivalent of choosing which of the eight centres of symmetry within the unit cell is to be the origin. The best reflexions are those which enter into a large number of strongly-determined Σ_2 relationships. The algorithm for determining these is described in the program documentation. In addition, the user is allowed to start the phase refinement with each permuted reflexion set alternatively positive and negative. Where N is the number of permuted phases, 2^N phase refinements are undertaken. The value of N is limited by practical considerations of use of computer time. The indices of the reflexions to be permuted are calculated within the CONVERGE procedure according to the criteria (1) they should enter into a large number of strongly-determined Σ_2 relationships and (2) they should be as Σ_2-independent of the origin-determining reflexions as possible. Since the signs of all reflexions are allowed to vary in the final stages of phase refinement, increasing the number of reflexions to be permuted does not necessarily lead to an increased number of independent solutions (see below).

During the CONVERGE procedure the initial unphased set of strongest E(hkl)'s have been condensed to a small starting set of reflexions for which the signs have at least initially been determined. The FASTAN procedure is essentially a reversal of this process with the phases of the starting set being propagated through the unphased set by the weighted Σ_2 formula

$$s\{E_h\} = s\{B_h\}$$

where

$$B_h = \sum_{h'} \omega_{h'}\omega_{h-h'} \left|E_{h'}\right| \left|E_{h-h'}\right| s\{E_{h'}\} s\{E_{h-h'}\}$$

and

$$\omega_{h'} = \tanh\left(\tfrac{1}{2} \left|E_{h'}\right| B_{h'}\right)$$

The vectors of type $\underline{h}$ refer to the reflexions from the planes with Miller indices $\underline{hkl}$. The summation is taken over all three indices. Originally only the starting set are phased and weighted (ω_h=1 for origin-fixing and permuted reflexions; ω_h=2(p-1/2) for the Σ_1 reflexions). The reflexions are phased in the reverse order to that in which they were eliminated from the search for strong Σ_2-contributors. Once a first-approximation set of phases has been determined, the procedure can be restarted with the summations taking place over all E(hkl)'s. The relexions are allowed to change in sign when the weight-determination procedure returns a weight ω_h>2(p-1/2). The process is repeated until it has essentially converged.

The phases of the other starting set reflexions are held constant until the last few cycles. When these are allowed to change the result sometimes produced is a duplication of phase sets, often origin-shifted.

Details of the computation of the figures of merit are given in the program documentation and the literature cited therein:

ABS FOM: The absolute figure of merit tests the internal consistency of the sign determinations. With satisfactory recycling the ω_h's increase and these are compared to those for a random structure. A correct set of phases will give ABS FOM a value of about 1.2. A set of phases with ABS FOM less than 0.8 is highly unlikely to be correct.

PSI ZERO: This figure of merit is defined by Cochran and Douglas (1954)

$$\psi_o = \sum_{h} \left| \sum_{h'} E_h E_{h-h'} \right|$$

where the outer summation is over a separately-input set of very weak reflexions. For these it is expected that the Σ_2 phase indications will be very weak and an unusually high ψ_o is a diagnostic feature of a pathological phase determination -- eg. setting all phases to the same value.

RESID: This is the Karle R-factor in the form

$$R_K = \frac{\sum (|E_{obs}| - |E_{calc}|)}{\sum |E_{obs}|}$$

(Karle and Karle,1966). The calculated E-values are computed according to

$$E_h = k \langle E_{h'} \; E_{h-h'} \rangle_{h'}$$

where k is a scale factor. For a reasonably correct set of phases RESID should be less than about 30 per cent. MULTAN has been implemented on the ICL 1904S at Aston University by Dr. C.H.Schwalbe. A revised version of MULTAN employing magic integers (Woolfson,1977) has become available on the CDC7600 at UMRCC.

2.4 EEES

An alternative centrosymmetric direct methods approach has recently been made available with the implementation of SHELX on the CDC7600 at U.M.R.C.C. Here the approach, rather than recycling, is to start with a very large number of permutations of signs (of the order of 2^{10} to 2^{20}) and to eliminate early on during sign expansion those sets which are giving poor agreement (Sheldrick,1978). The test applied is

$$\mathbf{M}(\mathrm{abs}) = \frac{\Sigma\, \alpha - \Sigma\, \langle \alpha^2 \rangle_r^{1/2}}{\Sigma\, \langle \alpha^2 \rangle_e^{1/2} - \Sigma \langle \alpha^2 \rangle_r^{1/2}}$$

Where the quantities on the right-hand side have been defined elsewhere (Karle and Karle,1966; Germain,et al,1970). At any stage if M(abs) is less than a threshold

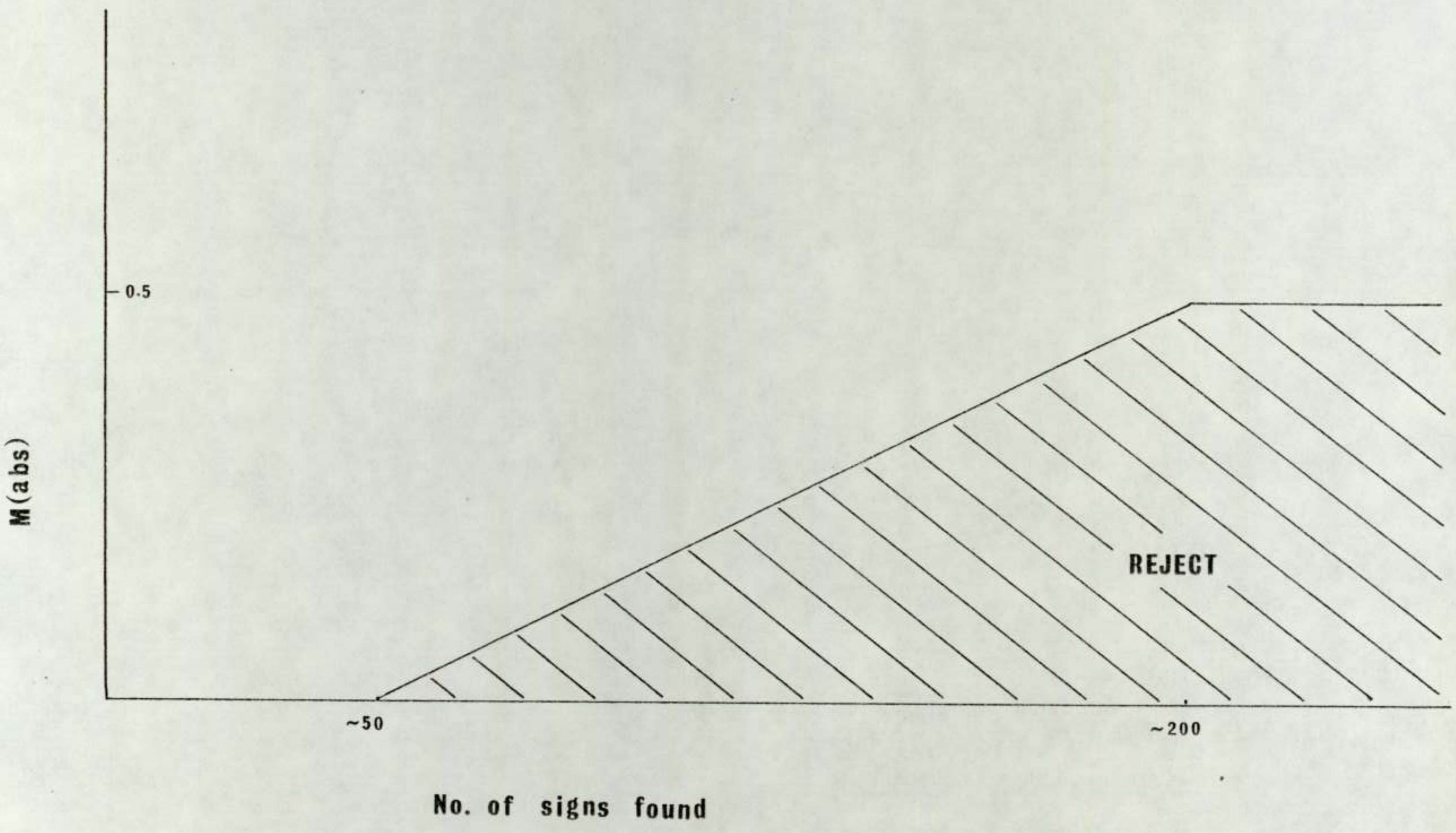


Fig 2.4-1

value (which itself increases during expansion) then the expansion is discontinued and the set rejected as a possible starting set (see Fig 2.4-1). E-maps are computed and figures of merit calculated for the surviving sets.

2.5 Least-Squares Refinement

2.5.1 ORFLS

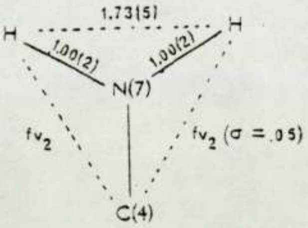
ORFLS is a general-purpose crystallographic least-squares program (Busing,et al,1962) widely cited in published structural papers, particularly in the 1960's. The program has rigid sin θ minimum and maximum and |Fobs| minimum cut-offs under user control. Several different weighting schemes are allowed. The University of Aston version, implemented by Dr. C.H.Schwalbe on the 1904S is subject to the following limitations: a maximum of 110 parameters to be refined for a maximum of 44 atoms.

2.5.2 SHELX

Two least-squares routines are available on the SHELX system. In addition to the normal least-squares refinement (L.S.) there is an accelerated refinement (AFLS) where the normal matrix is not recomputed and reinverted between refinement cycles. It is useful where the structure has been essentially established (i.e. at the end of isotropic refinement) and rapid computation of estimates of the final anisotropic parameters is desired. The version currently implemented on the CDC7600 at U.M.R.C.C allows for the refinement of up to 306 parameters simultaneously with the option of blocking (instruction BLOC) where more parameters are to be refined or computation time is to be reduced. There is only one weighting scheme allowed, $w=1/\left[\sigma^2(F)+g\,|F|^2\right]$ although the user can impose his own weighting scheme by altering the standard deviations. The macro CSWTEX, written by the author, allows the user to do this easily. All that need be supplied is a Fortran statement giving the weight (W) in terms of the structure factor (F) and standard deviation (S). The method is described in Section 3.7. The following additional features are incorporated into the SHELX least-squares routines:

(a) Rigid-body refinement (AFIX). Some groups of atoms may be refined as a rigid group (for details see the program documentation). Most hydrogen postions included in this study have been refined as part of rigid groups: as benzene-type CH's, as aliphatic CH_2's, or as methyl CH_3's -- in each case with the hydrogens riding on the appropriate carbon position. In addition, rings may be refined as rigid groups, and some phenyl rings have been treated in this manner.

(b) Fixing interatomic distances (DFIX). Refinement may be influenced toward maintaining certain interatomic distances by the addition of observational equations into the refinement matrix with the DFIX instruction. The atoms, the interatomic distance and the standard



DFIXed refinement of the C(4) amino group in Cycloguanil Hydrochloride (X-ray data). The fixed distances are shown with standard deviations in brackets. The N-H distances are fixed and an H-N-H angle of approximately 120° ($2 \sin^{-1} 0.365$) is assured by fixing the H...H distances to 1.73 (2 × 0.865). Symmetric refinement about the C-N bonds is assured by fixing the C(4)-H distances to the same free variable. Thus bending in and out of plane is allowed.

Fig 2.5.2-1

SHELX: Definition of R-factors:

$$R = \frac{\sum \Delta}{\sum |Fobs|}$$

$$Rw = \frac{\sum w^{1/2} \Delta}{\sum w^{1/2} |Fobs|}$$

$$Rg = \frac{\sum w \Delta^2}{\sum w |Fobs|^2}$$

where

$$\Delta = \big| |Fobs| - |Fcalc| \big|$$

Table 2.5.2-2

deviation of the distance must be specified. The lower the standard deviation the greater the weight the distance is given in the refinement. Several distances may be refined together with use of free variables. An example of such a case (the symmetrical refinement of the NH_2's in Cycloguanil Hydrochloride) is given in Fig 2.3.2-1. The DFIXing procedure has, in some cases, enabled the satisfactory refinement of hydrogen atoms where the parameters would otherwise have assumed unreasonable values. The process is, in effect, a method of including chemical knowledge in the refinement.

(c) Damping (DAMP). Where correlation presents a problem during refinement (correlation coefficients $|r_{ij}|>0.5$ are printed in the output) the problem may be partially overcome by damping the oscillations in the parameter values. The damping factor DAMP is optionally included in the L.S. instruction. DAMP is undefined in the program documentation but has a value 0 for no damping, 10 for moderate damping and 1000 for extreme damping.

(d) High-angle cutoff (SMAX). The user may specify the maximum value of $\sin\theta$ to be used in refinement with the SMAX parameter to the L.S. instruction.

(e) Elimination of 'less thans' and unwanted reflexions (OMIT). Weak reflexions ($F<n\sigma(F)$) may be eliminated from refinement with the instruction OMIT n. Particular reflexions may be eliminated with the instruction OMIT h k l.

(f) Isotropic extinction. The refinement of an isotropic extinction factor with the F's adjusted according to the relation

$$F' = F(1 - 10^{-4} \underline{x}\ F^2/\sin\theta)$$

is permitted where x is the parameter to be refined.

2.6 Least-Squares Planes Calculation

Currently there are several least-squares planes calculation programs available to University of Aston users:

(a) The Gottingen Least-Squares Planes Program. Brought by Dr. C.H.Schwalbe from the Max Planck Institute for Experimental Medicine and implemented on the 1904S it calculates the planes by an iterative procedure. Deviations of all atoms from the plane and coordinates of their projection onto the plane are output.

(b) The XRAY-72 system implemented at U.M.R.C.C. contains a least-squares program. It also calculates X^2 for the fit of the atoms to the plane to test the hypothesis of planarity of the atomic positions forming the plane.

(c) The GEOM program included in the software for handling the Cambridge database (see Sec 2.8) can be used for least-squares calculation. In conjunction with the FRAG instruction least-squares planes through atoms forming a particular fragment wherever it appears in the structure -- or set of structures -- may be calculated.

2.7 ORTEP

The thermal ellipsoid drawing program ORTEP (Johnson,1965) has been frequently cited in crystallographic structural reports. The program permits graphical representation of the anisotropic vibrations of molecules by plotting ellipsoids corresponding to a defined probability of enclosure of atomic position. The following conventions have been followed in producing the ORTEP plots in this study:

(a) Ellipsoids for non-hydrogen atoms have been drawn at the 50 per cent. probability level with one octant cut away to display the axes of the ellipsoid and the magnitude of vibration along each axis.

(b) Hydrogen atomic positions have been represented by circles of fixed radius.

(c) Bonds between non-hydrogens have been drawn with multiple lines, bonds to hydrogen atoms have been drawn with simple double lines.

The instructions for a typical ORTEP run (a plot of CGT viewed perpendicular to the triazine plane) are given in Fig 2.7-1. The author's program CSHORT transfers coordinates and temperature factors from SHELX card-image

```
ATTACH(ØRTEP,S:APPLAINS,ØRTEPS,ST=S19,FA=ASIS)
ØRTEP(PL=3000)
DISPØSE(TAPE15,PT,ST=CCPND1)
EXIT,
\\\\S
 CYCLØGUANIL HYDRØCHLØRIDE
  8,873   10,391   17,140   90,000   115,24   90,000
1             1,                          1,                          1,
CL1                               -0,3087  0,92724  0,05309
0 0,08132  0,12303  0,04833 -0,02578 -0,00663  0,03611          8
N1                                0,06605  0,79791  0,42293
0 0,03490  0,03661  0,03265 -0,00685  0,00718  0,00553          8
C2                                0,22195  0,87245  0,47198
0 0,03411  0,04042  0,04347 -0,00749  0,00736  0,00690          8
N3                                0,26217  0,85038  0,56308
0 0,04466  0,04011  0,03916 -0,01186  0,00319  0,00277          8
C4                                0,24506  0,73196  0,58945
0 0,03432  0,03966  0,03636 -0,00346  0,00963  0,00207          8
N5                                0,13441  0,64804  0,53716
0 0,03818  0,03698  0,03196 -0,00857  0,00540  0,00385          8
C6                                0,04131  0,68618  0,45538
0 0,03295  0,03636  0,03357 -0,00402  0,01009  0,00280          8
C9                                0,36386  0,82531  0,45117
0 0,04153  0,07263  0,07459 -0,00653  0,02238  0,00638          8
C10                               0,18847  1,01440  0,45339
0 0,05442  0,03975  0,05886 -0,01344  0,01119  0,00732          8
N7                                0,33579  0,70238  0,67159
0 0,05082  0,04827  0,03520 -0,01256  0,00005  0,00598          8
N8                               -0,08218  0,61052  0,40603
0 0,04962  0,04612  0,03259 -0,01795  0,00007  0,00721          8
C11                              -0,02763  0,82659  0,33232
0 0,03589  0,03654  0,03585 -0,00332  0,01099  0,00822          8
C12                               0,02289  0,77763  0,27250
0 0,04601  0,05767  0,04267  0,00435  0,01569  0,00492          8
C13                              -0,06444  0,80844  0,18587
0 0,06025  0,07420  0,04166 -0,00816  0,02042  0,00275          8
C14                              -0,20209  0,88728  0,10146
0 0,04771  0,06120  0,04180 -0,01432  0,00402  0,01736          8
C15                              -0,25609  0,93405  0,22006
0 0,03974  0,05757  0,06028  0,00501  0,00428  0,01743          8
C16                              -0,16750  0,90316  0,30660
0 0,04006  0,04931  0,04984  0,00487  0,01383  0,00659          8
HN3                               0,35936  0,89088  0,60468
0 0,50000                                                       8
H91                               0,34262  0,85387  0,38671
0 0,50000                                                       8
H92                               0,37610  0,72193  0,45690
0 0,50000                                                       8
H93                               0,47676  0,86981  0,49725
0 0,50000                                                       8
H101                              0,17835  1,03668  0,38979
0 0,50000                                                       8
H102                              0,29562  1,06301  0,50122
0 0,50000                                                       8
H103                              0,07729  1,04617  0,45867
0 0,50000                                                       8
H12                               0,13067  0,71562  0,29312
0 0,50000                                                       8
H13                              -0,02561  0,77144  0,13844
0 0,50000                                                       8
H15                              -0,36571  0,99408  0,19921
0 0,50000                                                       8
H16                              -0,20800  0,93908  0,35366
0 0,50000                                                       8
H81                              -0,11085  0,53457  0,43033
0 0,50000                                                       8
H82                              -0,15084  0,63118  0,34683
0 0,50000                                                       8
H71                               0,42892  0,75483  0,70467
0 0,50000                                                       8
H72                               0,32428  0,62239  0,69286
1 0,50000                                                       8
      201
      301   10,      10,      20,      1,0
      401   155501 -3155501
      501   355501   655501   355501   755501   555501                  1
      604
  2   511
  2         1 17  1 17  4  1,0  1,75  ,04
            1 17 18 31  1  0,8  1,2   ,01
  1   701
                                  1        17
  1   704
                                 18        41
  2   812
  2         1 17  1 17  4  1,0  1,75  ,04
            1 17 18 31  1  0,8  1,2   ,01
       /
      -1
\\\\S
```

Fig 2.7-1

output and puts them in a form suitable for input into ORTEP (see Sec 3.7).

2.8 The Cambridge Database

The Cambridge Database and associated software have recently been implemented on the CDC7600 at U.M.R.C.C. The system enables bibliographic references to be obtained for searches based on either connectivity of a fragment contained within the molecule (CONNSER) or character string contained in the compound name, authors, journal,etc. (BIBSER). Six-letter codes are retrieved corresponding to crystal structures meeting the test supplied. Then either bibliographic references (RETRIEV) or a file containing the geometrical data for each structure (RDAT) are retrieved. A number of geometrical calculations (GEOM78) can be carried out on the data retrieved -- eg. bond distances, angles and torsion angles, least-squares planes, direction cosine vectors, centroids, etc. Atoms may be referred to by their order of appearance either in the original data file or in a chemical fragment defined by the user. Users may define their own parameters for the tabulation of results. The program PLUTO (see Sec 2.9) can be used to plot the structures from the Cambridge database.

The author's macro CSCAMEX (see Sec 3.7) can be used to run any of the above programs, either with coordinates from the database or user-supplied coordinates.

2.9 PLUTO

The molecular plotting program PLUTO has recently been implemented on the CDC7600 at U.M.R.C.C. The program allows plotting of either unit cell contents or individual molecules, with options for either projection, perspective or stereo representation. A number of orientation options are allowed, the default being an approximately - calculated minimum-overlap orientation.

The program may be run from the macro CSPLTEX (see Sec 3.7)

2.10 Fourier Synthesis

2.10.1 PHUSIS/FURSUM

The electron density at any point with fractional coordinates x,y,z is given by

$$\rho(xyz) = \frac{1}{V}\sum_h\sum_k\sum_l F(hkl)\ \cos 2\pi\left(hx+ky+lz\right)$$

in the case of a centrosymmetric structure (Woolfson,1970 - p119). The summations in the above expression are taken from minus infinity to plus infinity. F(hkl) may be either positive or negative and the signs must be estimated either

(a) by calculating the structure factor from the best-known atomic positions and applying the sign of Fcalc(hkl) to |Fobs(hkl)| ("Fourier synthesis"), or (b) by applying the signs from a sign-expansion process such as MULTAN or EEES ("E-map"). During the early stages of structure analysis errors in the sign are the main cause of inaccuracy in the Fourier syntheses, although once the structure has been refined successfully there remain inaccuracies due to (1) errors in the determination of |Fobs(hkl)|, which -- apart from random errors (see Sec 3.1) -- may arise due to absorption, extinction or double-diffraction ("Renninger effect"), and (2) the triple summation above takes place over a limited number of measured reflexions, thus data are confined to a limited range $h_{min} \leq h \leq h_{max}$,etc. This cutting off of data ("series termination errors") leads to ripples around the maxima in the Fourier synthesis. During the later stages of structure analysis the correctness of the structure can be tested by a "Difference Fourier Synthesis":

$$\Delta\rho(xyz) = \frac{1}{V}\sum_h\sum_k\sum_l \Delta F(hkl)\cos\ 2\pi(hx+ky+lz)$$

where

$$|\Delta F(hkl)| = |Fobs(hkl)| - |Fcalc(hkl)|$$

and ΔF(hkl) has the sign of Fcalc(hkl) (Woolfson,1970 - pp341,342). In addition to the above the unphased

Patterson synthesis may be of use in determining heavy-atom positions for initial phasing:

$$P(xyz) = \frac{1}{V}\sum_h\sum_k\sum_l \left|F_{obs}(hkl)\right|^2 \cos 2\pi(hx+ky+lz)$$

All four of the above options -- Fourier synthesis, E-map, difference Fourier map and Patterson synthesis are available as options in the PHUSIS/FURSUM programs, obtained from the Max Planck Institute for Experimental Medicine in Gottingen, and implemented on the ICL 1904S at Aston University by Dr. C.H.Schwalbe. Output is in the form of scaled integers with the maximum value (usually 999) to be supplied by the user. Output in the form of pseudo magnetic tape can be used to generate a graph-plotter contoured map (with use of the program KONTUR -- see Sec 3.4) or as input for a peak-search (program PEAKS -- see Sec 3.3). Running the programs consecutively the calculations:

Fourier map ⟶ Peak search ⟶ Bond distances and angles

can be done in a single run).

2.10.2 FMAP (SHELX)

All of the above options are available in the FMAP program in the SHELX system. Here, there is additionally a sharpened Patterson function computed on the basis of a summation of the terms |E(hkl)||F(hkl)|. Output is either in the form of arrays of integers or of peak positions. Using the PLAN instruction these peaks can be plotted on the lineprinter in the form of least-squares planes through "molecules" where a "molecule" is defined as more than two peak positions connected by "bonds" which are in turn defined to be interatomic distances b_{ij} such that

$$b_{ij} < r_i + r_j + 0.5 \text{ Å}$$

where $r_i = 0.65$ Å or 1.25 Å. The larger "covalent radius" is given to peaks strong enough to indicate possible heavy atom positions.

Chapter 3: Developed Crystallographic Software

3.1 Data Reduction

The program BAKSUB was written to reduce raw four-circle diffractometer data (ω-2θ scan) on DIPB. The program subtracts the background, applies Lorentz and polarisation corrections and calculates structure factors. Statistics are output for the number of reflexions as a function of sinθ with average low-angle and high-angle backgrounds for each setting to detect anomalies due to missetting or beam-stop blocking. The backgrounds relative to other reflexions in the same range in sinθ, the Lp^{-1} correction, the corrected peak intensity (I) and its standard deviation (σ(I)) along with the ratio I/σ(I) are output onto the lineprinter, while structure factors (F) and standard deviations (σ(F)) are output into a card-image file for input into the Wilson Plot program, etc.

(a) Background subtraction -- The method of background subtraction for counter data has been described elsewhere (Stout and Jensen,1968 - p456). The method may be extended to generalised counting times for peak and background as follows:

$$N_{pk} = N_T - r(N_{b1} + N_{b2})$$

where N_T=total count, N_{pk}=peak count and N_{b1} and N_{b2} are the background counts each collected over a period 1/r X peak count time. The standard deviation due to counting statistics is calculated by

$$\sigma_{pk}^2 = \sigma_T^2 + \sigma_{b1}^2 + \sigma_{b2}^2$$

where $\sigma_T^2 = N_T$ and $\sigma_{b1} = r\sqrt{N_{b1}}$. The final standard deviation of the intensity must include an allowance for the variation in intensity of the main beam with time, thus:

$$\sigma_I^2 = \sigma_{pk}^2 + (f N_{pk})^2$$

where f is a parameter which depends on the constancy of the X-ray beam intensity and is dependent on the particular combination of generator and mains supply.

Generally, during data collection a small number of reflexions are measured repeatedly at intervals throughout data collection. These must be checked during the period of collection of data for monotonic decrease indicating a deterioration of the crystal in the X-ray beam, or for sudden drop-off, indicating a change in crystal alignment. Where data collection has proceeded without any overall trend in the intensities of the check reflexions, the spread of measurements may be used to estimate the parameter f by attributing that part of the variation in measurements not accountable for by counting statistics to variation in intensity of the main beam. If N is the mean count for n measurements and $\sigma^2(N)$ the variance of the counts (whose expected variance on the basis of counting statistics alone is $\frac{\bar{N}}{n-1}$), then

$$\sigma^2(N) = \frac{\bar{N}}{n-1} + (f\bar{N})^2$$

or

$$f = \frac{1}{N}\sqrt{\sigma^2(N) - \frac{\bar{N}}{n-1}}$$

The program allows the user the option to supply a value for *f* (Stout and Jensen give 0.01 as a generally-acceptable value for most apparatus) or have the program calculate *f* as above.

Peaks which, after background subtraction, have a negative intensity, are assigned a zero intensity and structure factor.

(b) *Lorentz and polarisation corrections* -- Intensities must also be corrected for factors of the geometry of crystal movement (Lorentz factor) and polarisation of the diffracted beam. For the geometry of the ω-2θ scan (see *International Tables*, Vol *IV*, p276) the rotation axis (φ-axis) is perpendicular to the plane of the incident and diffracted beam. Under these conditions the Lorentz factor is a function of 2θ alone (*International Tables*, Vol *II*, p266), *viz*.:

$$L = \frac{1}{\sin 2\theta}$$

The polarisation factor is independent of the method of data collection (Stout and Jensen, 1968 - p196), viz.:

$$p = \frac{1 + \cos^2 2\theta}{2}$$

Lorentz-polarisation correction and structure factor calculation can proceed according to the equation

$$F_{hkl} = \sqrt{(Lp)^{-1} I_{hkl}}$$

where I_{hkl} is the background-corrected intensity, and combining the above results

$$(Lp)^{-1} = \frac{2 \sin 2\theta}{1 + \cos^2 2\theta}$$

The factor $(Lp)^{-1}$ is output for each reflexion. The structure factors are then on an arbitrary scale and must be rescaled during normalisation and refinement.

3.2 Molecular Geometry Calculations

The program MOLJOM was developed to provide calculations of molecular geometry during the early stages of structure analysis to determine the chemical reasonableness of the coordinates from Fourier maps and refinements. The features include

a) calculation of specified bond distances
b) calculation of specified bond angles
c) calculation of specified torsion angles
d) calculation of an approximate plane fitted to specified atoms

The approximation of the plane was obtained by summing the vector products at each atom, viz.

$$\underline{\ell} = \sum_{i=1}^{n} \underline{b}_{i\,i+1} \times \underline{b}_{i+1\,i+2}$$

where $\underline{b}_{ij}$ is the vector between the ith and jth atom in the plane and numbering is modulo $\underline{n}$ (i.e. $\underline{r}_{n+1} = \underline{r}_1$). The direction cosines ($\underline{\lambda}$) of the plane simply describe a unit vector along $\underline{l}$, viz.

$$\underline{\lambda} = \frac{\underline{\ell}}{|\underline{\ell}|}$$

and where $\underline{r}$ are the Cartesian coordinates of the atoms, the parameter $\underline{d}$ in the plane equation $\underline{\lambda} \cdot \underline{\mathbf{r}} = \underline{d}$ is calculated by

$$\mathbf{d} = \frac{1}{n} \sum_{i=1}^{n} \underline{\lambda} \cdot \underline{r}$$

The program was later modified to include symmetry and to allow for the calculation of general bond distances (b_{ij}) and angles (θ_{ijk}) which meet the criteria

$$\mathbf{b}_{\min} \leq \mathbf{b}_{ij} \leq \mathbf{b}_{\max}$$

and

$$\theta_{\min} \leq \theta_{ijk} \leq \theta_{\max}$$

where the minima and maxima are parameters supplied by the user. The program could thus handle input coordinates which had not been chemically identified, e.g. coordinates resulting from a peak search of a Fourier map (see

Sec 3.3).

The method of specifying symmetry operations has been kept consistent throughout this set of programs. The new fractional coordinates (x',y',z') are related to the old (x,y,z) by the operations

$$x' = R_1 u_i + t_1$$
$$y' = R_2 u_j + t_2$$
$$z' = R_3 u_k + t_3$$

where $u_1=x$, $u_2=y$ and $u_3=z$. On a card of Fortran FORMAT(10X,6F10.0,7X,3I1) the parameters are input in the order $R_1, t_1, R_2, t_2, R_3, t_3, i, j, k$. Where the last three columns are zero or blank the values i=1,j=2,k=3 are assumed. This system is sufficient for handling any of the space groups included in this study.

3.3 Peak Search

The program PEAKS was developed to facilitate the location of peaks in Fourier maps from the PHUSIS/FURSUM programs. With the facilities of MOLJOM the peak locations could in turn be used to calculate "bond lengths" and "bond angles" in the structure.

The program locates peaks in the Fourier map output in three-dimensional array form from the PHUSIS/FURSUM programs. A peak is defined by

$$\rho(i,j,k) \geq \max\left\{\rho(l,m,n)\right\}$$

where l,m and n are allowed to take on any value in the range $i-1 \le l \le i+1$, $j-1 \le m \le j+1$, $k-1 \le n \le k+1$ and ρ refers to the electron density at the grid point (i,j,k) within the unit cell. Interpolation is carried out in the x-direction by fitting a parabola to the points $\rho(i-1,j,k)$, $\rho(i,j,k)$ and $\rho(i+1,j,k)$ and determining the position of the maximum. Similar interpolations are carried out along the y and z axes.

Peaks are stored in a one-dimensional array in order of decreasing intensity. Once the number of peaks specified by the user has been entered into the array, the weakest peak is discarded each time a new peak is encountered. The facility exists for the search for negative peaks.

3.4 Contoured Fourier Output

KONTUR is a general-purpose contouring program, but has been specifically adapted to handling output from PHUSIS/FURSUM. Contouring can be done either on an absolute scale or on a scale relative to the maximum peak height. Negative peaks are indicated with dashed lines. A grid can be superimposed on the plot for the purpose of measuring fractional coordinates of peak positions etc. In the current version only rectangular plots may be drawn. The user scales the vertical and horizontal axes by specifying the distance in millimetres between grid points. Although a curve-smoothing procedure is incorporated in the program, it is not recommended for use on Fourier outputs because (a) it greatly increases the computation time and graphplotter file size, and (b) the artifacts of curve-smoothing may cause curves from adjacent contours to overlap each other.

3.5 Representation of Unit Cell Contents

The program CELPIC was written to give a graphical representation in stick diagram form of the unit-cell contents for structures of monoclinic or higher symmetry. The features included are

(a) bonds either specifically declared by the user or calculated on the basis of covalent radii.

(b) plotting of symmetry-related molecules. Translations may be made relative to a symmetry-related molecule whose centroid is within the unit cell. Separate molecules may be identified using dashed or heavy lines.

(c) automatic calculation and plotting of hydrogen bonds.

(d) Van der Waals spheres for atoms shown on sections through the unit cell. (Under the present version sections must be perpendicular to an axis which coincides with its reciprocal axis.)

(e) choice of projection without perspective (AXON3) or perspective (PROJ3 or FROM3) -- see Gino-F User Manual(1975). Stereo diagrams can be made from a suitable combination of two projections.

3.6 Determination of Crystal Density and Linear Absorption Coefficient

The program ABSORB was written for the purpose of carrying out the routine calculation of cell volume, density as determined from unit cell contents and linear absorption coefficient for X-rays.

Unit cell volumes (V_c) are calculated as described in the International Tables, Vol I, p13. The molecular weight of the molecule is determined by

$$M = \sum n_i A_i$$

where n_i is the number and A_i the atomic weight of each atomic species in the molecule. For calculations of densities and absorption coefficients the summation must be over the atoms in one asymmetric unit. The density from X-ray data (D_x) is then determined by

$$D_X = \frac{Z M m}{V_c}$$

where m = 1 atomic mass unit (1.660×10^{-24} g) and Z is the number of times the asymmetric unit is repeated in the unit cell. The fraction, f_i, by mass of each atomic species, is calculated by

$$f_i = \frac{n_i A_i}{M}$$

and the mass absorption coefficient (μ^*) of the crystal by

$$\mu^* = \sum f_i \mu_i^*$$

where μ_i^* is the mass absorption coefficient for each atomic species. These coefficients are tabulated for all elements up to atomic number 83 for a variety of radiations in the International Tables, Vol III, pp162-165. The linear absorption coefficient is then calculated by

$$\mu = D_x \mu^*$$

Atomic weights and mass absorption coefficients for CuKα and MoKα radiation for some commonly-found elements have been stored within the program. It is easily amended to include other atomic species and other radiations.

3.7 Manchester Programs and Macros

A number of macros were written in order to facilitate the running of the various programs implemented at U.M.R.C.C. (see Chapter 2).

The system consists of the CDC7600 computer front-ended by an ICL 1904S computer. Thus the file-handling and editing facilities of the George 3 operating system are available to the user. The macros facilitate the file-handling and supply the required CDC instructions for running the programs on the main computer.

There are a number of different groups within Aston university sharing a single U.M.R.C.C. user number, with the files pertaining to each group identifiable by a two-letter prefix. The prefix for the Department of Pharmacy Crystallography Group is CS. The macros are therefore designed to operate on files with this prefix, although amendment to enable handling of files with other prefixes should be a comparatively trivial matter. In the description that follows the designation <CSfn> will refer to the full file name and <fn> will refer to the file name with the CS prefix removed.

(a) CSPROGEX

This macro facilitates the compiling and running of FORTRAN programs on the CDC7600. There are three compulsory parameters (which must be the first three) and a number of optional ones.

Parameter 1: <fn1>: File containing either the FORTRAN listing or the binary version of the program where the execution of a previously-compiled program is required. The first card in the FORTRAN program contains the input-output instructions: see U.M.R.C.C. JOINT SYSTEM MANUAL, Sec III.1.

Parameter 2: <fn2>: Card-image file containing input data.

Parameter 3: <fn3>: Card-image file for output or output of the binary program where compilaton alone is required.

Optional parameters:

#COMP: The program is compiled and a binary version stored in <fn3>.

#EX: The binary version of the program is executed.

#FASTEX: The program is compiled OPT=2 for fast execution with slow compilation.

#FASTCOMP: The program is compiled OPT=0 for fast compilation with slow execution.

(default): Program compiled (OPT=1, a compromise compilation) and executed

(b) CSHEX

This macro facilitates the running of SHELX jobs. The instructions and data are kept in separate files. The conventions that are followed in naming the files are as follows:

Instruction File name: CSxxnf where
xx = two-letter code name for identifying the structure.
n = any digit
f = the letter F, G or H

Data File Name: CSxxDF
This name may be altered in which case the appropriate <fn> must be specified in the second parameter when running CSHEX.

The Instruction File must begin with the TITL instruction, contain all the instructions for running the program, and end with the HKLF instruction. The Data File must begin with the HKLF instruction, contain the intensity data in the format specified and terminate with the END instruction. The two files are merged into the file CSXXT and run. The separation of the instruction and data files

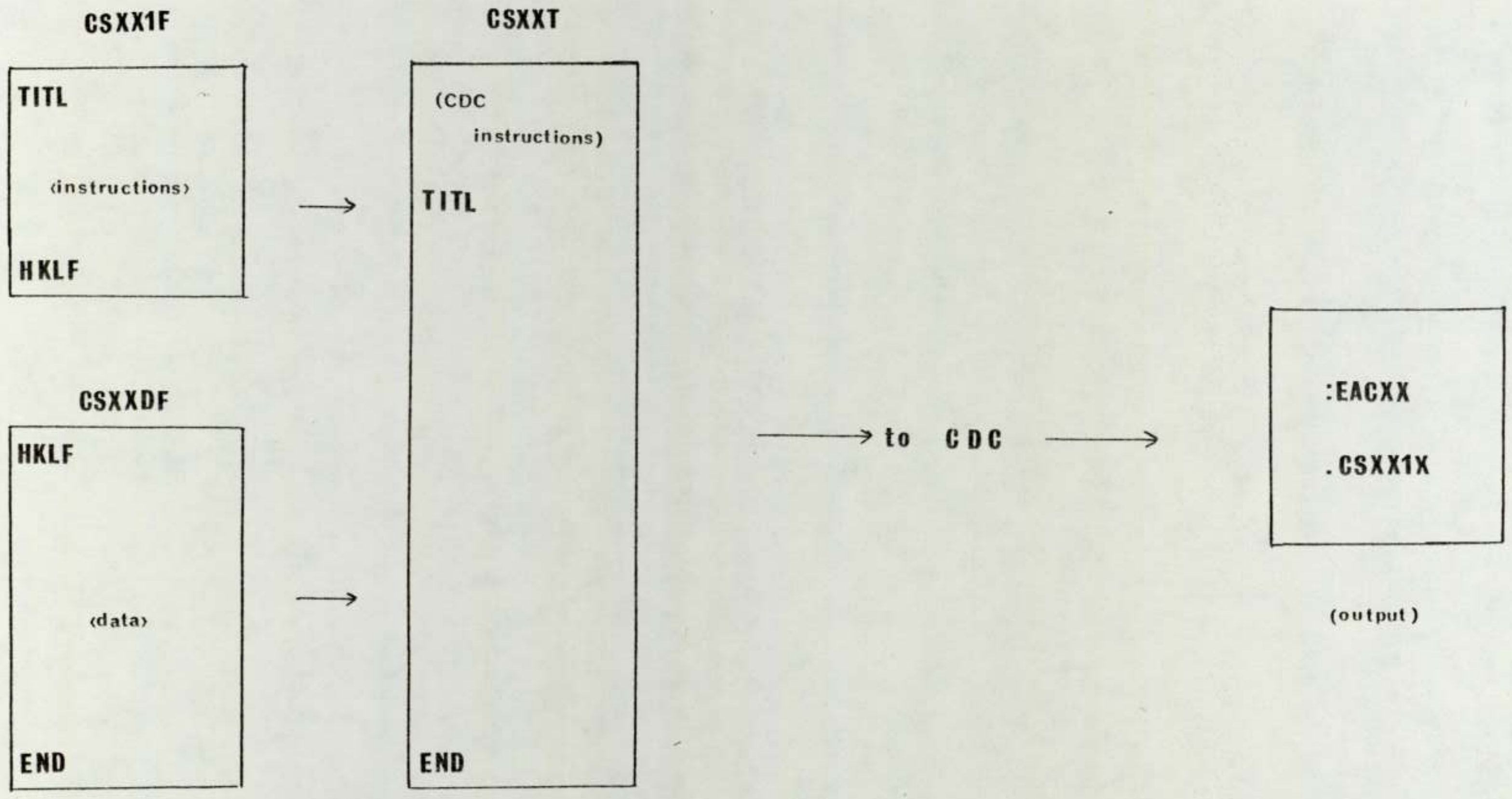

CSXX1F
TITL
(instructions)
HKLF
CSXXDF
HKLF
(data)
END
CSXXT
(CDC
instructions)
TITL
END
to CDC
:EACXX
.CSXX1X
(output)

Fig 3.7-1

enables the instructions to be changed without editing the data. The file CSXXT is a temporary one and should be erased after use. The default time is 1200 octal seconds and the default priority P0000. These may be altered by adding additional parameters after the first two, eg., #P2000,#T500. For example

```
CSHEX XX1F,,#P2000
```

will run a job with the instructions contained in the file CSXX1F, the data in the file CSXXDF at a priority P2000. The name of the CDC job will be CSXX1X.

(c) CSCAMEX

This macro facilitates the running of programs associated with the Cambridge crystallographic data base. There are two parameters. The first is a single digit to identify the structure or question. Since several jobs may be run in sequence in following up a single question the same digit must be used throughout, and it is essential that during that time no other jobs be run with this macro and the same digit. The second digit identifies the program to be run, viz.:

CONS: generates REFCODES in response to a connectivity search.

RETV: retrieves bibliographic references corresponding to previously-generated REFCODES.

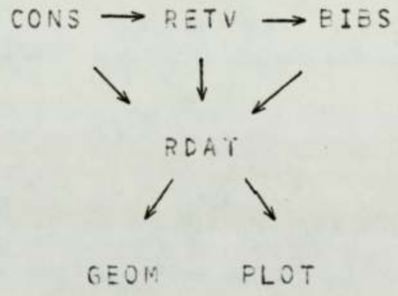
BIBS: generates bibliographic references in response to a search for character strings in the title, author names, etc.

RDAT: retrieves the raw geometrical data corresponding to previously-generated REFCODES.

GEOM: calculates specific geometrical parameters for either (i) raw geometrical data previously retrieved, or (ii) input atomic coordinates. In the latter case the <fn> containing the coordinates must be specified as the third parameter.

PLOT: plots PLUTO stick diagrams for the structure whose geometrical data has been previously retrieved or for the structure whose coordinates are input, in which case the appropriate <fn> must appear as the third parameter.

The programs must be run in sequence, possible pathways for which are shown:



The macro permits the running in parallel, where there is logic in doing so, with the combining of names in the second parameter (the order is unimportant). The combinations allowed are:

RETV AND RDAT

PLOT AND GEOM

where the parameters CONS, BIBS or GEOM are specified data must be entered into the file CSCAMDATA. A final card containing the character string 'END OF DATA' must be added at the end of the data.

The REFCODES are stored in the file CSEEKn and the raw geometrical data in the file CSEELn where n is the first parameter digit. The following sequence, run in different jobs, should run a connectivity search, retrieve the bibliographic references, calculated the required geometrical parameters and output stick plots:

```
JOB :EACXX,CSJOB1
IN CSCAMDATA,T////
<data here>
END OF DATA
////
CSCAMEX 7,CONS
EJ
****


JOB :EACXX,CSJOB2
CSCAMEX 7,RETV AND RDAT
EJ
****


JOB :EACXX,CSJOB3
IN CSCAMDATA,T////
<data here>
END OF DATA
////
CSCAMEX 7,GEOM AND PLOT
EJ
****
```

(d) CSPLTEX

This macro facilitates the running of PLUTO on the CDC7600 computer. There are two parameters. The first is a single digit to identify the job, the second is the name (without the prefix CS) of the file containing the atomic coordinates or raw geometrical data. The instructions for the plot are entered in the file CSPLTDATA, terminated in the same manner as CSCAMDATA. Thus after the running of CSJOB2 above the following job could be issued:

```
JOB :EACXX,CSJOB4
IN CSPLTDATA,T////
<data here>
END OF DATA
////
CSPLTEX 4,EEL7
EJ
****
```

Note that the RDAT file is identified by the digit in the second parameter, not the first.

(e) CSHORT

This program accepts coordinates and temperature factor data from SHELX refinements and outputs these in a format suitable for ORTEP. The program may be run with use of the CSPROGEX macro:

```
CSPROGEX HORT,<fn1>,<fn2>
```

where <fn1> is the SHELX coordinates file (normally of the form CSXXSC) and <fn2> is the output filename. The input file must first be edited with the left-justified character string 'END 1' (the digit must appear in column 5) at the end of the data. There is no need to edit out the AFIX or dummy atom cards.

(f) CSHFIX

This program alters the coordinates output from SHELX refinements to allow various parameters to be fixed and also permits conversion of temperature factors from anisotropic to isotropic form (on the basis of the mean of the elements of the diagonal of the matrix). The input data is identical to that for CSHORT above, except that the digit following 'END' determines the type of calculation, viz.:

1...fix coordinates
2...fix coordinates and temperature factors
3...convert anisotropic temperature factors to isotropic
4...convert temperature factors and fix coordinates
5...convert and fix temperature factors and fix coordinates

The program may be run with use of the CSPROGEX macro as follows:

```
CSPROGEX HFIX,<fn1>,<fn2>
```

where <fn1> and <fn2> contain the input data and output respectively.

(g) CSWTEX

This macro facilitates the alteration of standard deviations in a SHELX data file of the form CSxxDF where xx is the two-letter code identifying the structure. The altered standard deviations are entered into the file CSxxDFW. The weight (W) may be specified as a function of the structure factor (F) or standard deviations of the structure factor (S) in a FORTRAN statement or series of statements. The standard deviation may be altered directly, in which case the value of the variable IS must be set to 1 in the statements. There is one parameter to the macro -- the two-letter structure identification code. The format of the job is as follows:

```
JOB :EACXX,CSJOB5
IN CSXXWT,T////
<FORTRAN statements here>
RETURN
END
////
CSWTEX XX
EJ
****
```

Chapter 4: 3,4-Dihydro-3-Isopropyl-4-Phenylimino-1,2,3-Benzotriazine (DIPB)

4.1 Introduction

The principal medicinal interest in the 1,2,3-benzotriazines has been the quinidine-like effect on muscular contraction. This has led to speculation that some members of the series may be therapeutically useful as anti-arrhythmic agents. The phosphorodithioate derivative (4.1-VI) is a powerful inhibitor of rat acetylcholinesterase (Rohrbaugh,et al,1976). As far as is known the title compound (4.1-I) has no biological activity.

The following 1,2,3-benzotriazine structures are known to have been solved crystallographically (on the basis of a connectivity search of the Cambridge database conducted on the CDC7600 computer at UMRCC on 26.3.79):

4.1-II: 1,2,3-benzotriazine-4(3H)-one (Hjortas,1973)

4.1-III: 4-oxo-2-phenyl-1,2,3-benzotriazinium-1-oxide (Ballard and Norris,1975)

4.1-IV: anhydro-2-methyl-4-o-nitroanilino-
1,2,3-benzotriazinium hydroxide (Schwalbe,1975)

4.1-V: 2-propyl-4-anilino-1,2,3-benzotriazinium iodide
(Schwalbe,1975)

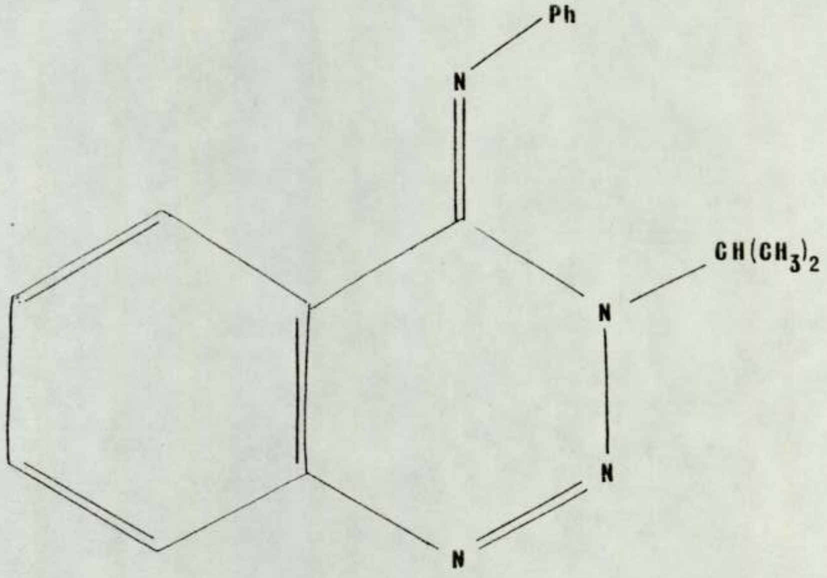
4.1-VI: O,O-dimethyl-S-(4-oxo-1,2,3-benzotriazin-3-yl)
methyl phosphorodithioate (Rohrbaugh,et al,1976)

4.1-VII 2-(2,4-dibromophenyl)-4-oxo-1,2,3-benzotriazin-
2-ium-3-ide (Hamid and Hargreaves,1976)

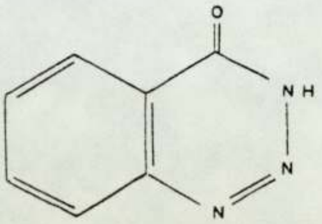
The crystallographic stacking arrangement in compounds 4.1-I to 4.1-V has been investigated (Schwalbe and Hunt,1976). The stacking arrangement symmetries with distances and angles between adjacent planes are listed in Table 4.1-1.

4.2 Crystal Data

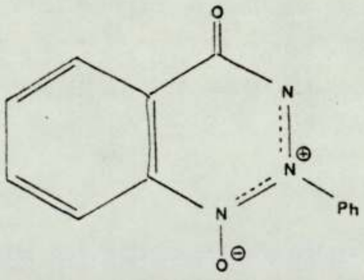
3,4-Dihydro-3-isopropyl-4-phenylimino-1,2,3-benzotriazine ($C_{16}H_{16}N_4$) crystallises in space group $P2_1/n$ with a=8.929(1) Å, b=20.080(3) Å, c=8.979(1) Å, β=114.05(1)°, Z=4, V =1470.1(3) $Å^3$. The molecular weight is 264.332 and the density calculated from unit cell contents 1.194 g cm^{-3}. The absorption coefficients for CuKα radiation are μ^*=4.965 cgs units, μ=5.928 cm^{-1}.



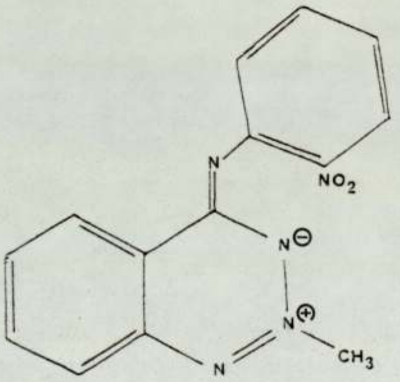
4.1-I



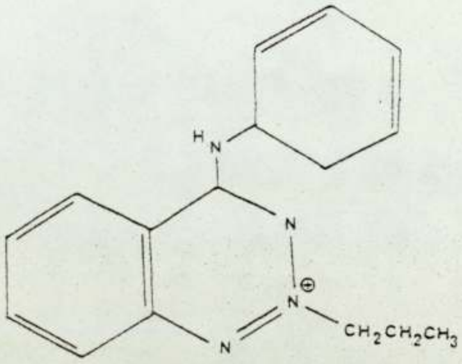
4.1-II



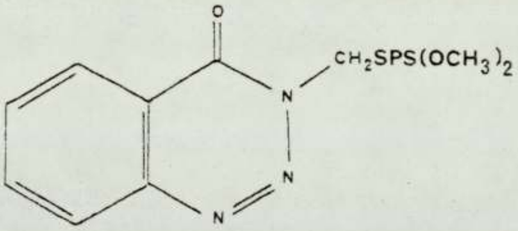
4.1-III



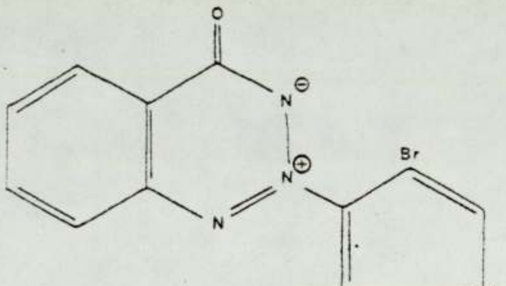
4.1-IV



4.1-V



4.1-VI



4.1-VII

Stacking for Structures 4.1-I to 4.1-V

Structure	Rings	Extent	Symmetry	Distance	Angle
I	(no stacking)	----	----	----	----
II	Benzotriazine	Columns	1+x	3.42 Å	0
III	Benzotriazine	Columns	n	3.27 Å	4.8
	Phenyl	Pairs	$\bar{1}$	3.61 Å	0
IV	Benzotriazine	Columns	$\bar{1}$ and 1+x	3.56 Å	0
	Phenyl	Columns	2_1	3.76 Å	37.5
V	Benzotriazine	Pairs	$\bar{1}$	3.60 Å	0

Table 4.1-1

4.3 Structure Analysis

4.3.1 Data Collection

DIPB crystallises in the form of colourless prisms. One crystal was mounted along the unique axis on a Stoe four-circle diffractometer in the Chemistry Department of the Max Planck Institute for Experimental Medicine in Göttingen, West Germany. The crystal was irradiated with Ni-filtered CuKα radiation ($\lambda=1.54182$ Å) and intensities measured using an ω-2θ scan of 80 steps of $\Delta\omega=0.01^{\circ}$ for each peak. The total peak count time was 48 seconds with a 6-second background collection on either side of the peak. Data were collected for 2065 unique reflexions (1940 $F>2\sigma(F)$). The peak intensities were corrected for background contribution and Lorentz and polarisation effects and structure factors were calculated with use of the program BAKSUB (see Sec 3.1). Data were initially collected in the non-standard space group $B2_1/a$. $P2_1/n$ was chosen as the space group for publication because of the extremely obtuse angle ($\beta=146.9^{\circ}$) of the corresponding $P2_1/c$ unit cell. The transformation

$$\begin{bmatrix} h' \\ k' \\ l' \end{bmatrix} \qquad \begin{bmatrix} \frac{1}{2} & 0 & \frac{1}{2} \\ 0 & 1 & 0 \\ -\frac{1}{2} & 0 & \frac{1}{2} \end{bmatrix} \begin{bmatrix} h \\ k \\ l \end{bmatrix}$$

converts the indices from $B2_1/a$ to $P2_1/n$. Here and in subsequent discussion the primed quantities refer to the

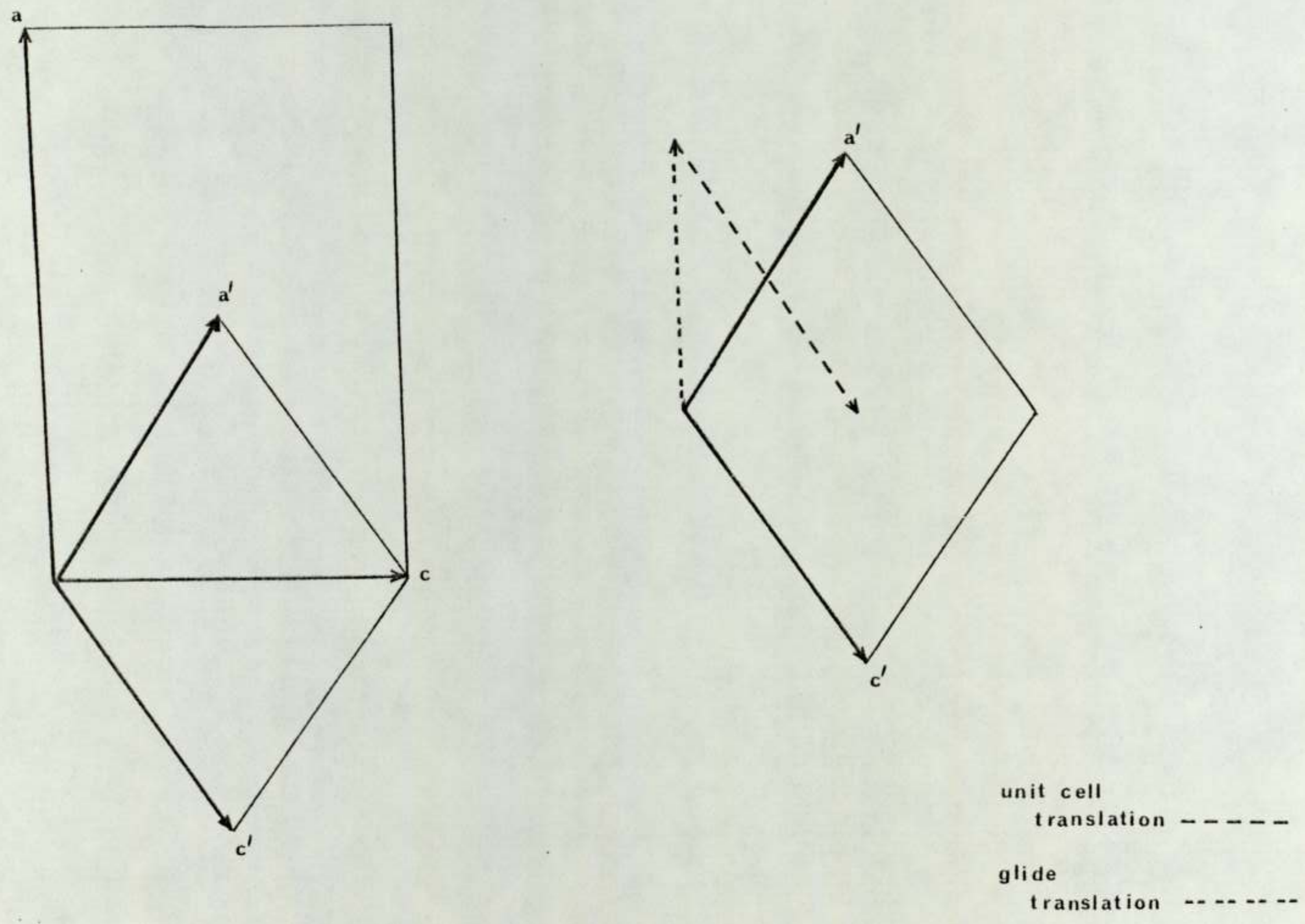


Fig 4.3.1-1

latter space group. Fig 4.3.1-1 shows the relation between the two unit cells, and (in dotted lines) it is shown that

$$\underline{a}\text{ glide} + \underline{c}'\text{ translation} = \underline{n}'\text{ glide}$$

The original cell dimensions $a=15.023$ Å, $b=20.081$ Å, $c=9.746$ Å, $\beta=90.35^{\circ}$ were transformed into the published unit cell with use of the following equations of transformation:

$$(2a')^2 = a^2 + c^2 + 2ac\cos\beta$$

$$b' = b$$

$$(2c')^2 = a^2 + c^2 - 2ac\cos\beta$$

$$\cos\beta' = (a'^2 + b'^2 - a^2)/(2a'c')$$

4.3.2 Solution

Normalised structure factors were calculated using a modified Wilson Plot method (see Sec 2.2). Two rigid fragments were input: one naphthalene and one benzene fragment per asymmetric unit with bond lengths fixed at 1.4 Å. The curves according to the Wilson calculation and the Debye calculation are shown in Fig 4.3.2-1 along with the least-squares fit to the Debye calculation. Values calculated from the gradient and intercept were

$$2B=6.7379$$

$$k=0.9415$$

Phase determination was undertaken with use of the program MULTAN (see Sec 2.3) on the basis of 299 reflexions

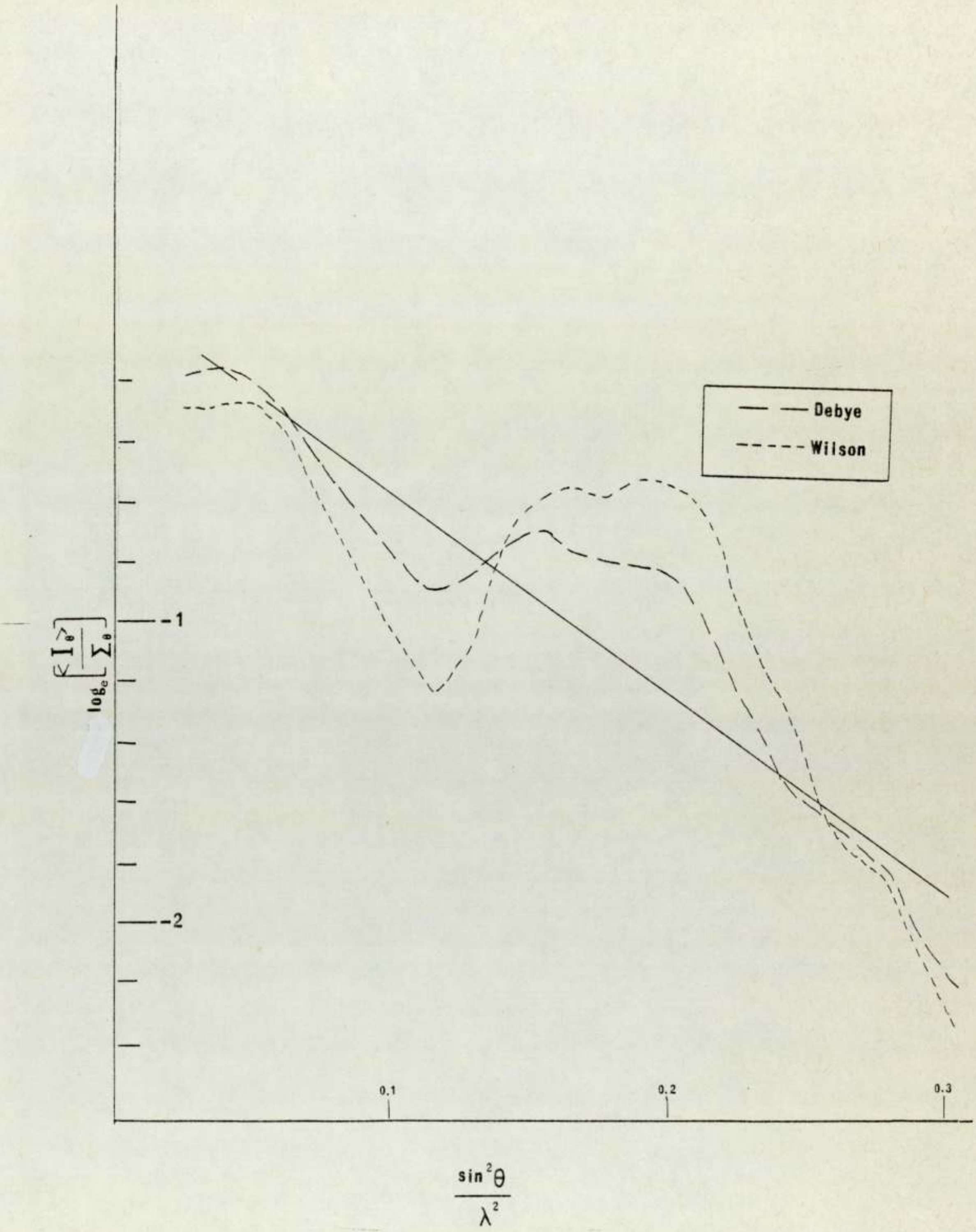

Debye
Wilson
-1
-2
$\log_e\left[\frac{\langle I_\theta \rangle}{\Sigma_\theta}\right]$
0.1
0.2
0.3
$\frac{\sin^2\theta}{\lambda^2}$

Fig 4.3.2-1

Distribution of E-values for DIPB

	Experimental	Theoretical	
		Centric	Acentric
$<E^2-1>$	0.9848	0.9860	0.7360
$<E>$	0.7993	0.7980	0.8660
%E>0.5	61.6	61.7	77.9
%E>1.0	29.7	31.7	36.8
%E>2.0	5.2	4.6	1.8

Table 4.3.2-2

Figures of Merit for the Starting Set:

7 16 4 (+), 19 6 7 (+), 12 9 3 (+)

ABS FOM	1.2421	(First)
PSI ZERO	1208	(Fourth Highest)
RESID	34.88	(Least)
COMB FOM	2.2991	(First)

Table 4.3.2-3

obeying the condition $|E| > 1.39$. 1600 unique Σ_2 relationships were obtained for which

$$|E_h||E_k||E_{h-k}|>1.75$$

The sign of the reflexion 0 18 0 (+) was determined with a probability of 99.8 per cent. by the Σ_1 formula. The CONVERGE procedure produced the following origin-fixing reflexions: 0 16 1 (+), 3 15 2 (+), 18 7 6 (+). Eight starting sets were obtained by permuting the signs of the reflexions 7 16 4, 19 6 7 and 12 9 3. The set with the signs respectively +,+ and - produced an E-map from which the two principal features of the structure -- the phenyl and benzotriazine rings -- could easily be distinguished. The figures of merit for this starting set are given in Table 4.3.2-3.

When the 17 atomic positions determined from the E-map were used to phase a Fourier synthesis, the remaining atoms (the isopropyl group) could all be distinguished, although with a lower intensity than with the input atomic positions.

4.3.3 Refinement

Initial isotropic refinement was undertaken at Aston using the least-squares program ORFLS (see Sec 2.5.1). After 3 cycles, with all atoms entered as carbons and $\sin\theta<0.75$, $R=0.27$, $Rg=0.35$. Unusually low temperature factors were noted at the following positions:

1,2,3,4 and 41' -- with B-values 1.68,1.95,0.86,1.94 and 0.57 respectively. The low temperature factors at the 1,2,3 and 41' positions strongly support the designation of these atoms as nitrogens on the basis of organic synthesis. The low temperature factor at the 4-position is at least partially attributable to the stabilising effect of attachment of the phenylimino moiety.

Subsequent refinement was undertaken at UMRCC Manchester using the full-matrix least-squares option in SHELX. During refinement it became apparent that a number of intense reflexions had serious discrepancies between the observed and calculated structure factors with $|F_{obs}|<|F_{calc}|$. An isotropic extinction factor of the form (Sheldrick,1976)

$$|F|' = \left[1 - \frac{10^{-4}\chi|F|^2}{\sin\theta}\right]|F|$$

was applied to the observed structure factors. The parameter $\underline{x}$ was refined as a free variable to the value $\underline{x}=0.106$. The observational equations were weighted by $1/\sigma^2(F)$ with 1940 reflexions of the type $|F|>2\sigma(F)$ included in the refinement. Serious discrepancies were observed for the low-angle reflexions 0 4 0, $\bar{1}$ 1 1, 1 1 1 and 1 4 1. In each of these cases the observed structure factor was much less than the calculated magnitude. Because of the possibility that the beam stop had prevented the detection of some of the intensity of these reflexions, they were eliminated from the refinement and the calculation of the structure factors and residuals.

All carbon and nitrogen atoms were refined with anisotropic temperature factors whilst isotropic temperature factors were refined for the hydrogen atoms in fixed positions, riding on the bonded carbon atoms. The carbon atoms in the phenyl ring were refined as a rigid hexagon. A total of 193 parameters were refined, and of the 37056 correlation coefficients, r_{ij}, 44 had values $|r_{ij}| > 0.5$. The highest value of $|r_{ij}|$ was 0.76 with refinement of the rigid CH_3 groups providing the greatest difficulty. The maximum absolute value of shift/e.s.d. for the final cycle of refinement was 0.80, but apart from the methyl group parameters none were greater than 0.09. The final cycles of refinement were weakly damped (DAMP=1.0). The final agreement factors were R=0.072, Rw=0.094 and Rg=0.110.

The strongest peak in the final difference Fourier synthesis, 0.54 $e\mathring{A}^{-3}$, occurs at a possible hydrogen position in the C(32) methyl group. This peak, along with the refinement difficulties described above, indicates that there is considerable disorder in the methyl groups, with considerable freedom of rotation -- even in the crystalline state -- about the C-C σ-bonds. All other density in the final difference map is within the range $-0.28e\mathring{A}^{-3}$ to $0.25e\mathring{A}^{-3}$.

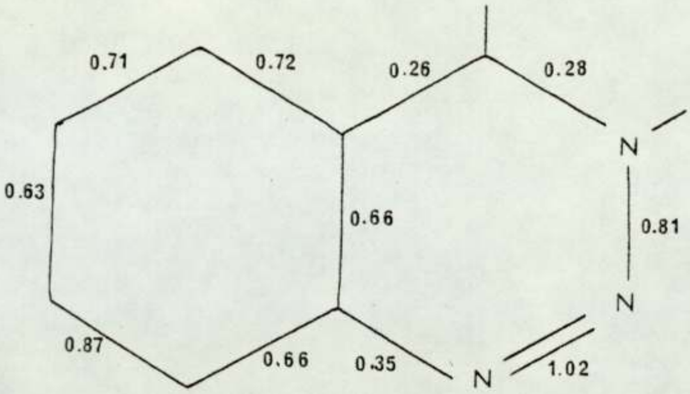
4.4 Discussion

Although, in common with other 1,2,3-benzotriazine structures investigated crystallographically, DIPB exhibits considerable delocalisation in the fused ring system, the N(1)-N(2) bond is extremely short and the $\pi[N(1)-N(2)]$ orbital can be considered to be fully occupied. A similar effect is found in the 3-phosphorodithioate structure of Rohrbaugh, et al (1976) and may be a consequence of substitution at the 3-position. There is, however, some double-bond character to the N(2)-N(3) bond in both these structures. The π-bond orders for the benzotriazine moiety of DIPB are shown in Fig 4.4-1. These have been calculated on the basis of the empirical formulae of Roos and Skancke (1967) and Fischer-Hjalmars and Sundbom (1968). With estimated standard deviations in the bond lengths of the order of 0.004 Å, the uncertainties in the calculated π-bond orders are about 0.02 (excluding uncertainties in the approximation method).

On the basis of CNDO/2 calculations (Pople and Beveridge, 1970 -- pp 75-80) there is some residual charge on the atoms of the benzotriazine ring (Fig 4.4-2). The atom N(41') is also charged (+0.245 electrons). The net charges were calculated on the basis of

$$-q_{net} = \sum_{i=1}^{N_s} q_i - N_s'$$

where Ns is the number of atomic orbitals in the valence shell and Ns' is the total population of the valence shell for the uncharged species (5 for nitrogen, 4 for carbon) and q_i is the population of each orbital.



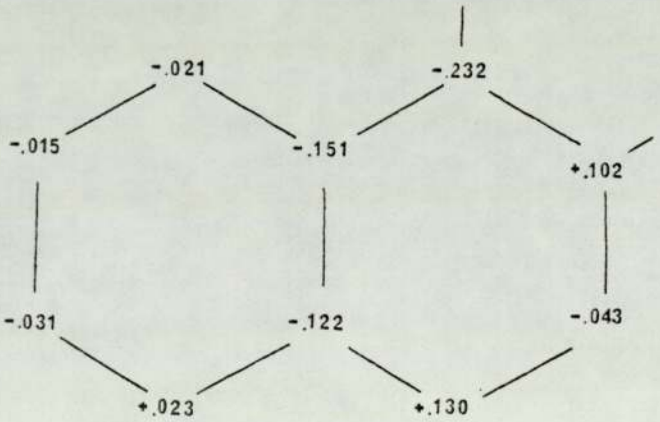
DIPB: π-bond orders calculated from bond lengths

$$p = \frac{A - d}{.18}$$

p = π-bond order d = bond length

A = 1.517 (C-C); 1.458 (C-N); 1.453 (N-N)

Fig 4.4-1



Charge distribution about the 1,2,3-benzotriazine ring according to CNDO/2 calculations.

Fig 4.4-2

All atoms in the benzotriazine moiety are within ±0.08 Å of the least-squares plane through them. With estimated standard deviations of the atomic positions of the order of 0.003 Å, the displacement of some atoms from the plane is significant. There is a slight inclination (4.0°) between the fused benzene ring and the 1,2,3-triazine ring. A similar inclination was found in the structure 1,2,3-benzotriazin-4-(3H)-one (Hjortas,1973).

The phenyl substituent is in an approximate "Stilbene trans" conformation (see Sec 9.1) with approximately 180° torsion about the bonds C(4A)-C(4)=N(41')-C(1') (see Sec 9.1). although on the basis of bond length (1.274 Å) the bond C(4)-N(41') is a pure double bond, there is some torsion about this bond and, in addition, the atom N(41') deviates by 0.18 Å from the benzotriazine plane. These distortions may be a consequence of steric hindrance from the phenyl ring (see Chapter 9). The phenyl ring is inclined to the benzotriazine ring at an angle of 76.6°. The least-squares planes for this structure are listed in Table 4-6.

The molecules are arranged pairwise in infinite columns along the direction [101]. The pairs are related by n-glide symmetry. The effect is shown perpendicular to the glide (Fig 4.4-8) and along the direction of the glide (Fig 4.4-7). The motif is repeated at intervals of 7.9 Å along the [101] direction. This arrangement leaves the phenyl rings sandwiched nearly perpendicular between two [101] translated triazines. In a survey of five related

1,2,3-benzotriazine structures (Schwalbe and Hunt,1976) DIPB was the only one found where the benzotriazine moiety did not stack. The packing arrangement is inefficient since the space between the translated fused benzene fragments is largely unoccupied, although there is some intrusion by an n-glide-related H(8) between C(5) and C(5)' and a [100] translated isopropyl group between C(7) and C(7)'. These effects can best be seen in Fig 4.4-9. The Van der Waals spheres of the atoms are shown in the form of a section along the glide plane in Fig 4.4-11. The void between the benzotriazine rings has dimensions approximately 6Å X 2Å X 2Å.

The pairwise column arrangements are separated from each other by hydrophobic contacts between the isopropyls and symmetry-related C(6)-H and C(7)-H groups, the contacts occuring approximately at the (101) planes. In the [010] direction, separation occurs at the (020) planes. No bonds pass through these planes. The charged nitrogens are kept distant from each other by the interleaving arrangement of the benzotriazines, with the N(1) atoms between [101] translated C(8) atoms.

Illustrations

4.4-3 ORTEP with numbering scheme. Ellipsoids are drawn at the 50 per cent. probability level.

4.4-4 ORTEP stereo viewed approximately along the plane of the benzotriazine rings.

4.4-5 ORTEP stereo viewed perpendicular to the plane of the benzotriazine rings.

4.4-6 Unit cell contents viewed along [100]. The symmetry operation required to generate each molecule is indicated by the type of line:

x,y,z	heavy line
1-x,1-y,1-z	light line
-x,1/2+y,3/2-z	dots and dashes
x,1/2-y,-1/2+z	dashed line

In diagrams 4.4-7 and 4.4-8 the first two operations are shown in light outline and the last two in heavy outline.

4.4-7 Unit cell contents viewed along [101].

4.4-8 Unit cell contents viewed along [010].

4.4-9 Stereo view of the unit cell contents viewed approximately along the a axis.

4.4-10 Stereo view of the unit cell contents viewed along the n glide

4.4-11 A section through the unit cell at y=0.25 showing the Van der Waals radii of the atoms.

