PYRROLOTRIAZINES AS POTENTIAL INHIBITORS OF DIHYDROFOLIC REDUCTASE

BY

JOHN RICHARD TRAYNOR

A thesis presented for the degree of

DOCTOR OF PHILOSOPHY

in the

University of Aston in Birmingham

October, 1973

Department of Pharmacy

University of Aston in Birmingham

SUMMARY

The chemistry of the known pyrrolotriazines is reviewed and the biochemical reasons for the synthesis of such systems are discussed.

The work described in this thesis is concerned with the preparation and properties of pyrrolo[1,2-a][1,3,5]triazines and the attempted preparation of pyrrolo[2,1-f][1,2,4] triazines. The synthesis of the pyrrolo[1,2-a][1,3,5] triazine system was approached by two main routes.

(i) From 1,3,5-triazines:

The preparation and properties of various 1,3,5-triazines are discussed, together with their suitability, as potential precursors, of the bicyclic system. Special reference is made to the high carbonyl stretching vibrational bands found in the infra-red spectra of the 1,3,5-triazin-2,4(1H,3H)-diones. The structures of 6-dicarbethoxymethyl-1,3,5-triazin-2,4(1H,3H)-dione and 2,4,6-tris(dicarbethoxymethyl)-1,3,5-triazine are re-assigned, on the basis of spectroscopic evidence, as 6(1H)-dicarbethoxymethylene-1,3,5-triazin-2,4 (3H,5H)-dione and 2,4,6(1H,3H,5H)-tris(dicarbethoxymethylene)-1,3,5-triazine, respectively.

Reaction of 6-methyl- and 6-benzyl-1,3,5-triazin-2,4 (1H,3H)-dione with ethyl bromopyruvate gave ethyl pyrrolo [1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylate and ethyl 8-phenylpyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-

7-carboxylate respectively. Difficulties were experienced when other α-halogeno-ketones were used in the above reaction.

The potassium salt of 6-methyl-1,3,5-triazin-2,4(1H,3H)-dione and phenacyl bromide afforded 6-methyl-1,3,5-triazin-2,4(1H,3H)-dione and 6-methyl-1,3-diphenacyl-1,3,5-triazin-2,4(1H,3H)-dione as the major products. The latter compound, on treatment with acetic anhydride, gave 3-phenacyl-7-phenyl-pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione.

Plausible mechanisms for, and the limitations of, the above reactions are discussed.

Bromination of ethyl 1,3-dimethylpyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylate afforded a mixture of the 8-bromo-, and 6,8-dibromo-derivatives.

(ii) From 2-aminopyrroles

2-Aminopyrroles, containing electron-withdrawing groups in positions 3 and 4, and alkyl (or aryl) isocyanates afforded 3,7,8-trisubstitutedpyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-diones. A possible mechanism for, and the limitations of, the reaction are discussed and 1-alkyl (or aryl)-3(3,4-disubstitutedpyrrol-2-yl)ureas are shown to be intermediates.

The spectroscopic properties of the pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-diones are discussed.

The synthesis of the pyrrolo[2,1-f][1,2,4]triazines was attempted by an extension of the Tschitschibabin indolizine

synthesis. Alkyl- and arylalkyl-1,2,4-triazines form quaternary salts with methyl iodide. Reaction of 3-amino-5,6-dimethyl-1,2,4-triazine with ethyl bromopyruvate gave diethyl 4-methylpyrrolo[2,1-f]imidazo[1',2'-b][1,2,4]triazine-2,7-dicarboxylate or the isomeric diethyl 4-methylpyrrolo[1,2-d]imidazo[1',2'-b][1,2,4]triazine-2,8-dicarboxylate. Both of these compounds are derivatives of previously unreported ring systems, although which isomer was present is unconfirmed.

The mass spectra of most of the compounds mentioned in the thesis are discussed and possible fragmentation patterns are suggested.

The author would like to thank Professor D. G. Wibberley for his help and encouragement during the course of this work, and the staff and postgraduates (1970-1973) of the pharmaceutical chemistry section for useful discussion.

The author also acknowledges the help of the technical staff and thanks Mr. M. J. Horton for running the mass spectra.

The author is greatly indepted to his wife for typing this thesis.

"We shall finish up better because we've had our setbacks. This isn't the end, this is the beginning."

C. P. Snow (The New Men, 1954)

To Carol

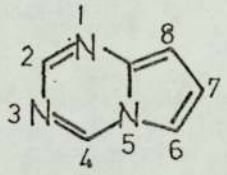
INDEX

EXPERIMENTAL

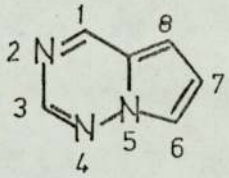
INTRODUCTION

A. The Pyrrolotriazines

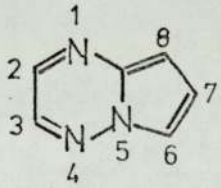
There is only one pyrrolo[1,3,5], or s-, triazine system, the pyrrolo[1,2-a][1,3,5]triazines (1). There are, however, four different pyrrolo[1,2,4], or as-, triazine systems which contain a bridgehead nitrogen atom. These are the pyrrolo[2,1-f][1,2,4]triazines (2), the pyrrolo[1,2-b][1,2,4]triazines (3), the pyrrolo[2,1-c][1,2,4]triazines (4) and the pyrrolo[1,2-d][1,2,4]triazines (5). The pyrrolo[2,1-f][1,2,4] triazine system is the only one which is completely unknown.



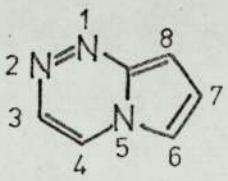
(1)



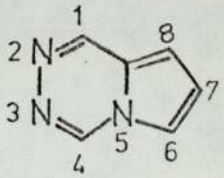
(2)



(3)



(4)



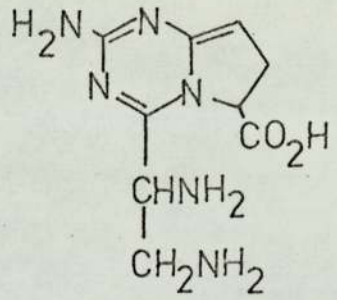
(5)

(i) Pyrrolo[1,2-a][1,3,5]triazine

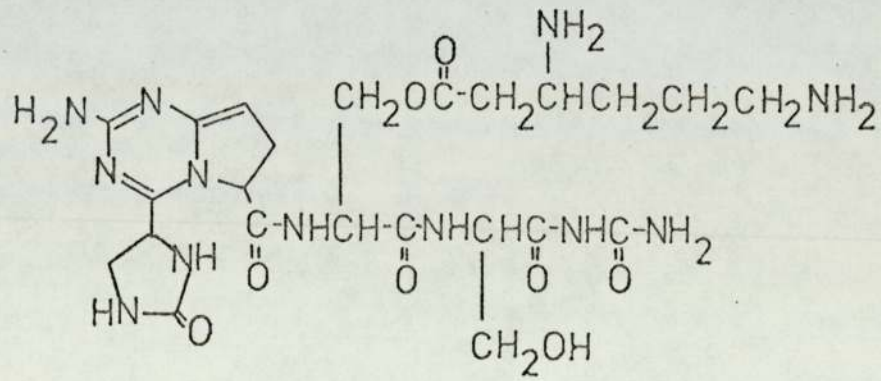
The fully saturated derivative and two benzhydro derivatives of this system have been reported in the literature, but the fully aromatic species (1) is unknown.

In 1964 a dipeptide component ("peptide A") was

isolated from a partial acid-hydrolysate of the streptomyces antibiotic viomycin[1]. The structure (6) was proposed for this dipeptide and it was believed to be responsible for the ultra-violet absorption of the antibiotic[2]. The compound was claimed as the first example of the pyrrolo[1,2-a][1,3,5]triazine ring system and the structure (7) proposed for viomycin, a structure which was later reproduced in a standard text[3].

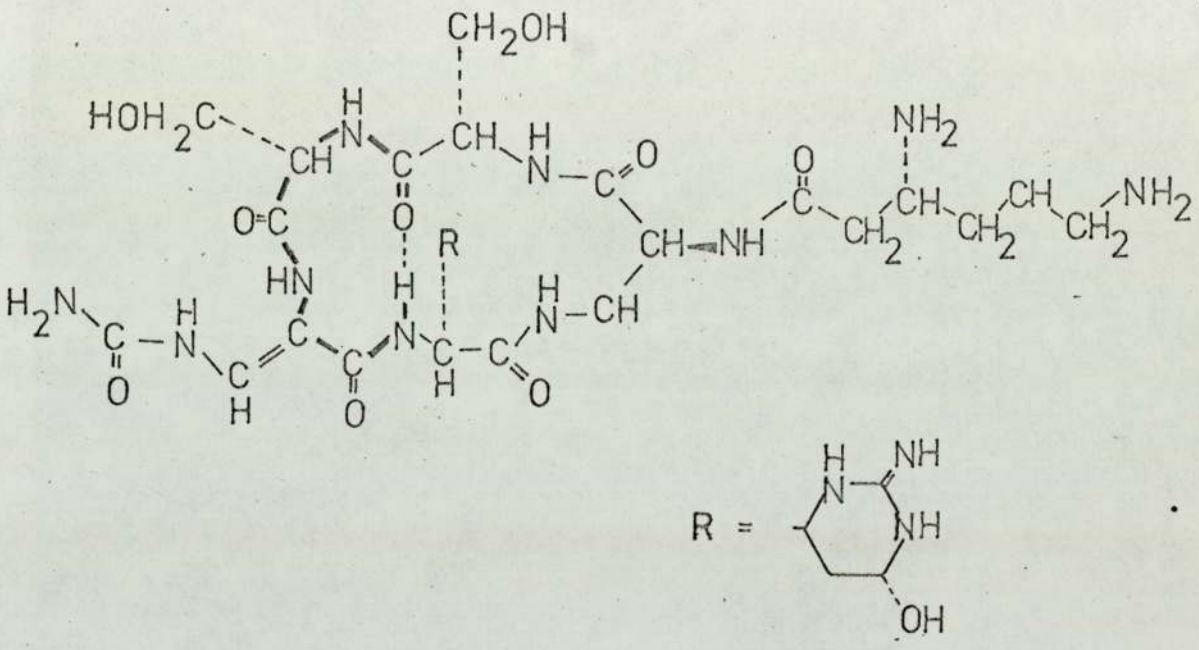


(6)

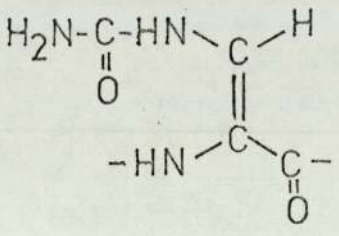


(7)

Later work has, however, shown "peptide A" to be a mixture[4] and based on much spectroscopic, including X-ray, data the structure of viomycin has been elucidated as the quinazahexadecane (8)[5,6] and the moiety responsible for the ultra-violet chromophore as the dehydroserine ureide (9)[5,7].



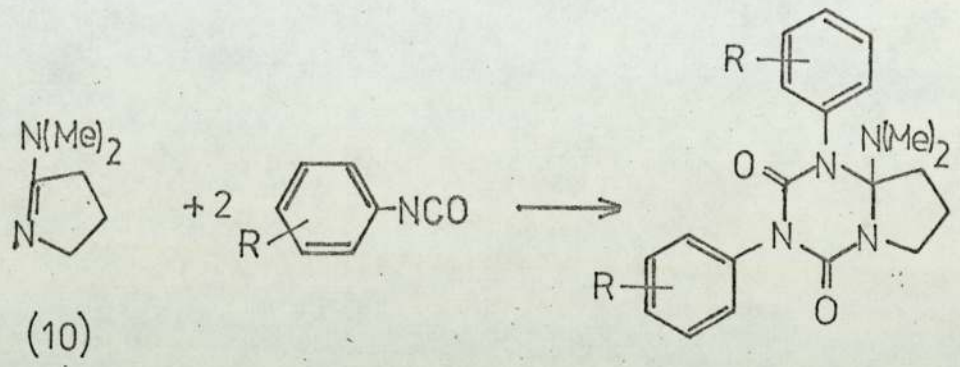
(8)



(9)

The first authenticated pyrrolo[1,2-a][1,3,5]triazine was synthesised by Richter[8]. He reported that aromatic isocyanates underwent addition to the "-C=N-" moiety of fully

substituted amidines in a 2:1 ratio to give hexahydrotriazine derivatives; reaction of the amidine (10) gave the 8a-dimethylamino-2,4-dioxo-1,3-diaryl-perhydro-pyrrolo[1,2-a][1,3,5] triazines (11-13).



(10)

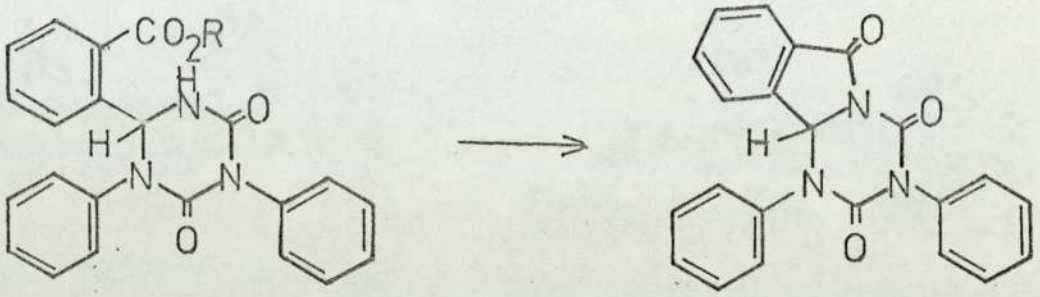
(11) R=H

(12) R=p-Cl

(13) R=m-Cl

The benz-derivatives mentioned in the literature are both derivatives of the isoindolo[1,2-a][1,3,5]triazine system. The triazinoisoindole (16) was obtained by treatment of the acid (14) with strong acid or by heating the ester (15) in refluxing benzonitrile[9].

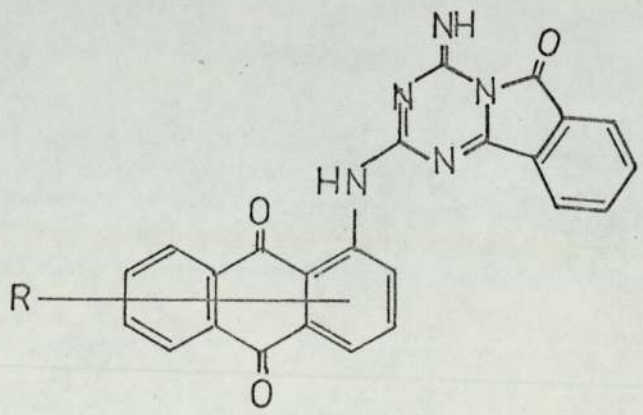
1,9-diimino-3-amino-isoindolo[2,3-a][1,3,5]triazine reacts with 1-chloroanthraquinone derivatives to give dyes of the type (17), where R is H, amino, or substituted amino[10]. A synthesis of the ring system is not reported.



(14) R=H

(15) R=Me

(16)

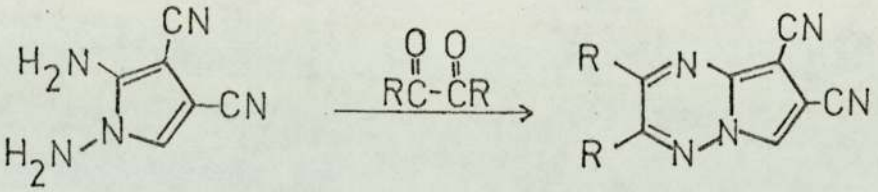


(17)

(ii) Pyrrolo[1,2-b][1,2,4]triazine

Two similar methods to the synthesis of this system have been reported, both of which involve the formation of a "triazine ring" by cyclisation to a 2-aminopyrrole precurser.

1,3,5-triamino-3,4-dicyanopyrrole (18) readily condenses with symmetrical diketones to give the pyrrolo[1,2-b][1,3,5] triazines (19-21)[11].

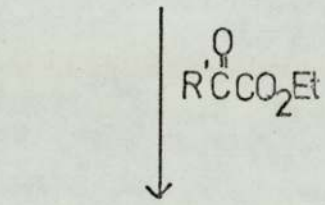


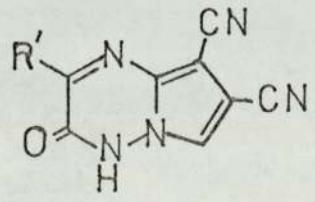
(18)

(19) R=H

(20) R=Me

(21) R=Ph



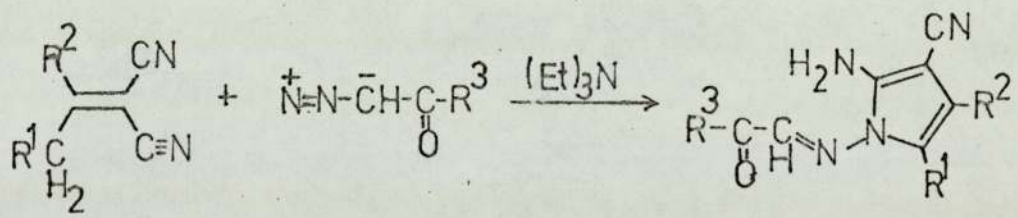


(22) R'=Me

(23) R'=CO_2Et

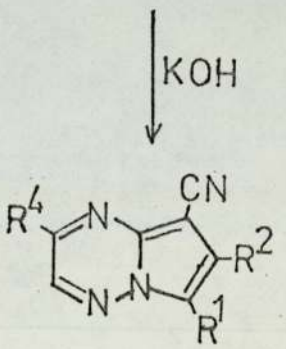
Ethyl pyruvate or ethyl oxomalonate react with (18) to give the same ring system and only one compound is isolated in each case, although there are two possible isomers. The structures (22-23) were assigned on the basis that the most reactive carbonyl group (the keto group) would react with the most reactive amino group (the 2-amino group).