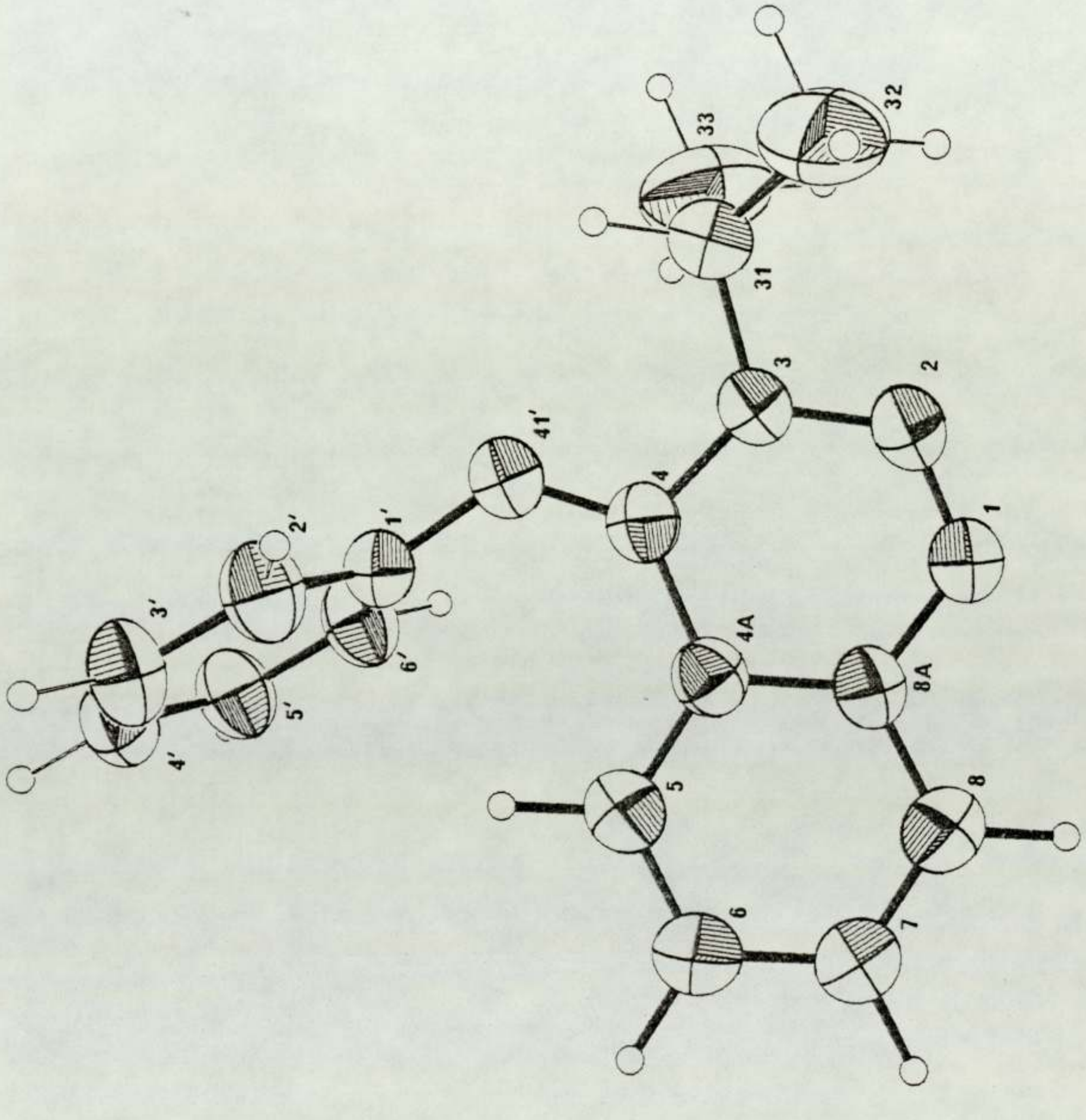


Fig 4.4-3

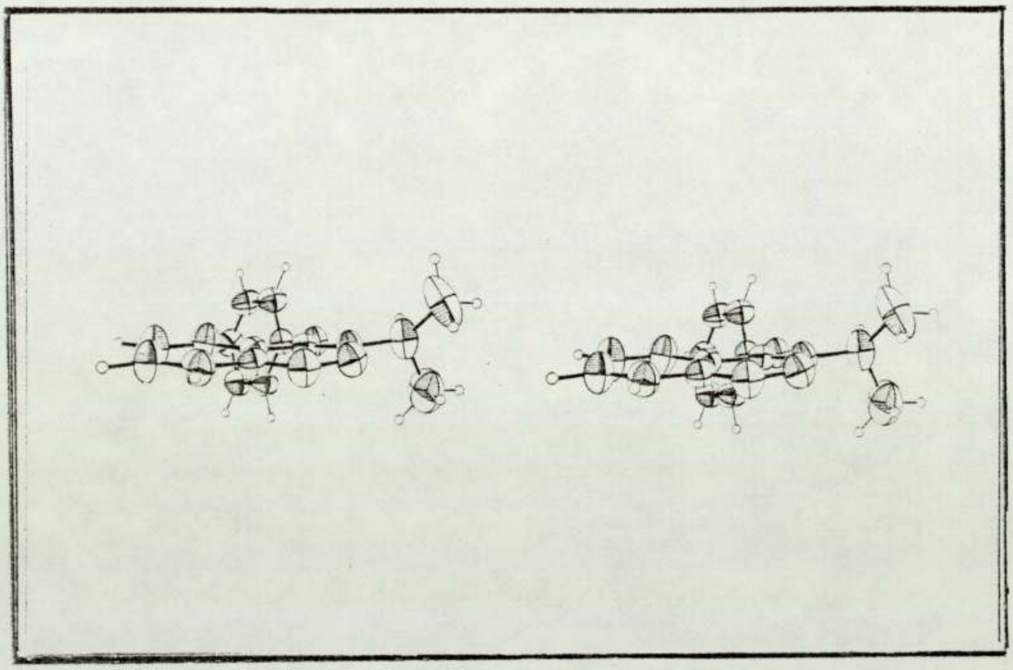


Fig 4.4 - 4

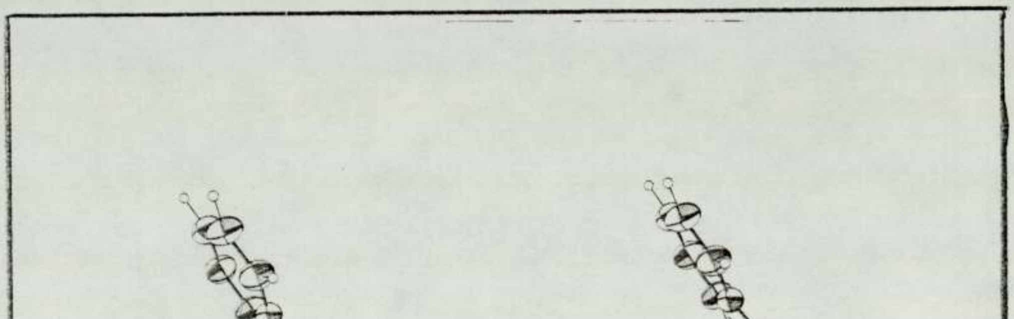


Fig 4.4 -5

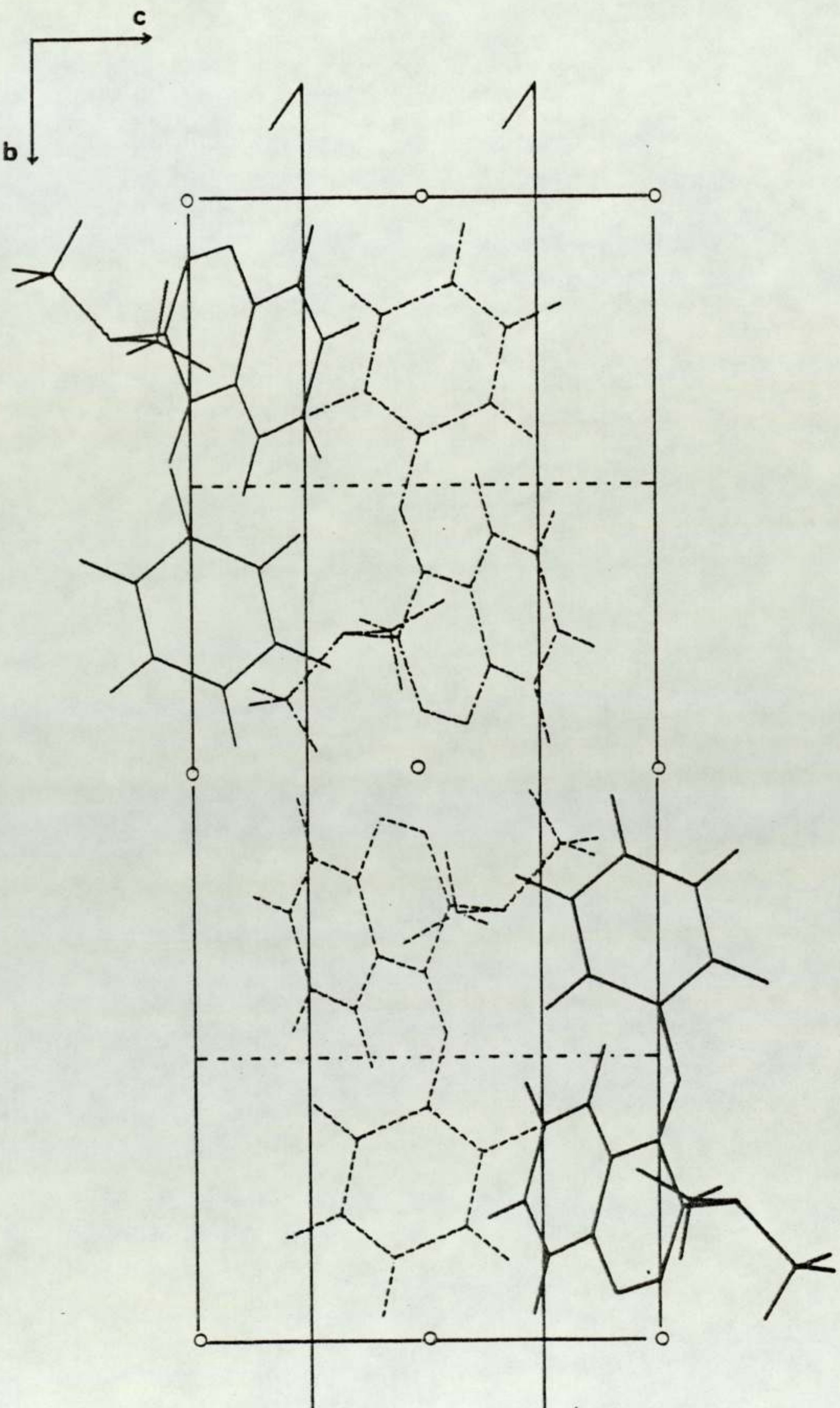


Fig 4.4-6

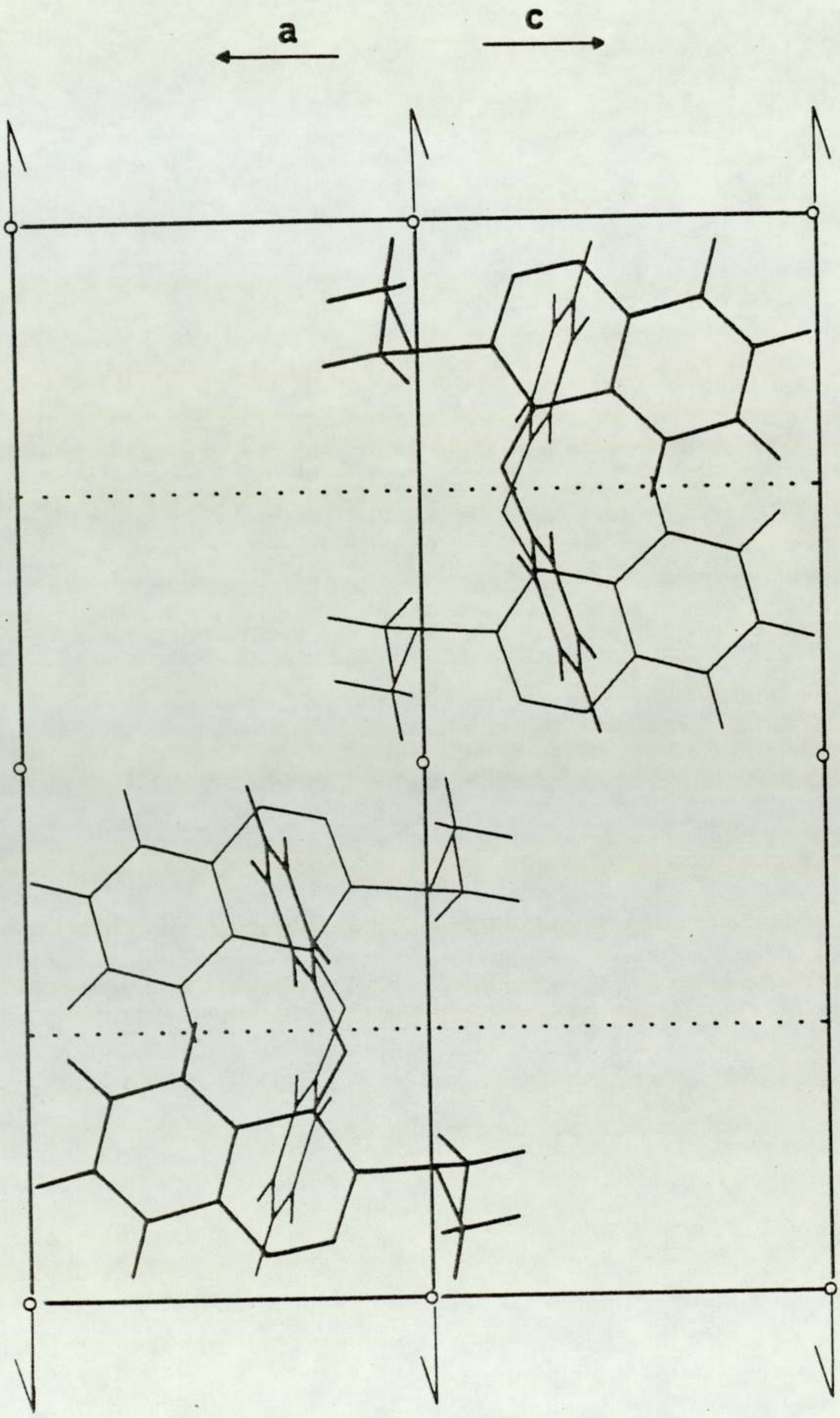


Fig 4.4-7

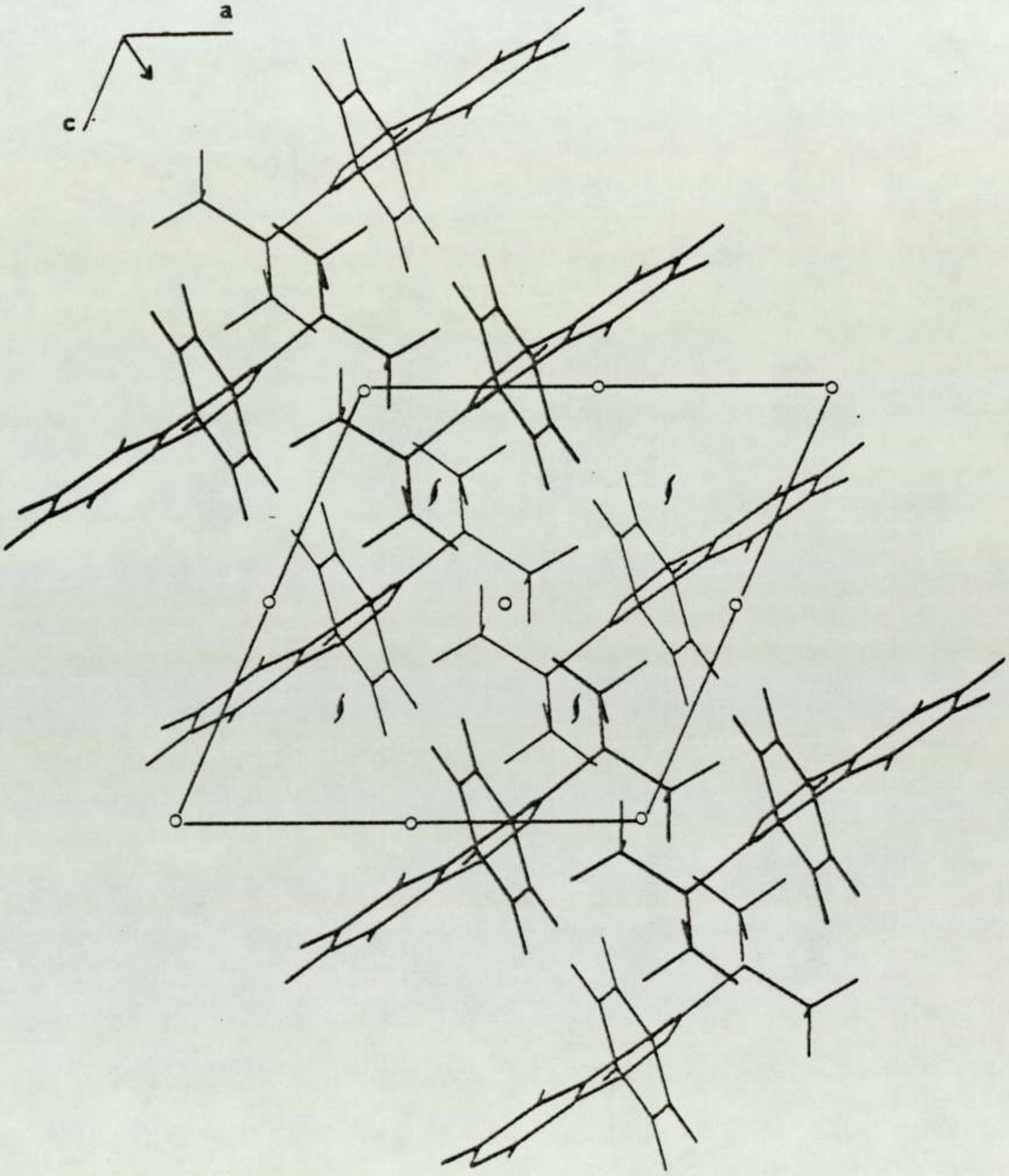


Fig 4.4-8

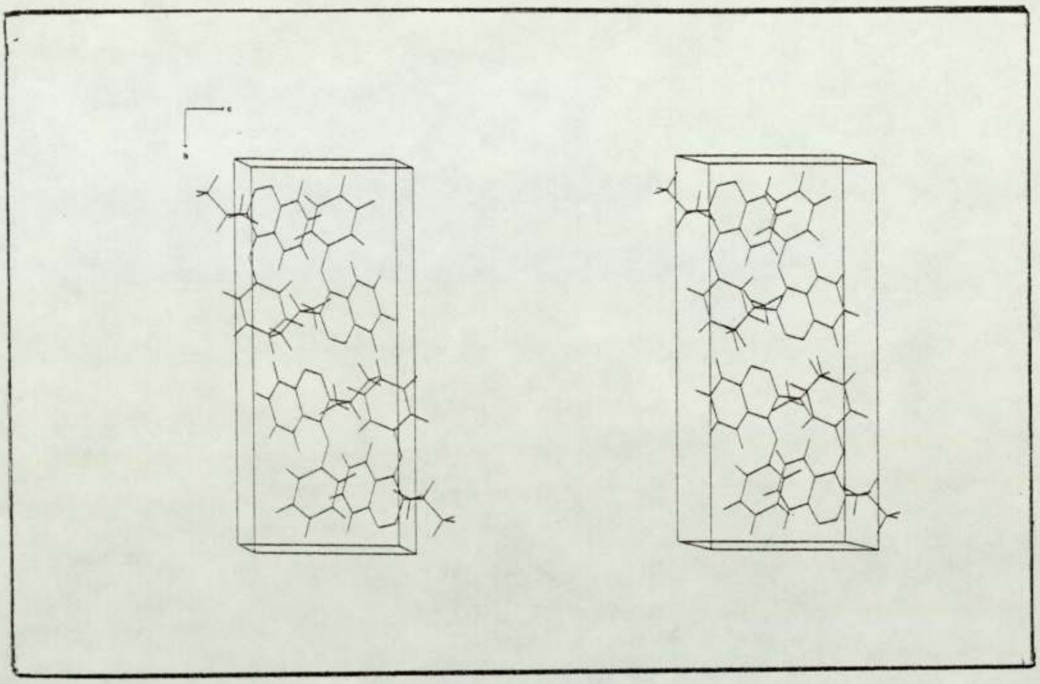


Fig 4.4-9

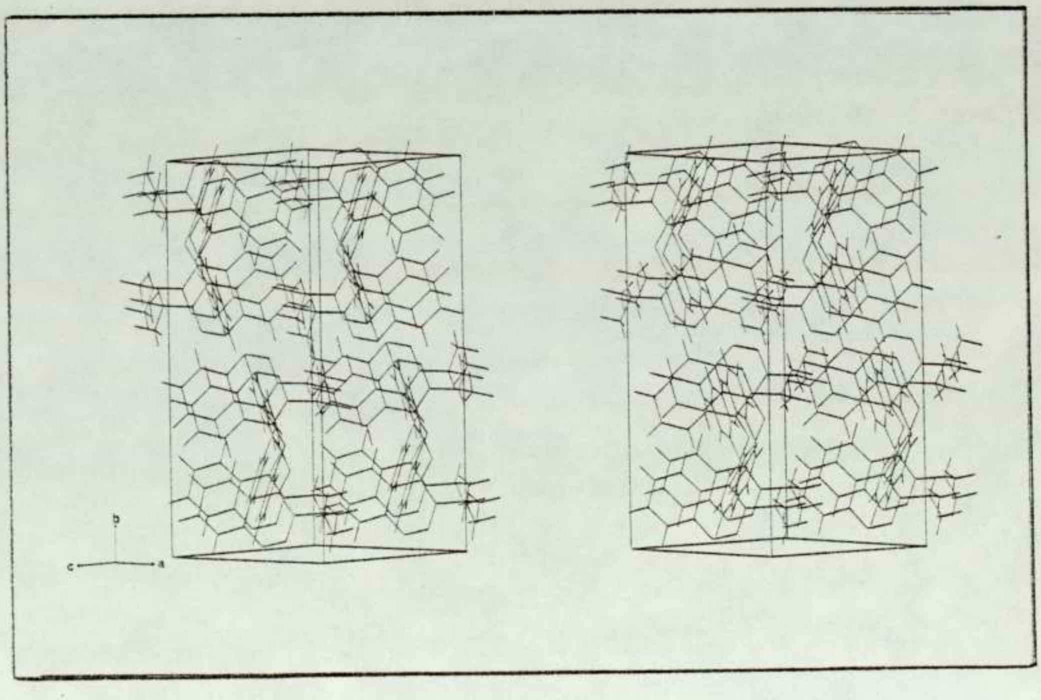


Fig 4.4-10

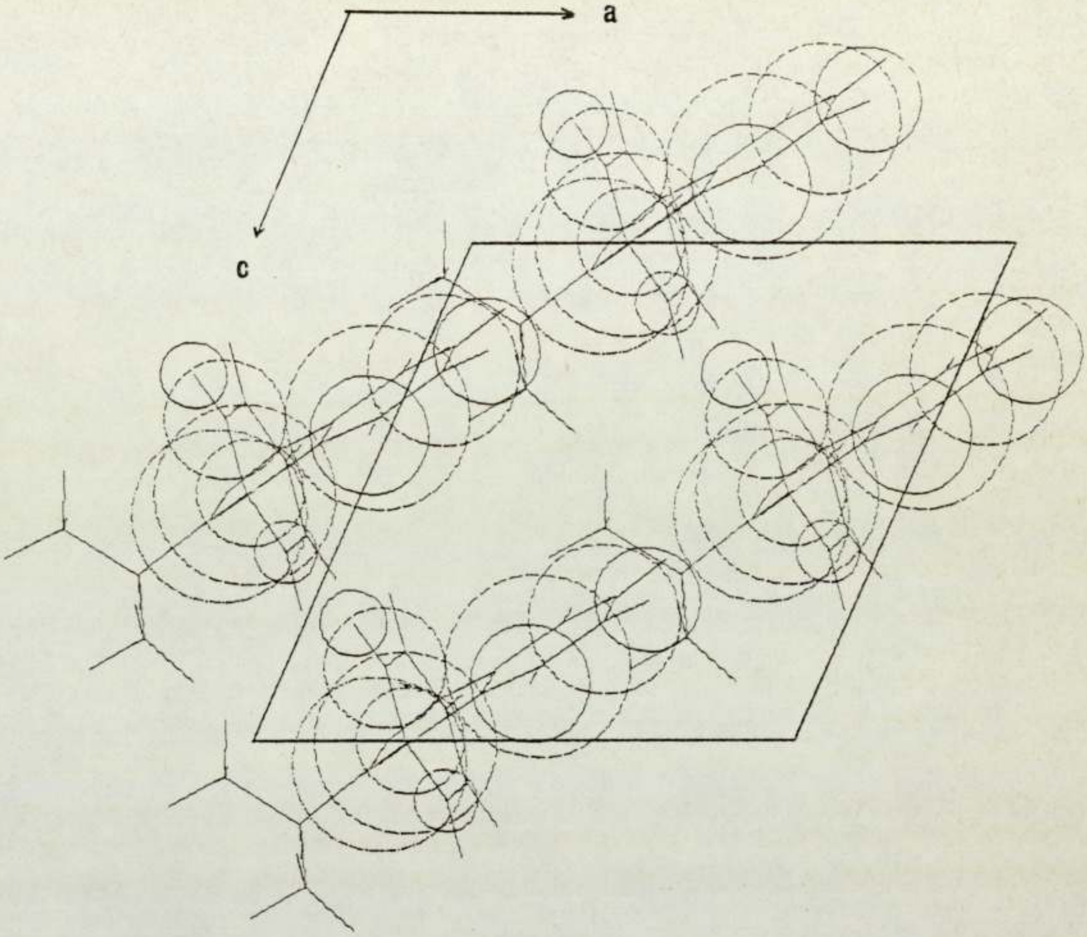


Fig 4.4.11

DIPB: FRACTIONAL COORDINATES

	X	Y	Z
N(1)	0.3182(3)	-0.0412(1)	-0.0932(3)
N(2)	0.2491(3)	-0.0539(1)	0.0024(3)
N(3)	0.2419(3)	-0.1169(1)	0.0533(3)
C(4)	0.2922(3)	-0.1749(1)	-0.0012(3)
C(4A)	0.3840(3)	-0.1599(1)	-0.1011(3)
C(5)	0.4669(4)	-0.2072(2)	-0.1512(5)
C(6)	0.5505(5)	-0.1890(2)	-0.2459(5)
C(7)	0.5507(5)	-0.1220(2)	-0.2912(5)
C(8)	0.4747(4)	-0.0748(2)	-0.2382(4)
C(8A)	0.3900(3)	-0.0933(1)	-0.1436(3)
N(41')	0.2549(3)	-0.2300(1)	0.0456(3)
C(1')	0.2856(2)	-0.2944(1)	0.0032(2)
C(2')	0.4071(2)	-0.3332(1)	0.1189(2)
C(3')	0.4294(2)	-0.3991(1)	0.0834(2)
C(4')	0.3301(2)	-0.4263(1)	-0.0679(2)
C(5')	0.2086(2)	-0.3874(1)	-0.1836(2)
C(6')	0.1863(2)	-0.3215(1)	-0.1481(2)
C(31)	0.1564(5)	-0.1211(2)	0.1659(5)
C(32)	0.2172(8)	-0.0637(3)	0.2938(6)
C(33)	-0.0233(6)	-0.1230(3)	0.0694(7)

Table 4-1

DIPB: ANISOTROPIC TEMPERATURE FACTORS

	U11	U22	U33	U23	U13	U12
N(1)	0.0753(17)	0.0452(13)	0.0715(16)	0.0038(11)	0.0394(14)	0.0025(11)
N(2)	0.0730(17)	0.0435(13)	0.0656(15)	-0.0028(10)	0.0319(13)	0.0021(11)
N(3)	0.0667(15)	0.0421(12)	0.0580(14)	-0.0024(9)	0.0327(12)	0.0021(10)
C(4)	0.0475(15)	0.0452(15)	0.0460(14)	0.0006(11)	0.0156(11)	0.0000(11)
C(4A)	0.0481(15)	0.0467(14)	0.0496(14)	-0.0037(11)	0.0178(11)	-0.0019(11)
C(5)	0.0856(23)	0.0516(17)	0.1050(27)	-0.0017(17)	0.0607(21)	0.0019(15)
C(6)	0.1058(29)	0.0634(20)	0.1124(29)	-0.0003(19)	0.0773(25)	0.0036(19)
C(7)	0.0870(25)	0.0615(19)	0.0923(25)	0.0047(17)	0.0568(21)	0.0014(16)
C(8)	0.0684(19)	0.0611(18)	0.0677(19)	0.0071(14)	0.0347(15)	-0.0014(14)
C(8A)	0.0493(15)	0.0440(15)	0.0522(15)	0.0008(11)	0.0169(12)	0.0020(11)
N(41')	0.0662(16)	0.0449(13)	0.0629(15)	-0.0011(10)	0.0316(12)	0.0008(10)
C(1')	0.0534(15)	0.0414(14)	0.0521(15)	0.0011(11)	0.0233(12)	-0.0010(11)
C(2')	0.0601(18)	0.0508(16)	0.0666(19)	-0.0046(13)	0.0153(14)	-0.0028(12)
C(3')	0.0649(19)	0.0517(17)	0.0754(20)	0.0072(14)	0.0159(16)	0.0092(14)
C(4')	0.0649(19)	0.0462(16)	0.0786(20)	-0.0035(14)	0.0278(16)	0.0006(13)
C(5')	0.0696(20)	0.0520(17)	0.0653(19)	-0.0093(13)	0.0198(16)	0.0007(13)
C(6')	0.0646(19)	0.0537(17)	0.0569(17)	-0.0007(13)	0.0119(14)	0.0083(13)
C(31)	0.0997(26)	0.0565(18)	0.0869(23)	-0.0014(16)	0.0624(22)	0.0029(16)
C(32)	0.1935(57)	0.1242(40)	0.0975(33)	-0.0332(31)	0.0956(39)	-0.0246(38)
C(33)	0.0994(36)	0.1639(52)	0.1223(40)	-0.0126(36)	0.0713(32)	-0.0160(33)

Table 4-2

DIPB: HYDROGEN FRACTIONAL COORDINATES
AND ISOTROPIC TEMPERATURE FACTORS

	X	Y	Z	UISO
H(5)	0.4667	-0.2587	-0.1163	0.0741
H(6)	0.6149	-0.2260	-0.2845	0.0691
H(7)	0.6117	-0.1080	-0.3685	0.0612
H(8)	0.4797	-0.0231	-0.2693	0.0686
H(2')	0.4840	-0.3122	0.2360	0.0707
H(3')	0.5235	-0.4292	0.1731	0.3270
H(4')	0.3474	-0.4773	-0.0953	0.0599
H(5')	0.1318	-0.4084	-0.3007	0.0808
H(6')	0.0923	-0.2915	-0.2378	0.0911
H(31)	0.1864	-0.1668	0.2354	0.1395
H(32)	0.1414	-0.0762	0.3577	0.1057
H(33)	0.1715	-0.0188	0.2238	0.1549
H(34)	0.3419	-0.0559	0.3809	0.6870
H(35)	-0.1001	-0.1346	0.1327	0.2277
H(36)	-0.0687	-0.1487	-0.0463	0.1485
H(37)	-0.0253	-0.0699	0.0488	0.0607

NOTES:
(1) H(5) TO H(31) REFINED RIDING ON BONDED CARBON ATOMS
(2) H(32) TO H(37) REFINED AS RIGID METHYL GROUPS.
(3) HYDROGEN ATOMS OF RIGID METHYL GROUPS ORIGINALLY INPUT IN STAGGERED POSITIONS.

Table 4-3

DIPB: BOND DISTANCES

N (2)	-	N (1)	1.270(3)
N (3)	-	N (2)	1.355(3)
C (4)	-	N (3)	1.407(3)
C (4A)	-	C (4)	1.471(4)
C (5)	-	C (4A)	1.388(4)
C (6)	-	C (5)	1.390(5)
C (7)	-	C (6)	1.404(4)
C (8)	-	C (7)	1.360(4)
C (8A)	-	N (1)	1.395(3)
C (8A)	-	C (4A)	1.398(4)
C (8A)	-	C (8)	1.399(4)
N (41')	-	C (4)	1.274(3)
C (1')	-	N (41')	1.407(2)
C (2')	-	C (1')	1.395*
C (3')	-	C (2')	1.395*
C (4')	-	C (3')	1.395*
C (5')	-	C (4')	1.395*
C (6')	-	C (1')	1.395*
C (6')	-	C (5')	1.395*
C (31)	-	N (3)	1.497(4)
C (32)	-	C (31)	1.561(6)
C (33)	-	C (31)	1.481(7)

* BOND DISTANCES FIXED AS A CONSEQUENCE OF RIGID-BODY REFINEMENT

Table 4-4

DIPB: BOND ANGLES

N (2) - N (1) - C (8A)	118.8(2)
N (1) - N (2) - N (3)	121.3(2)
N (2) - N (3) - C (4)	126.1(2)
N (2) - N (3) - C (31)	112.9(2)
C (4) - N (3) - C (31)	120.8(2)
N (3) - C (4) - C (4A)	112.2(2)
N (3) - C (4) - N (41')	116.1(2)
C (4A) - C (4) - N (41')	131.7(2)
C (4) - C (4A) - C (5)	124.1(2)
C (4) - C (4A) - C (8A)	117.1(2)
C (5) - C (4A) - C (8A)	118.8(3)
C (4A) - C (5) - C (6)	120.5(3)
C (5) - C (6) - C (7)	119.6(3)
C (6) - C (7) - C (8)	120.5(3)
C (7) - C (8) - C (8A)	119.8(3)
N (1) - C (8A) - C (4A)	123.7(2)
N (1) - C (8A) - C (8)	115.6(2)
C (4A) - C (8A) - C (8)	120.7(3)
C (4) - N (41) - C (1')	127.0(2)
N (41') - C (1') - C (2')	119.4(1)
N (41') - C (1') - C (6')	120.4(1)
C (2') - C (1') - C (6')	120.0*
C (1') - C (2') - C (3')	120.0*
C (2') - C (3') - C (4')	120.0*
C (3') - C (4') - C (5')	120.0*
C (4') - C (5') - C (6')	120.0*
C (1') - C (6') - C (5')	120.0*
N (3) - C (31) - C (32)	109.6(3)
N (3) - C (31) - C (33)	109.6(3)
C (32) - C (31) - C (33)	114.7(4)

* BOND ANGLES FIXED AS A CONSEQUENCE OF RIGID-BODY REFINEMENT

Table 4-5

DIPB: LEAST-SQUARES PLANES

(a) Equations of planes in the form $AX+BY+CZ+D=0$ where X,Y and Z are the orthogonal coordinates in Å along a,b and c*:

Plane(1): $0.5608X + 0.1279Y + 0.8180Z - 1.0819 = 0$
Plane(2): $0.5911X + 0.1083Y + 0.7993Z - 1.2101 = 0$
Plane(3): $0.5399X + 0.1447Y + 0.8292Z - 0.9122 = 0$
Plane(4): $0.8804X + 0.2994Y - 0.3677Z - 0.4561 = 0$

(b) Deviations in A of atoms from planes:

Plane(1): N(1) -.028, N(2) .038, N(3) .077, C(4) -.074
C(4A) -.041, C(5) .020, C(6) .045, C(7) .007,
C(8) -.006, C(8A) .037, N(41')* -.184, C(1')* -.393
Plane(2): N(1) -.029, N(2) -.002, N(3) .046, C(4) -.054,
C(4A) .025, C(8A) .015
Plane(3): C(4A) -.013, C(5) .008, C(6) .007, C(7) -.016,
C(8) .010, C(8A) .004
Plane(4): C(1'),C(2'),C(3'),C(4'),C(5') and C(6')# .000,
N(41')* -.119

(c) Dihedral angles in degrees between the planes:

(1) - (2) 2.3, (1) - (3) 1.7, (1) - (4) 76.6,
(2) - (3) 4.0, (2) - (4) 75.0, (3) - (4) 77.7

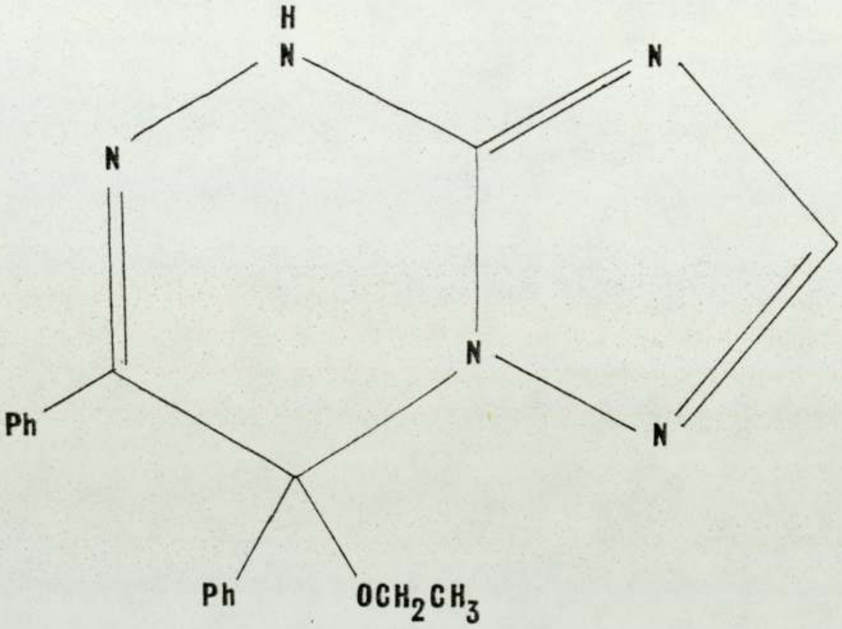
*Atoms marked with an asterisk not included in the definition of the plane.
#Atoms preceding a hash-mark have a zero deviation from the plane as a consequence of rigid-body refinement.

Table 4-6

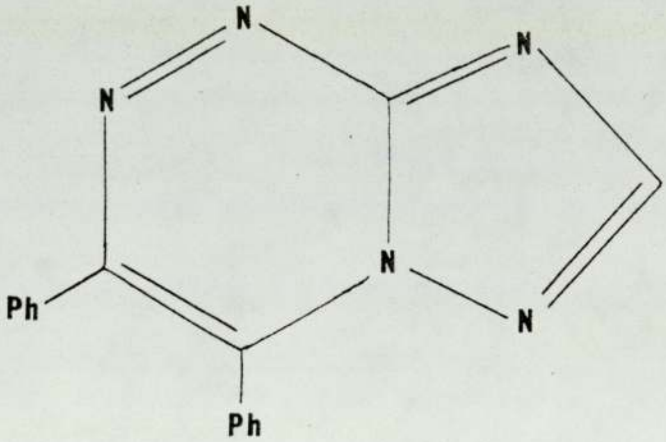
Chapter 5: 4,7-Dihydro-6,7-Diphenyl-7-Ethoxy [1,2,4]Triazolo[5,1-c][1,2,4]Triazine (DETT)

5.1 Introduction

6,7-Diphenyl[1,2,4]triazolo[5,1-c][1,2,4]triazine (DTT) and its 7-ethoxy adduct (DETT) were synthesised as potential purine antimetabolites (Gray,1976,p1). DTT was formed from the condensation of 3,4-diamino-5-hydrazino-1,2,4-triazole dihydrochloride with benzil (Bz). Two paths of cyclisation were proposed (Gray and Stevens,1976) with possible Dimroth rearrangement between the two isomers (see Fig 5.1-1). On the basis of Dimroth rearrangements in similar compounds it was believed that [5,1-c] was the more stable isomer. The 7-position was assigned as the site of attachment of the ethoxy adduct on the basis of NMR spectra (Gray and Stevens,1976). Crystallographic investigation of the two structures was undertaken to confirm the cyclic arrangement and the site of attachment of the ethoxy group. The structure of DTT has been previously reported (Schwalbe,et al,1978).



5.1-I



5.1-II

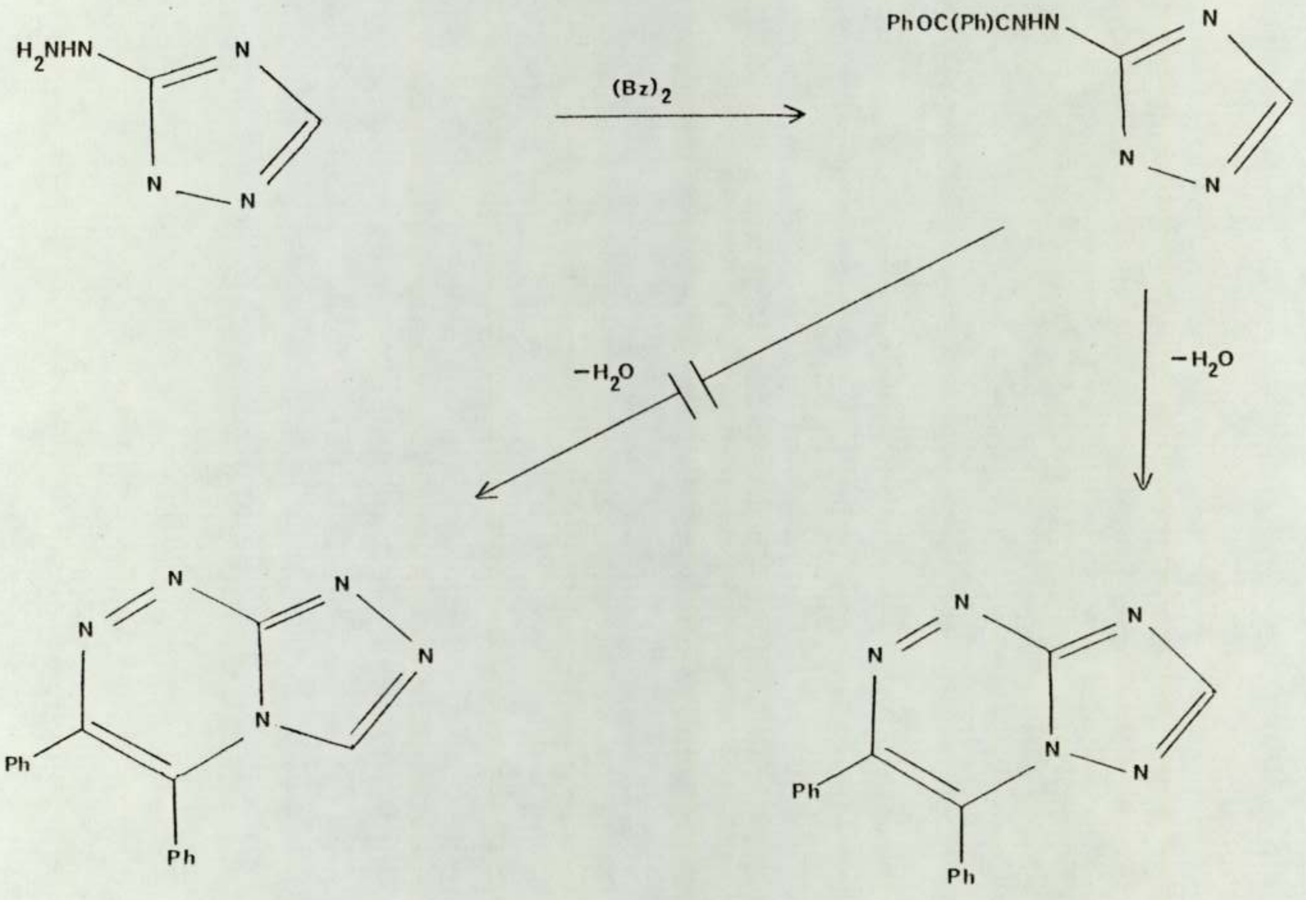


Fig 5.1-1

5.2 Crystal Data

6,7-Dihydro-6,7-diphenyl-7-ethoxy[1,2,4]triazolo[5,1-c][1,2,4]triazine ($C_{18}H_{17}N_5O$) crystallises in space group $P2_1/c$ with $a=11.329(2)$ Å, $b=9.333(2)$ Å, $c=16.094(3)$ Å, $\beta=104.48(1)^\circ$, $Z=4$, $V_c=1647(1)$ Å^3.

The molecular weight is 319.368 and the density calculated from unit cell contents 1.237 g cm^{-3}.The density determined by flotation in a solution of bromobenzene and m-xylene is 1.28 g cm^{-3}. The absorption coefficients for MoKα radiation are $\mu^*=0.710$ cgs units, $\mu=0.914$ cm^{-1}.

5.3 Structure Analysis

5.3.1 Data Collection

DETT crystallises in the form of colourless prisms. One crystal of approximate dimensions 0.6mm X 0.3mm X 0.3mm was mounted along the unique axis on a Syntex four-circle diffractometer in the Department of Molecular Sciences at Warwick University in Coventry. Crystal alignment, data collection and data reduction were done automatically with use of the Syntex system. 3394 unique MoKα diffraction peaks were recorded of which 2769 satisfied the condition $|F|>2\sigma(F)$. Refinement of the orientation matrix, the axial lengths and the angle β yielded the above cell dimensions.

5.3.2 Solution

Normalised structure factors were calculated according to the modified Wilson Plot procedure described in Section 2.2. Three rigid fragments were input: one fused 6 and 5-membered ring system, with all atoms entered as carbons and all bond distances 1.4 Å and two phenyl rings per asymmetric unit. The curves according to the Wilson calulation and the Debye calculation are shown in Fig 5.3.2-1 along with the least-squares fit to the Debye calculation. Values calculated from the gradient and intercept were

$$2B=6.4787$$

$$k=0.0548$$

The E-value statistics correspond closely to those for a randomly-distributed centrosymmetric structure (see Table 5.3.2-2).

Phase determination was undertaken with use of the program MULTAN (see Sec 2.3). 295 reflexions for which $|E|>1.70$ were input and 1600 Σ_2 relationships used in the phase refinement. On the basis of a Σ_1 calculation the following invariant phases were determined:

$2\ 4\ 8$ (+) p = 99.7 per cent.

$12\ 0\ \bar{8}$ (+) p = 95.3 per cent.

The CONVERGE procedure produced the following origin-determining reflexions: $1\ 8\ \bar{1}$ (+), $1\ 2\ 4$ (+) and $6\ 7\ \overline{10}$ (+). Eight starting sets were obtained by permuting

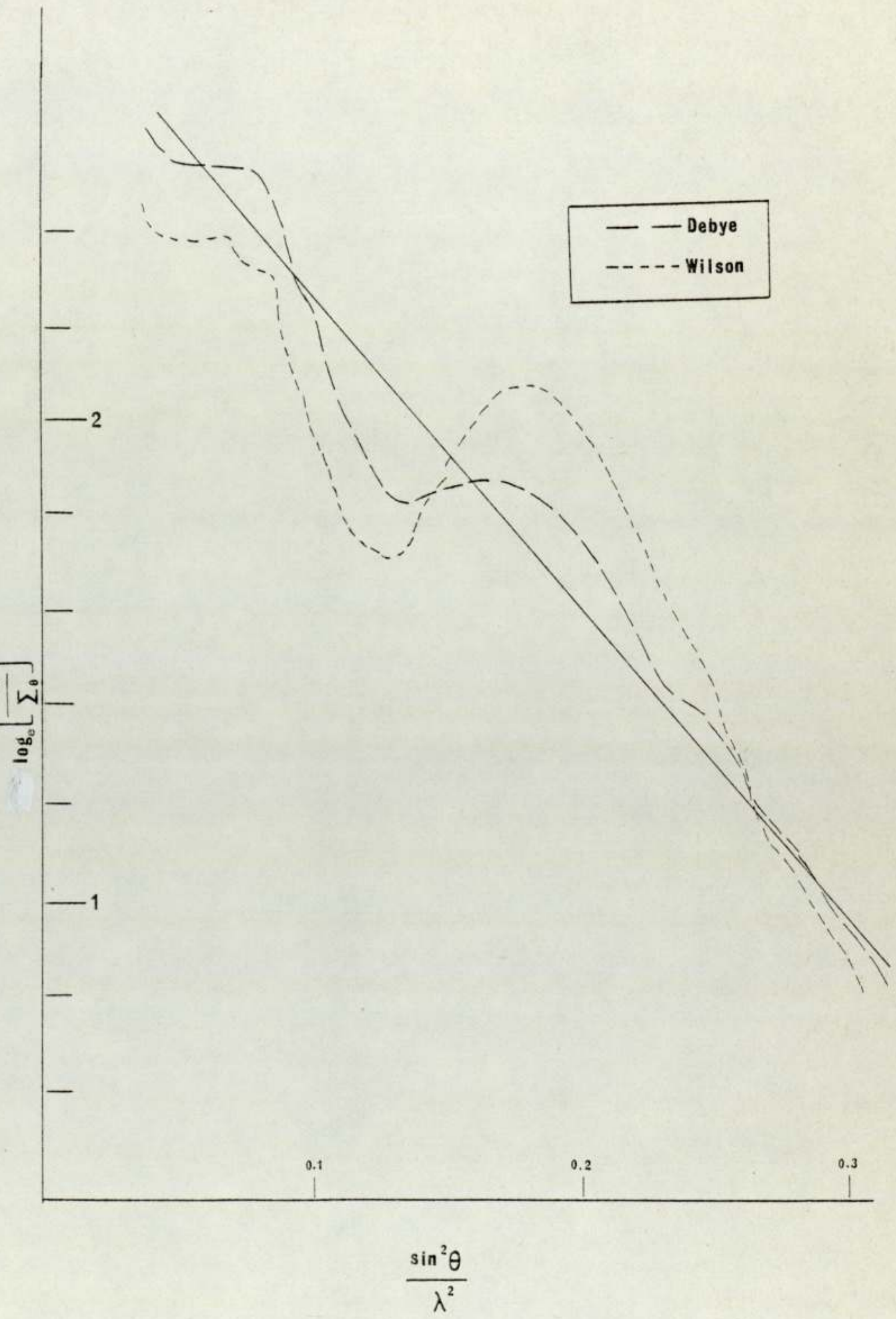

Debye
Wilson
2
1
$\log_e \left[\frac{\langle I_\theta \rangle}{\Sigma_\theta} \right]$
0.1
0.2
0.3
$\frac{\sin^2\theta}{\lambda^2}$

Fig 5.3.2-1

Distribution of E-values for DETT

	Experimental	Theoretical	
		Centric	Acentric
$<E^2-1>$	1.0183	0.9860	0.7360
$<E>$	0.7767	0.7980	0.8660
%E>0.5	58.8	61.7	77.9
%E>1.0	30.2	31.7	36.8
%E>2.0	5.0	4.6	1.8

Table 5.3.2-2

Figures of Merit for the Starting Set:

1 3 5 (+), 2 4 12 (-), 8 4 $\bar{2}$ (+)

ABS FOM	1.1117	(First)
PSI ZERO	2088	(Second Highest)
RESID	29.54	(Least)
COMB FOM	2.3859	(First)

Table 5.3.2-3

the signs of the reflexions 1 3 5, 2 4 12 and 8 4 $\bar{2}$. The set of signs +, - and + respectively produced an E-map in which, from the set of 29 peaks with density greater than half the maximum density, the triazolotriazine rings and 5 out of 6 of the carbons on each phenyl ring could be distinguished. The figures of merit for this starting set are given in Table 5.3.2-3. Isotropic refinement of these atomic positions followed by a difference Fourier synthesis yielded the remainder of the structure.

5.3.3 Refinement

Initial isotropic refinement was undertaken at Aston using the least-squares program ORFLS (see Sec 2.5.1). Some difficulty was encountered in refining all positions in the phenyl groups. When, however, the phenyl groups were refined as rigid hexagons on the SHELX system (see Sec 2.5.2(a)) all non-hydrogen atomic positions refined in a satisfactory manner.

The phenyl groups with their attached hydrogens were kept as rigid groups throughout anisotropic refinement. Additionally, the hydrogen at C(2) was refined riding on the attached carbon while the CH_2 group at C(22) and the methyl group at C(23) were refined as rigid groups. For the low-angle reflexion 1 0 0, |Fobs| was less than |Fcalc| with poor agreement. This reflexion was therefore eliminated from the later stages of refinement. During the final cycles of refinement an isotropic extinction factor of the type described in Section 2.5.2(f) was applied. The parameter x refined to a value 0.00423. The final refinement involved 217 parameters with 2768 reflexions for which $|F|>2\sigma(F)$ included in the refinement. Of the 46872 correlation coefficients r_{ij}, 11 were of the type $|r_{ij}|>0.5$. The r_{ij} of greatest magnitude (0.721) was between the scale factor and the isotropic extinction factor. All density in the final difference Fourier synthesis was in the range -0.25 eÅ^{-3} to $+0.32$ eÅ^{-3}. Two of the three greatest peaks were associated with the methyl group. The remainder of the seven greatest peaks were associated with carbons in the phenyl groups. The final agreement parameters were R=0.060, Rw=0.049, Rg=0.047.

During refinement atoms identified as nitrogens on the basis of the proposed ring closure scheme (see Fig 5.1-1) were refined with nitrogen atomic scattering factors. To test the validity of this scheme, the structure was refined with isotropic temperature factors (a) with the atomic species indicated and (b) with all ring nitrogens refined with carbon atomic scattering factors. The agreement factors and isotropic temperature factors for the two refinements are shown in Table 5.3.3-1. All indications from these refinements are that the identification of the positions of the ring nitrogens is correct. The agreement factors are worsened by the replacement of nitrogen with carbon, as would be expected on the basis of a correct identification of atomic types. With the exception of N(1), all nitrogen positions which were refined as carbon atoms have an associated Uiso<0.04 whilst the remaining

DETT: Comparison of Isotropic Refinements

		(a)	(b)
Agreement factors:			
	R	.139	.157
	Rw	.126	.142
	Rg	.125	.142
Isotropic temperature factors:			
	N(1)	.0555	.0426
	C(2)	.0550	.0636
	N(3)	.0474	.0348
	C(3A)	.0386	.0496
	N(4)	.0464	.0352
	N(5)	.0424	.0325
	C(6)	.0328	.0410
	C(7)	.0365	.0431
	N(8)	.0385	.0277

(a) Normal refinement.
(b) Refinement with the nitrogen atoms given carbon scattering factors.

Table 5.3.3-1

positions refine with Uiso>0.04. That the temperature factor at N(1) is of the same order as that at C(6) and C(7) in spite of the wrong-species refinement is hardly surprising since N(1) is at the edge of the molecule, well away from the anchoring effect of the substituents. Moreover, the alternative ring-closure system would have C(2) identified as a nitrogen position, which is unlikely on the basis of the all-carbon refinement since its temperature factor is the highest in the ring system.

5.4 Discussion

X-ray structure analysis has confirmed the predicted cyclic arrangement and the site of attachment of the ethoxy group. The effects of the addition of the ethoxy group can be observed by comparing the structures DTT and DETT. In DETT the carbon C(7) is sp^3 hybridised: the bond C(7)-C(8) is a pure single bond, while the remaining bonds to C(7) have very little double-bond character. This carbon atom deviates considerably (0.12 Å) from the plane of the remaining atoms in the triazolotriazine rings, which are all coplanar to ±.03 Å. The same degree of planarity is observed in DTT (Schwalbe,et al,1978). The arrangement of the phenyl substituents is very different in the structures DTT and DETT. In DTT neither of the phenyl substituents is coplanar with the triazolotriazine ring: they are inclined in a propeller-blade arrangement which avoids steric hindrance between the two phenyl groups. The sp^3

Interplanar Angles

	DTT	DETT
TT - C(6)-Ph	56.2°	6.2°
TT - C(7)-Ph	50.8°	82.4°
C(6)-Ph - C(7)-Ph	62.5°	86.8°

TT = Triazolotriazine

Table 5.4-1

hybridisation of C(7) of DETT forces all atoms in the ethoxy and C(7)-phenyl groups away from the triazolotriazine plane, leaving space for the C(6)-phenyl to adopt a relatively coplanar arrangement.

The bond angle at N(4) is slightly greater than 120° consistent with protonation at that site (see Sec 1.2). In DTT, where N(4) is unprotonated, the angle is 117°. There is also a significant lengthening of the bond N(4)-N(5). Two bonds in the triazolotriazine rings approach double-bond character: these are N(5)=C(6) and N(1)=C(2). With the exception of the bonds at C(7) mentioned above, the remaining bonds are of intermediate character. Delocalisation appears to be less complete in this structure than in DTT. The difference between the lengths of the two C-N bonds formed at C(2) -- a feature consistent with the molecular formula in Fig 5.1-1 -- is observed in both structures, but is less pronounced in DTT than in DETT. The near-double bond N(5)=C(6) appears to be a consequence of the sp^3 hybridisation of C(7). It is not found in DTT.

The triazolotriazine rings are loosely stacked in a herringbone arrangement along the 2_1 axes. The C(7)-phenyls are stacked in pairs across the centres of symmetry at the Wyckoff <u>d</u> positions (1/2,0/1/2) and (1/2,1/2,0) while the C(6)-phenyls are similarly arranged at the Wyckoff <u>b</u> positions (1/2,0,0) and (1/2,1/2,1/2).

Illustrations

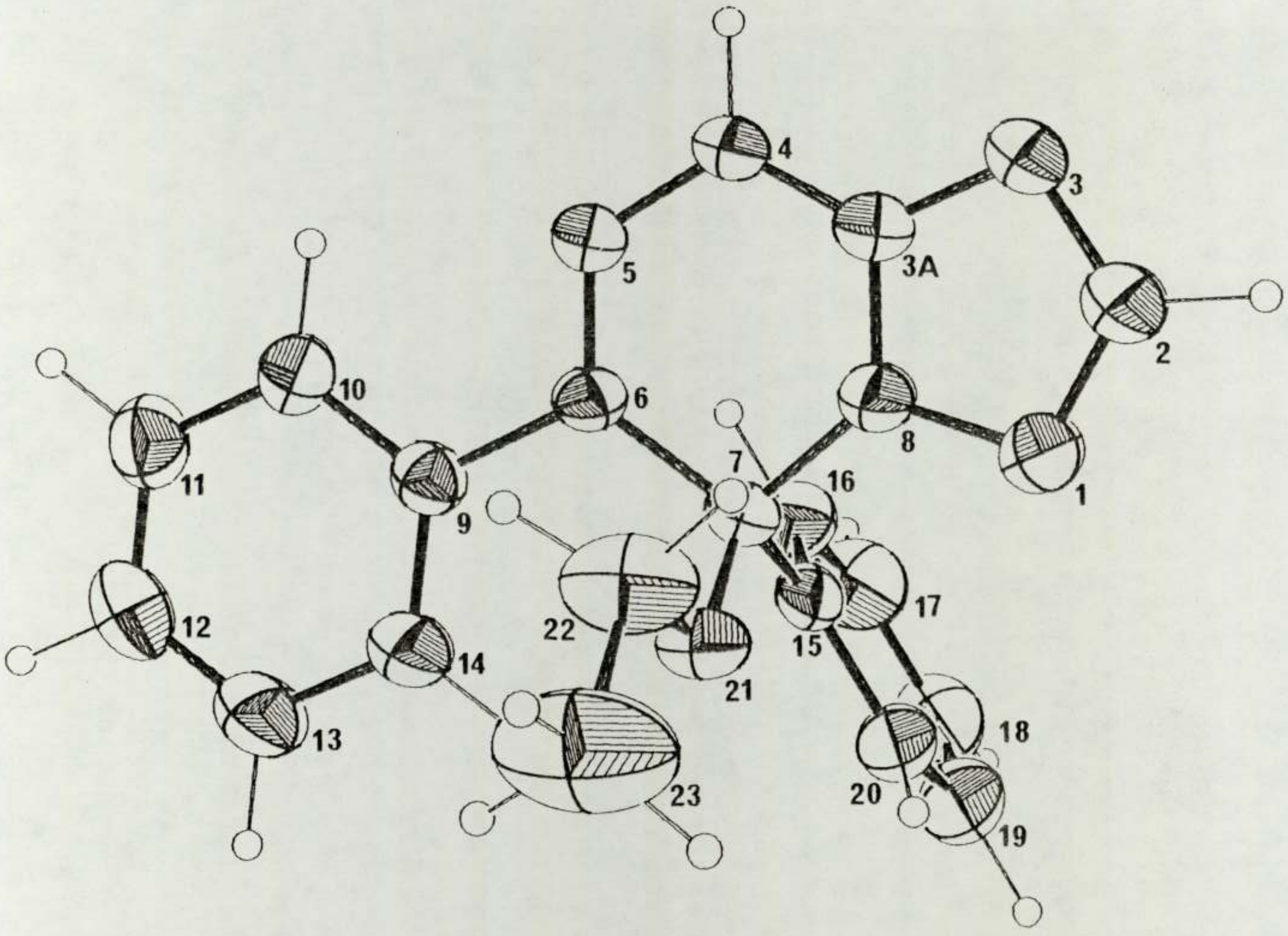


Fig 5.4-2

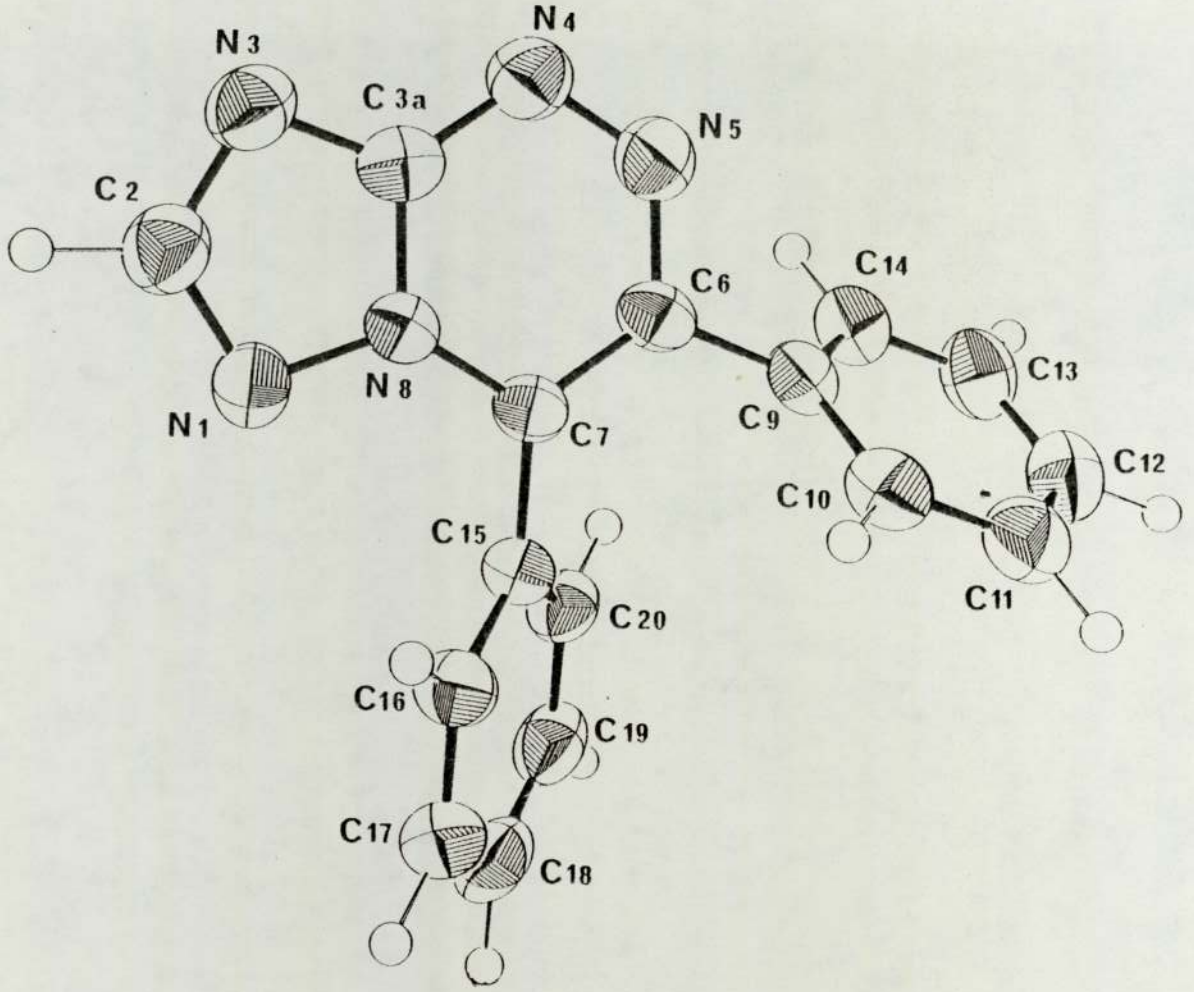

N 3
N 4
C 3a
N 5
C 2
C 14
C 6
C 13
N 8
N 1
C 9
C 7
C 12
C 10
C 15
C 11
C 20
C 16
C 19
C 17
C 18

Fig 5 4-3

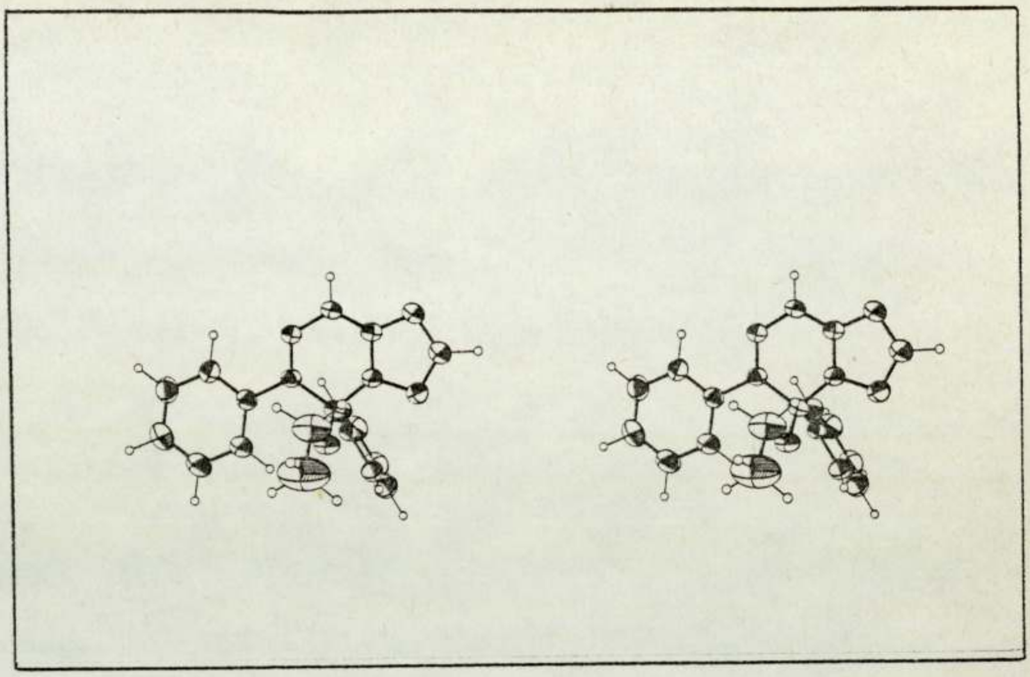


Fig 5.4 -4

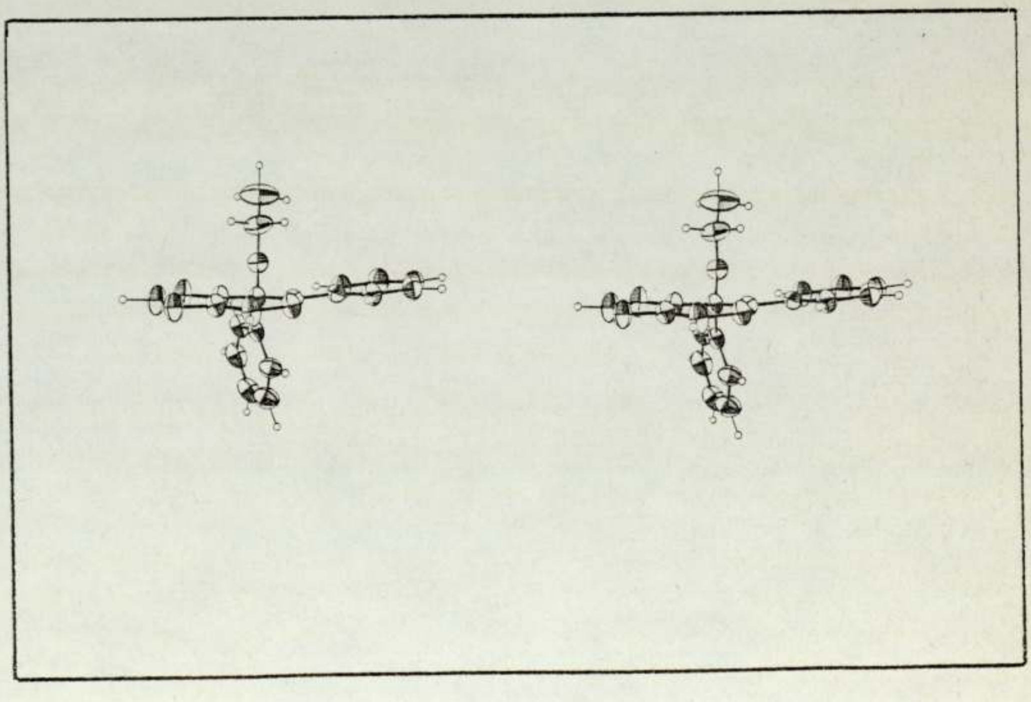


Fig 5.4 -5

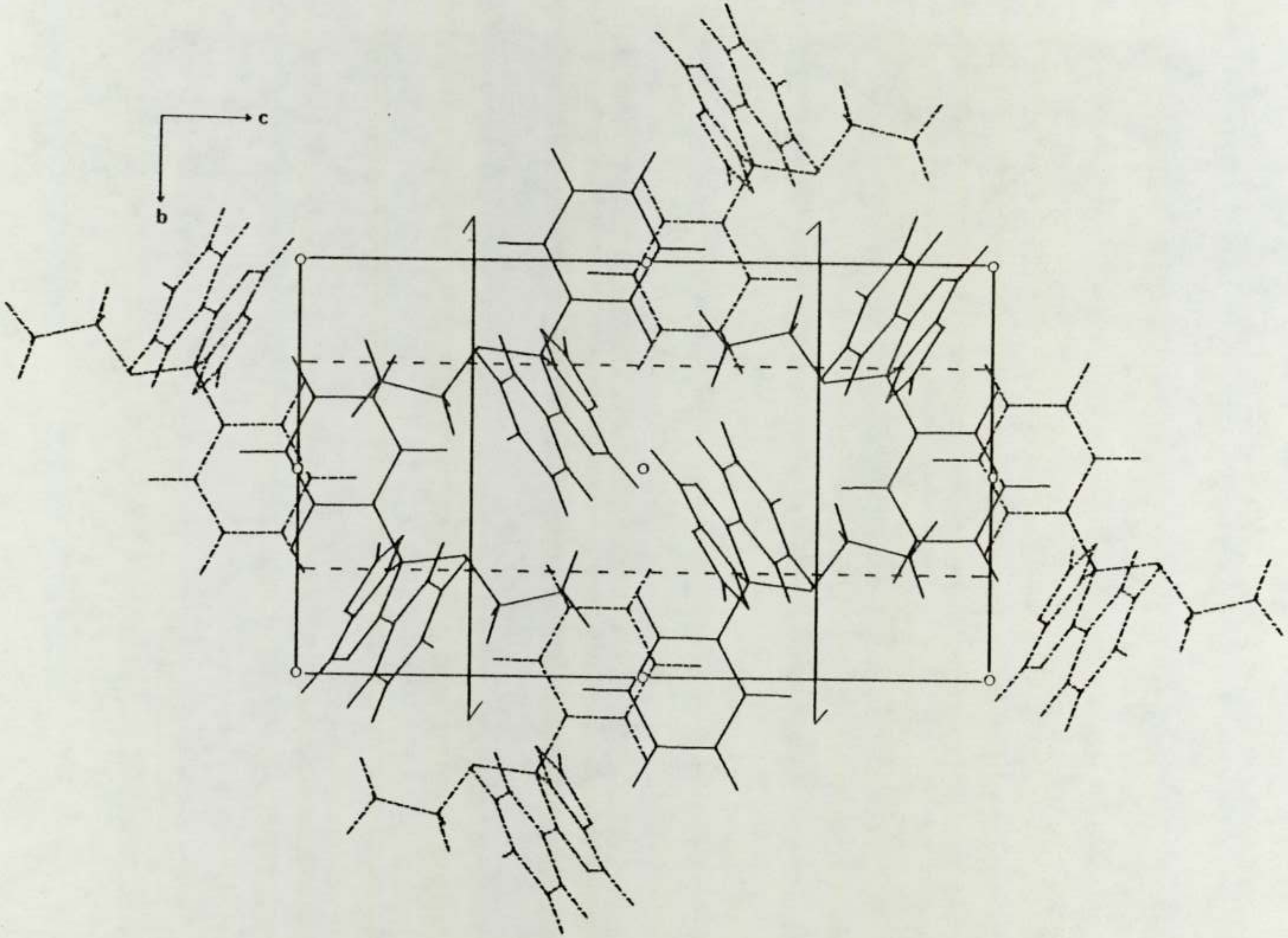


Fig 5.4-6

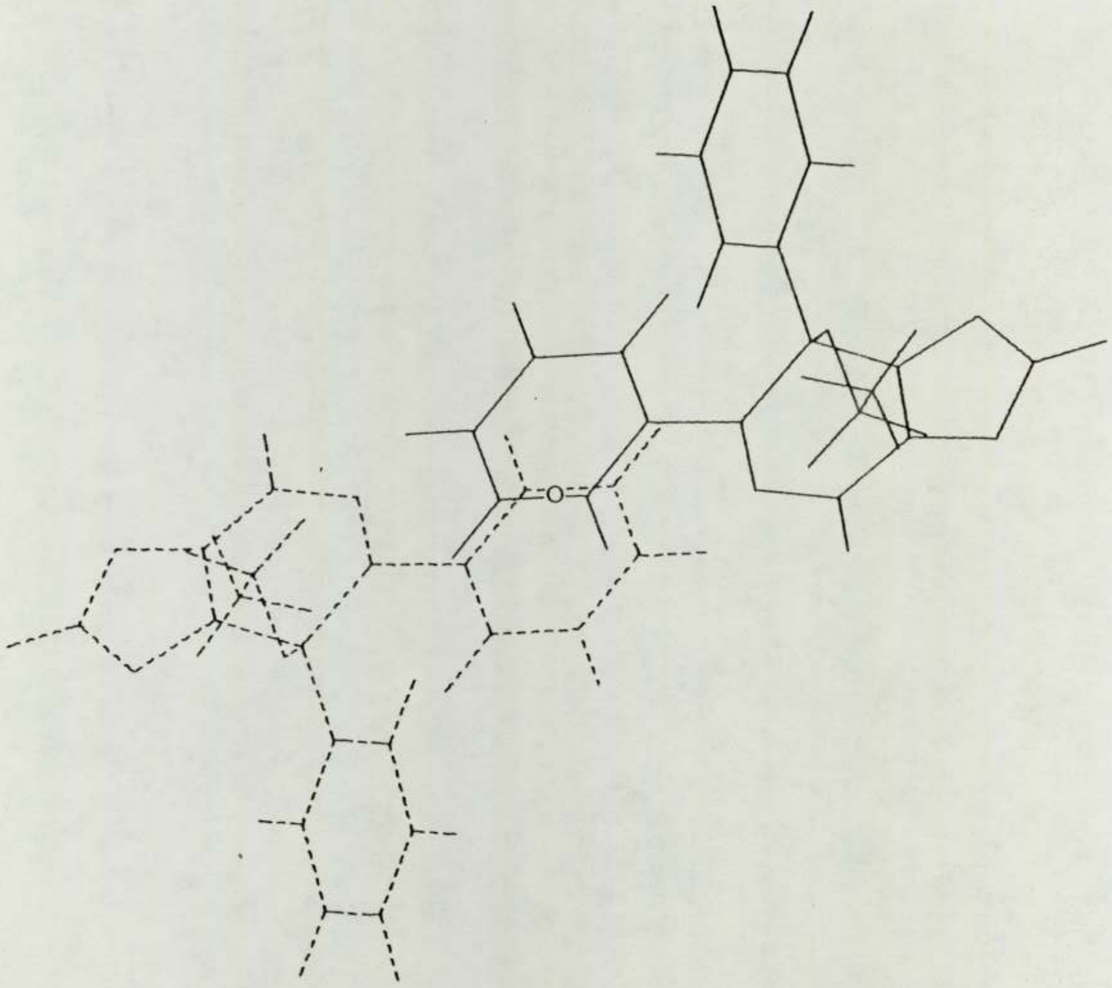


Fig 5.4-7

DETT: FRACTIONAL COORDINATES

	X	Y	Z
C(10)	0.4607(1)	0.5008(1)	0.3874(1)
C(11)	0.5723(1)	0.5210(1)	0.3672(1)
C(12)	0.6150(1)	0.4188(1)	0.3185(1)
C(13)	0.5461(1)	0.2964(1)	0.2902(1)
C(14)	0.4345(1)	0.2761(1)	0.3104(1)
C(9)	0.3918(1)	0.3783(1)	0.3590(1)
C(16)	0.2141(1)	-0.0383(1)	0.3503(1)
C(17)	0.2550(1)	-0.1658(1)	0.3932(1)
C(18)	0.3268(1)	-0.1621(1)	0.4773(1)
C(19)	0.3578(1)	-0.0310(1)	0.5186(1)
C(20)	0.3169(1)	0.0965(1)	0.4758(1)
C(15)	0.2451(1)	0.0929(1)	0.3916(1)
N(1)	-0.0233(2)	0.1664(2)	0.3478(1)
C(2)	-0.1000(2)	0.2281(2)	0.3853(1)
C(3A)	0.0504(2)	0.3633(2)	0.4178(2)
N(3)	-0.0611(2)	0.3503(2)	0.4296(1)
N(4)	0.1344(2)	0.4641(2)	0.4480(1)
N(5)	0.2436(1)	0.4649(2)	0.4262(1)
C(6)	0.2709(2)	0.3631(2)	0.3802(1)
C(7)	0.1918(2)	0.2305(2)	0.3481(1)
N(8)	0.0750(1)	0.2578(2)	0.3692(1)
O(21)	0.1712(1)	0.2110(1)	0.2592(1)
C(22)	0.1186(3)	0.3318(3)	0.2071(1)
C(23)	0.1052(5)	0.2956(4)	0.1177(2)

Table 5-1

DETT: ANISOTROPIC TEMPERATURE FACTORS

	U11	U22	U33	U23	U13	U12
C(10)	0.0469(13)	0.0408(12)	0.0571(14)	-0.0003(10)	0.0177(11)	-0.0029(10)
C(11)	0.0476(14)	0.0579(14)	0.0647(16)	0.0018(12)	0.0184(12)	-0.0069(12)
C(12)	0.0437(13)	0.0758(17)	0.0613(15)	0.0083(13)	0.0212(12)	0.0023(13)
C(13)	0.0508(14)	0.0715(16)	0.0726(17)	-0.0128(14)	0.0299(13)	0.0012(13)
C(14)	0.0482(13)	0.0529(13)	0.0659(15)	-0.0134(12)	0.0266(12)	-0.0007(11)
C(9)	0.0395(11)	0.0386(11)	0.0387(11)	0.0030(9)	0.0128(9)	0.0045(9)
C(16)	0.0564(14)	0.0353(11)	0.0723(17)	-0.0039(11)	0.0292(13)	0.0005(11)
C(17)	0.0777(18)	0.0368(13)	0.0938(20)	0.0010(14)	0.0388(16)	0.0020(13)
C(18)	0.0833(19)	0.0432(14)	0.0973(21)	0.0188(15)	0.0461(17)	0.0170(14)
C(19)	0.0834(19)	0.0623(16)	0.0688(18)	0.0168(14)	0.0240(15)	0.0172(15)
C(20)	0.0668(16)	0.0446(12)	0.0511(14)	0.0045(11)	0.0162(13)	0.0054(12)
C(15)	0.0397(12)	0.0304(10)	0.0579(14)	-0.0001(10)	0.0261(11)	0.0034(9)
N(1)	0.0417(11)	0.0540(11)	0.0932(15)	-0.0291(11)	0.0265(11)	-0.0090(10)
C(2)	0.0423(13)	0.0548(14)	0.0872(18)	-0.0207(13)	0.0272(13)	-0.0031(13)
C(3A)	0.0437(11)	0.0354(11)	0.0507(13)	-0.0051(10)	0.0199(10)	0.0035(9)
N(3)	0.0419(12)	0.0485(11)	0.0745(13)	-0.0154(10)	0.0276(11)	-0.0007(10)
N(4)	0.0500(11)	0.0434(10)	0.0793(14)	-0.0238(10)	0.0376(10)	-0.0075(9)
N(5)	0.0439(10)	0.0356(9)	0.0579(11)	-0.0068(9)	0.0243(9)	-0.0006(8)
C(6)	0.0395(11)	0.0275(9)	0.0415(12)	0.0005(9)	0.0149(10)	0.0064(9)
C(7)	0.0386(11)	0.0356(10)	0.0444(12)	-0.0059(9)	0.0186(9)	0.0015(9)
N(8)	0.0363(10)	0.0358(9)	0.0596(12)	-0.0116(8)	0.0183(8)	-0.0001(8)
O(21)	0.0526(9)	0.0386(8)	0.0446(8)	-0.0068(7)	0.0146(7)	0.0068(7)
C(22)	0.0848(19)	0.0656(16)	0.0505(15)	0.0052(13)	0.0063(14)	0.0284(16)
C(23)	0.1782(40)	0.1055(28)	0.0508(19)	0.0090(18)	0.0210(22)	0.0407(29)

Table 5-2

DETT: HYDROGEN FRACTIONAL COORDINATES
AND ISOTROPIC TEMPERATURE FACTORS

	X	Y	Z	UISO
H(10)	0.4277	0.5799	0.4251	0.0685
H(11)	0.6256	0.6159	0.3892	0.0821
H(12)	0.7014	0.4345	0.3029	0.0660
H(13)	0.5792	0.2172	0.2525	0.0990
H(14)	0.3812	0.1813	0.2884	0.0877
H(16)	0.1585	-0.0411	0.2852	0.0937
H(17)	0.2310	-0.2673	0.3612	0.1006
H(18)	0.3585	-0.2608	0.5105	0.0870
H(19)	0.4134	-0.0281	0.5837	0.1050
H(20)	0.3409	0.1981	0.5077	0.0778
H(2)	-0.1895	0.1842	0.3812	0.0855
H(21)	0.0302	0.3557	0.2177	0.1562
H(22)	0.1773	0.4240	0.2240	0.1753
H(31)	0.0652	0.3850	0.0779	0.1223
H(32)	0.0544	0.1993	0.0952	0.2856
H(33)	0.1987	0.2821	0.1145	0.1769
H(4)	0.1208	0.5393	0.4879	0.0971

NOTES: (1) H(10) TO H(20) REFINED AS PART OF RIGID PHENYL GROUPS

(2) H(2), H(21) AND H(22) REFINED RIDING ON BONDED CARBON ATOMS

(3) DISTANCE N(4)-H(4) DFIXED

(4) C(23), H(31), H(32) AND H(33) REFINED AS A RIGID PHENYL GROUP.

(5) HYDROGEN ATOMS OF RIGID METHYL GROUPS ORIGINALLY INPUT IN STAGGERED POSITIONS.

Table 5-3

DETT BOND-LENGTHS

C(11) - C(10)	1.395*
C(12) - C(11)	1.395*
C(13) - C(12)	1.395*
C(14) - C(13)	1.395*
C(9) - C(10)	1.395*
C(9) - C(14)	1.395*
C(17) - C(16)	1.395*
C(18) - C(17)	1.395*
C(19) - C(18)	1.395*
C(20) - C(19)	1.395*
C(15) - C(16)	1.395*
C(15) - C(20)	1.395*
C(2) - N(1)	1.309(3)
N(3) - C(2)	1.359(3)
N(3) - C(3A)	1.328(2)
N(4) - C(3A)	1.341(3)
N(5) - N(4)	1.367(2)
C(6) - C(9)	1.499(2)
C(6) - N(5)	1.288(2)
C(7) - C(14)	1.514(2)
C(7) - C(6)	1.540(3)
N(8) - N(1)	1.376(2)
N(8) - C(3A)	1.330(2)
N(8) - C(7)	1.469(2)
O(21) - C(7)	1.402(2)
C(22) - O(21)	1.442(3)
C(23) - C(22)	1.449(3)

* FIXED AS A CONSEQUENCE OF RIGID-BODY REFINEMENT

Table 5-4

DETT: BOND ANGLES

C(11) - C(10) - C(9)	120.0*
C(10) - C(11) - C(12)	120.0*
C(11) - C(12) - C(13)	120.0*
C(12) - C(13) - C(14)	120.0*
C(13) - C(14) - C(9)	120.0*
C(10) - C(9) - C(14)	120.0*
C(10) - C(9) - C(6)	118.1(1)
C(14) - C(9) - C(6)	121.9(1)
C(17) - C(16) - C(15)	120.0*
C(16) - C(17) - C(18)	120.0*
C(17) - C(18) - C(19)	120.0*
C(18) - C(19) - C(20)	120.0*
C(19) - C(20) - C(15)	120.0*
C(16) - C(15) - C(20)	120.0*
C(16) - C(15) - C(7)	120.0*
C(20) - C(15) - C(7)	119.8(1)
C(2) - N(1) - N(8)	101.6(2)
N(1) - C(2) - N(3)	116.4(2)
N(3) - C(3A) - N(4)	128.8(2)
N(3) - C(3A) - N(8)	111.3(2)
N(4) - C(3A) - N(8)	119.9(2)
C(2) - N(3) - C(3A)	101.3(2)
C(3A) - N(4) - N(5)	121.1(2)
N(4) - N(5) - C(6)	120.4(2)
C(9) - C(6) - N(5)	115.2(2)
C(9) - C(6) - C(7)	119.2(1)
N(5) - C(6) - C(7)	125.6(2)
C(15) - C(7) - C(6)	113.3(1)
C(15) - C(7) - N(8)	108.5(1)
C(15) - C(7) - O(21)	107.9(1)
C(6) - C(7) - N(8)	105.4(1)
C(6) - C(7) - O(21)	112.4(1)
N(8) - C(7) - O(21)	109.2(1)
N(1) - N(8) - C(3A)	109.3(1)
N(1) - N(8) - C(7)	123.7(1)
C(3A) - N(8) - C(7)	126.8(1)
C(7) - O(21) - C(22)	115.5(1)
O(21) - C(22) - C(23)	108.7(1)

* FIXED AS A CONSEQUENCE OF RIGID-BODY REFINEMENT

Table 5-5

DETT: LEAST-SQUARES PLANES

(a) Equations of planes in the form AX+BY+CZ+D=0 where X,Y and Z are the orthogonal coordinates in Å along a,b and c*:

Plane(1): 0.2637X - 0.4780Y + 0.8378Z - 3.7896 = 0
Plane(2): -0.9392X - 0.0379Y + 0.3413Z - 0.9223 = 0
Plane(3): 0.1719X - 0.5399Y + 0.8240Z - 3.3372 = 0
Plane(4): 0.1741X - 0.5206Y + 0.8358Z - 3.4895 = 0
Plane(5): 0.9336X + 0.3553Y + 0.0463Z - 1.7305 = 0
Plane(6): 0.1787X + 0.5433Y + 0.8203Z - 3.2959 = 0

(b) Deviations in A of atoms from planes:

Plane(1): C(9),C(10),C(11),C(12),C(13) and C(14)# .000, C(6)* -.039
Plane(2): C(15),C(16),C(17),C(18),C(19) and C(20)# .000, C(7)* .121
Plane(3): N(1) .004,C(2) -.001, N(3) -.003, C(3A) .006, N(8) -.006
Plane(4) C(3A) -.006,N(4) .042, N(5) -.016, C(6) -.033, C(7) .059, N(8) -.045
Plane(5): C(7) .006, O(21) -.007, C(22) -.005, C(23) .006
Plane(6) N(1) .009,C(2) -.007, N(3) -.013, C(3A) .004, N(4) .027, N(5) -.019, C(6) -.002, C(7)* .122, N(8) .002, C(9)* -.090

(c) Dihedral angles in degrees between the planes:

(1) - (2) 86.8, (1) - (3) 6.4, (1) - (4) 5.7,
(1) - (5) 83.4, (1) - (6) 6.2, (2) - (3) 81.9,
(2) - (4) 81.9, (2) - (5) 151.0, (2) - (6) 82.4,
(3) - (4) 1.3, (3) - (5) 89.6, (3) - (6) 0.5,
(4) - (5) 89.1, (4) - (6) 1.6, (5) - (6) 89.3

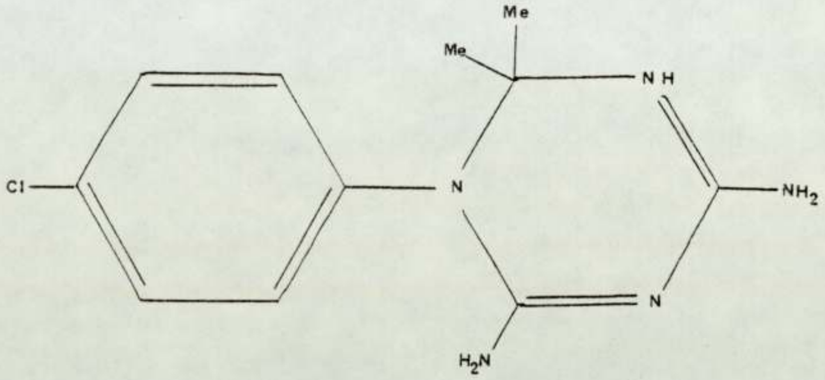
*Atoms marked with an asterisk not included in the definition of the plane.
#Atoms preceding a hash-mark have a zero deviation from the plane as a consequence of rigid-body refinement.