Reaction of the alkylidene malononitriles (24) with diazocarbonyl compounds (25) in the presence of triethylamine afforded the 2-amino-N-substituted pyrroles (26) which under basic aqueous conditions gave the pyrrolotriazines (27)[12].



(24) (25) (26)

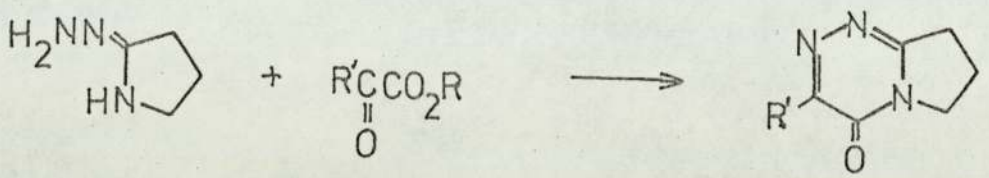
R^1	R^2	R^3	R^4
$-(CH_2)_4-$		Ph	Ph
$-(CH_2)_4-$		$PhNO_2$(p)	$PhNO_2$(p)
H	Ph	$PhNO_2$(p)	$PhNO_2$(p)
$-(CH_2)_4-$		OEt	OH



(27)

(iii) Pyrrolo[2,1-c][1,2,4]triazine

Reaction of the amidrazone (30) with α-ketocarboxylic acid esters (31-32) gave the 3-substituted-4-oxo-4,6,7,8-tetrahydropyrrolo[2,1-c][1,2,4]triazines (33-34)[13].

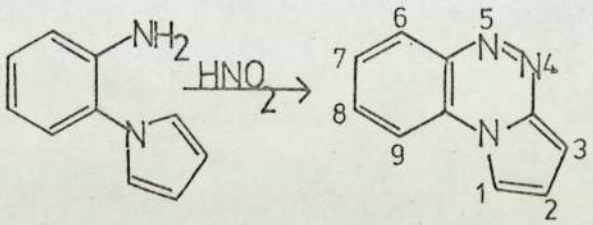


(30) (31) R'=Me (32) R'=Ph (33) R'=Me (34) R'=Ph

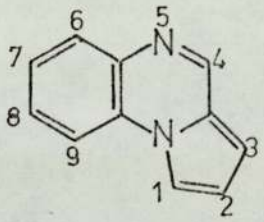
The aromatic bicyclic system is unknown but the benzo analogue pyrrolo[2,1-c][1,2,4]benzotriazine (36) is readily formed on diazotisation of 1-(2-aminophenyl)pyrrole (35) in aqueous acidic media[14].

The reactivity of this system to typical electrophiles has been recently investigated and compared to the pyrroloquinoxaline system (37)[15]. The preferred site of halogenation was found to be position 1, with C-3 the second most favoured position, these experimentally determined values agreeing with those predicted by molecular orbital calculations. Both systems underwent sulphonation at position 3, but the pyrrolobenzotriazine required much more forcing conditions, (concentrated sulphuric acid at 130°) than the

pyrroloquinoxaline (concentrated sulphuric acid at ambient temperature), thus demonstrating the deactivating effect of the additional ring nitrogen atom in compound (36).



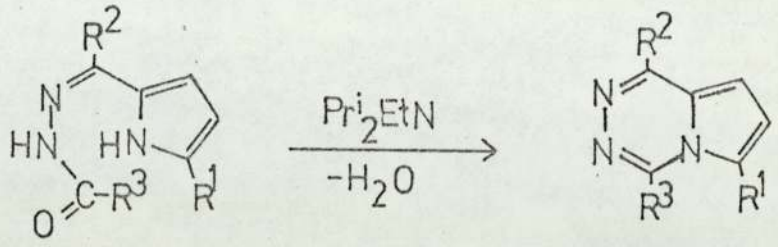
(35) (36)



(37)

(iv) Pyrrolo[1,2-d][1,2,4]triazine

The parent compound of this system (42) has been synthesised from pyrrole-2-carboxaldehyde formylhydrazone (38) by a base-catalysed cyclodehydration reaction. Various methyl derivatives of the system (43-45) were similarly obtained from the corresponding pyrroles (39-41)[16].



(38) $R^1=R^2=R^3=H$

(39) $R^1=R^2=H$, $R^3=Me$

(40) $R^1=R^3=H$, $R^2=Me$

(41) $R^1=Me$, $R^2=R^3=H$

(42) $R^1=R^2=R^3=H$

(43) $R^1=R^2=H$, $R^3=Me$

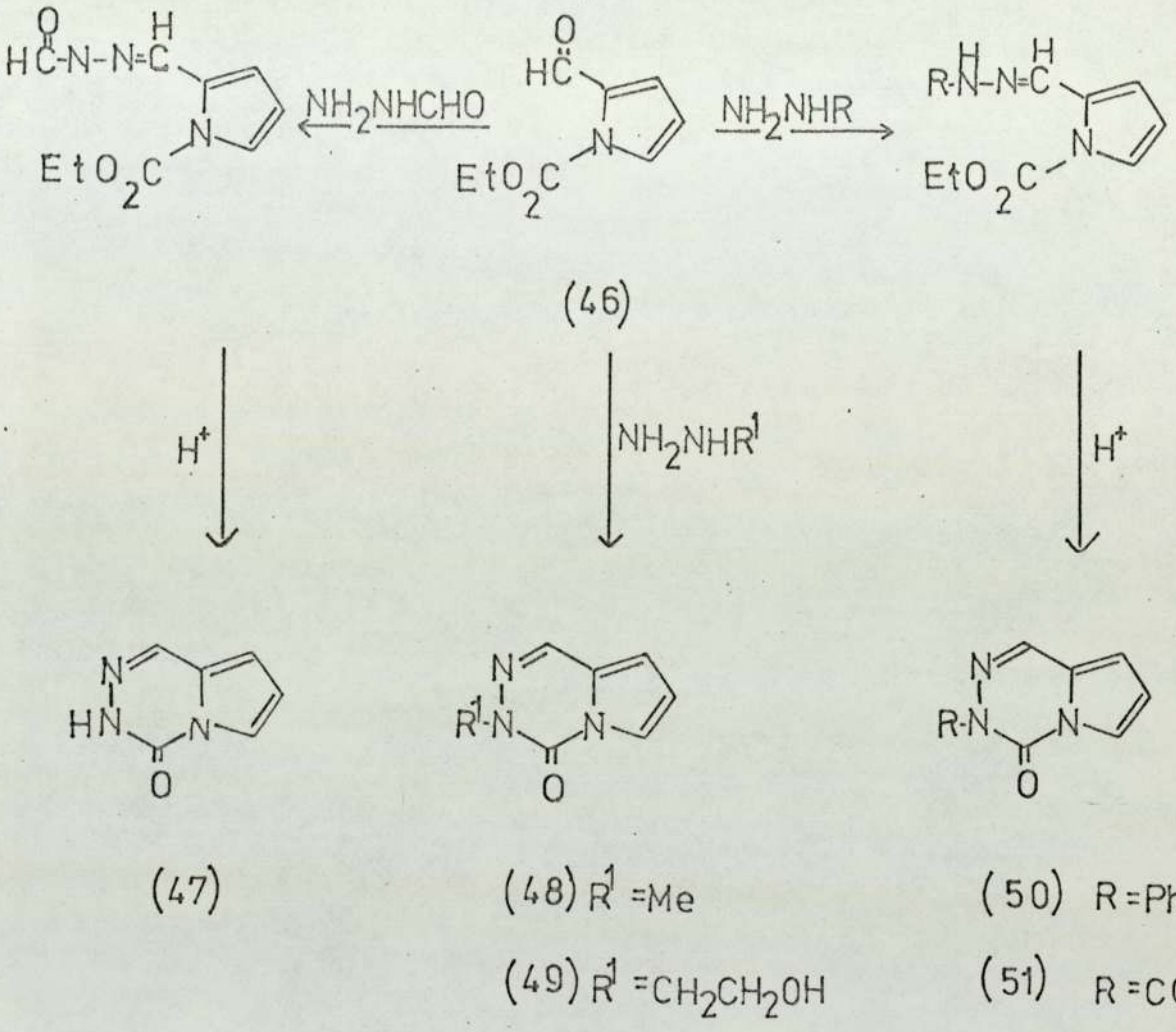
(44) $R^1=R^3=H$, $R^2=Me$

(45) $R^1=Me$, $R^2=R^3=H$

Reaction of (42) with N-bromosuccinimide in dichloromethane gave the 6-bromopyrrolo[1,2-d][1,2,4]triazine.

The 3H-pyrrolo[1,2-d][1,2,4]triazin-4-ones (47-51) were formed by ring closure of N-carbethoxy-2-formylpyrrole (46) with various substituted hydrazines[17]. In the case of the less reactive hydrazines the intermediate hydrazones were isolated and ring closure was effected under acidic conditions (scheme 1).

Scheme 1



(47)

(48) R^1 = Me

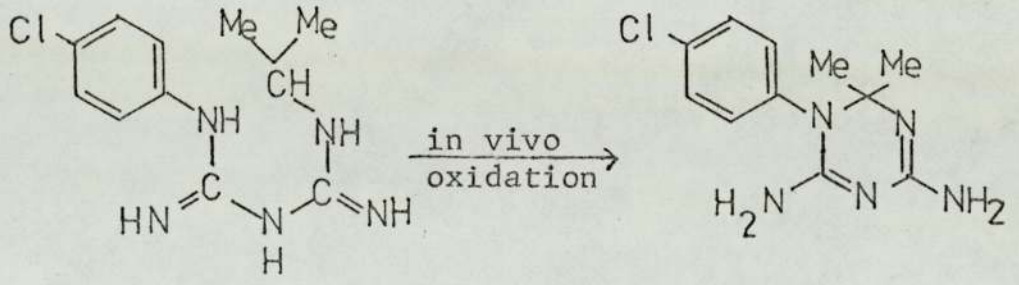
(49) R^1 = CH_2CH_2OH

(50) R = Ph

(51) R = CO_2Et

B. The "raison d'être"

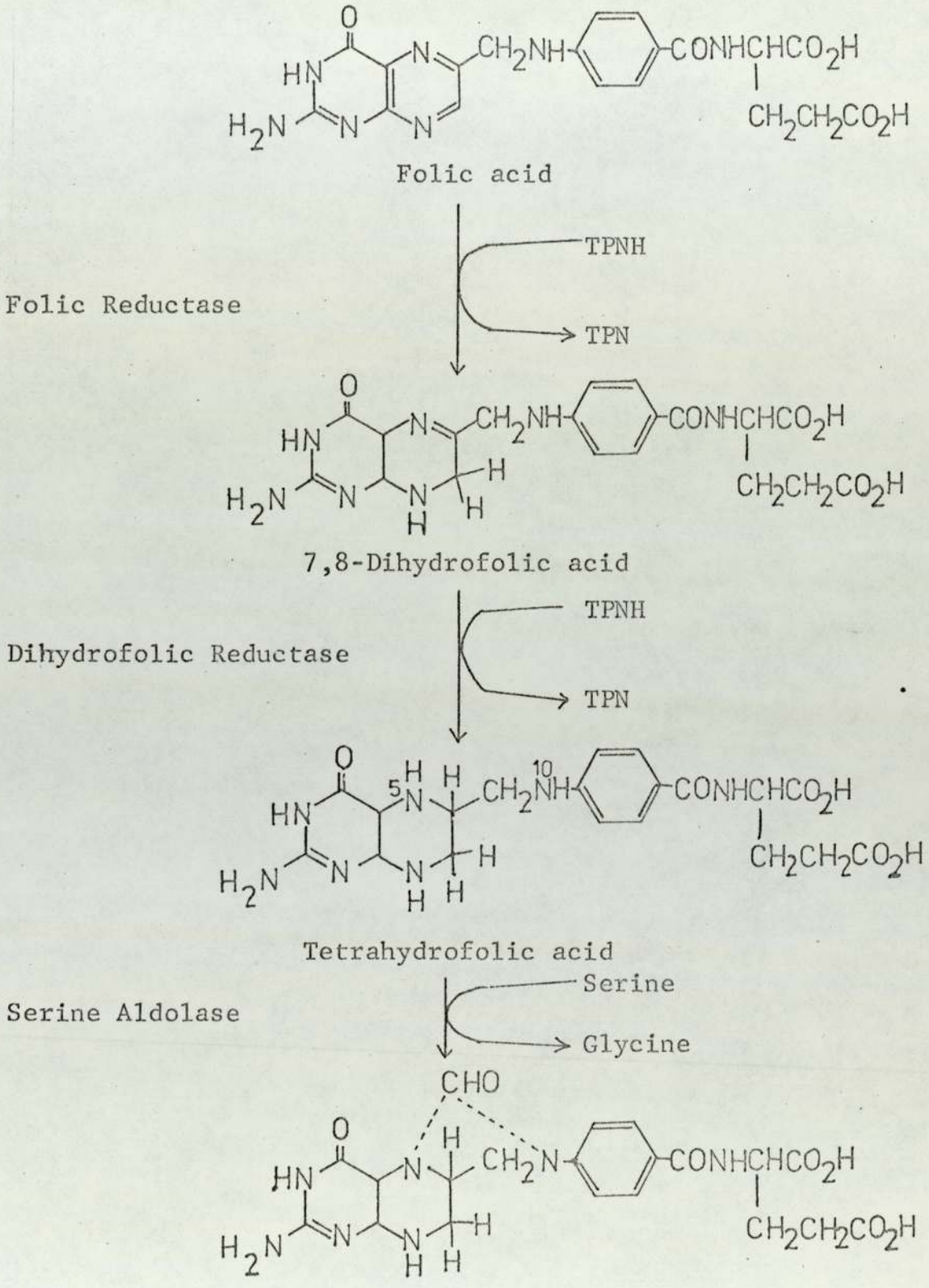
The pyrrolotriazines so far synthesised have no recorded biological activity although triazine derivatives have value as antimetabolites as aza-analogues of nucleic acid derivatives[18,19,20], and dihydrotriazines have antibacterial and antitumour activity in experimental systems[21]. Perhaps the best known dihydrotriazine is 4,6-diamino-1-(4 -chloro-phenyl)-1,2-dihydro-2,2-dimethyl-1,3,5-triazine (53), the active metabolite of the antimalerial drug proguanil (52) which acts by depriving the malerial parasite of citrovorum factor (scheme 2), the formyl derivative of tetrahydrofolic acid[22].



(52) (53)

Tetrahydrofolic acid is formed in the cell by enzymatic reduction of folic acid via the 7,8-dihydroderivative, the enzyme dihydrofolic reductase, also known as folic reductase, catalysing both steps which are dependant on reduced triphosphopyridine nucleotide (scheme 2). It is these reduced forms of folic acid which take part in the biosynthetic reactions in the cell leading to the formation of D.N.A.

Scheme 2



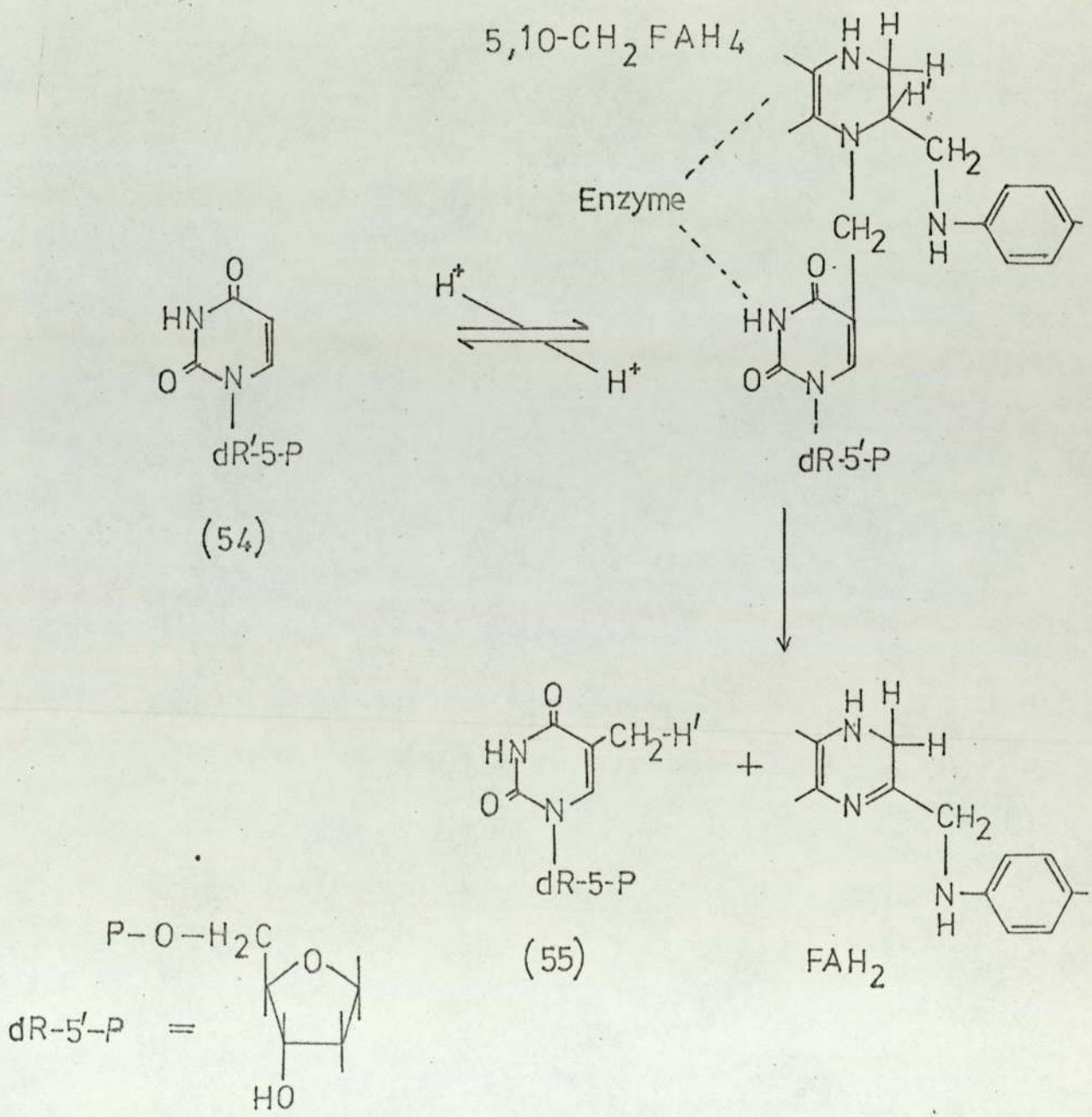
TPN=Triphosphopyridine nucleotide
TPNH=Reduced triphosphopyridine nucleotide

Any one of five different enzymes present in the cell can then catalyse the attachment of a one-carbon fragment, at the formaldehyde or formic acid oxidation level, at N^5 or N^{10} or both, of tetrahydrofolic acid to give citrovorum factor (scheme 2).

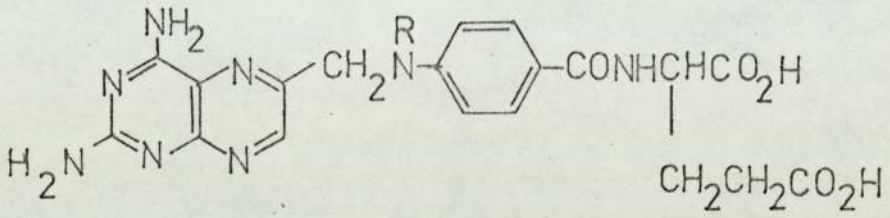
A further six enzymes are then able to interconvert the oxidation level of the one-carbon fragment or its position on tetrahydrofolic acid. Citrovorum factor is involved in four one-carbon transfer reactions, three of which occur in pyrimidine or purine biosynthesis, for example the biosynthesis of 2'-Deoxythymine 5'-monophosphate (dTMP)(55) from 2'-Deoxyuridine 5'-monophosphate (dUMP)(54), which involves the methylation of the pyrimidine ring. The enzyme thymidylate synthetase catalyses the conversion of dUMP to dTMP with a concomitant oxidation of 5,10-methylene-tetrahydrofolic acid (5,10-CH_2-FAH_4) to dihydrofolic acid (FAH_2). In this reaction the hydrogen atom at C-6 of 5,10-CH_2-FAH_4 is transferred to the methylene carbon to form the methyl group of dTMP[23].

Thus it can be seen that inhibition of dihydrofolic reductase will lead to a blockage of D.N.A. synthesis and as a consequence blockage of this enzyme has become an important target for the design of antimetabolites as active chemotherapeutic agents. There is also evidence to suggest that there may be differences in the primary, secondary, and tertiary structures of the enzyme in normal tissue in

comparison with those of dihydrofolic reductase in a tumour cell, particularly in the case of virus-induced cancers[24,25]. The active-site-directed irreversible enzyme inhibitors[26] take advantage of the similarity of the active-site for reversible complexing, and also of the less functional parts of the enzyme surface for irreversible covalent bond formation, thus adding an extra magnitude of specificity.



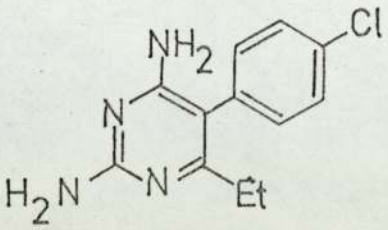
Close analogues of folic acid, containing a 4-amino function, such as aminopterin (56) and methotrexate (57), produce a reversible block of dihydrofolic reductase by competing with folic acid for the enzyme[21].



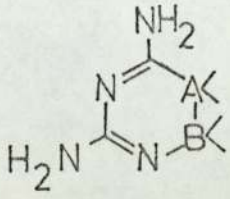
(56) R = H

(57) R = Me

A study of analogues of the pyrimidine base thymine showed their action to be "antifolic" rather than "antithymine" in nature[27] and further studies on 5-substituted pyrimidines and derivatives of condensed systems showed the main criterion for inhibition to be the diamino pyrimidine nucleus[28]. The antimalerial drug pyrimethamine (58), for example, acts by depriving the maleria parasite of citrovorum factor at a time when this metabolite is most needed, that is, during division of the nucleus[29]. With the discovery of the 1,3,5-triazine (53) as the active metabolite of proguanil (52)[30,31] and that 1,2,4-triazines possessed similar properties[32] the general requirements for antifolic activity were further extended as shown in formula (59).



(58)

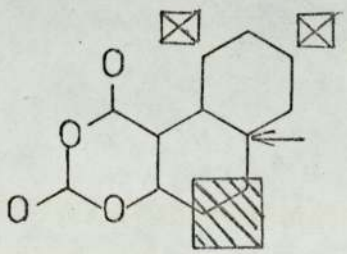


A–B= C=C; C=N; N=C.

(59)

Studies on the comparative activities of several series of pyrimidines, triazines, quinazolines and pyrido[2,3-d] pyrimidines enabled Hitchings and Burchenall to construct a schematic representation of the enzyme surface (figure 1)[33].

Figure 1



O binding sites common to all inhibitors

⊠ binding sites where species differences have been detected

▨ geometrical limitations - any substituent positioned here is detrimental to activity

→ the pteridine-6-position; this is relatively open and optimum activity is obtained with sizable groups in this position

DISCUSSION

AIMS AND OBJECTS OF THE WORK

It was of interest to synthesise some potential inhibitors of dihydrofolic reductase modelled on the biological data available. Much work has been carried out on the simpler pyrimidines and triazines, the so-called "small molecule" inhibitors of dihydrofolic reductase[26,33], and in view of the limited knowledge of the pyrrolo[1,2-a][1,3,5]triazine and pyrrolo[2,1-f][1,2,4]triazine systems it was decided to investigate synthetic routes to these. Although both satisfy the requirements for binding if substituted with amino groups in the 2- and 4- positions of the triazine ring, the pyrrolo[1,2-a][1,3,5]triazine system was of greater interest due to the biological significance of the symmetrical triazines.

SYNTHESIS OF PYRROLO[1,2-a][1,3,5] TRIAZINES FROM SYMMETRICAL TRIAZINE PRECURSORS

A. Extension of the Tschitschibabin Indolizine Synthesis

Alkyl and aryl indolizines can be prepared by Tschitschibabin's[34,35,36] method in which α-picoline or a derivative is quaternised with α-halogeno-ketones and then treated with aqueous alkali. This method has been extended to other 5,6-bicyclic systems containing a pyrrole ring with a bridgehead nitrogen atom, for example the pyrrolo[1,2-c] pyrimidine[37], the pyrrolo[1,2-a]pyrimidine[38] and the pyrrolo [1,2-a]pyridazine[39] systems, and it was proposed to extend the scope of this reaction to include the synthesis of the pyrrolo[1,2-a][1,3,5]triazine system.

(i) Synthesis, Properties, and Suitability of Potential Precursors

(a) Alkyl-1,3,5-triazines

Symmetrical trialkyltriazines have been known for many years and are usually synthesised by trimerisation of the corresponding nitrile under extreme pressure[40] but Schaefer has recently reported an easier laboratory synthesis of trimethyl-1,3,5-triazine by treatment of ethyl acetimidate with glacial acetic acid[41]. Synthetic methods to mono- and di-alkyl-1,3,5-triazines have long been sought after although of late preparations of these compounds have been reported[42-46]. Several of these methods are expensive if workable amounts of starting materials are required[42-45],

and do not provide pure products[42], while other methods proved difficult to repeat[42,44,46]; in one case[44] no experimental details were given.

A comparison of various monocyclic nitrogen heteroaromatic compounds shows a decreasing basicity in the order pyridine> pyridazine> pyrimidine> pyrazine> triazine*[47], due to the insertion of extra ring-nitrogen atoms which have similar inductive and mesomeric effects to those of similarly positioned exocyclic nitro-groups both qualitatively and quantitatively[48]. Thus 1,3,5-triazines would be expected to undergo quaternisation only with extreme difficulty and in fact no quaternary salts of this heterocycle or its derivatives have been reported, although the more basic 2,4-diamino-6-methyl-1,3,5-triazine (60) does undergo N-oxidation at position 3[49] (page 24). Steric effects also play an important role in quaternisation reactions[50] and Taylor and Wibberley used this to advantage in the synthesis of pyrrolo [1,2-c]pyrimidines by blocking N-1 with a 6-phenyl substituent[37]. 2,4,6-Trimethyl-1,3,5-triazine would obviously suffer greatly from steric effects although the quaternisation of 2,4,6-trimethylpyrimidine with phenacyl bromide and cyclisation to 7-phenylpyrrolo[1,2-a]pyrimidine has been reported[38]. Later work has not, however, substantiated this, although the reaction does occur with ethyl bromopyruvate[51].

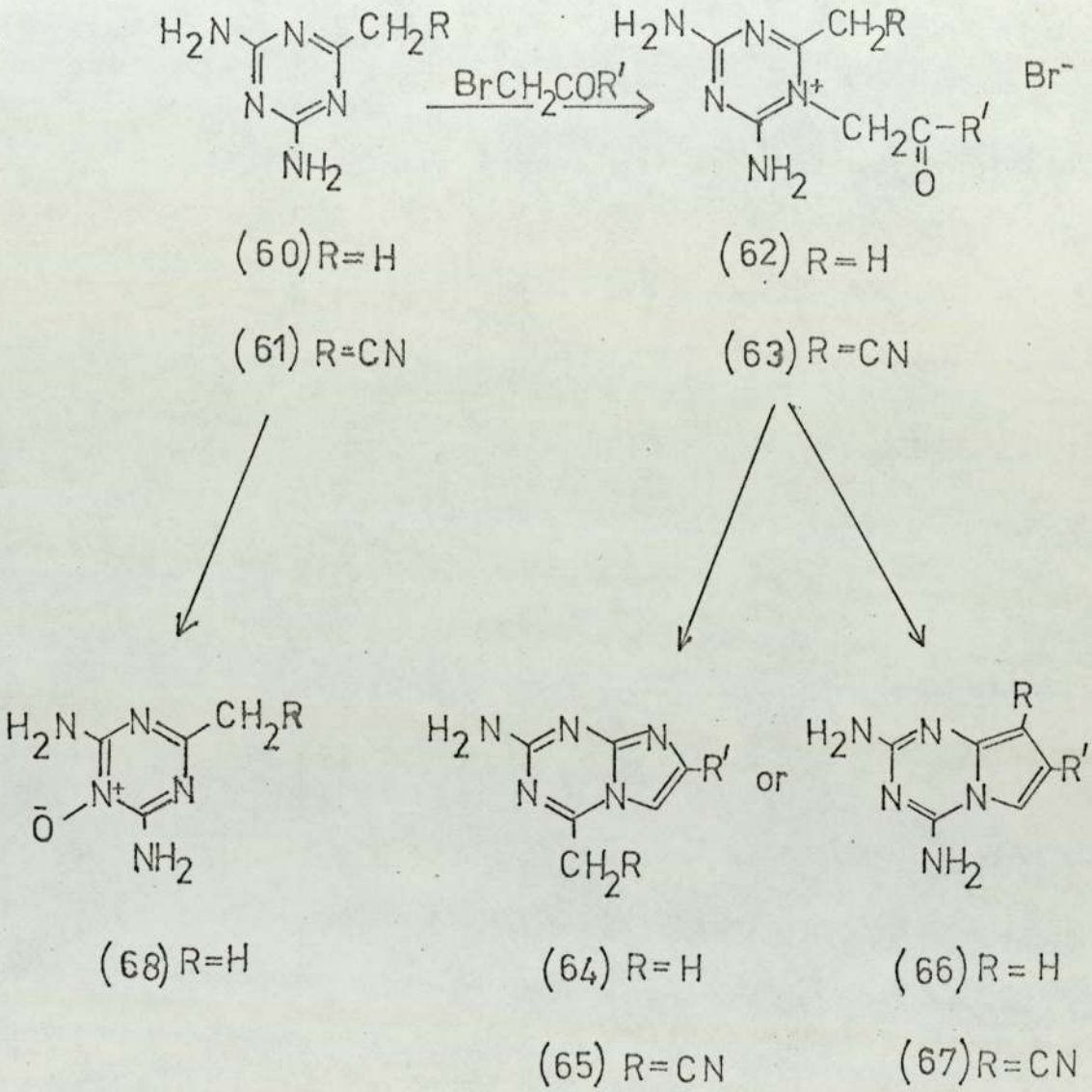
* Albert, Goldacre and Phillips[47] could obtain no pK_a value for this very weak base which was almost completely destroyed by water.

From a biochemical viewpoint the alkyl-1,3,5-triazines are not particularly interesting if one is considering blockage of dihydrofolic reductase and for this reason, and the more obvious preparative and quaternisation difficulties which are involved, it was decided to look for more readily available starting materials.

(b) 2,4-Diamino-6-methyl (substituted methyl)-1,3,5-triazines

These triazines have received much attention, especially in industry, due to their resin-forming properties. They are readily prepared by reaction of biguanide with esters, acid chlorides, acid anhydrides, lactones, imides, amides, ortho-esters, and amidines, by reaction of cyanoguanidine with nitriles or by miscellaneous methods from guanidines, tris(trihalomethyl)-1,3,5-triazines, halotriazines, and by reaction of urea with nitriles, amides, and acids in the presence of ammonia[52].

If the 2,4-diamino-1,3,5-triazines (60-61) could be quaternised with α-halogeno-ketones at position 1, followed by cyclisation to the reactive methyl substituent at position 6 then the compounds (66-67) obtained could prove to be very interesting in the search for inhibitors of dihydrofolic reductase. There are, however, several drawbacks in this hypothesis which must firstly be considered.

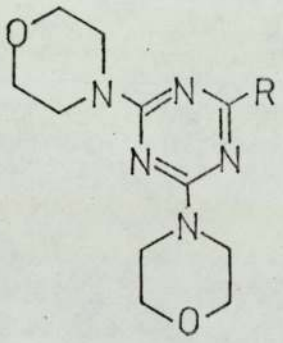


The quaternisation stage presents obvious difficulties for although the diamino-1,3,5-triazines are more basic (2,4-diamino-1,3,5-triazine has pK_a 3.91[53]) than the corresponding alkyl-1,3,5-triazines they too will suffer from strong steric effects. 6-Methyl-2,4-diamino-1,3,5-triazine (60) has been oxidised with perbenzoic acid to

give the N-3-oxide (68)[49], which would indicate that this triazine may possibly quaternise at N-3, but difficulties could be expected as N-oxidation suffers much less from steric effects than quaternisation[54]. Assuming that the N-1 quaternary salts could be obtained then cyclisation to the 2-amino function to give the imidazo[1,2-a][1,3,5] triazines (64-65) is much more likely to occur than cyclisation to the 6-methyl (or substituted methyl) function to give the pyrrolo[1,2-a][1,3,5]triazines (66-67).