Table 5-6

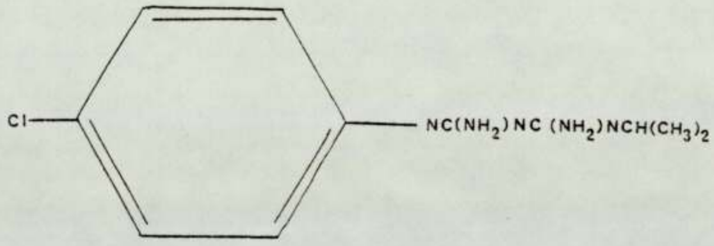
Chapter 6: Cycloguanil Hydrochloride

6.1 Introduction

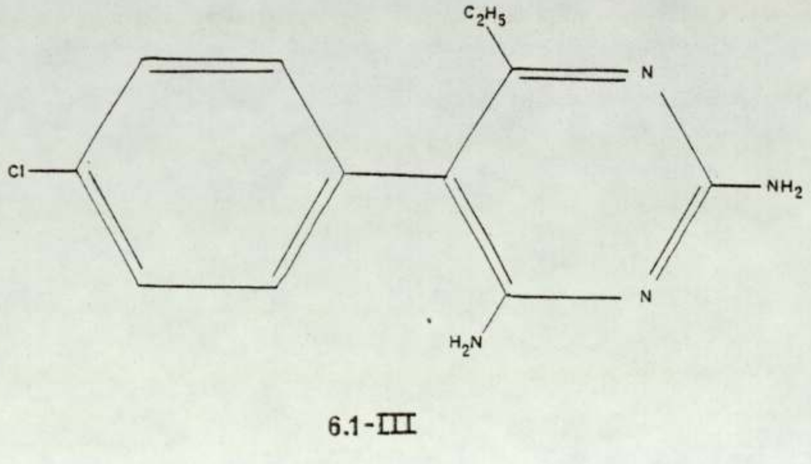
Cycloguanil (6.1-I) has been identified as the active metabolite of the antimalarial drug Proguanil,BP (6.1-II) (Carrington,et al,1951). Its synthesis, along with melting point and ultraviolet absorption characteristics, has been described elswhere (Thompson,et al,1963). The properties of cycloguanil have been investigated on several mammalian hosts for a variety of *plasmodia* (see Table 6.1-1). It has been used extensively in Guatemala (Clyde,1969). The characteristics of cycloguanil observed in clinical trials are similar to those of Proguanil,BP and Pyrimethamine,BP (6.1-III) offering no protection to strains resistant and cross-resistant to these drugs (Clyde,1969). Its principal use clinically appears to be in the treatment of strains resistant to Chloroquine,BP and -- when injected intramuscularly in the pamoate form (6.1-IV) -- to offer protection for a period of months to uninfected individuals (Coatney,et al,1964). Cycloguanil pamoate has also been found useful in the treatment of cutaneous leishmaniasis in Central America (Peña-Chavarria,et al,1965).



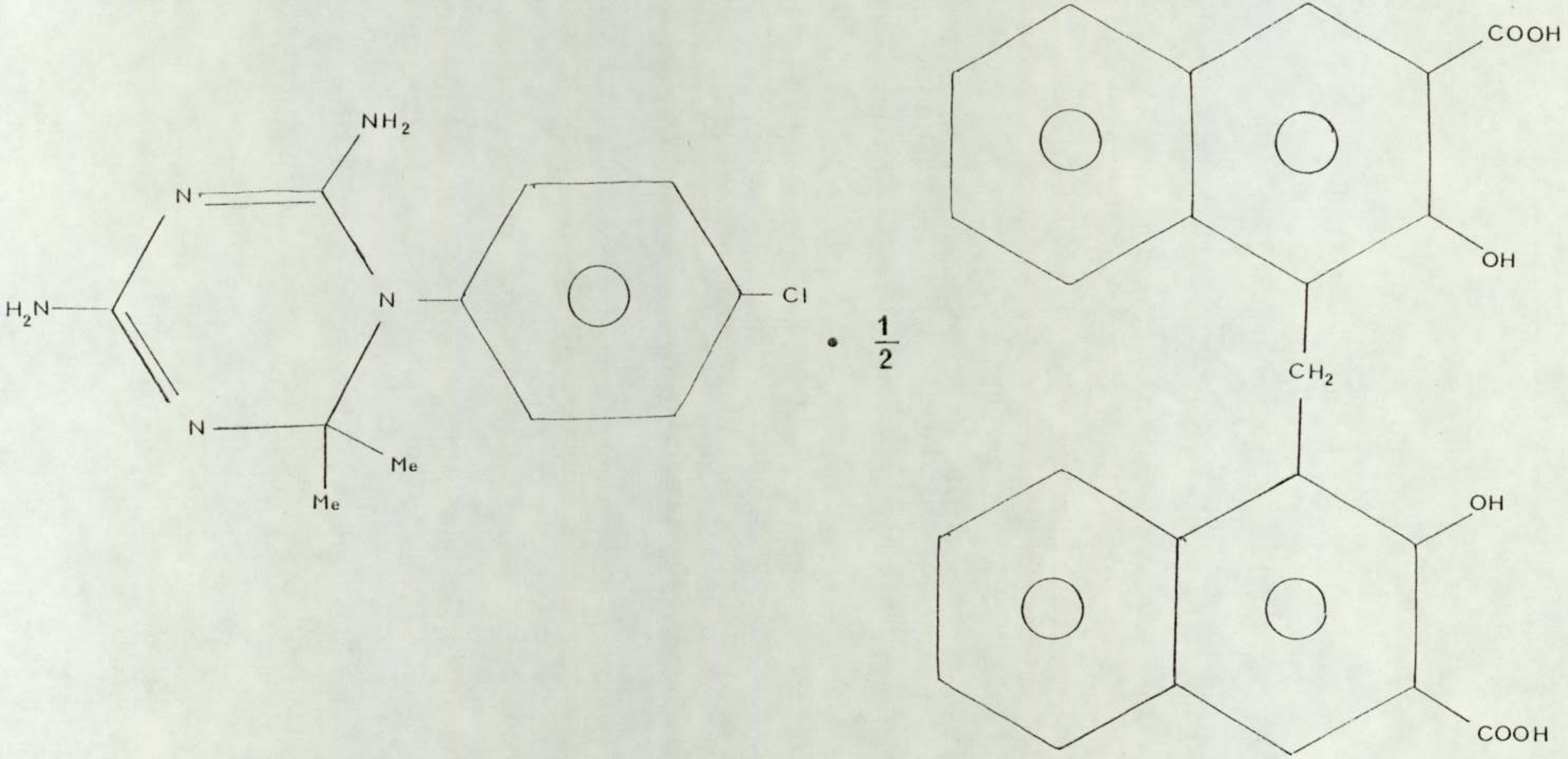
6.1-I



6.1-II



6.1-III



6.1-IV

Summary of *in vivo* investigations of Cycloguanil

Host	Plasmodium	Form Administered	Reference
Mouse	P.berghei	Pamoate	Thompson,et al,1963
Rhesus Monkey	P.cynomolgi	Pamoate	Thompson,et al,1963
Rhesus Monkey	P.cynomolgi	Pamoate and and Hydrochloride	Schmidt,et al,1963
Man	P.falciparum	Hydrochloride	Robertson,1957
Man	P.vivax	Pamoate	Coatney,et al,1963
Man	P.vivax	Pamoate	Coatney,et al,1964
Man	P.vivax	Pamoate	Powell,et al,1965
Man	P.falciparum	Pamoate	Contacos,et al,1964
Man	P.falciparum	Pamoate	McGregor,et al,1966
Man	P.falciparum	Pamoate	Lunn,et al,1964
Man	P.malariae	Pamoate	McGregor,et al,1966
Man	P.ovale	Pamoate	McGregor,et al,1966

Table 6.1-1

The chemistry and pharmacology of cycloguanil has been extensively reviewed by Thompson and Werbel (1972 -- pp 251 - 265).

The crystal structures of cycloguanil hydrochloride and cycloguanil hydrobromide have been solved and refined in projection (Bailey,1954).

6.2 Crystal Data

4,6-Diamino-1-p-chlorophenyl-1,2-dihydro-2,2-dimethyl-s-triazine hydrochloride ($C_{11}H_{15}N_5Cl_2$) crystallises in Space Group $P2_1/c$ with a=8.87(2) Å, b=10.39(2) Å, c=17.14 Å, β=115.2(1)°, V_c=1430(10) $Å^3$, Z=4. The molecular weight is 288.182 (251.721 for the free base) and the density calculated from unit cell contents 1.339 g cm^{-3}. The crystal density determined by flotation in a solution of bromobenzene and m-xylene is 1.336 g cm^{-3}. Since both density determinations are accurate to about ±.01 g cm^{-3}, the difference between them is not significant. The absorption coefficients for MoKα radiation are μ =3.334 c.g.s. units and μ^*=4.463 cm^{-1}.

6.3 Structure Analysis (X-ray)

6.3.1 X-ray Data Collection

3659 independent reflexions (3040 with $|F|>2\sigma(F)$) were collected on the Stoe 2-circle diffractometer in the Department of Chemistry at the University of Birmingham.

With the crystal mounted about the b-axis data were collected in layers of k=0 to k=12 using monochromated MoKα radiation (λ=0.71069 Å, monochromator 2θ=12°). Peak intensities were collected by scanning in ω over a range $\Delta\omega$ given by

$$\Delta\omega = A + B \frac{\sin\mu}{\tan\theta'}$$

where μ is the equi-inclination angle and θ' is half the angle between the diffracted ray and the direct beam when projected onto a plane perpendicular to the axis of rotation and where A and B were set as follows:

levels 0 - 2 A=1.20°, B=0.0°
levels 3 - 12 A=0.90°, B=0.5°

The maximum 2θ was set to 55° up to and including level 3, then subsequently reduced by one degree per level. Data on all levels were thus collected at least to the limit of the copper sphere. The stepping time was set at 1 sec. with ω incremented .01° between each step. Background intensities were collected for 30 sec. on either side of the stepping range. The zero level check reflexions 0 0 8, 2 0 $\bar{4}$, 3 0 6 and 1 0 $\overline{14}$ were collected after completion of each level. The reflexion 3 12 $\overline{17}$, incorrectly transcribed onto paper tape, was eliminated from the data set. Data were reduced with use of a program supplied by Dr. T.A.Hamor with σ(F) values calculated on the basis of a Poisson counting distribution and a variation in the main beam intensity of 4 per cent.

6.3.2 Solution

E-values were calculated according to the modified Wilson Plot procedure described in Section 2.1 with the 299 reflexions with greatest E-values used for the purpose of phase determination with the program MULTAN (Main, et al, 1971). Starting with the origin-fixing reflexions 1 3 8, 4 9 $\bar{9}$ and 5 7 $\bar{3}$ (all set to +) and -- by permuting the reflexions 4 1 5, 3 9 13 and 4 7 $\bar{2}$ -- two equivalent origin-shifted solutions with ABS FOM=1.0431 (First), PSI ZERO=5210 (Second) and RESID=30.27 (Least) were obtained. The equivalents were formed as a result of sign changes in the starting set under tangent formula refinement. The two sets are related by a reversal of sign of the parity groups *guu* and *uuu*.

The E-map corresponding to these starting sets revealed the two chlorine atoms in the asymmetric unit. A Fourier sythesis phased on the chlorine atoms revealed five of the six carbon atoms in the phenyl ring. No further chemically-reasonable peaks were found until the sixth phenyl carbon, N(1) and C(4) had been placed in calculated positions. A peak, identified as either an the equatorial methyl carbon or as N(8) suggested that the rings were nearly perpendicular. The triazine ring was placed in a calculated position consistent with the above peak identification and both rings refined ($\sin\theta < .25$) as rigid hexagons. The subsequent Fourier synthesis revealed a peak

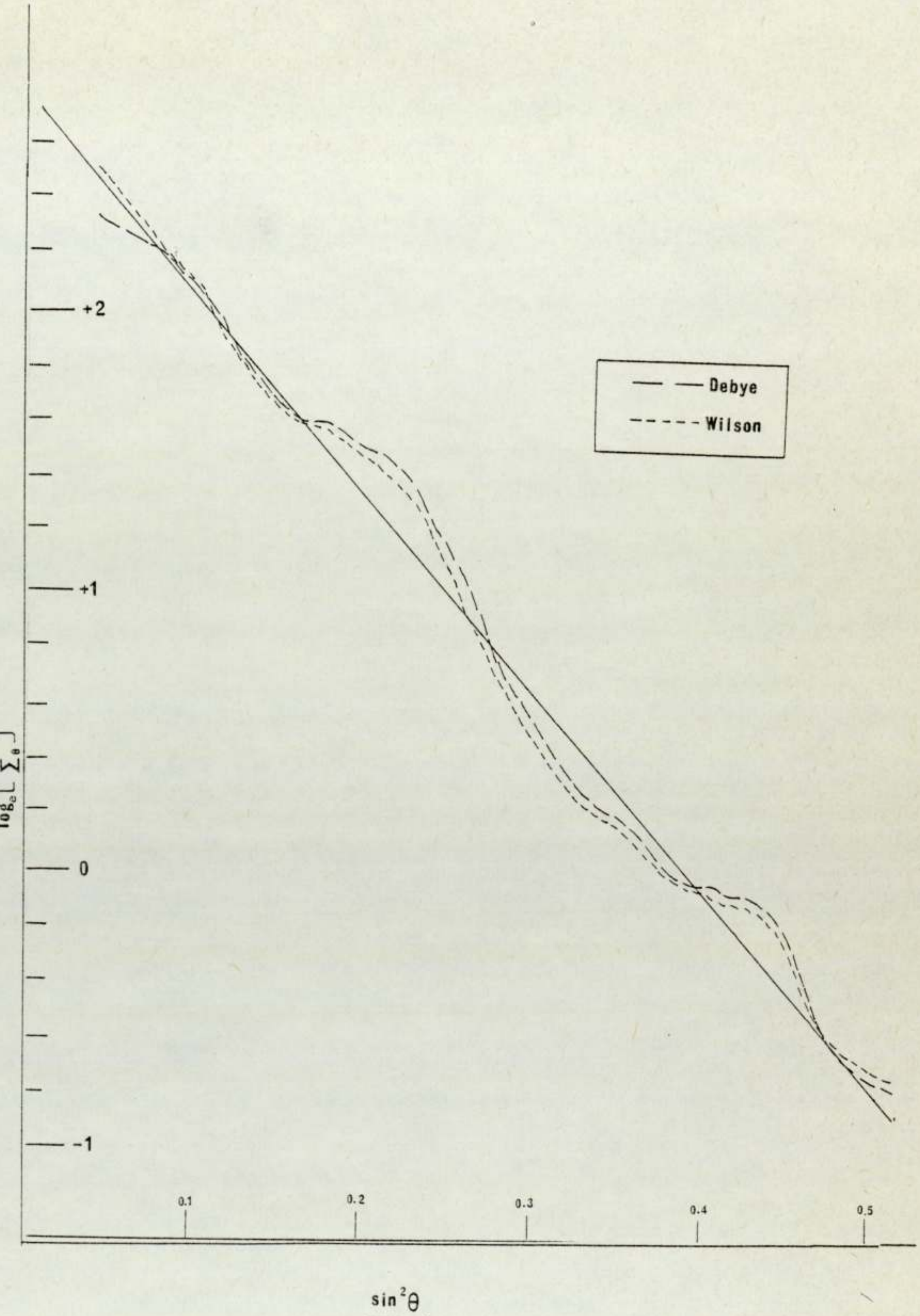

+2
+1
0
-1
$\log_e\left[\frac{\langle I_\theta\rangle}{\Sigma_\theta}\right]$
0.1
0.2
0.3
0.4
0.5
$\frac{\sin^2\theta}{\lambda^2}$
Debye
Wilson

Fig 6.3.2-1

Distribution of E-values for CGT

	Experimental	Theoretical	
		Centric	Acentric
$<E^2-1>$	0.994	0.9860	0.7360
$<E>$	0.783	0.7980	0.8660
%E>0.5	61.1	61.7	77.9
%E>1.0	30.0	31.7	36.8
%E>2.0	4.9	4.6	1.8

Table 6.3.2-2

identified on the basis of the short distance to the ring as N(8). Further refinement, relaxing the restrictions on the triazine ring, enabled the positions of the remaining non-carbon atoms to be determined.

The solution of the structure was again examined, this time with use of MULTAN78 which had become available at U.M.R.C.C. The structure factors were normalised as before and the 315 reflexions with $|E_h|>1.7$ were employed in the phase refinment. The origin-fixing reflexions selected by the program were 7 0 4 (+), 5 4 13 (+) and 0 3 6 (+) and sixteen phase sets were generated by permuting the signs of the reflexions 3 2 11, 1 5 12, 4 1 5 and 5 1 7. 2400 Σ_2 relationships where

$$|E_h||E_k||E_{h-k}|>3.02$$

were used to refine the phases. Of the sixteen phase sets, nine were origin-shifted duplicates. Of the seven independent phase sets the second showed clearly the best figures of merit. The figures of merit for this set and the fifth phase set, which on the basis of both ABS FOM and RESID was the second best, are shown in Table 6.3.2-3.

The E-map calculated from the second phase set revealed the entire structure. The two strongest peaks, with densities greater than twice that of the third greatest, corresponded to the positions of the chlorine atoms. Of the next 21 peaks in order of intensity, 16 corresponded to the remaining non-hydrogen atomic positions

CGT: MULTAN78

Reflexions given with E-values and rank in magnitude.

Origin-fixing reflexions:

7 0 4 (+) ($|E|=3.66$, 5th)
5 4 13 (+) ($|E|=3.64$, 6th)
0 3 6 (+) ($|E|=2.43$,76th)

Σ_1 reflexions: none with $p>.95$

Permuted reflexions:

3 2 11 ($|E|=4.21$, 1st)
1 5 12 ($|E|=3.33$,13th)
4 1 5 ($|E|=3.30$,14th)
5 1 7 ($|E|=3.19$,16th)

Set 2: phases −,+,+,+ respectively
Set 5: phases +,+,−,+ respectively

	Min	Max	Set 2	Set 5
ABS FOM	0.6994	1.1313	1.1313	1.0742
PSI ZERO	1446	2100	1884	2100
RESID	25.90	45.06	25.90	29.88
COMB FOM	0.6217	2.3299	2.3299	1.6602

Table 6.3.2-3

while the other five (17th, 19th, 20th, 21st and 22nd in order of magnitude) were spurious.

The structure was independently solved by Dr. C.H.Schwalbe using Patterson methods.

6.3.3 Refinement

Refinement of the structure was carried out on the CDC7600 computer at U.M.R.C.C. with use of the least-squares procedure (L.S.) in SHELX (see Sec 2.5.2). Final agreement factors were R=0.057, Rw=0.056 and Rg=0.062 for 3040 independent reflexions for which $|F|>2\sigma(F)$. The observational equations were weighted by $1/\sigma^2(F)$. The low angle reflexions $\bar{1}\ 0\ 4$, $\bar{2}\ 0\ 2$, $1\ 0\ 2$ and $2\ 0\ \bar{2}$ with poor agreement of the form $|Fobs|<<|Fcalc|$ were omitted from the refinement. Anisotropic temperature factors were refined for all non-hydrogen atoms, whilst isotropic temperature factors were refined for all hydrogen atoms. The carbon atoms of the phenyl substituent were refined independently but the bonded hydrogen atoms were AFIXed in positions consistent with the requirement of sp^2 hybridisation. The two methyl groups were refined as rigid bodies. The amino group hydrogen positions were refined subject to the following constraints: (a) N-H distances DFIXed at 1.00(2) Å, (b) H-H distances DFIXed at 1.73(5) Å, and the C-H contact distances were tied to a single free variable for each groups with a standard deviation of 0.05 Å. The free variables refined to 1.967 Å for the group at C(4) and 1.998 Å for the group at C(6). The N(3)-H(N3) bond length

CGT: Constrained Distances

	Fixed	Observed
N(3) - H(N3)	0.95(5)	0.95(2)
N(7) - H(71)	1.00(2)	0.95(2)
N(7) - H(72)	1.00(2)	0.93(2)
N(8) - H(81)	1.00(2)	0.98(2)
N(8) - H(82)	1.00(2)	0.96(2)
H(71) - H(72)	1.73(5)	1.62[c]
H(81) - H(82)	1.73(5)	1.66
C(4) - H(71)[a]	1.97(5)	1.97
C(4) - H(72)[a]	1.97(5)	1.97
C(6) - H(81)[b]	2.00(5)	2.00
C(6) - H(82)[b]	2.00(5)	2.00

Notes:

a) parameter tied to free variable no. 2

b) parameter tied to free variable no. 3

c) standard deviations not calculated for contact distances

Table 6.3.3-1

was DFIXed at 0.95(5) Å. The refined values of the constrained distances are listed in Table 6.3.3-1.

No element of the correlation matrix was greater in magnitude than 0.52 and all densities in the final difference Fourier synthesis were within the range -0.53 eÅ^{-3} to $+.0.27$ eÅ^{-3}.

6.4 Structure Analysis (Neutron)

6.4.1 Neutron Data Collection

Neutron data were collected at A.E.R.E. Harwell for one week during the summer of 1977. Because of the time limitation intensities were measured for only 291 independent reflexions with large calculated neutron structure factors. A crystal of approximate dimensions 2mm x 2mm x 1mm was mounted on a Grubb-Parsons Mk VI diffractometer in Dido reactor and positioned in a beam of monochromated neutrons, $\lambda = 1.1803$ Å. Peaks were scanned $(\omega-2\theta)$ in 40 steps of 0.02° in ω initially (first 99 reflexions) then in 32 steps of 0.02° in ω when results showed that the peaks were sufficiently well centred. Backgrounds on either side were measured in 5 steps of .02° in ω. The standard reflexion 0 0 8 was measured every 10th reflexion initially, then every 20th. The monitor count was set to 2×10^5 throughout. Data collection and reduction were carried out under the Harwell Andromache system.

6.4.2 Neutron Refinement

Hydrogen positions and isotropic temperature factors were refined, with non-hydrogen positions and anisotropic temperature factors fixed at values determined from X-ray refinement. The low angle reflexions 0 2 0 and 2 1 2 were omitted because of poor agreement with the calculated structure factors, with $|Fobs|<|Fcalc|$.

Two separate refinements were undertaken (a) with all hydrogen positions free and (b) with the phenyl hydrogens AFIXed and methyl hydrogens refined as a rigid group. Results of the two refinements are shown in Table 6.4.2-1. Application of Hamilton's R factor ratio test (Hamilton,1965) on the Rg's suggests that the hypothesis that the constrained refinement is correct can be rejected ($p<.005$). With both refinements the temperature factors are generally reasonable, although one methyl hydrogen attains the high value of $Uiso>0.2$. Bond distances and angles from the free refinement are listed in Table 6.4.2-2. The hydrogen fractional coordinates and temperature factors resulting from this refinement are listed in Table 6-3.

6.4.3 Discussion of the Neutron Structure

The neutron data show clearly that the structure is protonated at the same relative position as the other antifolate drugs. The NH and NH_2 units are involved with hydrogen bonding. The hydrogen bonding scheme with angles and distances resulting from the free hydrogen refinement

Neutron Hydrogen Parameter Refinements

	Np	No	R	Rw	Rg
Free	61	289	.0598	.0458	.0382
AFIXed	37	289	.0678	.0541	.0452

Np = number of parameters

No = number of observations

Table 6.4.2-1

Selected Bond Distances and Angles

N(3) - H(N3)	1.03(3) Å
C(2) - N(3) - H(N3)	113(2)°
C(4) - N(3) - H(N3)	117(2)°
N(7) - H(71)	0.99(3) Å
N(7) - H(72)	1.06(3) Å
C(4) - N(7) - H(71)	114(2)°
C(4) - N(7) - H(72)	119(1)°
H(71) - N(7) - H(72)	124(2)°
N(8) - H(81)	0.97(3) Å
N(8) - H(82)	1.03(2) Å
C(6) - N(8) - H(81)	115(2)°
C(6) - N(8) - H(82)	125(2)°
H(81) - N(8) - H(82)	119(2)°

Table 6.4.2-2

are shown in Fig 6.4.3-1. The amino groups are essentially sp^2 hybridised and planar (sum of bond angles at N(7) is $S_7=358.6^\circ$; at N(8) $S_8=357.4^\circ$). However the bond angles deviate as much as 5° ($=3\sigma$) from the expected 120°. Another neutron diffraction structure of an antifolate drug, unprotonated trimethoprim (Koetzle and Williams,1976) similarly shows sp^2 hybridisation ($S_7=347.4^\circ$, $S_8=358.6^\circ$ with the atom numbering altered to correspond to the cycloguanil nomenclature), but all bond angles are much nearer to 120°. It is also possible to have partial sp^3 hybridisation as in 2,4,6-triamino-5-chloroquinazoline (Rogan and Williams,1979) with S values of 339° and 356°. Thus it appears that the amino groups can easily undergo deformation either in-plane or out-of-plane. Such flexibility may be of great importance in good hydrogen bonding to dihydrofolate reductase whose natural substrate has a carbonyl oxygen in the 6-position and greater bulk in the side groups.

6.5 Discussion

The sp^3 hybridisation of C(2) and consequent deviation from planarity of the s-triazine ring (see Table 6-6) does not appear to be an important factor in DHFR inhibition since the biological activity of cycloguanil is very simialar to the sp^2 hybridised pyrimethamine. The deviation of C(2) from the plane of the remaining five ring atoms is 0.486 Å. The remaining atoms show significant deviation from coplanarity (assuming a standard deviation in position of 0.002 Å for all atoms, $X^2=1400$; for $X^2>14$ with two degrees of freedom the hypothesis of coplanarity can be rejected with $p<0.001$). The two amino nitrogen atoms deviate from the plane, one on either side. The deviation of N(8) is 0.228 Å. It is interesting that such large movements appear to little affect the binding properties of the molecule. The methyl carbon C(9) is in an axial position with respect to the ring while C(10) is equatorial. The bonds in the ring are considerably delocalised with even the bonds to C(2) exhibiting some weak π-bond character. The phenyl ring is coplanar to within ±0.001 Å, although the bonded chlorine Cl(1) deviates significantly (0.041 Å) from the ring plane. The two planes are inclined at an angle of 100.4°.

The molecules are hydrogen-bonded in pairs across centres of symmetry at the Wyckoff a̲ positions (0,0,0) and (1/2,1/2,1/2). This type of hydrogen bonding is ubiquitous in the crystal structures of DHFR inhibitors (see Sec 10.3). All four amino nitrogens and the proton at N(4) take part in hydrogen bonding (see Fig 6.4.3-1).

There is no ring stacking in the structure, although there is a weak association of phenyl rings related by 2_1-symmetry. The rings are inclined to each other at an angle of 49°. Viewed down the glide plane, the s-triazine rings appear superimposed on each other (See Fig 6.5-3), but there are no close contacts.

Illustrations

Note: Subscripts refer to symmetry operations:

1st digit: Space group symmetry operation in the order given in the International Tables, Vol I, p99

2nd, 3rd and 4th digits: Unit cell translations along a, b and c respectively.

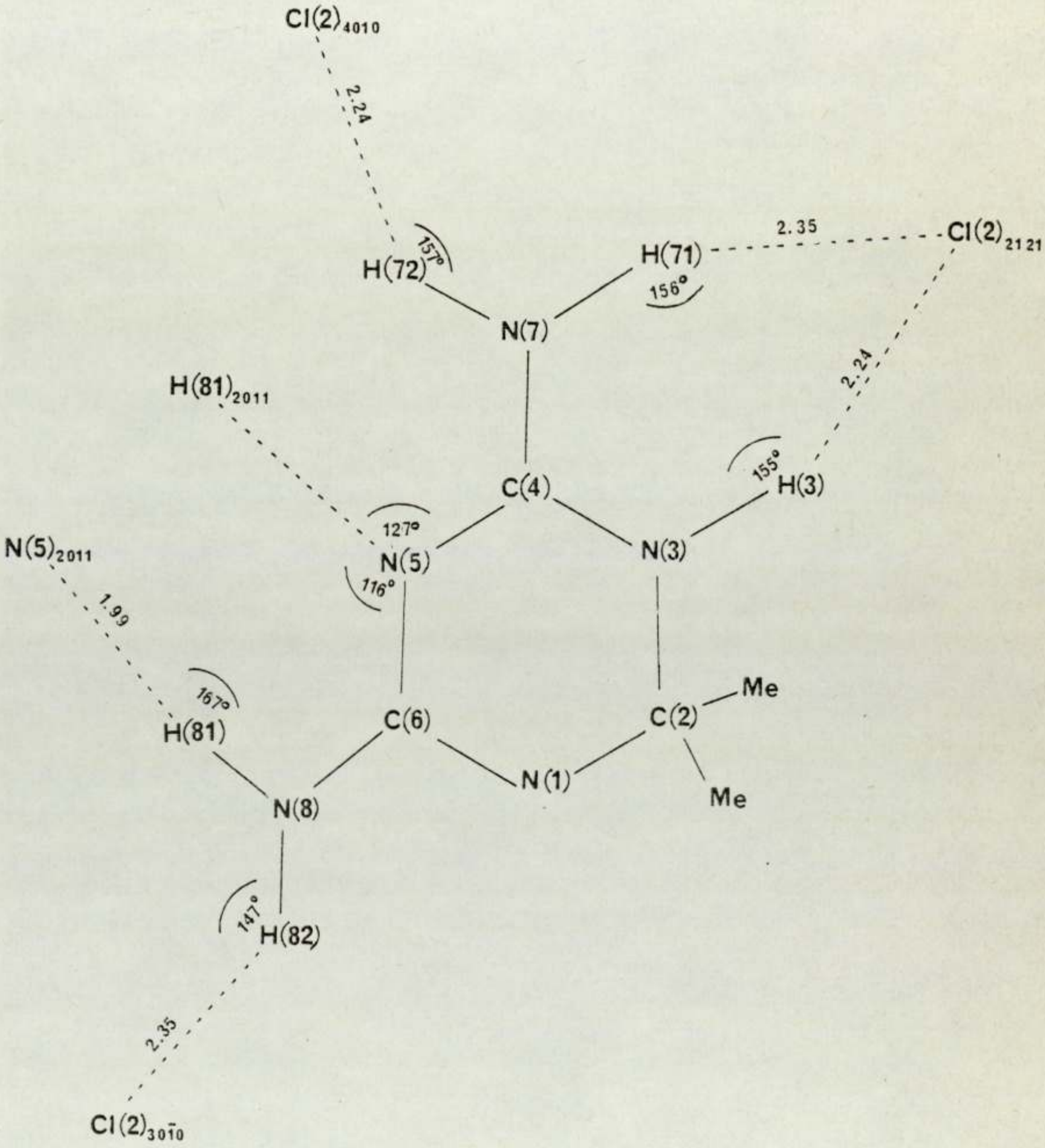


Fig 6.4.3-1

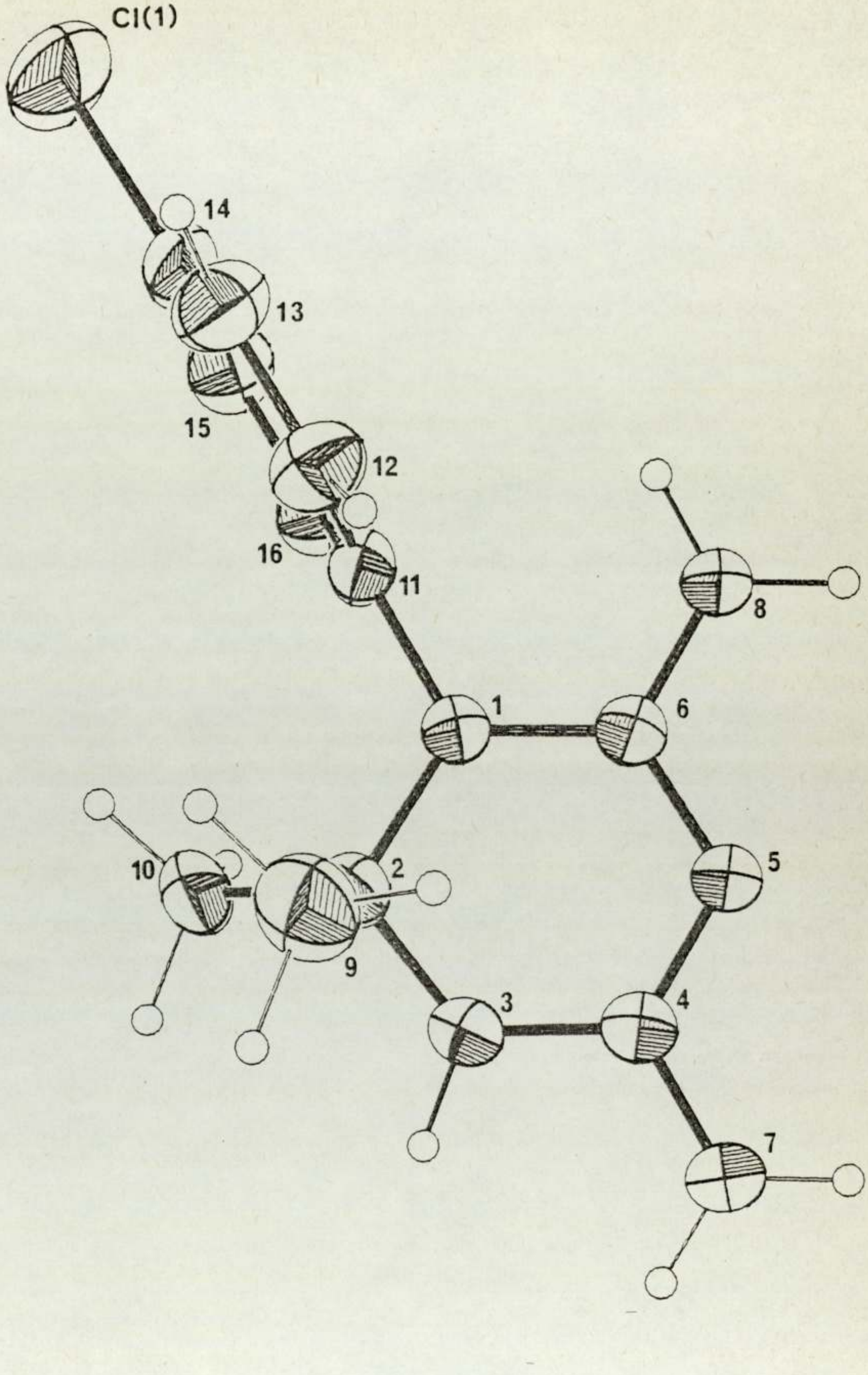


Fig 6.5-1

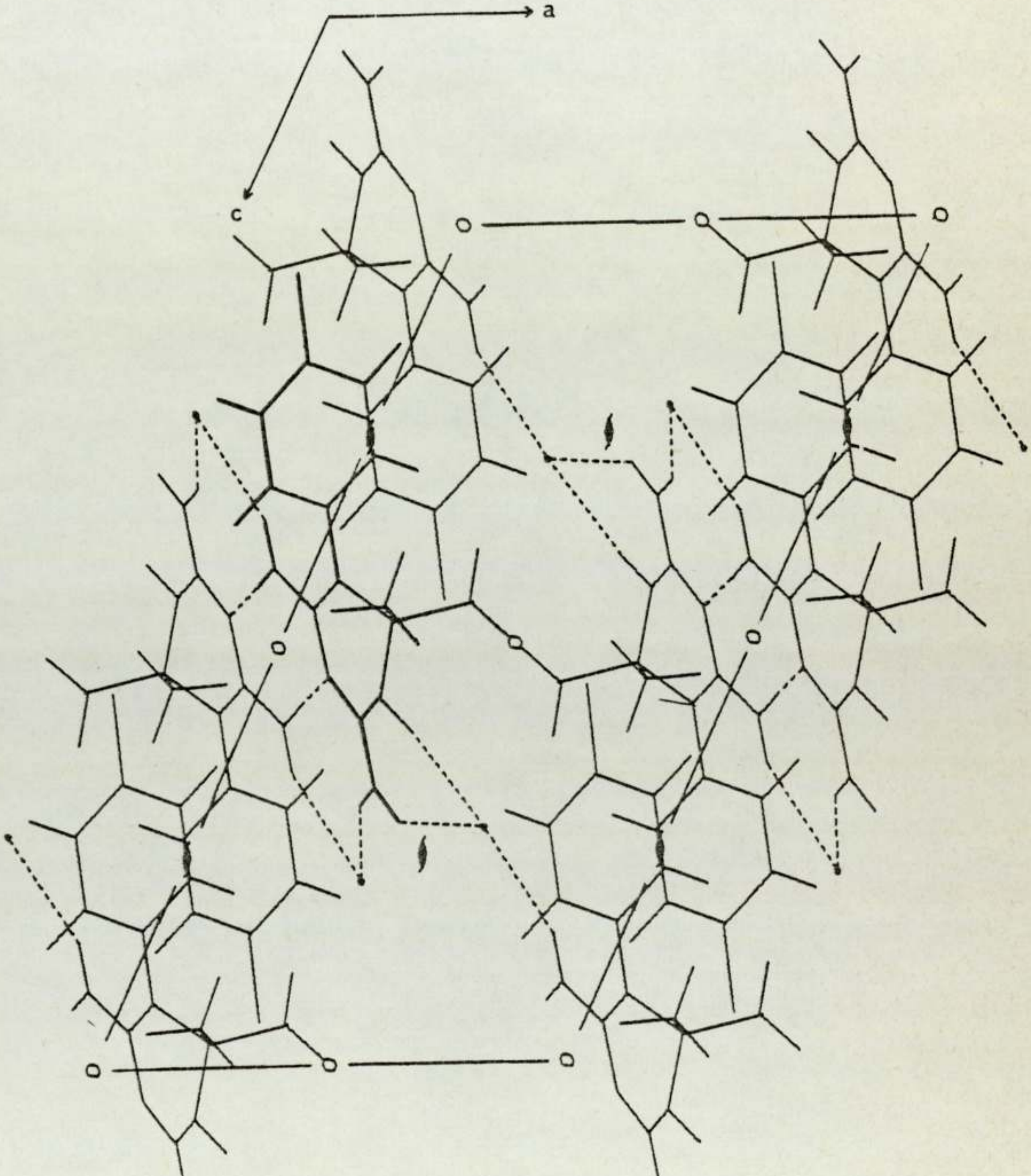


Fig 6.5-2

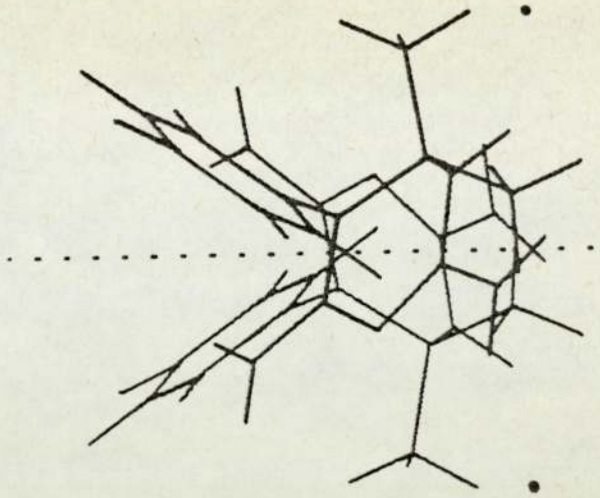


Fig 6.5-3

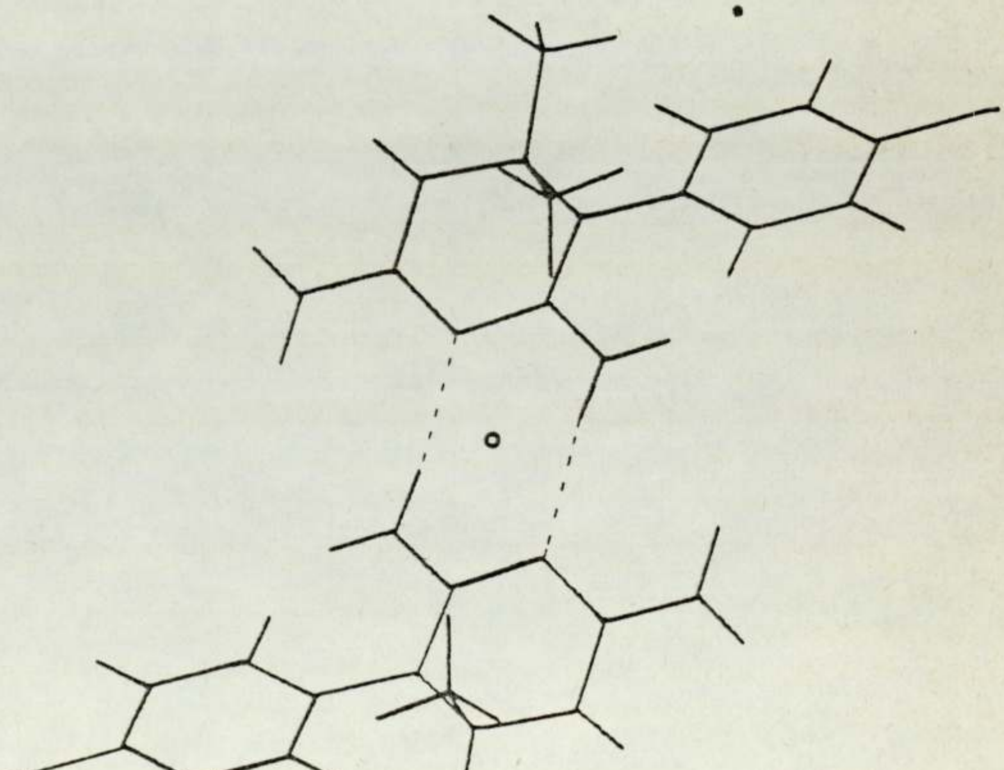


Fig 6.5-4

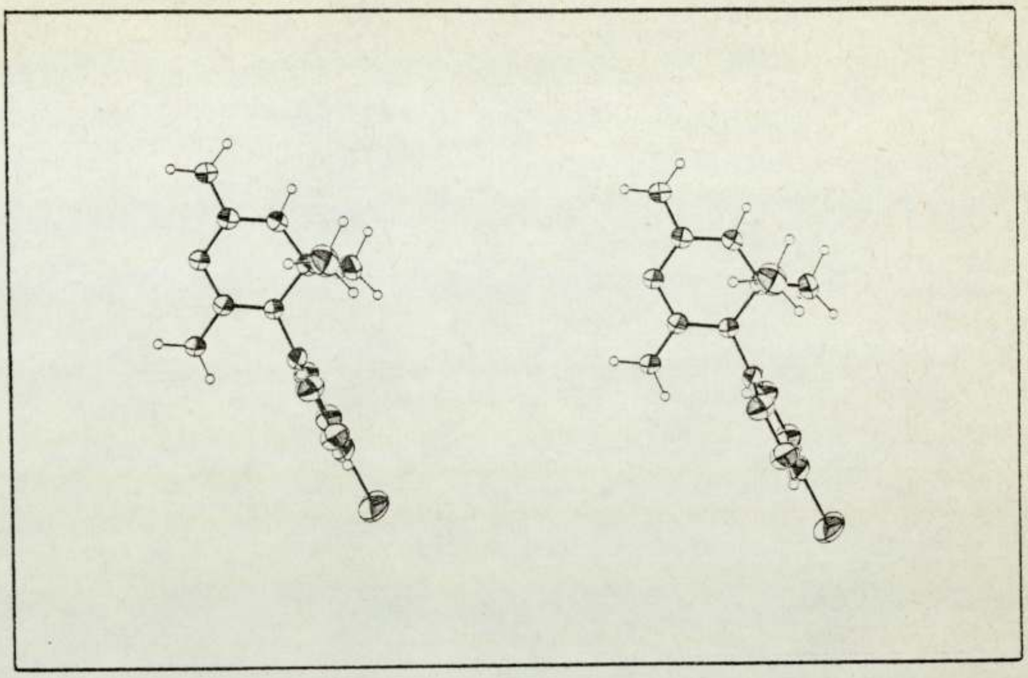


Fig 6.5 -5

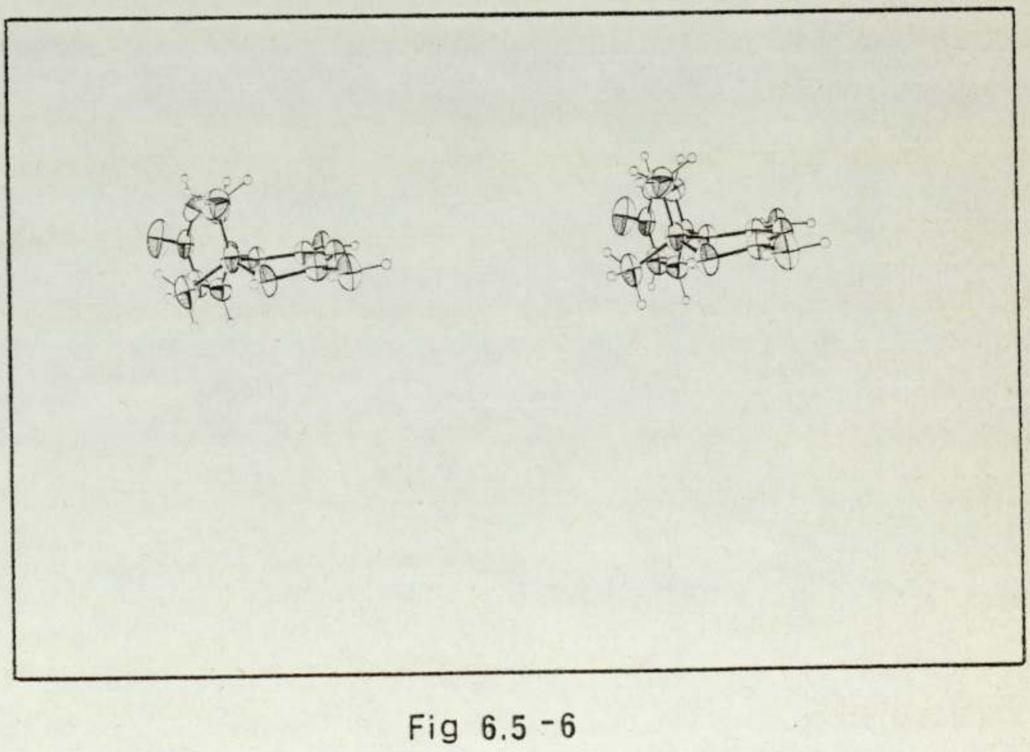


Fig 6.5 -6

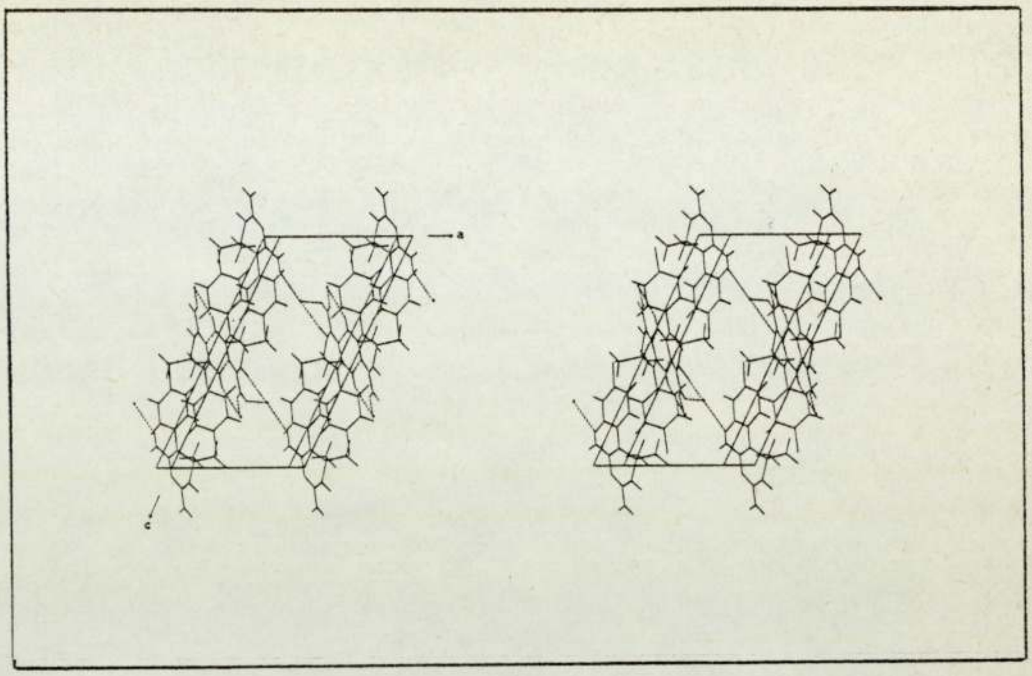


Fig 6.5 -7

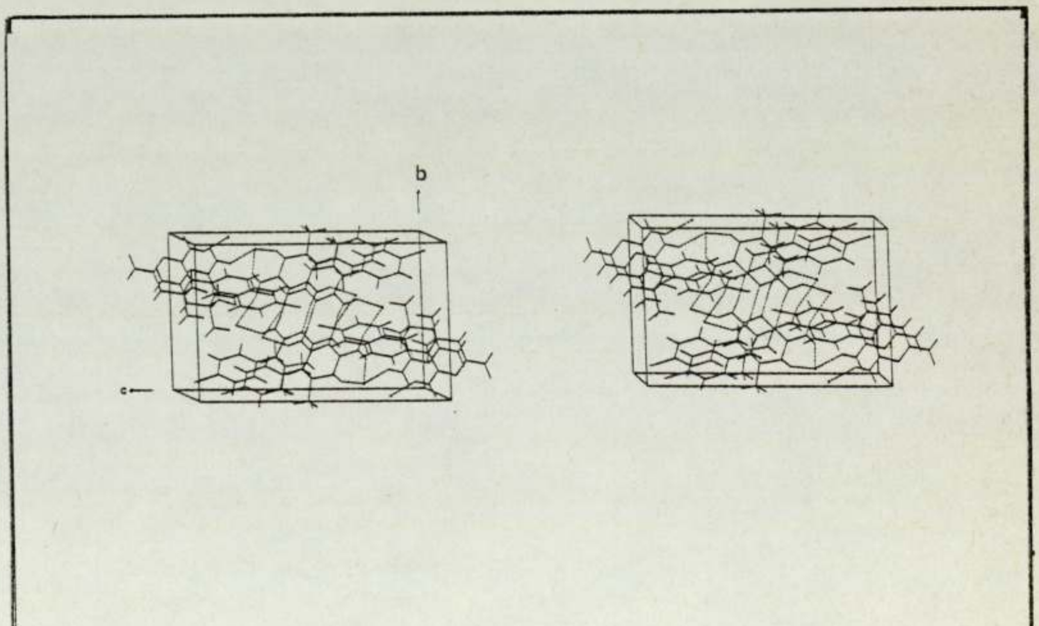


Fig 6.5 - 8

CGT: FRACTIONAL COORDINATES

	X	Y	Z
CL(1)	0.6913(1)	0.9272(1)	0.0531(1)
CL(2)	0.6045(1)	0.9386(1)	0.7193(1)
N(1)	0.0661(2)	0.7979(1)	0.4229(1)
C(2)	0.2219(2)	0.8725(2)	0.4720(1)
N(3)	0.2622(2)	0.8504(2)	0.5631(1)
C(4)	0.2451(2)	0.7320(2)	0.5894(1)
N(5)	0.1344(2)	0.6480(1)	0.5372(1)
C(6)	0.0413(2)	0.6862(2)	0.4554(1)
C(9)	0.3639(3)	0.8253(3)	0.4512(2)
C(10)	0.1885(3)	1.0144(2)	0.4534(2)
N(7)	0.3358(2)	0.7024(2)	0.6716(1)
N(8)	-0.0822(2)	0.6105(2)	0.4060(1)
C(11)	-0.0276(2)	0.8266(2)	0.3323(1)
C(12)	0.0229(3)	0.7776(2)	0.2725(1)
C(13)	-0.0644(3)	0.8084(3)	0.1859(1)
C(14)	-0.2021(3)	0.8873(2)	0.1615(1)
C(15)	-0.2561(3)	0.9341(2)	0.2201(2)
C(16)	-0.1675(2)	0.9032(2)	0.3066(1)

Table 6-1

CGT: ANISOTROPIC TEMPERATURE FACTORS

	U11	U22	U33	U23	U13	U12
CL(1)	0.0813(5)	0.1230(7)	0.0483(4)	0.0361(4)	-0.0066(3)	-0.0258(4)
CL(2)	0.0489(3)	0.0506(3)	0.0438(3)	-0.0087(2)	-0.0001(2)	-0.0068(2)
N(1)	0.0349(8)	0.0366(8)	0.0327(8)	0.0055(6)	0.0072(6)	-0.0068(6)
C(2)	0.0341(10)	0.0404(10)	0.0435(11)	0.0069(8)	0.0074(8)	-0.0075(8)
N(3)	0.0447(10)	0.0401(9)	0.0392(9)	0.0028(7)	0.0032(7)	-0.0119(7)
C(4)	0.0343(9)	0.0397(9)	0.0364(9)	0.0021(7)	0.0096(8)	-0.0035(7)
N(5)	0.0382(8)	0.0370(8)	0.0320(8)	0.0039(6)	0.0054(6)	-0.0086(6)
C(6)	0.0329(9)	0.0364(9)	0.0336(9)	0.0028(7)	0.0101(7)	-0.0040(7)
C(9)	0.0415(12)	0.0726(17)	0.0746(17)	0.0064(13)	0.0224(12)	-0.0065(11)
C(10)	0.0544(13)	0.0397(11)	0.0589(13)	0.0073(10)	0.0112(11)	-0.0134(10)
N(7)	0.0508(10)	0.0483(10)	0.0352(9)	0.0060(8)	0.0000(8)	-0.0126(8)
N(8)	0.0496(9)	0.0461(8)	0.0326(8)	0.0072(7)	0.0001(7)	-0.0179(8)
C(11)	0.0359(9)	0.0365(9)	0.0359(9)	0.0082(7)	0.0110(8)	-0.0033(7)
C(12)	0.0460(11)	0.0577(13)	0.0427(11)	0.0049(9)	0.0157(9)	0.0043(10)
C(13)	0.0602(14)	0.0742(16)	0.0417(12)	0.0027(11)	0.0204(11)	-0.0082(12)
C(14)	0.0477(12)	0.0612(13)	0.0418(11)	0.0174(10)	0.0040(10)	-0.0143(10)
C(15)	0.0397(11)	0.0576(13)	0.0603(14)	0.0174(11)	0.0043(10)	0.0050(10)
C(16)	0.0401(11)	0.0493(11)	0.0498(12)	0.0066(9)	0.0138(9)	0.0049(9)

Table 6-2

CGT: HYDROGEN FRACTIONAL COORDINATES
AND ISOTROPIC TEMPERATURE FACTORS

	X	Y	Z	UISO
H(3)	0.3622	0.8996	0.6046	0.0661
H(91)	0.3416	0.8352	0.3949	0.1705
H(92)	0.3783	0.7216	0.4601	0.0845
H(93)	0.4781	0.8488	0.4944	0.1244
H(101)	0.1837	1.0444	0.3985	0.0908
H(102)	0.2993	1.0844	0.5008	0.0870
H(103)	0.0900	1.0611	0.4591	0.1060
H(12)	0.1333	0.7057	0.2949	0.0747
H(13)	-0.0299	0.7803	0.1366	0.0833
H(15)	-0.3733	0.9904	0.1960	0.0765
H(16)	-0.2090	0.9340	0.3529	0.0823
H(81)	-0.0913	0.5332	0.4331	0.0697
H(82)	-0.1576	0.6297	0.3423	0.0345
H(71)	0.4331	0.7613	0.7018	0.0568
H(72)	0.3251	0.6126	0.6940	0.0356

NOTE: HYDROGEN PARAMETERS FREELY REFINED
FROM NEUTRON DATA

Table 6-3

CGT: BOND DISTANCES

C(2)	-	N(1)	1.493(2)
N(3)	-	C(2)	1.464(3)
C(4)	-	N(3)	1.342(2)
N(5)	-	C(4)	1.333(2)
C(6)	-	N(1)	1.345(2)
C(6)	-	N(5)	1.348(2)
C(9)	-	C(2)	1.528(3)
C(10)	-	C(2)	1.512(3)
N(7)	-	C(4)	1.326(2)
N(8)	-	C(6)	1.321(2)
C(11)	-	N(1)	1.446(2)
C(12)	-	C(11)	1.379(3)
C(13)	-	C(12)	1.388(3)
C(14)	-	CL(1)	1.738(2)
C(14)	-	C(13)	1.379(4)
C(15)	-	C(14)	1.373(4)
C(16)	-	C(11)	1.379(4)
C(16)	-	C(15)	1.388(3)

Table 6-4

CGT: BOND ANGLES

C(2) - N(1) - C(6)	119.4(1)
C(2) - N(1) - C(11)	117.9(1)
C(6) - N(1) - C(11)	120.1(1)
N(1) - C(2) - N(3)	105.4(1)
N(1) - C(2) - C(9)	111.1(2)
N(1) - C(2) - C(10)	109.6(2)
N(3) - C(2) - C(9)	110.4(2)
N(3) - C(2) - C(10)	108.3(2)
C(9) - C(2) - C(10)	111.8(2)
C(2) - N(3) - C(4)	119.5(2)
N(3) - C(4) - N(5)	122.0(2)
N(3) - C(4) - N(7)	117.8(2)
N(5) - C(4) - N(7)	120.1(2)
C(4) - N(5) - C(6)	117.1(1)
N(1) - C(6) - N(5)	123.2(2)
N(1) - C(6) - N(8)	119.1(2)
N(5) - C(6) - N(8)	117.7(2)
N(1) - C(11) - C(12)	120.1(2)
N(1) - C(11) - C(16)	119.3(2)
C(12) - C(11) - C(16)	120.6(2)
C(11) - C(12) - C(13)	120.0(2)
C(12) - C(13) - C(14)	118.7(2)
CL(1) - C(14) - C(13)	118.3(2)
CL(1) - C(14) - C(15)	119.8(2)
C(13) - C(14) - C(15)	121.9(2)
C(14) - C(15) - C(16)	119.0(2)
C(11) - C(16) - C(15)	119.8(2)

Table 6-5

CGT: LEAST-SQUARES PLANES

(a) Equations of planes in the form $AX+BY+CZ+D=0$ where X,Y and Z are the orthogonal coordinates in Å along a,b and c*:

Plane(1): $-0.8954X + 0.3790Y + 0.2336Z - 6.9573 = 0$
Plane(2): $0.5764X + 0.8071Y + 0.1278Z - 6.0384 = 0$

(b) Deviations in A of atoms from planes:

Plane(1): N(1) -.036, C(2)* -.486, N(3) .034, C(4) -.029, N(5) -.012, C(6) .047, C(9)* -2.011, C(10)* .150, C(11)* -.104, N(7)* -.031, N(8)* .228
Plane(2): C(11) .011, C(12) -.008, C(13) -.003, C(14) .009, C(15) -.006, C(16) -.005, N(1)* .048, Cl(1)* .041

(c) Dihedral angles in degrees between the planes:

(1) - (2) 100.4

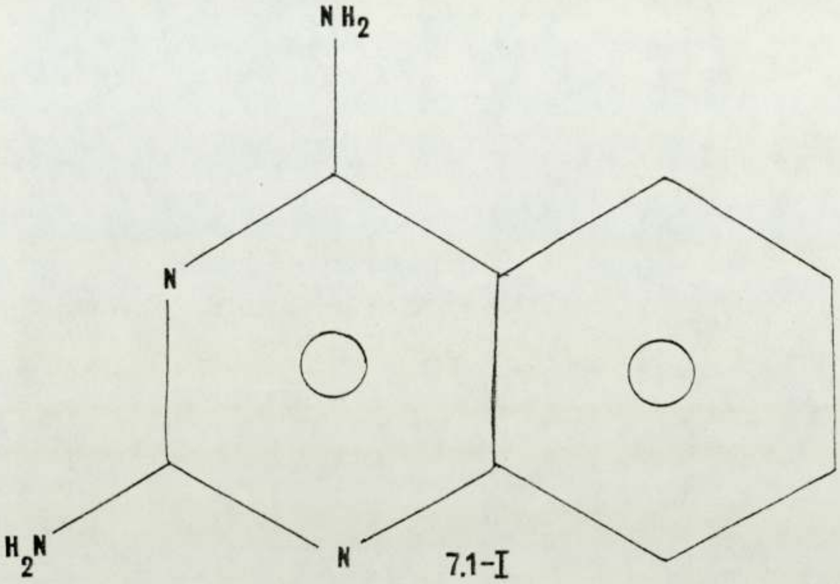
*Atoms marked with an asterisk not included in the definition of the plane.

Table 6-6

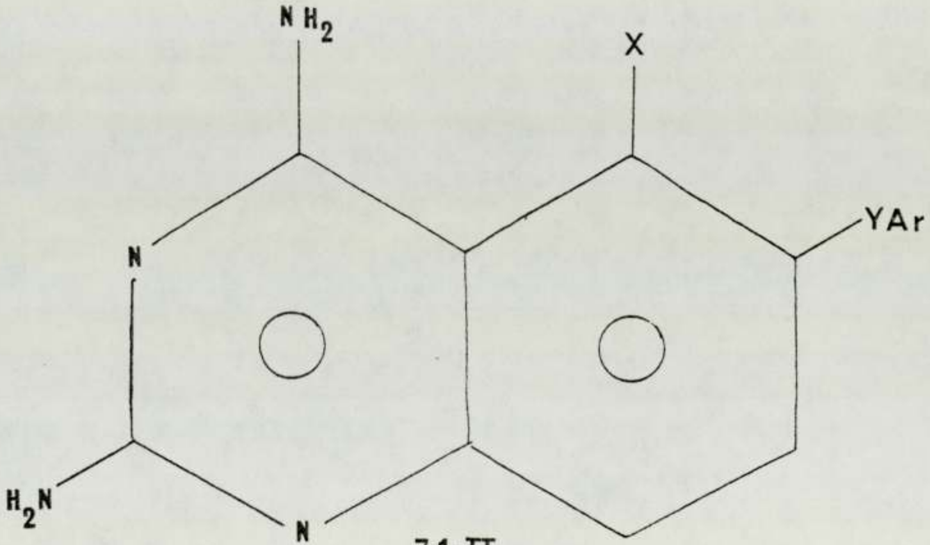
Chapter 7: 2,4-Diaminoquinazoline

7.1 Introduction

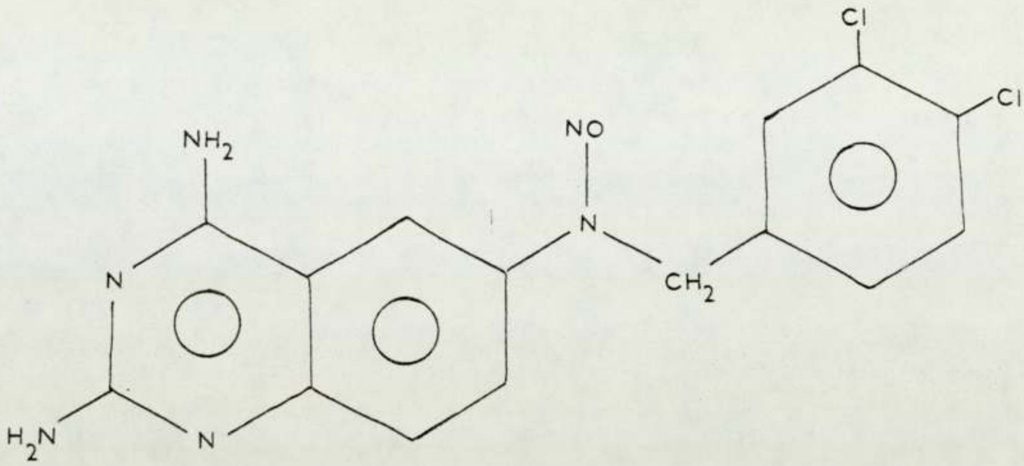
Some substituted 2,4-diaminoquinazolines have been found to be potent inhibitors of DHFR from various sources and have been investigated as possible antimalarial, antitumour and antileukaemic agents. 2,4-Diaminoquinazoline (7.1-I) itself is a moderate inhibitor of DHFR (Ashton,et al,1973) with 50 per cent. inhibition (for rat liver DHFR) at a concentration of 22μM compared to .07 μM for Pyrimethamine. Inhibitory activity is enhanced by the presence of an aromatic substituent at the 6-position (Hynes,et al,1974) and with the addition at the 5-position of a hydrophobic group (Davoll,et al,1972) or an electronegative atom (Ashton,et al,1973). Some members of the disubstituted series (7.1-II) have shown activity against P.berghei and P.gallinaceum (Hynes and Ashton,1975). 2,4-Diamino-6-[(3,4-dichlorobenzyl) nitrosamino] quinazoline (7.1-III) has been found to be active against P.berghei and P.cynomolgi including chloroquine, cycloguanil, pyrimethamine and DDS resistant strains (Thompson,et al,1970).



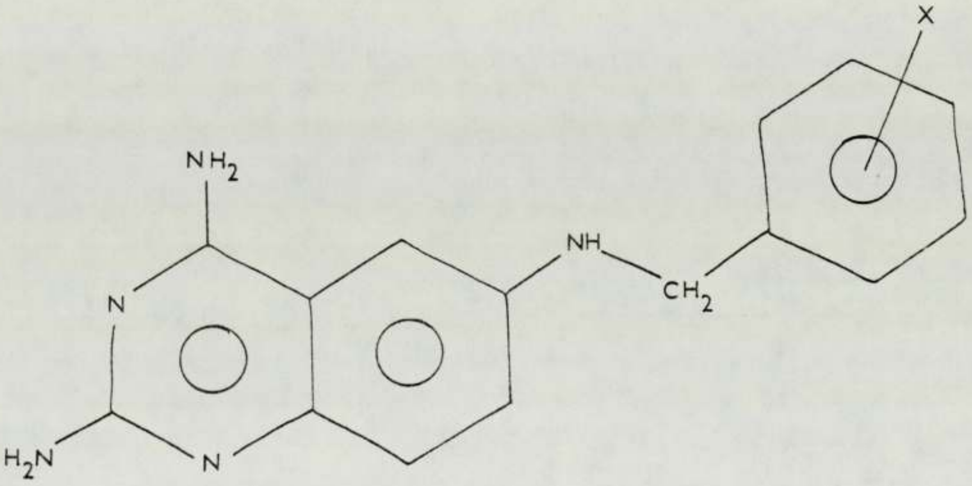
7.1-I



7.1-II



7.1-III



7.1-IV

Activity is believed to result from the quinazoline ring system acting as an analogue for the pteridine moiety of folic acid. Quinazoline analogues of isofolic acid were not found to be active against L1210 mouse leukaemia (Hynes and Garrett,1975) although the series 7.1-IV inhibited DHFR from rat liver and L1210 cells with 50 per cent. inhibition at concentrations of the order of 0.1µM for the most potent (Richter and McCormack,1974).

7.2 Crystal Data

2,4-Diaminoquinazoline ($C_8H_8N_4$) crystallises in space group $I4_1/a$. The conditions limiting possible reflexions for this space group are: hkl,h+k+l=2n; hk0,h=2n and k=2n; 00l,l=4n. There are, however, some exceptions for which no satisfactory explanation has been found. Refinement in alternative space groups has, however, been unconvincing. The unit cell dimensions are $a \equiv b = 21.59(1)$ Å, $c=7.55(2)$ Å,$V_c=3520(10)$ Å^3. Crystallisation occurs in the monohydrate form DAQ·H_2O; M=160.180 for the free base and M=178.195 for the monohydrate. There are 16 formula units per unit cell. The density determined from unit cell size and contents is 1.345 g cm^{-3}; the density determined by flotation in a mixture of bromobenzene and m-xylene is 1.33 g cm^{-3}. The difference between the two density determinations is within the range of experimental error. The absorption coefficients for MoKα radiation are $\mu^*=0.764$ cgs units; $\mu=1.027$ cm^{-1}.

7.3 Structure Analysis

7.3.1 Data Collection

Crystals grown from ethanol and water formed colourless prisms with adjacent faces inclined at an angle of 45°. One crystal measuring approximately 0.2 mm X 0.2 mm X 0.2 mm was mounted along the unique axis on the Stoe two-circle diffractometer at the Department of Chemistry of the University of Birmingham. Data were collected for levels $l=0$ to $l=8$ (2289 reflexions, 1516 with $|F|>\sigma(F)$) from a monochromated MoKα source in the same manner as for CGT (see Sec 6.3.1) with the settings $A=1.20^\circ, B=0.0^\circ$ for levels 0 and 1 and $A=1.00^\circ$, $B=0.5^\circ$ for the remaining levels. The scan time was set initially at 1 second but was increased to 1.5 seconds for levels 7 and 8. The great number of reflexions with $|F|<\sigma(F)$ results largely from poor counting statistics as a result of using a replacement tube with a lower beam intensity than that of the normal tube. On the basis of previously-taken Weissenberg and precession photographs the space group had been assigned as $I4_1/a$. Data were collected in one octant of reciprocal space for points with $h+k+l=2n$. Significant intensities were measured for a few reflexions extinct in the above space group (see Sec 7.3.4).

7.3.2 Solution

The data were reduced using a program supplied by Dr T.A.Hamor of Birmingham University and E-values were calculated using the Wilson Plot Program (see Sec 2.2) with one rigid group per asymmetric unit input: a naphthalene ring with all bond distances set to 1.4 $\mathring{A}^2$ and all bond angles to 120°. The Wilson Plot is shown in Fig 7.3.2-1. The overall temperature factor (2B) was 6.04 $\mathring{A}$ and scale multiplier 3.39. The distribution of E-values approximated that of a centric distribution (see Table 7.3.2-2).

The E-values were then input into MULTAN (299 $|E_h|>1.35$, 2500 $\Sigma_2$relationships). Two phases $\overline{10}$ 4 2,p=0.92 and $\overline{20}$ 0 0,p=0.98 were accepted initially from the Σ_1 calculation. The origin was determined by setting the phase of the reflexion $\bar{5}$ 2 1 (+). Only one origin-setting reflexion was required because there are only two non-equivalent centres of symmetry in $I4_1/a$. The starting set of phases [set 4: $\overline{10}$ 10 4 (−), $\overline{15}$ 8 3 (−), $\overline{17}$ 4 1 (+); ABS FOM=1.0382 (highest), RESID=41.31 (lowest) and PSI ZERO=1101 (third of eight)] yielded an E-Map from which the fused rings could be unambiguously identified.

7.3.3 Refinement

The data were then transmitted to U.M.R.C.C. and atomic positions were refined with the use of SHELX. The structure refined isotropically to R=0.190,Rw=0.156,Rg=0.141 for $|F|>\sigma(F)$, refining the non-hydrogen atoms only. Anisotropic refinement reduced the agreement factors to R=0.130,Rw=0.098, Rg=0.087 for $|F|>2\sigma(F)$. The reflexions 0 20 4 and $\bar{2}$ 20 4, which had previously shown poor agreement with $|Fobs|<|Fcalc|$, were omitted. An extinction correction was included (see Sec 2.5.2) but refined to a low value (4.6×10^{-4}). The

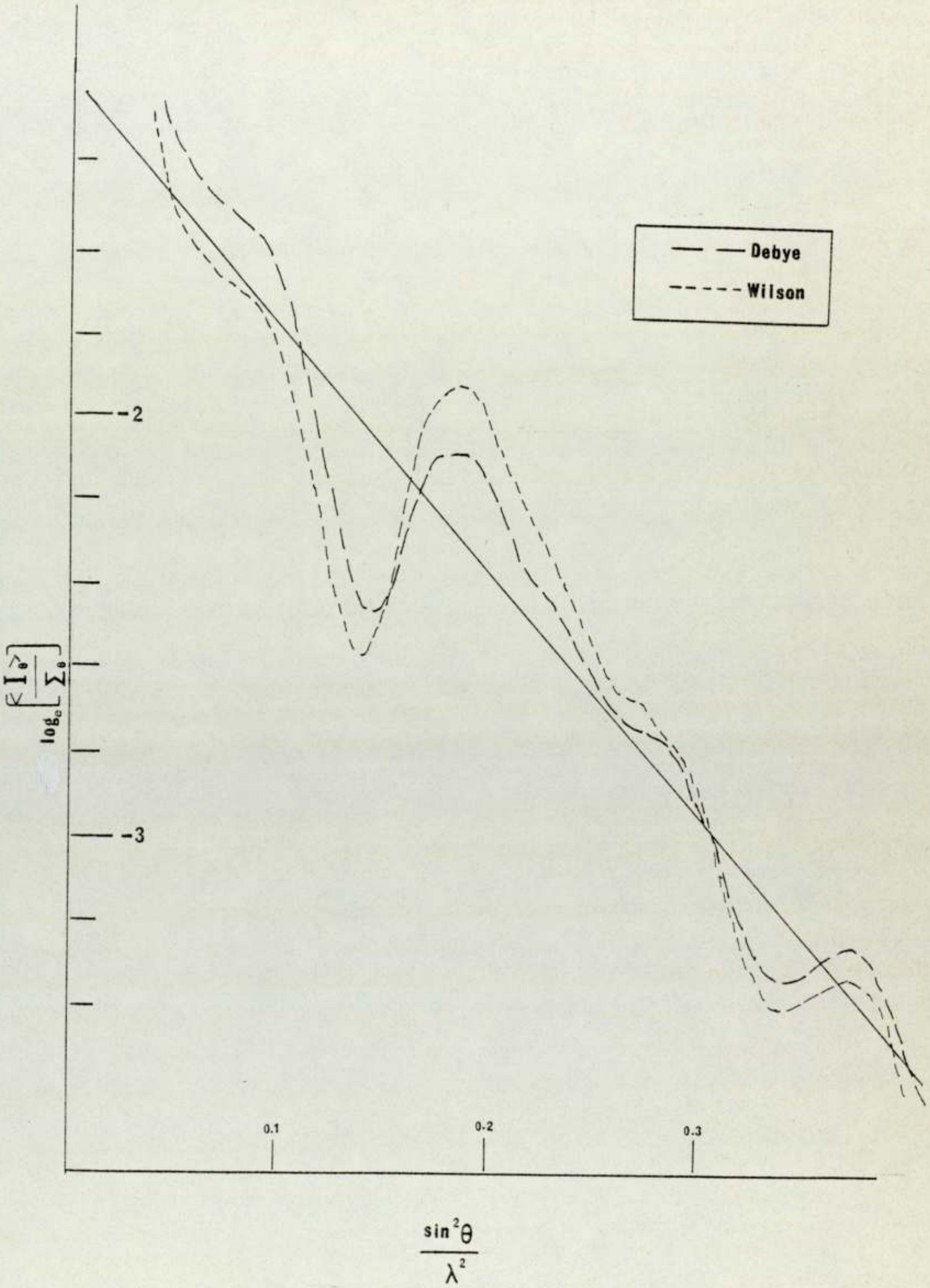

Debye
Wilson
-2
-3
$\log_e \left[\frac{\langle I_\theta \rangle}{\Sigma_\theta} \right]$
0.1
0.2
0.3
$\frac{\sin^2\theta}{\lambda^2}$

Fig 7.3.2-1

Distribution of E-values for DAQ

	Experimental	Theoretical	
		Centric	Acentric
$<E^2 - 1>$	1.0194	0.9860	0.7360
$<E>$	0.7487	0.7980	0.8660
%E>0.5	59.3	61.7	77.9
%E>1.0	30.9	31.7	36.8
%E>2.0	4.9	4.6	1.3

Table 7.3.2-2

observational equations were weighted by $1/\sigma^2(F)$. The ring hydrogens were AFIXed, the O-H and water H...H distances were DFIXed and in the amino groups the N-H and H...H distances were DFIXed. The C(2)...H(21) and C(2)...H(22) distances were DFIXed with the value of the distance refined as a free variable. The amino group at C(4) was treated in an identical manner. The final values of the free variables were 2.03(2) Å for the C(4) amino group and 2.04(2) Å for the C(2) amino group. The density in the final difference Fourier map was within the range -0.11 to +0.10 $e\text{Å}^{-3}$. Fifty reflexions showed poor final agreement to the extent that |Fobs-Fcalc| was greater than 2σ(|Fobs-Fcalc|). The differences among the three parity groups were small, with generally poorer agreement at the higher angles of reflexion. The structure factors and analysis of variance are listed in Appendix A.

7.3.4 Forbidden Reflexions on the Zero Level

Solution of the structure in space group $I4_1/a$ leaves unexplained the presence on the zero level of reflexions which violate the conditions limiting possible reflexion. The a glide condition requires that both h and k be even; I-centring requires that only the sum of h+k be even. When diffractometer data were collected for all h+k even on the zero level, a number of reflexions with h and k both odd were measured with significant intensities. The highly significant reflexions ($|F|>3\sigma(F)$) are listed in Table 7.3.4-1.

Reflexion	$\lvert F \rvert$	$\lvert F \rvert / \sigma(F)$
$\overline{17}$ 17 0	7.23	7.5
$\bar{3}$ 25 0	7.40	6.2
$\overline{11}$ 5 0	5.99	5.7
$\overline{15}$ 17 0	6.11	4.8
$\bar{1}$ 5 0	4.06	4.3
$\bar{7}$ 5 0	4.52	3.7
$\bar{9}$ 15 0	5.29	3.6
$\bar{9}$ 5 0	4.57	3.5
$\overline{15}$ 19 0	5.38	3.4
$\bar{3}$ 27 0	5.63	3.3
$\overline{25}$ 9 0	5.34	3.3
$\overline{13}$ 13 0	4.92	3.3
$\overline{25}$ 1 0	5.01	3.1
$\overline{23}$ 11 0	4.97	3.0
$\bar{5}$ 17 0	4.74	3.0

Table 7.3.4-1

Weissenberg photographs for levels $l=0$ to $l=4$ taken with CuKα radiation were indexed and densitometered by the S.R.C. film scanning service. In the zero level Weissenberg films, a number of spots violated both the glide and body-centring conditions, but only the reflexion 5 9 0 appeared in more than one symmetry-related position. Moreover, closer inspection shows that the remaining reflexions are poorly indexed and may, therefore, be discounted as spurious density on the film. That the reflexion 5 9 0 appears at the three symmetry-equivalent positions scanned with a variation in intensity of ±20 per cent. is strong evidence that it is a genuine reflexion.

Attempts were made to explain these forbidden reflexions (a) by assuming that the true space group symmetry is lower than $I4_1/a$ and (b) by looking at the diffraction geometry with possible Renninger double diffraction in mind.

Any explanation of the $\underline{uu0}$ reflexions in terms of a twin (which was not observed on examination of the crystal) may be rapidly discounted. Because of the high symmetry of the crystal with faces 45° apart, any twinning must involve a rotation of 45° about the $\underline{c}$-axis. Any reflexion HKL of the twin would be indexed hkl where

$$\begin{bmatrix} h \\ k \\ l \end{bmatrix} = \begin{bmatrix} 1/\sqrt{2} & 1/\sqrt{2} & 0 \\ -1/\sqrt{2} & 1/\sqrt{2} & 0 \\ 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} H \\ K \\ L \end{bmatrix}$$

By considering the indices in the hypothetical twin giving rise to the observed uu0 reflexions, only the reflexion $\overline{17}$ 17 0, which could be the reflexion 24 0 0 in the twin (angular separation $\Delta\omega = .06^\circ$), could be explained in this way. Indices in the hypothetical twin giving rise to the other forbidden reflexions would be non-integral. Moreover, the films do not show evidence of the large number of new diffraction spots which would be introduced by the twin.

7.3.5 Refinement in Alternative Space Groups

In order to account for the forbidden uu0 reflexions in the diffractometer data, consideration was given to the possibility that the true space group was of lower symmetry than $I4_1/a$.

There is no reason to suspect that the structure is not tetragonal. The crystal faces are 45° apart and the axes 90° apart and of equal length on Weissenberg films (to the accuracy that these parameters can be measured). Fourfold symmetry dictates that $F(h0l)=F(0hl)$ and pairwise comparison of these reflexions from the zero level did not indicate violation of this symmetry, with $\Delta = 1.3$ where

$$\Delta = \left\langle \frac{|I_{h00} - I_{0h0}|}{\sigma(I_{h00} - I_{0h0})} \right\rangle_h$$

where $\sigma(I) = .03N + \sqrt{N}$ (see Sec 3.1). The expression was averaged over even-indexed reflexions from 6 0 0 to 28 0 0.

2,4-Diaminoquinazoline: Refinement of Isotropic Models

	No	Np	R	Rw	Rg	Nr
$I4_1/a$	1516	53	0.206	0.162	0.144	1
$I\bar{4}$	1516	105	0.173	0.134	0.116	47
$I4_1$	1516	104	0.175	0.135	0.118	>100
$P\bar{4}$	1516	170	0.149	0.114	0.098	48
$P4_1$	1516	169	0.151	0.115	0.100	40

Notes

No=no. of observations. $h+k+l=2n$ only collected. Reflexions of type $hk0$, h or $k=2n$ included in the calculation of R-factors for space group $I4_1/a$. Weak reflexions of $|F|<\sigma(F)$ have been excluded from the refinements.

Np=no. of parameters. In the primitive space groups temperature factors of pseudosymmetry-related atoms are tied to a single free variable -- otherwise some temperature factors refine to negative values. In $I\bar{4}$ and $I4_1$ temperature factors are refined freely, but for some atoms the temperature factors refine to values outside the normally-expected range

Nr=No. of correlation coefficients $|r|>0.5$. There is strong correlation between pseudosymmetry-related atoms. All refinements were executed with SHELX damping factor 10.0, except $P4_1$ where, because of oscillation during refinement, the damping factor was increased to 100.0

Table 7.3.5-1

Considering possible subgroups of $I4_1/a$ we have the two body-centred space groups $I\bar{4}$ and $I4_1$ and the two primitive space groups $P\bar{4}$ and $P4_1$. $P4_3$ is enantiomorphically related to $P4_1$ and, in the absence of anomalous scattering, is indistinguishable from the latter.

Results of the isotropic refinement of DAQ in $I4_1/a$ and the four subgroups are shown in Table 7.3.5-1. In order to reflect the disagreement for the $\underline{uu0}$ reflexions for $I4_1/a$, these reflexions were included in the calculation of the R-factors. Correlation was a problem throughout the refinements in the lower symmetry groups, particularly between atoms equivalent in $I4_1/a$. In the primitive space groups, the temperature factors of the atoms symmetry related in $I4_1/a$ had to be tied to a single free variable in order to prevent the temperature factors of some atoms going negative. In the body-centred space groups all temperature factors were refined freely, but some of these refined to values well outside the normally-expected range. Damping was used throughout these refinements.

Since it is inevitable that R-factors will decrease with an increase in the number of parameters, a test has been devised (Hamilton,1965) to determine whether the additional parameters significantly improve the model. In the present case every reduction in symmetry brought about a significant improvement in the model on the basis of the Hamilton test, with the primitive space groups -- negative temperature factors included -- coming out better. The

DAQ: Hamilton's R-factor Ratio Test

Hypothesis: Alteration of space group symmetry from S.G.1 to S.G.2 does not improve the fit to the observed data.

S.G.1	S.G.2	n-m	b	$\mathbb{R}$	Hypothesis
$I4_1/a$	$I\bar{4}$	1463	52	1.241	reject $p<.005$
$I\bar{4}$	$P\bar{4}$	1417	65	1.184	reject $p<.005$
$I4_1$	$I\bar{4}$	1463	1	1.017	reject $p<.005$
$P4_1$	$P\bar{4}$	1417	1	1.020	reject $p<.005$

$$\mathbb{R}_{b,n-m,.005}$$

n-m b	1000	1500
1	1.0039	1.0026
40	1.0333	1.0222
60	1.0457	1.0305
80	1.0574	1.0384

For explanation of method see

W.C.Hamilton, *Acta.Cryst.*(1965). 18,502

Table 7.3.5-2

test does, however, depend on the linearity of the observational equations. This condition, when applied to crystallographic structures, is only approximately true over a limited region of parameter space. Because the lower-symmetry space groups result in structures which are not physically realistic, no further consideration was given to them, and the space group was kept as $I4_1/a$.

7.3.6 Possible Renninger Effect Contribution to Forbidden Reflexions

A necessary condition for double diffraction to occur is that two points of the reciprocal lattice enter the sphere of reflexion simultaneously (Renninger,1937). If hkl are the indices of a reflexion being measured and $h_1k_1l_1$ the indices of a reciprocal lattice point in the sphere of reflexion at the same time, then the doubly-diffracted ray from the sets of planes $h_1k_1l_1$ and $h_2k_2l_2$ where

$$h\ k\ l = h_1k_1l_1 + h_2k_2l_2$$

emerges in the direction of the ray hkl. This phenomenon has the following detrimental effects during structure determination: (a) to contribute to the intensity of the reflexion hkl, increasing discrepancies between observed and calculated structure factors, and (b) where F(hkl) is zero because of space group symmetry and $F(h_1k_1l_1)$ and $F(h_2k_2l_2)$ are not, to contribute intensity to extinct reflexions, thus causing apparent violations of space group limitations. Thus the Renninger effect is a possibility which must be considered in attempting to explain the forbidden uu0 reflexions. The absence of all forbidden reflexions but one on the Weissenberg photographs taken with CuKα radiation enhances the likelihood of double diffraction being the mechanism producing them.

Since in space group $I4_1/a$ only reflexions of the type gg0 are present in the zero level, then a contribution of any two of these cannot contribute to a reflexion of the type uu0. Any double-diffraction contributing to these reflexions must involve upper level reflexions, thus:

$$h\ k\ 0 = h_1 k_1 l_1 + h_2 k_2 \bar{l}_1$$

All parity groups permitted by the condition of body-centring may contribute to the uu0 reflexions (see Table 7.3.6-1).

Since interference does not appear to take place between the primary and doubly diffracted beams (Lipscomb,1949) the intensity of the reflexion hkl can be expected to have two components: one proportional to $|F(hkl)|$ and the other proportional to $|F(h_1 k_1 l_1)|^2 \cdot |F(h_2 k_2 l_2)|^2$ (Hirshfeld,1955). As noted by Speakman (1965), for normal beam Weissenberg diffraction geometry, the two reciprocal lattice points must be in the sphere of reflexion at the same angle ω. In order to look for possible Renninger contributors a search was made in the following manner: (1) the angle ω for all reflexions was calculated (for normal beam geometry since we are

Parity Groups Contributing to $\underline{uu0}$ Reflexions

$$u\,u\,0 = \begin{cases} g\,u\,u \quad + \quad u\,g\,\bar{u} \\ u\,g\,u \quad + \quad g\,u\,\bar{u} \\ \\ u\,u\,g \quad + \quad g\,g\,\bar{g} \\ g\,g\,g \quad + \quad u\,u\,\bar{g} \end{cases}$$

Table 7.3.6-1

Forbidden hk0 reflexion	Possible Contributors
$\bar{1}\ 5\ 0$ $F=4.2\sigma$ $\omega=14.73^\circ$	$F^2(\bar{1}\ 16\ 1)=69$ $\omega=14.73^\circ$
	$\rightarrow F^2(0\ \overline{11}\ \bar{1})=28$
	$F^2(6\ \overline{13}\ 1)=163$ $\omega=14.75^\circ$
	$\rightarrow F^2(\bar{7}\ 18\ \bar{1})=0$
	$F^2(12\ \overline{18}\ 4)=80$ $\omega=14.80^\circ$
	$\rightarrow F^2(\overline{13}\ 23\ \bar{4})$ not measured
	$F^2(3\ \bar{6}\ 3)=219$ $\omega=14.63^\circ$
	$\rightarrow F^2(\bar{4}\ 11\ \bar{3})=58$
	$F^2(1\ 22\ 3)=62$ $\omega=14.65^\circ$
	$\rightarrow F^2(\bar{2}\ \overline{17}\ \bar{3})=6$
	$F^2(1\ 19\ 4)=86$ $\omega=14.62^\circ$
	$\rightarrow F^2(\bar{2}\ \overline{14}\ \bar{4})=0$
$\bar{3}\ 21\ 0$ $F=2.8\sigma$ $\omega=22.50^\circ$	$F^2(11\ \overline{15}\ 2)=73$ $\omega=22.48^\circ$
	$\rightarrow F^2(\overline{14}\ 36\ \bar{2})$ not measured
	$F^2(13\ \overline{16}\ 3)=203$ $\omega=22.66^\circ$
	$\rightarrow F^2(\overline{16}\ 37\ \bar{3})$ not measured
	$F^2(1\ 9\ 6)=73$ $\omega=22.75^\circ$
	$\rightarrow F^2(\bar{4}\ 12\ \bar{6})=80$
$\bar{3}\ 25\ 0$ $F=6.2\sigma$ $\omega=23.97^\circ$	$F^2(\bar{2}\ 20\ 4)=96$ $\omega=23.84^\circ$
	$\rightarrow F^2(\bar{1}\ 5\ \bar{4})=0$
	$F^2(\bar{2}\ 9\ 3)=293$ $\omega=24.14^\circ$
	$\rightarrow F^2(\bar{1}\ 16\ \bar{3})=0$

Table 7.3.6-2

interested in contributors to the zero level) and the indices, structure factor and ω-angles were listed in order of ascending ω; (2) for significant forbidden reflexions a search was made for reflexions of the type $h_1 k_1 l_1$, $l_1 \neq 0$ which enter or leave the sphere of reflexion at approximately the same ω. A check at $\pm 90^{\circ}$ was made for Laue-related reflexions; (3) where possible contributors were found, their structure factors were noted along with $|F(h_2 k_2 \bar{l}_1)|$. Where both structure factors are great in magnitude, the double diffraction hypothesis is a reasonable one. The results of this search are shown for three reflexions (Table 7.3.6-2). Whilst this method appears to offer a reasonable explanation for the reflexion $\bar{1}$ 5 0, no reflexions could be found to account for the particularly intense ($F>6\sigma(F)$) reflexion $\bar{3}$ 25 0. Although this observation does not preclude the presence of the Renninger effect generally in the data set -- the worst agreements are almost all of the type $|F_{obs}|>|F_{calc}|$ -- it does not appear to be the sole mechanism producing the forbidden <u>uu0</u> reflexions.

7.4 Discussion

Examination of bond distances for the heterocyclic rings shows that there is considerable delocalisation with the bonds of intermediate character. The bond N(1)-C(2) does however approach pure double-bond character, while the bond C(2)-N(3) is significantly longer than the bond N(3)-C(4) (difference approximately three standard deviations). The bonds C(5)-C(6) and C(7)-C(8) are shorter than C(4A)-C(5) and C(8)-C(8A). These observations regarding the bond lengths are consistent with the simple resonance theory for naphthalene presented in Section 1.6. In the amino groups, the bond to N(2) is significantly longer than that to N(4) (difference approximately three standard deviations). The N(2) amino group donates a hydrogen bond to the water oxygen atom, while the N(4) amino group is involved in base pairing (see below).

The fused rings are planar to ±.03 Å. There is significant deviation from planarity in the pyrimidine moiety ($X^2=45$ assuming positional standard deviations of .005 Å; for three degrees of freedom $p<.001$) but not in the benzene moiety. The two rings are inclined slightly to each other (2°). Examination of the hydrogen bonding scheme shows the same N(4)-H...N(3)' type of base pairing that has been observed in the crystal structures of other DHFR inhibitors (see Sec 10.3). The pairing occurs across centres of symmetry at the Wyckoff c positions (see International Tables, Vol I, p178). The water molecules are hydrogen bonded in the form of infinite spirals along the 4_1 and 4_3 axes. The DAQ molecules are hydrogen bonded to the spiral at two points: the donation of a hydrogen bond N(2)-H...O and the receipt of a hydrogen bond O-H...N(1) from a water molecule three-quarters of a turn down the screw axis from the first. The hydrogen bonding contacts are listed in Table 7.4-1.

DAQ: Hydrogen Bonding Contacts

O(1)-H(01)...N(1)'	O(1)...N(1)'	2.71 Å	3/4+y,3/4-x,-1/4+z
O(1)-H(02)...O(1)'	O(1)...O(1)'	2.82 Å	3/4+y,3/4-x,-1/4+z
N(2)-H(22)...O(1)'	N(2)...O(1)'	2.94 Å	3/2-x, -y,-1/2+z
N(4)-H(41)...N(3)'	N(4)...N(3)'	3.03 Å	1-x, -y, 1-z
N(4)-H(42)...O(1)'	N(4)...O(1)'	3.24 Å	1/2+x, y, 3/2-z

Notes:

(1) The long contact N(4)-H...O(1) has not been drawn as a hydrogen bond.

(2) The hydrogen H(21) does not partake in hydrogen bonding.

Table 7.4-1

The DAQ molecules are stacked pairwise across centres of symmetry at the Wyckoff _d_ positions (see _International Tables_, Vol I, p178). This arrangement stacks the benzene ring above the pyrimidine ring and vice versa. Similar arrangements of benzene rings stacked with heterocyclic rings have been observed in purines and unprotonated pyrimidines (Bugg, et al, 1971) and have been attributed to electrostatic interaction of a partial bond moment in the heterocyclic ring with a polarisable π-electron system (dipole-induced dipole stacking). There is also a contact between the heterocyclic ring and the benzene moiety of the molecule formed by a minus one application of the 4_1 axis followed by an _a_ glide translation (Fig 7.4-11). In this case the benzene ring approaches the pyrimidine ring edge-on.

Illustrations

7.4-2 ORTEP with numbering scheme. Ellipsoids are drawn at the 50 per cent. probability level.

7.4-3 Base-pairing across the centre of symmetry at (1/2,0,1/2) viewed along [010]. Here and in subsequent diagrams the molecule formed by the listed coordinates is shown in heavy outline.

7.4-4 The 4_1 axis at (3/4,0,z) viewed along [001].

7.4-5 The 4_1 axis at (3/4,0,z) viewed along [100].

7.4-6 ORTEP stereo viewed perpendicular to the quinazoline rings.

7.4-7 ORTEP stereo viewed approximately along the plane of the quinazoline rings.

7.4-8 Stereo view of the 4_1 axis viewed along [001].

7.4-9 Stereo view of the 4_1 axis viewed along [100].

7.4-10 Stereo view of the unit cell contents viewed along [001].

7.4-11 Stereo view of the edge-on association of the benzene moiety with the pyrimidine moiety of a symmetry-related molecule.

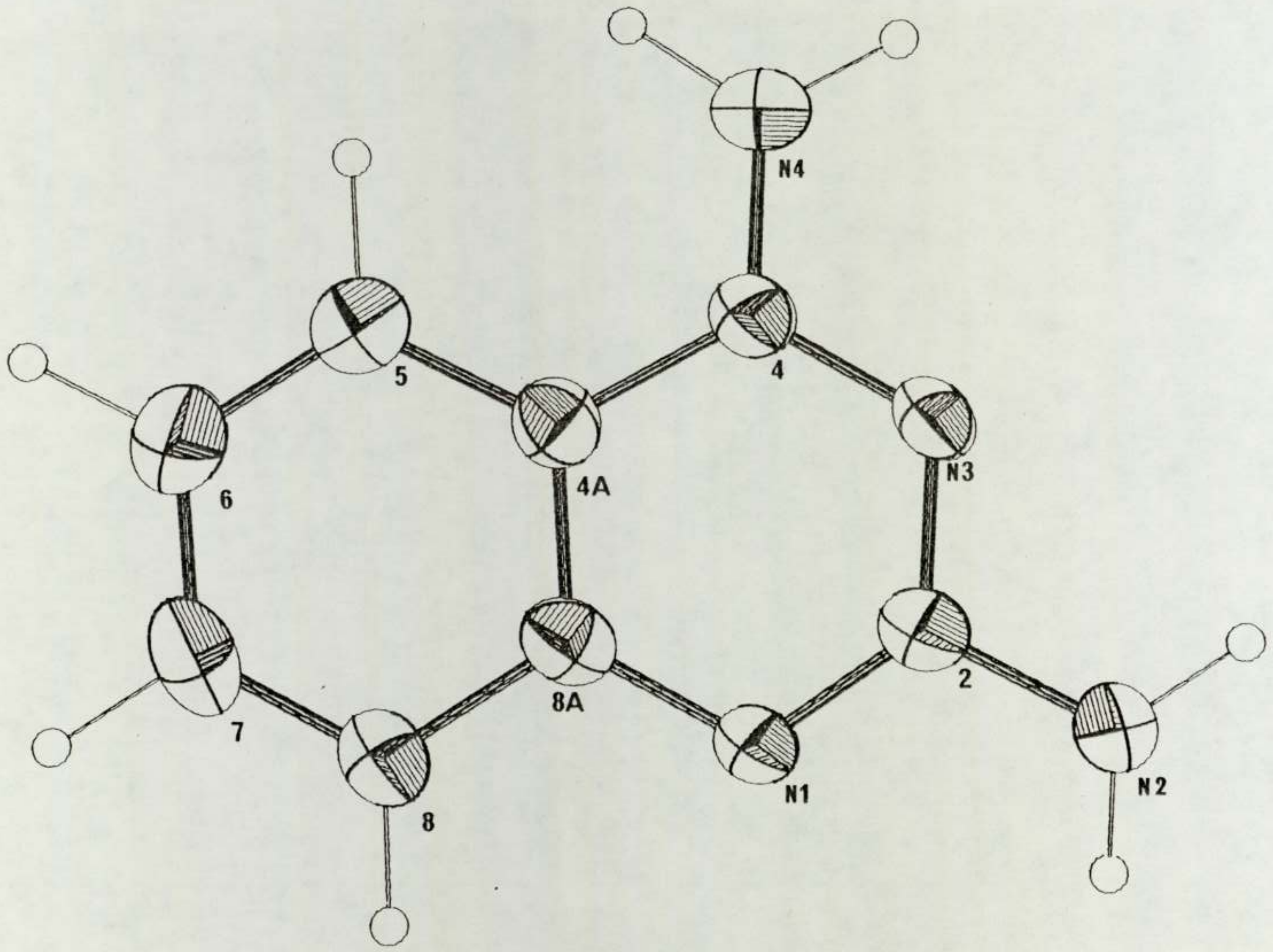


Fig 7.4-2

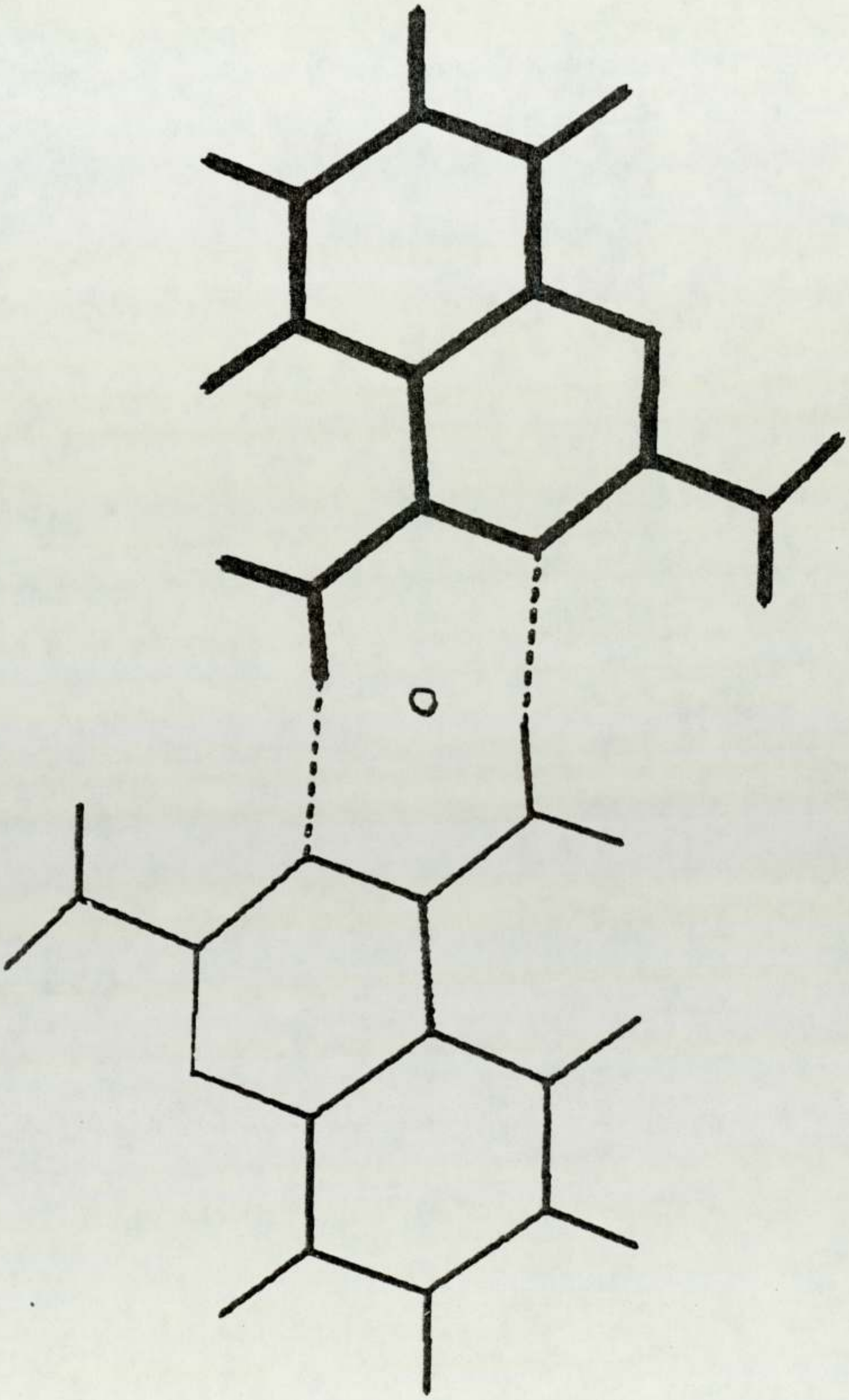


Fig 7.4-3

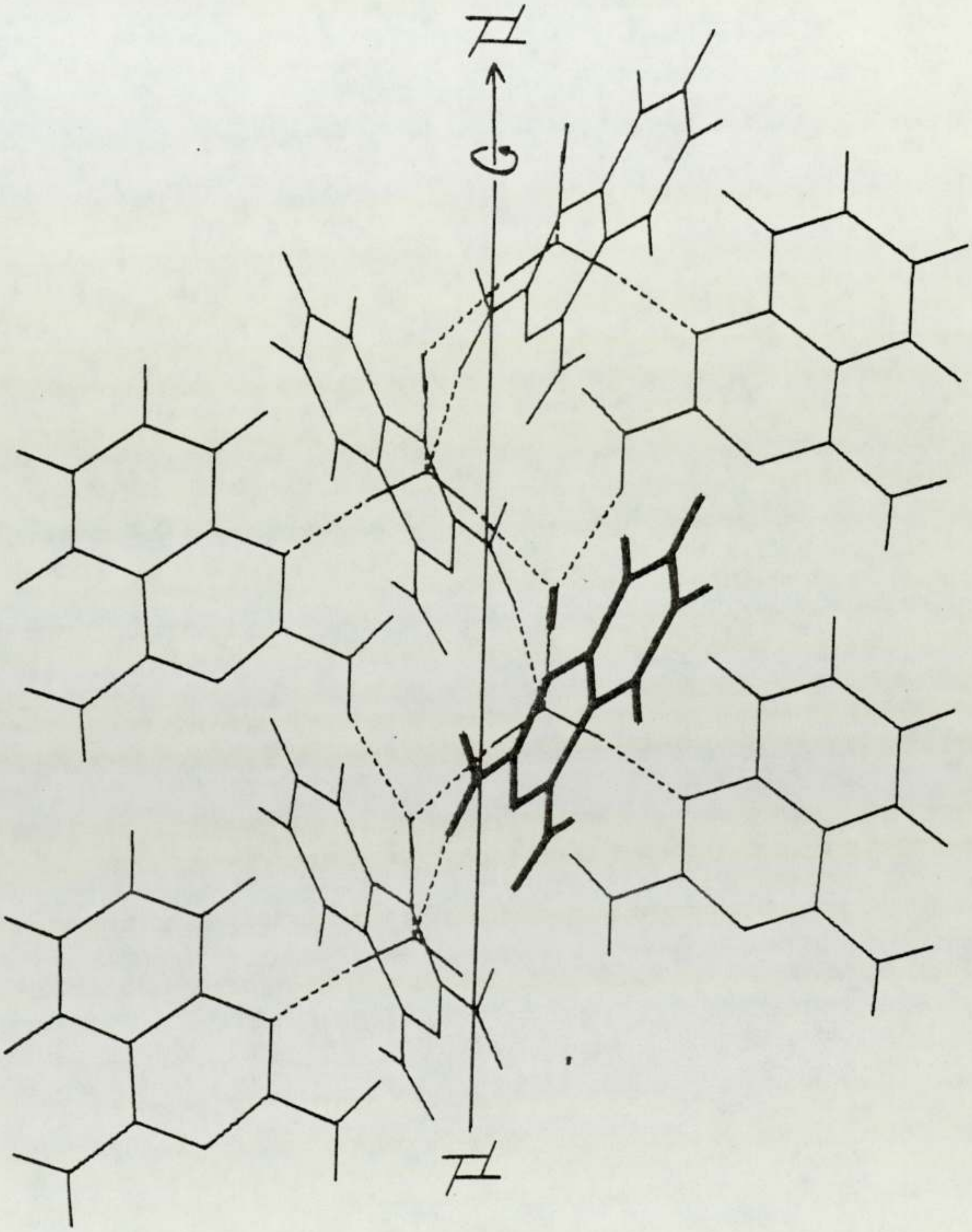


Fig 7.4-4

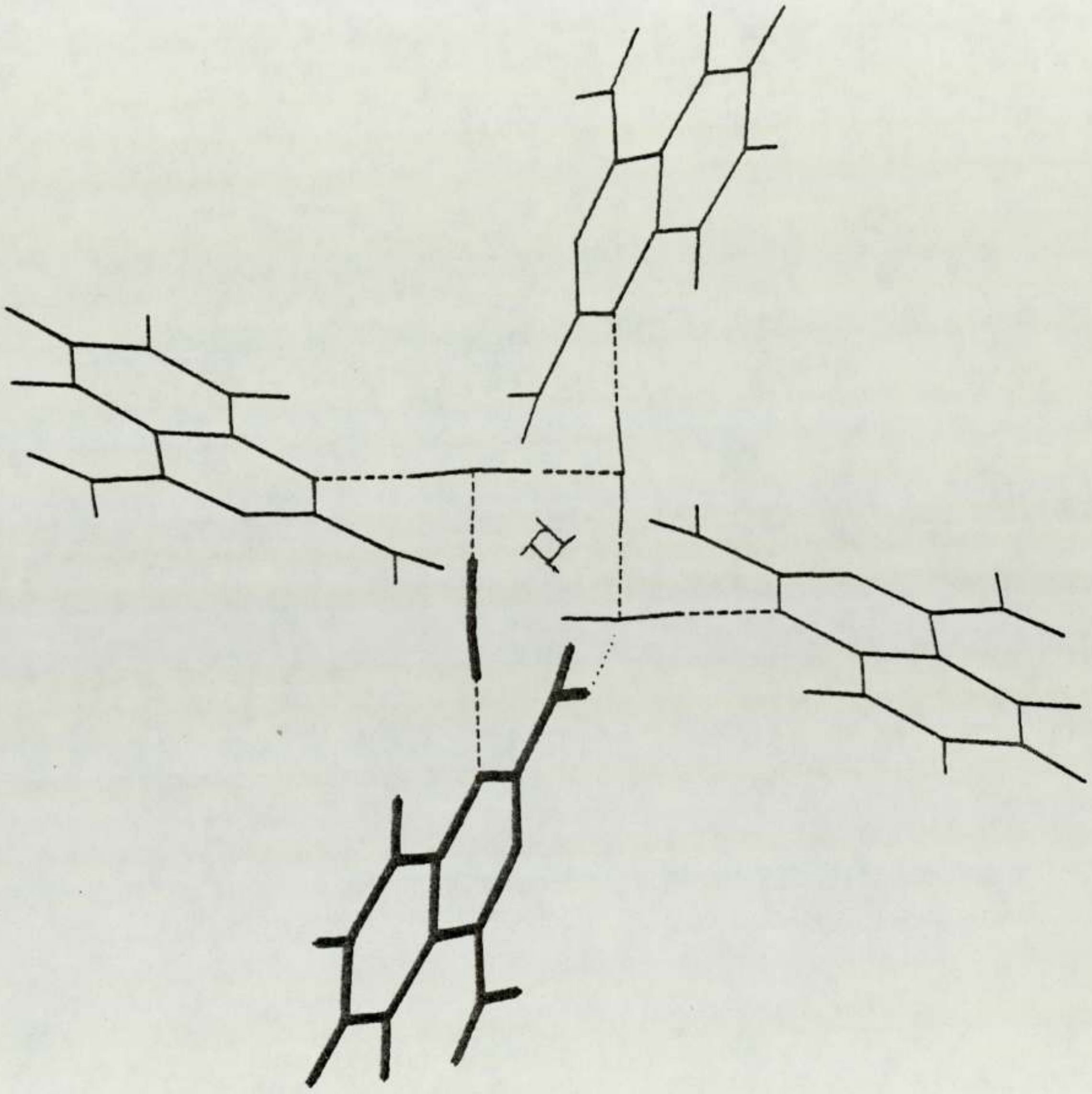


Fig 7.4-5

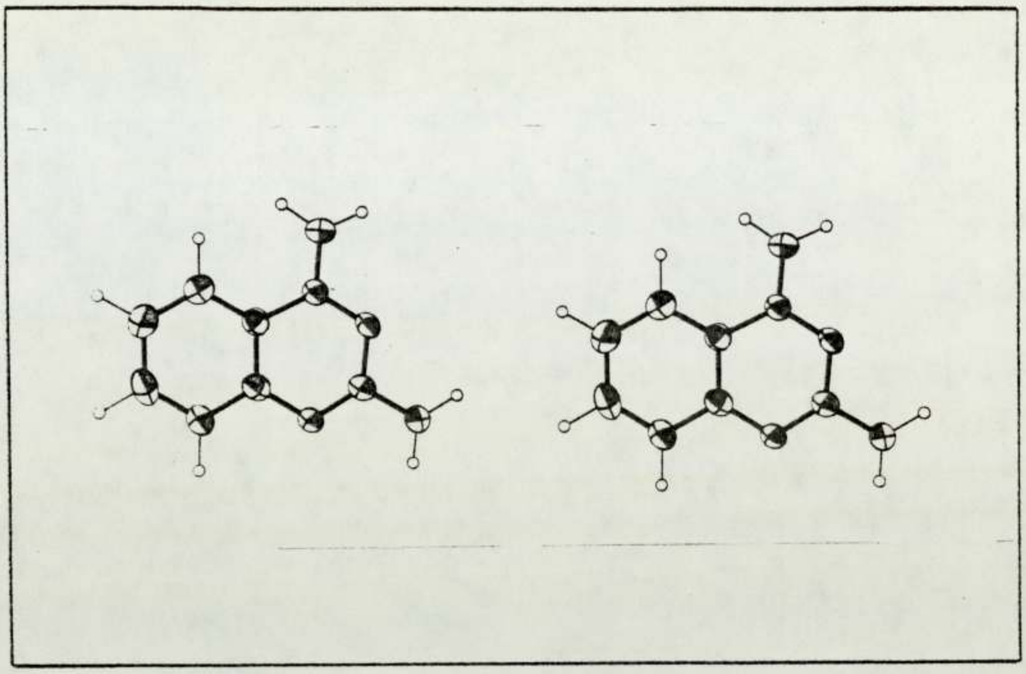


Fig 7.4 - 6

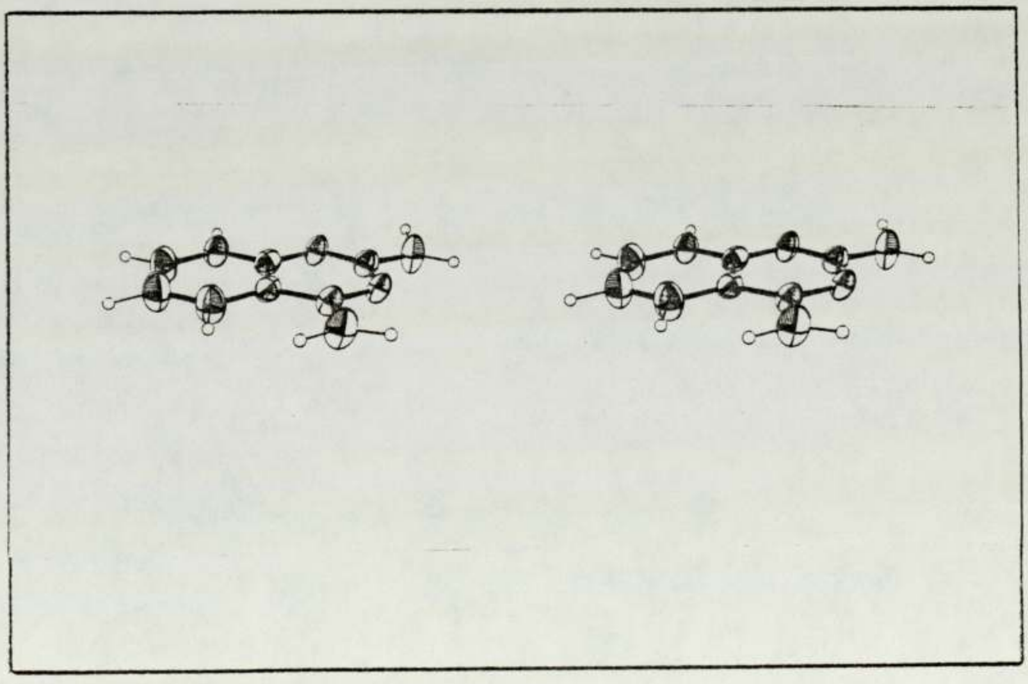


Fig 7.4 -7

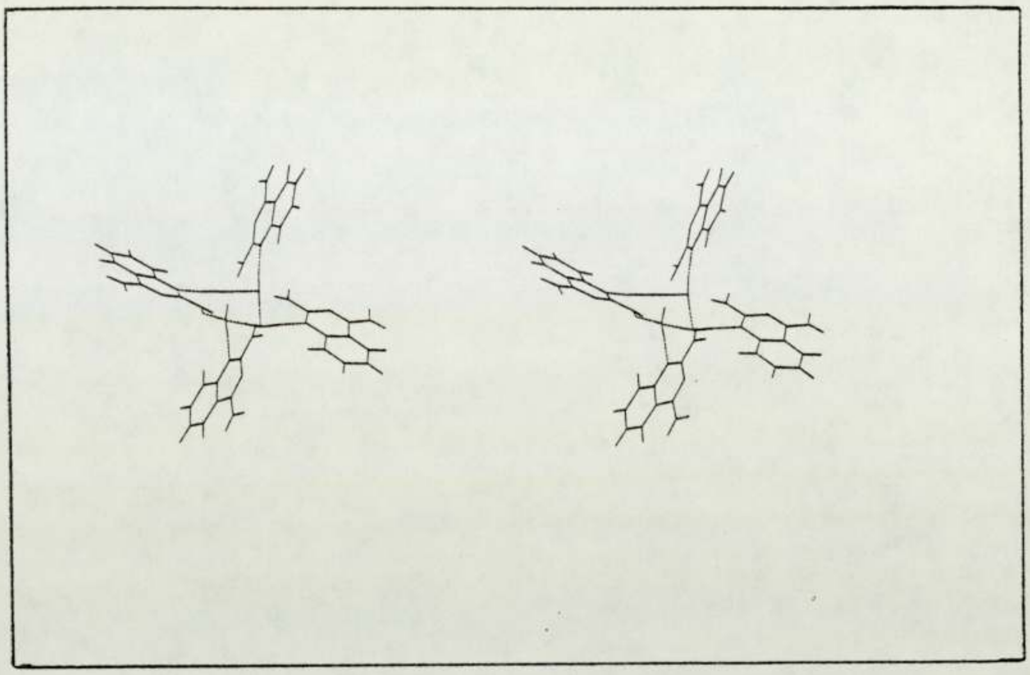


Fig 7.4-8

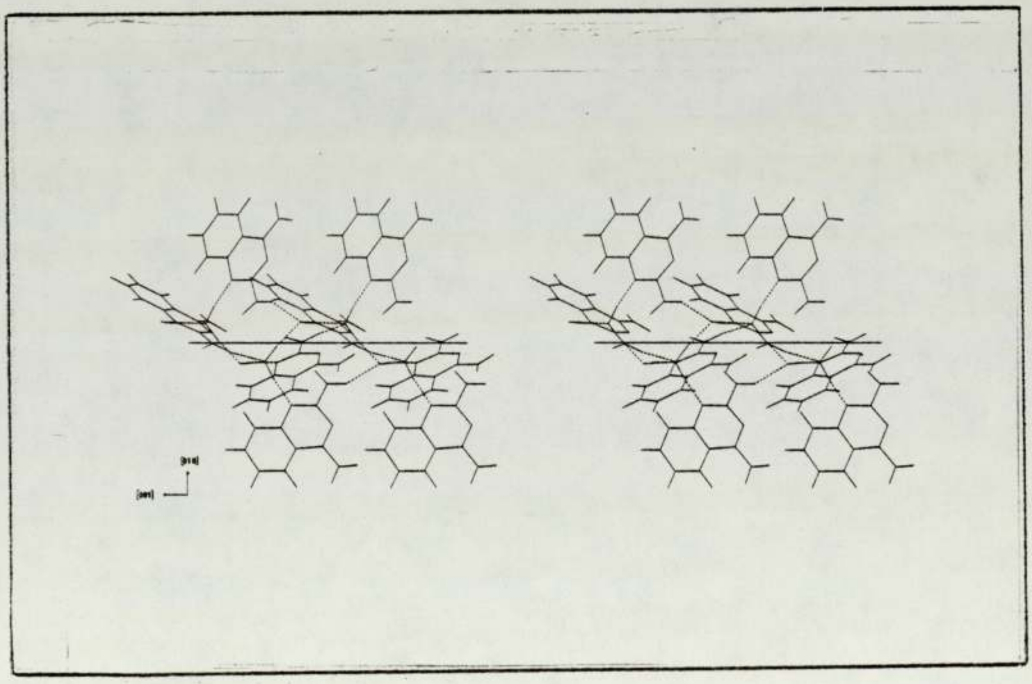


Fig 7.4-9

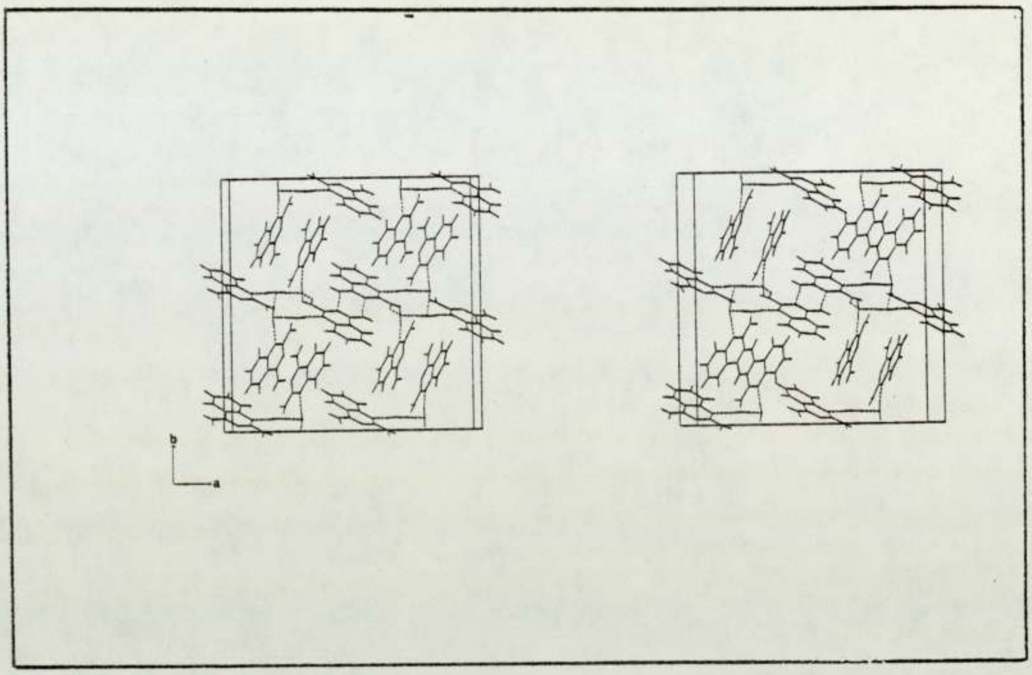


Fig 7.4 -10

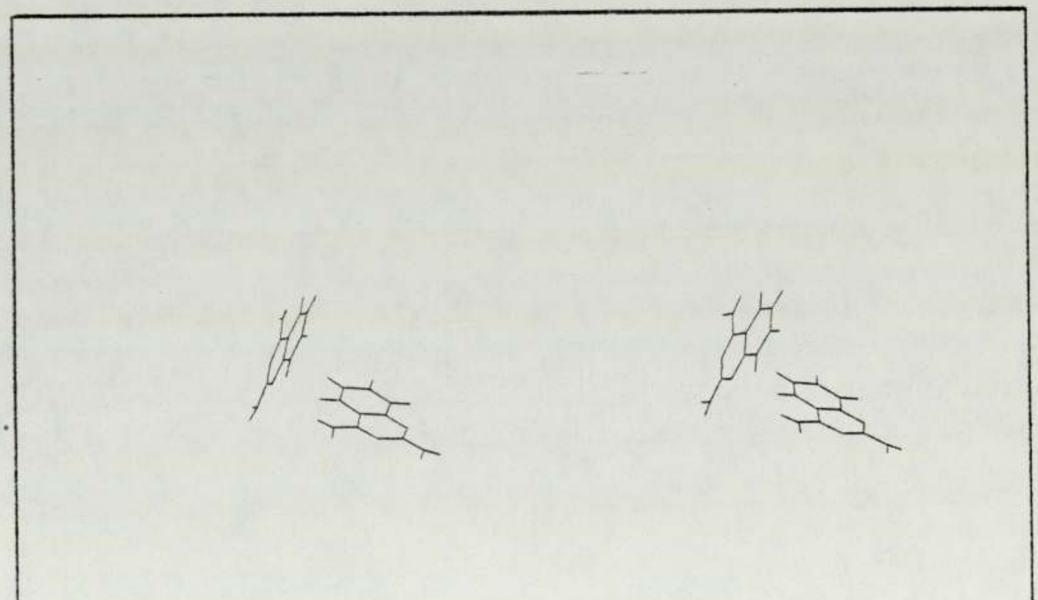


Fig 7.4 - 11

DAQ: FRACTIONAL COORDINATES

	X	Y	Z
N(1)	0.4022(2)	0.0479(2)	0.9751(5)
C(2)	0.4027(2)	0.0248(3)	0.8165(6)
N(3)	0.4500(2)	0.0253(2)	0.6993(5)
C(4)	0.5023(3)	0.0521(2)	0.7502(6)
C(4A)	0.5073(3)	0.0821(2)	0.9178(6)
C(5)	0.5595(3)	0.1142(3)	0.9762(8)
C(6)	0.5611(3)	0.1417(3)	1.1381(8)
C(7)	0.5089(3)	0.1370(3)	1.2458(8)
C(8)	0.4565(3)	0.1055(3)	1.1944(7)
C(8A)	0.4553(3)	0.0778(2)	1.0280(6)
N(2)	0.3498(2)	-0.0027(2)	0.7570(6)
N(4)	0.5497(2)	0.0510(3)	0.6376(6)
O(1)	0.1987(2)	0.0459(2)	0.9151(5)

Table 7-1

DAQ: ANISOTROPIC TEMPERATURE FACTORS

	U11	U22	U33	U23	U13	U12
N(1)	0.0311(27)	0.0590(33)	0.0257(22)	-0.0046(21)	0.0035(20)	-0.0042(24)
C(2)	0.0372(33)	0.0454(37)	0.0299(29)	-0.0006(25)	0.0030(25)	-0.0025(29)
N(3)	0.0343(26)	0.0500(30)	0.0219(22)	-0.0043(19)	0.0003(20)	0.0017(23)
C(4)	0.0327(31)	0.0458(36)	0.0277(26)	-0.0012(25)	0.0016(25)	-0.0004(28)
C(4A)	0.0394(34)	0.0395(33)	0.0294(25)	0.0003(25)	-0.0035(25)	-0.0008(27)
C(5)	0.0496(41)	0.0759(49)	0.0466(36)	-0.0088(33)	0.0051(32)	-0.0187(38)
C(6)	0.0524(43)	0.0817(53)	0.0505(37)	-0.0109(36)	-0.0010(34)	-0.0226(40)
C(7)	0.0728(48)	0.0632(44)	0.0435(33)	-0.0209(34)	-0.0017(35)	-0.0092(37)
C(8)	0.0481(37)	0.0529(39)	0.0345(29)	-0.0089(28)	0.0008(29)	0.0022(32)
C(8A)	0.0398(33)	0.0392(33)	0.0303(27)	0.0005(24)	0.0042(25)	0.0042(28)
N(2)	0.0375(30)	0.0802(40)	0.0397(26)	-0.0235(29)	0.0034(25)	-0.0140(30)
N(4)	0.0387(31)	0.0815(42)	0.0383(27)	-0.0087(26)	0.0094(24)	-0.0133(29)
O(1)	0.0598(28)	0.0471(27)	0.0391(22)	0.0130(22)	0.0067(20)	-0.0004(24)

Table 7-2

DAQ: HYDROGEN FRACTIONAL COORDINATES
AND ISOTROPIC TEMPERATURE FACTORS

	X	Y	Z	UISO
H(5)	0.5995	0.1173	0.8909	0.0676
H(6)	0.6017	0.1666	1.1820	0.1175
H(7)	0.5097	0.1588	1.3745	0.0483
H(8)	0.4170	0.1024	1.2816	0.0540
H(21)	0.3183	-0.0140	0.8497	0.0908
H(22)	0.3494	-0.0226	0.6375	0.0741
H(41)	0.5458	0.0272	0.5236	0.0842
H(42)	0.5904	0.0697	0.6732	0.0734
H(01)	0.2020	0.0872	0.8545	0.0948
H(02)	0.2010	0.0087	0.8345	0.1013

Table 7-3

DAQ: BOND DISTANCES

C(2) - N(1)	1.297(6)
N(3) - C(2)	1.351(6)
C(4) - N(3)	1.326(6)
C(4A) - C(4)	1.426(7)
C(5) - C(4A)	1.395(7)
C(6) - C(5)	1.361(8)
C(7) - C(6)	1.392(8)
C(8) - C(7)	1.376(8)
C(8A) - N(1)	1.374(6)
C(8A) - C(4A)	1.402(7)
C(8A) - C(8)	1.393(7)
N(2) - C(2)	1.361(6)
N(4) - C(4)	1.333(6)

Table 7-4

DAQ: BOND ANGLES

C(2) - N(1) - C(8A)	116.2(5)
N(1) - C(2) - N(3)	127.4(5)
N(1) - C(2) - N(2)	117.7(5)
N(3) - C(2) - N(2)	114.9(4)
C(2) - N(3) - C(4)	117.2(4)
N(3) - C(4) - C(4A)	121.4(5)
N(3) - C(4) - N(4)	117.5(5)
C(4A) - C(4) - N(4)	121.1(5)
C(4) - C(4A) - C(5)	124.7(5)
C(4) - C(4A) - C(8A)	115.7(5)
C(5) - C(4A) - C(8A)	119.6(5)
C(4A) - C(5) - C(6)	121.3(6)
C(5) - C(6) - C(7)	118.3(6)
C(6) - C(7) - C(8)	122.6(5)
C(7) - C(8) - C(8A)	118.8(5)
N(1) - C(8A) - C(4A)	121.9(4)
N(1) - C(8A) - C(8)	118.6(5)
C(4A) - C(8A) - C(8)	119.5(5)

Table 7-5

DAQ: LEAST-SQUARES PLANES

(a) Equations of planes in the form $AX+BY+CZ+D=0$ where X,Y and Z are the orthogonal coordinates in Å along a,b and c:

Plane(1): $.3528X + .8502Y - .3907Z - 2.5683 = 0$
Plane(2): $.3388X + .8605Y - .3806Z - 2.4749 = 0$
Plane(3): $.3651X + .8418Y - .3976Z - 2.6199 = 0$

(b) Deviations in A of atoms from planes:

Plane(1): N(1) -.010, C(2) .030, N(3) .024, C(4) -.033, c(4A) -.014, C(5) .005, C(6) .021, C(7) .014, C(8) -.014, C(8A) -.024, N(2)* .103, N(4)* -.083
Plane(2): N(1) -.013, C(2) .010, N(3) .009, C(4) -.022, C(4A) .017, C(8A) .000
Plane(3): C(4A) .001, C(5) -.002, C(6) .000, C(7) .002, C(8) -.003, C(8A) .001

(c) Dihedral angles in degrees between the planes:

(1) - (2) 1.2 (1) - (3) 1.0 (2) - (3) 2.0

*Atoms marked with an asterisk not included in the definition of the plane.

Table 7-6

- -

Chapter 8: 3-Hydroxy-4-Oxy-1,2,3-Benzotriazine

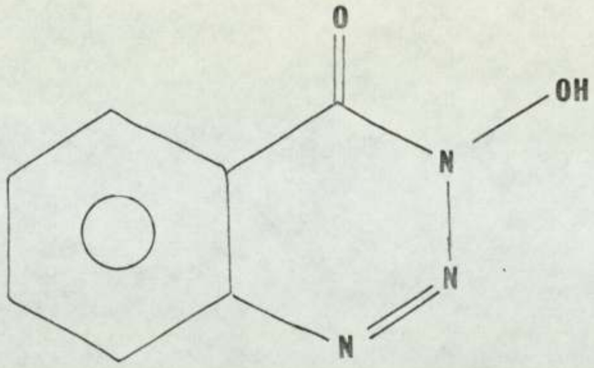
- -

8.1 Introduction

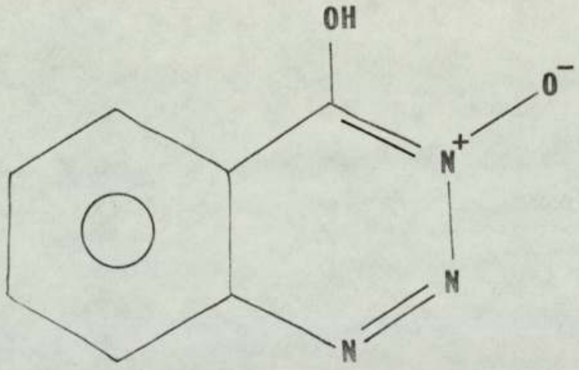
3-Hydroxy-4-oxy-1,2,3-benzotriazine was believed to exist in one of the three possible tautomeric forms shown (8.1-I,8.1-II,8.1-III) (Vaughan,1979). Crystal structure determination was undertaken to discover which of the tautomeric forms existed in the crystalline state and to correlate crystallographic results with structural information obtained from decomposition of the molecule under thermolysis.

8.2 Crystal Data

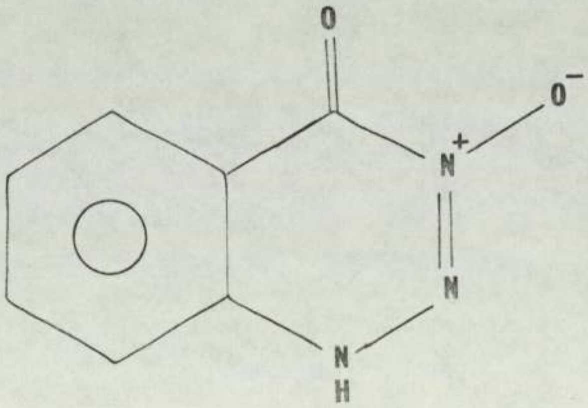
3-Hydroxy-4-oxy-1,2,3-benzotriazine (HOB) - $C_7H_5N_3O$ - crystallises in space group $P2_1/n$ with the following conditions limiting possible reflexions: h0l,h+l=2n and 0k0,k=2n with no restrictions on general hkl reflexions. The unit cell dimensions are a=15.04(1) Å, b=4.29(2) Å, c=10.95(1) Å, β=103.2(1)° and V_c = 688(4) $Å^3$. There are 4 formula units per unit cell; M=163.136; D_x=1.576 g cm^{-3} and μ=1.30 cm^{-1}.



8.1-I



8.1-II



8.1-III

8.3 Structure Analysis

8.3.1 Data Collection

HOB crystallises in the form of colourless needles extending along the [010] direction. One long crystal of cross-section approximately 0.14 mm X 0.24 mm was mounted along the b-axis. The crystal faces were of the type {101}. A cross – sectional diagram of the crystal is shown in Fig 8.3.1-1. Diffracted intensities for MoKα radiation were collected on the Stoe Two-circle Diffractometer in the Chemistry Department of Birmingham University. Data for levels k=0 to k=4 were taken in a manner similar to that described in Section 6.3.1. Raw intensity data were transferred to the ICL 1904S computer at Aston University and data reduction was carried out with use of a program supplied by Dr. T. A. Hamor of Birmingham University. A total of 1637 independent reflexions were measured of which 1038 satisfied the condition $|F|>2\sigma(F)$.

8.3.2 Solution

Normalised structure factors were calculated according to the modified Wilson Plot procedure described in Section 2.2. One rigid fragment was input per asymmetric unit: a regular naphthalene fragment with all atoms entered as carbons and all interatomic distances set to 1.4 Å. The curves according to the Wilson calculation and the Debye calculation are shown in Fig 8.3.2-1 along with the least-squares fit to the Debye calculation. Values calculated

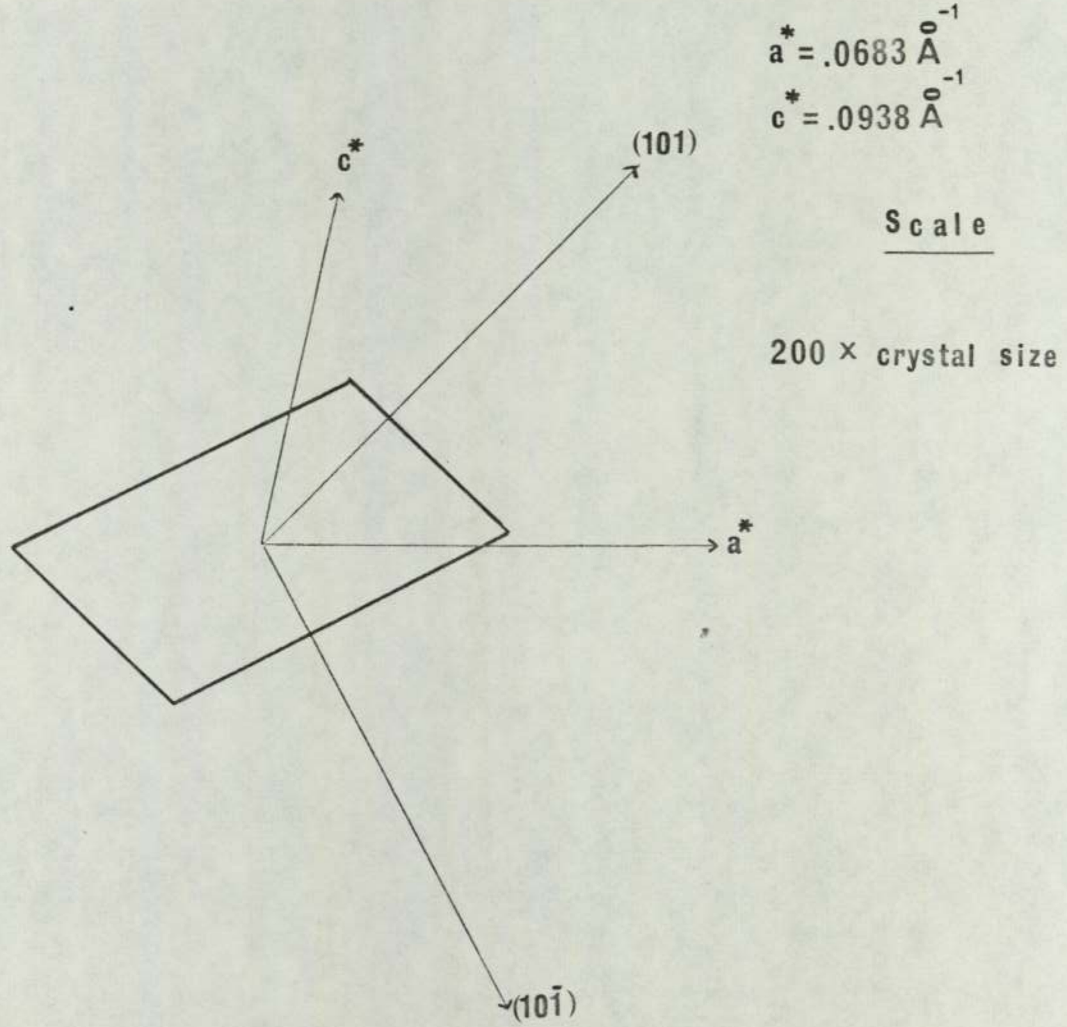

$a^* = .0683\ \mathring{A}^{-1}$
$c^* = .0938\ \mathring{A}^{-1}$
Scale
200 × crystal size
c*
(101)
a*
(10$\bar{1}$)

Fig 8.3.1-1

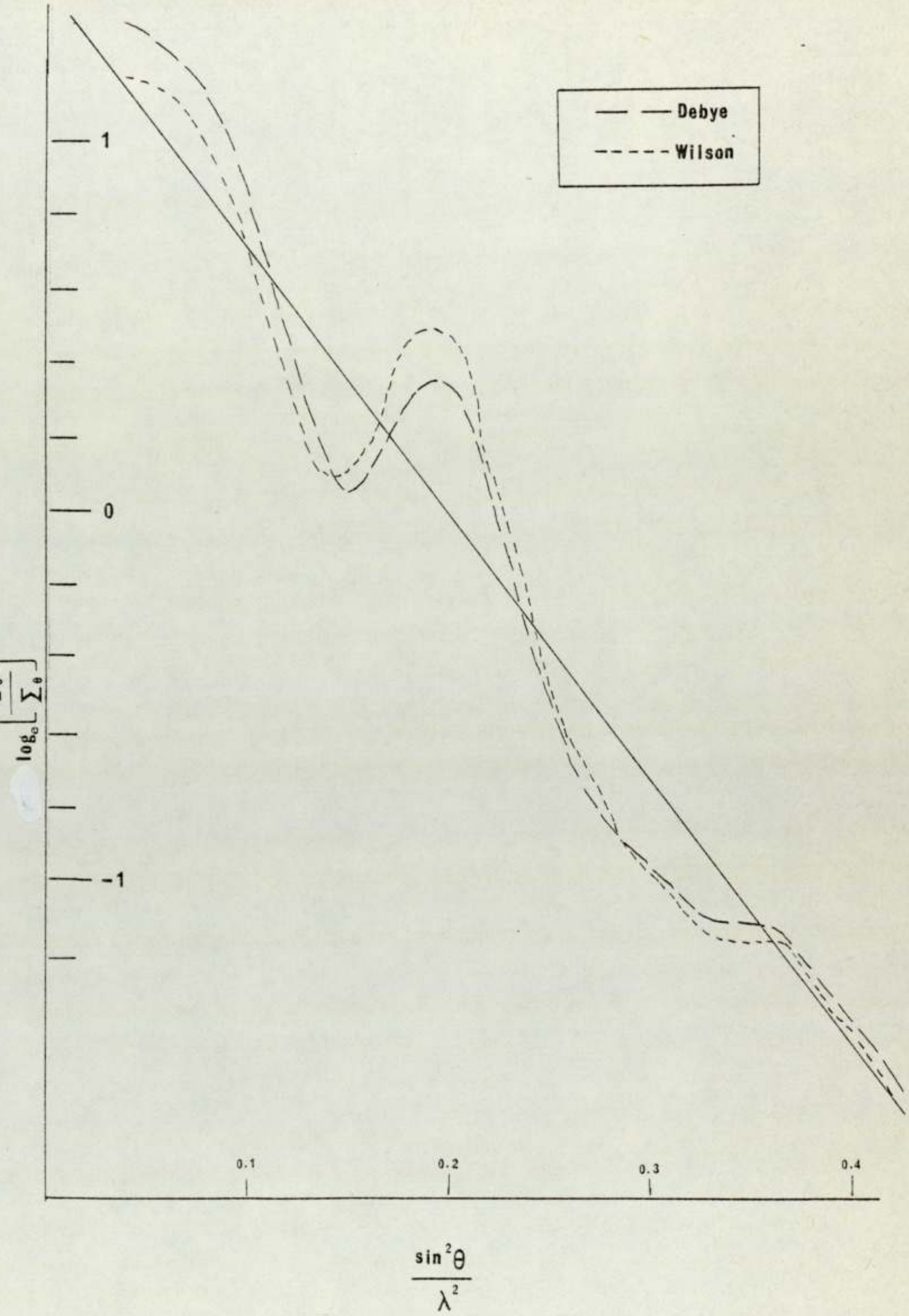

Debye
Wilson
1
0
-1
$\log_e\left[\frac{\langle I_\theta\rangle}{\Sigma_\theta}\right]$
0.1
0.2
0.3
0.4
$\frac{\sin^2\theta}{\lambda^2}$

Fig 8.3.2-1

Distribution of E-values for HOB

	Experimental	Theoretical	
		Centric	Acentric
$<E^2-1>$	1.0530	0.9860	0.7360
$<E>$	0.7419	0.7980	0.8660
%E>0.5	57.9	61.7	77.9
%E>1.0	29.1	31.7	36.8
%E>2.0	5.3	4.6	1.8

Table 8.3.2-2.

from the gradient and intercept were

$$2B = 7.1563$$

$$k = 0.2423$$

The distribution of E-values conformed approximately to that of a random centrosymmetric structure (see Table 8.3.2-2). The values of $<E^2>$ showed little variation between the parity groups, the highest being $<E^2>=1.21$ for $\underline{uuu}$ and the lowest $<E^2>=0.83$ for group $\underline{ugg}$.

Phase determination was attempted with the program MULTAN (see Sec 2.3). 299 reflexions for which $|E_h|>1.29$ were input and -- making use of expanded dimensioning within the program -- 2500 Σ_2 relationships were used in the phase refinement. On the basis of the Σ_1 calculation the following invariant phases were determined:

$6\ 4\ \bar{8}$ (+) p = 99.2 per cent.

$6\ 0\ \bar{8}$ (-) p = 98.3 per cent.

The CONVERGE procedure produced the following origin-determining reflexions: $2\ 3\ \bar{4}$ (+) and 10 1 4 (+). Eight starting sets were determined by permuting the signs of the reflexions: 12 0 2, $1\ 0\ \overline{11}$ and 13 0 1. None of the four origin-shifted solutions (maximum ABS FOM 0.9826, minimum RESID 40.11) produced a satisfactory E-map. Meanwhile an alternative approach was attempted with the SHELX centrosymmetric direct-methods program EEES (see Sec 2.4). The maps produced exhibited a characteristic 'chicken wire' effect, with two molecules appearing to be superimposed upon one another. Eventually averaging atomic positions between the separate images yielded the structure.

8.3.3 Refinement

All refinement was undertaken with use of the SHELX system on the CDC7600 computer at UMRCC. The hydrogen atoms attached to carbons C(5),C(6),C(7) and C(8) were refined riding on the carbon atoms with their positions fixed by the requirement of sp^2 hybridisation (see Sec 2.5.2(a)). All non-hydrogen atoms were refined with anisotropic temperature factors. An isotropic extinction factor of the type described in Section 2.5.2(f) was refined, the final value being x=-0.05169(5). The negative value of this parameter indicates that it is the weaker rather than the stronger reflexions which are suffering from errors of the form |Fobs|<|Fcalc|. Although there is no obvious physical explanation for this phenomenon, the factor was kept in the refinement.

Of particular interest in this refinement is the site of protonation. Unfortunately the quality of data is such that the position of the hydrogen atom must remain somewhat uncertain. The bond N(3)-O(3) is the length (1.37 Å) of a single bond, while that of C(4)-O(4) is close to that of a double bond. It would seem reasonable to expect that the hydrogen is attached to O(3). Because of this evidence of the protonation site, a hydrogen atom was refined DFIXed (see Sec 2.5.2(b)) attached to O(3) with a bond distance of 1.00(5) Å. The isotropic temperature factor monotonically increased during refinement from Uiso= 0.05 -- the arbitrary initial value -- to Uiso=0.22 after 5 cycles of refinement. In this case, the resulting N(3)-O(3)-H(O3) angle was considerably less than could be expected on the basis of sp^3 hybridisation (86°). The hydrogen position is, however, reasonably consistent with intramolecular hydrogen bonding (H(O3) ... O(4) 1.81 Å). This model, however, offers no explanation for the short intermolecular O(3) ... O(4) contact (see Sec 8.4).

The final agreement factors for the DFIXed refinement were R=0.120,Rw=0.108 and Rg=0.104. All density in the final difference Fourier synthesis was in the range from -0.16 to +0.11 $eÅ^{-3}$. The terms in the synthesis were weighted on the basis of $\exp(-z \sin \theta)$ where the value of z is such that the weight is half the maximum for $\sin \theta/\lambda = 0.3$.

8.4 Discussion

Of the three possible tautomeric forms, crystallographic evidence strongly favours 8.1-I. The double bond N(1)=N(2) indicates a contribution from the $2p_z$ orbital of N(1) to the π-bonding system and hence indicates lack of protonation (see Sec 1.2). The double-bond C(4)=O(4) indicates that there is no hydrogen atom bonded to O(4). O(3) is left as the likely site of attachment, although unfortunately there is no clear evidence of the hydrogen position in the difference Fourier synthesis.

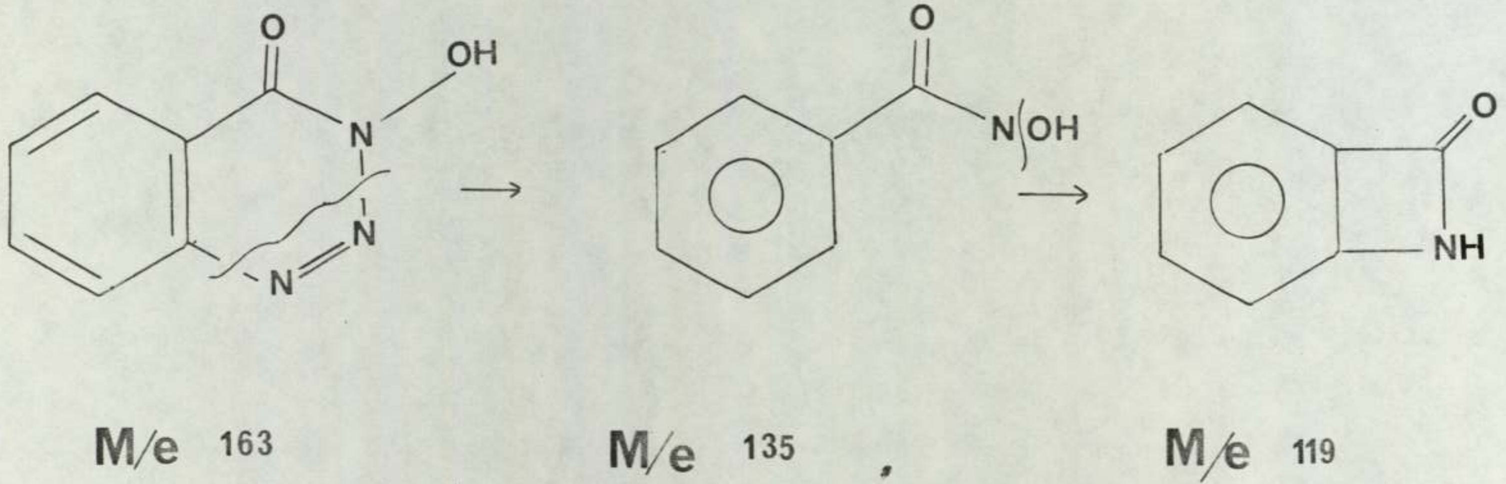


Fig 8.4-1

The short intermolecular contact O(3) ... O(4) (2.57 Å) -- about 0.2 Å shorter than the minimum expected Van der Waals contact -- requires some explanation, the most likely of which is hydrogen bonding. The oxygen atoms could approach more closely than the sum of their Van der Waals radii if they carried charges of opposite signs. There is a resonance form of the tautomer 8.1-II, with the double bond shifted from N(3)-C(4) to C(4)-O(4), which satisfies this condition (Vaughan,1979). Unfortunately the evidence from bond lengths is unable to distinguish between this resonance form and the tautomer 8.1-I. The charge separation would, however, render this resonance form less favourable. A detailed examination of the difference Fourier synthesis shows a peak of density 0.11 eÅ^{-3} vaguely in the region between the two oxygen atoms. The peak is fairly symmetrical, of approximate radius 0.6 Å when contoured at half its maximum. Its point of maximum density is located 1.37 Å from O(3) and 1.87 Å from O(4)' with an angle O(3)-Peak-O(4)' of 104°. These values lie well outside the range of O-H ... O geometries collected from neutron data (Brown,1976). The region in the difference Fourier synthesis along a line between the oxygen atoms is, however, mainly negative. The alternative hypothesis of internal hydrogen bonding is partially supported with some density between O(3) and O(4), but placing the hydrogen atom at the point of maximum density gives an even more extreme geometry than the one above: 2.04 Å to O(3), 1.56 Å to O(4) and O(3)-Peak-O(4) 95°. In view of the above problems there must remain some doubt about the hydrogen bonding scheme.

Intermolecular hydrogen bonding of the type (O(3)-H...O(4)') appears the most likely arrangement and in the stacking diagrams the hydrogen atom has been located on the axis between the two oxygen atoms. The effect of these hydrogen bonds is to create an infinite spiral of linked molecules arranged along the 2_1 axes. This arrangement is similar to the hydrogen bonding in 1,2,3-benzotriazin-4(3H)-one (Hjortas,1973), the only difference being the N(3)-H...O(4) form of the bond in the latter structure. The planes are stacked pairwise across centres of symmetry at the Wyckoff a positions (see International Tables, Vol I - p99). The planes are inclined at an angle of 39° to the b-axis.

The fused rings are planar to within .025 Å. Since the standard deviations of bond lengths are of the order of .005 Å, the larger deviations from the least- squares plane are significant. There is a small angle (1.3°) between the least-squares planes for the two rings. Both O(3) and O(4) deviate considerably more than the ring atoms from the plane; both oxygen atoms lie on the same side of the plane.

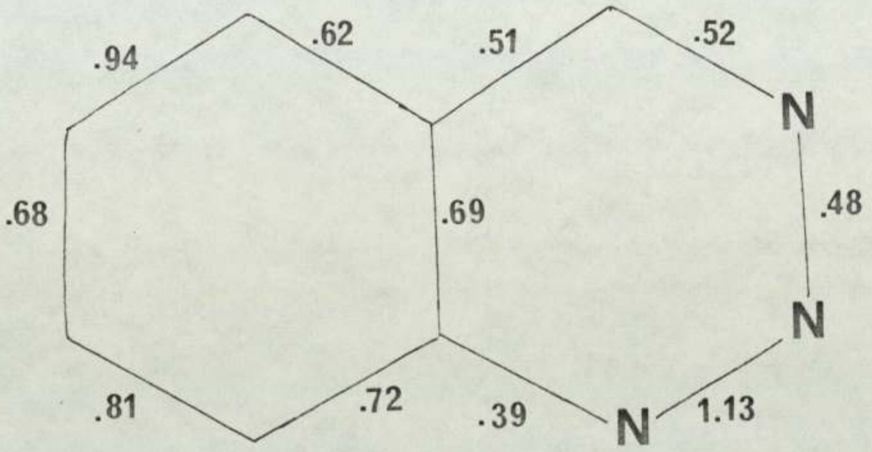
Mass-spectroscopic analysis of decomposition during thermolysis indicates that the loss of N_2O is a two step process via the intermediate shown in Fig 8.4-1. There is very little N_2O gas in the decomposition products indicating that the concerted loss of N_2O is only a minor contribution to the overall reaction (Ahren,et al,1977).

This result is not surprising in view of the crystallographic evidence for the double bond N(1)=N(2) which would have to be broken in such a reaction. The intermediate with a ratio M/e of 147 was also observed in the mass spectrum, indicating that the breakdown also occurs in the reverse order to that shown in Fig 8.4-1. Calculations of the π-bond orders according to the equations of Roos and Skancke (1967) and Fischer-Hjalmars and Sundbom (1968) indicate that the lowest orders in the fused ring system are for N(2)-N(3) and C(8A)-N(1) (see Fig 8.4-2). Crystallographic evidence therefore predicts the separate evolution of N(1)=N(2) and O(3) observed in the thermolysis experiment.

The distribution of π-bond orders about the fused benzene ring follows the pattern expected from the simple resonance theory for naphthalene (see Sec 1.6).

Illustrations

8.4-3	ORTEP with numbering scheme. The ellipsoids have been drawn at the 50 per cent. probability level. The hydrogen atom for which no definite position can be assigned is omitted.
8.4-4	Stereo view of the unit cell along [010]. In all stereo illustrations of this structure the problematic hydrogen atom has been placed in a position consistent with a linear O-H...O intermolecular bond.
8.4-5	Stereo view of the unit cell contents along [101].
8.4-6	Stereo illustration of the unit cell contents viewed perpendicular to the (100) plane.
8.4-7	Stereo view of the unit cell contents along [001]. All stereo illustrations in this section have been produced with use of the program PLUTO.



$d = A - 0.180\ p$

d=bond distance

p=π-bond order

A = 1.517 (C-C)
A = 1.458 (C-N)
A = 1.453 (N-N)

Fig 8.4-2

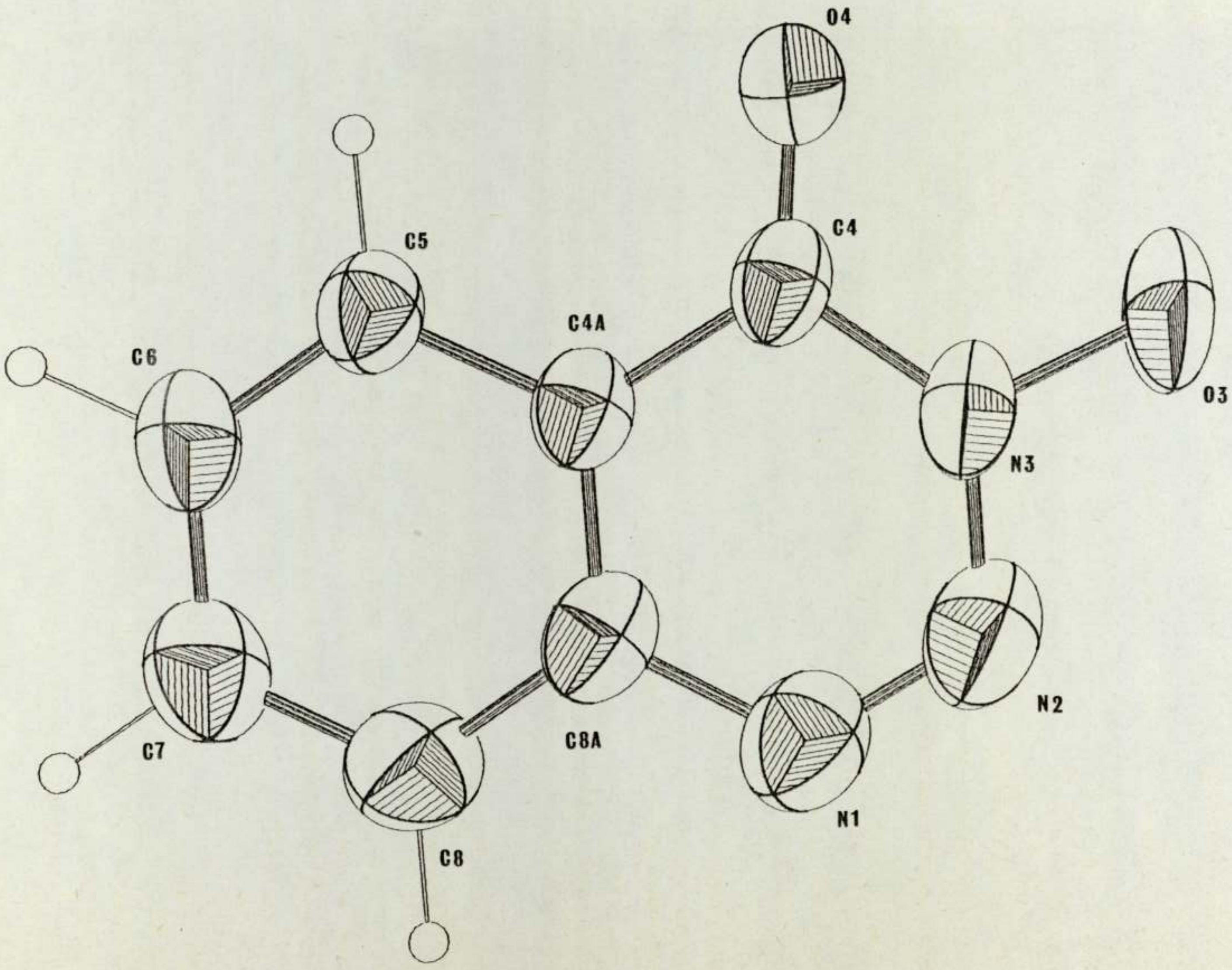


Fig 8.4-3

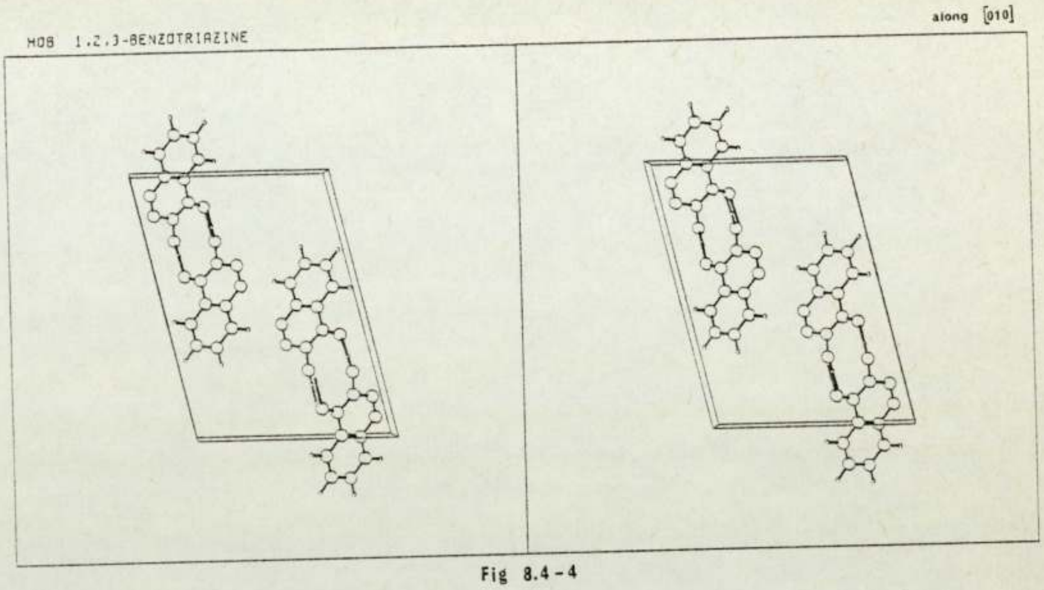


Fig 8.4-4

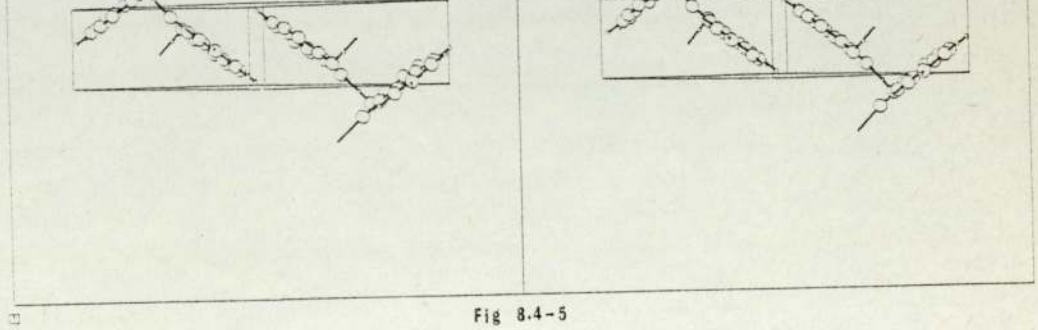


Fig 8.4-5

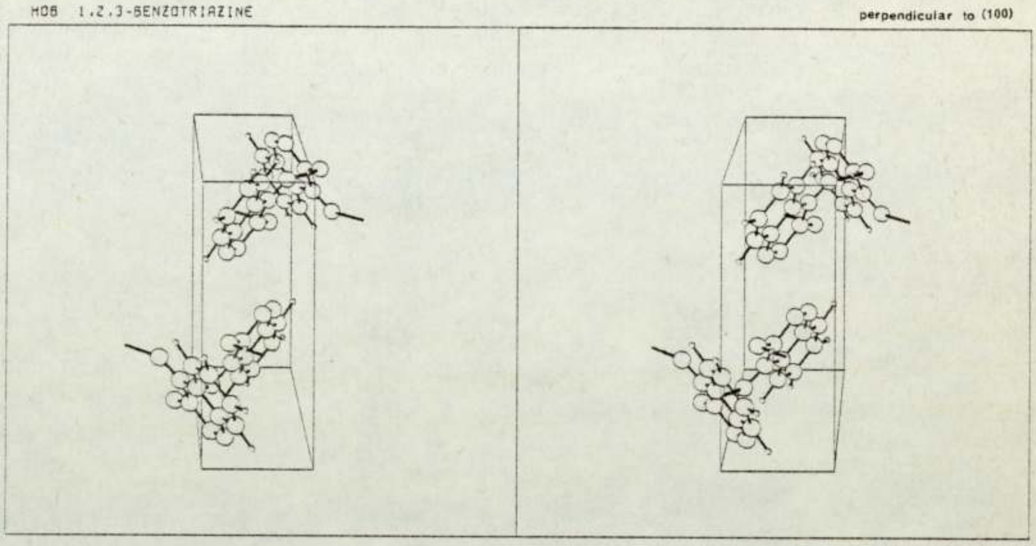


Fig 8.4-6

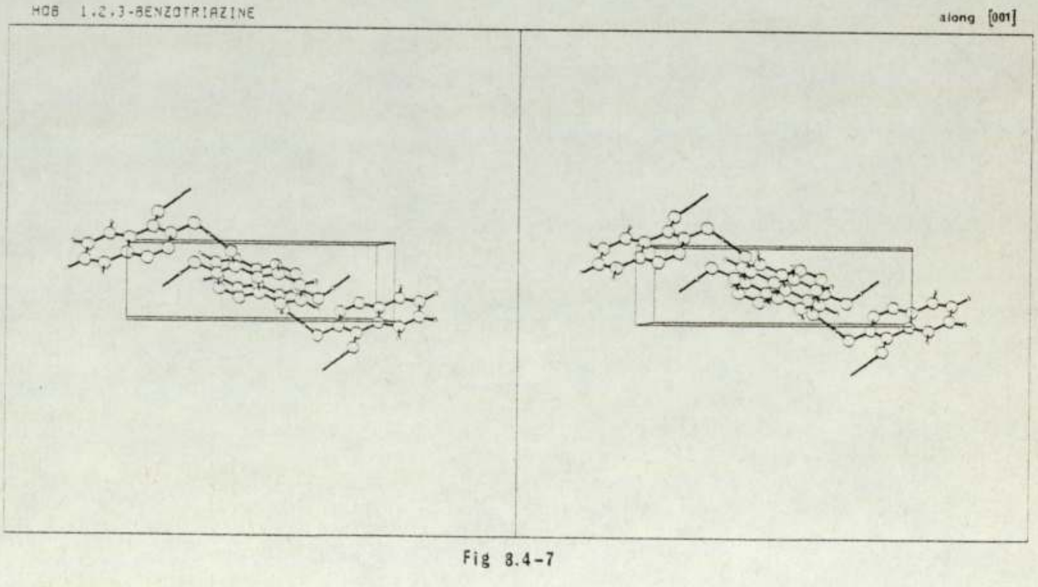


Fig 8.4-7

HOB: FRACTIONAL COORDINATES

	X	Y	Z
N(1)	.5740(3)	.7140(14)	.4174(4)
N(2)	.6511(3)	.5963(15)	.4249(4)
N(3)	.6615(2)	.4037(12)	.3297(4)
O(3)	.7469(2)	.2729(12)	.3512(4)
C(4)	.5973(3)	.3135(14)	.2264(5)
O(4)	.6151(2)	.1254(11)	.1521(3)
C(4A)	.5106(3)	.4547(13)	.2204(4)
C(5)	.4355(3)	.4075(15)	.1189(5)
C(6)	.3549(3)	.5452(15)	.1192(5)
C(7)	.3455(4)	.7411(16)	.2171(5)
C(8)	.4185(4)	.7888(16)	.3165(5)
C(8A)	.5010(3)	.6532(14)	.3171(5)

Table 8-1

HOB: ANISOTROPIC TEMPERATURE FACTORS

	U11	U22	U33	U23	U13	U12
N(1)	.0629(29)	.0927(44)	.0603(30)	-.0052(28)	.0157(24)	-.0129(30)
N(2)	.0579(30)	.0995(46)	.0546(29)	.0017(30)	.0039(23)	-.0137(31)
N(3)	.0360(22)	.0764(36)	.0501(26)	.0094(25)	.0021(18)	-.0077(24)
O(3)	.0349(19)	.1076(40)	.0705(27)	.0188(26)	-.0089(17)	.0023(22)
C(4)	.0406(27)	.0603(38)	.0424(29)	.0095(26)	.0052(22)	-.0100(26)
O(4)	.0422(20)	.0918(32)	.0600(24)	-.0133(23)	.0069(16)	.0032(21)
C(4A)	.0374(25)	.0567(36)	.0456(28)	.0069(25)	.0113(21)	-.0104(24)
C(5)	.0413(27)	.0733(41)	.0491(31)	.0014(29)	.0098(22)	-.0047(29)
C(6)	.0384(27)	.0760(45)	.0683(36)	.0063(33)	.0062(24)	-.0011(28)
C(7)	.0492(33)	.0829(51)	.0764(41)	.0041(36)	.0221(30)	-.0029(32)
C(8)	.0635(35)	.0880(49)	.0630(38)	-.0096(36)	.0303(29)	-.0095(35)
C(8A)	.0504(30)	.0630(41)	.0473(30)	.0055(28)	.0116(24)	-.0176(29)

Table 8-2

HOB: HYDROGEN COORDINATES
AND ISOTROPIC TEMPERATURE FACTORS

	X	Y	Z	UISO
H(5)	.4421	.2608	.0413	.0830
H(6)	.2968	.5030	.0425	.0484
H(7)	.2810	.8552	.2144	.1338
H(8)	.4106	.9328	.3943	.0993
H(03)	.7223	.1485	.2681	.2178

NOTES:
(1) H(5),H(6),H(7) AND H(8) REFINED RIDING ON BONDED CARBON ATOMS
(2) H(03) REFINED DFIXED TO O(3): DIST=1.00(5)

Table 8-3

HOB: BOND DISTANCES

N(2)	-	N(1)	1.250(6)
N(3)	-	N(2)	1.367(7)
O(3)	-	N(3)	1.372(5)
C(4)	-	N(3)	1.363(6)
O(4)	-	C(4)	1.218(6)
C(4A)	-	C(4)	1.426(7)
C(5)	-	C(4A)	1.405(7)
C(6)	-	C(5)	1.349(7)
C(7)	-	C(6)	1.395(8)
C(8)	-	C(7)	1.372(7)
C(8A)	-	N(1)	1.387(6)
C(8A)	-	C(4A)	1.392(7)
C(8A)	-	C(8)	1.369(7)

Table 8-4

HOB: BOND ANGLES

N(2) - N(1) - C(8A)	122.0(5)
N(1) - N(2) - N(3)	117.5(4)
N(2) - N(3) - O(3)	112.5(4)
N(2) - N(3) - C(4)	128.4(4)
O(3) - N(3) - C(4)	118.9(5)
N(3) - C(4) - O(4)	121.3(5)
N(3) - C(4) - C(4A)	112.6(5)
O(4) - C(4) - C(4A)	126.1(5)
C(4) - C(4A) - C(5)	122.4(5)
C(4) - C(4A) - C(8A)	118.6(4)
C(5) - C(4A) - C(8A)	119.0(5)
C(4A) - C(5) - C(6)	119.6(5)
C(5) - C(6) - C(7)	121.0(5)
C(6) - C(7) - C(8)	119.7(5)
C(7) - C(8) - C(8A)	120.0(6)
N(1) - C(8A) - C(4A)	121.0(5)
N(1) - C(8A) - C(8)	118.4(5)
C(4A) - C(8A) - C(8)	120.6(5)

Table 8-5

HOB: LEAST-SQUARES PLANES

(a) Equations of planes in the form $AX+BY+CZ+D=0$ where X,Y and Z are the orthogonal coordinates in Å along a,b and c*:

Plane(1): $0.3806X + 0.7787Y - 0.4987Z - 3.0562 = 0$
Plane(2): $0.3902X + 0.7864Y - 0.4789Z - 3.1999 = 0$
Plane(3): $0.3856X + 0.7830Y - 0.4881Z - 3.1443 = 0$

(b) Deviations in A of atoms from planes:

Plane(1): N(1) -.004, N(2) -.003, N(3) -.011, C(4) -.010, C(4A) -.003, C(8A) .004
Plane(2): C(4A) -.011, C(5) .007, C(6) -.004, C(7) .006, C(8) -.010, C(8A) .013
Plane(3): N(1) .006, N(2) .012, N(3) .013, C(4) -.024, C(4A) -.016, C(5) .016, C(6) .009, C(7) .008, C(8) -.022, C(8A) -.002, O(3)* -.063, O(4)* -.094

(c) Dihedral angles in degrees between the planes:

(1) - (2) 1.3, (1) - (3) 0.7, (2) - (3) 0.6

*Atoms marked with an asterisk not included in the definition of the plane.