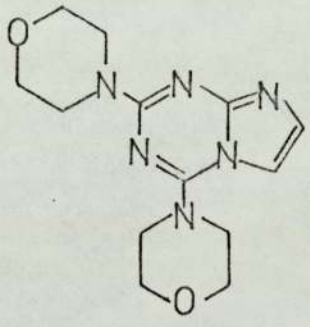
Preliminary experiments were carried out by the author to determine the validity or otherwise of the above theoretical observations. The diamino-1,3,5-triazines (60) and (61) were synthesised by literature methods[55,56]. Neither of these two compounds could be made to react, under a variety of conditions, with methyl iodide or dimethylsulphate to give quaternary methiodides, nor could quaternary salts be obtained by reaction of these triazines with phenacyl bromide or ethyl bromopyruvate although in these latter cases hydrobromides of the starting materials were obtained when the reactions were carried out in the absence of any solvent. Reaction of 2,4-diamino-6-methyl-1,3,5-triazine (60), a similar reaction using (61) was not carried out, with bromoacetaldehyde gave an inseparable mixture of four (or possibly five) compounds together with the starting material hydrobromide. The mixture did not contain ionic bromine ($AgNO_3$ test) and it is probable that this mixture did in fact contain all the

bicyclic and tricyclic products possible. To overcome the production of complex mixtures 6-methyl-2,4-dimorpholino-1,3,5-triazine (69) was prepared by an adaptation of the method of preparation of 6-amino-2,4-dimorpholino-1,3,5-triazine (70)[57], but this failed to react with bromoacetaldehyde, ethyl bromopyruvate or phenacyl bromide. This was puzzling since 6-amino-2,4-dimorpholino-1,3,5-triazine (70) had recently been reported to react with bromoacetaldehyde to give the imidazo[1,2-a][1,3,5]triazine (71)[58].



(69) R=Me

(70) R=NH_2



(71)

This reaction was repeated successfully but reaction of 6-amino-2,4-dimorpholino-1,3,5-triazine with other bromocarbonyl compounds resulted in the formation of 2-amino-4,6-dimorpholino-1,3,5-triazine hydrobromide only. 6-Methyl-4,6-dimorpholino-1,3,5-triazine presumably did not react because of the lower basicity of the ring nitrogen atom at position 1, or because initial reaction may have taken place

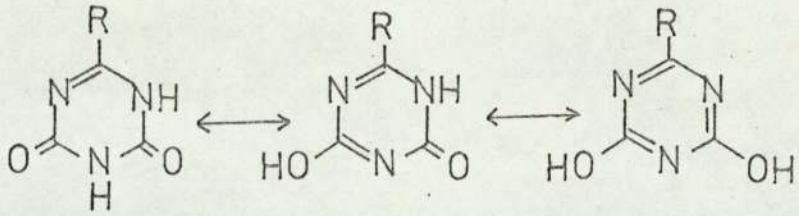
at the exocyclic nitrogen in the 6-amino compound. It may be, however, that quaternisation of 2,4-diamino-6-methyl-1,3,5-triazine, like N-oxidation, occurs at position 3, which is very sterically hindered in 6-methyl-2,4-dimorpholino-1,3,5-triazine and thus no reaction would be expected. If this were the case the complex mixture of products obtained by reaction of bromoacetaldehyde and (60) would not be expected to contain any pyrrolotriazine.

It is perhaps worthy of note that both 2,4-diamino-6-methyl-1,3,5-triazine and 6-amino-2,4-dimorpholino-1,3,5-triazine underwent quaternisation and subsequent cyclisation with bromoacetaldehyde but similar reactions with other α-halogeno-ketones gave only the unchanged starting materials or their hydrobromides.

The drawbacks mentioned above made these compounds unattractive for immediate use as possible precursors of the pyrrolo[1,2-a][1,3,5]triazine ring system.

(c) 6-Substituted-1,3,5-triazin-2,4(1H,3H)-diones

6-Methyl-1,3,5-triazin-2,4(1H,3H)-dione (72) was prepared by an acid hydrolysis of 2,4-diamino-6-methyl-1,3,5-triazine by the method of Necki[59]. The infra-red spectrumof this 1,3,5-triazindione was of interest due to the high carbonyl absorption it exhibited (see table 1). For this reason and for a later mass spectral study (page 98) and also as potential intermediates several other 1,3,5-triazindiones were prepared.



(72) R = Me

(73) R = Ph

(74) R = CH_2Ph

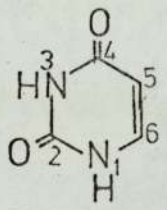
(75) R = $CH_2PhCl(o)$

(76) R = H

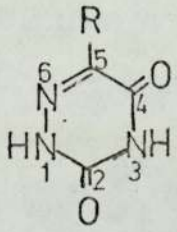
6-Phenyl- (73) and 6-benzyl- (74) 1,3,5-triazin-2,4 (1H,3H)-diones were prepared by literature methods[60,61] by treatment of the corresponding acyl biguanides with aqueous base; this method was extended to include the preparation of 6-(2 -chlorobenzyl)-1,3,5-triazin-2,4(1H,3H)-dione (75) and is a good general method for the synthesis of 6 (substituted) phenyl- and 6(substituted) benzyl-1,3,5-triazin-2,4(1H,3H)-diones. This method, however, cannot be used for the preparation of 6-methyl- (72) and 6-unsubstituted- (76)1,3,5-triazin-2,4(1H,3H)-diones due to their greater susceptibility to hydrolysis, a finding which was later explained by the low electron density at C-6 due to the simultaneous influence of the uracil configuration and the presence of the nitrogen atom at C-5[62]. 1,3,5-Triazin-2,4(1H,3H)-dione (5-azauracil)(76), an antimetabolite the mechanism of action of which has been studied in detail,[63] is prepared by the reaction of ethyl

orthoformate with urea in the presence of acetic anhydride[64].

6-Methyl-1,3,5-triazin-2,4(1H,3H)-dione (72) is very water soluble and amphoteric and forms a variety of metal salts and salts with mineral acids. The fact that the metal salts contained only a single equivalent of a metal atom led Ostrogovich and Cadariv[65] to propose that the structure was mainly in the monoenolic form(77). A survey of the literature revealed that a group of Czech workers had published much ultra-violet and infra-red data on 1,3,5-triazindiones and related compounds[66,67,68], which confirmed that these compounds did, in fact, exist in the diketo-form (72-76).

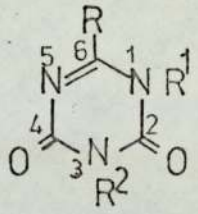


(79)



(80) R = H

(81) R = Me



(82) R = R^2 = H, R^1 = Me

(83) R = R^1 = H, R^2 = Me

(84) R = H, R^1 = R^2 = Me

(85) R = R^1 = R^2 = Me

Table 1 gives a comparison of the carbonyl stretching frequencies of some 1,3,5-triazin-2,4(1H,3H)-diones and related compounds.

Table 1

Compound[a]	ν C=Ocm^{-1}(Dioxan)	νC=Ocm^{-1}(Nujol)
Uracil(79)	1722,1694[c]	1730-1715,1670
6-azauracil(80)	1731,1703[c]	
5-methyl-6-azauracil(81)	1728,1708[c]	1720,1675
5,6-dihydro-5-methyl-6-azauracil	1723[c]	
5-azauracil(76)	1753,1721[b]	1740,1710[f]
6-methyl-5-azauracil(72)	1745,1720[d,e]	1760,1705
6-phenyl-5-azauracil(73)		1740,1690
6-benzyl-5-azauracil(74)		1750,1670
5,6-dihydro-6-methyl-5-azauracil	1727[b]	
1-methyl-5-azauracil(82)	1746,1721[b]	
3-methyl-5-azauracil(83)	1749,1696[b]	
1,3-dimethyl-5-azauracil (84)	1739,1692[b]	
1,3,6-trimethyl-5-azauracil(85)		1720,1670

a The trivial 'azauracil' nomenclature is used, together with the uracil numbering for easier comparison.

b Ref. 66

c Ref. 67

d Ref. 66 gives 1753, 1730cm^{-1}

e Shoulder at 1695cm^{-1}

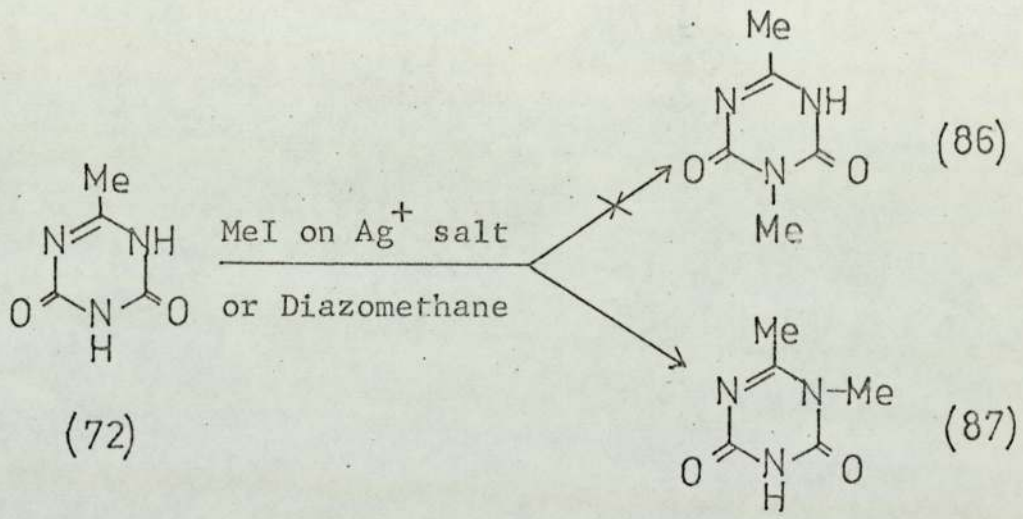
f Shoulder at 1690cm^{-1}

The occurrence of two frequencies in the carbonyl stretching region of these compounds has been explained by an inequality of the two carbonyl groups[69] although the Czech workers have suggested that a better interpretation may be presented by taking into account a possible "coupling effect" between both carbonyl groups in the molecule (because of the weak-coupling effect in the dihydrocompounds the two C=O bands are superimposed). The infra-red spectra of the aza-analogues of uracil differ from the spectrum of uracil in that the carbonyl stretching frequencies are displaced to higher wave numbers. This is explained by differing electronegativities of the carbon and nitrogen; the more electronegative nitrogen atom drawing electrons away from the carbonyl grouping, thus increasing the bond order and causing an increase in the C=O stretching frequency. This is a general effect for all types of carbonyl groups[70].

It is concluded that the CO-N(R)-CO moiety acts toward electronic changes in its vicinity as an internally compensating system[67]. A mass-effect is shown when alkyl groups are substituted at N-1 and N-3 which leads to frequency changes, often in individual bands.

Substitution of a phenyl group at the 6-position of 1,3,5-triazin-2,4(1H,3H)-dione causes a lowering of the frequency of absorption of the C=O grouping due to conjugation, but it is unclear as to why the benzyl group, in the 6-benzyl derivative, should cause a lowering of the position of absorption of the lower C=O band.

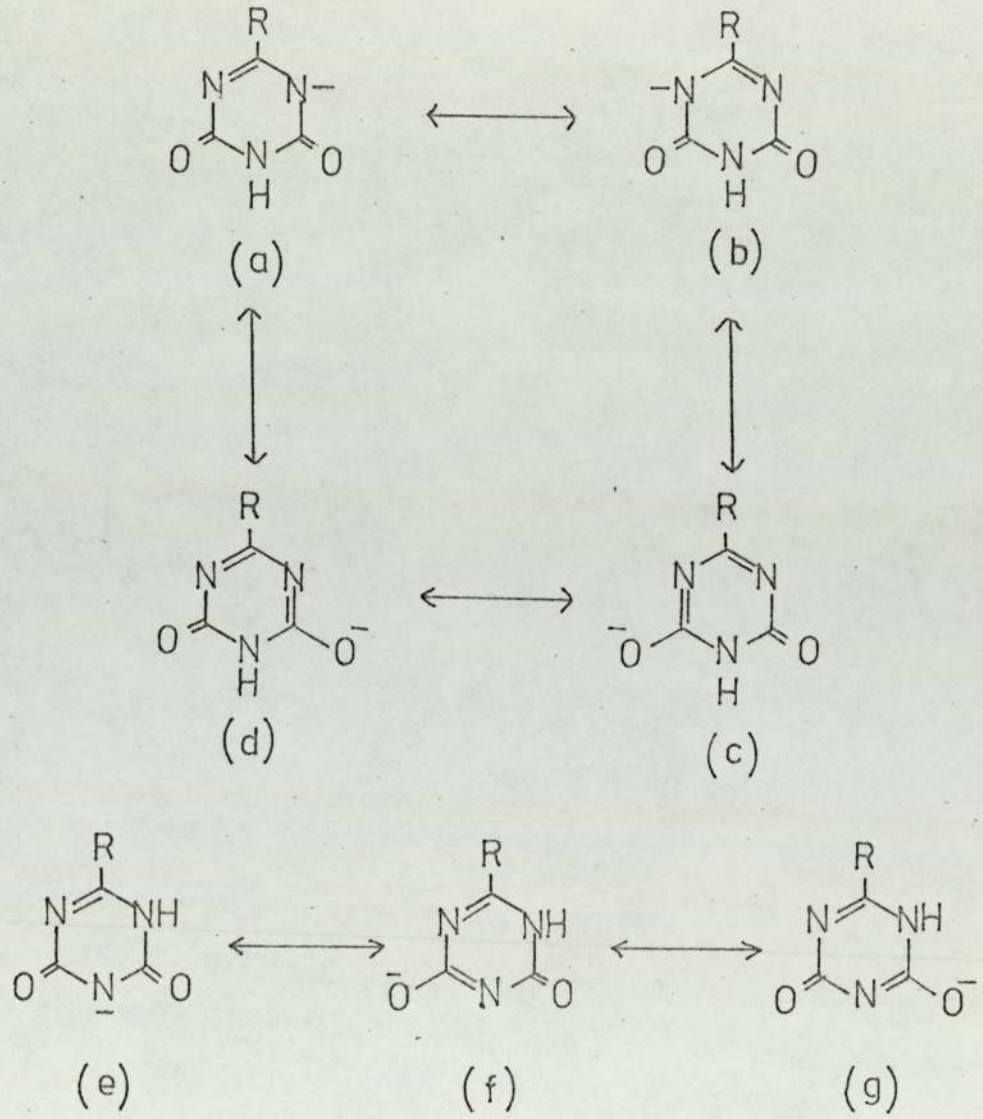
Ostrogovich[71] claimed that reaction of the silver salt 6-methyl-1,3,5-triazin-2,4(1H,3H)-dione (72) gave the N-3 methyl derivative (86), he presented no evidence for this, however, and later workers showed that reaction of (72) with one equivalent of diazomethane gave the N-1 methyl compound (87), identical to that obtained by Ostrogovich[68].



The above experimental findings have been confirmed by a determination of the dissociation constants of uracil and its 6-aza and 5-aza analogues and their derivatives[66,72] (table 2). It has been shown that the hydrogen atom at position 1 ionises first, followed by that at position 3 for uracil (79) and 1,3,5-triazin-2,4(1H,3H)-dione(5-aza-uracil) (76) but follows the reverse order for 1,2,4-triazin-3,5(2H,4H)-dione(6-azauracil) (80). These results were later supported by theoretical calculations[62], although a consideration of the contributing canonical forms of the anion indicates that the proton at position 1 would ionise

first. For the removal of a proton at position 1 four structures, with the negative charge spread over five atoms, can be drawn compared with the anion produced by removal of a proton at position 3 for which only three contributing forms can be drawn (scheme 3).

Scheme 3



The infra-red spectrum of the potassium salt of 6-methyl-1,3,5-triazin-2,4(1H,3H)-dione; obtained as a stable white solid by the action of alcoholic potassium hydroxide on an

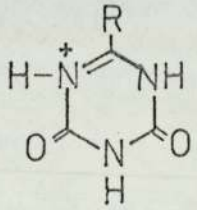
alcoholic solution of the free base, shows striking differences from the spectrum of the free base. The high carbonyl absorptions at 1760 and 1705 cm^{-1}(Nujol) of the free base are absent, but are replaced by a broad carbonyl stretching frequency at 1640-1660 cm^{-1}, indicative of a conjugated carbonyl grouping adjacent to a negatively charged nitrogen atom, and the C=N absorbance due to the localisation of this bond in the free base is absent. A study of the spectra of the sodium salts of pyridinones and pyrimidinones has shown the carbonyl stretching frequencies of these compounds to occur near 1600 cm^{-1} [73].

From a study of the ultra-violet spectrum of 1,2,4-triazin-3,5(2H,4H)-dione Jonas and Gut[74] found it impossible to decide whether the negative charge produced by dissociation of a proton resides largely or wholly on the oxygen or nitrogen atoms. The anion of 6-azauracil was, however, stable and did not undergo hydrolysis in alkaline media, indicating that stabilisation of the anion through pseudo-aromatic structures had occurred. Preliminary results of a Raman-spectra study favoured structures with the negative charge on the oxygen atoms. It may be expected that of the canonical forms possible for the structure of the anion of 1,3,5-triazin-2,4(1H,3H)-diones (Scheme 3) (c) and (d) should make a greater contribution to the overall structure than forms (a) and (b) due to the electron affinity of oxygen being higher than that of nitrogen[75]. This is supported by

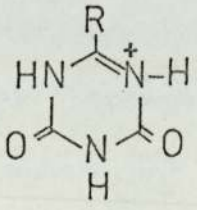
experimental observations in the 2- and 4-hydroxypyrimidine series since a spectral study of the anions of these compounds showed them to have essentially structures in which the negative charge resided on the oxygen atoms[76].