Table 8-6

Chapter 9: Steric and Electronic Control of Conformation in the 1,2,3-Benzotriazines

9.1 Introduction

Of the crystallographic investigations of the 1,2,3-benzotriazine structures reported to date (see Chapter 4) three structures contain anilino substituents in the 4-postion. These three will be denoted as follows:

DIPB:	3,4-Dihydro-3-isopropyl-4-phenylimino-1,2,3-benzotriazine (4.1-I)
AMNB:	Anhydro-2-methyl-4-o-nitroanilino-1,2,3-benzotriazinium hydroxide (4.1-IV)
PAB:	2-Propyl-4-anilino-1,2,3-benzotriazinium iodide (4.1-V)

The numbering scheme to be used in this discussion is identical to that for DIPB (see Fig 4.4-3). Torsion angles will be denoted by listing all four atoms involved, with the torsion occurring about the bond between the second and third atoms in the list.

The C(4)-N(41') bond in each of these compounds contains considerable double bond character, the bond length being in all three cases shorter than 1.34 Å. The

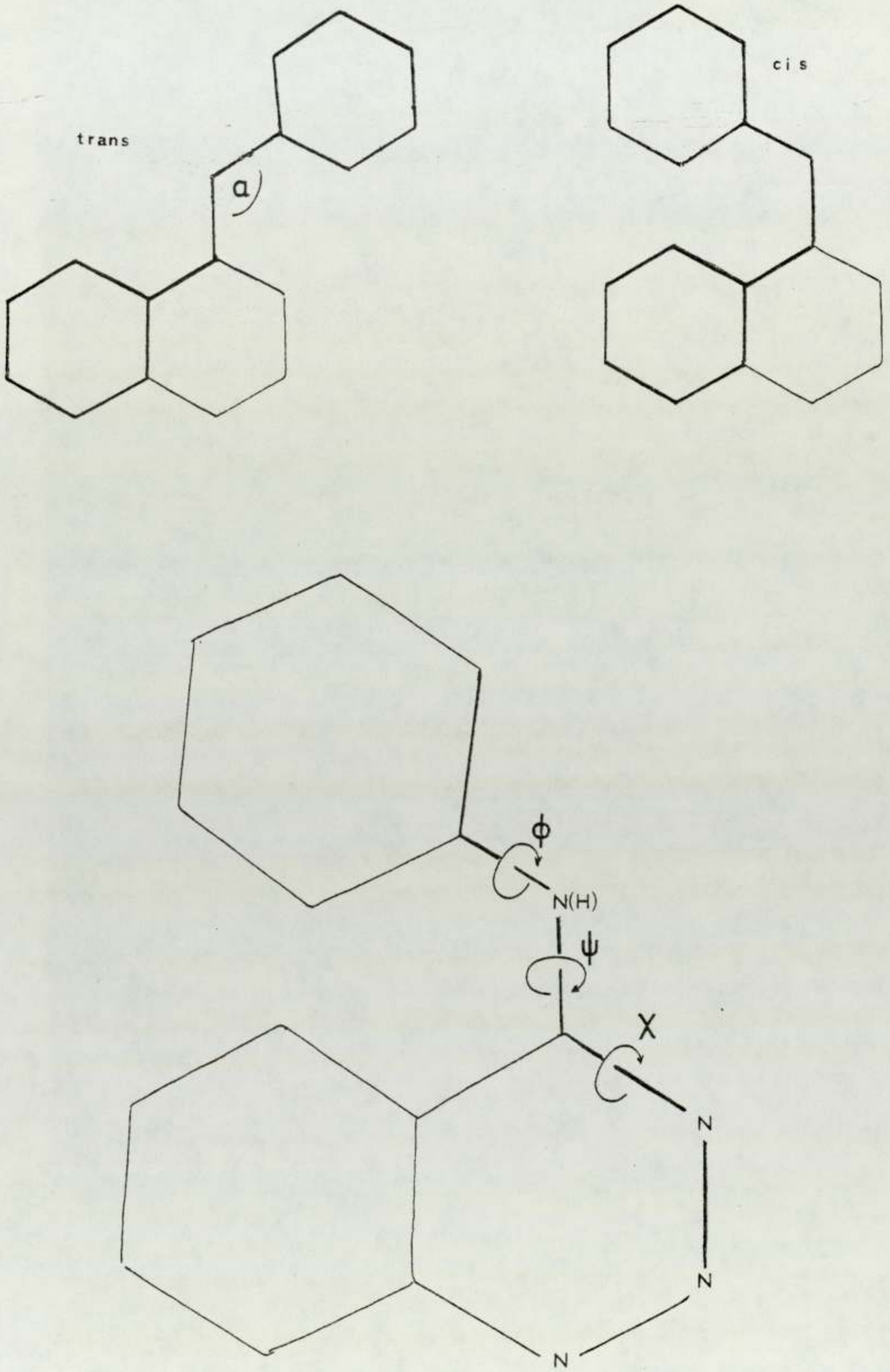
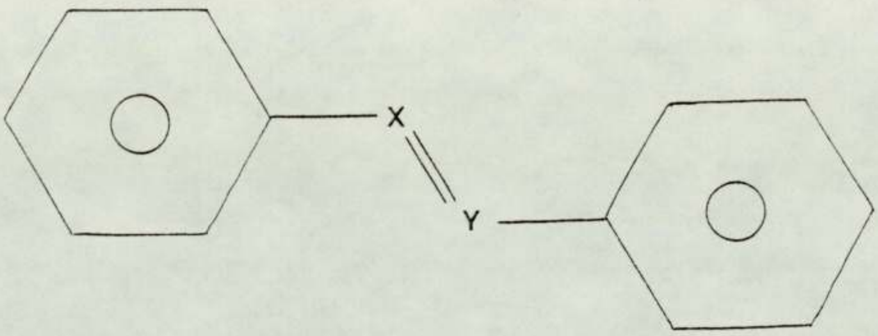


Fig 9.1-1



X= C	Y= C	Stilbene
X= C	Y= N	N-benzylideneaniline
X= N	Y= N	Azobenzene

Fig 9.1-2

Selected Conformational Parameters

	D	Δ	X	ψ	φ	θ
DIPB	1.274	0.38	-171	-177	73	77
AMNB	1.280	0.09	-178	-6	118	72
PAB	1.331	0.50	-176	+12	50	51

D = Bond distance C(4)-N(41') in Å.
Δ = Deviation in Å of C(1') from the least-squares plane through the benzotriazine rings.
X = Torsion angle along N(2)-N(3)--C(4)-N(41') in degrees.
ψ = Torsion angle along N(3)-C(4)--N(41')-C(1') in degrees.
φ = Torsion angle along C(4)-N(41')--C(1')-C(2') in degrees.
θ = Angle between the normals to the phenyl and benzotriazine rings.

Table 9.1-3

X-ray structure analyses of these compounds show that there is very limited torsion about the bond and that C(1') is approximately coplanar with the benzotriazine rings. Correlation of the C(1') deviation with the C(4)-N(41') bond distances (see Table 9.1-3) indicates that the greatest deviation is in PAB whose C(4)-N(41') bond has the weakest double-bond character, while the low deviation in AMNB is consistent with the strong double bond character associated with such a short bond length. The relatively large deviation of DIPB is quite unexpected on this basis and is a steric effect primarily produced by torsion about the bond N(2)-N(3)--C(4)-N(41') (see Table 9.1-3). The character of the bond C(4)-N(4') is influenced by the protonation state of N(41'). Protonation at N(41') in PAB has been identified in a difference Fourier synthesis, while lack of protonation in DIPB and AMNB can be inferred from the short bond length C(4)-N(41').

The restriction on rotation about the bond C(4)-N(41') limits these structures to two possible isomeric forms (see Fig 9.1-1). By analogy with the simpler molecules azobenzene, N-benzylideneaniline and stilbene (see Fig 9.1-2) these isomeric forms will be referred to by the names "stilbene-cis" and "stilbene-trans". CNDO molecular orbital calculations on azobenzene (Ljunggren and Wettermark,1971) and N-benzylideneaniline (Warren,et al,1971) indicate that cis-trans isomerisation takes place by the opening up of the X-Y-C bond (see Fig 9.1-2) rather than by rotation about the X-Y bond. The two forms can thus be considered as distinct isomers rather than two different conformations of the same isomer. In this study the term conformation will be used to describe changes in the torsion angles indicated in Figure 9.1-2, other than changes of approximately $\pm 180^{\circ}$ in ψ.

9.2 Discussion of Torsion

The program COORD (Dewar and Baird, University of Texas) was modified by Dr. C.H.Schwalbe of Aston University to allow for variable torsion about up to three bonds. (The modified version has been designated "ROTACORD".) All interatomic distances are recalculated after each rotation and non-bonded contacts flagged as "rare" if $r_1 \leq r_{ij} \leq r_2$ and "impossible" if $r_{ij} \leq r_1$ where r_1 and r_2 are the distances listed in columns 1 and 2 respectively of Table 9.2-1.

The geometry of the 4-anilino substituted 1,2,3-benzotriazines can be described principally in terms of three torsion angles:

(i) χ about N(2)-N(3)--C(4)-N(41'),

(ii) ψ about N(3)-C(4)--C(N41')-C(1')

(iii) ϕ about C(4)-N(41')--C(1')-C(2')

(see Fig 9.1-1). The right-hand screw is positive sign convention is used throughout. The value of χ can be expected to be close to 180° because of the sp^2 hybridisation of C(4). Because of the double-bond

ROTACORD

Programmed: M.J.S.Dewar and N.C.Baird

Modified: C.H.Schwalbe

Modified version allows variable torsion angles.

Following contact distances flagged:

	"Rare"	"Impossible"
H...H	2.0 Å	1.8 Å
C...H	2.5	2.3
C...C	3.0	2.8
N...H	2.45	2.25
N...C	2.95	2.75
N...N	2.9	2.7
O...H	2.35	2.15
O...N	2.80	2.60
O...C	2.80	2.65

Table 9.2-1

ROTACORD CONTACTS

DIPB

$\phi=90^\circ$ no contacts

$\phi=80^\circ$ C(2')...H(5) 2.47 Å (R)

$\phi=70^\circ$ C(2')...H(5) 2.27 Å (I)

Observed $\phi=72.6^\circ$

Observed H(5)...C(1') 2.38 Å

Observed H(5)...C(2') 2.81 Å

AMNB

$\phi=140^\circ$ N(3)...C(6') 2.71 Å (I)
N(3)...H(6') 2.25 Å (R)
C(4)...C(6') 2.87 Å (R)

$\phi=125^\circ$ N(3)...C(6') 2.90 Å (R)
C(4)...C(6') 2.96 Å (R)

$70 < \phi < 120^\circ$ no contacts

$\phi=65^\circ$ N(3)...O(1) 2.63 Å (R)

$\phi=60^\circ$ N(3)...O(1) 2.45 Å (I)

Observed $\phi=117.9^\circ$

Observed N(3)...C(6') 3.20 Å

PAB

$62^\circ < \phi < 90^\circ$ no contacts

$\phi=58^\circ$ N(3)..C(2') 2.90 Å (R)

$\phi=46^\circ$ N(3) ..C(2') 2.70 Å (I)

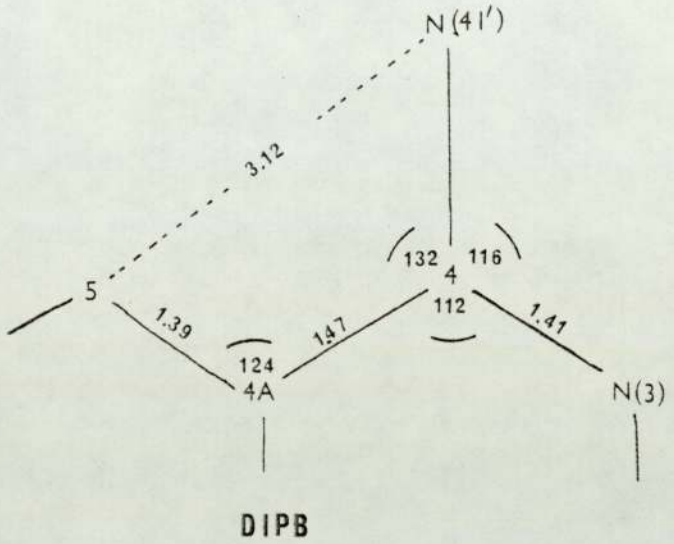
Observed $\phi=49.8^\circ$

Observed N(3)...C(2') 2.88 Å

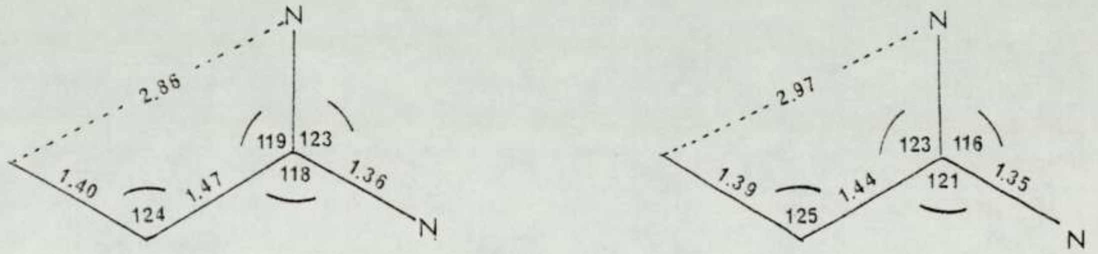
Sterically limiting contact distances generated by rotation about N(41')--C(1').

DIPB and AMNB are symmetric about $\phi=90^\circ$.

Table 9.2-2



DIPB



AMNB

PAB

Fig 9.2-3

character of C(4)-N(41') ψ can be expected to take values near either 0 or 180° . Torsion ϕ about N(41')-C(1') is the greatest factor in bringing the phenyl substituent out of coplanarity with the benzotriazine rings: the single-bond character of this bond indicates that the rotation is subject only to steric hindrance.

The extent to which torsion can occur along the bond N(41')-C(1') was explored using ROTACORD. Starting with a model derived from our observed crystallographic bond distances and angles and a completely planar benzotriazine moiety with N(41') and C(1') in the same plane as the benzotriazine rings, coordinates were generated for various values of and sterically-limiting contacts noted (Table 9.2-2).

DIPB

The observed ϕ is lower than can be expected on the basis of avoidance of steric hindrance, the observed contact H(5)...C(2') being much longer than that expected on the basis of a planar benzotriazine moiety. Minor distortions in the plane of the benzotriazine rings relieve steric hindrance and allow the phenyl to move into a position of greater coplanarity. As can be seen in Table 9.1-3 the principal distortion is torsion about N(3)-C(4) (χ =-171°) rather than torsion about C(4)-N(41') (ψ =-177°). The strong double-bond character prevents large deviation from ψ =180°. The torsion angle about

N(2)-N(3)--C(31)-C(32) is -82° which brings the C(31)-C(32) AND C(31)-C(33) bonds in the isopropyl group into a position where they are pointing away from the phenyl substituent. The close contact H(5)...C(1') is unaffected by the variation in ϕ; nevertheless comparison between the structures suggests that some bond-stretching and bond angle bending may be involved in the relief of this steric effect (see Fig 9.2-3).

AMNB

The observed ϕ is within the range of values giving geometries completely clear of steric hindrance (Table 9.2-2). The observed contact distance N(3)...C(6') of 3.20 Å indicates that the phenyl substituent could be brought into greater coplanarity with the benzotriazine rings. Crystal packing forces may account for the large ϕ since the observed arrangement allows stacking of the benzotriazine rings with a separation of 3.56 Å (Schwalbe and Hunt,1976). AMNB is the least crowded of these structures. Since $\phi > 90^{\circ}$ the nitro group is on the opposite side of the phenyl ring to the benzotriazine moiety. There is very little torsion about C(4)-N(41') ($\psi = -6^{\circ}$) and N(41') is close to being coplanar with the benzotriazine moiety ($X = -178^{\circ}$). Both these effects may be explained in terms of the lack of need for distortion to overcome steric hindrance. The nitro group is sharply inclined to the phenyl substituent, the torsion angle C(1')-C(2')--N(2')-O(1) being -38°. The unit C(2')-NO_2 is almost coplanar, the deviation of C(2') from the plane of the other three atoms -- 0.02 Å (Schwalbe,et al,1978) -- is of the same order of magnitude as the positional uncertainties.

<u>PAB</u>

The observed ϕ is lower than that expected on the basis of planar geometry of the benzotriazine rings. The observed N(3)...C(2') is 2.88 Å at ϕ=49.8° while a planar calculation gives a contact of 2.90 Å at ϕ=58° (Table 9.2-2). Steric hindrance is relieved mainly by torsion (ψ=12°) about C(4)-N(41'). The n-propyl substituent is far from being planar with torsion angles 113° about N(3)-N(2)--C(21)-C(22) and -63° about N(2)-C(21)--C(22)-C(23).

9.3 Possible cis-trans Isomerism

Of the three 1,2,3-benzotriazine structures included in this survey, two exist in the "stilbene-trans" isomeric form, while one, DIPB, exists in the "stilbene-cis" isomeric form. This observation begs the question as to whether considerations of minimisation of electronic energy determine the form adopted, or whether steric hindrance prevents the molecules from taking on the opposite isomeric form.

To explore the question of steric influences in possible cis-trans isomerism the coordinates for the opposite isomers were generated by rotating the C(4)-N(41') bond through 180°. When the interatomic distances were calculated, a number of forbidden contacts for each isomer were noted, for example:

DIPB trans: H(31) ... C(1') 1.28 Å
AMNB cis: H(5) ... C(1') 1.62 Å
PAB cis: H(5) ... C(1') 1.97 Å

In the calculation of the above contact distances, no allowance was made for alterations in the bond distances and angles to alleviate these steric effects. It would appear that the molecules AMNB and PAB adopt the "stilbene-trans" isomeric form to avoid the contact between H(5) and C(1'). Neither of these molecules has substituents at the 3-postition; thus the trans isomer is left unhindered. In the case of DIPB, however, the contact between the phenyl group and the isopropyl group creates even greater steric problems. The molecule, therefore adopts the cis isomeric form. The steric problems of contact between H(5) and C(1') are relieved by minor alterations in the intervening bonds-- mainly stretching along C(4A)-C(4) and increasing the bond angle C(4A)-C(4)-N(41') (see Fig 9.2-3).

9.4 Molecular Orbital Calculations

The investigation of the steric influences on conformation in the 1,2,3-benzotriazines was complemented with the calculation of the electronic energies for selected conformations. The CNDO/2 approximation method, the theory of which is described elsewhere (Pople and Beveridge, 1970 - pp75-79) was employed in the calculations, which were carried out on the CDC7600 computer at U.M.R.C.C. employing a version of the CNDO/2 program written by Segal (1966). The program calculates the electronic and electrostatic repulsion energies separately, with the electronic energy (E) and total energy (T) output in atomic units of energy (a.u.) where

$$1 \text{ a.u.} = 4.36 \times 10^{-18} \text{ J}$$

or, more usefully, 1 a.u. of energy per molecule is the equivalent of approximately 2700 kJ/mol. In the tables the atomic units have been kept, but since the magnitudes of the energies involved are very great in comparison with the differences between them -- the latter being of interest in the present study -- the energies have been referred to an arbitrary baseline (E_o and T_o).

Because the calculation is done on the basis of atomic positions alone and without reference to the bonds between them -- the resonance integrals corresponding to chemical bonding are calculated within the program -- the method is influenced by pseudo-bonding effects, i.e. significant resonance integrals for pairs of atoms which are geometrically close, but not chemically bonded. Care must, therefore, be taken in interpreting energies where the conformation is sterically crowded.

The cis-trans isomerisation of DIPB was investigated (a) by considering the process of rotation about the double bond C(4)-N(41') and (b) by opening up the bond angle C(4)-N(41')-C(1') (inversion) (see Table 9.4-1). The calculations show that the "stilbene cis" isomer is electronically the high energy one, but when repulsion effects are considered, the total energy is lower than in the "stilbene-trans" isomer. This observation is further evidence that DIPB adopts the cis isomeric form in order to relieve steric hindrance between the phenyl and isopropyl groups. The calculations indicate an energy barrier to rotation (maximum total energy aproximately 145 kJ/mol above the total energy for the "stilbene trans" isomer, 360 kJ/mol above that for the cis isomer). For inversion, going from the trans to the cis form, there is a rapid decrease in energy, followed by a low potential barrier (approximately 90 kJ/mol above the total energy for the cis form). Comparing the energies for the PAB-cis and -trans forms (see Tables 9.4-2 and 9.4-3), in the idealised form $\phi=90^{\circ}$, $\psi=0^{\circ}$ or 180° the total energy is slightly less (approximately 10kJ/mol) for the trans than for the cis form. The electronic energy is, however, considerably lower for the "stilbene-cis" isomeric form. Once again the molecule appears to adopt the form less favoured electronically out of steric considerations. A similar situation occurs in the comparison of isomeric forms for AMNB (see Table 9.4-5). The total energy for the "stilbene-trans" form is lower (by approximately 85 kJ/mol), although the "stilbene-cis" isomeric form has the lower electronic energy. In all three cases, therefore, the electronically-favoured form does not occur in the crystal structure, further confirmation that it is steric rather than electronic effects which govern the isomeric form of these molecules.

Further calculations were undertaken to study the deprotonation of the nitrogen N(41') of PAB, which is the only protonated molecule in the survey. It exists in the crystalline state in the iodide form. The calculations show that considerable energy (approximately 1840 kJ/mol) is required to remove the proton. The above discussion, of course, neglects solvent effects.

DIPB

Resistance to isomerisation by rotation ψ about C(4)-N(41') (top table) and by inversion by varying the angle a, C(4)-N(41')-C(1'). Conformations near $\psi=0$ or $a=234^\circ$ ("stilbene trans") are influenced by pseudo-bonding effects. $E_o=-950$ a.u., $T_o=-175$ a.u. $X=180^\circ$ and $\phi=90^\circ$ throughout.

ψ	180°	150°	120°	90°	60°	30°	0°
$E - E_o$	30.6880	30.6542	29.5936	24.1675	15.3653	5.8434	2.1334
$T - T_o$	2.3469	2.3588	2.3904	2.4165	2.4798	2.4631	2.4258

(cis) rotation (trans)

a	126°	153°	180°	207°	234°
$E - E_o$	30.6880	42.6994	42.7221	30.7115	2.1334
$T - T_o$	2.3469	2.3654	2.3794	2.3656	2.4258

(cis) inversion (trans)

Table 9.4-1

PAB

Comparison of selected "stilbene-cis" and "stilbene-trans" conformations. $\phi=72.5^\circ$, $\psi = -168^\circ$ represents the sterically optimised "stilbene-cis" conformation with an allowance of ±12° torsion about C(4)-N(41'). Torsion angles in the n-propyl group and χ are held at 180 throughout the calculations. $E_0=-950$ a.u., $T_0=-175$ a.u..

(cis)	$\phi=90^\circ$ $\psi=180^\circ$	$\phi=72.5^\circ$ $\psi=-168^\circ$
$E - E_0$	26.2551	26.7521
$T - T_0$	1.6957	1.6941

(trans)	$\psi=0^\circ$			$\psi=12^\circ$
	$\phi=0^\circ$	$\phi=70^\circ$	$\phi=50^\circ$	$\phi=50^\circ$
$E - E_0$	31.6235	36.2399	34.9602	34.9076
$T - T_0$	1.6939	1.6915	1.6898	1.6917

Table 9.4-2

PA8

Effect of deprotonation.

Deprotonation was considered in two steps:
(1) removal of the hydrogen
(2) reduction of the C(4)-N(41') bond length from 1.33 to 1.28 Å.

$E_0=-950$ a.u., $T_0=-175$ a.u.

$\Phi=90^\circ$, $\chi=180^\circ$ and $\Psi=0^\circ$ throughout.

(trans)	Protonated D=1.33 Å	Deprotonated D=1.33 Å	Deprotonated D=1.28 Å
$E - E_0$	36.6942	52.3742	50.1887
$T - T_0$	1.6921	2.3706	2.3745

Table 9.4-3

DIPB

Effects of torsion of the "stilbene-cis" isomer.

Because of steric hindrance the phenyl substituent is constrained to near perpendicularity to the benzene rings. The third column represents the crystallographically-observed conformation. $E_0=-950$ a.u., $T_0=-175$ a.u.

(cis)	$\Psi=180^\circ$		$\Psi=-177^\circ$
	$\chi=180^\circ$		$\chi=-171^\circ$
	$\Phi=90^\circ$	$\Phi=80^\circ$	$\Phi=73^\circ$
$E-E_0$	30.6880	30.5566	30.5660
$T-T_0$	2.3469	2.3470	2.3490

Table 9.4-4

AMNB

Effects of torsion in the "stilbene-trans" isomer.

Comparison of cis and trans form for $\Phi=90^\circ$.

$E_0=-1050$ a.u., $T_0=-205$ a.u.

	(trans)		(cis)	
	$\Psi=0^\circ$		$\Psi=180^\circ$	
	$\Phi=60^\circ$	$\Phi=90^\circ$	$\Phi=117^\circ$	$\Phi=90^\circ$
$E - E_0$	46.0927	37.9899	44.9372	9.2556
$T - T_0$	8.8659	1.9236	1.9236	1.9545

Note

$X=180^\circ$ throughout.

Table 9.4-5

The energies involved for minor conformational changes of the crystallographically observed isomeric form were calculated. The variations in energy involved in these conformational changes were very small -- within about 5 kJ/mol -- and there is no clear indication from these calculations why the molecule takes the particular conformation which is observed. There is very little difference in energy between the sterically-permitted conformations.

Chapter 10: Crystallographic Studies of DHFR Inhibitors

10.1 Introduction

The objectives of studying inhibitors of DHFR crystallographically are as follows:

(1) to observe the pattern of protonation, particularly bearing in mind the importance of protonation at N(1) to some models of DHFR inhibition;

(2) to observe the patterns of hydrogen-bonding with the object of using these as possible models for the enzyme-inhibitor complex;

(3) to observe the spatial distribution of the hydrophobic and polar components of the molecules in order to elucidate the shape of the active site and discover possible secondary sites of bonding, with particular interest in species differences;

(4) to observe subtle changes in the geometry of the molecule brought about with small chemical alterations in order to model the type of accommodation the molecules may undergo on entry into the active site.

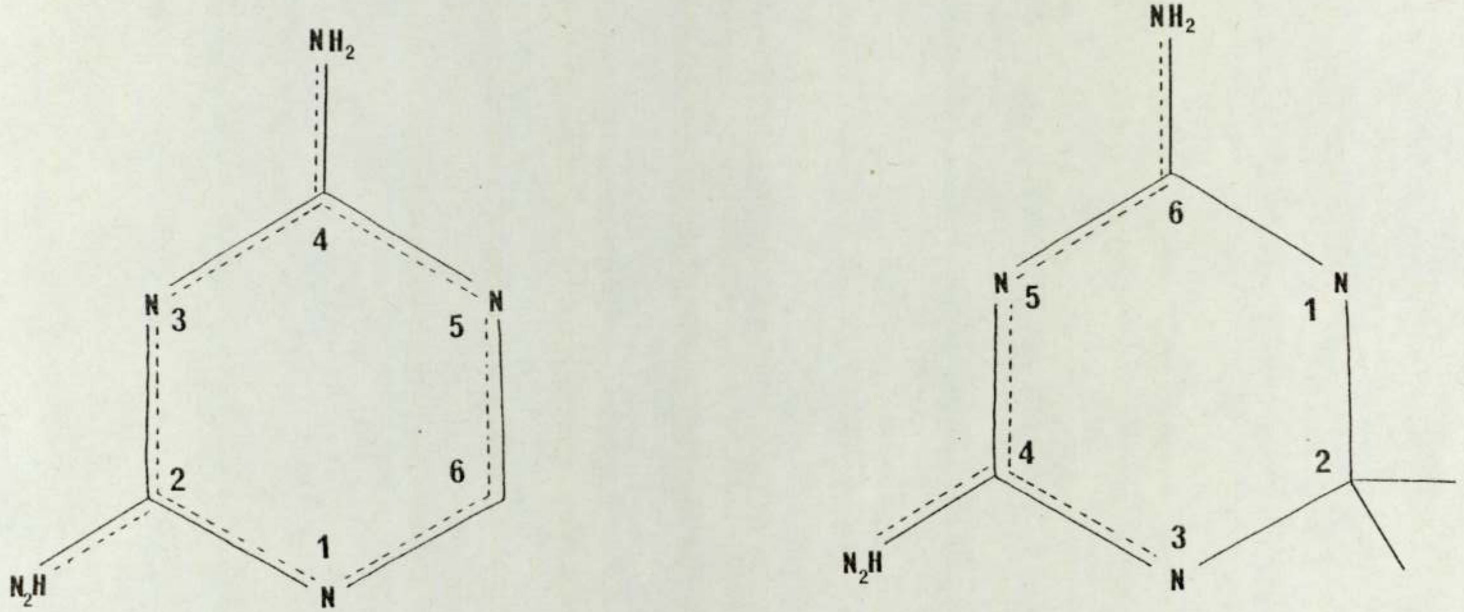
Unfortunately, of all the compounds known to have DHFR-inhibitory activity, only a small number have been investigated crystallographically. Conclusions must, therefore, be tentative, but they do give some idea about the range of values of the parameters determining the geometrical structure of these compounds. The structures with their bibliographic references are listed in Table 10-1.

10.2 Nomenclature

Discussion of the comparative geometry of these structures is, unfortunately, complicated by differences in the numbering schemes for different ring systems. The numbering scheme for the pteridines with 2 and 4 as the sites of amination is followed in the pyrimidine ring system, but not in the 1,2-dihydro- s-triazines where the sites of amination are numbered 4 and 6 (see Fig 10.2-1). In this discussion, unless otherwise stated, atoms will be referred to by their pyrimidine numbers, regardless of the ring system.

10.3 Base Pairing

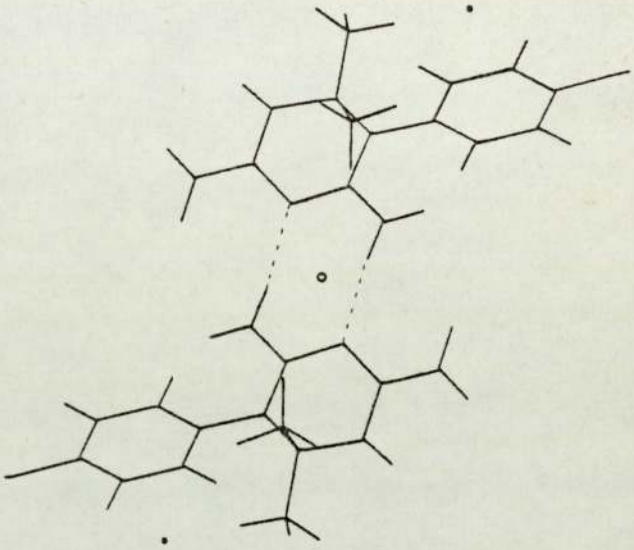
The triclinic space group $P\bar{1}$ has eight non-equivalent centres of symmetry, the monoclinic space groups $P2_1/c$ and $C2/c$ have four and the tetragonal space group $I4_1/a$ has two. In all known DHFR inhibitors one of these centres is used for base pairing of the type N(4)-H...N(3)' and



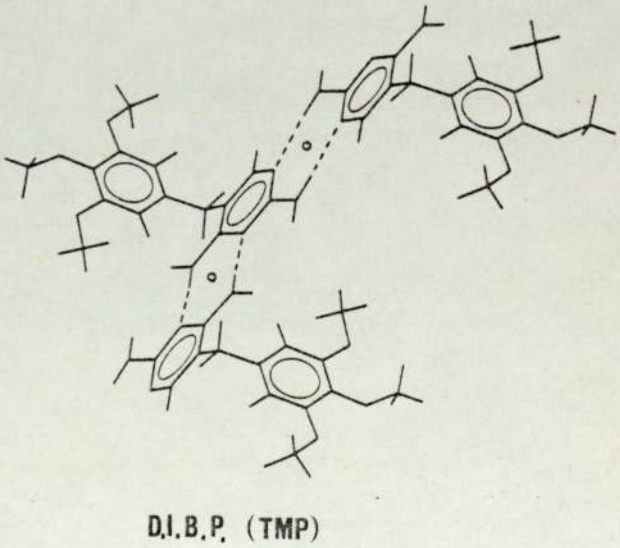
Pyrimidine Numbering Scheme

1,2 Dihydro-s-triazine Numbering Scheme

Fig 10.2-1



S.I.B.P. (CGT)



D.I.B.P. (TMP)

Fig 10.3-1

N(4)'-H'...N(3). (The primes refer to the centrosymmetrically-related atoms.) In some of the unprotonated structures base pairing of the type N(2)-H...N(1)' and N(2)'-H'...N(1) occurs across a second non-equivalent centre of symmetry, thus setting up an infinite chain of hydrogen-bonded molecules. Both types of base-pairing are illustrated in Fig 10.3-1. The former -- to be referred to as single-inversion base pairing (S.I.B.P.) -- is illustrated with the example of cycloguanil hydrochloride (top) and the latter -- double-inversion base pairing (D.I.B.P.) -- with trimethoprim (Koetzle and Williams,1976). The lower part of Fig 10.3-1 has been taken from an illustration in their paper. The protonation state and type of base pairing for each of the structures are listed in Table 10-4.

10.4 Delocalisation

A survey of the geometries of s-triazine and pyrimidine rings for these structures shows that the bonding is considerably delocalised. The N(1)-C(2) bond in unprotonated TMP and DVD and of all the protonated structures is of intermediate character, but with a π-bond order greater than 50 per cent. for all structures on the basis of the empirical equation of Fischer-Hjalmars and Sundbom (1968)

$$d = 1.458 - .18\ p$$

where d = bond distance and p = π-bond order. The endocyclic bonds C(2)-N(3) and N(3)-C(4) are clearly resonance hybrids with the π-bond orders ranging from 50 to 80 per cent. The exocyclic C-N bonds, too, exhibit intermediate character between single and double bonds. There are important differences between the structures which may result from intermolecular interactions (see Sec 10.5). The geometry about C(6) clearly depends on the hybridisation state of the carbon atom. In the sp^3-hybridised structures (TZT and CGT) the bonds approach single bond lengths and the planarity of the ring system is perturbed (see Table 10-10). The naphthalene characteristic (see Sec 1.6) of N(2)-C(2) is found in the fused ring systems DAQ and TCQ, although not in DMBH, perhaps because the protonated nitrogen is less like the benzene C-H than the unprotonated species. As expected on the basis of VSEPR theory (see Sec 1.2) the bond angles at N(1) are greater for the protonated than for the unprotonated molecules. However, because of the enlargement of the intracyclic angles at C(2) and C(4) with amination, the angles at N(1) are less than that expected on the basis of Chatar Singh's survey (1965).

The bond lengths C(2)-N(2) are in all cases longer for the unprotonated species than for the protonated species, although this result is of marginal significance statistically, since the observed difference between the groups (Table 10.4-1) could be expected with a probability of about 10 per cent. if both came from the same population. The standard deviations were estimated here on

Distribution of C(2)-N(2) Bondlengths

	N	mean	e.s.d	Difference of means	e.s.d. of difference
Protonated	6	1.3303	.0116		
Unprotonated	4	1.3595	.0192	.0292	.0224

Table 10.4-1

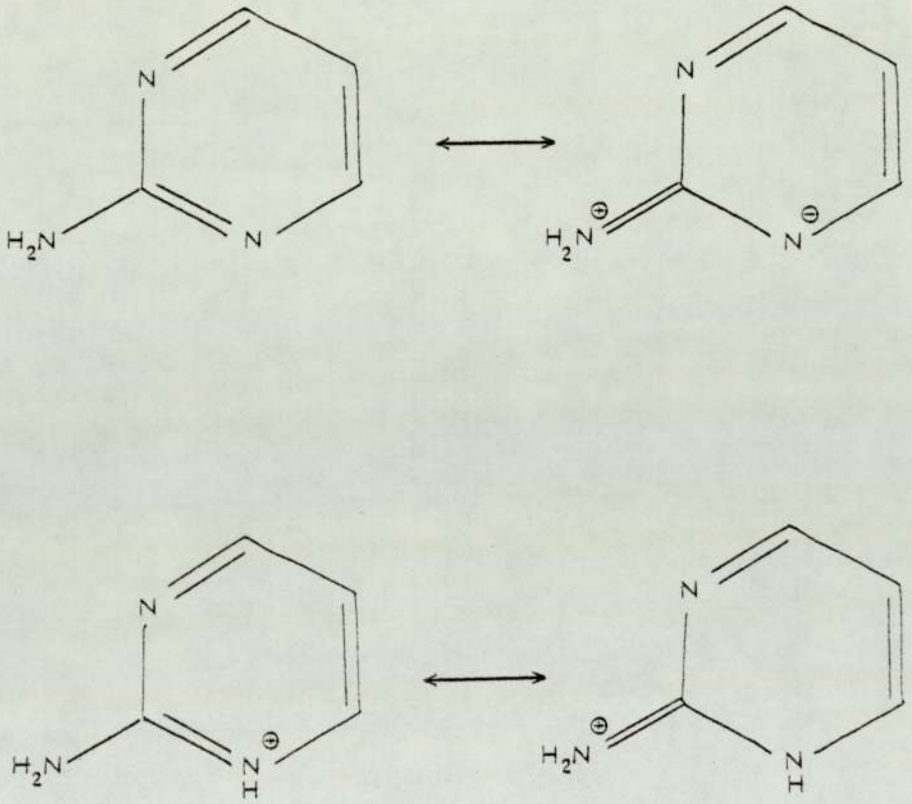


Fig 10.4-2

the basis of the distribution of published bond lengths without regard for published standard deviations, which in some cases were missing. If we assume standard deviations in the bond lengths of .005 Å on the basis of refinement, then the C(2)-N(2) bond lengths are distributed as follows: χ^2=131.7, 10 degrees of freedom (df) for all structures listed; χ^2=44.2, 3 df for the unprotonated subgroup; χ^2=26.9, 5 df for the protonated subgroup. On this basis not even the subgroups can be regarded as coming from a single population. The difference between the two groups is, however, consistent with the resonance formulae (Fig 10.4-2) where the double-bond model for the unprotonated species is rendered unfavourable by the charge separation involved. The unprotonated sub-group contains the hydrogen-bond donor-acceptor N(2)H of TCQ. The oxide TMP-O has not been included in either group. The statistical methods utilised in the discussion in this paragraph have been described elswhere (Stout and Jensen,1968 - pp 419-424).

10.5 Geometrical Flexibility

The ability of the DHFR inhibitors to take up conformations compatible with the active site of the enzyme is a prerequisite for their activity. The spatial distribution of ionic and hydrophobic components may give some clues as to the nature of the active site of the enzyme. It may also be possible to determine the range of values within which certain geometrical parameters must

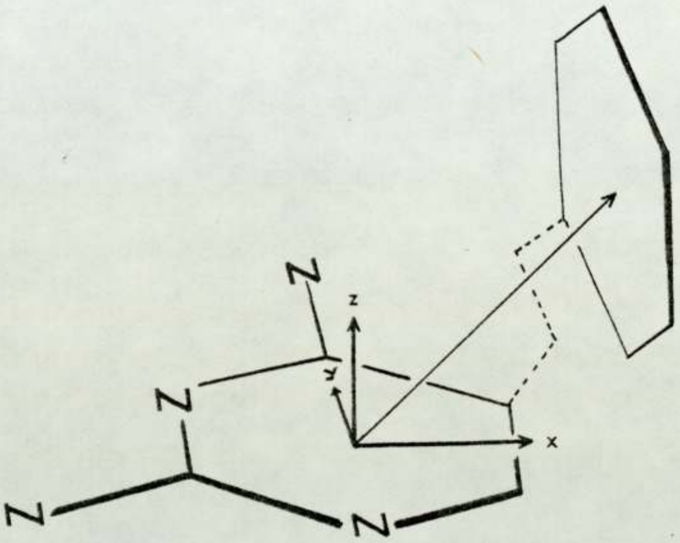


Fig 10.5 -1

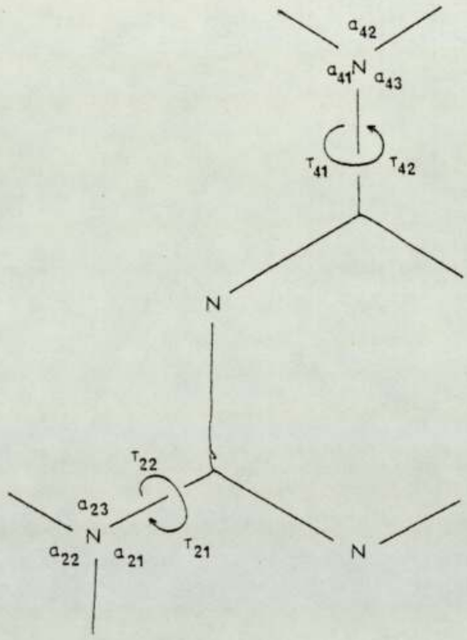
fall if the molecule is to be considered a candidate for DHFR inhibition.

The active site of DHFR consists of at least one polar and one hydrophobic locus (see Sec 1.5.4 and Sec 1.5.5). All the structures surveyed have one 2,4-diamino-substituted heterocycle and at least one aryl component, sometimes with polar subtituents. In the native folate and methotrexate the components are linked through the two-atom bridge (Pteridine-CH_2-NH-Phenyl) thus offering three degrees of freedom -- the torsion about the three linking bonds. In two of the compounds surveyed the phenyl component is fused to the heterocyle thus effectively fixing the spatial arrangement of the two components. It is probable that, on complexing to the enzyme, the quinazoline ring occupies the site of the pteridine ring and that the complexing takes place without the benefit of interaction at the hydrophobic site. In the antimalarials CGT and PMA, there is one degree of freedom about the single bond linking the two components. The antileukaemic agent TZT is similarly arranged and in addition has a second aryl component attached in the para position through a further -O-CH_2- linkage. It has been postulated that this component is active at a second hydrophobic site (Camerman, et al,1978). In the antibacterial TMP and the closely related DVD the components are linked by the two-bond -CH_2- linkage, offering two rotational degrees of freedom. Conformation analysis has shown (Koetzle and Williams,1976) that the torsion about the bond to the heterocyle (τ_1) is highly constrained while torsion about the second bond (τ_2) is relatively free. For $\tau_1=\pm 90^{\circ}$, τ_2 can take on any value. In the case of DMBH the phenyl is linked to the fused ring system by a $-CH_2-$ linkage.

In order to investigate systematically the orientation of the hydrophobic ring with respect to the heterocycle, the coordinate system shown in Fig 10.5-1 was set up. The origin is the centroid of the six-atom heterocylic ring. The x-axis lies along the extension of the midpoint of C(2)-N(3) to origin, the y-axis lies along a line from the origin to C(4) and the z-axis is perpendicular to all non-hydrogens of the heterocycle, including the amino nitrogens, with the sense of the vector chosen to make a right-handed system. Defined in this manner the angles between the axes are not exactly 90°. (The calculation of vector products is a feature unfortunately missing from the GEOM78 program.) The angles between the axes -- α_{xy}, etc -- are listed in Table 10-11. The vector $\underline{D}$ joins the centroids of the two rings and β_x, etc. are the angles that it makes with the axes. ψ is the angle between the normals of the planes. β_z and ψ are arbitrarily chosen to lie in the range 90° to 180°. There are two degrees of freedom in the model which permit this arbitrary choice: (1) the arbitrary sense of the vector perpendicular to the plane of the hydrophobic moiety and (2) the arbitrary choice of enantiomorph (all these structures are centrosymmetric).

With the exception of DAQ and TCQ -- which are unlikely to be active at the hydrophobic site of the enzyme in any case -- the parameters fall within fairly restricted ranges ($26^{\circ} < \beta_x < 53^{\circ}$; $53^{\circ} < \beta_y < 95^{\circ}$; $90^{\circ} < \beta_z < 118^{\circ}$; $4.1\ \text{Å} < D < 6.9\ \text{Å}$; $90^{\circ} < \psi < 110^{\circ}$). It will be an interesting matter as more materials are tested for DHFR-inhibitory activity and as more of these are studied crystallographically to correlate these parameters with inhibition of DHFR from various sources.

Because of the importance of hydrogen bonding in the formation of the enzyme-inhibitor complex, it would be an interesting matter to observe the geometrical arrangement of the hydrogen atoms in the amino groups. Unfortunately only two structures have been studied by neutron diffraction. The bond angles (α_{21},etc.) and torsion angles (τ_{21} ,etc.) are shown in Fig 10.5-2. The torsion angles have been defined to take on the range of values near 0° and to involve bonds on the same side of C-N as that on which the symbol appears in the diagram. The standard deviations for TMP are approximately 0.1°, while those for CGT are approximately 2°. Examination of the values of these parameters shows that each of the nitrogen atoms is sp^2 hybridised. The range of in-plane bending that is allowed appears to be about 5°, with perhaps as much as 20° torsion along the C-N bonds. This degree of flexibility may be an important feature which enhances the binding of this group of compounds to the DHFR enzyme.



	a_{21}	a_{22}	a_{23}	a_{41}	a_{42}	a_{43}	τ_{21}	τ_{22}	τ_{41}	τ_{42}
TMP	119	118	121	119	119	121	-14	6	-3	12
CGT	114	124	119	115	119	125	18	-3	2	-4

Fig 10.5-2

TMP

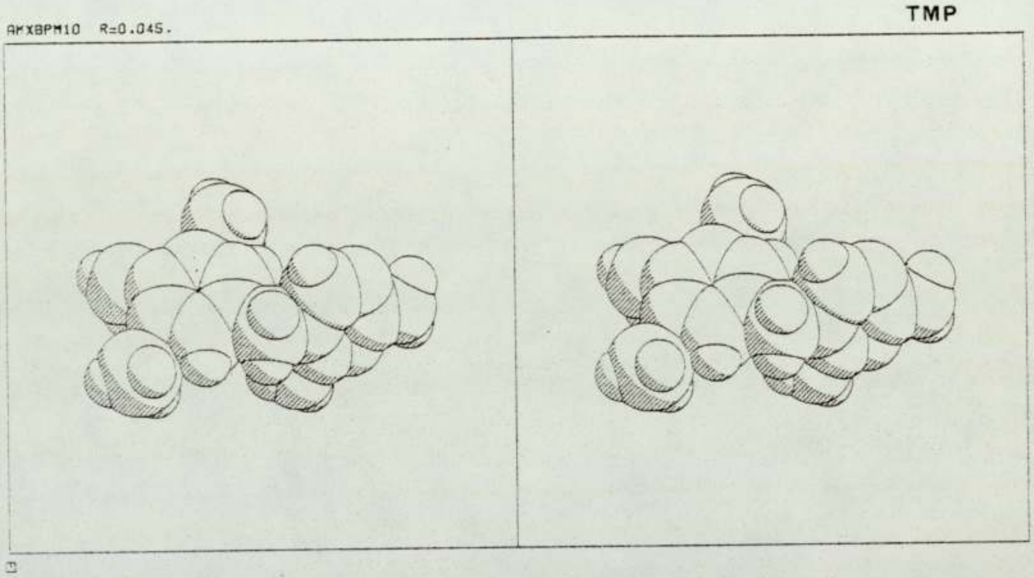


Fig 10.5-3

TMP-O

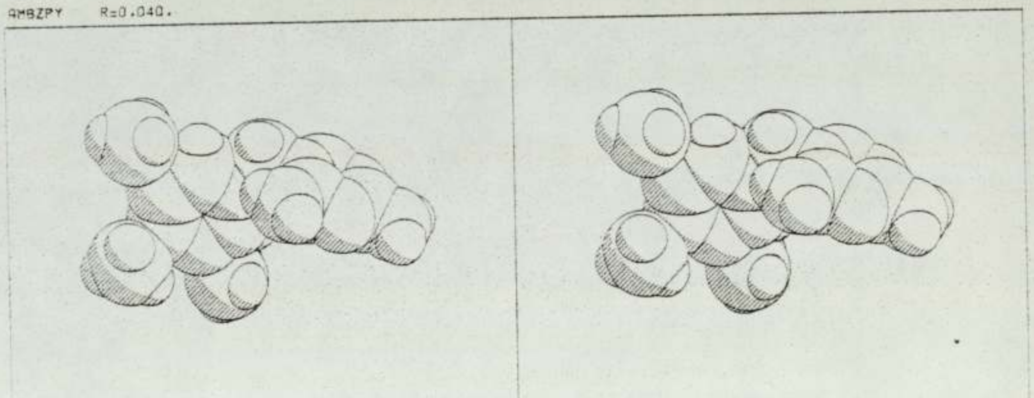


Fig 10.5-4

DMBH

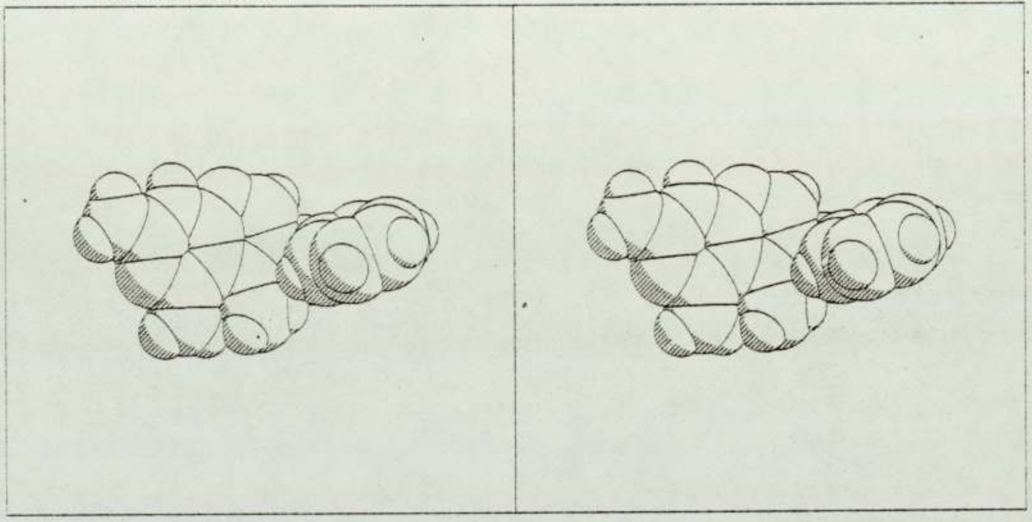


Fig 10.5-5

TCQ

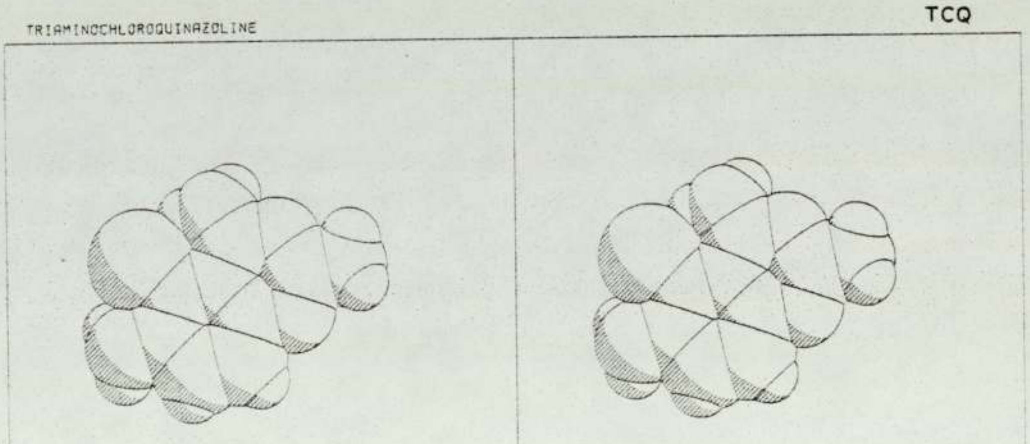


Fig 10.5-6

DAQ

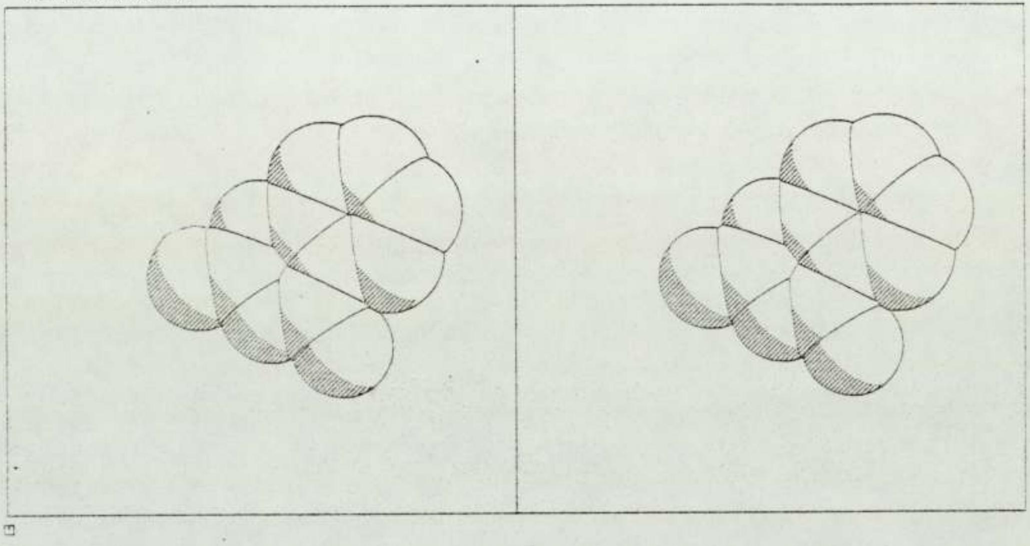


Fig 10.5-7

CGT

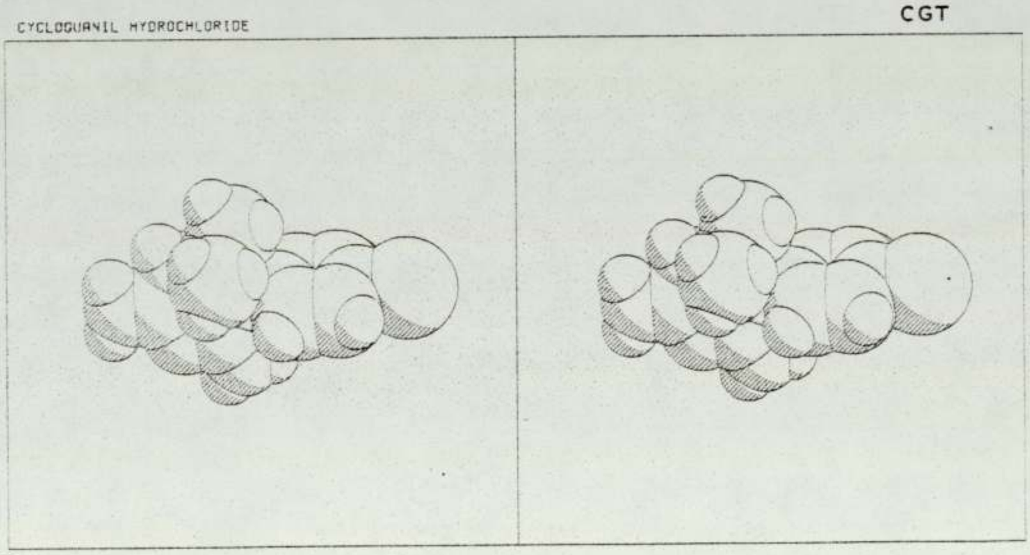
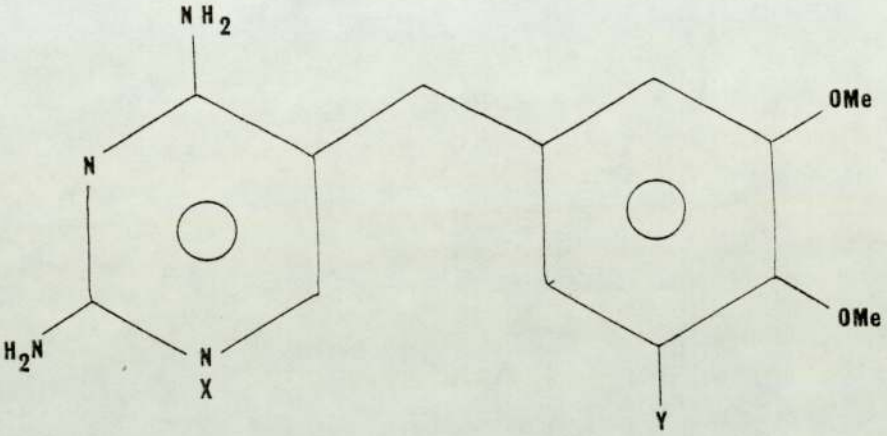
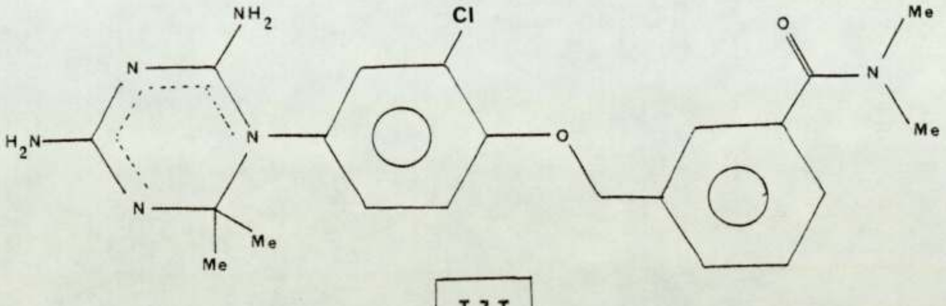


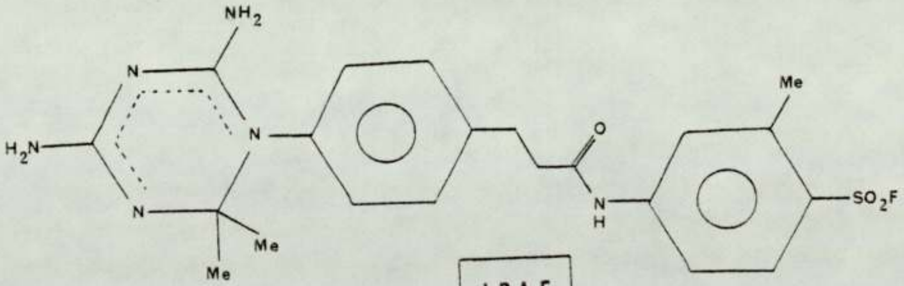
Fig 10.5-8



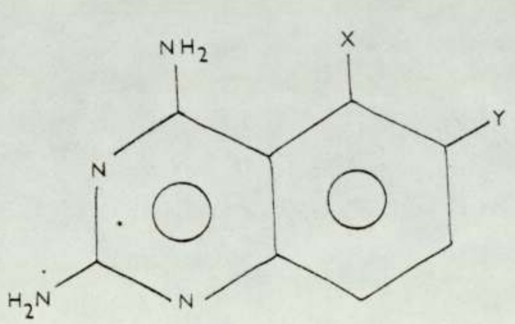
	X	Y
TMP	—	OMe
TMP-A	H	OMe
TMP-HBR	H	OMe
TMP-O	O	OMe
DVD	—	H



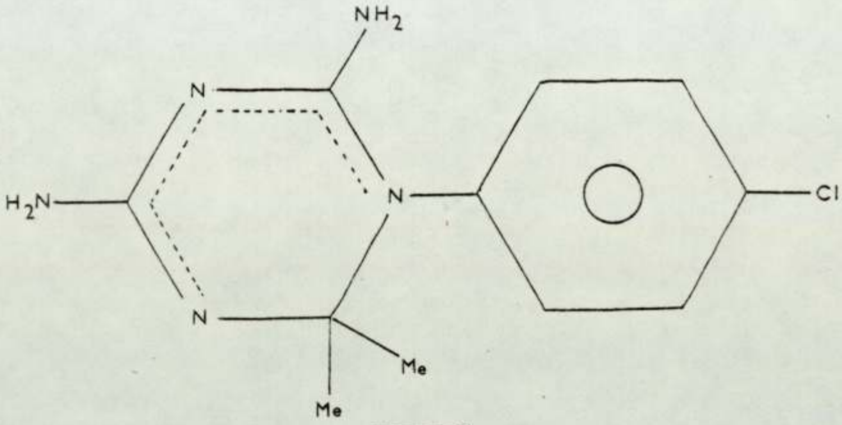
TZT



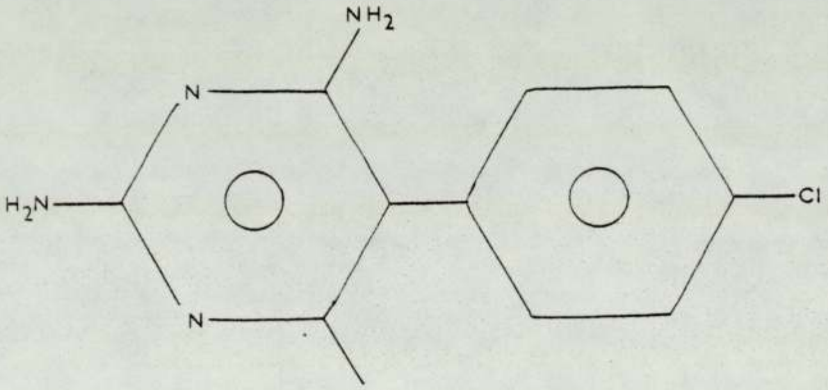
IBAF



	X	Y
TCQ	Cl	NH_2
DAQ	H	H



CGT



PMA

Structure	Trivial Name	Reference	Code[a]
TMP	Trimethoprim	Koetzle and Williams,1976	AMXBPM10
TMP-A	Trimethoprim Acetate	Haltiwanger,1971[b]	----
TMP-HBR	Trimethoprim Hydrobromide	Phillips and Bryan,1969	TMPRIM
TMP-O[c]	Trimethoprim Oxide	Oberhansli,1970	AMBZPY
DVD	Diaveridine	Koetzle and Williams,1978	----
TZT[d]	Triazinate	Camerman,et al,1978	----
IBAF[d]	"Insoluble Baker's Antifol"	Camerman,et al,1978	----
DMBH	-----	Sternglanz and Bugg,1973	MZPYPM
TCQ	Triaminochloroquinazoline	----	----
DAQ	Diaminoquinazoline	----	----
CGT	Cycloguanil Hydrochloride	Schwalbe and Hunt,1978	CYGUAN
PMA	Pyrimethamine	Phillips and Bryan,1969	DARAPR

a) Code assigned by the Cambridge Crystallographic Data Centre. Entries up to February 1979 are listed.
b) A copy of this MSc thesis was supplied by Dr T.F.Koetzle.
c) This compound is a natural metabolite of Trimethoprim.
d) Geometrical data for these compounds were supplied by Dr H.W.Smith.

Table 10-1

Structure	Chemical Name
TMP	2,4-diamino-5-(3,4,5-trimethoxybenzyl)-pyrimidine
TMP-A	2,4-diamino-5-(3,4,5-trimethoxybenzyl)-pyrimidine acetate
TMP-HBR	2,4-diamino-5-(3,4,5-trimethoxybenzyl)-pyrimidine hydrobromide
TMP-O	2,4-diamino-(3,4,5-trimethoxybenzyl)-pyrimidine-1-oxide dihydrate
DVD	2,4-diamino-5-(3',4'-dimethoxybenzyl)-pyrimidine
TZT	1-[3-chloro-4-(N-dimethyl-carbamoylbenzyloxy)] phenyl-4,6-diamino-1,2-dihydro-2,2-dimethyl-*s*-triazine ethanesulphonate
IBAF	1-[4-(N-[3'-methyl-4'-fluorosulphonyl]phenyl) propanamide] phenyl-4,6-diamino-1,2-dihydro-2,2-dimethyl-*s*-triazine ethanesulphonate dihydrate
DMBH	2,4-diamino-5-methyl-6-benzylpyrido[2,3-d] pyrimidine hydrobromide
TCQ	2,4,7-triamino-6-chloroquinazoline
DAQ	2,4-diaminoquinazoline
CGT	4,6-diamino-1-*p*-chlorophenyl-1,2-dihydro-2,2-dimethyl-*s*-triazine hydrochloride
PMA	2,4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine hydrobromide

Table 10-2

Structure	S.G.	Cell Dimensions					
TMP	$P\bar{1}$	10.52	11.22	8.07	101.2	112.2	112.6
TMP-A	$P2_1/c$	11.06	19.09	9.63	90.0	122.6	90.0
TMP-HBR	$P2_1/c$	21.88	5.03	14.48	90.0	90.7	90.0
TMP-O	$P\bar{1}$	7.85	10.70	10.40	100.1	97.4	75.8
DVD	$C2/c$	18.14	12.80	12.33	90.0	114.78	90.0
TZT	$P\bar{1}$	11.52	10.72	11.47	110.8	111.5	87.8
IBAF	$P\bar{1}$	12.93	17.52	6.57	99.1	90.4	94.1
DMBH	$P2_1/c$	23.78	5.06	14.45	90.0	120.7	90.0
TCQ	$C2/c$	29.96	3.85	17.74	90.0	109.4	90.0
DAQ	$I4_1/a$	21.59	21.59	7.55	90.0	90.0	90.0
CGT	$P2_1/c$	8.87	10.39	17.14	90.0	115.2	90.0
PMA	$P2/c$	10.89	8.56	15.23	90.0	100.2	90.0

Table 10-3

	Protonation	Base Pairing	Heterocyclic Ring System
TMP	none	DIBP	pyrimidine
TMP-A	N(1)	SIBP	pyrimidine
TMP-HBR	N(1)	(a)	pyrimidine
TMP-O	(b)	SIBP	pyrimidine
DVD	none	DIBP	pyrimidine
TZT	N(1)[c]	SIBP	s-triazine
IBAF	N(1)[c]	(a)	s-triazine
DMBH	N(1)	SIBP	pyrido [2,3-d]pyrimidine
TCQ	none	SIBP	quinazoline
DAQ	none	SIBP	quinazoline
CGT	N(1)[c]	SIBP	s-triazine
PMA	N(1)	(a)	pyrimidine

a) no coordinates or base-pairing scheme published
b) oxidised at N(1)
c) refers to pyrimidine numbering scheme - N(3) in the original

Table 10-4

BOND DISTANCES

Structure	N(1)-C(2)	C(2)-N(3)	N(3)-C(4)
TMP[a]	1.343	1.346	1.343
TMP-A[b]	1.34	1.34	1.35
TMP-HBR[c]	---	---	---
TMP-O[a]	1.355	1.332	1.343
DVD[b]	1.340	1.347	1.346
TZT[d]	1.334	1.336	1.351
IBAF[d]	1.335	1.328	1.342
TCQ[d]	1.305	1.355	1.324
DAQ[e]	1.297	1.351	1.327
DMBH[a]	1.338	1.316	1.360
CGT[e]	1.342	1.333	1.348
PMA[b]	1.35	1.34	1.35

a) bond distances calculated using GEOM78 with coordinates from the Cambridge database
b) bond distances taken from publication
c) no coordinates or bond distances published
d) bond distances taken from a pre-publication manuscript
e) structure solved at Aston

Table 10-5

ENDOCYCLIC BOND ANGLES

Structure	C6-N1-C2	N1-C2-N3	C2-N3-C4	N3-C4-X5[a]
TMP[b]	115.4	125.4	117.5	121.6
TMP-A[c]	119	123	118	122
TMP-HBR[d]	---	---	---	---
TMP-O[b]	119.6	121.8	119.3	121.2
DVD[c]	114.1	126.8	116.8	121.4
TZT[e]	119.7	122.3	116.7	122.8
IBAF[e]	121.1	121.7	116.7	123.3
TCQ[e]	116.1	126.5	118.6	121.3
DAQ[f]	116.2	127.4	117.2	121.4
DMBH[b]	122.3	122.4	120.7	118.4
CGT[f]	119.5	122.0	117.1	123.2
PMA[c]	121	123	118	122

a) X = Carbon or Nitrogen
b) bond angles calculated using GEOM78 with coordinates from the Cambridge database
c) bond angles taken from publication
d) no coordinates or bond angles published
e) bond angles taken from a pre-publication manuscript
f) structure solved at Aston

Table 10-6

EXOCYCLIC BOND ANGLES

Structure	N1-C2-N2	N3-C2-N2	N3-C4-N4	X5[a]-C4-N4
TMP[b]	116.7	117.9	116.8	121.6
TMP-A[c]	118	119	117	121
TMP-HBR[d]	---	---	---	---
TMP-0[b]	117.4	120.5	117.0	121.7
DVD[c]	116.6	116.6	116.7	122.0
TZT[e]	118.2	119.5	116.9	120.3
IBAF[e]	120.2	118.0	116.8	120.0
TCQ[e]	118.5	114.9	114.7	124.0
DAQ[f]	117.7	114.8	117.5	121.1
DMBH[b]	118.2	119.3	117.1	124.4
CGT[f]	117.8	120.1	117.7	119.1
PMA[c]	117	120	116	121

a) X = Carbon or Nitrogen
b) bond angles calculated using GEOM78 with coordinates from the Cambridge database
c) bond angles taken from publication
d) no coordinates or bond angles published
e) bond angles taken from a pre-publication manuscript
f) structure solved at Aston

Table 10-7

TORSION ANGLES AND HETEROCYCLE WIDTH

Structure	C4-N3--C2-N2	C2-N3--C4-N4	Dist N1-N4
TMP[a]	174.7	178.2	4.10
TMP-A[b]	177.9	180.0	4.04
TMP-HBR[c]	---	---	---
TMP-O[a]	-179.6	-175.8	4.04
DVD[b]	-176.4	-178.2	4.11
TZT[c]	---	---	---
IBAF[e]	---	---	---
TCQ[d]	179.0	179.9	4.11
DAQ[e]	-179.4	-177.9	4.08
DMBH[a]	-177.7	-178.1	3.98
CGT[e]	177.3	-171.9	3.97
PMA[c]	---	---	---

a) parameters calculated using GEOM78 with coordinates from the Cambridge database
b) parameters calculated from published coordinates
c) no coordinates published
d) parameters calculated from coordinates contained in a pre-publication manuscript
e) structure solved at Aston

Table 10-8

GEOMETRY OF THE AMINO GROUPS

Structure	C(2)-N(2)	C(4)-N(4)	Deviation from L.S. Plane[a] N(2)	 N(4)
TMP[b]	1.349	1.351	-.069	.033
TMP-A[c]	1.332	1.330	-.007	-.002
TMP-HBR[d]	---	---	---	---
TMP-O[b]	1.327	1.335	-.010	.043
DVD[c]	1.353	1.351	.037	-.018
TZT[e]	1.322	1.319	---	---
IBAF[e]	1.317	1.320	---	---
DMBH[b]	1.335	1.261	-.027	.010
TCQ[f]	1.374[i]	1.347	.003	.012
DAQ[g]	1.362	1.332	.019	-.024
CGT[g]	1.326	1.321	-.033	.048
PMA[h]	1.35	1.33	---	---

a) plane defined by six-membered heterocyclic ring plus amino nitrogens
b) parameters calculated using GEOM78 with coordinates from the Cambridge database
c) parameters calculated from published coordinates
d) no coordinates or bond lengths published
e) bond lengths taken from a pre-publication manuscript -- deviations not calculated
f) parameters calculated with coordinates from a pre-publication manuscript
g) structure solved at Aston
h) bond distances taken from publication -- no coordinates published
i) this amino group is partially sp^3 hybridised and the site of hydrogen bond acceptance

Table 10-9

GEOMETRY AT C(6)

Structure	X5 - C6	N1 - C6	N1-C6-X5[a]	Deviation of C6[b]
TMP[c]	1.379	1.343	124.8	-.003
TMP-A[d]	1.363	1.346	122.9	.003
TMP-HBR[e]	---	---	---	---
TMP-O[c]	1.359	1.353	121.6	.002
DVD[d]	1.364	1.347	125.6	.003
TZT[f]	1.491	1.459	105.1	---[gk]
IBAF[f]	1.477	1.437	106.6	---[k]
DMBH[c]	1.381	1.366	118.9	.020
TCQ[h]	1.419	1.373	123.3	.008
DAG[i]	1.403	1.373	121.9	-.002
CGT[i]	1.492	1.464	105.4	-.224[k]
PMA[j]	1.38	1.37	119	---

a) X = Carbon or Nitrogen
b) from plane defined by six-membered heterocyclic ring plus amino nitrogen atoms
c) parameters calculated using GEOM78 with coordinates from the Cambridge database
d) parameters calculated from published coordinates
e) neither geometrical data nor coordinates published
f) parameters taken from a pre-publication manuscript
g) deviation of C(6) not calculated but known to be about 0.2 Å
h) parameters calculalated from coordinates taken from a pre-publication manuscript
i) structure solved at Aston
j) bond lengths and angle taken from publication -- no coordinates published
k) C(6) sp^3 hybridised

Table 10-10

POSITION OF THE HYDROPHOBIC GROUP

Structure	α_{xy}	α_{xz}	α_{yz}	β_x	β_y	β_z	D	ψ
TMP[a]	91.9	90.7	90.4	37.0	64.1	111.9	5.09	110.7
TMP-A[a]	91.0	90.4	90.8	43.5	59.9	117.9	5.02	93.1
TMP-HBR[b]	---	---	---	---	---	---	---	---
TMP-O[a]	91.7	89.7	90.6	45.6	54.5	115.6	5.06	92.2
DVD[a]	92.0	89.4	89.5	52.3	53.2	120.1	4.93	104.3
TZT[c]	---	---	---	---	---	---	---	---
IBAF[c]	---	---	---	---	---	---	---	---
DMBH[ad]	92.5	90.4	90.0	26.0	84.5	115.1	6.83	95.1
TCQ[ad]	92.6	89.6	89.9	1.6	94.2	90.1	2.42	178.8
DAQ[ad]	92.6	90.0	90.0	1.6	92.9	91.6	2.39	177.1
CGT[a]	91.7	87.6	90.1	32.2	59.6	90.5	4.18	93.0
PMA[b]	---	---	---	---	---	---	---	113[e]

a) Tabulation of the spatial distribution of phenyl components. α_{xy}, α_{xz} and α_{yz} are the angles between the molecular axes as defined in the text (see Fig 10.5-1) -- β_x, β_y and β_z are the angles that the inter-ring vector makes with the axes and D is its length. ψ is the dihedral angle between the planes: the definition of the heterocyclic plane includes the amino nitrogen atoms. Parameters have been calculated using GEOM78 with coordinates from sources given in the footnote to Table 10-9. Plane vector directions have been defined so that β_z and ψ are in the range 90° to 180°.

b) coordinates unavailable

c) parameters not calculated

d) phenyl fused to the heterocycle

e) interplanar angle taken from publication -- exact definition of the plane not given.

Table 10-11

Appendix A: Structure Factor Tables

Observed and calculated structure factors are listed. The agreement for various groups of reflexions is listed following the structure factors. The parameter V is defined by the equation:

$$V = 100 \left[\frac{N \sum \omega \Delta^2}{n \sum \omega} \right]^{\frac{1}{2}}$$

where $\Delta = |Fobs| - |Fcalc|$. The summation in the numerator is taken over the n reflexions in the group and the summation in the denominator is taken over all reflexions. N is the total number of reflexions.