6-Methyl-1,3,5-triazin-2,4(1H,3H)-dione hydrochloride was prepared for a comparison of its infra-red spectrum[77]. The general outline of the spectrum is quite different from that of the free base, the most notable feature being a change in the position of the carbonyl stretching vibrations. These are shifted to higher frequencies and occur at 1780 and 1725cm^{-1} (20cm^{-1} higher than the free base) and the lower of the two bands is much smaller. Similar results were found for the cations of 2- and 4-hydroxypyrimidines[78] and previous ultra-violet work on these compounds has shown that they are preferentially protonated on the nitrogen, rather than the oxygen, atom[79].

Scheme 4



(a)



(b)

That the infra-red spectrum of the hydrochloride changes quite markedly from that of the free base indicates that changes have occured in the molecule or bond orders of the molecule. This suggests that the cation formed is preferentially protonated at N-5 (rather than N-1 or N-3)

and, if so, would exist as a resonance hybrid of the two canonical forms (a) and (b) (Scheme 4).

Russian authors have discussed the changes in the infra-red spectra of amino- and oxo-amino-1,3,5-triazines on salt formation[80].

Table 2

Compound[a]	pK_{a1}	pK_{a2}
Uracil (79)	9.43	13.2
6-azauracil (80)	7.00	12.9
5-methyl-6-azauracil (81)	7.84	13.4
5-azauracil (76)	6.73	12.2
6-methyl-5-azauracil (72)	7.21	

a The 'azauracil' nomenclature is used, together with the uracil numbering system.

Table 2 clearly shows that the additional ring nitrogen atom in the aza analogues causes an increase in acidity of these compounds when compared to uracil. This increase has been explained in terms of the inductive effect of the extra ring-nitrogen which disturbs the amide (acid-weakening) resonance by drawing upon electrons necessary for its operation[47]. The aza analogues of uracil thus have both a greater acidity and a higher carbonyl absorption than uracil; effects which have been explained by the differing electronegativities of carbon and nitrogen. Acidity and carbonyl stretching frequency both follow the order

5-azauracil > 6-azauracil > uracil which, if the above hypothesis were true, is the expected order since the third nitrogen atom in 5-azauracil has to exert its inductive effect through one bond only, compared to two bonds in 6-azauracil.

Calculations of the electronic structure of uracil and its 5-aza and 6-aza analogues using the MO LCAO method[62] have confirmed that the third ring nitrogen atom alters the distribution of electron density around the molecule.

Crystal structures of uridine[81] and 6-azauridine[82] (the N-1 ribose derivatives of uracil and 6-azauracil respectively) have been determined and confirm the di-lactam structure of these compounds. Schwalbe and Saenger[82] investigated the electronic properties of 6-azauridine by the extended Huckel molecular orbital method, taking co-ordinates for the molecule from the crystal structure analysis, and compared them with similar calculations for uridine[83] (table 3).

Table 3

Position	Miliken net charges (electrons)	
	Uridine	6-Azauridine
1	-0.21	$\pm$0.00
5	-0.25	+0.24
6	+0.28	-0.47

These results agreed, in general, with the pattern obtained by the MO LCAO method, the most notable differences in

electron density between uridine and its 6-aza analogue occuring at position 6, where the third nitrogen atom of the aza derivative has replaced a -CH-, and positions 1 and 5 adjacent to this extra ring nitrogen.

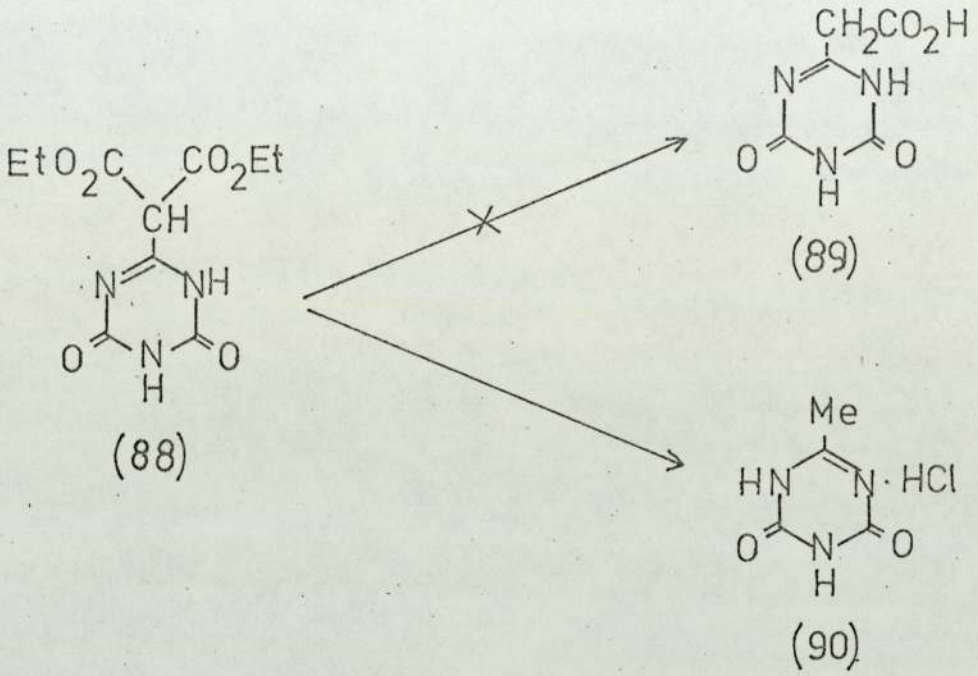
Unfortunately no similar studies have been reported for any 5-azauracil derivatives although at the present time work is being carried out in this laboratory on the crystal and electronic structure of 6-phenyl-1,3,5-triazin-2,4(1H,3H)-dione(6-phenyl-5-azauracil) (73)[84].

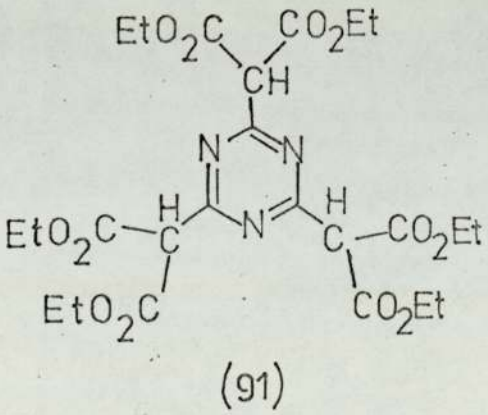
Another, potentially useful, triazindione mentioned in the literature is 6-carboxymethyl-1,3,5-triazin-2,4(1H,3H)-dione (89). This was synthesised by Kolb in 1894[85] by the hydrolysis and decarboxylation of 6-dicarbethoxymethyl-1,3,5-triazin-2,4(1H,3H)-dione (88) with strong hydrochloric acid at 130°.

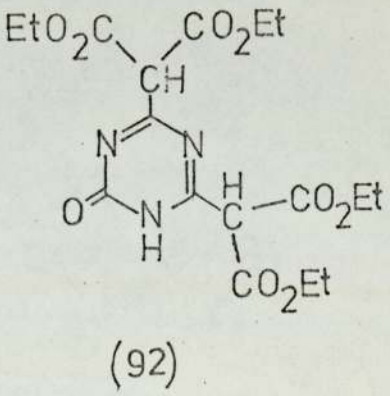
6-Dicarbethoxymethyl-1,3,5-triazin-2,4(1H,3H)-dione was prepared by the reaction of 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride) with one equivalent of sodium diethyl malonate, but attempted hydrolysis of this compound with varying concentrations of hydrochloric acid led either to isolation of the starting material (88), or to the production of 6-methyl-1,3,5-triazin-2,4(1H,3H)-dione hydrochloride (90).

Reaction of cyanuric chloride with three equivalents of sodium diethyl malonate afforded 2,4,6-tris(dicarbethoxymethyl)-1,3,5-triazine (91), although when two equivalents of sodium diethyl malonate were used only the tris(dicarbethoxymethyl)-

triazine (91) was obtained and no 2,6-bis(dicarbethoxymethyl)-1,3,5-triazin-4(3H)-one (92) could be isolated.

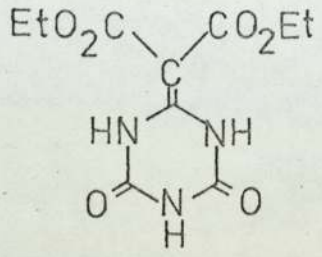




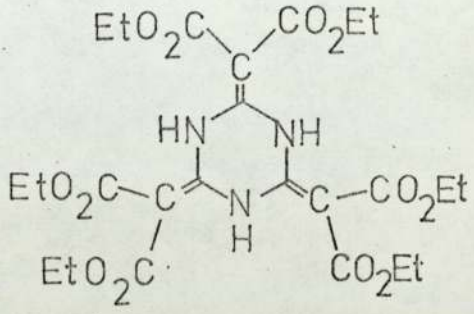


Examination of the spectra of 6-dicarbethoxymethyl-1,3,5-triazin-2,4(1H,3H)-dione and 2,4,6-tris(dicarbethoxymethyl)-1,3,5-triazine showed, in fact, that the formulae (88) and (91) did not represent the true structures of these compounds which were better represented by the structures

(93) and (94), namely 6(1H)-dicarbethoxymethylene-1,3,5-triazin-2,4(3H,5H)-dione and 2,4,6(1H,3H,5H)-tris(dicarbethoxymethylene)-1,3,5-triazine respectively (93,94).



(93)



(94)

The n.m.r. spectra of 6-dicarbethoxymethylenetriazindione (93) and 2,4,6-tris(dicarbethoxymethylene)triazine (94) showed no evidence of any resonance which could be attributed to the methine protons of the carbethoxymethyl-1,3,5-triazine structures (91) and (92). Examination of the structures (93) and (94) suggests that intramolecular hydrogen-bonding would be favoured in these compounds and indeed the marked downfield shifts of the N-H protons in the n.m.r. spectra of (93) and (94) indicates that this does occur. The N-H protons of 2,4,6(1H,3H,5H)-tris(dicarbethoxymethylene)-1,3,5-triazine (94) are equivalent and occur as a broad singlet at τ-3.8, but the N-H protons of the dicarbethoxymethylene-1,3,5-triazindione (93) are not equivalent, the two N-H protons adjacent to the dicarbethoxymethylene grouping occuring at τ-2.22, whilst the proton at the 3-position, that is the proton not involved in intramolecular hydrogen-

bonding, absorbs at τ 1.18.

Evidence for the structures 6(1H)-dicarbethoxymethylene-1,3,5-triazin-2,4(3H,5H)-dione (93) and 2,4,6(1H,3H,5H)-tris(dicarbethoxymethylene)-1,3,5-triazine is also afforded by their infra-red spectra in the region 1600-1800cm^{-1}. The dicarbethoxymethylene-1,3,5-triazindione (93) shows an ester C=O stretch at 1720cm^{-1}, although in the spectrum of the tris(dicarbethoxymethylene)triazine (94) the ester C=O stretching band is shifted to lower frequencies and absorbs at 1680cm^{-1}, presumably due to strong intramolecular hydrogen-bonding as well as conjugation. The carbonyl stretching frequency of methyl anthranilate, for example, which exhibits a similar N-H---O chelation occurs at 1685cm^{-1} [86].

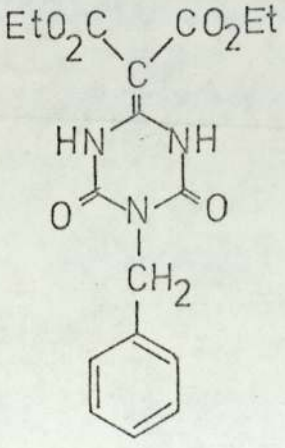
The amide C=O stretching vibration of the dicarbethoxymethylene-1,3,5-triazindione (93) occurs as a single, well defined band at 1760cm^{-1}. Comparison of this with the 6-substituted-1,3,5-triazin-2,4(1H,3H)-diones, which exhibit two carbonyl stretching bands (page 30), would suggest that the carbethoxymethyl-1,3,5-triazin-2,4(1H,3H)-dione structure (88), which contains a C=N bond, is incorrect.

The dicarbethoxymethylene-1,3,5-triazines (93-94) also exhibit strong, broad C=C stretching bands although the positions of these differ in the two compounds. The infra-red spectrum of 6(1H)-dicarbethoxymethylene-1,3,5-triazin-2,4(3H,5H)-dione (93) shows a C=C stretching vibration at 1635cm^{-1} but in the tris(dicarbethoxymethylene)-

triazine (94) this band is shifted to lower wavelengths due to conjugation, and occurs at 1605cm^{-1}.

The mass spectral breakdown of these compounds are quite different from the 1,3,5-triazindiones (page 105) and show no positive ion fragment corresponding to cleavage of a diethyl malonate grouping, as might be expected from the carbethoxymethyl-1,3,5-triazine structures (88) and (91).

The potassium salt of 6(1H)-dicarbethoxymethylene-1,3,5-triazin-2,4(3H,5H)-dione was stirred with benzyl bromide in dimethylformamide to give a mono-benzylated compound. The n.m.r. spectrum of this compound showed that the ester protons, and the protons at N-1 and N-5 absorbed at identical τ values to those same protons in the non-alkylated compound (93). The resonance assigned to the proton at N-3 in the non-alkylated compound was, however, absent and thus it was concluded that the benzyl derivative was, in fact, 3-benzyl-6(1H)-dicarbethoxymethylene-1,3,5-triazin-2,4 (3H,5H)-dione (95).



(95)

The potassium salt of the 3-benzyl derivative (95) could not be induced to react with a further molecule of benzyl bromide, nor could the potassium salt of 2,4,6(1H,3H,5H)-tris(dicarbethoxymethylene)-1,3,5-triazine (94). These failures are possibly due to steric hindrance by the dicarbethoxymethylene groupings.

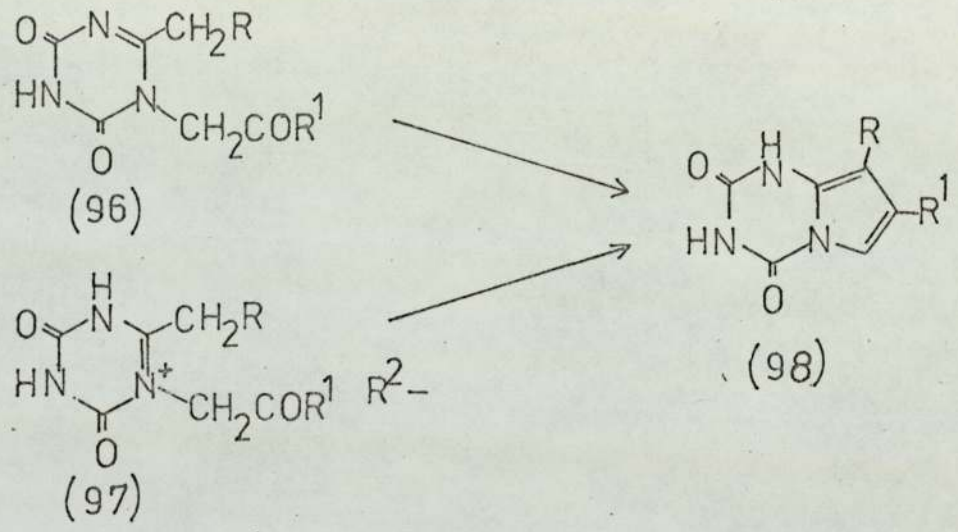
Attempts to extend this study by the synthesis of similar triazine derivatives using other active methylene compounds, such as ethyl cyanoacetate and ethyl phenylacetate were unsuccessful since these compounds failed to react with cyanuric chloride and only 1,3,5-triazin-2,4,6(1H,3H,5H)-dione, (cyanuric acid) formed by the ready hydrolysis of the chlorine atoms of cyanuric chloride, was isolated.

After completion of the above work a report was published[87] which confirmed the findings of the author regarding the structures of 6(1H)-dicarbethoxymethylene-1,3,5-triazin-2,4(3H,5H)-dione (93) and 2,4,6(1H,3H,5H)-tris(dicarbethoxymethylene)-1,3,5-triazine (94).

(ii) Reaction of 6-methyl-1,3,5-triazindiones with α-halogeno-ketones

The methyl, or substituted methyl, groups of 6-alkyl-1,3,5-triazin-2,4(1H,3H)-diones are very reactive and may be induced to condense with aldehydes, in the presence of base or acid, to give styrl compounds[56,88]. It is known that 6-methyl-1,3,5-triazin-2,4(1H,3H)-dione undergoes alkylation at position 1 (page 32) so that it should be

possible to prepare compounds of type (96). If such compounds, or the quaternary salts (97), can be synthesised it seems reasonable to suppose that these could be induced to ring close to the active methyl group at position 6 to give 7-substituted pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-diones (98).