These tables were compiled with use of the program SHELX.

```
OBSERVED AND CALCULATED STRUCTURE FACTORS FOR   DIPB 1,2,3-BENZOTRIAZINE - P21,N                                PAGE  1

H  K  L    FO   FC      H  K  L    FO   FC      H  K  L    FO   FC      H  K  L    FO   FC      H  K  L    FO   FC

2  0  0    47  -46      4  5  0    17   17      6  9  0     4    4      3 15  0    25  -24      3  0  1    36   32
4  0  0    38   34      5  5  0    11  -10      0 10  0    19   19      5 15  0    10    8      5  0  1     9   -8
6  0  0    11  -10      6  5  0    12  -12      1 10  0    19   18      6 15  0     3   -3      7  0  1    12   11
1  1  0    18  -18      8  5  0     6   -6      2 10  0    18   19      0 16  0     7    7     -8  1  1     5    5
2  1  0    33  -31      9  5  0     5    5      3 10  0     9  -10      1 16  0    19  -20     -7  1  1    12   13
3  1  0     1   -1      0  6  0    34  -36      4 10  0     3    3      2 16  0     6   -7     -6  1  1     3   -3
4  1  0    15  -13      1  6  0    18   22      5 10  0     5   -5      3 16  0    22   21     -5  1  1    17  -17
5  1  0     4   -5      2  6  0    11   12      6 10  0     2   -2      4 16  0    13   12     -4  1  1     5    5
8  1  0     5    5    - 3  6  0     1   -2      7 10  0     1    0      6 16  0     4    3     -3  1  1    42   43
9  1  0     3   -3      4  6  0    18  -17      8 10  0     3   -3      1 17  0     5    4     -2  1  1    26   27
0  2  0    12  -12      5  6  0    19   19      1 11  0     6   -6      2 17  0    13   12      0  1  1    36   37
1  2  0    34   34      6  6  0     3    4      2 11  0    20   20      3 17  0     5    5      2  1  1    56  -55
2  2  0    10  -12      7  6  0     5    5      3 11  0     3    3      4 17  0     5    5      3  1  1     5   -7
3  2  0    43  -42      8  6  0     4   -3      5 11  0     5   -4      5 17  0     8   -8      4  1  1    26   25
4  2  0     9   -9      1  7  0    21   24      6 11  0     3   -2      0 18  0    18   17      5  1  1    11   11
5  2  0     4   -4      2  7  0    21  -22      0 12  0    13  -15      2 18  0    17  -14      6  1  1     6   -6
6  2  0     8    8      3  7  0    24   23      1 12  0    23  -22      3 18  0    11  -11      8  1  1     9    9
7  2  0    13  -13      4  7  0    22   21      2 12  0    14   14      4 18  0     5    4     -9  2  1     5    5
9  2  0     6    6      5  7  0     4   -3      3 12  0     4    4      5 18  0     6    6     -8  2  1     1   -1
1  3  0    20   19      6  7  0     5   -4      4 12  0    20  -21      1 19  0     1    2     -7  2  1     6   -6
2  3  0    24  -23      7  7  0     4    4      5 12  0    14  -13      2 19  0     8    7     -6  2  1    14   13
3  3  0     7   -9      8  7  0     4    4      1 13  0     5    5      3 19  0     3    3     -4  2  1    10    8
4  3  0    20  -19      0  8  0    36  -37      2 13  0    13  -12      4 19  0     4   -4     -3  2  1     6    6
5  3  0     4    3      1  8  0    20   21      3 13  0     5   -7      5 19  0     2    2     -2  2  1    54  -51
6  3  0     9    7      2  8  0     8   10      4 13  0     9   -9      0 20  0     7   -6     -1  2  1     1    0
7  3  0     1   -2      3  8  0     7   -7      5 13  0     6    6      2 20  0     3    4      0  2  1    17  -20
8  3  0     5   -4      4  8  0     1   -1      6 13  0     7    7      4 20  0     1   -2      1  2  1    14   12
1  4  0    40   46      5  8  0     7   -6      7 13  0     3   -3      3 21  0     7    7      2  2  1    64  -60
2  4  0    18  -21      6  8  0     7   -6      0 14  0    18  -19      0 22  0     4   -4      3  2  1    16   17
3  4  0     8   -8      7  8  0     5    5      1 14  0     3   -2      2 22  0     2   -2      4  2  1    15   12
4  4  0    13   13      8  8  0     3    4      2 14  0    11   11     -9  0  1     4   -4      5  2  1     3    3
5  4  0    10    9      1  9  0     3    4      3 14  0     7    6     -7  0  1     2    2      6  2  1     6    7
6  4  0     4    4      2  9  0    15   12      4 14  0     3    3     -5  0  1    18   17      7  2  1     4   -5
1  5  0    31  -33      3  9  0    14  -12      5 14  0     2    2     -3  0  1    42   42     -9  3  1     1    1
2  5  0    19  -17      4  9  0     4    3      6 14  0     4    4     -1  0  1    35  -38     -8  3  1     2   -2
3  5  0     4    4      5  9  0    10   10      2 15  0    18  -18      1  0  1    39  -40     -7  3  1     7    7
```

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OBSERVED AND CALCULATED STRUCTURE FACTORS FOR   DIPS 1,2,3-BENZOTRIAZINE - P21,N                                 PAGE  2

 H  K  L   FO   FC     H  K  L   FO   FC     H  K  L   FO   FC     H  K  L   FO   FC     H  K  L   FO   FC

-6  3  1    6    6    -1  5  1    4   -4     3  7  1    2   -3    -8 10  1    9    9     3 12  1    9    9
-5  3  1   13   12     0  5  1    2   -1     4  7  1    2    1    -7 10  1    5    5     4 12  1    9    9
-4  3  1   10    8     1  5  1   23   26     5  7  1    2   -2    -6 10  1    6   -6     5 12  1    5    5
-3  3  1   22  -22     2  5  1   15   16     6  7  1   11   10    -4 10  1    9    8     6 12  1    2    2
-2  3  1   32  -34     3  5  1   30  -28     7  7  1    2    2    -3 10  1    7   -6    -8 13  1    2    2
-1  3  1    3   -4     4  5  1    2   -2    -9  8  1    4    4    -2 10  1    3    4    -7 13  1    3    3
 0  3  1   10  -15     5  5  1   14   13    -8  8  1    2   -2    -1 10  1    8   -7    -6 13  1    7   -7
 1  3  1   51   52     8  5  1    6   -5    -7  8  1    2    2     0 10  1   17   15    -5 13  1    2   -2
 2  3  1   18   16    -9  6  1    4   -4    -6  8  1    7    7     2 10  1    7    6    -4 13  1   18   19
 3  3  1    6   -7    -8  6  1    2    2    -5  8  1   11   10     3 10  1   12  -12    -3 13  1   14  -15
 4  3  1   12  -11    -7  6  1    4    5    -4  8  1   17  -16     4 10  1    5   -5    -2 13  1    5    5
 5  3  1    2   -2    -6  6  1    5   -5    -3  8  1   13  -12     5 10  1    2    1    -1 13  1   11  -11
 6  3  1    5   -4    -5  6  1    6    5    -2  8  1   41   41     6 10  1    2   -3     0 13  1    8   -7
 7  3  1    2    2    -4  6  1   17  -17    -1  8  1   38   41    -8 11  1    3   -3     1 13  1   10  -10
 8  3  1    7   -7    -3  6  1   22   21     0  8  1    2   -2    -6 11  1    1    1     2 13  1    6    6
-8  4  1    2   -2    -2  6  1    3    3     1  8  1   10   13    -5 11  1   12  -11     3 13  1   14   14
-7  4  1    3   -4    -1  6  1    2   -2     2  8  1    7    6    -4 11  1    4   -4     4 13  1   14  -15
-6  4  1    7   -7     0  6  1   27  -28     3  8  1   19  -19    -3 11  1   13   14     5 13  1   10   -9
-5  4  1   25  -25     1  6  1    5    7     4  8  1   18   15    -2 11  1   25   25     6 13  1    1   -1
-4  4  1    2    3     2  6  1    6   -7     5  8  1   11   10    -1 11  1    2    2    -7 14  1    3   -3
-3  4  1   13  -16     3  6  1   16  -15     6  8  1    4   -4     0 11  1   33  -34    -5 14  1   12  -12
-2  4  1    6   -8     4  6  1    8   -6     7  8  1    6   -7     1 11  1   14   14    -4 14  1    2    2
-1  4  1   12  -12     5  6  1    2   -2    -8  9  1    3    3     2 11  1   10    9    -3 14  1   11  -11
 0  4  1   20   23     6  6  1    7   -7    -7  9  1    2    2     3 11  1    2   -3    -2 14  1    8    9
 2  4  1   12   11     7  6  1    2    2    -4  9  1    2   -2     4 11  1   12  -12    -1 14  1    6    6
 3  4  1   11   12    -9  7  1    3    3    -3  9  1    7   -6     5 11  1    4    3     0 14  1    8   -8
 4  4  1    7   -6    -8  7  1    5   -5    -2  9  1    2   -2     6 11  1    3    3     1 14  1    3   -3
 5  4  1   14  -13    -7  7  1    9   -9    -1  9  1    2   -3     7 11  1    2    2     3 14  1   14   13
 7  4  1    3    3    -5  7  1   14   14     0  9  1    2   -3    -6 12       6    6     4 14  1   12   12
 8  4  1    3    3    -4  7  1   24  -23     1  9  1   10  -11    -5 12  1   11   11     6 14  1    3    4
-9  5  1    3   -4    -3  7  1    5    4     2  9  1    9   10    -4 12  1    7   -8    -5 15  1    7    7
-7  5  1    4   -4    -2  7  1    6   -7     3  9  1   16  -17    -2 12  1    7   -8    -4 15  1    2   -2
-6  5  1    3    4    -1  7  1   20  -21     4  9  1    1    2    -1 12  1   20  -20    -3 15  1   15  -15
-5  5  1    4    4     0  7  1    7   10     5  9  1    2    1     0 12  1    6   -6    -2 15  1    7    6
-3  5  1   14   12     1  7  1    8    7     7  9  1    4   -4     1 12  1    5   -6    -1 15  1   16   15
-2  5  1    3   -3     2  7  1    4   -4     8  9  1    2    3     2 12  1    9  -10     0 15  1   11  -11
```

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ØBSERVED AND CALCULATED STRUCTURE FACTØRS FØR   DIPB 1,2,3-BENZØTRIAZINE - P21,N                         PAGE  3

 H  K  L   FØ   FC      H  K  L   FØ   FC      H  K  L   FØ   FC      H  K  L   FØ   FC      H  K  L   FØ   FC

 1 15  1   12  -12      0 18  1   14   13      4  0  2   20   20     -8  3  2    2    3     -3  5  2   15   17
 2 15  1   27   27      1 18  1    4   -4      8  0  2    1   -1     -7  3  2    1   -1     -2  5  2   17  -16
 3 15  1   10   10      2 18  1    4   -4    -10  1  2    2   -2     -6  3  2    3   -3     -1  5  2   22  -24
 5 15  1    3   -3      3 18  1    4   -4     -8  1  2    3   -3     -5  3  2    5    4      0  5  2   34  -38
 6 15  1    3   -3      4 18  1    3   -3     -6  1  2    5    4     -4  3  2    8    7      1  5  2   11  -12
-7 16  1    2   -2     -5 19  1    3   -3     -5  1  2    3   -2     -3  3  2   40   43      2  5  2    2    2
-6 16  1    8   -7     -3 19  1    9    9     -4  1  2    3   -3     -2  3  2   52   56      3  5  2   11  -12
-5 16  1    2   -2     -2 19  1    5    6     -3  1  2   18  -18     -1  3  2   41  -45      4  5  2   10    8
-4 16  1    8    7     -1 19  1   10  -10     -2  1  2   48   52      0  3  2    8   -6      5  5  2    5   -5
-3 16  1    2    2      0 19  1    2    2     -1  1  2   36   38      1  3  2    8   -7      6  5  2    2    1
-2 16  1    7   -6      1 19  1    8    7      0  1  2    8   -7      2  3  2   21   19      7  5  2    2    2
-1 16  1   20   19      2 19  1    7   -6      1  1  2   46   44      3  3  2   41  -38      8  5  2    1    2
 0 16  1    7   -6      3 19  1    4   -3      2  1  2   31  -34      4  3  2    9    9     -9  6  2    4   -4
 1 16  1    4    5      4 19  1    4   -4      3  1  2   44   43      5  3  2    5   -5     -7  6  2    2    2
 2 16  1    9    8     -4 20  1    5    4      4  1  2   19   18      7  3  2    8    8     -6  6  2    8    7
 3 16  1   10  -10     -3 20  1    2   -2      5  1  2    5    5      8  3  2    3   -3     -5  6  2    8    8
 4 16  1   22  -21     -2 20  1    8   -8      6  1  2   18  -17     -7  4  2    7    6     -4  6  2    2   -2
 5 16  1    2   -2     -1 20  1    7   -7      7  1  2    5   -5     -6  4  2   13   14     -3  6  2    9    6
 6 16  1    3    3      0 20  1    4    3      8  1  2    4    4     -5  4  2    1    1     -2  6  2    9   -9
-6 17  1    5   -5      1 20  1    1   -1     -9  2  2    6    5     -4  4  2    9    7     -1  6  2    3   -3
-5 17  1    8    7      2 20  1    1   -1     -8  2  2    3   -4     -3  4  2   34   35      0  6  2    2   -3
-4 17  1    2    3      4 20  1    2   -2     -7  2  2    5    5     -2  4  2   23  -24      1  6  2    3   -4
-3 17  1    6    7     -3 21  1    2   -1     -6  2  2    2    2     -1  4  2    5   -5      2  6  2   21   19
-2 17  1   18  -19     -2 21  1    6   -5     -5  2  2   20  -19      0  4  2   21   19      3  6  2    9    8
-1 17  1   21   19      0 21  1    4    4     -4  2  2   36  -36      1  4  2   27  -27      4  6  2    6   -7
 0 17  1   12   12      1 21  1    2   -2     -3  2  2    7    9      2  4  2   13  -12      5  6  2    4    3
 1 17  1    4   -4      2 21  1    2   -2     -2  2  2   39   44      3  4  2   11  -11      6  6  2    2    2
 2 17  1   18  -16     -3 22  1    1    1     -1  2  2   41   41      4  4  2    3    2     -7  7  2    3    3
 3 17  1    3    3      1 22  1    3    2      0  2  2   11  -12      6  4  2    8   -7     -6  7  2    2   -2
 4 17  1   19   19      2 22  1    2    2      1  2  2   65   59      7  4  2    5   -5     -5  7  2    3   -3
 5 17  1    3   -2     -8  0  2   13   12      2  2  2    3   -1     -9  5  2    2   -2     -4  7  2   20  -21
-6 18  1    6    6     -6  0  2   28  -27      3  2  2   37  -35     -8  5  2    3    3     -3  7  2    4    4
-5 18  1    5    4     -4  0  2   17   19      4  2  2    5    5     -7  5  2    2   -2     -2  7  2   23   23
-4 18  1    3   -3     -2  0  2   45  -49      5  2  2    4    4     -6  5  2   12  -13     -1  7  2   19  -16
-2 18  1   12  -12      0  0  2   26   25      7  2  2    7   -7     -5  5  2    1   -1      0  7  2   44  -45
-1 18  1    1    1      2  0  2   67  -66     -9  3  2    3    3     -4  5  2   14  -16      1  7  2   21  -21
```

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OBSERVED AND CALCULATED STRUCTURE FACTORS FOR   DIPB 1,2,3-BENZOTRIAZINE - P21.N                        PAGE  4

  H  K  L   FO   FC      H  K  L   FO   FC      H  K  L   FO   FC      H  K  L   FO   FC      H  K  L   FO   FC

  2  7  2    5    4     -7 10  2    4    4      0 12  2    3   -4      0 15  2    8   -9     -3 19  2    9   -8
  3  7  2    6    5     -6 10  2    3   -3      1 12  2   10   11      1 15  2    1    0     -2 19  2    3    3
  4  7  2    4    5     -5 10  2    5    5      2 12  2   14   14      3 15  2   14  -13     -1 19  2   12  -11
  5  7  2    4   -5     -4 10  2    6    6      3 12  2    6   -6      4 15  2    5    4      0 19  2   10    9
  6  7  2    5   -5     -2 10  2    7   -6      4 12  2    9   -8      5 15  2   10   10      1 19  2    5    5
 -9  8  2    2    2     -1 10  2   17  -16      6 12  2    6    6      6 15  2    5    5      2 19  2    3   -3
 -7  8  2    3   -3      0 10  2   16  -17     -8 13  2    3   -3     -7 16  2    2    2      3 19  2    2    2
 -6  8  2    5   -6      1 10  2    6    6     -7 13  2   13   13     -6 16  2    1    1      4 19  2    2    1
 -5  8  2    3    2      2 10  2    4    4     -5 13  2    2    2     -5 16  2    8    7     -5 20  2    1   -1
 -4  8  2    8    8      3 10  2    5   -6     -4 13  2    6    6     -4 16  2    4    4     -3 20  2    2    3
 -3  8  2   28  -26      4 10  2    7   -6     -3 13  2    4   -4     -2 16  2   10  -11     -2 20  2    4    4
 -2  8  2   31   32      5 10  2   12   13     -2 13  2    8   10     -1 16  2   20   18     -1 20  2    4    4
 -1  8  2   15  -15      6 10  2    3    3     -1 13  2    9   -9      0 16  2    7   -7      0 20  2    2    2
  0  8  2    5   -4     -7 11  2   13   13      0 13  2    3   -2      1 16  2   31  -29      1 20  2    3    3
  1  8  2   12   11     -6 11  2    9    9      1 13  2    2    2      3 16  2   28   23      2 20  2    2    2
  2  8  2   19   17     -5 11  2    7   -7      2 13  2    4    6      5 16  2    7   -6     -3 21  2    3    3
  3  8  2    9  -10     -4 11  2    1    2      6 13  2    3   -3     -6 17  2    2    2     -2 21  2    3   -3
  4  8  2    4    4     -3 11  2   11  -12     -7 14  2    1   -1     -5 17  2    3   -3     -1 21  2    6   -7
  7  8  2    4    4     -2 11  2    2    0     -6 14  2    5    5     -4 17  2    2   -2      1 21  2    4    4
 -9  9  2    4    4     -1 11  2   10    8     -5 14  2    7   -7     -1 17  2   11   13     -3 22  2    2    3
 -8  9  2    6    6      0 11  2   15   15     -3 14  2    4    5      0 17  2    2    1     -2 22  2    1   -1
 -7  9  2   18  -17      1 11  2   10    9     -2 14  2    3    3      1 17  2   15  -14     -1 22  2    2   -2
 -6  9  2    3   -3      2 11  2    9   -8     -1 14  2    8    8      3 17  2    7    6      0 22  2    1    1
 -5  9  2    6    6      3 11  2    7    7      0 14  2    3   -2      4 17  2    1   -2     -9  0  3    3    3
 -4  9  2   13   14      4 11  2    7   -6      1 14  2    3    3      5 17  2    2   -2     -7  0  3    8   -8
 -3  9  2   27  -26      5 11  2    1    2      2 14  2    8   -8     -6 18  2    7   -7     -5  0  3    5   -5
 -2  9  2    5   -5      6 11  2    3   -4      3 14  2    4   -3     -5 18  2    6   -5     -3  0  3   16   17
 -1  9  2   38   39      7 11  2    6   -6      4 14  2    4   -4     -4 18  2    8    7     -1  0  3    8   -5
  0  9  2   24   24     -8 12  2    5   -6      5 14  2   14  -14     -3 18  2    5    5      1  0  3   19   20
  1  9  2   10   -9     -7 12  2   13  -12      6 14  2    2   -2     -2 18  2    6   -7      3  0  3   32   32
  2  9  2    3    2     -6 12  2    4   -4     -7 15  2    6   -6     -1 18  2   15  -17      5  0  3   32  -31
  3  9  2    3    3     -5 12  2    5    5     -6 15  2    4   -4      0 18  2   11   10      7  0  3   11   10
  4  9  2    4   -4     -4 12  2   10  -10     -5 15  2    1    2      3 18  2    1   -3    -10  1  3    3   -3
  5  9  2    5    5     -3 12  2   14  -15     -3 15  2   11   11      4 18  2    5    5     -9  1  3    4    4
  6  9  2    3    4     -2 12  2    2    2     -2 15  2   14  -15     -5 19  2    2    2     -8  1  3    7   -7
 -9 10  2    6   -6     -1 12  2    8    9     -1 15  2   14   16     -4 19  2    3   -3     -7  1  3   19   18
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OBSERVED AND CALCULATED STRUCTURE FACTORS FOR DIPB 1,2,3-BENZOTRIAZINE - P21,N

H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC
-6	1	3	17	-16	-3	3	3	20	-21	2	5	3	6	-7	-4	8	3	1	-1	0	10	3	7	7
-5	1	3	10	-9	-2	3	3	20	-22	3	5	3	14	-13	-3	8	3	28	-27	1	10	3	11	-11
-4	1	3	43	44	-1	3	3	10	10	4	5	3	7	-7	-2	8	3	35	32	2	10	3	6	-5
-3	1	3	41	43	0	3	3	16	-15	5	5	3	4	3	-1	8	3	16	16	3	10	3	9	8
-2	1	3	14	-15	1	3	3	13	-12	7	5	3	3	-3	0	8	3	27	-27	4	10	3	1	2
-1	1	3	19	-18	2	3	3	32	28	-9	6	3	6	-6	1	8	3	36	-34	5	10	3	3	-4
0	1	3	32	30	3	3	3	24	-25	-8	6	3	4	-4	2	8	3	2	-2	6	10	3	3	-3
1	1	3	5	3	4	3	3	6	7	-7	6	3	5	4	3	8	3	4	5	-9	11	3	3	4
2	1	3	38	-33	5	3	3	6	5	-6	6	3	9	-8	4	8	3	1	-1	-8	11	3	10	-10
3	1	3	36	-36	6	3	3	2	-2	-5	6	3	25	-23	5	8	3	4	5	-7	11	3	4	5
4	1	3	11	11	7	3	3	2	2	-4	6	3	1	0	6	8	3	3	-3	-6	11	3	10	9
5	1	3	8	8	-9	4	3	2	-3	-3	6	3	7	8	7	8	3	1	-2	-5	11	3	8	9
6	1	3	2	-2	-8	4	3	11	10	-2	6	3	2	2	-9	9	3	2	-2	-4	11	3	5	6
7	1	3	2	1	-6	4	3	7	7	-1	6	3	20	-19	-8	9	3	4	4	-3	11	3	2	2
-10	2	3	7	-7	-5	4	3	11	12	0	6	3	5	-6	-6	9	3	3	3	-2	11	3	4	3
-9	2	3	6	6	-4	4	3	4	-5	1	6	3	6	5	-5	9	3	2	2	-1	11	3	8	9
-8	2	3	4	3	-3	4	3	1	1	2	6	3	11	12	-4	9	3	8	8	0	11	3	4	-3
-7	2	3	5	-5	-2	4	3	9	8	3	6	3	6	6	-3	9	3	1	-1	1	11	3	9	-9
-5	2	3	23	22	-1	4	3	3	-1	4	6	3	8	-7	-2	9	3	1	2	2	11	3	3	-4
-4	2	3	39	41	0	4	3	1	-2	-8	7	3	4	-4	-1	9	3	20	20	3	11	3	4	4
-2	2	3	9	-9	1	4	3	12	12	-6	7	3	3	3	0	9	3	20	-18	4	11	3	7	-7
-1	2	3	29	-29	2	4	3	18	17	-5	7	3	3	-3	1	9	3	5	5	5	11	3	3	3
0	2	3	12	11	3	4	3	5	-5	-4	7	3	3	-3	2	9	3	10	12	6	11	3	5	6
1	2	3	22	21	4	4	3	2	-2	-3	7	3	3	-2	3	9	3	6	6	-8	12	3	2	2
2	2	3	17	16	5	4	3	10	10	-2	7	3	32	33	4	9	3	2	-2	-7	12	3	7	7
3	2	3	25	-25	-9	5	3	9	-9	-1	7	3	17	-18	5	9	3	2	2	-5	12	3	2	-2
4	2	3	16	15	-8	5	3	7	7	0	7	3	11	10	6	9	3	3	-3	-3	12	3	4	3
5	2	3	5	4	-7	5	3	1	1	1	7	3	15	14	-9	10	3	3	-3	-2	12	3	2	-1
6	2	3	8	7	-6	5	3	12	11	2	7	3	2	2	-8	10	3	13	12	-1	12	3	4	4
7	2	3	4	-4	-5	5	3	3	-5	3	7	3	5	-4	-7	10	3	5	5	0	12	3	4	-5
-10	3	3	3	-3	-4	5	3	32	-32	6	7	3	2	1	-6	10	3	26	-25	1	12	3	10	10
-8	3	3	8	8	-3	5	3	5	-5	-9	8	3	1	2	-5	10	3	12	-13	2	12	3	1	3
-7	3	3	3	3	-2	5	3	11	10	-8	8	3	9	-8	-4	10	3	2	-2	3	12	3	8	-8
-6	3	3	2	2	-1	5	3	33	-34	-7	8	3	5	-5	-3	10	3	9	8	4	12	3	1	-2
-5	3	3	1	1	0	5	3	5	-4	-6	8	3	6	6	-2	10	3	6	-4	5	12	3	8	-7
-4	3	3	27	-26	1	5	3	33	32	-5	8	3	7	8	-1	10	3	17	18	-8	13	3	4	-4

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ØBSERVED AND CALCULATED STRUCTURE FACTØRS FØR   DIPB 1,2,3-BENZØTRIAZINE - P21,N                                PAGE  6

 H  K  L   FØ   FC      H  K  L   FØ   FC      H  K  L   FØ   FC      H  K  L   FØ   FC      H  K  L   FØ   FC

-7 13  3    5   -5     -6 16  3    2    2     -4 20  3    2    2      7  1  4    1    2     -2  4  4    3    4
-6 13  3   11  -10     -5 16  3    3   -3     -2 20  3    4   -3    -10  2  4    2   -2      0  4  4   21   19
-3 13  3    9   -9     -4 16  3    7   -8     -1 20  3    2    3     -9  2  4    2    3      2  4  4   10   -9
-2 13  3    7   -8     -3 16  3    2    2      0 20  3    3   -2     -8  2  4    7    7      3  4  4    3    2
-1 13  3    9    9     -2 16  3    1    2      1 20  3    6    6     -7  2  4    3   -4      4  4  4   13  -13
 0 13  3    4   -4     -1 16  3    8   -7      2 20  3    3   -3     -6  2  4    6    6      5  4  4    8    9
 1 13  3   18  -17      0 16  3    9    8     -3 21  3    3    3     -5  2  4   18  -17      6  4  4    2   -2
 2 13  3    7    6      1 16  3    9   -9     -2 21  3    1    1     -4  2  4    9   -9     -9  5  4    2   -2
 3 13  3    3    2      2 16  3    9    7     -1 21  3    1   -1     -3  2  4   46   46     -8  5  4    5    4
 4 13  3    4   -3      3 16  3    6    6      1 21  3    2    2     -2  2  4   22   23     -7  5  4    5    6
 6 13  3    5    5      4 16  3    4   -4     -2 22  3    2   -3      0  2  4    6   -3     -6  5  4   14  -14
-8 14  3    3   -3     -6 17  3    5   -5     -1 22  3    1   -2      1  2  4   16   16     -5  5  4   19   19
-7 14  3    2    3     -5 17  3    2    2    -10  0  4    4   -6      2  2  4    6    7     -4  5  4   27   28
-6 14  3   17   17     -4 17  3   14   13     -8  0  4    7   -6      3  2  4    2   -1     -3  5  4    7    7
-5 14  3    8    8     -3 17  3    5   -6     -6  0  4   13  -12      4  2  4    5    5     -2  5  4    4    5
-4 14  3    5    5     -2 17  3   12  -13     -4  0  4   13   13      6  2  4    2   -2     -1  5  4    1   -1
-2 14  3   11  -11     -1 17  3    4   -4     -2  0  4   23  -22    -10  3  4    3    3      1  5  4   13   11
-1 14  3    3    3      0 17  3   27   25      0  0  4    6    5     -9  3  4    6   -6      2  5  4    4    4
 0 14  3    9   -9      1 17  3    1   -2      2  0  4   18  -18     -8  3  4   15   13      4  5  4   12  -11
 1 14  3    7    6      2 17  3   11  -10      4  0  4   40   39     -7  3  4    4   -5      5  5  4    3    3
 2 14  3    7   -7      3 17  3    4    4      6  0  4    2   -2     -6  3  4   11  -10     -9  6  4    2   -2
 3 14  3    1   -2      4 17  3    5    5     -9  1  4    7    7     -5  3  4   15  -14     -8  6  4    7   -6
 4 14  3    7    7     -2 18  3    5    5     -8  1  4    1    1     -4  3  4   27   28     -7  6  4   11  -10
 5 14  3    6    6     -1 18  3    4    5     -7  1  4    6   -6     -3  3  4    9    8     -5  6  4    5    5
-7 15  3    5   -6      0 18  3   22   21     -6  1  4    4   -4     -2  3  4   12   -9     -4  6  4   11  -10
-5 15  3    1    1      1 18  3    7   -7     -5  1  4   10   10     -1  3  4   12   12     -3  6  4   18  -18
-4 15  3    5   -5      2 18  3    5   -5     -4  1  4    5   -5      0  3  4    4    2     -2  6  4   10   11
-3 15  3    2   -1      3 18  3    3    4     -3  1  4   36  -34      2  3  4   14   14     -1  6  4   19  -18
-2 15  3    9   -8     -5 19  3    3   -3     -2  1  4   33  -34      3  3  4    5   -3      0  6  4    9   -9
-1 15  3    4    3     -3 19  3    5    5     -1  1  4    5   -6      6  3  4    4   -4      1  6  4    7   -4
 0 15  3   13  -12     -2 19  3    5    5      0  1  4   31   28     -9  4  4   10  -11      2  6  4    6   -7
 1 15  3    4    4     -1 19  3    5   -4      1  1  4   10   -8     -8  4  4   13   12      3  6  4   12  -12
 2 15  3   18   17      0 19  3    3   -3      2  1  4    2   -1     -7  4  4    7   -6      4  6  4    5   -5
 4 15  3    4   -3      2 19  3    6   -5      3  1  4    6   -6     -6  4  4    7   -7      6  6  4    1    2
 5 15  3    6   -6      3 19  3    2   -2      4  1  4   27   26     -5  4  4   16  -15     -9  7  4    5   -5
-7 16  3    4   -4     -5 20  3    1   -1      6  1  4   12  -11     -3  4  4    2    2     -8  7  4   10   -9
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OBSERVED AND CALCULATED STRUCTURE FACTORS FOR   DIPB 1,2,3-BENZOTRIAZINE - P21,N                         PAGE  7

  H  K  L   FO   FC      H  K  L   FO   FC      H  K  L   FO   FC      H  K  L   FO   FC      H  K  L   FO   FC

 -7  7  4    5    4      1  9  4    5   -5     -1 12  4    5    5      2 15  4    9    9      1 19  4    9    8
 -6  7  4   15   15      2  9  4    4   -3      0 12  4    9  -10      3 15  4    3   -3      2 19  4    9   -9
 -5  7  4    1   -3      3  9  4    5    5      2 12  4    2    1      4 15  4    3   -4     -2 20  4    6   -6
 -4  7  4   18  -19      4  9  4    3   -4      3 12  4    2    4     -7 16  4    4   -4     -1 20  4    2   -1
 -3  7  4   11   12      6  9  4    4    5      4 12  4    4    3     -6 16  4    3   -3      0 20  4    2   -2
 -2  7  4   13   12     -9 10  4    5   -5      5 12  4    3   -3     -5 16  4    8    9      1 20  4    1    1
 -1  7  4   23  -23     -8 10  4    5   -5     -7 13  4    7    6     -4 16  4    2   -2     -3 21  4    2   -2
  0  7  4   24  -23     -7 10  4    8    8     -6 13  4    8    7     -3 16  4    8   -8     -2 21  4    2   -1
  1  7  4   13   12     -6 10  4    5    4     -5 13  4   13  -14     -2 16  4    4    4     -9  0  5    4   -4
  2  7  4   11   10     -5 10  4    5    5     -4 13  4   14  -14     -1 16  4    7    7     -7  0  5    8   -8
  3  7  4    4    4     -4 10  4    9   -9     -3 13  4    4   -4      0 16  4   13   13     -5  0  5   11   10
  5  7  4    3   -3     -2 10  4   10  -10     -2 13  4    5   -5      1 16  4   17  -15     -3  0  5   28  -28
 -9  8  4    4    4     -1 10  4   21   20     -1 13  4   13   14      2 16  4    1    1     -1  0  5   45   43
 -8  8  4    6   -6      1 10  4    7   -7      0 13  4    4    4      3 16  4    4    4      1  0  5    5   -3
 -7  8  4    4    4      2 10  4   10    9      1 13  4   11  -11      4 16  4    1   -1      3  0  5    3    2
 -5  8  4    1    1      3 10  4    4    3      2 13  4    4    4     -5 17  4    6    6      5  0  5   12  -12
 -4  8  4    9   -9     -8 11  4    5   -5      3 13  4    4    4     -3 17  4    3   -3     -9  1  5    2   -2
 -3  8  4   10  -10     -7 11  4    9    8      4 13  4    3    3     -2 17  4   10    9     -7  1  5   11  -11
 -2  8  4   13  -13     -6 11  4   12  -12      5 13  4    3   -3     -1 17  4    4   -5     -6  1  5    3   -3
 -1  8  4    6   -4     -5 11  4   20  -19     -7 14  4    7   -7      0 17  4    4   -4     -5  1  5    2   -2
  0  8  4   15  -14     -4 11  4    4   -4     -6 14  4    3   -3      1 17  4    8   -8     -4  1  5    2    2
  1  8  4   17   14     -3 11  4    3    3     -5 14  4    7   -7      2 17  4    5   -5     -3  1  5   21   21
  2  8  4   13   12     -2 11  4    1   -1     -3 14  4    4   -5      3 17  4    5    5     -2  1  5   15  -14
  3  8  4    7   -7     -1 11  4    9   -9     -2 14  4    3   -2     -6 18  4    1   -2     -1  1  5    5   -5
  4  8  4    7   -8      0 11  4   12   10     -1 14  4    1   -1     -5 18  4    2   -2      0  1  5    3   -2
  5  8  4    2    2      1 11  4    1    1      0 14  4    9    8     -4 18  4    4    4      1  1  5    9   10
 -9  9  4    7    7      2 11  4    8   -7      1 14  4    3    2     -3 18  4   12   11      2  1  5   10    9
 -8  9  4    5    5      3 11  4    3   -3      2 14  4    3   -1     -2 18  4    8   -8      3  1  5   16  -15
 -7  9  4   14  -13      4 11  4    4    3      4 14  4    4   -5     -1 18  4   13  -12      4  1  5    2   -1
 -6  9  4    8   -8      5 11  4    2    2     -6 15  4    7    7      1 18  4    7    7      5  1  5    6    7
 -5  9  4   11   10     -8 12  4    2    2     -5 15  4    2    3      2 18  4    6   -6      6  1  5    2   -3
 -4  9  4   20   21     -6 12  4   12   12     -3 15  4    5    6     -5 19  4    3    3     -9  2  5    5   -5
 -3  9  4    2    3     -5 12  4    7    7     -2 15  4    5    4     -4 19  4    5    5     -8  2  5    7    7
 -2  9  4   13  -11     -4 12  4    9    9     -1 15  4    4    3     -2 19  4    5   -4     -7  2  5   16  -15
 -1  9  4   13   10     -3 12  4    5    5      0 15  4    3   -4     -1 19  4    1    1     -6  2  5    3    3
  0  9  4   10  -12     -2 12  4   11   11      1 15  4    7   -6      0 19  4    4    3     -5  2  5    3    3
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ØBSERVED AND CALCULATED STRUCTURE FACTØRS FØR   DIPB 1,2,3-BENZØTRIAZINE - P21,N

H	K	L	FØ	FC	H	K	L	FØ	FC	H	K	L	FØ	FC	H	K	L	FØ	FC	H	K	L	FØ	FC
-4	2	5	12	11	1	4	5	7	-7	-8	7	5	4	-4	3	9	5	4	5	-7	13	5	5	-5
-3	2	5	11	-10	2	4	5	8	-8	-7	7	5	4	4	4	9	5	6	-5	-6	13	5	8	8
-2	2	5	3	-4	3	4	5	3	2	-6	7	5	4	3	5	9	5	3	-3	-5	13	5	11	10
-1	2	5	12	-13	4	4	5	4	-5	-5	7	5	13	-13	-9	10	5	2	-2	-4	13	5	10	10
0	2	5	2	4	5	4	5	3	2	-4	7	5	3	-3	-8	10	5	4	4	-3	13	5	7	6
1	2	5	12	12	6	4	5	2	2	-2	7	5	6	-6	-7	10	5	2	1	-2	13	5	1	-2
2	2	5	.6	-6	-9	5	5	7	-6	-1	7	5	15	14	-6	10	5	11	-10	-1	13	5	7	7
3	2	5	11	-10	-8	5	5	1	-2	0	7	5	4	-5	-5	10	5	5	5	0	13	5	6	6
4	2	5	2	-2	-7	5	5	24	22	1	7	5	6	6	-4	10	5	30	31	1	13	5	4	-5
5	2	5	7	7	-6	5	5	16	-15	2	7	5	4	-6	-3	10	5	16	15	2	13	5	2	-2
6	2	5	6	-8	-5	5	5	3	-4	3	7	5	11	-11	-2	10	5	8	-8	3	13	5	5	-5
-9	3	5	6	-5	-4	5	5	4	-5	4	7	5	2	2	-1	10	5	5	6	4	13	5	1	2
-8	3	5	12	12	-3	5	5	9	-9	-9	8	5	2	2	0	10	5	8	9	-6	14	5	1	1
-6	3	5	3	4	-2	5	5	3	3	-8	8	5	8	-7	1	10	5	9	-8	-5	14	5	5	-4
-5	3	5	13	12	-1	5	5	3	4	-7	8	5	16	-16	4	10	5	3	4	-4	14	5	10	-11
-4	3	5	9	9	0	5	5	2	0	-6	8	5	5	4	5	10	5	1	-2	-3	14	5	2	3
-3	3	5	9	10	1	5	5	3	-3	-5	8	5	15	16	-8	11	5	4	-4	-1	14	5	14	-13
-2	3	5	22	22	2	5	5	4	-3	-4	8	5	5	-5	-7	11	5	4	-4	0	14	5	6	5
-1	3	5	17	16	3	5	5	6	5	-3	8	5	13	-13	-6	11	5	4	4	1	14	5	2	2
0	3	5	2	3	4	5	5	4	4	-1	8	5	13	13	-4	11	5	2	1	2	14	5	2	-2
1	3	5	4	-3	5	5	5	2	2	0	8	5	11	-10	-3	11	5	2	-2	3	14	5	1	-1
2	3	5	9	-9	-9	6	5	3	2	2	8	5	10	10	-2	11	5	6	-6	-7	15	5	3	3
4	3	5	2	2	-8	6	5	2	2	3	8	5	2	2	-1	11	5	20	-18	-6	15	5	2	2
5	3	5	8	8	-7	6	5	22	21	4	8	5	1	1	0	11	5	11	10	-4	15	5	5	-5
6	3	5	1	-2	-6	6	5	9	-9	5	8	5	1	2	2	11	5	5	6	-1	15	5	3	3
-10	4	5	1	3	-5	6	5	16	-16	-9	9	5	2	2	3	11	5	3	2	0	15	5	3	-3
-9	4	5	4	4	-3	6	5	7	7	-8	9	5	3	-3	4	11	5	3	-3	1	15	5	7	-8
-8	4	5	3	-3	-2	6	5	9	-8	-6	9	5	5	4	-8	12	5	2	1	3	15	5	2	3
-7	4	5	12	12	-1	6	5	1	-2	-5	9	5	9	-8	-5	12	5	19	-20	-6	16	5	2	2
-6	4	5	2	3	0	6	5	3	0	-4	9	5	15	-16	-4	12	5	3	-2	-5	16	5	6	6
-5	4	5	5	5	1	6	5	6	5	-3	9	5	5	-4	-3	12	5	4	5	-4	16	5	6	-6
-4	4	5	8	-7	2	6	5	4	4	-2	9	5	7	6	-2	12	5	9	9	-1	16	5	6	-4
-3	4	5	7	7	3	6	5	3	3	-1	9	5	3	3	0	12	5	9	-9	0	16	5	1	0
-2	4	5	8	-8	4	6	5	2	-2	0	9	5	12	-11	1	12	5	3	3	1	16	5	3	-3
-1	4	5	14	-12	5	6	5	2	-3	1	9	5	3	-4	2	12	5	2	2	2	16	5	2	3
0	4	5	3	4	-9	7	5	2	-2	2	9	5	7	6	4	12	5	2	-2	-5	17	5	2	3

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ØBSERVED AND CALCULATED STRUCTURE FACTØRS FØR   DIPB 1,2,3-BENZØTRIAZINE - P21.N                                   PAGE  9

  H   K   L    FØ    FC       H   K   L    FØ    FC       H   K   L    FØ    FC       H   K   L    FØ    FC       H   K   L    FØ    FC

 -4  17   5     5     5      -8   2   6    10    10      -6   5   6    13   -12      -4   8   6    10   -10      -1  11   6     9    -8
 -3  17   5     6    -6      -7   2   6     2    -2      -5   5   6     4     4      -3   8   6    19    18       0  11   6     8     7
 -2  17   5     9    -9      -6   2   6    11   -11      -4   5   6     4     4      -2   8   6     8    10       2  11   6     1    -2
 -1  17   5     3     3      -5   2   6     5     5      -3   5   6     3     5      -1   8   6     1    -1       3  11   6     1     1
  0  17   5     7     7      -3   2   6     2    -2      -2   5   6     1     0       0   8   6     3    -4      -8  12   6     1    -1
  1  17   5     5     5      -1   2   6    16   -13       1   5   6     7     8       1   8   6     3    -3      -7  12   6     4    -4
  2  17   5     2    -3       0   2   6    10   -10       2   5   6     3    -2       2   8   6     7     8      -6  12   6     4     3
 -4  18   5     3    -2       1   2   6     7    -7       3   5   6     5    -5       3   8   6     7    -7      -4  12   6     5    -5
 -3  18   5     7    -8       2   2   6     5     5       4   5   6     1    -2       4   8   6     5    -6      -3  12   6    15   -15
 -1  18   5     9     8       3   2   6     9     8      -9   6   5     6    -5      -9   9   6     3     3      -1  12   6     2     2
  0  18   5     2    -2       4   2   6     2    -2      -8   6   6    10   -10      -7   9   6     5    -4       0  12   6     6    -5
 -2  19   5     6     4       5   2   6     4     5      -7   6   6     7     7      -6   9   6     4    -4       1  12   6     2    -2
 -1  19   5     1     1      -8   3   6     6    -6      -6   6   6     9     8      -5   9   6    13    12       2  12   6     3    -3
  0  19   5     3    -3      -7   3   6     7     7      -5   6   6    22   -22      -4   9   6     7     7       3  12   6     5     4
 -3  20   5     5     6      -6   3   6    18   -18      -4   6   6     6     6      -3   9   6    25   -24      -7  13   6     2    -2
 -2  20   5     2     2      -5   3   6     7     7      -3   6   6    10    11      -2   9   6    10    -9      -5  13   6     2    -2
 -8   0   6     4     4      -4   3   6     3    -3      -2   6   6     3     3      -1   9   6     2     2      -4  13   6     5    -5
 -6   0   6     3    -2      -2   3   6     9    -9      -1   6   6     3     3       0   9   6     3     4      -3  13   6    12    11
 -4   0   6    10    10      -1   3   6     3    -5       0   6   6     3     3       1   9   6    10   -10      -2  13   6     4    -4
 -2   0   6    29   -29       0   3   6     2    -2       2   6   6     6    -5       2   9   6     2     2      -1  13   6     3     2
  0   0   6     2     2       1   3   6     8     8       4   6   6     3     4       3   9   6     4     4       0  13   6     2     1
  2   0   6    15   -14       2   3   6    13    11      -9   7   6     4    -4      -7  10   6     4    -4      -6  14   6     6    -6
  4   0   6     4     4       4   3   6     5    -5      -8   7   6     3    -3      -6  10   6     7     7      -5  14   6     7     5
 -9   1   6     3    -3       5   3   6     5     5      -7   7   6     3     3      -5  10   6     4     4      -3  14   6     6     7
 -7   1   6     5    -4      -9   4   6     2     2      -6   7   6    23    23      -4  10   6    10   -10      -2  14   6     3     3
 -6   1   6     5     4      -7   4   6    14    14      -5   7   6    12   -11      -3  10   6    21   -21      -1  14   6     3    -4
 -5   1   6     3    -2      -6   4   6    15   -15      -4   7   6     4    -4      -2  10   6     6    -6       0  14   6     1    -1
 -4   1   6    14    13      -5   4   6     3     3      -3   7   6     5    -6      -1  10   6    12    11       1  14   6     1    -1
 -3   1   6     1    -1      -4   4   6     6     7      -2   7   6     2     1       0  10   6     8     7       2  14   6     3     3
 -2   1   6    13   -12      -3   4   6    12    13       0   7   6     7    -7       1  10   6     6    -5      -5  15   6     3    -2
 -1   1   6     8     9      -2   4   6    10     9       1   7   6     1     1       2  10   6     1    -2      -4  15   6     8    -8
  0   1   6    14    14      -1   4   6     4    -4       3   7   6     2    -3      -7  11   6     3     2      -3  15   6     3    -2
  1   1   6    10   -10       1   4   6    10    11      -8   8   6     4    -4      -5  11   6     5    -6      -2  15   6     3     4
  3   1   6     2     2       2   4   6     7     5      -7   8   6     4     4      -4  11   6    11    11      -1  15   6     3    -3
  4   1   6     3     3       5   4   6     1    -1      -6   8   6    13    12      -3  11   6    26    25       0  15   6     1    -1
 -9   2   6     1    -1      -9   5   6     4     4      -5   8   6     8    -8      -2  11   6     5     4       1  15   6     7     7
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ØBSERVED AND CALCULATED STRUCTURE FACTØRS FØR   DIPB 1,2,3-BENZØTRIAZINE - P21,N                                  PAGE 10

  H  K  L   FØ   FC      H  K  L   FØ   FC      H  K  L   FØ   FC      H  K  L   FØ   FC      H  K  L   FØ   FC

 -5 16  6    2    3     -4  2  7    2   -2      0  5  7   10  -10      1  9  7    6   -6     -1 15  7    1    1
 -4 16  6    1   -1     -2  2  7    3   -3      1  5  7    4   -3      2  9  7    3    3     -4 16  7    1    2
 -3 16  6    2   -2     -1  2  7    4    4      2  5  7    4    3      3  9  7    3    3     -3 16  7    2   -3
 -1 16  6    2    2      0  2  7   20   20     -9  6  7    1   -2     -8 10  7    2    1     -2 16  7    5    5
  0 16  6    3    3      1  2  7    3    4     -8  6  7    6    6     -7 10  7    1   -1     -6  0  8    4   -4
  1 16  6    1    1      2  2  7    7   -6     -7  6  7    2    2     -6 10  7    5   -5     -4  0  8    2    3
 -5 17  6    4   -3      3  2  7    3   -3     -6  6  7    3    2     -5 10  7    4   -6     -2  0  8    2    2
 -3 17  6    2   -3      4  2  7    1    1     -5  6  7   16  -16     -4 10  7   12   11      0  0  8    4    5
 -2 17  6    4    4     -9  3  7    4   -3     -4  6  7    9    9     -3 10  7    2    1      2  0  8    2    2
 -1 17  6    2    3     -7  3  7    9    9     -3  6  7    5    5     -2 10  7   20  -18     -8  1  8    2   -2
  0 17  6    4   -3     -6  3  7   14  -14     -2  6  7    3    3     -1 10  7    7   -7     -7  1  8    1    2
 -4 18  6    5    6     -4  3  7   11   11     -1  6  7    5   -5     -6 11  7    3    3     -4  1  8    4   -4
 -3 18  6    4    3     -3  3  7    1    1      0  6  7    2   -2     -5 11  7    4    3     -3  1  8    1   -1
 -2 18  6    1   -2     -2  3  7    8   -7      1  6  7    1    1     -4 11  7    5   -5     -1  1  8    3    2
 -1 18  6    3   -2      0  3  7    4    4      2  6  7    2    2     -3 11  7    2   -2      1  1  8    9   -8
 -9  0  7    1   -1      1  3  7    3   -3     -9  7  7    2    3     -1 11  7    4    5      2  1  8    6   -6
 -7  0  7    1    1      2  3  7    6   -5     -6  7  7    3    4      0 11  7    3    3     -9  2  8    2   -2
 -3  0  7   20  -18     -9  4  7    2   -2     -5  7  7   15  -14     -7 12  7    2   -2     -8  2  8    1    1
 -1  0  7    8    7     -8  4  7    6   -6     -4  7  7    3   -3     -6 12  7    3    3     -7  2  8    5   -5
  1  0  7    8   -8     -7  4  7    3   -3     -3  7  7   15   15     -5 12  7    6    7     -6  2  8    6   -6
  3  0  7    1    2     -6  4  7    4   -4     -1  7  7   15  -15     -3 12  7    6    6     -5  2  8    4    4
 -8  1  7    2   -2     -5  4  7    3    4      0  7  7    4   -4     -2 12  7    6    6     -3  2  8    8   -7
 -7  1  7    2   -2     -4  4  7   11   11      1  7  7    7    7      1 12  7    4    3     -2  2  8    2    2
 -6  1  7    4   -4     -3  4  7    1   -2      3  7  7    3   -4      2 12  7    3   -3     -1  2  8    2   -2
 -5  1  7    2   -2     -1  4  7    4    4     -8  8  7    3   -3     -5 13  7    4    4      0  2  8    4   -4
 -4  1  7    6   -7      2  4  7    3   -2     -6  8  7    8    8     -4 13  7    2   -2     -9  3  8    1   -2
 -3  1  7    4    4      3  4  7    1    1     -4  8  7   18  -16     -3 13  7    3   -3     -8  3  8    2   -2
 -2  1  7    7   -7     -9  5  7    1   -1      1  8  7    4   -4     -2 13  7   10  -10     -7  3  8    5    4
 -1  1  7   10  -10     -8  5  7    8    8      2  8  7    6    5      1 13  7    2    1     -6  3  8    8    9
  0  1  7    7    6     -7  5  7    7    8     -8  9  7    5   -5     -5 14  7    3    3     -5  3  8    3    3
  1  1  7    5    5     -6  5  7    7    7     -6  9  7    5    4     -4 14  7    4   -3     -4  3  8    3    3
  2  1  7    2    2     -5  5  7   15  -14     -5  9  7    6    5     -2 14  7    8    7     -3  3  8    4   -4
 -8  2  7    2   -2     -4  5  7   19   18     -4  9  7   18  -18      0 14  7    2    2     -1  3  8    3   -3
 -7  2  7    4    4     -3  5  7    4    4     -2  9  7   25   23      1 14  7    2   -2      1  3  8    4    4
 -6  2  7    7   -6     -2  5  7    1    2     -1  9  7    9    9     -3 15  7    3   -3      2  3  8    1   -2
 -5  2  7   10   10     -1  5  7    1   -1      0  9  7    1   -1     -2 15  7    2    3     -7  4  8    2   -1
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ØBSERVED AND CALCULATED STRUCTURE FACTØRS FØR DIPB 1,2,3-BENZØTRIAZINE - P21.N

H	K	L	FØ	FC	H	K	L	FØ	FC	H	K	L	FØ	FC	H	K	L	FØ	FC	H	K	L	FØ	FC
-6	4	8	3	2	-4	7	8	4	-5	1	10	8	3	-3	-2	2	9	2	2	-2	7	9	4	-3
-5	4	8	12	-12	-3	7	8	10	9	-7	11	8	4	4	0	2	9	2	-1	-1	7	9	12	-12
-4	4	8	11	10	-2	7	8	4	4	-6	11	8	3	3	-6	3	9	4	-4	-6	8	9	6	6
-3	4	8	4	-4	-1	7	8	5	4	-5	11	8	2	-2	-5	3	9	9	-8	-5	8	9	3	3
-2	4	8	6	-6	0	7	8	2	2	-4	11	8	8	-7	-4	3	9	5	6	-4	8	9	5	-5
-1	4	8	7	-7	1	7	8	1	2	-3	11	8	3	3	-3	3	9	2	-2	-3	8	9	3	-4
0	4	8	4	3	-7	8	8	2	2	-2	11	8	4	-4	-2	3	9	2	-2	-2	8	9	2	2
1	4	8	6	5	-6	8	8	3	3	-1	11	8	6	-6	-1	3	9	4	4	-1	8	9	2	3
2	4	8	1	-1	-5	8	8	3	-2	0	11	8	3	-3	0	3	9	2	2	-6	9	9	1	2
-7	5	8	4	-4	-4	8	8	16	-15	-1	12	8	2	2	-7	4	9	1	2	-5	9	9	3	3
-6	5	8	2	2	-3	8	8	15	14	0	12	8	4	4	-6	4	9	4	5	-4	9	9	3	-4
-5	5	8	7	-6	-2	8	8	9	9	-4	13	8	1	1	-5	4	9	2	2	-3	9	9	7	-6
-4	5	8	11	11	-1	8	8	8	-7	-3	13	8	2	2	-3	4	9	2	-1	-2	9	9	7	7
-3	5	8	2	-3	0	8	8	13	-12	-2	13	8	5	4	-2	4	9	4	4	-1	9	9	2	-2
-2	5	8	9	-8	-7	9	8	5	-5	-1	13	8	3	-3	-1	4	9	4	3	-5	10	9	2	-2
-1	5	8	4	4	-5	9	8	11	11	-2	14	8	1	1	0	4	9	3	-3	-4	10	9	3	3
0	5	8	5	4	-4	9	8	1	-1	-7	0	9	2	3	-6	5	9	2	2	-3	10	9	3	-3
1	5	8	2	1	-3	9	8	7	-7	-5	0	9	9	-9	-5	5	9	3	-3	-3	11	9	1	-2
-7	6	8	3	3	-2	9	8	2	-3	-3	0	9	5	4	-4	5	9	5	-5	-4	0	10	3	3
-4	6	8	2	3	0	9	8	5	5	-1	0	9	3	-3	-3	5	9	7	7	-2	0	10	4	-4
-3	6	8	8	7	-7	10	8	1	-1	-8	1	9	2	1	-2	5	9	1	-2	-4	1	10	3	-4
-2	6	8	12	-12	-6	10	8	1	1	-5	1	9	1	-1	-1	5	9	3	3	-3	1	10	2	2
0	6	8	9	8	-5	10	8	2	-2	-4	1	9	3	3	-5	6	9	4	4	-2	1	10	1	2
1	6	8	1	-1	-4	10	8	1	1	0	1	9	2	2	-3	6	9	11	11	-4	2	10	5	5
-8	7	8	5	-5	-3	10	8	4	-3	-7	2	9	1	2	-2	6	9	6	-6	-3	2	10	2	2
-7	7	8	3	2	-2	10	8	7	7	-5	2	9	4	-5	-1	6	9	3	-3	-5	3	10	2	-2
-6	7	8	2	-1	-1	10	8	8	8	-4	2	9	5	-5	-7	7	9	4	6	-5	4	10	2	-2
-5	7	8	4	-3	0	10	8	2	-1	-3	2	9	4	-8	-3	7	9	11	11	-3	4	10	5	6

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ANALYSIS OF VARIANCE FOR  DIPB 1,2,3-BENZOTRIAZINE - P21,N

                  GGG    UGG    GUG    UUG    GGU    UGU    GUU    UUU    ALL

       N          259    225    227    249    231    262    246    241   1940

       V           54     58     56     55     63     55     58     56     57


SIN THETA     0.00 -  .40 -  .50 -  .57 -  .63 -  .68 -  .73 -  .78 -  .81 -  .85 -  .89

       N          209    197    193    184    189    215    215    163    205    170

       V           74     70     71     60     53     51     49     44     45     48


SQRT(F/FMAX)  0.00 -  .16 -  .20 -  .23 -  .25 -  .28 -  .32 -  .36 -  .42 -  .52 - 1.00

       N          210    229    212    136    200    190    181    201    195    186

       V           64     73     73     54     54     57     50     49     40     35


      ABS(H)        0      1      2      3      4      5      6      7      8      9     10     11     12     13      -
    REST

       N          150    291    292    267    244    221    176    135     93     63      8      0      0      0      0

       V           61     62     62     61     50     54     44     43     38     33     63      0      0      0      0


      ABS(K)        0      1      2      3      4      5      6      7      8      9     10     11     12     13      -
    REST

       N           70    124    130    127    119    121    117    111    116    114    106    100     84     86    415

       V           54     52     63     61     62     62     71     56     53     55     47     64     53     49     52


      ABS(L)        0      1      2      3      4      5      6      7      8      9     10     11     12     13      -
    REST

       N          138    288    281    277    248    224    179    133    104     58     10      0      0      0      0

       V           53     60     59     56     59     68     54     45     45     46     41      0      0      0      0
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ØBSERVED AND CALCULATED STRUCTURE FACTØRS FØR  DETT                                                                PAGE  1

H  K  L   FØ   FC     H  K  L   FØ   FC     H  K  L   FØ   FC     H  K  L   FØ   FC     H  K  L   FØ   FC

0  0  2   15   16     0  2 16    2   -2     0  3  8    1   -1     0  4  3   23  -23     0  5  4    3    2
0  0  6   11  -11     0  2 15    2    1     0  3  7    4    5     0  4  2   22  -22     0  5  5    5   -4
0  0  8   43   43     0  2 13   14  -14     0  3  6   13   13     0  4  1    5    6     0  5  6   23   23
0  0 12   13  -13     0  2 12    3    4     0  3  5   11  -10     0  4  0   26   26     0  5  7   10  -10
0  0 14    4    3     0  2 11    2    2     0  3  4   60   59     0  4  1    5    6     0  5  8    2    1
0  0 16    7    6     0  2  9   26  -26     0  3  3   14  -14     0  4  2   22  -22     0  5 10    6    6
0  0 18    5   -5     0  2  8   21  -23     0  3  2   10    9     0  4  3   23  -23     0  5 11    3    3
0  1 19    3   -3     0  2  7    6    7     0  3  1   45   45     0  4  4    6   -5     0  5 12   10   10
0  1 18    5    4     0  2  6    1    0     0  3  1   46   45     0  4  5    7   -6     0  5 13    7   -7
0  1 17    5    5     0  2  5    6    7     0  3  2   10    9     0  4  6    7    5     0  5 15    4    3
0  1 16    3    3     0  2  4    6    6     0  3  3   14  -14     0  4  7    2    4     0  6 15    3   -2
0  1 15   11   11     0  2  3   44   45     0  3  4   60   59     0  4  8   10   10     0  6 14    6    6
0  1 14    3    3     0  2  2   84   84     0  3  5   11  -10     0  4  9    8    7     0  6 13    6   -5
0  1 12   13  -13     0  2  1   72   72     0  3  6   13   13     0  4 10   11  -11     0  6 11    4    4
0  1  9   21  -20     0  2  0   49  -52     0  3  7    4    5     0  4 11   31  -32     0  6 10    3    2
0  1  8    8    8     0  2  1   71   72     0  3  8    2   -1     0  4 12    3   -2     0  6  9   12  -12
0  1  7   34  -35     0  2  2   83   84     0  3  9   13   13     0  4 13    2    2     0  6  8    5   -4
0  1  5   53  -53     0  2  3   45   45     0  3 10    6   -6     0  4 14    2   -2     0  6  7   20   20
0  1  4   24  -25     0  2  4    6    6     0  3 11    7   -6     0  4 16    5    4     0  6  6   13  -14
0  1  3   32  -31     0  2  5    6    7     0  3 12   13   13     0  4 17    2   -2     0  6  5    2    3
0  1  1   30   32     0  2  7    6    7     0  3 13    5   -5     0  5 16    2   -2     0  6  4    2   -1
0  1  1   29   32     0  2  8   22  -23     0  3 15    5   -5     0  5 15    3    3     0  6  3    2    1
0  1  3   31  -31     0  2  9   26  -26     0  3 17    3    4     0  5 13    7   -7     0  6  2   12   11
0  1  4   24  -25     0  2 11    2    2     0  4 16    4    4     0  5 12   11   10     0  6  1    9   -8
0  1  5   52  -53     0  2 13   14  -14     0  4 15    2   -2     0  5 11    4    3     0  6  0   17   17
0  1  6    6   -6     0  2 16    3   -2     0  4 14    2   -2     0  5 10    5    6     0  6  1    8   -8
0  1  7   34  -35     0  2 17    5    5     0  4 13    2    2     0  5  7   10  -10     0  6  2   12   11
0  1  8    8    8     0  3 18    2    2     0  4 12    2   -2     0  5  6   22   23     0  6  5    3    3
0  1  9   21  -20     0  3 17    4    4     0  4 11   31  -32     0  5  5    4   -4     0  6  6   13  -14
0  1 12   13  -13     0  3 16    2    0     0  4 10   11  -11     0  5  4    3    2     0  6  7   19   20
0  1 15   11   11     0  3 15    5   -5     0  4  9    8    7     0  5  3   17   18     0  6  8    4   -4
0  1 16    2    3     0  3 13    5   -5     0  4  8   10   10     0  5  2   10   10     0  6  9   12  -12
0  1 17    5    5     0  3 12   12   13     0  4  7    3    4     0  5  1    2   -3     0  6 10    3    2
0  1 18    4    4     0  3 11    7   -6     0  4  6    7    5     0  5  1    2   -3     0  6 11    4    4
0  1 19    4   -3     0  3 10    6   -6     0  4  5    7   -6     0  5  2   10   10     0  6 13    6   -5
0  2 17    5    5     0  3  9   13   13     0  4  4    6   -5     0  5  3   18   18     0  6 14    6    6
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OBSERVED AND CALCULATED STRUCTURE FACTORS FOR  DETT

 H  K  L   FO    FC      H  K  L   FO    FC      H  K  L   FO    FC      H  K  L   FO    FC      H  K  L   FO    FC

 0  6 15    3    -2      0  8  4   22   -23      0 10  6    2    -2     -1  1 19    4    -3     -1  2 16    4    -4
 0  7 14    2     3      0  8  3   22    21      0 10  5    3    -4     -1  1 17    4    -5     -1  2 15    8     8
 0  7 13    4     4      0  8  2    6     6      0 10  4    7     7     -1  1 15    2    -3     -1  2 14    8     8
 0  7 12    6    -6      0  8  1   17    17      0 10  3    9     9     -1  1 14    8     8     -1  2 12    5     5
 0  7 11    5    -4      0  8  0   11    12      0 10  2    7    -7     -1  1 13   17    16     -1  2 11    5    -5
 0  7 10   14   -15      0  8  1   17    17      0 10  1    3     3     -1  1 12   18   -18     -1  2 10   14    14
 0  7  9    9     9      0  8  2    6     6      0 10  0    9    -8     -1  1 11   14    13     -1  2  9   20   -20
 0  7  8    5    -5      0  8  3   22    21      0 10  1    3     3     -1  1 10   17   -16     -1  2  8   31   -30
 0  7  7    2     2      0  8  4   23   -23      0 10  2    7    -7     -1  1  9    4    -5     -1  2  7   14    13
 0  7  6   23    24      0  8  5   18    18      0 10  3    9     9     -1  1  8   35    34     -1  2  6    1     2
 0  7  5   29   -31      0  8  7   10   -10      0 10  4    7     7     -1  1  7   24   -24     -1  2  5   13    12
 0  7  4   13    14      0  8  8   11    11      0 10  5    4    -4     -1  1  6   48   -49     -1  2  4   30    31
 0  7  3    7    -7      0  8 11    4    -4      0 10  6    3    -2     -1  1  5   22   -23     -1  2  3   41    40
 0  7  2   25   -27      0  8 13    3     3      0 10  8    3     3     -1  1  4   44    45     -1  2  2   24   -24
 0  7  1   20    20      0  9 12    5    -4      0 10  9    5    -4     -1  1  3   81    80     -1  2  1   15    18
 0  7  1   20    20      0  9 10    4    -3      0 11  5    4     4     -1  1  2   13   -11      1  2  0   89   -87
 0  7  2   25   -27      0  9  9    4     4      0 11  4    5     4     -1  1  1   15    15      1  2  1   44   -43
 0  7  3    7    -7      0  9  7    7     6      0 11  3    3    -1      1  1  0   72   -72      1  2  2   13    13
 0  7  4   13    14      0  9  6    5    -5      0 11  1   10   -10      1  1  1   12   -13      1  2  3   37    38
 0  7  5   29   -31      0  9  5    2     2      0 11  1   10   -10      1  1  2   65    67      1  2  4   97    98
 0  7  6   23    24      0  9  4   14    14      0 11  4    4     4      1  1  4   64    64      1  2  5   69    71
 0  7  7    3     2      0  9  3   12   -12      0 11  5    4     4      1  1  5   31    32      1  2  6    7     8
 0  7  8    5    -5      0  9  2   12    12     -1  0 18    2     1      1  1  6   22   -23      1  2  7   24   -25
 0  7  9    9     9      0  9  1    5     5     -1  0 12   18    19      1  1  7   23   -24      1  2  8   49   -49
 0  7 10   15   -15      0  9  1    5     5     -1  0 10   33   -34      1  1  8    9    -9      1  2  9   11   -12
 0  7 11    5    -4      0  9  2   12    12     -1  0  8   15   -15      1  1  9   22   -22      1  2 10    4    -4
 0  7 12    6    -6      0  9  3   12   -12     -1  0  6   31   -31      1  1 10    7     6      1  2 11    3     5
 0  7 13    4     4      0  9  4   14    14     -1  0  4   90   -89      1  1 11    4     4      1  2 12    3     4
 0  7 14    4     3      0  9  6    5    -5      1  0  4    2     1      1  1 12    9    -9      1  2 13    3    -2
 0  7 15    2    -2      0  9  7    7     6      1  0  6   68   -66      1  1 13    3    -3      1  2 14    4    -3
 0  8 13    3     3      0  9  9    4     4      1  0  8   11    11      1  1 14    7     6      1  2 16    3    -2
 0  8 11    4    -4      0  9 10    4    -3      1  0 10    6    -7      1  1 15    2    -2      1  2 17    2     1
 0  8  8   11    11      0  9 11    2     1      1  0 12    3    -3      1  1 16    3    -3      1  2 18    2    -2
 0  8  7    9   -10      0  9 12    5    -4      1  0 14   12    12      1  1 18    4     4     -1  3 17    2    -2
 0  8  6    2    -1      0 10  9    4    -4      1  0 16    2    -1     -1  2 19    2     1     -1  3 15    2    -1
 0  8  5   18    18      0 10  8    3     3      1  0 18    3     2     -1  2 18    2     2     -1  3 14    5    -4
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ØBSERVED AND CALCULATED STRUCTURE FACTØRS FØR  DETT                                                          PAGE  3

 H  K  L   FØ   FC     H  K  L   FØ   FC     H  K  L   FØ   FC     H  K  L   FØ   FC     H  K  L   FØ   FC

-1  3 13   12  -13    -1  4  7    4   -5     1  5  0   17  -18     1  6  8   26  -27    -1  8 10    3    2
-1  3 12    8   -8    -1  4  6    5   -6     1  5  1   19  -18     1  6  9   24   24    -1  8  9    5   -4
-1  3 10    4   -2    -1  4  5   12   11     1  5  2   18  -17     1  6 10    5   -5    -1  8  8    5   -5
-1  3  9    4    4    -1  4  4   15   14     1  5  3   46   43     1  6 12    9    9    -1  8  7    5    6
-1  3  8   19  -20    -1  4  3    4   -3     1  5  4   10   -9     1  6 13    6   -6    -1  8  6    3    3
-1  3  7    4   -3    -1  4  2    1    0     1  5  5    6    6     1  6 15    2   -2    -1  8  4    7    7
-1  3  5   24  -24    -1  4  1   26   26     1  5  7   12   12     1  6 16    3   -3    -1  8  3    2    1
-1  3  4    1    1     1  4  0    9   -9     1  5  8    8    8    -1  7 14    3    3    -1  8  2    6   -5
-1  3  3   47  -46     1  4  1   18   17     1  5  9   23  -25    -1  7 11   11   11    -1  8  1   41   43
-1  3  2   37   37     1  4  2    5   -5     1  5 10   21   22    -1  7 10    4   -4     1  8  1   15  -14
-1  3  1    2    1     1  4  3    2    2     1  5 11   10   11    -1  7  9    9   -9     1  8  2   11   11
 1  3  0    4   -4     1  4  4   20  -19     1  5 12   10  -10    -1  7  8    6   -7     1  8  3    4    4
 1  3  1    6   -4     1  4  5    6   -5     1  5 13    6    6    -1  7  7   11  -11     1  8  4    5   -5
 1  3  2   56  -58     1  4  6   28   27     1  5 14    6   -6    -1  7  6    9   -9     1  8  5   11   12
 1  3  3   10  -10     1  4  7   13   15    -1  6 16    3    2    -1  7  5    5    5     1  8  6   12  -12
 1  3  4   27   27     1  4  8   16   16    -1  6 15    2    0    -1  7  4   14   14     1  8  7    2   -4
 1  3  5   87   85     1  4  9   19   20    -1  6 14    4    4    -1  7  3    4    5     1  8  8    3   -3
 1  3  6   38   38     1  4 10   29  -30    -1  6 13    8   -7    -1  7  1    8   -8     1  8  9    8   -9
 1  3  7    6    7     1  4 11   10   11    -1  6 12    6    5     1  7  0   19   20     1  8 10    3    3
 1  3  8   13  -14     1  4 12   18  -18    -1  6 11    7    7     1  7  1   24   25     1  8 12    3    3
 1  3 10   19  -20     1  4 13    8   -9    -1  6 10    4    4     1  7  2    5    7     1  8 13    4   -3
 1  3 11   13  -13     1  4 15    4   -2    -1  6  9    6    6     1  7  3    2   -2    -1  9 12    3   -3
 1  3 12   13   12     1  4 16    3    2    -1  6  8   15  -16     1  7  4    6   -7    -1  9 11    3   -3
 1  3 13    8    8    -1  5 16    3   -2    -1  6  7    4   -4     1  7  5    3    3    -1  9  8    9   -9
 1  3 14    3   -1    -1  5 15    4    4    -1  6  6    2    2     1  7  6   16   17    -1  9  6    3   -4
 1  3 16    2    1    -1  5 14   10   -9    -1  6  5   13  -14     1  7  7   21  -22    -1  9  5    9    9
 1  3 18    2   -2    -1  5 13    2   -1    -1  6  4    4    4     1  7  8   22   23    -1  9  4    4   -4
-1  4 18    3    2    -1  5 11   13  -14    -1  6  3   23   24     1  7  9    3    3    -1  9  3    5   -5
-1  4 15    7    7    -1  5 10    9    9    -1  6  1    6    8     1  7 10    4   -4    -1  9  2   12   12
-1  4 14    3   -3    -1  5  8    7   -6     1  6  0    2    3     1  7 11    7    6    -1  9  1    7   -7
-1  4 13   16   16    -1  5  7    6   -4     1  6  1   22  -23     1  7 12    4   -2     1  9  1    9   -9
-1  4 12   12   12    -1  5  6   33  -31     1  6  2    7   -8     1  7 13    4    3     1  9  2   12   12
-1  4 11   11  -11    -1  5  5    3   -2     1  6  3    3   -3     1  7 14    2   -2     1  9  3    9    8
-1  4 10    7    8    -1  5  4    4   -4     1  6  4   16   15    -1  8 14    5    4     1  9  4   14   14
-1  4  9    5    6    -1  5  2   16   16     1  6  5   10  -12    -1  8 12    3    2     1  9  5    4   -3
-1  4  8   17   17    -1  5  1   10  -10     1  6  7    9    8    -1  8 11    4   -4     1  9  8    2    2
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ØBSERVED AND CALCULATED STRUCTURE FACTØRS FØR  DETT                                                                   PAGE  4

 H  K  L   FØ   FC      H  K  L   FØ   FC      H  K  L   FØ   FC      H  K  L   FØ   FC      H  K  L   FØ   FC

 1  9  9    3   -4      2  0  2   47  -44      2  1 15    5   -5     -2  3 16    3    3     -2  4 13    7    7
 1  9 10    2    2      2  0  4   27  -26      2  1 16    5    4     -2  3 15    5    5     -2  4 12    7   -6
 1  9 11    4    3      2  0  6   17   17     -2  2 19    3   -2     -2  3 14    2    2     -2  4 11   11   11
-1 10  8    4    4      2  0  8    7   -6     -2  2 17    3    1     -2  3 13    3   -2     -2  4 10    4    5
-1 10  6    3   -1      2  0 12   15  -16     -2  2 15    3   -2     -2  3 12    9  -10     -2  4  8    2    2
-1 10  5    2   -3      2  0 14   11   13     -2  2 12   10  -10     -2  3 11   13   15     -2  4  7   19  -18
-1 10  4    8    8      2  0 18    3    0     -2  2 11   10   10     -2  3 10    8    8     -2  4  6    3    2
-1 10  2    5    3     -2  1 17    2   -2     -2  2 10    2   -2     -2  3  8   27  -27     -2  4  5    1    1
-1 10  1    9    8     -2  1 16    7    7     -2  2  9   29  -29     -2  3  7   49   48     -2  4  4   24  -22
 1 10  0   13  -13     -2  1 14    2   -3     -2  2  8   20   20     -2  3  5    8   -8     -2  4  3    7    7
 1 10  1    9   -9     -2  1 13    2   -2     -2  2  7    7   -6     -2  3  4    4    2     -2  4  2   34  -33
 1 10  2    8   -8     -2  1 12    2    0     -2  2  6   23  -22     -2  3  3   30  -29     -2  4  1    3    3
 1 10  3    9   10     -2  1 11    6   -7     -2  2  5   41   40     -2  3  2   12  -12      2  4  0   12   10
 1 10  4    7    7     -2  1 10   12  -12     -2  2  4   11  -11     -2  3  1   17  -17      2  4  1   41  -40
 1 10  5    5    4     -2  1  9   27   27     -2  2  2   53  -51      2  3  0   22   22      2  4  2   35   33
 1 10  6    4    4     -2  1  8   12   12     -2  2  1   15  -15      2  3  1   26  -27      2  4  3   20   19
 1 10  7    2    2     -2  1  7    4   -5      2  2  0   42  -40      2  3  2   39  -42      2  4  4   11  -10
 1 10  8    2   -3     -2  1  6    4   -5      2  2  1   16   16      2  3  3   32  -32      2  4  5   25  -25
-1 11  6    4   -3     -2  1  5   23  -23      2  2  2   42   42      2  3  4   27  -23      2  4  6   10    9
-1 11  5    7    6     -2  1  4   20   21      2  2  3   19  -20      2  3  5    3    3      2  4  7   10   11
-1 11  3    9    9     -2  1  3   29  -29      2  2  4   16   14      2  3  6    3   -2      2  4  8   37   38
-1 11  2    3   -2     -2  1  2   13   13      2  2  5   25   22      2  3  7   30   32      2  4  9   11   11
 1 11  0    9   -8     -2  1  1   31   32      2  2  6    8    9      2  3  8   32   34      2  4 10   28   30
 1 11  1    6   -7      2  1  0   60  -60      2  2  7    6    7      2  3  9   10    9      2  4 11   16   15
 1 11  2    8   -7      2  1  1   73   72      2  2  8   25   25      2  3 10   21  -22      2  4 12   28  -28
 1 11  3   11  -10      2  1  2   68   69      2  2  9    2    2      2  3 11   25  -25      2  4 13   10   10
-2  0 18    4   -4      2  1  3   11  -10      2  2 10    6   -6      2  3 12   14  -14      2  4 14    8   -8
-2  0 16    5    6      2  1  4   33  -33      2  2 11   10  -10      2  3 13   11  -12      2  4 15    3   -1
-2  0 14    3    1      2  1  5    4    4      2  2 12    9    9      2  3 14   11   11      2  4 16   11   11
-2  0 12    9    9      2  1  6   18   16      2  2 13    6    5      2  3 15    6   -5      2  4 17    5   -4
-2  0 10   16   15      2  1  7   29   28      2  2 14   11  -11      2  3 17    4    5     -2  5 17    4    3
-2  0  8   41  -41      2  1  8   11  -10      2  2 15    7    8     -2  4 18    5    5     -2  5 14    7   -8
-2  0  6   11  -12      2  1  9    6    5      2  2 17    2    1     -2  4 17    3   -2     -2  5 13   12   12
-2  0  4   11  -12      2  1 10    8   -7      2  2 18    3    2     -2  4 16    3   -3     -2  5 12    8    7
-2  0  2   29  -30      2  1 11    4    4     -2  3 19    6    5     -2  4 15    6   -6     -2  5 11   13  -13
 2  0  0   15  -16      2  1 13    4   -4     -2  3 17    2    1     -2  4 14   16  -16     -2  5 10    4   -4
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ØBSERVED AND CALCULATED STRUCTURE FACTØRS FØR  DETT

 H  K  L   FØ   FC     H  K  L   FØ   FC     H  K  L   FØ   FC     H  K  L   FØ   FC     H  K  L   FØ   FC

                       2  6  0   14   12     2  7 14    4    4     2  9  3    3   -3     3  0  6   39   39
-2  5  9    7    8     2  6  1    3   -4    -2  8 13    3    4     2  9  4    2   -3     3  0  8    9    8
-2  5  8    6    6     2  6  2   12  -12    -2  8 11    6   -6     2  9  6    2   -2     3  0 12    2   -1
-2  5  7   12   11     2  6  3   18  -19    -2  8 10    2    3     2  9  9    4   -4     3  0 14    2    1
-2  5  6   11  -10     2  6  4    5    5    -2  8  9   16  -16    -2 10  8    4    4    -3  1 19    3    3
-2  5  5   25   24     2  6  5    2    3    -2  8  8    3    3    -2 10  7    4   -4    -3  1 18    4   -4
-2  5  4   33  -33     2  6  7    3   -3    -2  8  7    2    0    -2 10  5    4   -4    -3  1 17    7    6
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 2  5 13   13  -13    -2  7  3   24   25     2  8 10    2   -1     2 11  1    9    8     3  1  1   16  -16
 2  5 14    7   -7    -2  7  2   18   18     2  8 11    3    0     2 11  2    7   -6     3  1  2   27   27
 2  5 16    6   -5    -2  7  1    2    0    -2  9 10    3    2     2 11  4    9   -8     3  1  3   28  -27
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-2  6  1   12   10
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ØBSERVED AND CALCULATED STRUCTURE FACTØRS FØR  DETT                                                              PAGE  6

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 -3  2 17    3   -3      -3  3 12    2    1      -3  4  7    5   -5      -3  5  3    9    9       3  6  3   18  -16
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  3  2 10    7    7       3  3 16    8    7      -3  5 14    4    3      -3  6  8    2    3       3  7  6    8   -8
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  3  2 17    5    6      -3  4 14    9    9      -3  5  8   11   11      -3  6  3   18  -18       3  7 12    3    2
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OBSERVED AND CALCULATED STRUCTURE FACTORS FOR  DETT                                                        PAGE  7

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 -3  8 11    7    8      3  9  6    7   -6      4  0 16    2    2     -4  2  5   20   21      4  3  2   18   17
 -3  8 10    2    1      3  9  7    4    2     -4  1  9   11   11     -4  2  4    4   -3      4  3  3    7    7
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 -3  8  7    4    3     -3 10  9    4    3     -4  1  5   33   34     -4  2  1   15  -15      4  3  6   15  -15
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  3  8  5    5   -6      3 10  7    6   -6      4  1  7   20  -19      4  2 12    4   -3     -4  4 15   16   16
  3  8  6    7   -6     -3 11  2    2   -2      4  1  8    8   -8      4  2 14    3    3     -4  4 14   17   17
  3  8  9    2   -1     -3 11  1    5   -5      4  1  9   15   15      4  2 15    2    1     -4  4 13   11  -12
  3  8 11    7    6      3 11  1    6   -6      4  1 10   12  -11     -4  3 17    8   -8     -4  4 12   17   18
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 -3  9 12    4   -3     -4  0 18    3    3      4  1 14    3   -3     -4  3 15    6   -5     -4  4  8   14  -15
 -3  9 11    2   -3     -4  0 16   13  -12      4  1 15    2    2     -4  3 14    9   -9     -4  4  6   22   20
 -3  9 10    2    2     -4  0 14    5    5     -4  2 19    4    4     -4  3 13    7    7     -4  4  5   13  -13
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ØBSERVED AND CALCULATED STRUCTURE FACTØRS FØR  DETT                                                      PAGE  8

  H  K  L    FØ   FC      H  K  L    FØ   FC      H  K  L    FØ   FC      H  K  L    FØ   FC      H  K  L    FØ   FC

  4  4  8    10  -10     -4  6 14     4   -4      4  7  4     6   -5      4  9  1     6    6      5  0 10    17  -18
  4  4  9     3    3     -4  6 13     7    7      4  7  6     3   -2      4  9  2     2    2      5  0 12    23   24
  4  4 11    10  -10     -4  6 11     9   -9      4  7  7     4    4      4  9  4     4    5     -5  1 19     6   -6
  4  4 12     3   -4     -4  6  9     5    5      4  7  8     4    3      4  9  5     2    1     -5  1 18     4   -5
  4  4 15     4    3     -4  6  8     4    4      4  7  9     3   -3      4  9  6     6    5     -5  1 17     7   -7
 -4  5 15     8   -8     -4  6  7     4   -4      4  7 11     6    5      4  9  8     7   -6     -5  1 16     6    7
 -4  5 14     8    7     -4  6  5     6    6      4  7 12     6   -5      4  9  9     4    3     -5  1 14     3    3
 -4  5 13     3   -3     -4  6  4    11  -12     -4  8 14     4   -4     -4 10  8     6   -6     -5  1 13    12  -12
 -4  5 12     5   -5     -4  6  3     3    3     -4  8 13     3   -3     -4 10  7     2   -1     -5  1 12     9   -9
 -4  5 11     6    7     -4  6  1     7    8     -4  8 12     2    1     -4 10  6     4   -4     -5  1 11    10   10
 -4  5 10    14  -14      4  6  0    12   12     -4  8 11    10   10     -4 10  5     3   -3     -5  1 10    10   10
 -4  5  9     6   -6      4  6  1    12   11     -4  8 10     4    2     -4 10  4     5    3     -5  1  9    15   14
 -4  5  8    11  -11      4  6  2     3   -4     -4  8  7     6   -6     -4 10  2     4    4     -5  1  8    11   11
 -4  5  7     3   -3      4  6  3     3   -3     -4  8  3    23.  24     -4 10  1     6    5     -5  1  7    10    9
 -4  5  6     2    3      4  6  4    17  -17     -4  8  2     5   -4      4 10  0     3   -2     -5  1  6    28   28
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 -4  5  4     3    3      4  6  7     3   -3      4  8  1     4    5      4 10  4     3    2     -5  1  4    54  -54
 -4  5  3     2    0      4  6  8     4    3      4  8  2     3    2      4 10  5     3    2     -5  1  3     4    4
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  4  5  1    33   32      4  6 13     4   -4      4  8  6     6   -5     -4 11  2     4    3      5  1  0    12   13
  4  5  2    21  -21     -4  7 15     2   -2      4  8  7     6   -5      4 11  0     2    0      5  1  1     3    3
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  4  5  7     3   -3     -4  7  7     8   -8     -4  9 11     3    3     -5  0 10    25  -25      5  1  6     2    2
  4  5  8     7   -6     -4  7  6     4    3     -4  9 10     4   -4     -5  0  8    25   24      5  1  7     4   -4
  4  5  9    21   22     -4  7  5     3    3     -4  9  9     4   -3     -5  0  6    75   71      5  1  8     4    4
  4  5 10     3   -4     -4  7  4    11  -12     -4  9  7     5    5     -5  0  4    26  -23      5  1  9     5   -5
  4  5 11     3   -2     -4  7  2    10  -11     -4  9  6     3   -3     -5  0  2    94  -91      5  1 10    11  -10
  4  5 12     2    1     -4  7  1    15   16     -4  9  5     9   -8      5  0  0    11   13      5  1 13     3    2
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  4  5 14     2    0      4  7  1     7   -7     -4  9  3     4   -3      5  0  4     2   -1      5  1 16     3   -1
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OBSERVED AND CALCULATED STRUCTURE FACTORS FOR DETT

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-5	2	15	2	3	-5	3	9	23	23	5	4	2	2	2	5	5	10	9	-9	-5	7	8	5	-6
-5	2	14	10	-11	-5	3	7	16	16	5	4	3	9	-10	5	5	12	2	3	-5	7	7	10	11
-5	2	13	5	6	-5	3	6	32	-32	5	4	4	17	17	5	5	14	2	-1	-5	7	6	7	7
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-5	3	19	5	-4	-5	4	6	3	-2	5	5	2	11	-11	5	6	13	4	-2	-5	8	2	6	-7
-5	3	18	5	4	-5	4	5	1	-2	5	5	3	3	1	-5	7	15	2	0	5	8	2	6	7
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-5	3	14	9	-9	-5	4	3	7	6	5	5	5	9	-9	-5	7	13	8	7	5	8	4	4	4
-5	3	13	13	12	-5	4	2	3	-2	5	5	6	3	4	-5	7	12	13	12	5	8	5	9	9
-5	3	12	12	12	-5	4	1	19	18	5	5	7	14	-14	-5	7	11	16	-16	5	8	6	3	2
-5	3	11	8	-7	5	4	0	5	5	5	5	8	2	-3	-5	7	10	6	6	5	8	7	3	-3

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OBSERVED AND CALCULATED STRUCTURE FACTORS FOR  DETT                                                                       PAGE 10

 H  K  L   FO   FC     H  K  L   FO   FC     H  K  L   FO   FC     H  K  L   FO   FC     H  K  L   FO   FC

 5  8  8    3   -4     6  0  8    5   -5    -6  2 16    3    0    -6  3  8    8    9    -6  4  1   25   24
 5  8  9    3   -3     6  0 10    6   -7    -6  2 15    2   -1    -6  3  7    7    7     6  4  0    3   -2
-5  9 11    3   -2     6  0 12    2   -2    -6  2 14    8   -7    -6  3  6    9   -9     6  4  1   18   18
-5  9  9    3   -3     6  0 14    3   -1    -6  2 13   13   14    -6  3  5    7    7     6  4  2    4    4
-5  9  8    8    7    -6  1 19   12   11    -6  2 12   12  -13    -6  3  4    2   -1     6  4  3   11  -11
-5  9  7    6    6    -6  1 18    7   -6    -6  2 11    5    5    -6  3  3    7    7     6  4  4    3   -4
-5  9  6    2    3    -6  1 17    2   -2    -6  2 10   29   29    -6  3  2    4   -4     6  4  6   14  -14
-5  9  5    4   -3    -6  1 16   11  -11    -6  2  9    3    2    -6  3  1   17   16     6  4  7   15  -15
-5  9  4    3    2    -6  1 15   22  -21    -6  2  8    6   -6     6  3  0   26   26     6  4  8    4    5
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-5  9  2    7   -7    -6  1 13   14  -14    -6  2  6   15   15     6  3  3   11  -10    -6  5 16    3    3
-5  9  1    5   -5    -6  1 12    6   -6    -6  2  5    9    8     6  3  4    2   -2    -6  5 15    2    1
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 6  0  4   35   35    -6  2 17   17  -17    -6  3  9    2   -2    -6  4  2   12  -12    -6  6 13    4   -5
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OBSERVED AND CALCULATED STRUCTURE FACTORS FOR  DETT

  H  K  L   FO   FC      H  K  L   FO   FC      H  K  L   FO   FC      H  K  L   FO   FC      H  K  L   FO   FC

 -6  6 12    9   -8      6  7  0   16   16     -6 10  2    2    2     -7  1  1   14   14      7  2  5    6   -6
 -6  6 11    7    8      6  7  1    3   -5     -6 10  1    5   -5      7  1  0    3    2      7  2  6    4   -5
 -6  6 10    6    7      6  7  2   11   12      6 10  0    4    4      7  1  1   12   12      7  2  8    6    7
 -6  6  9    7    8      6  7  4   13  -14      6 10  1    5   -4      7  1  2    5   -5      7  2 10    4   -3
 -6  6  8    9    8      6  7  5    5    5      6 10  2    3   -3      7  1  3    2   -3     -7  3 18    5   -4
 -6  6  7    2    0      6  7  6    6   -6     -7  0 16    9    9      7  1  4   15  -15     -7  3 17    3   -2
 -6  6  6    8   -7     -6  8 13    5    5     -7  0 14   18  -18      7  1  5   11  -11     -7  3 16    4   -4
 -6  6  5    3   -5     -6  8 12    6    6     -7  0 12   29  -29      7  1  6   11   11     -7  3 15    5    5
 -6  6  4    3    2     -6  8 11    3    3     -7  0 10    4   -4      7  1  7    5    4     -7  3 14    5   -4
 -6  6  3   10   10     -6  8 10    7    7     -7  0  8   11  -11      7  1  8    2   -1     -7  3 13   11   11
 -6  6  2    9    9     -6  8  9    9   10     -7  0  6   14  -15      7  1 10    4    3     -7  3 12   10  -10
 -6  6  1   11  -11     -6  8  8   15  -14     -7  0  4   25   24      7  1 11    2   -2     -7  3 11   20  -20
  6  6  0    4    4     -6  8  7   14   14     -7  0  2    8   -9      7  1 12    3   -4     -7  3 10   20   21
  6  6  1    4   -3     -6  8  5    5    4      7  0  0    3   -4      7  1 14    3    3     -7  3  9   24  -24
  6  6  2   12  -12     -6  8  4    6    7      7  0  2   21  -22     -7  2 18    3    3     -7  3  8    2   -2
  6  6  3    9   11     -6  8  3   24  -24      7  0  4    2    1     -7  2 17    4   -4     -7  3  7    6    6
  6  6  4   10  -10     -6  8  2    3   -1      7  0  6    8    8     -7  2 16    3    4     -7  3  6    2   -2
  6  6  5    5   -7     -6  8  1    3    2      7  0  8    2    0     -7  2 15   11  -11     -7  3  5    6   -6
  6  6  6   14   13      6  8  0    9   -9      7  0 10    4    4     -7  2 14    8    8     -7  3  4   18   19
  6  6  7    2   -1      6  8  1    2    0     -7  1 19    3    2     -7  2 13    5   -5     -7  3  3   10    9
  6  6  8    2    0      6  8  3    3   -3     -7  1 18    3   -3     -7  2 12   18  -18     -7  3  2    9    8
  6  6  9    2   -2      6  8  4    4    4     -7  1 17    8    8     -7  2 11   29   30     -7  3  1    8    7
  6  6 10    2   -1      6  8  5    3   -1     -7  1 16    4   -4     -7  2 10   13  -13      7  3  0   18   18
 -6  7 15    5   -5      6  8  7    2    3     -7  1 15   10   10     -7  2  9    2   -2      7  3  1   27   28
 -6  7 14   10  -10      6  8  9    7    6     -7  1 14   12  -11     -7  2  8    6    7      7  3  2    3    4
 -6  7 12    3    3     -6  9 10    2    1     -7  1 13   15  -16     -7  2  6    3   -3      7  3  3    9   -9
 -6  7 11    6    6     -6  9  7    7   -7     -7  1 12   21   21     -7  2  5    5    5      7  3  4    9   -9
 -6  7 10   20   20     -6  9  5    5   -6     -7  1 11   19  -19     -7  2  4    7   -8      7  3  5    4   -4
 -6  7  9    7   -7     -6  9  4    4   -4     -7  1  9   12   12     -7  2  3   12  -12      7  3  6   15  -16
 -6  7  8    6   -5     -6  9  3    8    7     -7  1  8    7    7     -7  2  2   20   20      7  3  7    3   -4
 -6  7  7    6   -7     -6  9  2    6   -7     -7  1  7   29   29     -7  2  1    8   -8      7  3  8   14   15
 -6  7  6   21  -21     -6  9  1    3    2     -7  1  6    3    2      7  2  0    5    6      7  3  9    3    4
 -6  7  5   17   18      6  9  2    3   -3     -7  1  5   24   23      7  2  1    2    2     -7  4 17    4    5
 -6  7  4    5    4      6  9  3    3    3     -7  1  4    8   -8      7  2  2    5    5     -7  4 16   10   10
 -6  7  2   15   15     -6 10  6    7   -7     -7  1  3    2   -1      7  2  3    3   -3     -7  4 15    7   -6
 -6  7  1   13  -12     -6 10  4    2   -3     -7  1  2   16  -15      7  2  4   18  -18     -7  4 14    4    3
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ØBSERVED AND CALCULATED STRUCTURE FACTØRS FØR  DETT

 H  K  L   FØ   FC     H  K  L   FØ   FC     H  K  L   FØ   FC     H  K  I   FØ   FC     H  K  L   FØ   FC

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-7  4 12    9    8     7  5  2    6    5    -7  7  8   15   14    -7  9  2    5   -4     8  1  0   10  -10
-7  4 11    4   -4     7  5  3    2    1    -7  7  7   17   17    -7  9  1    8    7     8  1  1    4    4
-7  4 10   11  -10     7  5  4    6    6    -7  7  6    8   -7     7  9  0    4    4     8  1  2    9   -9
-7  4  9   17   17     7  5  5    5   -5    -7  7  5    3   -3     7  9  1    4   -2     8  1  3    9    9
-7  4  8   18  -19     7  5  7    4    3    -7  7  4    9   -9     7  9  3    4   -3     8  1  4    3    0
-7  4  6   18   17     7  5  8    8   -9    -7  7  3    3    3    -8  0 18    9    7     8  1  5    3    2
-7  4  5   10   10     7  5  9    2    3    -7  7  2    4    3    -8  0 16    4    4     8  1  7    3    2
-7  4  4   19   18     7  5 10    2   -3    -7  7  1   10  -10    -8  0 14    4   -4     8  1  8    2   -1
-7  4  3    7   -8     7  5 11    2    2     7  7  0   10   11    -8  0 12    8   -7     8  1  9    4   -3
-7  4  2   17  -17    -7  6 15    3    3     7  7  1    4    3    -8  0 10    2    1     8  1 11    3   -3
-7  4  1    9   -8    -7  6 14    4    3     7  7  2    7    7    -8  0  8   14   14    -8  2 17    3   -1
 7  4  2   19   19    -7  6 13    5   -4     7  7  3    3    2    -8  0  6   16  -16    -8  2 16    2    1
 7  4  3   11   11    -7  6 12   11  -11     7  7  8    3   -3    -8  0  4   17  -17    -8  2 15    2   -1
 7  4  4    3    2    -7  6 10    7   -8     7  7  9    4    4    -8  0  2   15   14    -8  2 13    4   -4
 7  4  5   11   12    -7  6  9   10  -10    -7  8 12    3   -3     8  0  0    9   -8    -8  2 12    8    8
 7  4  6   23  -24    -7  6  8   18   19    -7  8 10    4    4     8  0  2    2    2    -8  2 11    4   -3
 7  4  8    8   -8    -7  6  7   23   22    -7  8  9    3    3     8  0  6    5    4    -8  2 10    2   -3
 7  4  9    2   -2    -7  6  6    4    3    -7  8  8    2    2     8  0  8   10  -10    -8  2  9   14   14
 7  4 10    8    8    -7  6  5   15   16    -7  8  7    7    7     8  0 10    8    8    -8  2  8   27  -29
 7  4 11    2   -2    -7  6  4   18  -18    -7  8  6    3    3    -8  1 18    3   -1    -8  2  7    7    8
 7  4 12    3    1    -7  6  1    6   -7    -7  8  5   16   17    -8  1 17    3    2    -8  2  6   10  -10
-7  5 15    2    1     7  6  0   10    9    -7  8  4    5   -4    -8  1 16    3   -4    -8  2  5   16  -16
-7  5 12    6   -6     7  6  1    3    3    -7  8  3    4   -4    -8  1 15    4   -4    -8  2  3   17  -17
-7  5 11    2   -1     7  6  2   10  -10    -7  8  2    5   -4    -8  1 14    3   -3    -8  2  2   13   13
-7  5 10   21  -22     7  6  3    4    3    -7  8  1    5   -6    -8  1 13    8    8    -8  2  1   13   13
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-7  5  4    5    4     7  6 10    3    2    -7  9  9    7    6    -8  1  6   20  -20     8  2  5    3    3
-7  5  3    9   -9    -7  7 14    3   -3    -7  9  8    3    3    -8  1  5   17   18     8  2  6    3    2
-7  5  2   13  -13    -7  7 13    3   -4    -7  9  7    5   -4    -8  1  4   14   14     8  2  8    3    2
-7  5  1   19   19    -7  7 12    9   -9    -7  9  5    5   -5    -8  1  3    5    5     8  2  9    5    4
 7  5  0   13  -13    -7  7 11    3   -3    -7  9  4    4   -3    -8  1  2   16  -16     8  2 10    6   -5
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ØBSERVED AND CALCULATED STRUCTURE FACTØRS FØR  DETT                                                          PAGE 13

   H   K   L    FØ    FC       H   K   L    FØ    FC       H   K   L    FØ    FC       H   K   L    FØ    FC       H   K   L    FØ    FC

   8   2  11     3     4      -8   4   5     5     4      -8   6  14     3     3      -8   8   5     7    -8      -9   1   8     7    -8
   8   2  12     2     2      -8   4   4    21    21      -8   6  13     4    -3      -8   8   4     6     6      -9   1   7    16   -15
  -8   3  16     3    -3      -8   4   3    19    19      -8   6  11    11   -10      -8   8   3     3     3      -9   1   6    12   -12
  -8   3  15    10     9      -8   4   2    35    36      -8   6   9     7    -7      -8   8   2     3    -3      -9   1   5     7    -8
  -8   3  13     3     3       8   4   0    13   -14      -8   6   8     7     7      -8   8   1     3     3      -9   1   3     9    -9
  -8   3  12     7    -7       8   4   1     7     7      -8   6   7    14   -13       8   8   0     5    -6      -9   1   2     2    -1
  -8   3  11    16    15       8   4   2     8     9      -8   6   6     2     2       8   8   3     6     7      -9   1   1    21   -20
  -8   3  10     5    -5       8   4   4    13    13      -8   6   5    19    20       8   8   4     3     3       9   1   0    11    12
  -8   3   9     6    -6       8   4   5     6     8      -8   6   3    16    16      -8   9   7     2    -1       9   1   2    17   -17
  -8   3   8     9     9       8   4   6     2     3      -8   6   2     2    -1      -8   9   6     6     6       9   1   3    15    15
  -8   3   7    28   -28       8   4   7    10     9      -6   6   1     4    -4      -8   9   5     2    -1       9   1   4     6    -6
  -8   3   6     2     3       8   4   8     9    -9       8   6   0     4     5      -8   9   4     3    -3       9   1   5     2     3
  -8   3   5    15   -16       8   4   9     4    -4       8   6   1    11    11      -8   9   2     2     2       9   1   6    11    11
  -8   3   4    22   -23       8   4  11     2     0       8   6   2     6    -5      -8   9   1     4     2       9   1   8     3     3
  -8   3   3    10     9      -8   5  15     8    -8       8   6   3     2     3       8   9   0     6    -6       9   1   9     5     4
  -8   3   2    33    34      -8   5  13    10    10       8   6   6     6     6       8   9   1     4    -4       9   1  10     5    -5
  -8   3   1    19    19      -8   5  11     7     7       8   6   9     2     0      -9   0  16     4     4      -9   2  17     5    -5
   8   3   0     4    -4      -8   5  10    16   -16      -8   7  13     8    -8      -9   0  14     9     9      -9   2  14     8     8
   8   3   2    16    17      -8   5   9     3     4      -8   7  12     7    -6      -9   0  12    17   -17      -9   2  13     6     6
   8   3   3    11   -11      -8   5   8    14   -13      -8   7  11     4     3      -9   0  10    15    15      -9   2  12    14    14
   8   3   5     3     3      -8   5   7    22   -22      -8   7  10     4    -4      -9   0   8    24    25      -9   2  10    14   -14
   8   3   6    10   -10      -8   5   6    15    15      -8   7   8    12    12      -9   0   6    22    22      -9   2   9     4    -5
   8   3   7    13   -13      -8   5   5    11   -10      -8   7   7     6     6      -9   0   4    26   -27      -9   2   8     8     9
   8   3   9     4    -5      -8   5   4    21    22      -8   7   6     6     6      -9   0   2     4    -2      -9   2   7     5     5
   8   3  10     3     4      -8   5   3    16    16      -8   7   5     2     2       9   0   0     2     0      -9   2   6     8    -8
  -8   4  17     9     8      -8   5   2     4     4      -8   7   4     9     9       9   0   2     8     7      -9   2   5     5     5
  -8   4  16     3     0      -8   5   1     6     5      -8   7   3     3    -3       9   0   4    21    21      -9   2   4     3    -4
  -8   4  15     2    -2       8   5   0     2     0      -8   7   2     7     8       9   0   6    12   -12      -9   2   3    18   -17
  -8   4  13     9    -9       8   5   1    10   -10      -8   7   1    11   -10       9   0  10     4     3      -9   2   2    16   -17
  -8   4  12     6     5       8   5   2     5     6       8   7   0     2    -2      -9   1  15     5    -5       9   2   0     8     8
  -8   4  11     8    -8       8   5   4     9     9       8   7   2     4     3      -9   1  14     7    -7       9   2   1    15   -15
  -8   4  10     3     3       8   5   5     6    -7      -8   8  11     6     5      -9   1  13     3     3       9   2   2    20    20
  -8   4   9     3    -3       8   5   6     3     4      -8   8  10     3     2      -9   1  12    10     9       9   2   3    18   -19
  -8   4   8    20   -20       8   5   7     5     5      -8   8   9     7    -6      -9   1  11     3     3       9   2   4     5    -5
  -8   4   7    16    16       8   5   8     7    -6      -8   8   7     7    -7      -9   1  10     6     6       9   2   5     7     6
  -8   4   6    31   -32       8   5   9     4    -5      -8   8   6     5     5      -9   1   9     4    -4       9   2   6     8    -8
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ØBSERVED AND CALCULATED STRUCTURE FACTØRS FØR  DETT                                                          PAGE 14

   H   K   L    FØ    FC       H   K   L    FØ    FC       H   K   L    FØ    FC       H   K   L    FØ    FC       H   K   L    FØ    FC

   9   2   8     7     6      -9   4   5     5     5      -9   6   2    13   -12      10   0   2    16   -16     -10   2   5     6    -5
   9   2   9     3     2      -9   4   4    25   -25      -9   6   1    18    17      10   0   4     4     5     -10   2   4     9     9
   9   2  10     5    -4      -9   4   3    27    27       9   6   1    11    11      10   0   6    25    25     -10   2   3    10   -10
  -9   3  16     3    -3      -9   4   2     4     4       9   6   2     3     3      10   0   8     5     4     -10   2   2    17   -18
  -9   3  15    11    10      -9   4   1     7    -6       9   6   3     2     0     -10   1  16     2    -1      10   2   0     8    -7
  -9   3  14     6     7       9   4   0    18    18       9   6   4     2     1     -10   1  15     2    -2      10   2   1     3    -3
  -9   3  13     3     2       9   4   1     9    -9      -9   7  11     4    -4     -10   1  13     5    -5      10   2   3     4    -4
  -9   3  12     5    -4       9   4   4    10   -10      -9   7  10    10   -10     -10   1  11    13    13      10   2   4     5     5
  -9   3  11     7    -7       9   4   5     7    -6      -9   7   9     4     4     -10   1  10    19    19      10   2   5    10    -9
  -9   3  10     2     1       9   4   8     3    -2      -9   7   8     9    -8     -10   1   9    19    20      10   2   6     3     2
  -9   3   9     3     4      -9   5  15     3     2      -9   7   7    11    10     -10   1   8     9    -9      10   2   7     2     2
  -9   3   7     7     6      -9   5  14     3    -3      -9   7   5     2     2     -10   1   6    16   -17      10   2   9     8     7
  -9   3   5    19   -20      -9   5  12     4     4      -9   7   4     3     3     -10   1   5     5    -4     -10   3  16     4     3
  -9   3   4     4    -3      -9   5  11     4     4      -9   7   3     5    -4     -10   1   4     2     4     -10   3  15     4     4
  -9   3   3    10   -10      -9   5  10     5    -4      -9   7   2     3     3     -10   1   3     4     3     -10   3  14     6    -6
  -9   3   2    16   -16      -9   5   8    13   -13      -9   7   1    11   -11     -10   1   2     5     5     -10   3  13     2     2
  -9   3   1    13    14      -9   5   5     5     5       9   7   0     5    -5     -10   1   1     8    -8     -10   3  12     2     3
   9   3   0    17   -17      -9   5   4     9    10       9   7   3     8     6      10   1   0     9     8     -10   3  10     4    -4
   9   3   1    19    20      -9   5   3    17   -17       9   7   5     3    -2      10   1   1     7    -7     -10   3   8     6     6
   9   3   2     7    -7      -9   5   2    12    13      -9   8   9     3     4      10   1   2     4    -3     -10   3   7     9    -9
   9   3   3     7     6      -9   5   1     3     3      -9   8   7     3    -1      10   1   3     6    -6     -10   3   6     6     6
   9   3   4    13    12       9   5   0     2     3      -9   8   5    10   -10      10   1   4    10    -9     -10   3   4    11   -12
   9   3   5     7    -7       9   5   1    15    14      -9   8   4     5     5      10   1   5    10    10     -10   3   3     4    -3
   9   3   6     5     4       9   5   2     3     3      -9   8   2     3    -1      10   1   6     6    -6     -10   3   2     7    -7
   9   3   7     3    -2       9   5   4     7     6      -9   8   1     4     5      10   1   7     8     8     -10   3   1    10    10
   9   3  10     3     3       9   5   5     2    -3       9   8   0     7    -6      10   1   8    14    14      10   3   0    11   -11
  -9   4  16     4     4       9   5   6     6     5       9   8   1    10   -10      10   1   9     4    -4      10   3   1     9    -9
  -9   4  15     5     5       9   5   7     2    -2     -10   0  16     5    -5     -10   2  15     4    -4      10   3   2     7    -6
  -9   4  14     7     7       9   5   8     2     0     -10   0  14     2    -1     -10   2  14     2    -3      10   3   3     4     4
  -9   4  13     6    -6      -9   6  14     3     3     -10   0  12    11   -11     -10   2  13     9     8      10   3   4     9    -8
  -9   4  11    10    -9      -9   6  11     5    -5     -10   0  10     4     3     -10   2  12     9    10      10   3   5     5     5
  -9   4  10     5     5      -9   6   9     6    -6     -10   0   8     7     8     -10   2  11     4     4      10   3   6     5     5
  -9   4   9     3    -4      -9   6   8     2     2     -10   0   6     2    -5     -10   2   9     2    -3     -10   4  15     4     4
  -9   4   8     4    -5      -9   6   7     7    -7     -10   0   4    16   -15     -10   2   8    12   -13     -10   4  14     3     2
  -9   4   7    15   -15      -9   6   6    10    10     -10   0   2     2    -2     -10   2   7     3    -4     -10   4  13     4    -2
  -9   4   6     9    -9      -9   6   3     8     8      10   0   0    13   -13     -10   2   6     5     6     -10   4  12     5     5
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OBSERVED AND CALCULATED STRUCTURE FACTORS FOR  DETT                                                          PAGE 15

   H  K  L   FO   FC      H  K  L   FO   FC      H  K  L   FO   FC      H  K  L   FO   FC      H  K  L   FO   FC

 -10  4 11    4    5     10  6  0    9   -9    -11  1 11    4   -5    -11  3  6    2   -1    -11  6  2    4   -4
 -10  4 10    7    6     10  6  1    9   -9    -11  1 10    9    9    -11  3  5    5   -5    -11  6  1    8   -7
 -10  4  9    4   -4     10  6  2    4   -5    -11  1  8    4   -3    -11  3  3    2    0     11  6  0    3   -2
 -10  4  8    2    3     10  6  3    5    4    -11  1  7   16   17    -11  3  2   10  -11     11  6  1    3    2
 -10  4  7    3   -4     10  6  4    7    7    -11  1  6    5   -5    -11  3  1    6    6     11  6  2    5    4
 -10  4  6    9   -9    -10  7 10    2   -2    -11  1  5    5    5     11  3  1    6   -6    -11  7  6    3   -2
 -10  4  5   13  -13    -10  7  9    4    4    -11  1  4    5   -5     11  3  2    7   -6    -11  7  5    4    3
 -10  4  4    6   -5    -10  7  8    4   -5    -11  1  3   10  -10     11  3  3    4   -5    -11  7  4    2   -1
 -10  4  2    3    4    -10  7  7    3    3    -11  1  2   12   12     11  3  4    3   -3    -11  7  3    6   -5
 -10  4  1    8    8    -10  7  6   10  -10    -11  1  1    6   -6     11  3  5    6   -5    -12  0 14    4   -4
  10  4  0    3    2    -10  7  5    5    5     11  1  0    8    8    -11  4 12    3   -1    -12  0 12    4   -3
  10  4  1    8    8    -10  7  4    5   -4     11  1  1    2    2    -11  4 11    2   -1    -12  0 10   12   12
  10  4  3    5    5    -10  7  3    5   -4     11  1  4    9   -8    -11  4  9    8    8    -12  0  8   16   16
  10  4  4    5   -5    -10  7  2    3   -4     11  1  5    2   -2    -11  4  8    2    2    -12  0  6   13  -13
  10  4  5    3   -3    -10  7  1    5    4     11  1  7    2   -1    -11  4  7    2    0    -12  0  4    4    4
 -10  5 13    3    3     10  7  0    3   -4    -11  2 15    5   -6    -11  4  6    3    2    -12  0  2   10   10
 -10  5 12    3   -4     10  7  1    7   -6    -11  2 14    2    1    -11  4  1    2   -2     12  0  2    5   -4
 -10  5 11    5    4     10  7  2    5   -5    -11  2 13    5    5     11  4  0   10   10     12  0  4    3   -3
 -10  5  9    4   -4     10  7  3    2    0    -11  2 11    4    4     11  4  4    3   -2    -12  1 14    4   -3
 -10  5  8    6   -5    -10  8  5   10   -9    -11  2 10    6   -5     11  4  5    2    2    -12  1 12    3    3
 -10  5  5    3   -2    -10  8  3    4   -4    -11  2  9    2    1    -11  5 10    5   -4    -12  1 11    7   -7
 -10  5  3   14   13    -10  8  2    6    5    -11  2  8    4   -4    -11  5  9    2    0    -12  1 10    4    4
 -10  5  2    5    4    -11  0 14    8   -7    -11  2  7    3    2    -11  5  7    2   -1    -12  1  9    5   -5
 -10  5  1   13  -13    -11  0 12    6    6    -11  2  6    9    9    -11  5  6    2   -1    -12  1  8    9   -8
  10  5  0    4   -4    -11  0 10    6    6    -11  2  5   12  -13    -11  5  4    3    3    -12  1  6    4   -4
  10  5  1    2   -2    -11  0  8    5    6    -11  2  4   10   10    -11  5  2    4    3    -12  1  5    3    4
  10  5  3    6    7    -11  0  6    3    4    -11  2  3    7   -7    -11  5  1    4   -4    -12  1  4    5    5
  10  5  5    5    5    -11  0  4    9   -9    -11  2  2    4   -5     11  5  0   12   11    -12  1  3    3    1
  10  5  6    4   -3    -11  0  2    3   -3     11  2  0   13  -13     11  5  2    3    3    -12  1  2    2   -3
 -10  6 12    5    4     11  0  0    4    3     11  2  1    3   -4     11  5  3    4   -4    -12  1  1    6   -6
 -10  6 11    7   -6     11  0  2   16  -16     11  2  2   10   10     11  5  4    5   -5     12  1  1    3   -2
 -10  6 10    3    2     11  0  4    3   -1     11  2  6    2   -3    -11  6 10    4    4     12  1  2    2    3
 -10  6  6    2    0     11  0  8   11   10     11  2  7    4   -3    -11  6  9    7   -6    -12  2 13    5   -5
 -10  6  5    3    2    -11  1 15    2   -1    -11  3 13    6    6    -11  6  8    7    6    -12  2 11    3    3
 -10  6  3    9   -8    -11  1 14    4    4    -11  3 10    3   -3    -11  6  6    3    2    -12  2 10    2    1
 -10  6  1    4    4    -11  1 13    3   -3    -11  3  8    6    5    -11  6  5    2    1    -12  2  9    4    4
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OBSERVED AND CALCULATED STRUCTURE FACTORS FOR  DETT                                                              PAGE 16

  H  K  L    FO    FC      H  K  L    FO    FC      H  K  L    FO    FC      H  K  L    FO    FC      H  K  L    FO    FC

-12  2  8     4    -3    -12  3  2     2    -2     12  4  2     4    -4    -13  1  8     3    -2    -13  2  1     3     2
-12  2  7     2     3    -12  3  1     8     8     12  4  3     4    -4    -13  1  7     2    -2     13  2  0     4     4
-12  2  6     3     3     12  3  0     3     3    -12  5  9     2    -1    -13  1  6     4    -3    -13  3  9     4     3
-12  2  5     3    -2     12  3  3     5    -4    -12  5  8     3    -2    -13  1  5     8     7    -13  3  8     6     6
-12  2  4     3     3     12  3  4     4     3    -12  5  7     3     2    -13  1  4     4     5    -13  3  7     2     0
-12  2  3     3    -3    -12  4 11     3    -2    -12  5  6     3     3    -13  1  3     3    -2    -13  3  6     4     3
-12  2  2     4     4    -12  4  8     6    -6    -12  5  1     4     3    -13  2  9     2    -2    -13  3  5     4    -4
-12  2  1     2    -2    -12  4  6     5    -5    -13  0  8     5     5    -13  2  8     2    -1    -13  3  4     9    -9
 12  2  0     5    -5    -12  4  5    12    11    -13  0  6     5    -5    -13  2  7     5     6    -13  3  3     5     4
 12  2  1    10   -10    -12  4  4     5     5    -13  0  4     4    -4    -13  2  6     7     6    -13  3  2     6     5
-12  3 12     4    -2    -12  4  3     4    -4     13  0  0     3     2    -13  2  5     2    -3     13  3  0     3    -4
-12  3 10     3     3    -12  4  2     3     0     13  0  2     2     0    -13  2  3     3    -3    -13  4  6     7    -7
-12  3  4     4    -3     12  4  0     3     2    -13  1 11     9     9    -13  2  2     5    -4    -13  4  5     2     3
-12  3  3     6     6     12  4  1     2     1    -13  1  9     3    -2
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ANALYSIS ØF VARIANCE FØR DETT

                    GGG    UGG    GUG    UUG    GGU    UGU    GUU    UUU    ALL
        N           385    382    349    333    337    280    366    336   2768
        V            71     65     65     66     64     69     61     61     65

SIN THETA     0.00 -  .20 -  .25 -  .28 -  .32 -  .34 -  .36 -  .38 -  .40 -  .42 -  .44
        N           318    288    230    381    227    250    251    288    263    272
        V            99     89     71     69     63     53     47     35     42     40

SQRT(F/FMAX)  0.00 -  .15 -  .18 -  .20 -  .22 -  .24 -  .27 -  .31 -  .36 -  .44 - 1.00
        N           292    402    263    241    198    274    272    285    280    261
        V            32     39     40     45     63     67     72     94     84     88

      ABS(H)   0      1      2      3      4      5      6      7      8      9     10     11     12     13      *
    REST
        N     274    292    287    285    252    254    233    217    190    155    139     95     62     33      0
        V      72     77     82     71     68     68     58     54     48     51     49     44     37     41      0

      ABS(K)   0      1      2      3      4      5      6      7      8      9     10     11     12     13      *
    REST
        N     180    356    356    341    322    292    254    234    186    132     86     29      0      0      0
        V      77     65     63     66     73     61     72     68     55     46     37     58      0      0      0

      ABS(L)   0      1      2      3      4      5      6      7      8      9     10     11     12     13      *
    REST
        N     109    212    226    199    220    200    198    173    192    156    158    132    135    107    351
        V      83     80     76     67     76     73     73     67     72     53     52     52     47     39     42
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ØBSERVED AND CALCULATED STRUCTURE FACTØRS FØR C'GT                                                            PAGE  1

  H  K  L   FØ   FC     H  K  L   FØ   FC     H  K  L   FØ   FC     H  K  L   FØ   FC     H  K  L   FØ   FC

  0  0  4   57   61    -2  0  6   60   61    -4  0  4   49  -53    -6  0  6    4   -5     9  0  4    8   -8
  0  0  6   41  -40    -2  0  8    1   -1    -4  0  6   33  -33    -6  0  8    5   -5     9  0  0   11  -11
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ØBSERVED AND CALCULATED STRUCTURE FACTØRS FØR   CGT                                                          PAGE  2

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-1 1 17   11   -11      -2 1 13    8    -8      -3 1 11    5    -5      -4 1 10   15   -15      -5 1 10    5    -3
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ØBSERVED AND CALCULATED STRUCTURE FACTØRS FØR C G T

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ØBSERVED AND CALCULATED STRUCTURE FACTØRS FØR CGT

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-1	2	9	38	-37	-2	2	6	38	40	-3	2	2	48	48	-4	2	2	29	28	-5	2	2	9	-9
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OBSERVED AND CALCULATED STRUCTURE FACTORS FOR   CGT                                                    PAGE  5

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 -6  2  3   10   11      -7  2 10   15   15      -8  2 19    4   -5     -10  2 10    6    6       1  3 10    6   -6
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 -6  2  8    6   -6      -7  2 14    7    7       9  2  3    2    0     -11  2  4    2    0       1  3  6    5    4
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 -6  2 11    6    5      -7  2 17    7   -6       9  2  0    4   -4     -11  2 13    6   -6       1  3  3   24  -21
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OBSERVED AND CALCULATED STRUCTURE FACTORS FOR   CGT                                                    PAGE  6

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  2  3  2   21  -21     3  3  0   23  -23    -4  3  2   45   45    -5  3  4   36  -37    -6  3  8   12   12
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OBSERVED AND CALCULATED STRUCTURE FACTORS FOR CGT

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 -7  3  7   12   13     -8  3 16    3   -3    -10  3 13    3   -3      1  4 12    7   -7      2  4 11   25   25
 -7  3  8    9   -9     -8  3 18    4    3    -10  3 17    2   -1      1  4 11   14   14      2  4 10    9   -8
 -7  3  9    5    5     -8  3 19    2    3    -11  3  4    4    4      1  4 10   10  -10      2  4  9   19  -19
 -7  3 10    6   -6     -8  3 20    2    0    -11  3  6    2   -1      1  4  9   32   31      2  4  8    5   -4
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 -7  3 13   10   10      9  3  3    2   -1    -11  3  8    3    3      1  4  7   12  -12      2  4  6   23   22
 -7  3 14    6   -6      9  3  1    3    3    -11  3 10    5   -5      1  4  6    2   -1      2  4  5   37  -36
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 -7  3 16    4    5     -9  3  1    2   -2    -11  3 12    2   -2      1  4  4   24   22      2  4  3    2    3
 -7  3 18    2   -1     -9  3  2    7   -7    -11  3 13    2   -1      1  4  3   46  -47      2  4  2   27   24
 -7  3 19    5   -4     -9  3  3    4    5    -11  3 14    3    2      1  4  2    4    4      2  4  1   44  -43
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  8  3  7    3   -4     -9  3  7    2   -2      0  4  3   28   28      1  4  0   12  -11     -2  4  1   57  -58
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 -8  3  5    9   10     10  3  0    4    4      0  4 14   11   11     -1  4 13   16  -16     -2  4 12   17  -17
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 -8  3 10    9   10    -10  3  5    2   -3      1  4 18    5    5     -1  4 20    3   -3     -2  4 17    6   -6
 -8  3 11    4   -5    -10  3  6    4    3      1  4 17   13  -13      2  4 17    9    8     -2  4 18    6    5
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OBSERVED AND CALCULATED STRUCTURE FACTORS FOR  CGT                                                              PAGE  8

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  3  4 12   12   12       4  4  9    8    8       5  4  5   26  -26      -6  4  3    2    1      -7  4 11   14  -14
  3  4 11   14  -14       4  4  8    2   -1       5  4  3   13   12      -6  4  4    6    6      -7  4 12    2    1
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  3  4  9   29   29       4  4  6   19  -19       5  4  1   19  -20      -6  4  6    4   -4      -7  4 15    6   -6
  3  4  7   28  -28       4  4  5   12   12       5  4  0    7    8      -6  4  7   18   18      -7  4 16    4   -4
  3  4  6   13   13       4  4  3    2   -3      -5  4  1   24  -24      -6  4  8    8    8      -7  4 17    8    9
  3  4  5   49   48       4  4  2    4    3      -5  4  2   11   11      -6  4  9   20  -20      -7  4 19    6    6
  3  4  4   10    9       4  4  1    7    8      -5  4  3    9    9      -6  4 10    4   -3      -7  4 20    2    1
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  3  4  2   14   13      -4  4  1   49   50      -5  4  5   22  -21      -6  4 12    3    3       8  4  7   10  -10
  3  4  1   22  -20      -4  4  2   13  -13      -5  4  6    9   -9      -6  4 13    7   -7       8  4  6    6    5
  3  4  0   18   16      -4  4  3    9   -9      -5  4  8    4    4      -6  4 14    3    4       8  4  5    3    0
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 -3  4  2   44  -44      -4  4  5   46   46      -5  4 10    6    6      -6  4 16    5    4       8  4  3    9   -8
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 -3  4  4    4   -4      -4  4  8   17   18      -5  4 12    2    1      -6  4 18    2    3      -8  4  1    2   -2
 -3  4  5   12   10      -4  4  9    4   -4      -5  4 13   15   14       7  4  9    3   -2      -8  4  2   10  -10
 -3  4  6   10    9      -4  4 10   15   15      -5  4 14    5   -4       7  4  8    2    2      -8  4  3    8    8
 -3  4  7   48   47      -4  4 11   12  -12      -5  4 15   10  -10       7  4  7   10    9      -8  4  5   16  -15
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 -3  4  9    6   -5      -4  4 13   22  -22      -5  4 17    8    7       7  4  5    4   -4      -8  4  7    2    2
 -3  4 11    8    8      -4  4 14   20  -20      -5  4 18    3   -3       7  4  4    2   -2      -8  4  9   18  -17
 -3  4 12    6   -7      -4  4 15    3   -4       6  4 11    7   -7       7  4  3   11   11      -8  4 10    3    3
 -3  4 13   27  -28      -4  4 16   10  -10       6  4 10    4   -4       7  4  2    3   -3      -8  4 11    3   -2
 -3  4 14   13  -13      -4  4 17    6   -6       6  4  8    3   -4       7  4  1    6   -5      -8  4 12    2    3
 -3  4 15   14  -14      -4  4 18    6   -6       6  4  7   20  -20      -7  4  1   16   17      -8  4 14    2   -2
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 -3  4 21    8    7       5  4 11    2    2       6  4  2    2    3      -7  4  5   15   14      -8  4 20    2    2
  4  4 15    8    8       5  4 10    4   -4       6  4  1   18   18      -7  4  7    4   -4       9  4  2    4   -4
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OBSERVED AND CALCULATED STRUCTURE FACTØRS FØR  CGT                                                          PAGE  9

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 -9  4  7    5   -6     0  5  9   13   13    -1  5 10   36  -37    -2  5 10   11  -10    -3  5 12   19  -19
 -9  4  8   10  -10     0  5 10   11   11    -1  5 11   18  -19    -2  5 11   23  -23    -3  5 13    2    2
 -9  4  9    2   -2     0  5 11    9    9    -1  5 12   11  -12    -2  5 13   21  -22    -3  5 14    2   -3
 -9  4 11    2    2     0  5 12   12  -12    -1  5 13   24  -25    -2  5 14   18  -18    -3  5 16   17  -16
 -9  4 12    3    4     0  5 13    4   -4    -1  5 14    7    7    -2  5 15   11   12    -3  5 17   11   11
 -9  4 13    2   -1     0  5 14    3    3    -1  5 16    2    2    -2  5 16    4    4    -3  5 18    3   -2
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-10  4 10    5   -5     1  5 12   32   33     2  5 10    2    0     3  5 10    8   -8     4  5  7    7    6
-10  4 11    4   -4     1  5 11    4    3     2  5  9    7   -7     3  5  9    3   -3     4  5  6    5   -4
-10  4 13    2    3     1  5 10    2    0     2  5  8    2   -2     3  5  7   12   12     4  5  5   29  -29
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-10  4 17    4    4     1  5  6   15  -15     2  5  4    4   -4     3  5  3    9   -7     4  5  1    8    7
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  0  5  2   35   35    -1  5  3   43   42    -2  5  3    5   -5    -3  5  4   14   16    -4  5  6   17  -16
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ØBSERVED AND CALCULATED STRUCTURE FACTØRS FØR  CGT                                                        PAGE 10

   H  K  L   FØ    FC       H  K  L   FØ    FC       H  K  L   FØ    FC       H  K  L   FØ    FC       H  K  L   FØ    FC

  -4  5  8   11    11      -5  5 16    6     5       7  5  8    3    -2       8  5  1    8     8      -9  5 16    2     2
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  -4  5 10   18   -18      -5  5 20    2     0       7  5  6    3    -3      -8  5  1    3     4     -10  5  2    5     5
  -4  5 12   16    16      -5  5 21    2     2       7  5  5   10   -10      -8  5  2    4    -4     -10  5  3    2    -3
  -4  5 13   10   -11       6  5 11   12    11       7  5  4    2     1      -8  5  3    2     2     -10  5  5    2    -2
  -4  5 14    6     6       6  5 10   16   -17       7  5  3    3     3      -8  5  4    7    -6     -10  5  6    5     5
  -4  5 15    7     8       6  5  9    4     3       7  5  2   18   -19      -8  5  5    5    -5     -10  5  7    6    -5
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  -4  5 17    6    -6       6  5  7    4     4       7  5  0   12    12      -8  5  7   10   -10     -10  5 10    2     2
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   5  5 10   11    11       6  5  5    2     3      -7  5  2   15    15      -8  5 10    6     6     -10  5 13    4     4
   5  5  9    8     8       6  5  4    7     6      -7  5  3    6    -6      -8  5 11    6     6     -10  5 14    4    -3
   5  5  8   11   -10       6  5  3    8    -8      -7  5  4   22   -23      -8  5 12    2    -2       0  6  2   36    37
   5  5  7    3     3       6  5  2    6     5      -7  5  5    8    -8      -8  5 13    5     5       0  6  3   26    26
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   5  5  5    7    -8      -6  5  1    3    -3      -7  5  7    3    -3      -8  5 16    2     2       0  6  5    7    -7
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  -5  5  1    4     4      -6  5  7   10   -10      -7  5 13    4     3      -9  5  2    5     5       0  6 11   26   -26
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  -5  5  6   19    19      -6  5 12    8    -8      -7  5 18    4    -3      -9  5  6    3    -3       0  6 16    7     7
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ØBSERVED AND CALCULATED STRUCTURE FACTØRS FØR  CGT                                                            PAGE 11

 H  K  L   FØ   FC       H  K  L   FØ   FC       H  K  L   FØ   FC       H  K  L   FØ   FC       H  K  L   FØ   FC

 1  6 11    5    5       2  6 10    3    2       3  6  8    5    5       4  6  6    8   -7       5  6  2   21   20
 1  6 10   18  -17       2  6  9    7   -6       3  6  7    5    5       4  6  5    7    6       5  6  1    8   -9
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-1  6 13    2   -3      -2  6 13   13   12      -3  6 15    3   -3      -4  6 17    2   -2      -5  6 20   10   10
-1  6 14    2   -1      -2  6 14    3   -2      -3  6 16    4    4      -4  6 18    2    3       6  6  9    3    4
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OBSERVED AND CALCULATED STRUCTURE FACTØRS FØR CGT

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-6	6	15	5	5	-8	6	8	6	-6	-10	6	11	3	-2	-1	7	6	13	-12	-2	7	8	8	-8
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OBSERVED AND CALCULATED STRUCTURE FACTORS FOR CGT

H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC
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-3	7	4	4	-4	-4	7	10	8	8	-5	7	20	3	-3	-7	7	7	5	4	-9	7	1	2	-2
-3	7	5	10	-11	-4	7	11	11	11	6	7	8	2	2	-7	7	8	2	-1	-9	7	2	4	-2
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-3	7	9	19	19	-4	7	16	9	9	6	7	3	3	-2	-7	7	11	2	-2	-9	7	5	4	-4
-3	7	10	4	-4	-4	7	18	6	6	6	7	1	10	11	-7	7	12	4	-3	-9	7	6	2	1
-3	7	11	6	-6	-4	7	20	2	-2	6	7	0	3	-3	-7	7	13	14	-14	-9	7	7	3	5
-3	7	12	10	-10	5	7	11	12	-12	-6	7	1	13	-13	-7	7	14	5	-4	-9	7	8	6	6
-3	7	13	16	17	5	7	10	6	6	-6	7	2	3	-4	-7	7	15	7	-8	-9	7	9	2	1
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4	7	13	5	5	5	7	2	5	6	-6	7	10	3	-1	8	7	2	5	5	-10	7	5	6	6
4	7	12	8	-7	5	7	0	4	-5	-6	7	11	3	3	8	7	1	5	5	-10	7	6	3	2
4	7	11	7	7	-5	7	2	17	-17	-6	7	12	3	-3	8	7	0	3	-2	-10	7	8	4	-4
4	7	10	3	3	-5	7	3	30	-30	-6	7	13	3	2	-8	7	1	3	-3	-10	7	9	4	5
4	7	9	8	-7	-5	7	4	2	-2	-6	7	14	5	-4	-8	7	2	9	-10	-10	7	10	3	3
4	7	7	18	19	-5	7	5	2	1	-6	7	15	6	-6	-8	7	3	4	4	-10	7	12	2	2
4	7	6	13	-15	-5	7	6	19	20	-6	7	17	3	3	-8	7	4	4	-4	-10	7	13	3	2
4	7	5	13	-12	-5	7	7	12	-11	-6	7	18	2	1	-8	7	7	3	2	0	8	2	23	24
4	7	4	11	11	-5	7	8	5	-5	-6	7	19	4	-3	-8	7	8	3	3	0	8	3	2	-2
4	7	3	6	5	-5	7	9	10	11	7	7	5	5	-3	-8	7	9	2	-3	0	8	4	14	-14
4	7	1	21	-21	-5	7	10	17	17	7	7	4	3	3	-8	7	10	3	3	0	8	5	6	-7
4	7	0	13	13	-5	7	11	4	-4	7	7	2	3	-3	-8	7	11	8	-8	0	8	6	5	5
-4	7	1	19	-20	-5	7	12	3	3	7	7	1	3	-3	-8	7	13	4	-3	0	8	7	7	-7
-4	7	2	31	-31	-5	7	13	8	8	7	7	0	5	5	-8	7	14	2	2	0	8	8	14	14
-4	7	3	7	-7	-5	7	14	6	-7	-7	7	1	8	7	-8	7	15	7	-7	0	8	9	11	11
-4	7	5	4	-4	-5	7	16	2	2	-7	7	2	5	4	-8	7	16	3	-4	0	8	10	4	3
-4	7	6	9	9	-5	7	17	4	5	-7	7	3	3	3	-8	7	17	5	5	0	8	11	2	3

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OBSERVED AND CALCULATED STRUCTURE FACTORS FOR   C G T                                                     PAGE 14

 H  K  L   FO   FC      H  K  L   FO   FC      H  K  L   FO   FC      H  K  L   FO   FC      H  K  L   FO   FC

 0  8 12    7    7     -1  8 15    4    4     -2  8 17    5   -5      4  8  6    8   -7     -5  8  3   16   16
 0  8 13    4    5     -1  8 16    6   -6     -2  8 18    4    3      4  8  5   14  -14     -5  8  4    2   -3
 0  8 14    8   -8     -1  8 18    2    3      3  8 13    4    4      4  8  4   11  -11     -5  8  5    5   -5
 0  8 16    3   -2      2  8 15    8   -8      3  8 12    6    5      4  8  3    9   -9     -5  8  6    4    4
 0  8 17    2   -1      2  8 13    5    5      3  8 11    3    3      4  8  2   14  -14     -5  8  7    4    4
 1  8 16    6   -6      2  8 12   12  -11      3  8 10    2   -1      4  8  1    2   -2     -5  8  8   11  -11
 1  8 15    5   -6      2  8 11    2   -3      3  8  9    4   -3      4  8  0   14   13     -5  8 10   14  -15
 1  8 14    8    8      2  8 10   13   13      3  8  8   16   16     -4  8  1    9   -8     -5  8 11    9  -10
 1  8 13    3   -3      2  8  9    8   -8      3  8  7   10  -10     -4  8  2    5    4     -5  8 12    2    1
 1  8 12    4    4      2  8  8    3   -2      3  8  6   16  -16     -4  8  3    7   -7     -5  8 13    3   -4
 1  8 11    3   -4      2  8  7    6    7      3  8  5   12  -12     -4  8  4   28   28     -5  8 14    2   -2
 1  8 10    2   -1      2  8  6   12   11      3  8  4    4   -4     -4  8  5   11  -11     -5  8 15    2   -2
 1  8  9    2    2      2  8  5    5   -4      3  8  2   17  -16     -4  8  6    2    2     -5  8 16    7    7
 1  8  8   25   25      2  8  4    8   -9      3  8  1   14   13     -4  8  7    4    5      6  8  9    3   -3
 1  8  7    9    9      2  8  3   15   16      3  8  0   34  -35     -4  8  8    7    7      6  8  8   11   11
 1  8  6   24  -24      2  8  2    4   -4     -3  8  1   13  -12     -4  8  9    6   -5      6  8  6    6   -6
 1  8  5    3   -2      2  8  1   23   23     -3  8  2    6    6     -4  8 10    6   -6      6  8  4   10   10
 1  8  4    5    5      2  8  0   19  -20     -3  8  3    1    1     -4  8 12    5   -5      6  8  2   11  -11
 1  8  3    9   10     -2  8  1    7   -7     -3  8  4    5   -6     -4  8 15    3    1     -6  8  2   11  -11
 1  8  2   23  -22     -2  8  2    9   -9     -3  8  6   15   15     -4  8 16    4   -4     -6  8  3   14   14
 1  8  0   13   14     -2  8  3    9    9     -3  8  7    9    9     -4  8 17    4    5     -6  8  4    7    7
-1  8  2    2    2     -2  8  4    7    6     -3  8  8   11   12     -4  8 18    2    1     -6  8  5    5    5
-1  8  3    3   -4     -2  8  5    3    4     -3  8  9    6   -5     -4  8 19    2    1     -6  8  6    4    4
-1  8  4   16   16     -2  8  6   20  -19     -3  8 10   21   20      5  8  9    3    2     -6  8  7    2   -1
-1  8  5   10   -9     -2  8  7   12   12     -3  8 11    5   -6      5  8  7    2    0     -6  8  8    8   -8
-1  8  6    8    8     -2  8  8   14   14     -3  8 12    3    3      5  8  6    5    4     -6  8  9    4   -3
-1  8  7    1    1     -2  8  9    4    3     -3  8 13    2   -2      5  8  5    5    5     -6  8 10    6    6
-1  8  8   17  -18     -2  8 10   11  -11     -3  8 14    5    4      5  8  4    5   -6     -6  8 11   10  -10
-1  8  9    3    3     -2  8 11    3   -3     -3  8 16    4    3      5  8  3    8   -7     -6  8 12    8   -9
-1  8 10    5    5     -2  8 12   13   13     -3  8 17    5    5      5  8  2    8    8     -6  8 13   10   -9
-1  8 11   10   10     -2  8 13    2   -1     -3  8 18    8   -9      5  8  1    3   -2     -6  8 14    3    2
-1  8 12   16  -16     -2  8 14    5    5      4  8 10    6    7      5  8  0    2   -3     -6  8 15    4    3
-1  8 13    8    8     -2  8 15    3    3      4  8  8    7   -7     -5  8  1    2   -2      7  8  6    3    3
-1  8 14    3    3     -2  8 16    7    7      4  8  7    2   -3     -5  8  2   19   20      7  8  5    5   -5
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ØBSERVED AND CALCULATED STRUCTURE FACTORS FØR   C GT                                                         PAGE 15

 H  K  L   FØ   FC      H  K  L   FØ   FC      H  K  L   FØ   FC      H  K  L   FØ   FC      H  K  L   FØ   FC

  7  8  4  10   -9     -9  8  8    2    2      1  9  1    3   -3     -2  9  2    5    5     -3  9 10    6   -6
  7  8  3   3    3     -9  8  9    2   -2      1  9  0   14   15     -2  9  3    7   -7     -3  9 11    5   -5
  7  8  2   6    6     -9  8 10    4    4     -1  9  2    8    8     -2  9  4    6    5     -3  9 13    4    4
 -7  8  1   6   -7     -9  8 12    4   -3     -1  9  3   16   16     -2  9  5   15   15     -3  9 14    5    4
 -7  8  2   6   -7     -9  8 13    4   -3     -1  9  4    3   -3     -2  9  6    7   -6     -3  9 15    6   -6
 -7  8  3   3   -1     -9  8 15    2    0     -1  9  5    8   -7     -2  9  7    8   -7     -3  9 16    4    4
 -7  8  4   9    9    -10  8  7    2   -2     -1  9  6   13   13     -2  9  8    8    8      4  9 12    6   -6
 -7  8  6   3   -3    -10  8  8    2   -1     -1  9  7   12   12     -2  9 10    2   -2      4  9 11   10   10
 -7  8  7   5    4    -10  8  9    2   -3     -1  9  8    6    6     -2  9 11    4    4      4  9 10    3   -4
 -7  8  8   6    6    -10  8 10    2   -2     -1  9  9   13  -13     -2  9 13    3   -3      4  9  9    5   -5
 -7  8  9   2    3      0  9  2    8    8     -1  9 10    2    2     -2  9 14    5    6      4  9  8    4   -4
 -7  8 10   3   -2      0  9  3   18  -18     -1  9 11    5    5     -2  9 15    8    8      4  9  7    7    8
 -7  8 12   2    3      0  9  4   18   18     -1  9 12    4    4     -2  9 16    4   -4      4  9  5   11  -11
 -7  8 14   7   -8      0  9  5    2    3     -1  9 13    3    3     -2  9 17    4   -4      4  9  4    2   -2
 -7  8 15   4    5      0  9  7    2   -3     -1  9 14    3    3      3  9 13   10  -10      4  9  3    4    4
 -7  8 16   4    4      0  9  9    7    6     -1  9 16    3   -3      3  9 11    5    5      4  9  2    3    3
 -7  8 17   2    0      0  9 10    7   -7     -1  9 17    4    4      3  9  8    4    4      4  9  1   13  -14
  8  8  2   5    5      0  9 11    5    5      2  9 15    7   -7      3  9  7    2   -1      4  9  0    5   -4
  8  8  1   3    3      0  9 13    7    7      2  9 14    6   -6      3  9  6    2   -1     -4  9  1   18   18
 -8  8  2   9    9      0  9 14    3   -3      2  9 13    3    2      3  9  5   20   20     -4  9  2    5    4
 -8  8  4   4   -4      0  9 15    6   -6      2  9 12    3    2      3  9  4    6    6     -4  9  3    2    1
 -8  8  6   5    6      0  9 16    4    4      2  9 11    8   -8      3  9  3   10  -10     -4  9  4    1   -2
 -8  8  7   9    8      0  9 17    3   -3      2  9 10    5    5      3  9  2   16  -17     -4  9  5    9   -9
 -8  8  8   2   -2      1  9 16    5   -5      2  9  9    4    5      3  9  1   15   16     -4  9  6    5   -5
 -8  8  9   5    5      1  9 13    2   -3      2  9  8    3    3      3  9  0   10  -10     -4  9  7    9    9
 -8  8 10   7    7      1  9 12    9   -9      2  9  7    5    5     -3  9  1    4   -4     -4  9  8    7   -8
 -8  8 11   5    5      1  9 11   17   17      2  9  6   15   16     -3  9  2    8    8     -4  9  9   21  -22
 -8  8 16   3    2      1  9  9    5   -5      2  9  5    3   -3     -3  9  3    5    5     -4  9 10    3   -3
 -8  8 17   3   -2      1  9  7   15   15      2  9  4    2   -1     -3  9  4    2    3     -4  9 11    5    5
  9  8  0   9    8      1  9  6    7    6      2  9  3    3    3     -3  9  5    5   -5     -4  9 13    4   -4
 -9  8  1   5    5      1  9  5   19  -19      2  9  2    1    1     -3  9  6   14  -14     -4  9 14    4    5
 -9  8  3   4    4      1  9  4   14   14      2  9  1   12  -13     -3  9  7    1   -2     -4  9 15    2    3
 -9  8  4   9    9      1  9  3   17  -16      2  9  0    3   -2     -3  9  8   12  -12     -4  9 16    3   -3
 -9  8  6   2   -1      1  9  2   13   13     -2  9  1   12   13     -3  9  9    2   -2     -4  9 17    4   -3
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OBSERVED AND CALCULATED STRUCTURE FACTORS FOR  C GT

  H  K  L    FO   FC     H  K  L   FO   FC     H  K  L   FO   FC     H  K  L   FO   FC     H  K  L   FO   FC

 -4  9 18     2   -1    -6  9  2    8    8    -8  9  2    3    3     1 10 14    4    4     4 10 10    2    2
 -4  9 19     2    2    -6  9  3    6    6    -8  9  3    3    3     1 10 13    6   -6     4 10  8    3   -4
  5  9 10     2   -2    -6  9  4    4   -4    -8  9  4    2    2     1 10 11    3    1     4 10  6    7    7
  5  9  9     4    4    -6  9  5    2    2    -8  9  5    4   -4     1 10 10    2    3     4 10  5    5    4
  5  9  7     4   -5    -6  9  6    3    3    -8  9  7    3   -3     1 10  8    2    3     4 10  4    4    4
  5  9  6     3    2    -6  9  7   13   13    -8  9  8    5    5     1 10  6    9   -8     4 10  3    9    8
  5  9  4     4   -3    -6  9  8    2   -2    -8  9  9    4    1    -2 10 16    4    3     4 10  1    3   -4
  5  9  3    10  -10    -6  9 10    2   -2    -8  9 10    2   -3    -2 10 17    2   -2     4 10  0    3    3
  5  9  1     8   -9    -6  9 11    2    3    -8  9 11    6   -6     3 10 13    6   -6    -4 10  1    3   -3
  5  9  0     2    3    -6  9 12    3   -2    -8  9 14    3   -3     3 10 11    4    5    -4 10  2    3   -3
 -5  9  1     9   10    -6  9 13    4    3    -8  9 16    2   -3     3 10 10    4   -4    -4 10  3   12   12
 -5  9  2     4    5    -6  9 15    3   -3    -9  9  1    3    2     3 10  9    6   -6    -4 10  4    9    9
 -5  9  3     3   -3     7  9  6    5    5    -9  9  2    4   -4     3 10  8    7    7    -4 10  6    5   -5
 -5  9  4     5    5     7  9  5    3   -2    -9  9  3    6   -6     3 10  7    6    6    -4 10  7    2    1
 -5  9  5    13   13     7  9  4    7   -7    -9  9  4    4   -4     3 10  6    2   -1    -4 10  8    5    5
 -5  9  7     5   -4     7  9  3    6    6    -9  9  5    5   -4     3 10  5    3    3    -4 10 10    4   -4
 -5  9  8     6    6     7  9  2    2   -1    -9  9  8    2   -2     3 10  4    2    3    -4 10 11    2    3
 -5  9 10     5   -6     7  9  1    4   -5    -9  9  9    2   -2     3 10  3    2    1    -4 10 12    6   -5
 -5  9 11     4   -3    -7  9  0    9   -8    -9  9 11    2    3     3 10  1    4   -4    -4 10 13    3    3
 -5  9 12     4   -4    -7  9  1    7    7    -9  9 12    2   -2     3 10  0    2    1    -4 10 15    4   -3
 -5  9 13     7    7    -7  9  2    3    3     0 10  2    2    3    -3 10  1    8    9    -4 10 16    7   -7
 -5  9 14     4   -4    -7  9  3    2   -2     0 10  3    8   -7    -3 10  2    9    9    -4 10 17    2    0
 -5  9 15     4    3    -7  9  5    6    5     0 10  4   11  -10    -3 10  3   12  -11     5 10 10   11  -10
 -5  9 16     4   -4    -7  9  7    5    4     0 10  5    6    6    -3 10  4    5   -4     5 10  9    6    6
 -5  9 17     3   -2    -7  9  8    4    3     0 10  6    7    7    -3 10  5    5    5     5 10  8    2   -1
 -5  9 18     5   -4    -7  9  9    3    2     0 10  7    7   -7    -3 10  6    4    4     5 10  7    4   -4
  6  9  8     6    6    -7  9 12    3    3     0 10  8    4   -5    -3 10  7   16  -17     5 10  6    6    5
  6  9  7     5    5    -7  9 13    5   -5     0 10  9    4    4    -3 10  8    6   -6     5 10  5    5    4
  6  9  6     3    4    -7  9 14    2    2     0 10 10    2    2    -3 10  9    3    3     5 10  4    2   -1
  6  9  4     5   -4    -7  9 16    4   -5     0 10 11    4    4    -3 10 14    5   -5     5 10  3    8   -8
  6  9  3     3   -3    -7  9 17    5   -4     0 10 12    7    7    -3 10 15    3   -3     5 10  2   13   13
  6  9  2     9   -9     8  9  2    5   -4     0 10 14    8   -8    -3 10 16    2   -3     5 10  0    3   -3
  6  9  0     3   -4     8  9  1    6    6     0 10 15    8    7    -3 10 17    3    1    -5 10  1   12   12
 -6  9  1     8   -8     8  9  0    3    3     0 10 16    3    3    -3 10 18    4   -4    -5 10  3    2    2
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OBSERVED AND CALCULATED STRUCTURE FACTORS FOR   CGT                                                          PAGE 17

  H  K  L    FO   FC       H  K  L    FO   FC       H  K  L    FO   FC       H  K  L    FO   FC       H  K  L    FO   FC

 -5 10  4     2   -1      -7 10  1     3   -2       0 11  9     4    4       2 11 11     3   -3       5 11  0     2    2
 -5 10  5     9    9      -7 10  3     3   -3       0 11 10     7   -7       2 11 10     2    0      -5 11  1     3   -3
 -5 10  6     2   -1      -7 10  4     3    3       0 11 11     5   -6       2 11  9     7    6      -5 11  4     5    6
 -5 10  8     2   -2      -7 10  6     2   -1       0 11 12     5    6       2 11  8     3    3      -5 11  5     3    2
 -5 10  9     5   -5      -7 10  8     6    5       0 11 16     3   -2       2 11  6     3    2      -5 11  6     2   -3
 -5 10 10     2    3      -7 10  9     3   -3       1 11 14     3    3       2 11  5     1    0      -5 11  7     5   -4
 -5 10 11     3   -2      -7 10 10     5   -4       1 11 13     2    2       2 11  4     4   -4      -5 11  8     4    5
 -5 10 12     2    2      -7 10 11     3    2       1 11 12     6   -5       2 11  3     3    3      -5 11  9     2    3
 -5 10 13     5   -5      -7 10 13     2    0       1 11 11     6    5       2 11  2     5    6      -5 11 10     4   -4
 -5 10 14     3   -1      -7 10 14     3   -2       1 11 10     6    6       2 11  1     2    2      -5 11 12     2    1
 -5 10 16     3    3      -7 10 15     3   -2       1 11  7     4    4       2 11  0    14  -14      -5 11 14     2   -2
 -5 10 18     2   -2      -7 10 16     3    2       1 11  6     3    3      -2 11  2     7   -8      -5 11 17     2    1
  6 10  6     2   -1       8 10  1     2    2       1 11  5     3   -3      -2 11  3     5   -5       6 11  7     3    3
  6 10  5     8   -8       8 10  0    10  -10       1 11  4     4   -4      -2 11  4     5    5       6 11  5     4   -5
  6 10  4     5    5      -8 10  2     2   -3       1 11  3     4    4      -2 11  5     3   -2       6 11  4     4    4
  6 10  2     5   -6      -8 10  3     5   -4       1 11  2    10  -11      -2 11  7    11  -11       6 11  2     6    6
  6 10  1     7   -6      -8 10  4     6   -6       1 11  1     4    5      -2 11  9     3    3       6 11  1     3   -2
  6 10  0     6    6      -8 10  5     6    6       1 11  0     2    3      -2 11 12     5   -4       6 11  0     7    6
 -6 10  1     3    3      -8 10  6     3    3      -1 11  2     7    7      -2 11 13     3   -3      -6 11  1     5   -6
 -6 10  2     6   -7      -8 10  7     4   -3      -1 11  3     6    6      -2 11 14     4   -3      -6 11  2     7    7
 -6 10  3     6   -6      -8 10 14     3    2      -1 11  4    14  -15      -2 11 16     4   -3      -6 11  3     4    5
 -6 10  4     3    3      -9 10  2     5   -5      -1 11  5     5   -6       3 11 12     5    5      -6 11  4     3   -3
 -6 10  5     3    3      -9 10  7     2    2      -1 11  6     4    3       3 11 11     3   -3      -6 11  5     3   -4
 -6 10  6     4    4      -9 10  8     3    3      -1 11  7     3   -4       3 11 10     3   -3      -6 11  6     5    5
 -6 10  7     3   -4      -9 10  9     2   -2      -1 11  8     4   -3       3 11  8     2    2      -6 11  8     4   -4
 -6 10  8     3   -4      -9 10 10     3   -2      -1 11  9     2    1       3 11  6     8   -7      -6 11  9     3    3
 -6 10  9     3   -2      -9 10 11     2   -1      -1 11 10     3    2      -4 11 17     2    3      -6 11 10     2   -1
 -6 10 10     5    6       0 11  2     7   -8      -1 11 11     9   -8       5 11  9     3    4      -6 11 13     3    2
 -6 10 11     5   -4       0 11  3     1    1      -1 11 12     5   -4       5 11  8     5    4      -6 11 14     4    3
 -6 10 12     2   -2       0 11  4     8   -8      -1 11 13     4   -4       5 11  6     3   -3      -6 11 15     2   -1
 -6 10 15     2   -4       0 11  5     5    5      -1 11 14     4   -4       5 11  4    10   10      -6 11 16     3    3
 -6 10 17     2    3       0 11  6    12  -13       2 11 14     3   -2       5 11  3     2    0       7 11  2     6    5
  7 10  4     2   -2       0 11  7     3   -3       2 11 13     3    3       5 11  2     5    5      -7 11  1     3   -2
  7 10  0     8   -8       0 11  8    15   15       2 11 12     2    3       5 11  1     3    2      -7 11  2     5   -6
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OBSERVED AND CALCULATED STRUCTURE FACTORS FOR CGT

H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC
-7	11	4	6	6	1	12	6	5	5	-2	12	6	7	8	-4	12	1	6	-7	6	12	0	2	2
-7	11	6	3	-3	1	12	5	8	-8	-2	12	7	4	4	-4	12	3	7	7	-6	12	1	2	-2
-7	11	7	7	-6	1	12	3	4	3	-2	12	8	5	6	-4	12	4	2	-1	-6	12	2	4	3
-7	11	9	2	0	1	12	2	4	-4	-2	12	9	7	-7	-4	12	5	6	-6	-6	12	3	3	-2
-7	11	13	3	3	1	12	1	6	-6	-2	12	10	3	-3	-4	12	6	2	-1	-6	12	5	6	-5
-7	11	14	6	5	-1	12	1	6	-6	-2	12	11	6	6	-4	12	7	5	4	-6	12	6	3	-2
-7	11	15	7	7	-1	12	2	1	-2	-2	12	12	3	2	-4	12	8	4	-4	-6	12	7	5	-5
-7	11	16	3	2	-1	12	3	1	-2	-2	12	13	2	0	-4	12	9	2	2	-6	12	9	2	1
8	11	1	3	3	-1	12	4	2	0	3	12	12	2	0	-4	12	10	3	-1	-6	12	11	2	3
-8	11	1	5	-5	-1	12	5	8	-8	3	12	11	5	5	-4	12	14	2	1	-6	12	13	10	9
-8	11	2	3	2	-1	12	6	5	5	3	12	9	3	-3	-4	12	17	2	0	-6	12	14	5	4
-8	11	7	4	-3	-1	12	9	3	2	3	12	8	3	3	5	12	6	3	-2	-6	12	15	3	4
-8	11	8	3	-2	-1	12	11	2	-2	3	12	7	9	9	5	12	5	4	4	7	12	3	2	-1
-8	11	10	4	-3	-1	12	13	4	4	3	12	5	2	-2	5	12	4	3	-3	7	12	1	2	3
-8	11	11	2	-1	-1	12	15	5	-5	3	12	4	4	2	5	12	2	5	-4	-7	12	1	4	-4
-8	11	13	3	3	-1	12	16	3	3	3	12	3	2	2	5	12	1	7	7	-7	12	2	2	3
-9	11	7	2	0	2	12	12	3	2	3	12	2	2	0	-5	12	1	5	5	-7	12	3	2	2
-9	11	8	4	-4	2	12	11	3	-4	3	12	1	2	-2	-5	12	2	3	3	-7	12	5	3	-3
0	12	3	11	-11	2	12	10	2	-1	3	12	0	2	2	-5	12	3	7	-7	-7	12	7	2	1
0	12	5	6	-5	2	12	9	4	4	-3	12	1	6	6	-5	12	4	3	-3	-7	12	8	2	-3
0	12	9	5	-5	2	12	7	6	-6	-3	12	2	3	4	-5	12	5	4	-4	-7	12	9	2	-2
0	12	10	3	-4	2	12	6	3	4	-3	12	14	3	-2	-5	12	7	1	0	-7	12	11	3	3
0	12	11	3	-2	2	12	5	7	7	-3	12	15	3	2	-5	12	11	8	8	-7	12	12	2	2
0	12	12	2	-3	2	12	3	4	-4	4	12	10	4	3	-5	12	12	5	4	-7	12	15	2	2
0	12	13	4	-2	2	12	2	4	-4	4	12	9	2	1	-5	12	14	3	3	8	12	0	3	2
0	12	15	3	2	-2	12	1	3	3	4	12	7	2	2	-5	12	15	3	3	-8	12	4	3	-3
1	12	14	3	-2	-2	12	2	2	3	4	12	5	2	1	6	12	6	2	-1	-8	12	5	4	2
1	12	11	5	-5	-2	12	3	2	2	4	12	4	6	-6	6	12	5	4	-3	-8	12	9	3	2
1	12	9	9	-8	-2	12	4	2	-2	4	12	3	6	6	6	12	4	2	1	-8	12	10	3	-2
1	12	8	2	-1	-2	12	5	6	-6	4	12	1	6	-6	6	12	3	5	4	-8	12	11	2	-2

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ANALYSIS ØF VARIANCE FØR   CGT

              GGG    UGG    GUG    UUG    GGU    UGU    GUU    UUU    ALL

      N       417    432    384    377    344    344    378    364   3040

      V        61     62     62     59     59     62     61     62     61


SIN THETA    0,00 -  .22 -  .28 -  .32 -  .35 -  .38 -  .40 -  .42 -  .45 -  .47 -  .55

      N       319    337    336    313    328    245    261    404    260    237

      V        98     66     56     61     58     53     51     50     48     44


SQRT(F/FMAX) 0,00 -  .15 -  .17 -  .19 -  .21 -  .23 -  .26 -  .30 -  .36 -  .44 - 1,00

      N       426    284    293    275    250    311    308    326    273    297

      V        46     50     54     62     68     66     76     67     53     67


       ABS(H)   0      1      2      3      4      5      6      7      8      9     10     11     12     13     -
    REST

      N       182    352    384    350    341    336    312    276    211    169     93     34      0      0      0

      V        63     75     71     59     62     61     52     53     54     47     46     49      0      0      0


       ABS(K)   0      1      2      3      4      5      6      7      8      9     10     11     12     13     -
    REST

      N       159    319    315    308    292    285    272    250    224    214    143    127    132      0      0

      V        79.    69     64     69     65     57     57     54     51     54     54     51     52      0      0


       ABS(L)   0      1      2      3      4      5      6      7      8      9     10     11     12     13     -
    REST

      N        69    170    200    185    202    181    200    174    192    171    182    157    151    133    653

      V        73     70     72     71     67     70     62     61     60     55     57     51     46     61     55
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OBSERVED AND CALCULATED STRUCTURE FACTORS FOR  CGT(neutron)                                               PAGE  1

  H  K  L   FO   FC       H  K  L   FO   FC       H  K  L   FO   FC       H  K  L   FO   FC       H  K  L   FO   FC

 -1  0 12   10    9      -4  7  2   12  -11      -2  1 10    8    8       1  2  2    7    7      -2  3 15    7   -7
 -2  0 10   13   13       3  8  0   10  -11       3  1  1    5   -6      -1  2  4    7   -6       3  3  6    8    8
  3  0  8   13  -12      -4  4  5   12   12      -3  1  3    2    2       2  2 13    7   -7      -3  3  5    7   -7
 -5  0  4   14   15       0  0  4    7    6      -3  1  4    5   -4       2  2  9   11  -11       4  3  1    7    7
  6  0  6   14   15       0  0  6    9   -8       3  1  5    5   -5       2  2  8    6    7      -4  3  2    6    6
 -6  0  2    8   -7       0  0 10    9   -9      -3  1  7    6   -5       2  2  4    5   -5      -4  3  4    7   -7
 -6  0 10   11  -11       0  0 16    6   -6      -3  1  9    7   -7       2  2  3    7    7      -5  3  4    7   -8
  7  0  4   12   12       0  4  0    9   -9      -3  1 12    8    7       2  2  2    4   -4      -5  3  6    7   -6
 -7  0  4    7   -7       0  8  0    5   -5      -3  1 13    6   -4       2  2  0    4   -4      -5  3 14    6    5
 -8  0  8    8    7       0 10  0    3    2       4  1  0    5    5      -2  2  2    6    5      -5  3 16    7   -7
 -2  1  3   12   13      -1  0 10    1   -1       4  1  9    6    7      -2  2  4    6   -6      -6  3  4    6    6
 -2  1 12   13   12       2  0  8   12   12       4  1  8    9   -9       3  2  1    4    3      -6  3  7    4    5
 -3  1  1    9   10       2  0  4    5   -6       4  1  5   13   13       3  2  0    9   -9       7  3  3    8   -7
  5  1  6   13  -14       2  0  2    8   -8       4  1  4    8    7      -3  2  5    7   -8       8  3  4    5   -7
 -5  1  1    8   -8       2  0  0    6   -6       4  1  0    5    5      -4  2  5    2   -2       1  4  4   10   10
  0  2  7   14   15       3  0 10   10   -9      -4  1  3    6   -6      -4  2  6    8    7      -1  4 14    7    7
  1  2  3   10  -10       3  0  0    7    7      -4  1  7   10  -10      -5  2  6    6    6       2  4 11    8    8
 -2  2  3    9   -9      -3  0 12   10   10      -4  1 13    7    7      -5  2  7    5   -4       2  4  6    8    7
  3  2 11   11  -11      -4  0  6   11  -11       5  1  7    7    7      -5  2 13    4    5       2  4  4   10   10
 -3  2  2   10   11      -4  0 14    9    8       5  1  2    3    3      -6  2  1    7    6       2  4  1    9   -9
 -4  2  7   15  -15       5  0  6   13   12      -5  1  2    7   -7      -6  2  2    9    9      -2  4  2    5   -4
 -4  2 15    9    9      -5  0  2    5   -5      -5  1  5   10  -10     -10  2  9    4    4      -2  4  9    9    9
 -7  2  8    9  -11       6  0  0    6   -6      -5  1 13    5    5       1  3 13   10   10      -2  4 11    6   -5
  0  3 13    7    7      -7  0  2    3   -4       7  1  4   10   10       1  3  8   10   10      -2  4 15    6   -5
  0  3 12   15  -15      -9  0 10    5   -6      -7  1  4    9    9       1  3  3    5   -6       3  4  9    9    9
 -1  3  3   12  -12       0  1  5    7   -7      -8  1  4    3    5      -2  3  3    7   -7       3  4  7    8   -8
 -2  3  7   10   10       0  1  7    7    6      -8  1  6    5    6       2  3  0    5    5       3  4  5    8    8
  3  3  3   14   15      -1  1  8    5    4       0  0  8   19  -19      -2  3  5    8   -8      -3  4  1    9   -9
 -5  3 15    9  -10      -1  1 10    8    7       1  0 10   10   10      -2  3 12    6    6      -3  4  1    9   -9
  1  5  4    9   -8       2  1 13    5   -5       1  0  6    6    6       4  1  8    9   -9      -3  4  2   10   -9
 -5  5  7   13  -13       2  1  6    9   -9      -1  0  8    9   -9      -2  2  5    8   -7      -3  4 13   10  -10
  0  6  2   10   10       2  1  2    7   -7       2  0  6    5   -5       3  2  5    7    7      -3  4 14    8   -8
  0  6  9   13  -13       2  1  1    7    7      -8  1  8    7   -6       3  2  4    7   -7      -4  4  1    7    7
 -3  6  1   12   12      -2  1  1    4   -5       0  2 12    8   -8       4  2  3    8   -8      -4  4 13    8   -8
 -5  5  1    3   -2      -2  1  4    8   -8       1  2  7    9    9      -1  3  6    8   -7      -5  4  6    8   -7
 -2  7  1   11   11      -2  1  6    4    3       1  2  6    9    9       2  3 11    6    6      -6  4  9    7   -6
1
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 OBSERVED AND CALCULATED STRUCTURE FACTORS FOR   GGT(neutron)                                                                   PAGE  2

  H  K  L   FO   FC       H  K  L   FO   FC       H  K  L   FO   FC       H  K  L   FO   FC       H  K  L   FO   FC

 -7  4  9    7   -7      -2  6  2    2   -9       2  8  1    8    9       7  0  0    4   -5       3  2  6    8   -8
-10  4  9    5   -6      -3  6  3    5    5       2  8  0    7   -8      -9  0  2    6    5      -5  3  7   12   12
  0  5  5    8    7      -3  6  4    7   -7      -3  8  1    6   -6      -9  0  8    6    7      -5  3  7   13   12
  1  5 12    8    8      -5  6  1   10  -11      -3  8  7    6    6       0  1  4    4   -3      -5  2  1    9    9
  1  5  8    6    5      -5  6  3    7   -7      -3  8  8    7    7       1  1 14    7   -6       0  3  6    7    7
 -1  5  3    5    5      -5  6  4    7   -6      -3  8  4    3    3      -1  1  9    8    7       2  3 11    6    6
 -1  5  4    9    9      -6  6  4    9  -10       0  9  4    9    9       2  1  8    4    4       2  3  3    4   -3
 -1  5  6    5   -6      -6  6  5    7   -6       0  9  5    4   -4      -2  1  5    5    5      -2  3  2    3    3
 -1  5  7   11   11      -6  6  6    7   -7      -2  9  5    6    6       2  1  5    5   -5      -2  3  4    3   -3
  2  5  3    6    6      -6  6  9    4    4      -3  9  6    6   -5      -3  1  2    5   -6      -2  3 13    4    5
  4  5  5    7   -7      -7  6  9    5    6      -4  9  1    6    6       4  1 10    6   -6       3  3 11    6   -7
 -4  5  3    5    6       1  7  7    7   -6      -4  9  9    6   -6       5  1  1    4   -4       3  3  8    7   -8
 -6  5  4    5    4       2  7  7   10  -10      -5  9  5    4    5      -5  1  8    5   -4       3  3  1    6    6
 -6  5  8    4    4       2  7  6    8   -8      -1 10  4    7   -7      -5  1 11    4    3      -3  3  1    4    4
 -7  5  4    6   -6       3  7  6    9  -10      -2 10  6    9   -8       7  1  3    4    5      -3  3  2    3    2
  0  6 10    7   -8      -3  7  2    7   -7      -1 12  5    2   -3      -7  1  2    5    5      -3  3  3    3   -3
  1  6  9    9   -9      -3  7  3    4    4       0  6  0    4    5      -7  1 11    6   -6      -3  3  9    4   -3
  1  6  1    6    6      -4  7  1    9   -8       8  0  0    2    1      -8  1  8    6   -6      -3  3  1    4    4
 -1  6  7    7   -7      -4  7  6    6    5       2  0  6    6   -5       0  2  8    5    5      -3  3 10    5    5
 -1  6 12    5   -4      -5  7  2    7   -7      -3  0  8    6    6       2  2 10    7    6      -3  3 13    5    5
 -1  6 15    4    5      -5  7  3    8   -8      -5  0 12    5   -5      -2  2  1    3   -4       0  0  8   19  -19
  2  6  8    7   -7       0  8  2    8    7      -6  0 18    4    4      -2  2  9    5    4
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ANALYSIS OF VARIANCE FOR  CGT(neutron)

                 GGG   UGG   GUG   UUG   GGU   UGU   GUU   UUU   ALL

       N          49    42    34    33    28    28    35    40   289

       V          59    46    34    48    37    29    36    41    44


SIN THETA     0.00 - .23 - .29 - .33 - .37 - .41 - .46 - .50 - .54 - .57 - .71

       N          33    29    28    30    24    31    29    38    18    29

       V          44    36    35    70    46    45    38    38    32    38


SQRT(F/FMAX)  0.00 - .47 - .52 - .55 - .59 - .61 - .64 - .67 - .71 - .77 - 1.00

       N          32    32    25    35    20    38    23    30    25    29

       V          61    36    34    39    30    41    54    40    44    47


      ABS(H)       0     1     2     3     4     5     6     7     8     9    10    11    12    13     -
   REST

       N          26    36    64    56    31    34    16    14     7     3     2     0     0     0     0

       V          41    42    52    42    31    44    35    39    59    46    29     0     0     0     0


      ABS(K)       0     1     2     3     4     5     6     7     8     9    10    11    12    13     -
   REST

       N          43    60    43    47    26    16    22    12     9     7     3     0     1     0     0

       V          41    45    46    38    29    35    73    31    42    38    34     0    20     0     0


      ABS(L)       0     1     2     3     4     5     6     7     8     9    10    11    12    13     -
   REST

       N          16    27    26    22    33    21    28    19    24    17    13     8    10    12    13

       V          34    35    70    37    42    33    46    42    46    34    36    36    60    44    33
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OBSERVED AND CALCULATED STRUCTURE FACTORS FOR   2,4-DIAMINOQUINAZOLINE                              PAGE  1

 H  K  L   FO   FC      H  K  L   FO   FC      H  K  L   FO   FC      H  K  L   FO   FC      H  K  L   FO   FC

 0  6  0   23  -24      6 14  0   22   24     12 24  0   15   14    -14 22  0   15    9      3 14  1   12   -1
 0  8  0   93  -91      6 16  0   20   18      0 14  0   24  -23    -16 22  0   16   12      3 16  1   32   30
 0 10  0   51  -53      6 18  0   12  -21     -2 14  0   16   16     -2 24  0   16  -15      3 18  1   34  -35
 0 12  0   67  -68      6 20  0   11   -8     -4 14  0   61   62     -4 24  0   16  -12      3 20  1   32   31
 0 14  0   25  -23      6 22  0   18   20     -6 14  0   63   64     -6 24  0   26   27      3 22  1   15   -9
 0 16  0   13    9      6 24  0   17   22     -8 14  0   58   54     -8 24  0   22  -24      3 24  1   15   -7
 0 18  0   43  -44      0  8  0   94  -91    -10 14  0   27  -28     -4 26  0   13   -4     -1  4  1   11   12
 0 20  0   86   87     -2  8  0   37   34     14 14  0   33   32     -8 26  0   20   -6     -3  4  1   19   17
 0 22  0   24  -22     -4  8  0    8    5     14 16  0   43   42      0  5  1  125  127      4  5  1  133  134
 0 24  0   11    7     -6  8  0  105 -105     14 22  0   11    4      0  7  1  129  131      4  9  1   28  -30
 0 28  0   13   -6      8  8  0   23  -21      0 16  0   14    9      0  9  1   35   32      4 11  1  115 -113
 2  6  0  162 -165      8 10  0   89   89     -2 16  0   23  -23      0 11  1   13  -10      4 13  1   15  -12
 2  8  0   54   54      8 12  0   36   39     -6 16  0   39   37      0 13  1   26   24      4 15  1   23   25
 2 10  0   12  -11      8 14  0   30  -30     -8 16  0   15    7      0 17  1   10    2      4 17  1   75  -76
 2 12  0   36  -37      8 18  0   10    0    -14 16  0   28  -28      0 19  1   15  -15      4 19  1   21   22
 2 14  0   14  -10      8 22  0   15   17     16 16  0   13    3      0 21  1   13    8      4 21  1   13   -7
 2 16  0   30   30      8 24  0   11    5     16 18  0   10    8      0 23  1   14   -9      0  5  1  126  127
 2 18  0   40  -42      0 10  0   53  -53     16 22  0   13    3      1  4  1  205  209     -2  5  1   86   88
 2 20  0   31  -36     -2 10  0   29  -28      0 18  0   42  -44      1  6  1  216  221     -4  5  1   57  -56
 2 24  0   14    3     -4 10  0   24  -23     -2 18  0   39   38      1  8  1   38   35      5  6  1   61   64
 4  4  0  211 -208     -8 10  0   36   38     -4 18  0   27  -26      1 12  1   54  -54      5  8  1   27   26
 4  6  0  162 -161     10 10  0  113 -112     -6 18  0   13   13      1 14  1   57  -58      5 10  1   57  -59
 4  8  0   77  -76     10 12  0   52  -51    -16 18  0   11  -10      1 16  1   21  -15      5 12  1   82  -82
 4 10  0   52  -54     10 14  0   16   10     18 20  0   17  -10      1 18  1   16   11      5 14  1   19  -16
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 4 16  0   68  -69     10 20  0   24   23     -4 20  0   28   28      2 11  1   85   83      5 20  1   23  -24
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OBSERVED AND CALCULATED STRUCTURE FACTORS FOR   2,4-DIAMINOQUINAZOLINE                                                    PAGE  2

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  0  7  1   130   131      -2 11  1    14   -10      -1 16  1    20    19      -8 23  1    13    10       3 13  2    21    18
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OBSERVED AND CALCULATED STRUCTURE FACTØRS FØR   2,4-DIAMINØQUINAZØLINE                                        PAGE  3

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OBSERVED AND CALCULATED STRUCTURE FACTORS FOR 2,4-DIAMINOQUINAZOLINE

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OBSERVED AND CALCULATED STRUCTURE FACTORS FOR 2,4-DIAMINOQUINAZOLINE