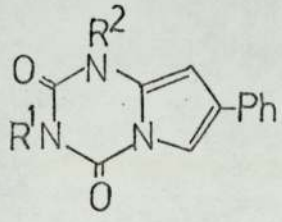


(a) Synthesis of pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-diones via quaternary salts of type (97).

6-Methyl-(72) or 6-benzyl-(74) 1,3,5-triazin-2,4(1H,3H)-dione failed to react with phenacyl bromide when the reaction was carried out under reflux in a variety of polar solvents (acetone, methanol, ethanol, and 2-ethoxyethanol). 6-Methyl-1,3,5-triazin-2,4(1H,3H)-dione, however, did react with phenacyl bromide in refluxing dimethylformamide to give a dark brown product which decomposed slowly above 300° and which could not be further purified. The infra-

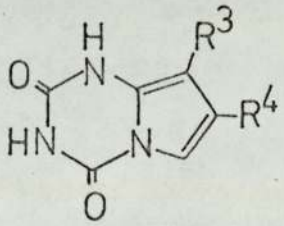
red, n.m.r., and mass spectral data of the crude product were consistent with the structure 3-, or 1-phenacyl-7-phenylpyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione (99a,b). Variation of the reaction conditions in attempts to obtain a purer product, and consequently a more useful method, failed, yielding either a similarly crude product or often only the starting materials.

Ethyl bromopyruvate (100) reacted with 6-methyl-(72) and 6-benzyl-(74) 1,3,5-triazin-2,4(1H,3H)-dione in refluxing ethanol or refluxing 1,2-dimethoxyethane (6-benzyl-1,3,5-triazin-2,4(1H,3H)-dione undergoes alcoholysis in ethanol or methanol) respectively, over three days, to give the corresponding pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-diones (101-102).



(99) a. $R^1 = CH_2COPh, R^2 = H$

b. $R = H, R^2 = CH_2COPh$



(101) $R = H, R = CO_2Et$

(102) $R = Ph, R = CO_2Et$

The mechanism for the synthesis of indolizines from α-picolines and α-halogeno-ketones, outlined by Bragg and Wibberley[89], is also pertinent to this reaction (scheme 5). The initial step is the formation of the quaternary salt (103); loss of a proton from this gives the carbanion-betaine (104)

which can cyclise by an intramolecular aldol-type reaction. Alternatively the cyclisation can be visualised as proceeding via the eneamine resonance structure (105) as shown on page 47.

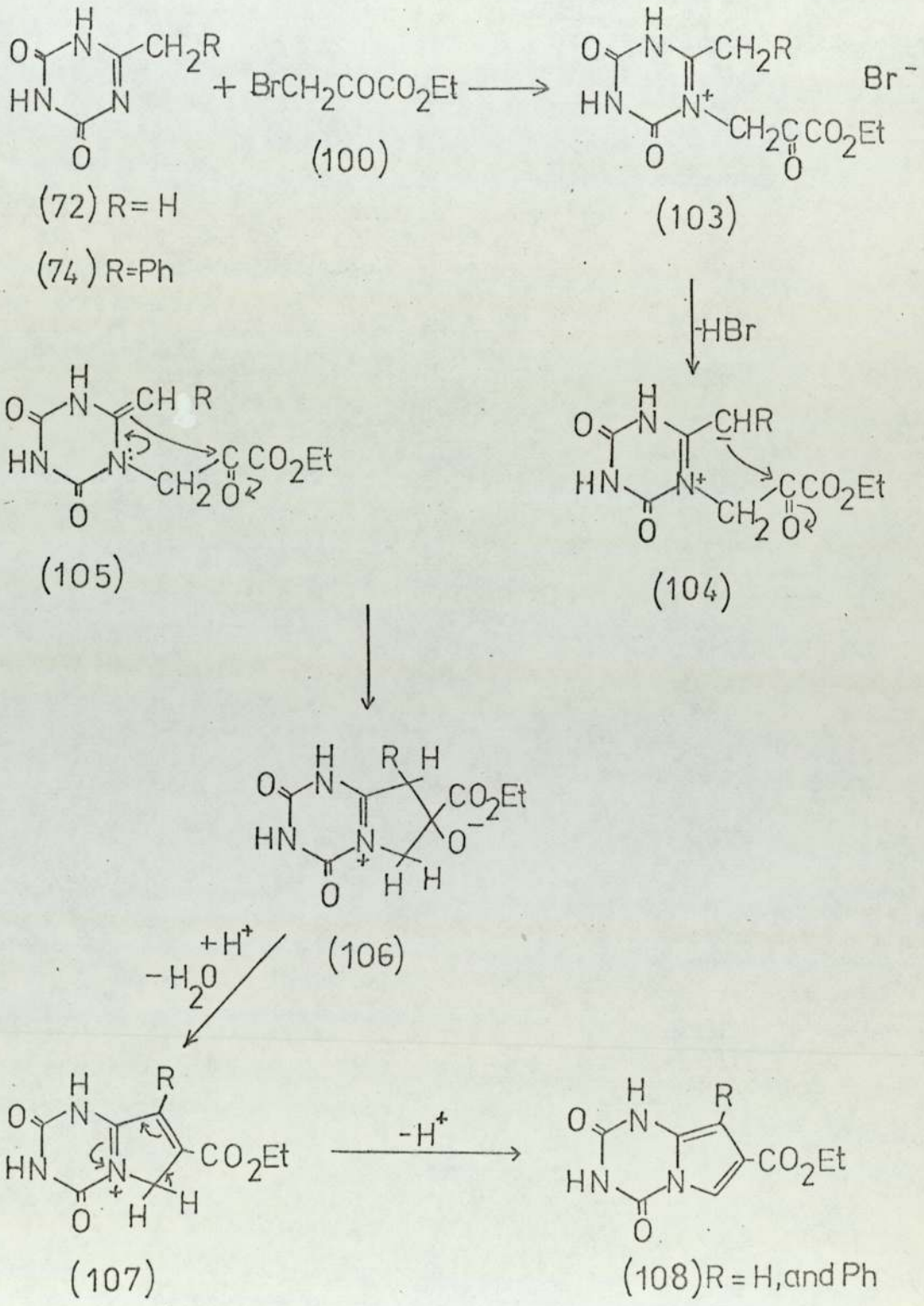
Removal of water from the product (106) gives the cation (107) from which pyrrolotriazine (108) is liberated. A second molecule of the triazindione is used as a catalyst in the removal of a proton from the quaternary salt. The quaternary salts (103) were not isolated in this synthesis.

In the synthesis of indolizines from ethyl 2-pyridyl-acetate and ethyl bromopyruvate no quaternary salts were isolated, although in this case the authors were able to show that the heterocyclic base did form quaternary salts with alkyl halides[87].

2- and 4-Pyrimidone are more basic than pyrimidine[90], the basic centre being the nitrogen atom not involved in tautomerism. Thus 6-methyl-1,3,5-triazin-2,4(1H,3H)-dione (72) could be expected to have a higher basic strength than 1,3,5-triazine and perhaps be more basic than the alkyl-1,3,5-triazines, since its basic strength will also be increased by the +I effect of the 6-methyl substituent and by resonance stabilisation (scheme 4, page 35). The availability of the lone pair on the nitrogen atom at position 5 of 6-methyl-1,3,5-triazin-2,4(1H,3H)-dione (72) is still, however, very low.

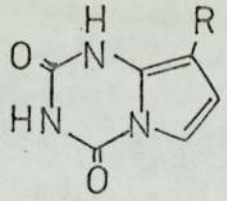
It is suggested that 6-methyl-1,3,5-triazin-2,4(1H,3H)-dione (72) and ethyl bromopyruvate (100) do react to form a

Scheme 5


+ BrCH2COCO2Et
(100)
(72) R= H
(74) R=Ph
(103)
Br⁻
-HBr
(105)
(104)
(106)
+H⁺
-H2O
(107)
-H⁺
(108) R = H, and Ph

quaternary salt, though perhaps to a very small extent, but that any intermediate salt so formed rapidly cyclises due to the highly reactive keto-carbonyl of the pyruvate moiety.

In the attempted preparation of pyrrolo[1,2-a][1,3,5] triazin-2,4(1H,3H)-dione (109) no reaction occurred between bromoacetaldehyde and 6-methyl-1,3,5-triazin-2,4(1H,3H)-dione (72). Reaction did, however, occur between the more reactive 6-benzyl-1,3,5-triazin-2,4(1H,3H)-dione (74) and bromoacetaldehyde to give an unstable purple compound. This was identified from its infra-red spectrum and mass spectrum (M^+, 227.068941, $C_{12}H_9N_3O_2$) as 8-phenylpyrrolo[1,2-a][1,3,5] triazin-2,4(1H,3H)-dione (110).



(109) R=H

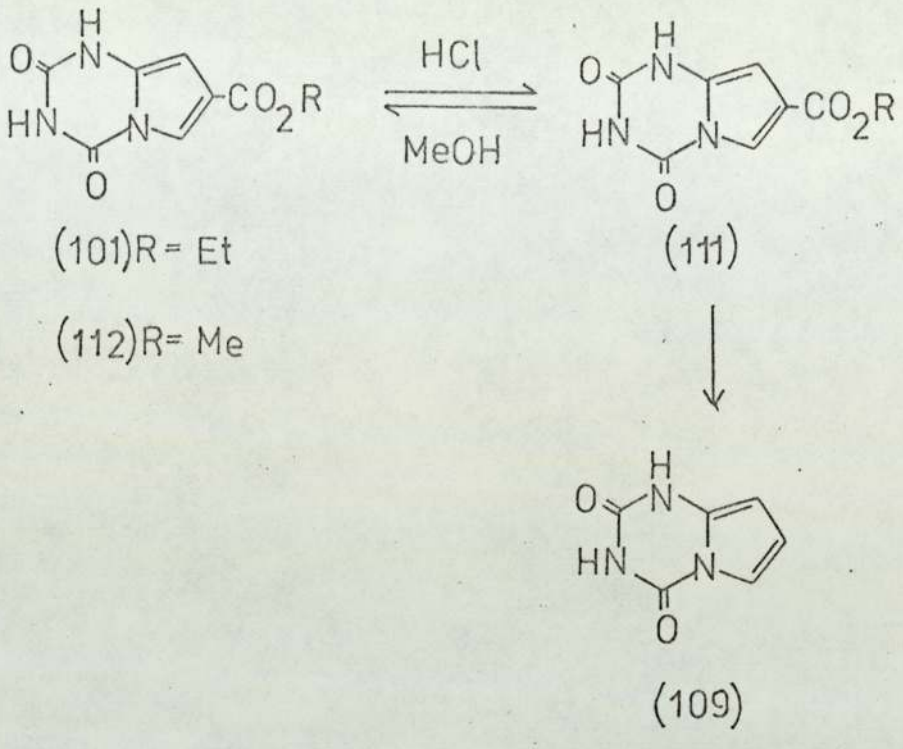
(110) R=Ph

Reaction of 6-methyl-1,3,5-triazin-2,4(1H,3H)-dione (72) with either phenacyl bromide or ethyl bromopyruvate in the absence of any solvent gave good yields of the hydrobromide salt of the starting material. This is not unprecedented and is known to occur in the reactions of other N-heteroaromatic compounds, such as quinaldine[91,92] and 2,4,6-trimethyl-pyrimidine[51], with phenacyl bromide. This reaction may be

due to elimination of hydrobromic acid from the α-halogeno-ketone rather than the required substitution, at least in the cases where no other nucleophiles are present (i.e. in the absence of any solvent).

It is interesting to note that the reaction of 2,4,6-trimethylpyrimidine with phenacyl bromide results in the production of 2,4,6-trimethylpyrimidine hydrobromide whereas a similar reaction using ethyl bromopyruvate results in the isolation of the required pyrrolopyrimidine[51]. These results are consistant with the above findings regarding the reactivity of the α-halogeno-ketones.

For a spectroscopic study of the pyrrolo[1,2-a][1,3,5] triazin-2,4(1H,3H)-diones (page79) it was necessary to synthesise several derivatives of the system, especially the compound (109) which is unsubstituted in the pyrrole ring. It has been previously noted that this compound could not be prepared directly by the action of the bromoacetaldehyde on 6-methyl-1,3,5-triazin-2,4(1H,3H)-dione (page 48) but an alternative route to this compound would be an hydrolysis and decarboxylation of the pyrrolotriazine ester (101). On warming with 6N hydrochloric acid the ester readily gave pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylic acid (111) which proved difficult to decarboxylate. This was finally achieved by sublimation from a mixture of the acid and copper bronze (1:1) at 280°.



(101)R = Et

(112)R = Me

(111)

(109)

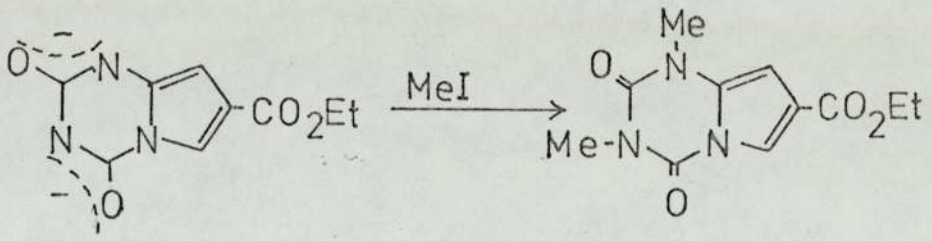
Pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione (109) was extremely unstable, being very sensitive to air and organic solvents, so that a n.m.r. spectrum of the compound could not be obtained. The structure of the compound was formulated by consideration of its infra-red spectrum (lack of carboxylic acid OH and C=O absorptions) and mass spectrum (M^+, 151.038092, $C_6H_5N_3O_2$).

The difficulty experienced in decarboxylating the pyrrolotriazine-7-carboxylic acid (111), or indeed the fact that the pyrrolotriazine (109) could not be prepared by the more direct method may be related to the inherent instability of pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione (109).

Pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylic

acid (111) was re-esterified to give the methyl ester (112) by refluxing in methanol containing a little concentrated sulphuric acid.

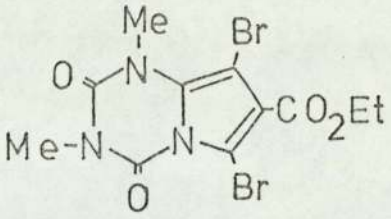
Addition of an alcoholic potassium hydroxide solution, containing two equivalents of potassium hydroxide, to an ethanolic solution of ethyl pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylate (101) gave the dipotassium salt (113) which was isolated as a stable colourless solid. This was stirred with two equivalents of methyl iodide in dimethylformamide, a solvent known to increase the yields and shorten reaction times of S_N2 reactions of this type[93], to give ethyl 1,3-dimethylpyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylic acid (114).



(113) (114)

Bromination of the ethyl pyrrolo[1,2-a][1,3,5]triazindione carboxylate (114) with N-bromosuccinimide in chloroform afforded a mixture of the 8-monobromo- (115) and 6,8-dibromo- (116) derivatives. Chromatographic analysis of the crude material showed no other brominated derivatives to be present. The structures of these compounds were assigned on the basis of their n.m.r. spectra (page 79).

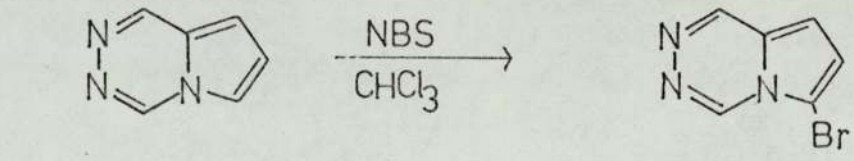
(115)

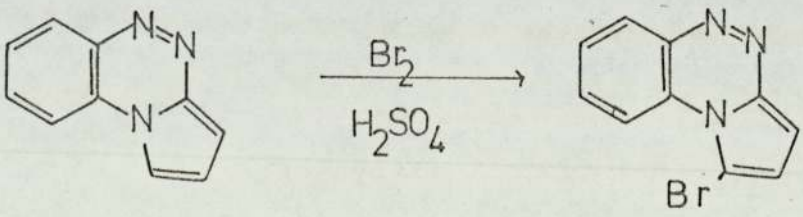


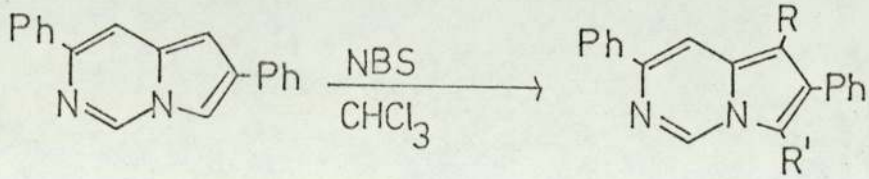
(116)

Similar studies on related pyrrolotriazines have shown that in these cases bromination occurs at the position adjacent to the bridgehead nitrogen atom (Scheme 13),[15,16] although bromination of 3,6-diphenylpyrrolo[1,2-c]pyrimidine (117) with N-bromosuccinimide in chloroform gave a mixture of 5- (118) and 7-monobromo- (119) and 5,7-dibromo derivatives (120), in the yields 15.5, 11.1, and 39% respectively.[137]

Scheme 13







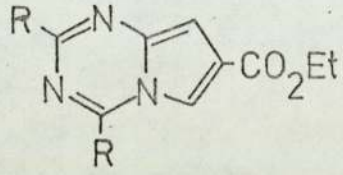
(117)

(118) R = Br, R′ = H

(119) R = H, R′ = Br

(120) R = R′ = Br

It was hoped that ethyl 2,4-diaminopyrrolo[1,2-a][1,3,5] triazine-7-carboxylate (122) could be prepared from ethyl pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylate (101) via the dichloro compound (121).



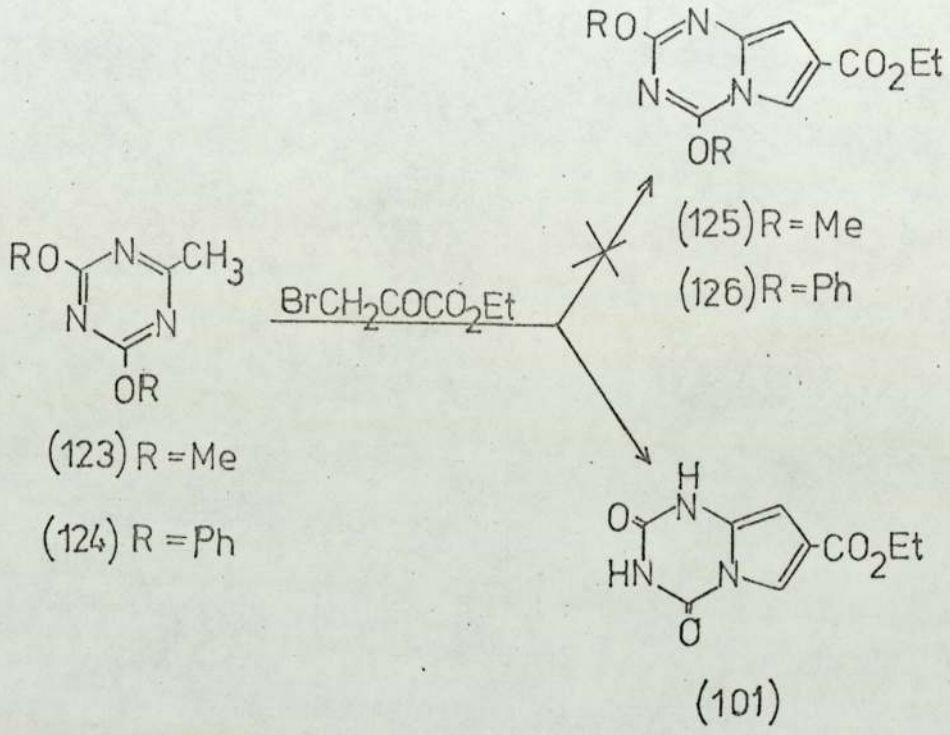
(121) R = Cl

(122) R = NH_2

Attempts to prepare (121) were, however, unsuccessful since the action of phosphorus oxychloride or phosphorus oxychloride and dimethylaniline under reflux, and thionyl chloride and dimethylformamide at 80°, gave only intractable tars. Milder conditions resulted in recovery of the starting material.

As a useful synthetic method to the pyrrolo[1,2-a] [1,3,5]triazin-2,4(1H,3H)-dione system the one-step reaction between an α-halogeno-ketone and a 6-methyl-, or substituted methyl-1,3,5-triazin-2,4(1H,3H)-dione is thus rather restricted by the availability of suitable 1,3,5-triazindiones and by the fact that ethyl bromopyruvate is the only α-halogeno-ketone which is sufficiently reactive. To increase the scope of this reaction it was hoped that the 2,4-dialkoxy-6-methyl-1,3,5-triazines (123) and (124) could be induced to

react with ethyl bromopyruvate to give the pyrrolotriazines (125-126).



The compounds (123-124) are presumably sufficiently basic to react due to the +M effect exerted by the -OR grouping, but the reaction might well be hindered by steric effects.

Reaction of 2,4-dimethoxy-6-methyl-1,3,5-triazine (123) with ethyl bromopyruvate gave ethyl pyrrolo[1,2-a][1,3,5]-2,4(1H,3H)-dione-7-carboxylate (101) in 11% yield, with no evidence of any ethyl 2,4-dimethoxypyrrolo[1,3,5]triazin-7-carboxylate (125). The mother liquors afforded 6-methyl-1,3,5-triazin-2,4(1H,3H)-dione (72) in 25% yield and spectroscopic evidence of the starting material, although

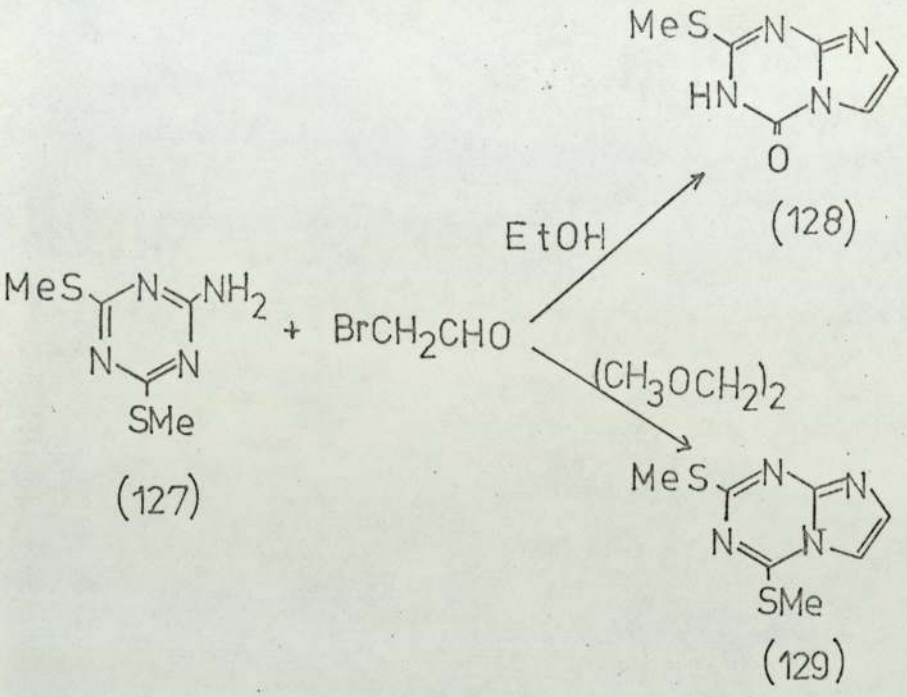
this was not isolated.

A similar result was obtained for 6-methyl-2,4-diphenoxy-1,3,5-triazine (124).

The absence of any 2,4-dimethoxypyrrolo[1,2-a][1,3,5] triazine and the recovery of 6-methyl-1,3,5-triazin-2,4 (1H,3H)-dione hydrochloride indicate that hydrolysis of 2,4-dimethoxy-6-methyl-1,3,5-triazine (123) occured prior to cyclisation. The reaction was repeated in 1,2-dimethoxy-ethane, a non-hydrolytic solvent, and afforded only 3% of the pyrrolotriazindione (101), no evidence of the dimethoxypyrrolotriazine (125) was found and the unreacted 2,4-dimethoxytriazine (123) was recovered. These facts further substantiate that hydrolysis occured prior to cyclisation and the lower yield of ethyl pyrrolo[1,2-a][1,3,5] triazin-2,4(1H,3H)-dione-7-carboxylate (101) obtained when the reaction was repeated in the non-hydrolytic solvent is explained by the lesser amount of 6-methyl-1,3,5-triazin-2,4(1H,3H)-dione produced.

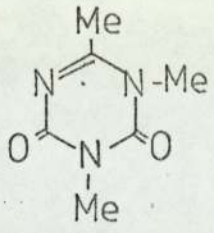
A similar hydrolysis was observed in the synthesis of the imidazo[1,2-a][1,3,5]triazine ring system[58]. Reaction of 6-amino-2,4-bismethylthio-1,3,5-triazine (127) with bromo-acetaldehyde in 1,2-dimethoxyethane gave 5,7-bismethylthio [1,2-a][1,3,5] triazine (128) whereas the reaction in ethanol afforded 7-methylthio imidazo[1,2-a][1,3,5] triazin-5(6H)-one (129), although in this case prior formation of 6-amino-2-methylthio-1,3,5-triazin-4(5H)-one was not necessary for

cyclisation to occur.

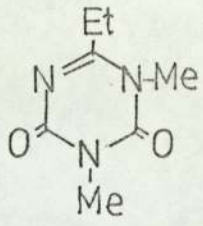


(b) Synthesis of pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-diones via N-1 alkylated compounds of type (96)

Reaction of 6-methyl-1,3,5-triazin-2,4(1H,3H)-dione (72) with excess diazomethane, using dioxan as solvent, afforded 1,3,6-trimethyl-1,3,5-triazin-2,4(1H,3H)-dione (130). Chromatographic analysis of the crude product showed no evidence of any other methylated triazines. The infra-red spectrum of the compound exhibited two carbonyl absorptions at 1720cm^{-1} and 1670cm^{-1} and the general outline of the spectrum was very similar to that of the starting material, indicating that O-methylation had not taken place. The two sets of N-CH_3 protons appeared as two singlets in the n.m.r. spectrum at τ 6.60 and τ 6.55.



(130)



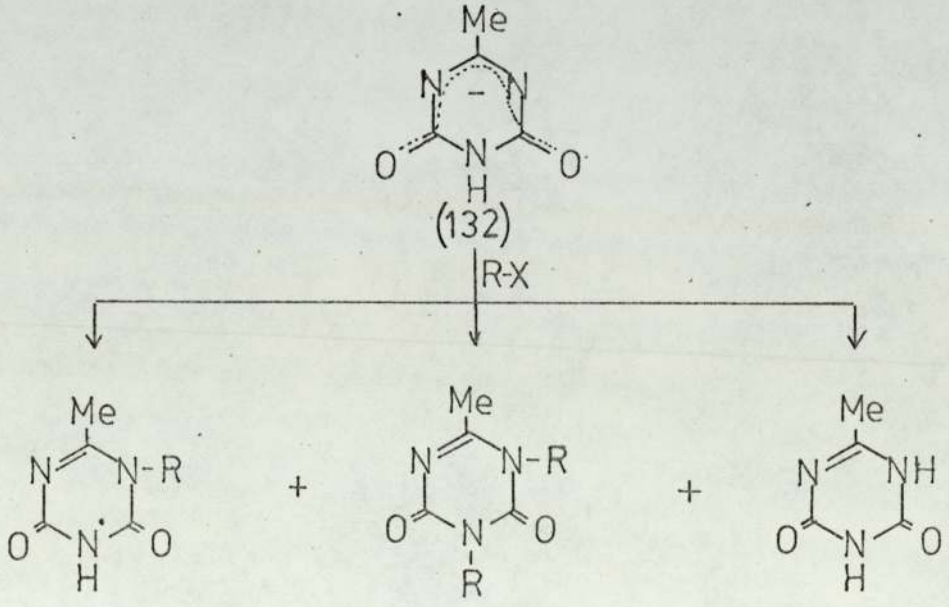
(131)

When the reaction was carried out in ether suspension much starting material was recovered and only 22% of the trimethylated product (130) was obtained. A chromatographic analysis of the crude material showed the presence of a second, very minor, component and a mass spectrum of the crude product showed a very small peak at m/e 169. It is suggested that this compound may be 6-ethyl-1,3-dimethyl-1,3,5-triazin-2,4(1H,3H)-dione (131) and that replacement of all the acidic protons in the molecule had occured.

Methylation of uracil[94], 5-azauracil[68], 6-azauracil[95] and their derivatives using diazomethane similarly yielded only N-methylated products in non-polar solvents, although in the presence of small amounts of polar solvents varying amounts of O-methylated derivatives were also obtained.

The potassium salt of 6-methyl-1,3,5-triazin-2,4(1H,3H)-dione (132) and methyl iodide refluxed in methanol afforded 1,3,6-trimethyl-1,3,5-triazin-2,4(1H,3H)-dione (130), identified by comparison with an authentic sample, as the major product and 1,6-dimethyl-(133) and 6-methyl-(72)-1,3,5-triazin-2,4(1H,3H)-diones as the minor products.

Reaction of the same potassium salt with phenacyl bromide in dimethylformamide at room temperature also afforded a mixture of compounds. The major products were 6-methyl-1,3,5-triazin-2,4(1H,3H)-dione (72) and 6-methyl-1,3-diphenacyl-1,3,5-triazin-2,4(1H,3H)-dione (135). A third minor component which was unidentified showed a single broad carbonyl absorption at 1700cm^{-1} in its infra-red spectrum and protons at τ 7.75(3H) and τ 6.58(3H), possibly C-CH_3 and N-CH_3 respectively, at τ 5.18(1H) and τ 5.08(1H), and at τ 2.28 and τ 1.90, possibly benzoyl protons. The mass spectrum of this compound showed a large peak at m/e 161, possibly phenacyl isocyanate ($PhCOCH_2NCO$), but was generally poorly defined and showed smaller peaks at higher values than this, up to m/e 280.



(133) R=Me (130) R=Me (72)

(134) R=CH_2COPh (135) R=CH_2COPh

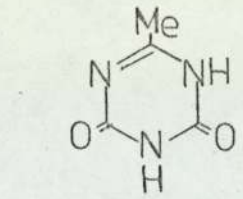
The reaction was repeated, using two equivalents of phenacyl bromide, to give a similar mixture, although the minor product in this case was identified as 1-phenacyl-6-methyl-1,3,5-triazin-2,4(1H,3H)-dione hydrobromide (134·HBr).

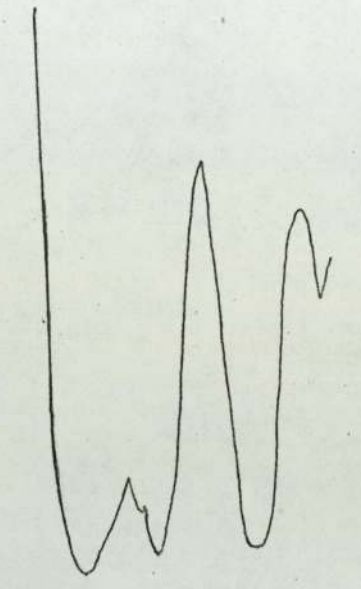
The infra-red spectra of these N-alkylated compounds were of interest in view of the previous discussion regarding the carbonyl stretching frequencies of the 1,3,5-triazin-2,4(1H,3H)-diones (page 29).

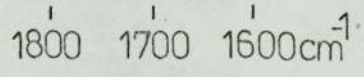
The infra-red spectra of 6-methyl-1,3,5-triazin-2,4(1H, 3H)-dione (72) and its 1,3-diphenacylated and 1,3-dimethylated derivatives showed striking differences in the region 1600-1800cm^{-1} (fig.2), the most notable being a change in the intensities of absorption of the two carbonyl bands.