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-5	11	4	10	6	15	17	4	19	-17	-4	24	4	15	-14	4	13	5	26	27	9	22	5	12	-1
-7	11	4	10	-4	-2	16	4	9	-6	0	3	5	38	40	4	15	5	11	-14	-1	10	5	16	16
-9	11	4	84	85	-4	16	4	16	15	0	7	5	32	31	4	17	5	17	-14	-3	10	5	23	-23
11	11	4	30	29	-6	16	4	18	17	0	13	5	31	-32	4	19	5	11	17	-5	10	5	65	71
11	13	4	33	34	-8	16	4	22	22	0	15	5	10	-4	0	5	5	8	-3	-7	10	5	15	-12
11	17	4	18	-23	-12	16	4	18	-15	0	17	5	26	-32	5	6	5	10	9	-9	10	5	18	23
11	19	4	11	-7	-14	16	4	12	10	0	21	5	25	18	5	8	5	38	-39	10	11	5	38	-41
0	12	4	23	26	16	18	4	16	-5	1	2	5	24	-25	5	10	5	46	47	10	13	5	33	-32
-2	12	4	50	-52	-1	17	4	18	13	1	6	5	16	17	5	12	5	40	-41	10	15	5	12	-4
-4	12	4	29	-31	-9	17	4	10	-7	1	8	5	10	9	5	14	5	16	20	10	17	5	11	-12
-8	12	4	24	-25	-15	17	4	22	-13	1	10	5	12	-1	5	20	5	10	-9	10	21	5	15	10
12	12	4	36	-41	-2	18	4	11	12	1	12	5	10	2	-5	6	5	45	45	0	11	5	9	-6
12	14	4	13	-6	-4	18	4	17	-22	1	14	5	11	11	6	7	5	8	2	-4	11	5	9	-1
12	16	4	17	16	-6	18	4	10	6	1	18	5	13	3	6	9	5	36	-36	-6	11	5	28	30
12	18	4	18	19	-8	18	4	10	9	1	20	5	11	-15	6	11	5	20	19	-8	11	5	23	-22

```
ØBSERVED AND CALCULATED STRUCTURE FACTØRS FØR   2,4-DIAMINØQUINAZØLINE

   H  K  L   FØ   FC      H  K  L   FØ   FC      H  K  L   FØ   FC      H  K  L   FØ   FC      H  K  L   FØ   FC

 -10 11  5   38  -38    -13 18  5   12    2     -2  4  6   20   22     -7  9  6   34   35     -8 16  6   11   -6
  11 12  5   27   28      0 19  5   11   -6      4  6  6   20   20      9 13  6   20  -17    -10 16  6   17   15
  11 14  5   18   20     -5 20  5   15  -15      4  8  6   10   13      9 15  6   11  -14    -12 16  6   20  -19
  11 16  5   19   10    -13 20  5   12    6      4 10  6   50   50      0 10  6   23  -23     16 16  6   14    1
  -1 12  5   15   15      0 21  5   14   18      4 12  6   24  -23     -2 10  6   26   29     -3 17  6   11    2
  -3 12  5   11   -6     -2 21  5   15  -12      4 14  6   17  -15     -4 10  6   38   39     -5 17  6   14   13
  -7 12  5   16   11     -6 21  5   13    8      4 22  6   16   11     -6 10  6   24  -25     -9 17  6   15   -5
  -9 12  5   25   30     -1 22  5   11    2     -1  5  6   57   61     -8 10  6   13   10      0 18  6   13   -1
 -11 12  5   18  -20      0 23  5   14    6      5  5  6   21   17     10 12  6   19   16     -4 18  6   25   22
  12 19  5   12    5      0  4  6   24   25      5  9  6   13   -4     10 18  6   12    8     -6 18  6   18  -11
   0 13  5   33  -32      0  6  6   57  -63      5 11  6   21   19     10 20  6   13   -6     -8 18  6   19   19
  -2 13  5   21   25      0  8  6   40   43      5 15  6   11  -12     -1 11  6   14   22     -1 19  6   10    6
  -4 13  5   10   12      0 10  6   21  -23      0  6  6   57  -63     -3 11  6   17  -16     -5 19  6   10   -3
  -6 13  5   22   19      0 12  6   16   14     -2  6  6   73   77     -5 11  6   17   19    -11 19  6   14   -2
 -10 13  5   11    7      0 14  6   44  -47     -4  6  6    8   -4     -9 11  6   13  -11    -13 19  6   14   -5
  13 14  5   11   -5      1  1  6    8   -6      6  8  6    9   -4     11 11  6   22  -25      0 20  6   11   -8
  -1 14  5   20   23      1  5  6   42  -43      6 12  6   26   26     11 15  6   14  -12     -8 20  6   13   -1
  -5 14  5    9    5      1  7  6   30   33      6 14  6   16   -2      0 12  6   14   14    -10 20  6   12    2
  -7 14  5   23  -23      1  9  6   21  -23      6 16  6   13   10     -2 12  6   32  -33    -11 21  6   17    1
 -11 14  5   15   10      1 13  6   41   45      6 22  6   16  -14     -4 12  6   22   26     -5 23  6   11    8
  14 17  5   14   -1      1 15  6   14   -8     -1  7  6   59  -65     12 20  6   15   12      0  3  7   21  -18
  -2 15  5   15  -20      1 21  6   11    1     -3  7  6   26   24     -1 13  6   12  -17      0  5  7    9   -3
  -4 15  5   14   15      2  2  6   18  -21     -5  7  6   16   18     -3 13  6   22   22      0  7  7   10  -14
 -10 15  5   27  -24      2  4  6   24  -23      7 11  6   14  -11     -5 13  6    9    3      0  9  7   38   37
 -14 15  5   10   -9      2  6  6   11   14      7 13  6   26  -28    -11 13  6   21  -24      0 11  7   18   16
  -1 16  5   14  -12      2  8  6   21  -20      7 19  6   11  -12     13 13  6   13  -12      0 13  7   17   11
  -5 16  5   12   -9      2 18  6   11   10      7 21  6   11   10     13 19  6   10   -8      0 15  7   17    7
  -7 16  5   12    6     -1  3  6   15  -18      0  8  6   41   43      0 14  6   44  -47      1  8  7   27   21
 -11 16  5   10   13      3  3  6   16   16     -4  8  6   10  -10     -2 14  6   20   17      1 10  7   12    0
   0 17  5   28  -32      3  5  6   16  -16     -6  8  6   28   27     -6 14  6   10   -9      1 14  7   17  -12
  -2 17  5   11   -9      3  7  6   10   -7      8  8  6   32   36    -12 14  6   12  -13      2  3  7   12   11
  -4 17  5   11  -15      3  9  6   23   25      8 10  6   15   17     -1 15  6   46   50      2  7  7   18   17
 -10 17  5   19  -16      3 11  6   14  -11      8 14  6   10   -5     -7 15  6   17   19      2  9  7   13   16
  -1 18  5   20  -22      3 13  6   12   10      8 16  6   28  -27    -13 15  6   17   -7      2 13  7   15  -12
  -9 18  5   16   12      3 21  6   13   -9      8 20  6   13    4     -2 16  6   19  -19      2 17  7   18  -12
 -11 18  5   13   -3      0  4  6   24   25     -5  9  6   22  -23     -4 16  6   21   18      0  3  7   18  -18
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OBSERVED AND CALCULATED STRUCTURE FACTORS FOR   2,4-DIAMINOQUINAZOLINE                                        PAGE  7

  H  K  L   FO    FC       H  K  L   FO    FC       H  K  L   FO    FC       H  K  L   FO    FC       H  K  L   FO    FC

 -2  3  7   16   -14      -2  9  7   37    34      -9 16  7   16   -13       3 21  8   14    -9      10 10  8   18    -8
  3  4  7   60    56      -6  9  7   14   -13     -11 16  7   22   -15      -2  4  8   26   -27      -1 11  8   21   -17
  3  6  7   27   -22      -8  9  7   21    18      -4 17  7   12     1       4  8  8   14     5      -7 11  8   20    15
  3  8  7   12   -11       9 12  7   12     7      -6 17  7   30    24      -3  5  8   22    22      -9 11  8   17     4
  3 16  7   13    -4       9 16  7   16    -5      -8 17  7   20   -14       5  5  8   25   -19      11 11  8   21   -11
  3 22  7   17    -7       9 18  7   18   -10     -12 17  7   14    -2       5  7  8   12     3      11 13  8   15    10
 -1  4  7   15    -7      -5 10  7   16     8     -14 17  7   19    -1       5 11  8   14   -10      11 15  8   15     2
 -3  4  7   30   -25      -7 10  7   14    -9      -9 18  7   33   -26       6 15  8   13     1       0 12  8   14     9
  4  5  7   31   -29      10 17  7   14     7      -1 20  7   13     0       0  6  8   13    -9      -2 12  8   23   -21
  4  9  7   14   -14       0 11  7   13    16      -3 20  7   16    11      -2  6  8   19    18      -4 12  8   24   -18
  4 13  7   11     7      -2 11  7   34    33      -1 22  7   13     1      -4  6  8   20   -19      -6 12  8   12    -9
 -2  5  7   20   -18      -4 11  7   14    14       0  6  8   10    -9       6  6  8   28    22      12 12  8   25   -15
 -4  5  7   53   -49      -6 11  7   16   -10       0 16  8   21    19      -5  7  8   13     9      -1 13  8   12     4
  5  6  7   66    60      11 18  7   26   -18       1  3  8   23    21       7  7  8   15   -13      -5 13  8   13   -10
  5 14  7   11     8      -1 12  7   40    33       1  7  8   18   -16       7  9  8   21   -18      13 17  8   14   -12
  5 18  7   19    -5      -3 12  7   23   -18       1  9  8   17   -13       7 11  8   16     9      -4 14  8   13     2
 -1  6  7   11    -2      -5 12  7   17    12       1 11  8   14   -14       7 17  8   16     2      -6 14  8   13     6
 -3  6  7   51   -47      -7 12  7   12     6       1 13  8   18   -13       0  8  8   13     7     -12 14  8   11     2
 -5  6  7   19   -17      -9 12  7   12     9       1 17  8   18    11      -2  8  8   35   -33      14 14  8   16    -3
  6  7  7   23   -22     -11 12  7   16    13       1 21  8   17    -9      -6  8  8   13    -2      -5 15  8   16    10
  6 11  7   15    11       0 13  7   12    11       0  2  8    8    -7       8 14  8   22   -17     -13 15  8   14    -7
  6 13  7   12   -10      -6 13  7   14     7       2  4  8   16    16      -1  9  8   12   -17      15 15  8   18    -5
  0  7  7   12   -14      -8 13  7   18   -11       2  6  8   12    -1      -3  9  8   19   -15      -6 16  8   17    12
 -2  7  7   28    26      13 14  7   12    -2       2 10  8   17   -14       9 11  8   19    13      -3 17  8   14    12
 -4  7  7   23   -22      -5 14  7   32    29       2 12  8   18   -13       9 15  8   12     7     -13 17  8   18     9
  7 12  7   13     7      -7 14  7   28   -27       2 14  8   26    24       9 17  8   15    -1       0 18  8   14     5
  7 16  7   14    10      -9 14  7   18    13       2 18  8   15     9       9 19  8   20    -3      -8 18  8   20    12
  7 20  7   22   -12       0 15  7   12     7      -1  3  8   10    -8       0 10  8   11   -10     -10 18  8   19   -10
 -1  8  7   36   -33      -2 15  7   19    14       3  3  8   26   -24      -2 10  8   37   -34      -9 19  8   13     1
 -3  8  7   17   -16      -8 15  7   15    13       3  5  8   23    23      -4 10  8   23   -20       0 20  8   14    10
 -5  8  7   16   -13      -3 16  7   15    14       3 11  8   16    13      -6 10  8   19   -11      -4 20  8   14    -5
  8 11  7   16   -12      -5 16  7   38   -33       3 15  8   15     6      -8 10  8   14    -6      -1 21  8   12    -4
  0  9  7   36    37
```

DAQ

```
                 GGG    UGG    GUG    UUG    GGU    UGU    GUU    UUU    ALL

      N          394      0      0    262      0    284    301      0   1241

      V          337      0      0    368      0    355    316      0    343


SIN THETA     0.00 -  .19 -  .24 -  .28 -  .31 -  .34 -  .36 -  .39 -  .41 -  .44 -  .52

      N          125    131    125    127    147    100    150     98    138    100

      V          282    277    288    349    318    316    318    326    382    544


SQRT(F/FMAX)  0.00 -  .20 -  .21 -  .22 -  .24 -  .25 -  .28 -  .30 -  .34 -  .43 - 1.00

      N          179    100    101    177     68    170     91    111    136    108

      V          294    365    402    378    367    367    289    300    308    347


     ABS(H)        0      1      2      3      4      5      6      7      8      9     10     11     12     13      -
   REST

      N          136    119    126     99    117    103    106     72     81     60     52     46     36     28     60

      V          342    357    278    316    300    367    326    322    335    308    343    400    308    404    450


     ABS(K)        0      1      2      3      4      5      6      7      8      9     10     11     12     13      -
   REST

      N            0      1      8     22     29     33     50     47     57     57     71     74     80     68    644

      V            0    266    287    294    347    275    385    326    336    296    343    293    325    281    364


     ABS(L)        0      1      2      3      4      5      6      7      8      9     10     11     12     13      -
   REST

      N          116    184    176    178    160    131    119     92     85      0      0      0      0      0      0

      V          272    299    338    304    316    353    403    424    438      0      0      0      0      0      0
```

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OBSERVED AND CALCULATED STRUCTURE FACTORS FOR    HOB                                                         PAGE  1

  H  K  L   FO   FC      H  K  L   FO   FC      H  K  L   FO   FC      H  K  L   FO   FC      H  K  L   FO   FC

  0  0  4   51  -52     -4  0 12    4   -4     -7  0  1   23   23     10  0  8    2   -1    -15  0  9    4    2
  0  0  6    7    7     -4  0  6   30   29      7  0  1   26  -24    -11  0 13    2   -2    -15  0  7    2   -3
  0  0  8    7   -6     -4  0  4   29  -26      7  0  3    2    2    -11  0  9    8   -9    -15  0  5    5   -6
 -1  0 13    2   -3     -4  0  2   24   23      7  0  5   10   10    -11  0  7   10   10    -15  0  1    2    3
 -1  0 11   21   25      4  0  0   50  -52      7  0  7    5    5    -11  0  5    2    1     15  0  1    7   -7
 -1  0  9   17  -20      4  0  2   31  -30      7  0  9   11  -12    -11  0  3    2    4     15  0  3    2    1
 -1  0  7   16  -17      4  0  4   46   44      7  0 11    3    3    -11  0  1    2   -2     15  0  5   11   10
 -1  0  5   13   13      4  0  6    4   -5     -8  0 10    2   -3     11  0  1   12   12    -16  0  6    7    8
 -1  0  3   11  -10      4  0  8    2   -2     -8  0  6    7    7     11  0  3   16  -15    -16  0  4   10  -12
  1  0  3   35   33      4  0 10    3    2     -8  0  4   18   16    -12  0 10    7    9    -16  0  2    2   -2
  1  0  5   17  -18     -5  0 13    3    3     -8  0  2   59  -60    -12  0  8   15  -15     16  0  2    5    4
  1  0  7    3    2     -5  0 11    4   -5      8  0  0   27   26    -12  0  6    2    2    -17  0  9    2    2
  1  0  9   15  -16     -5  0  9    6   -7      8  0  2    8    8    -12  0  4    5   -5    -17  0  5    3   -1
  1  0 11    3    4     -5  0  7   28   28      8  0  4   18  -17    -12  0  2   12   12    -18  0  6    4    5
 -2  0 12    4   -4     -5  0  5    4   -3      8  0  6   14   13     12  0  0   27   28    -18  0  4    3   -2
 -2  0 10   10   11     -5  0  3   15  -15      8  0 10    5   -5     12  0  2   35  -34     18  0  2    4   -4
 -2  0  8    6    6     -5  0  1    3    3     -9  0 13    6   -7     12  0  6    3    4    -19  0  3    2    2
 -2  0  6    6   -5      5  0  1   15   15     -9  0 11    4    4     12  0  8    2    0    -19  0  1    2   -2
 -2  0  4   28  -27      5  0  3   36  -35     -9  0  9    4    5    -13  0 11    4    6      0  1  3    8   -9
  2  0  2   29   31      5  0  5    7    6     -9  0  7    7   -8    -13  0  9   14  -17      0  1  4   11  -11
  2  0  4   49   50      5  0  7    4    3     -9  0  5   10   11    -13  0  7    6    6      0  1  5    4    3
  2  0  6   14  -14     -6  0 12    2    1     -9  0  3    4    4    -13  0  5    5    6      0  1  6    8   -9
  2  0  8   19  -11     -6  0  8   16  -16     -9  0  1   23  -23    -13  0  3    8   -8      0  1  7    4    4
  2  0 10    2    3     -6  0  6    7    7      9  0  1    5    4    -13  0  1    6   -7      0  1  8    9    9
  2  0 12    2    1     -6  0  4   28   26      9  0  3   12   11     13  0  1   26   25      0  1  9   16  -17
 -3  0 11    5    5     -6  0  2   27  -25      9  0  5   15  -15     13  0  3    8   -8      0  1 10    2    3
 -3  0  9    5    6      6  0  0    3   -4      9  0  7   10   10     13  0  5    4   -3      0  1 11    5    7
 -3  0  7   11   11      6  0  2    2    3      9  0  9    5    4    -14  0 12    3    0      0  1 13    3    2
 -3  0  5   25  -23      6  0  4   11    9    -10  0 12    3   -3    -14  0 10    9   10     -1  1 13    5   -4
 -3  0  3   14  -12      6  0  6    5   -6    -10  0 10    3    2    -14  0  8    7   -8     -1  1 12    2   -2
  3  0  1    7   -7      6  0  8    4   -4    -10  0  8    5   -6    -14  0  6    3   -3     -1  1 10    6    6
  3  0  3   23  -19      6  0 10    4    4    -10  0  4   21   20    -14  0  2    6   -5     -1  1  9    5    5
  3  0  5   30   29     -7  0 13    3   -4    -10  0  2    4    6     14  0  0    8    8     -1  1  8    4   -4
  3  0  7    3    4     -7  0  9    2    3     10  0  0   14  -14     14  0  2    8    8     -1  1  7   10   10
  3  0 11    5   -5     -7  0  5   12  -13     10  0  2   26  -23     14  0  4    2   -1     -1  1  6    3   -2
  3  0 13    2   -2     -7  0  3   12   12     10  0  4   18   17     14  0  6    8   -7     -1  1  5    3   -2
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                                                                                              PAGE  2
OBSERVED AND CALCULATED STRUCTURE FACTORS FOR   HOB

   H  K  L   FO   FC       H  K  L   FO   FC       H  K  L   FO   FC       H  K  L   FO   FC       H  K  L   FO   FC

  -1  1  3   25  -27      -3  1  2   60  -65      -5  1  9    4   -4       6  1  8    3   -4       8  1  5    5   -4
   1  1  3    3    2       3  1  1   19   20      -5  1  8    5   -5       6  1 11    5    3       8  1  6    6   -6
   1  1  4    3   -2       3  1  2   10   11      -5  1  7    6    6      -7  1 14    2    0       8  1  7   10   10
   1  1  5   10  -10       3  1  3   14  -16      -5  1  6   17   15      -7  1 11    5   -4       8  1  9    4   -4
   1  1  6   16  -18       3  1  4   12   12      -5  1  5    6    6      -7  1 10    3    4      -9  1 11    2   -2
   1  1  7   18  -20       3  1  5   11   11      -5  1  4    6   -6      -7  1  8    5   -5      -9  1 10    2    4
   1  1  8    3    4       3  1  6    5   -5      -5  1  3   15  -13      -7  1  7    5    5      -9  1  7    3   -3
   1  1  9   16   16       3  1  7    9  -10      -5  1  2    4    6      -7  1  6    2   -1      -9  1  5    3    1
   1  1 12    2   -1       3  1  8    5    4      -5  1  1    9   10      -7  1  5    4   -4      -9  1  4   18   18
   1  1 13    3    0       3  1 11    2   -1       5  1  0   24   26      -7  1  4    4   -3      -9  1  3    2   -1
  -2  1 11    7    8       3  1 13    3    2       5  1  1   32  -32      -7  1  3    7    6      -9  1  2   13  -13
  -2  1  9    3    3      -4  1 13    4   -3       5  1  2   36  -34      -7  1  2   11  -10      -9  1  1   11   12
  -2  1  7    2   -2      -4  1 12    4   -5       5  1  3   34   31      -7  1  1    6   -6       9  1  0   14  -14
  -2  1  6   16   17      -4  1  9    4    4       5  1  4    3    3       7  1  0   24   23       9  1  1    6    6
  -2  1  5   21  -19      -4  1  8    2    3       5  1  6    6    6       7  1  1    4   -4       9  1  2    3    3
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  -2  1  3   26   22      -4  1  6    4   -4       5  1  8    4   -5       7  1  3    2    2       9  1  5    6    6
   2  1  2    3   -3      -4  1  5   16  -10       5  1  9    4   -4       7  1  4    3    3       9  1  6    6   -6
   2  1  3    1    2      -4  1  4   16   15       5  1 12    3    2       7  1  5    3   -4       9  1  7    5   -6
   2  1  4   16   18      -4  1  3   18   18      -6  1 11    4    5       7  1  7    4    4     -10  1 13    2   -2
   2  1  5   14   15      -4  1  2   17   18      -6  1 10    3    3       7  1  8    4   -6     -10  1  9    2    0
   2  1  6   19  -19      -4  1  1    3   -3      -6  1  9    9   -8       7  1  9    3   -2     -10  1  8    3    4
   2  1  7    9    9       4  1  0   14   17      -6  1  8   12  -12      -8  1 13    2   -2     -10  1  7   13   13
   2  1  8    3   -3       4  1  1   13  -16      -6  1  6    6    6      -8  1 11    5    5     -10  1  6   11  -12
   2  1  9   11  -12       4  1  2   33   34      -6  1  5   11   11      -8  1 10    2    2     -10  1  5   13  -11
   2  1 10    3    3       4  1  3    6   -6      -6  1  4    3    2      -8  1  9    3   -2     -10  1  4   15   15
   2  1 11    2   -1       4  1  4    8   -7      -6  1  3    3   -3      -8  1  6    9   -8     -10  1  2   12  -12
   2  1 13    2    0       4  1  5    5    4      -6  1  2   22   21      -8  1  4    8    9     -10  1  1    5    4
  -3  1 13    7   -8       4  1  6   11  -12      -6  1  1    2    0      -8  1  3    9  -10      10  1  0    7   -7
  -3  1 12    3   -4       4  1  8    4    5       6  1  0   23   23      -8  1  2   12   11      10  1  1    4   -4
  -3  1 11    6    7       4  1  9    3    4       6  1  1   15   16      -8  1  1    2    0      10  1  2   20  -20
  -3  1  7   10  -10       4  1 11    3    2       6  1  2    2    2       8  1  0    4    3      10  1  3    5   -4
  -3  1  6   17   14       4  1 12    4   -4       6  1  3    9   -8       8  1  1   14   15      10  1  4   24   23
  -3  1  5   26   27      -5  1 14    3    2       6  1  4    6   -6       8  1  2    8    8      10  1  7    3    2
  -3  1  4   15   15      -5  1 11    3   -4       6  1  5    5   -5       8  1  3    5   -5      10  1  8    5   -4
  -3  1  3   22   21      -5  1 10    3   -4       6  1  6    6    6       8  1  4    6    5     -11  1 12    2    0
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OBSERVED AND CALCULATED STRUCTURE FACTORS FOR   HOB                                                        PAGE  3

  H  K  L   FO   FC      H  K  L   FO   FC      H  K  L   FO   FC      H  K  L   FO   FC      H  K  L   FO   FC

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-11  1  8    8   -8    -13  1  3    5   -5     16  1  0    4    4      1  2  5   10    9     -3  2  6    4   -4
-11  1  7   16  -17    -13  1  2    2   -1     16  1  5    3    2      1  2  6   11  -11     -3  2  5    2   -1
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-11  1  3   11   12     13  1  1   12  -12    -17  1  1    5    5      1  2  9    4   -4     -3  2  2   29  -29
-11  1  2    3    4     13  1  2    6   -6     17  1  0    2   -2      1  2 10    2   -2     -3  2  1   10  -11
-11  1  1    6   -6     13  1  3    2    3     17  1  2    3   -2      1  2 13    2    2      3  2  0   17   21
 11  1  1    4    5     13  1  4    7   -6     17  1  3    6    5     -2  2 13    2   -3      3  2  2   12  -14
 11  1  2   16  -17     13  1  7    4   -4    -18  1  8    3   -2     -2  2 12    3   -2      3  2  3    3    3
 11  1  3   17  -17     13  1  8    3    3    -18  1  6    4    5     -2  2 11    2    3      3  2  4    4    3
 11  1  4    5    6    -14  1 11    3    3    -18  1  1    3    2     -2  2 10    2   -3      3  2  5   20  -19
 11  1  5    9    9    -14  1 10    5    7     18  1  0    3    2     -2  2  9    2   -3      3  2  6    5    5
 11  1  7    4    4    -14  1  9    3   -3     18  1  1    3    1     -2  2  8    3    3      3  2  7   16   16
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 12  1  0    7   -7     14  1  3    5    4      0  2  9    3    3      2  2  3   11   13     -4  2  3   22   21
 12  1  1    6    7     14  1  5    2    1      0  2 11    4    3      2  2  4    3   -5     -4  2  2    7   -7
 12  1  2    3    3    -15  1 11    4    4      0  2 12    4   -1      2  2  5    4    4     -4  2  1    8    8
 12  1  3    3   -2    -15  1 10    4    4     -1  2  9    3    4      2  2  6    3   -1      4  2  0    2   -2
 12  1  4    3   -3    -15  1  4    6   -6     -1  2  8   11   12      2  2  7   21  -20      4  2  1    2    1
 12  1  7    5   -3    -15  1  2    2   -2     -1  2  7    4   -4      2  2  8    6    6      4  2  2   11  -13
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-13  1 12    2   -1     15  1  0    3    3     -1  2  5    4   -3      2  2 11    3    2      4  2  4    5    6
-13  1 11    5    4     15  1  4    2    1     -1  2  4    2   -2     -3  2 13    2   -3      4  2  5    9    9
-13  1 10    4    5    -16  1  7    2   -1     -1  2  3   23   23     -3  2 12    3   -2      4  2  6    6   -5
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OBSERVED AND CALCULATED STRUCTURE FACTORS FOR    HOB .                                                          PAGE  4

  H  K  L   FO   FC      H  K  L   FO   FC      H  K  L   FO   FC      H  K  L   FO   FC      H  K  L   FO   FC

  4  2 12    3   -2      6  2  6    2    1      8  2  2    6    5    -11  2  6   12  -12     14  2  0    4    5
 -5  2 13    2   -2      6  2  7    7    7      8  2  3    3   -2    -11  2  4    8    9     14  2  1    2    1
 -5  2  9    5   -5      6  2  9    3   -3      8  2  4   10   10    -11  2  3    5   -5     14  2  3    2   -2
 -5  2  8    5   -5      6  2 10    3   -2      8  2  6   13  -11    -11  2  2    2    1     14  2  5    3   -2
 -5  2  7    4    3      6  2 11    2   -1      8  2  7    3   -2    -11  2  1    2   -2    -15  2  7    2    1
 -5  2  6    7   -7     -7  2 13    2    1     -9  2 12    3   -3     11  2  0    3    2    -15  2  4    2    2
 -5  2  5    9   -8     -7  2 11    3    3     -9  2 10    4    3     11  2  1    2    2    -15  2  3    7    8
 -5  2  4   21   18     -7  2 10    2    3     -9  2  9    4    3     11  2  2    6   -6    -15  2  2    8   -9
 -5  2  3    6    5     -7  2  9    5   -5     -9  2  8    3    2     11  2  3    5    6    -15  2  1    9   -9
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  5  2  0    5    5     -7  2  4    5   -5     -9  2  5   19  -18    -12  2  9    2   -1     15  2  4    3    2
  5  2  1    8   -9     -7  2  1    7   -8     -9  2  4    5    5    -12  2  8    4    4    -16  2  7    4   -3
  5  2  2   10  -12      7  2  0    8   -8     -9  2  3    8    8    -12  2  7    3    2    -16  2  4    6    6
  5  2  3    3   -3      7  2  1   19   21     -9  2  2    2    1    -12  2  6    7   -7    -16  2  3    9    9
  5  2  4    6    6      7  2  2    9   10     -9  2  1    2   -2    -12  2  5    7   -8    -16  2  1    6   -6
  5  2  5    4   -5      7  2  3    4   -4      9  2  0    5   -5    -12  2  4    3    3     16  2  4    4    4
  5  2  6    4    3      7  2  4    4    3      9  2  2    4    3    -12  2  2    4    4    -17  2  5    3   -4
  5  2  7    2    2      7  2  5    2   -3      9  2  4   11   12    -12  2  1    7    8    -17  2  3    5    5
  5  2  8    3   -3      7  2  6   13  -14      9  2  5    3    3     12  2  0    5   -6     17  2  1    3   -1
  5  2 10    3    3      7  2  8    4    4      9  2  6    9   -8     12  2  1    4    4    -18  2  6    3    1
  5  2 11    6    5      7  2  9    2   -1    -10  2 10    2    0     12  2  3    3   -3    -18  2  1    4    1
 -6  2 11    3   -3      7  2 10    4    3    -10  2  9    2   -3     12  2  5    2   -1     18  2  0    2    2
 -6  2  9    6    5      7  2 11    3    1    -10  2  8    2    2     12  2  8    2    0      0  3  2    6   -6
 -6  2  8    5   -4     -8  2 12    2   -1    -10  2  7    6   -5    -13  2  2    7   -8      0  3  3    7    7
 -6  2  6    2   -2     -8  2 10    7    6    -10  2  5   12   11    -13  2  1    3   -4      0  3  4    2    2
 -6  2  5    8   -8     -8  2  9    3   -1    -10  2  4    4   -2     13  2  0    7   -7      0  3  5    3    3
 -6  2  4    6   -5     -8  2  8    6   -7     10  2  1    3   -3     13  2  1    3   -3      0  3  7    2   -2
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  6  2  0   26   28     -8  2  5   18   17     10  2  5    9    9    -14  2 11    3    2      0  3 12    3    2
  6  2  1    8   -9     -8  2  4    6   -5     10  2  7    5   -4    -14  2  8    3    2     -1  3 11    2    0
  6  2  2   10  -10     -8  2  3    7   -7    -11  2 11    3   -2    -14  2  5    2   -2     -1  3 10    2   -3
  6  2  3    7   -8     -8  2  2    3   -3    -11  2 10    2    1    -14  2  4    3   -2     -1  3  8    5    5
  6  2  4    6   -7     -8  2  1   15  -15    -11  2  8    3    3    -14  2  2    3   -3     -1  3  7    3   -2
  6  2  5    4    3      8  2  1    7   -8    -11  2  7    6    6    -14  2  1    4   -5     -1  3  5    2    0
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OBSERVED AND CALCULATED STRUCTURE FACTORS FOR   HOB                                                    PAGE  5

  H  K  L   FO   FC      H  K  L   FO   FC      H  K  L   FO   FC      H  K  L   FO   FC      H  K  L   FO   FC

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 -1  3  2    5    5     -3  3  1    1    3      5  3  0    2    0      7  3  5    2    0     10  3  5    3   -2
  1  3  1   13   16      3  3  0    2   -3      5  3  1    4   -4      7  3  6    7   -7    -11  3  9    2   -1
  1  3  2    4   -5      3  3  1    2   -4      5  3  2    2   -3      7  3  8    6    6    -11  3  6    3   -2
  1  3  3    3   -3      3  3  2    5   -5      5  3  3   10  -11      7  3  9    5    3    -11  3  5    3   -3
  1  3  5    7   -7      3  3  3    7    7      5  3  4    4    5     -8  3 10    3    3    -11  3  3    6    6
  1  3  6    3    2      3  3  4    4    5      5  3  5   14   14     -8  3  6    2    0     11  3  0    3   -3
  1  3  7    4    3      3  3  5    8    8      5  3  6    5   -5     -8  3  5    7   -6     11  3  1    4    4
  1  3  9    2   -2      3  3  6    3   -3      5  3  8    2    3     -8  3  4    4    3     11  3  2    2    2
  1  3 10    2    1      3  3  7    5   -5      5  3  9    3   -2     -8  3  3   11   12     11  3  3    3   -2
 -2  3 11    2   -1      3  3  9    3   -2     -6  3  8    6    6     -8  3  2    9   -9     11  3  4    2    1
 -2  3 10    5   -4      3  3 10    3    2     -6  3  7    6    7     -8  3  1    8   -8     11  3  7    3    0
 -2  3  9    3   -2      3  3 11    2    2     -6  3  6   19  -16      8  3  1    2   -1    -12  3 11    2   -1
 -2  3  8    3    2     -4  3  9    4   -3     -6  3  5   12  -11      8  3  2    2   -2    -12  3  9    2    0
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 -2  3  1    3    6     -4  3  4   13   12      6  3  0    3    2     -9  3 10    2    1     12  3  3    3    4
  2  3  0    2   -1     -4  3  3    2    2      6  3  2    3    3     -9  3  7    2    0    -13  3  9    2   -2
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  2  3  3    1    2     -4  3  1    2    3      6  3  4    8   -8     -9  3  4    2   -3    -13  3  5    2    1
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  2  3  6    5   -5      4  3  2    7   -8      6  3  7    2    2      9  3  1    2    2     13  3  1    3    4
  2  3  7    4    4      4  3  3    5    6      6  3  8    9    7      9  3  3    2   -3     13  3  3    4   -4
  2  3  8    3    1      4  3  4    3    2     -7  3  8    2    2      9  3  6    3   -1     13  3  5    3    1
  2  3  9    3    2      4  3  5   10  -10     -7  3  7   10    8      9  3  7    2    0    -14  3  8    4    4
  2  3 10    2    0      4  3  6    5    5     -7  3  6    3   -2      9  3  8    2    1    -14  3  7    4    3
 -3  3 11    2    0      4  3  7    4    4     -7  3  5    2    2    -10  3 12    2   -2    -14  3  6    3   -2
 -3  3 10    3   -3     -5  3  9    3    2     -7  3  4    3   -2    -10  3 11    3    0    -14  3  4    2   -1
 -3  3  8    3    2     -5  3  8    2    2     -7  3  3   19  -18    -10  3  9    3    2    -14  3  3    2    1
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 -3  3  3    5    5     -5  3  4    9    9      7  3  1    2   -3     10  3  0    2   -3    -15  3  2    3   -3
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OBSERVED AND CALCULATED STRUCTURE FACTORS FOR   HOB                                                              PAGE  6

  H   K   L    FO   FC      H   K   L    FO   FC      H   K   L    FO   FC      H   K   L    FO   FC      H   K   L    FO   FC

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-16   3   5     4   -4     -2   4   1     3    5      4   4   1     2    2      6   4   3     6   -6      9   4   0     2   -2
-16   3   4     3    4      2   4   0     2   -2      4   4   5     3    4      6   4   4     3    3      9   4   2     3    2
-16   3   3     6    5      2   4   1     2    3      4   4   8     3    1      6   4   5     3    3      9   4   7     3    1
-16   3   2     3   -3      2   4   2     1    1      4   4  10     3   -3     -7   4   9     2   -2      9   4   8     3   -2
-16   3   1     3   -1      2   4   3     4    4     -5   4  12     4    2     -7   4   8     4    4    -10   4   4     2    2
 16   3   0     2    0      2   4   4     2    2     -5   4   7     2    1     -7   4   7     3    4    -10   4   3     4    5
 16   3   1     2   -1      2   4   5     3   -3     -5   4   6     4   -4     -7   4   6     3   -3    -10   4   1     2   -2
 16   3   2     3   -3      2   4   6     3   -2     -5   4   4     2    3     -7   4   3     2    3     10   4   0     2   -1
-17   3   5     5   -5      2   4   8     2    0     -5   4   1     7   -8     -7   4   2     2    0     10   4   2     3    3
-17   3   3     5    6     -3   4  12     3    1      5   4   0     2    2      7   4   0     2   -2     10   4   6     3   -2
-17   3   2     3    0     -3   4  11     2   -1      5   4   1     2    2      7   4   1     5   -5    -11   4   9     2    1
-17   3   1     2    0     -3   4  10     3   -2      5   4   3     6    6      7   4   2     3    5    -11   4   5     4   -3
  0   4   1     1    1     -3   4   9     2    1      5   4   4     4   -4      7   4   3     5    4    -11   4   3     5    4
  0   4   3     2    0     -3   4   7     2    1      5   4   5     3   -3      7   4   4     3   -3     11   4   2     2    0
  0   4   4     4    3     -3   4   6     4   -3      5   4   7     2    0      7   4   6     3   -2    -12   4   8     2    0
  0   4   6     2   -2     -3   4   1     2    5      5   4   8     4    4     -8   4  11     2    1    -12   4   7     2    1
  0   4   7     2    1      3   4   1     2   -1      5   4  10     2   -2     -8   4  10     2   -1    -12   4   6     2    1
  0   4  11     2    0      3   4   2     3   -3     -6   4   9     2   -1     -8   4   9     3   -3     12   4   0     3    1
 -1   4   9     2   -1      3   4   4     4    4     -6   4   8     4    4     -8   4   8     3    4    -13   4   7     2    1
 -1   4   8     2    0      3   4   7     4   -2     -6   4   7     4    5     -8   4   7     7    5    -13   4   5     3   -2
 -1   4   7     4    3      3   4   8     3    2     -6   4   6     4   -4     -8   4   3     3   -1     13   4   1     2   -2
 -1   4   6     2    1      3   4  10     3   -2     -6   4   5     5   -4     -8   4   1     2   -2     13   4   2     2    1
 -1   4   5     2   -3     -4   4  12     2    1     -6   4   3     5   -6      8   4   2     2   -2     13   4   5     3   -1
 -1   4   1     2    4     -4   4   7     3   -1     -6   4   2     2    2      8   4   3     4   -4    -14   4   8     2    2
  1   4   5     3   -3     -4   4   4     3   -2     -6   4   1     5    6      8   4   4     2    0    -14   4   1     3    2
 -2   4  12     2    1     -4   4   3     3   -4      6   4   0     2   -2      8   4   6     2   -1     14   4   0     3    0
 -2   4   5     3    3     -4   4   1     4    8      6   4   1     4    4
```

```
ANALYSIS OF VARIANCE FOR  HOB

              GGG    UGG    GUG    UUG    GGU    UGU    GUU    UUU    ALL

      N       174     91    121    116    102    178    131    125   1038

      V        93    103     90     88    101     93     98     91     94


SIN THETA   0.00 -  .20 -  .26 -  .29 -  .32 -  .34 -  .37 -  .39 -  .42 -  .45 -  .52

      N       106    140     86    117     75    134     82    112     91     95

      V       139    125     87     80     82     72     79     71     84     85


SQRT(F/FMAX) 0.00 - .19 -  .20 -  .22 -  .24 -  .26 -  .29 -  .32 -  .39 -  .50 - 1.00

      N       138     81    131    106     84    104     85    111     96    102

      V        62     70     79     87     81     86     73     88    137    148


     ABS(H)     0      1      2      3      4      5      6      7      8      9     10     11     12     13      -
  REST

      N        36     69     83     83     81     83     79     77     68     59     51     52     49     45    123

      V        84    104    109    124    120    101     98     73     83     75     84     75     75     78     80


     ABS(K)     0      1      2      3      4      5      6      7      8      9     10     11     12     13      -
  REST

      N       162    287    258    206    125      0      0      0      0      0      0      0      0      0      0

      V       104     91     98     93     83      0      0      0      0      0      0      0      0      0      0


     ABS(L)     0      1      2      3      4      5      6      7      8      9     10     11     12     13      -
  REST

      N        52    112    103    106    106     99     87     87     79     67     46     44     27     21      2

      V       107    110    101    103    105     95     95     79     70     81     66     98     72     62     89
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- -

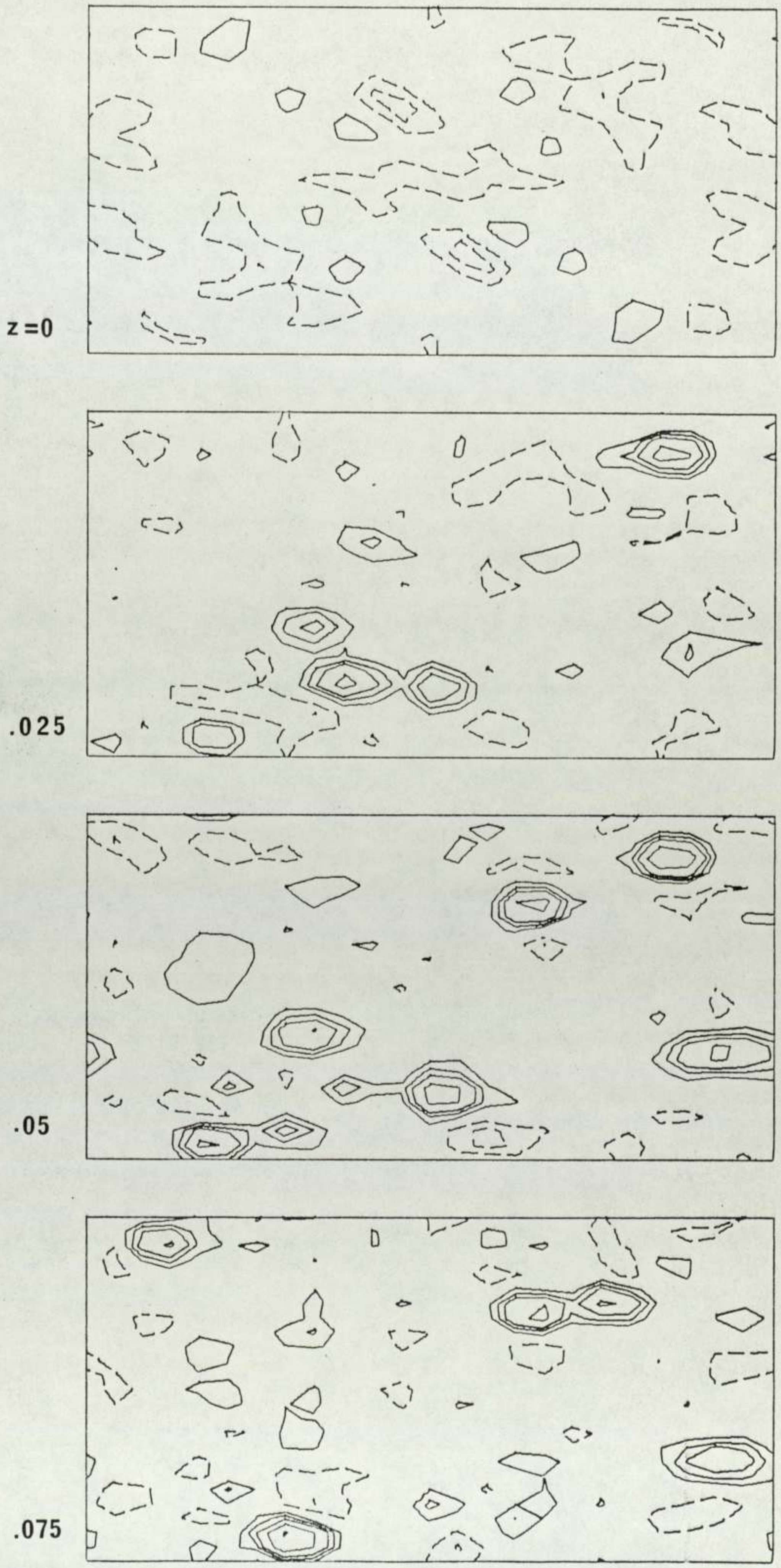
Appendix B: Cycloguanil Hydrochloride: Difference Fourier Synthesis

- -

The Fourier synthesis for 291 neutron reflexions phased on X-ray atomic positions is shown.

The synthesis is shown in sections of constant _z_ from z=0 to z=0.5. The entire length of the _a_ and _b_ axes are shown with _a_ lengthwise and _b_ widthwise with respect to the A4 page. The axes are not drawn to scale.

These plots were produced with use of the program KONTUR.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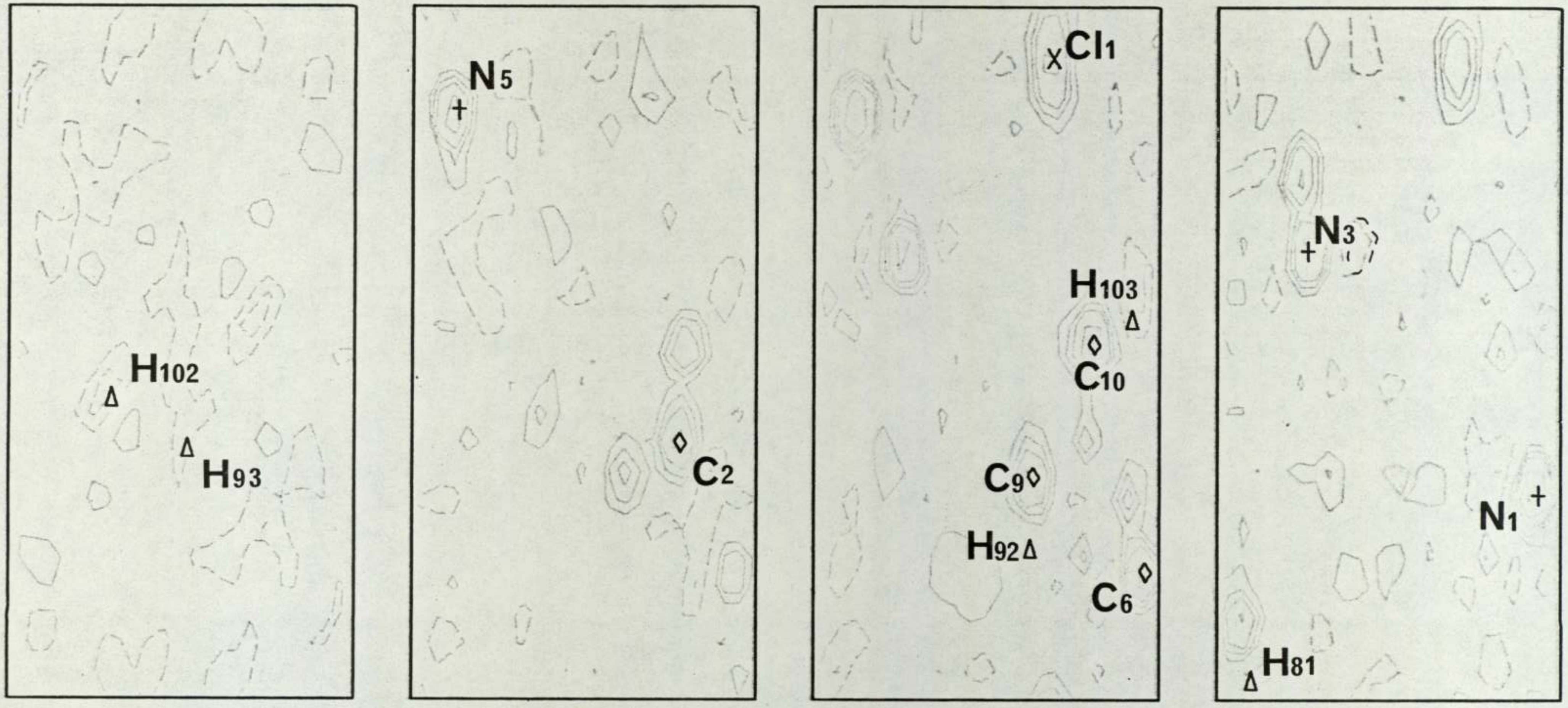
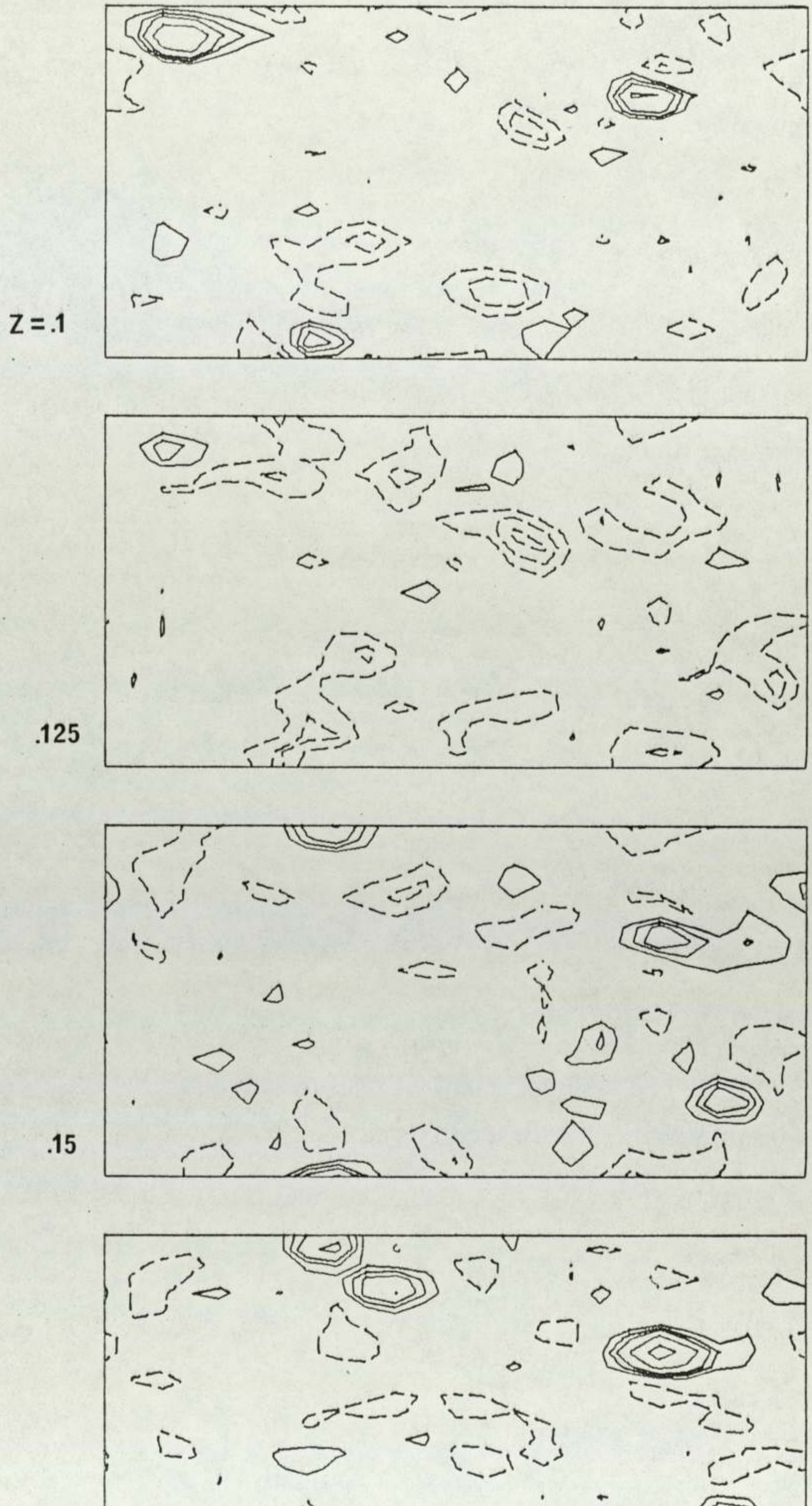
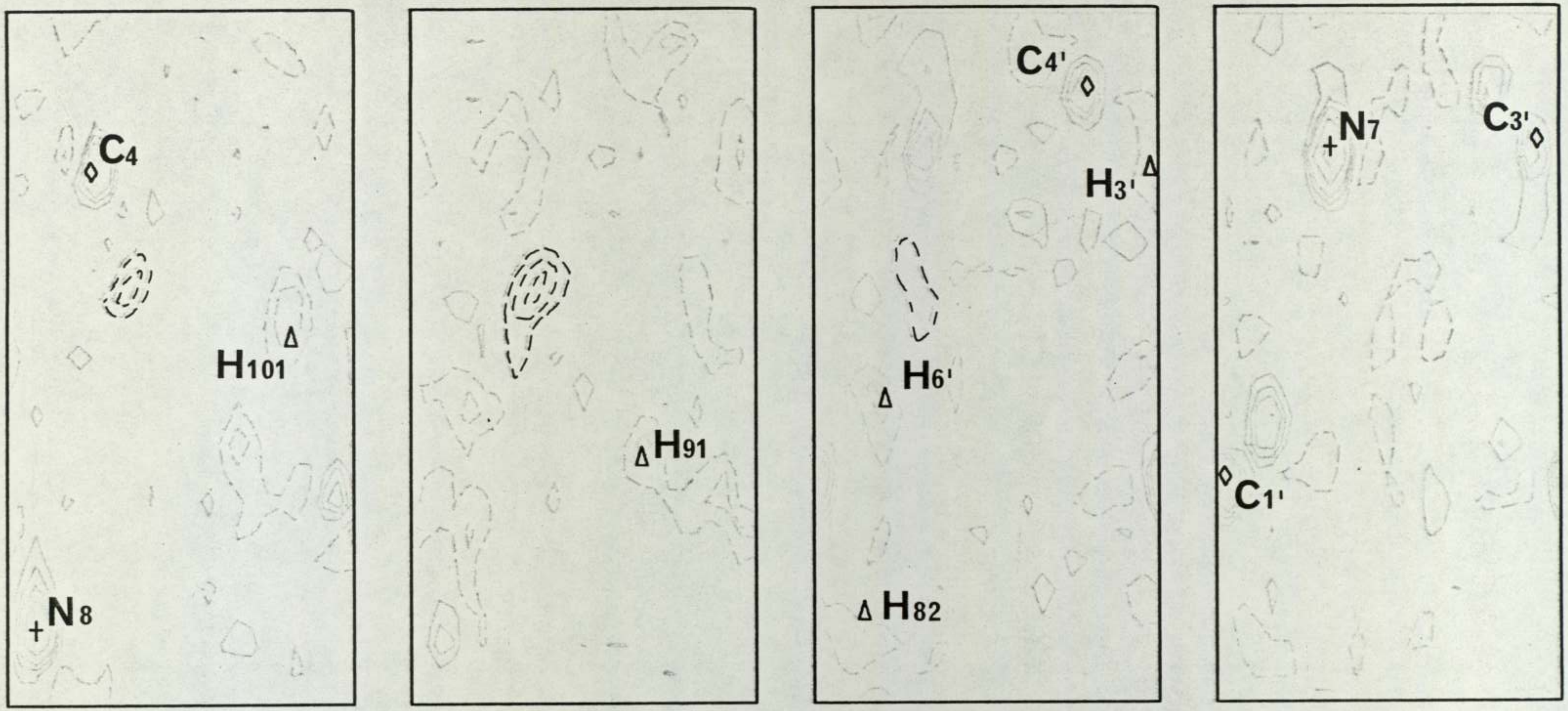
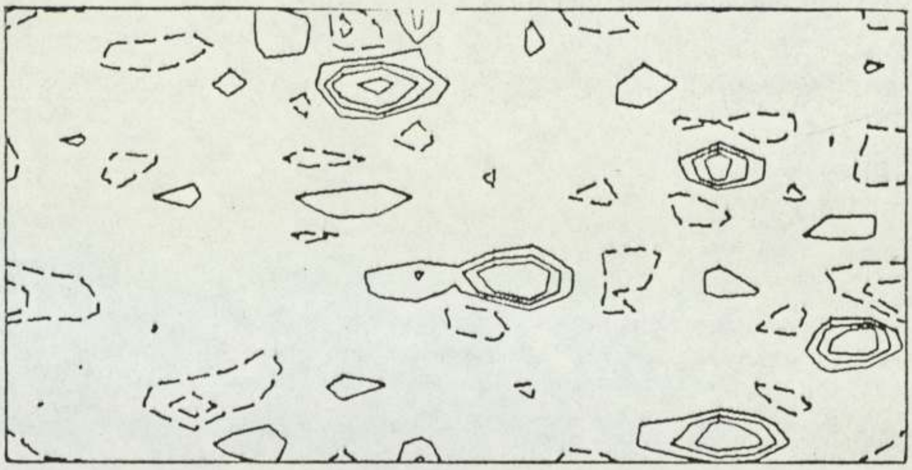
.025
.05
.075

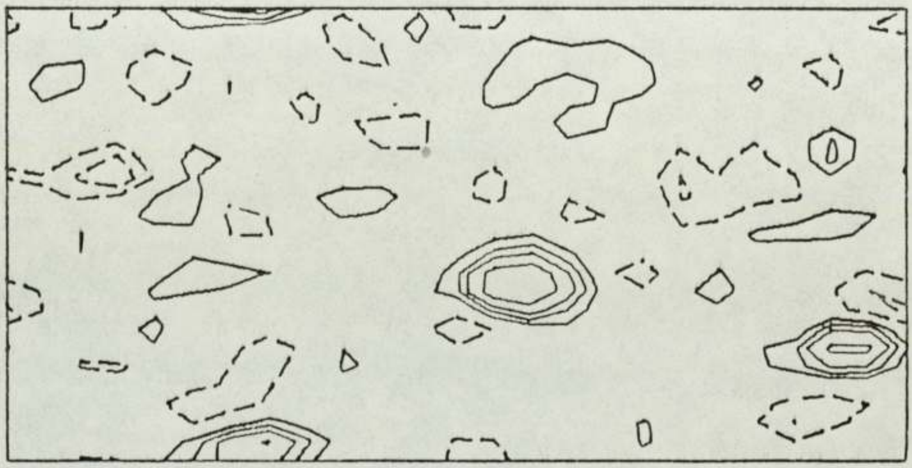

H102
H93
N5
C2
Cl1
H103
C10
C9
H92
C6
N3
N1
H81


Z = .1
.125
.15
.175

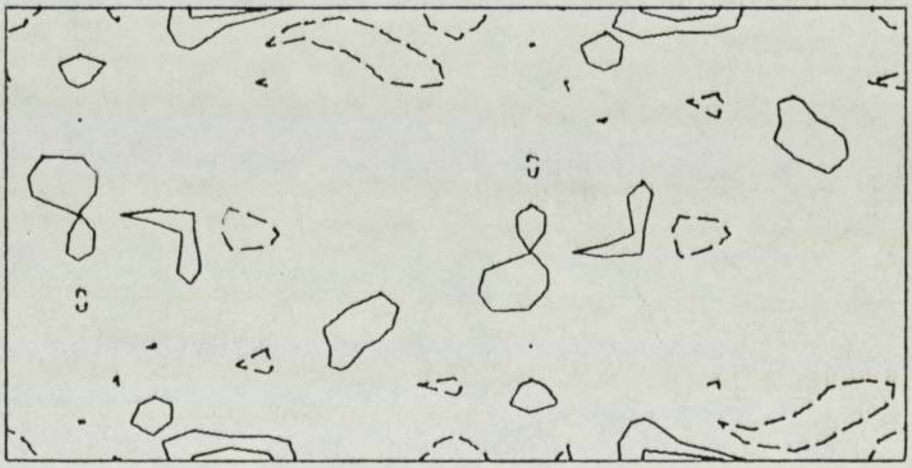

C4
H101
N8
H91
C4'
H3'
H6'
H82
N7
C3'
C1'



Z=.2



.225



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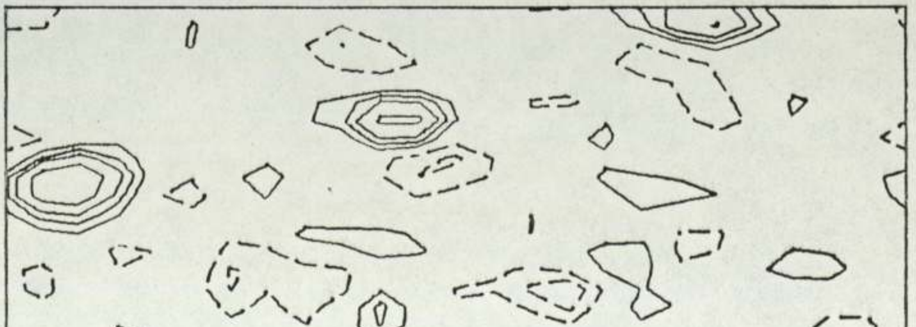

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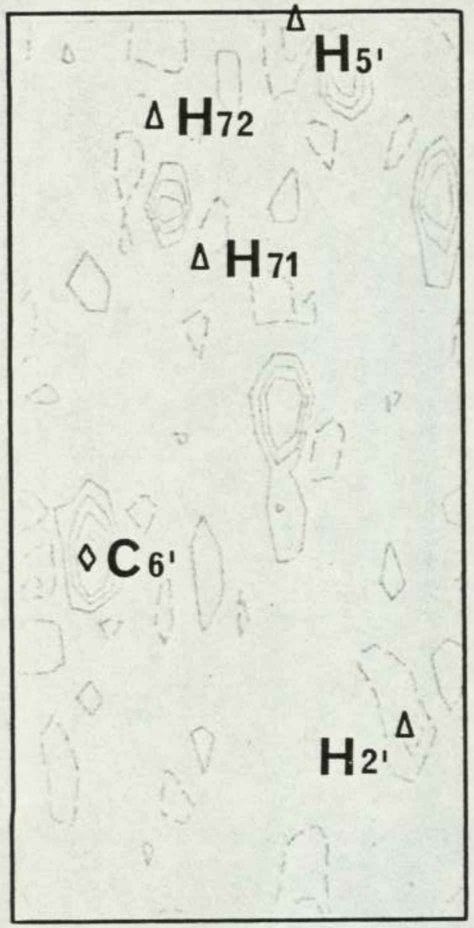
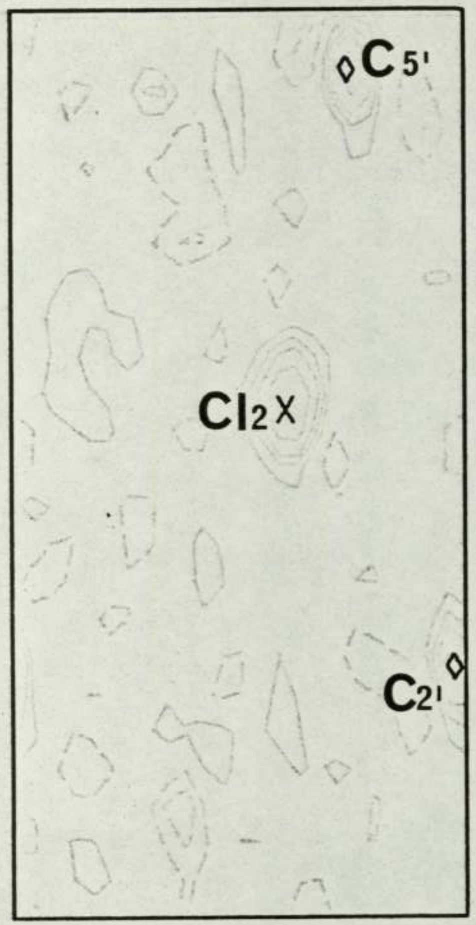
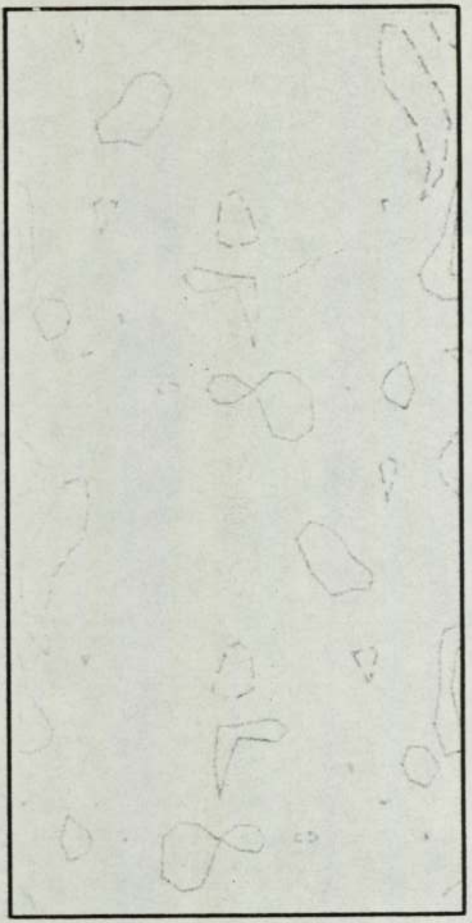
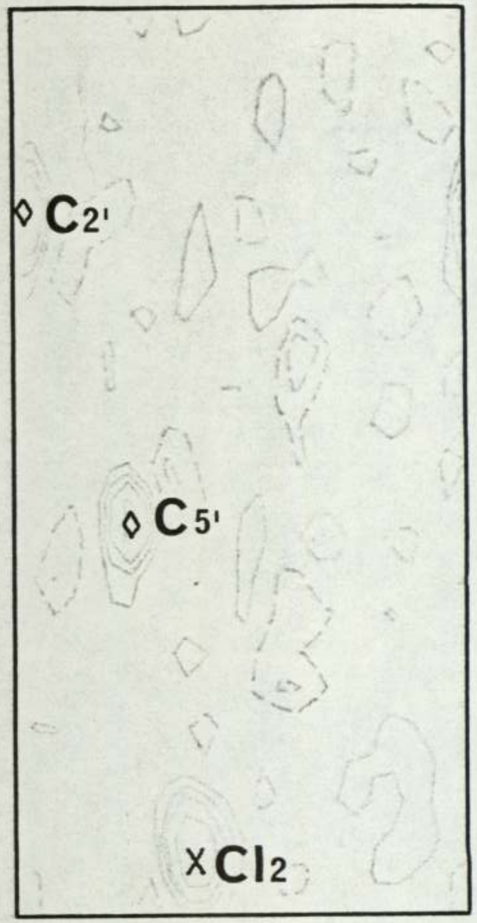
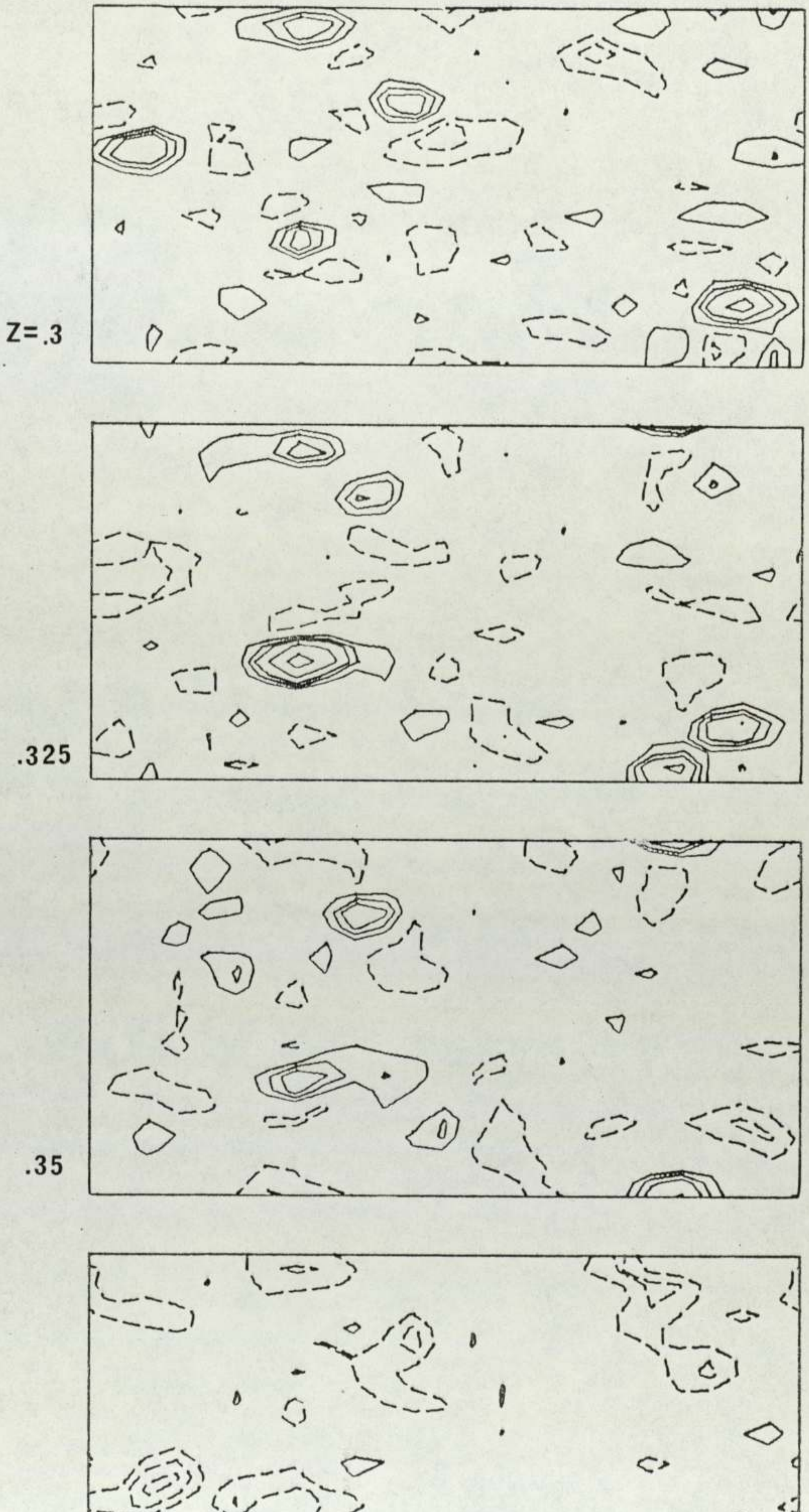
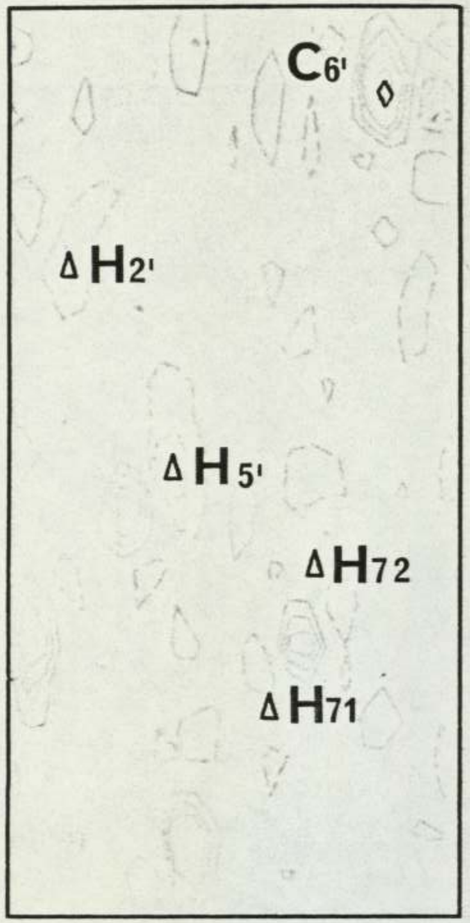

H5'
H72
H71
C6'
H2'

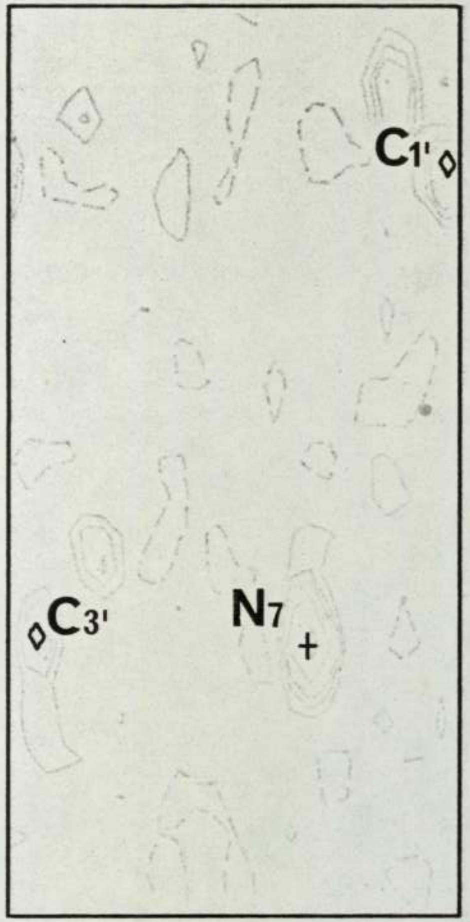

C5'
Cl2
C2'

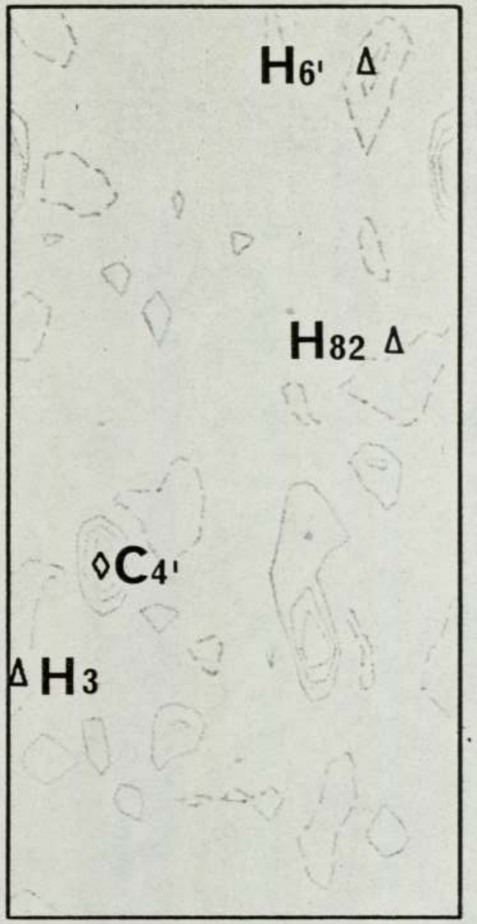


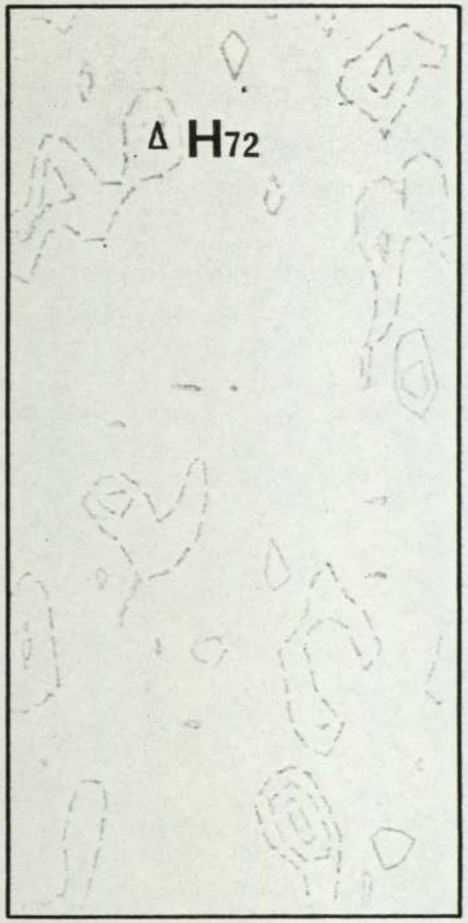

C2'
C5'
Cl2

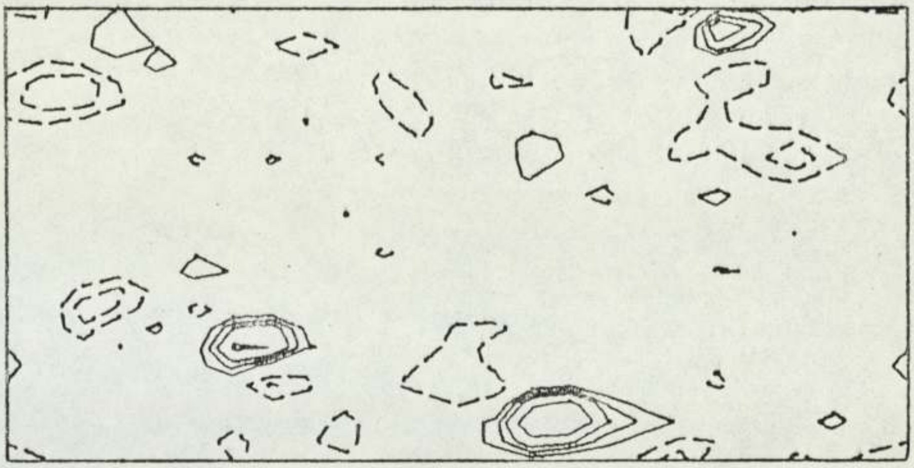

Z=.3
.325
.35
.375


$C_{6'}$
$H_{2'}$
$H_{5'}$
H_{72}
H_{71}

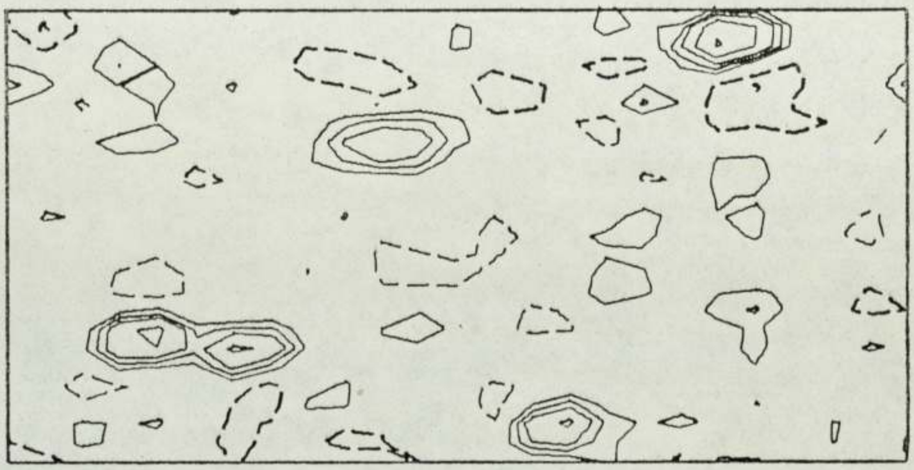

$C_{1'}$
$C_{3'}$
N_7


$H_{6'}$
H_{82}
$C_{4'}$
H_3


H_{72}



Z=.4



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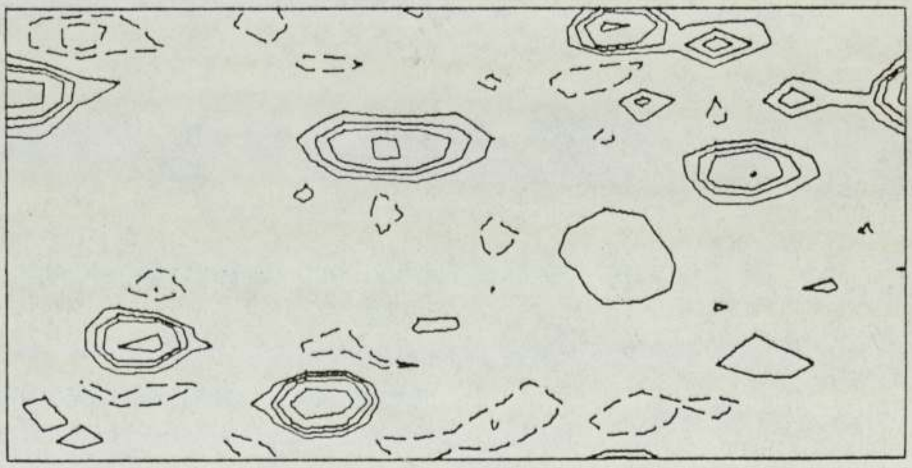

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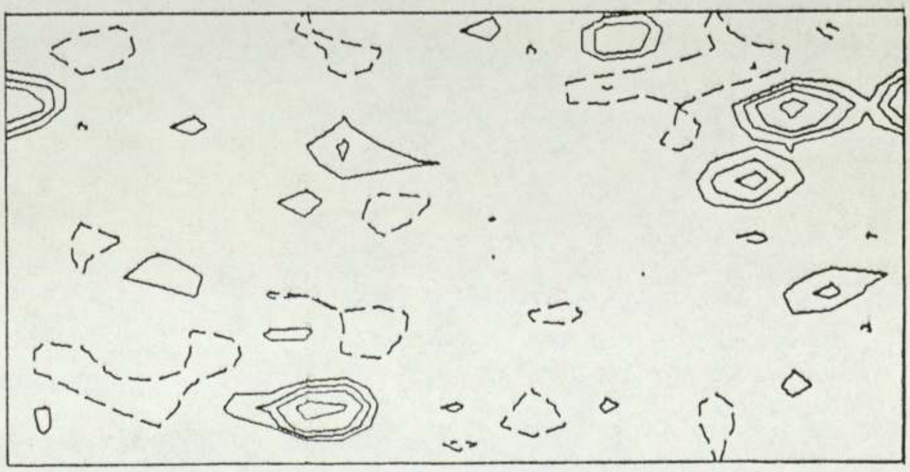

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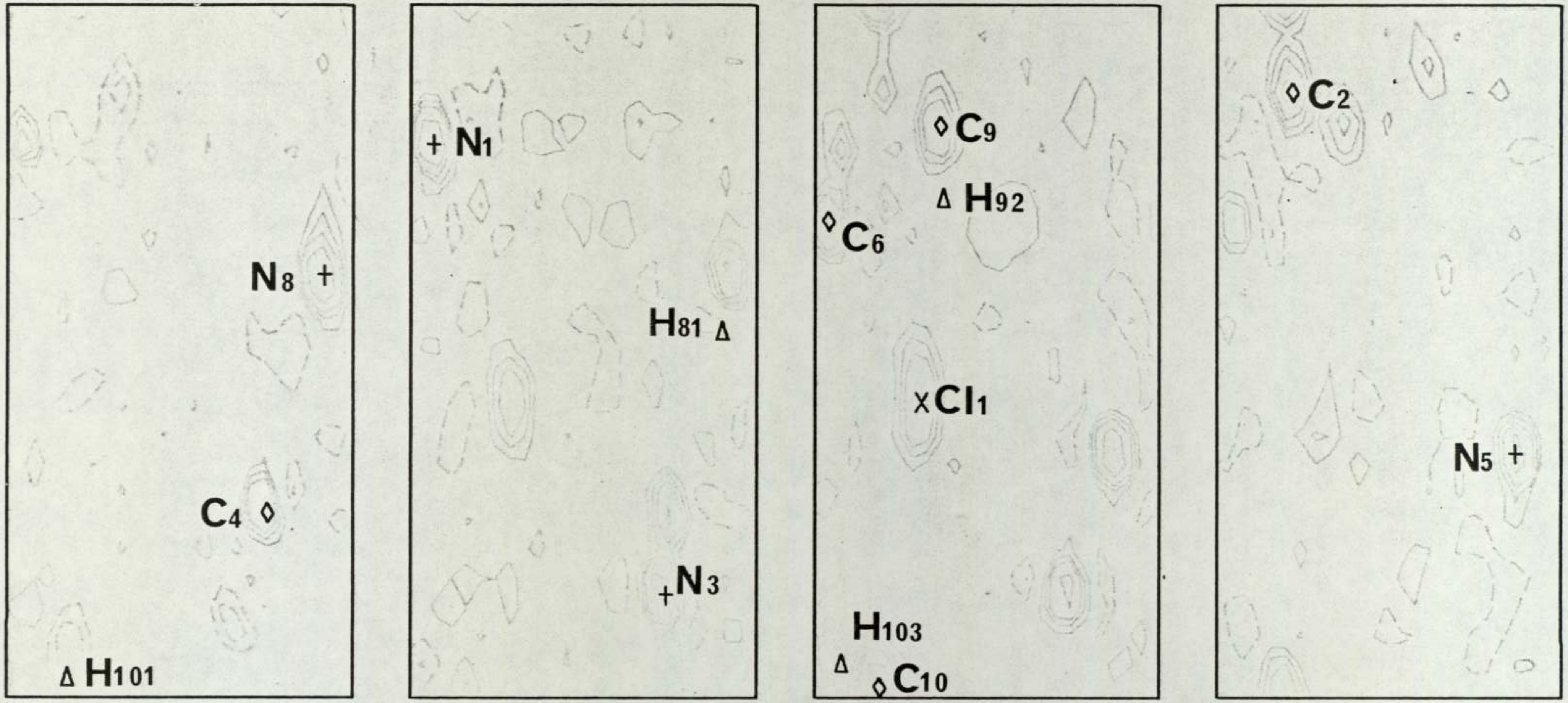
N8
C4
H101
N1
H81
N3
C9
H92
C6
Cl1
H103
C10
C2
N5

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PLUTO: Motherwell,----

SHELX: Sheldrick,1976

X-RAY 72: Stewart,et al,1972

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