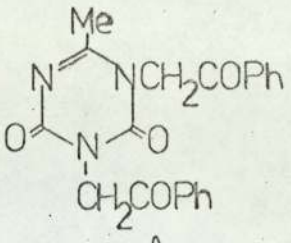
The spectrum of the monophenacylated-6-methyl-triazin-2,4(1H,3H)-dione hydrobromide shows the expected shift of the carbonyl stretching frequencies to higher values (page 35) but no alteration in the intensity of the absorptions. Previous workers have drawn attention to the mass-effects of N-alkyl groups on the carbonyl stretching frequencies of 1,2,4[67]- and 1,3,5[66]-triazin-diones and have shown that substituents at the 3- position cause considerable changes in the relative intensities of the carbonyl stretching frequencies. Examination of the spectrum of the monophenacylated derivatives (fig.2) suggests, therefore, that the phenacyl substituent is sited at position -1. Further, though far from conclusive, evidence that this is so is given

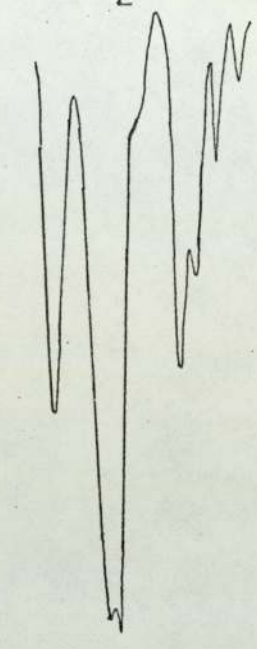
Fig. 2

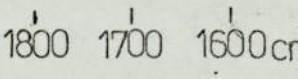


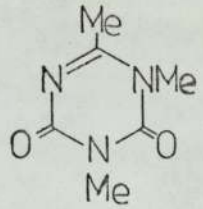


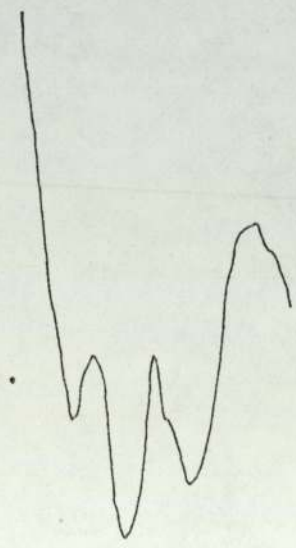


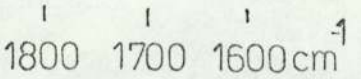


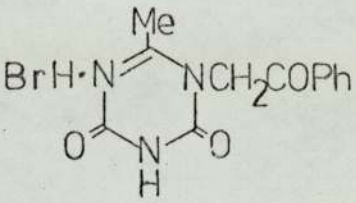


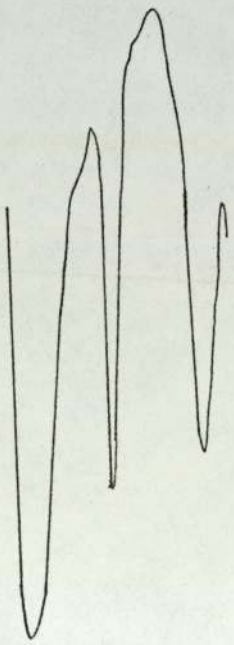


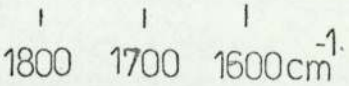






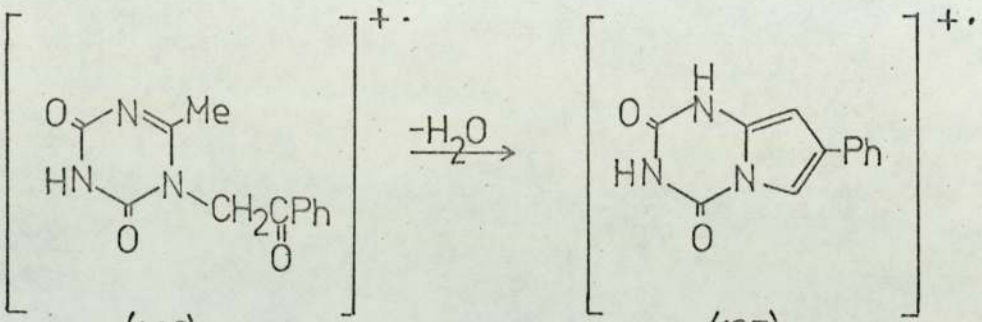






All spectra recorded as Nujol mulls

by the mass spectral breakdown pattern of the compound. This shows a very small molecular ion at m/e 245, consistent with the assigned structure (134), which by loss of water affords the base-peak at m/e 227 ($C_{12}H_9N_3O_2$). One of the ways this compound could lose water is, in fact by cyclisation, in the envisaged manner to the pyrrolotriazine (137).



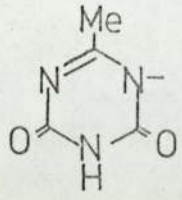
(136) (137)

The n.m.r. spectrum of 6-methyl-1,3-diphenacyl-1,3,5-triazin-2,4(1H,3H)-dione showed that the two sets of-CH_2-protons were not equivalent, one -CH_2- occuring at τ 5.03, and the other at τ 4.60 ($CDCl_3$); the most deshielded of the protons being attributed to the phenacyl grouping at N-3. The CH_2COPh protons of 6-methyl-1-phenacyl-1,3,5-triazin-2,4(1H,3H)-dione hydrobromide occured as a singlet at τ 4.12 (CF_3COOH).

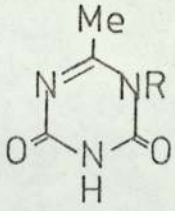
The reasons why mixtures of compounds are obtained in these reactions are now discussed.

If as is expected, (page 32) the 1st alkylation occurs at N-1 to give the species (ii) (scheme 6) then both species (i) and (ii) will be present during reaction. The differences in acidic pK_a value between (ii) and (iii) is approximately 1 pK_a unit, (iii) having the most easily removed proton.

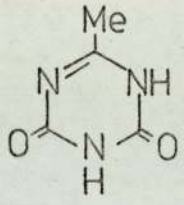
Scheme 6



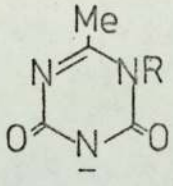
(i)



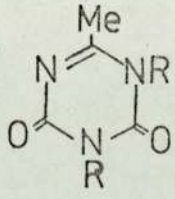
(ii)



(iii)



(iv)



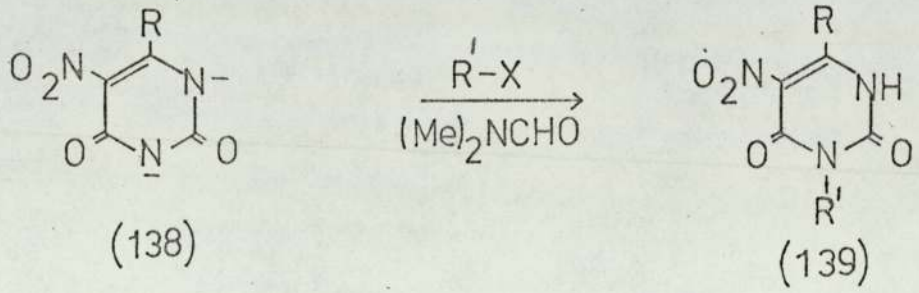
(v)

For example the pK_a of 6-methyl-1,3,5-triazin-2,4(1H,3H)-dione is 7.23, compared to a value of 8.27 for the 1,6-dimethyl-1,3,5-triazin-2,4(1H,3H)-dione[68]. Thus presumably an equilibrium will exist between the anion (i) and the anion (iv), (i) being in the greater concentration. However (iv) might be expected to be the more basic and therefore possibly the most nucleophilic anion since although its basicity will be decreased by the inductive effect of N-5, it will be increased by +I effect of the 1-alkyl substituent, whereas the basicity of (i) will be decreased by both the inductive effect of the nitrogen atom at N-5 and mesomerism with N-5. The anion of 6-methyl-1-substituted-1,3,5-triazin-2,4(1H,3H)-dione (iv) will therefore rapidly react with any alkyl halide present causing production of a 1,3-disubstituted

product (v) and an unsubstituted product (iii) and causing the equilibrium between the 1- (i) and 3-anions (iv) to shift.

Other factors must also be involved. For example in scheme 6 the negative charges are depicted as residing on the nitrogen atoms, and in fact only N-alkyl compounds are isolated, whereas presumably the negative charge will be delocalised and will reside mainly on the oxygen atoms (page 33). The percentage of any N-3 anion present would have to be considered and also the steric effects of the 6-methyl group as well as such factors, as for example, the choice of solvent.

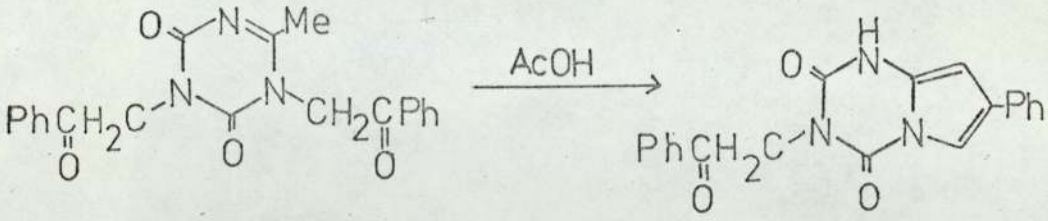
A comparable finding has been reported in the electronically similar 5-nitrouracils[96], where a 1,3-di-anion (138) was preferentially alkylated at position 3 to give (139). This was explained by the greater nucleophilicity of the N-3 anion compared to the N-1 anion.



(138) (139)

Cyclisation of 6-methyl-1,3-diphenacyl-1,3,5-triazin-2,4(1H,3H)-dione (135) to 3-phenacyl-7-phenylpyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione(140) in the presence of refluxing glacial acetic acid showed that this method does

provide a route to the pyrrolo[1,2-a][1,3,5]triazines.



(135) (140)

The infra-red spectrum of the 3-phenacyl-7-phenyl-pyrrolotriazindione (140) was very similar to that exhibited by its diphenacylated triazine precursor (135) in the carbonyl stretching region, but showed the presence of an N-H stretching frequency at 3050cm^{-1} and a C=C band at 1640cm^{-1}. The spectrum was generally much more complicated. The structure of the pyrrolotriazine (140) was further proved by analysis and an accurate mass determination of its molecular ion ($\underline{M}^{+}$, 345.111598, $C_{20}H_{15}N_3O_3$).

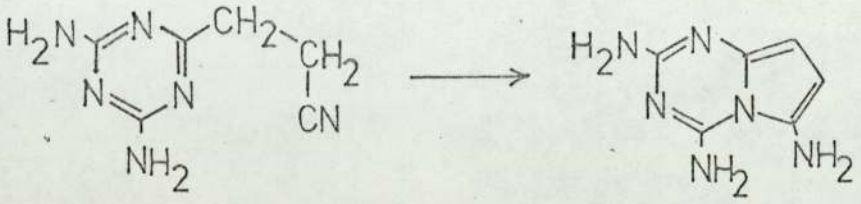
B. Intramolecular Cyclisation of Suitably Substituted 3-(1,3,5-triazin-6-yl)propane derivatives

Treatment of 3-(2,4-diamino-1,3,5-triazin-6-yl)propiontrile (141), 3-(2,4-diamino-1,3,5-triazin-6-yl)propionic acid (142) and 3-(2,4-diamino-1,3,5-triazin-6-yl)propan-2-one (143) with reagents such as acetic anhydride, phosphorus oxychloride, or polyphorphorus acid afforded none of the required pyrrolo-triazines (144-146).

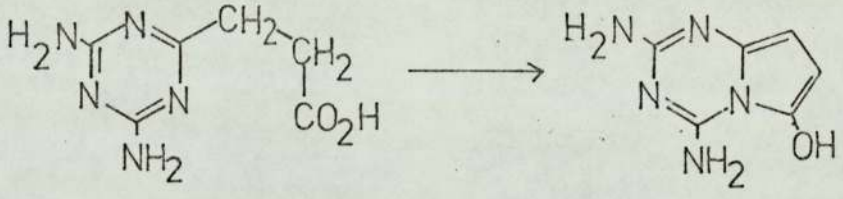
This type of reaction depends on the availability of the lone pair of electrons on the attacking nitrogen atom and thus previous workers[105] have found that the lesser basicity of pyrimidines compared to pyridines renders the preparation of pyrrolo[1,2-c]pyrimidines from 3-pyrimidin-4yl-propan-1-ols much more difficult than that of indolizines from 3-2'-pyridylpropan-1-ols. Taylor and Wibberley[37] could not effect the cyclisation of diethyl di-(6-phenylpyrimidin-4-ylmethyl) malonate or 4-(2-acetylethyl)-6-phenylpyrimidine to the corresponding pyrrolo[1,2-c]pyrimidines with acetic anhydride.

In the attempted synthesis of the pyrrolo[1,2-a][1,3,5] triazine system the 2- and 4-amino-substituents of the precursors might be expected to enhance the basicity of the ring nitrogen atoms although it is probable that prior reaction of the cyclising agent with the exocyclic amino-group will reduce the electron donating effects of these groups, and in fact, in the attempted cyclisation of the triazinylpropionic acid with acetic anhydride, the diacetyl

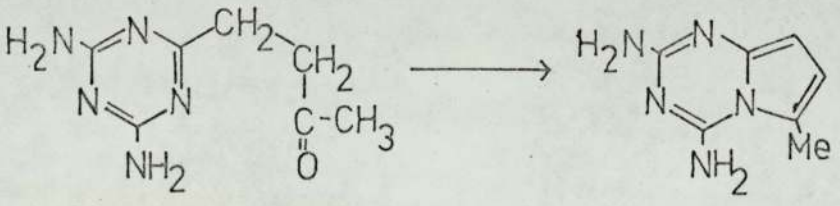
derivative was obtained in good yield.



(141) (144)



(142) (145)

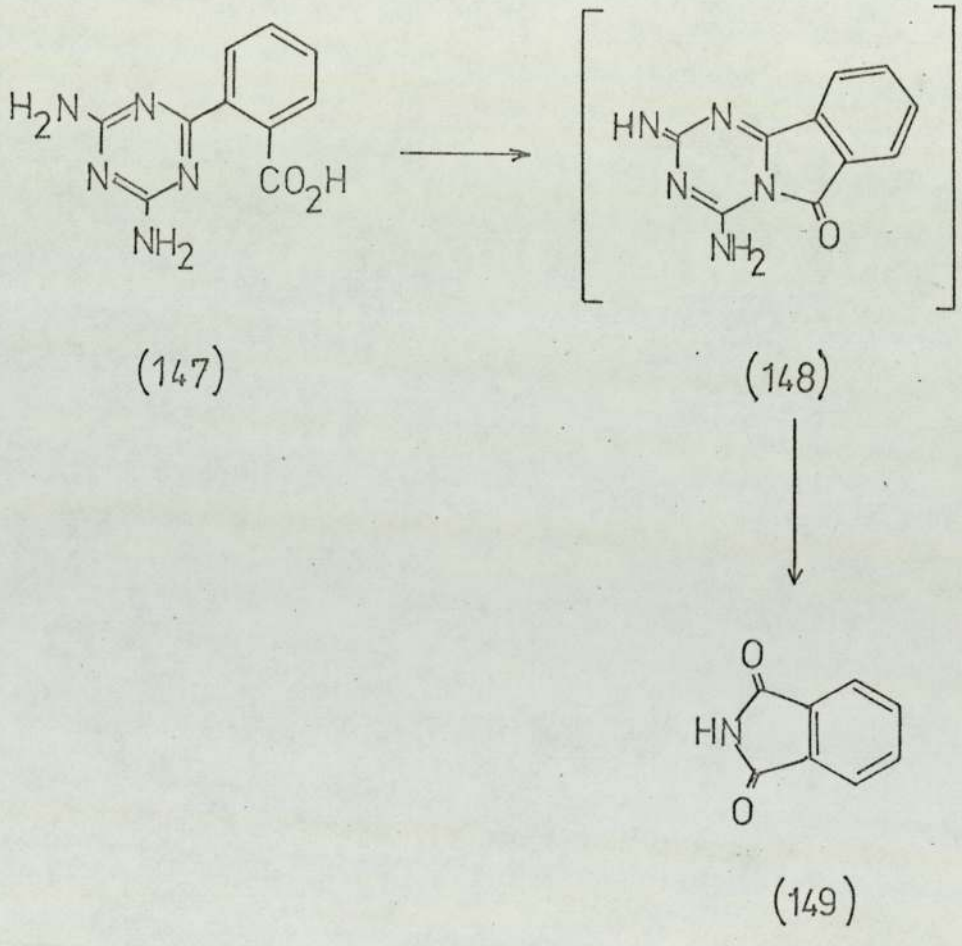


(143) (146)

Mackenzie[97] was unable to cyclise 2,4-diamino-6-(2-cyanophenyl)-1,3,5-triazine to the corresponding 1,3,5-triazino[2,1-a]isoindole by treatment of this compound with ethanol containing piperidine, with glacial acetic acid, or by sublimation but when the triazine was boiled in 2N hydrochloric acid and allowed to stand for 1 week phthalimide

(149) was obtained.

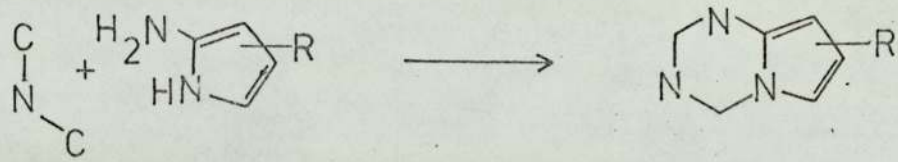
Initial hydrolysis of the cyano group to give 2-(4,6-diamino-1,3,5-triazin-2-yl)benzoic acid (147) was thought to occur and the 1,3,5-triazino[2,1-a]isoindolone (148) was proposed as a possible intermediate.



(147) (148) (149)

SYNTHESIS OF PYRROLO[1,2-a][1,3,5]TRIAZINES FROM 2-AMINO-PYRROLE PRECURSORS

The pyrrolo[1,2-b], [2,1-c], and [1,2-d][1,2,4] triazine systems have been synthesised from various substituted pyrrole derivatives, as discussed in the introduction, and the 8a-dimethylamino-2,4-dioxo-1,3-diaryl-perhydro-pyrrolo [1,2-a][1,3,5] triazines have been synthesised from 2-dimethyl-amino-Δ-pyrroline (page 5). A possible route from pyrrole derivatives to the pyrrolo[1,2-a][1,3,5] triazine system (151) would involve the prior synthesis of a 2-aminopyrrole (150) and addition of a C-N-C moiety to this.



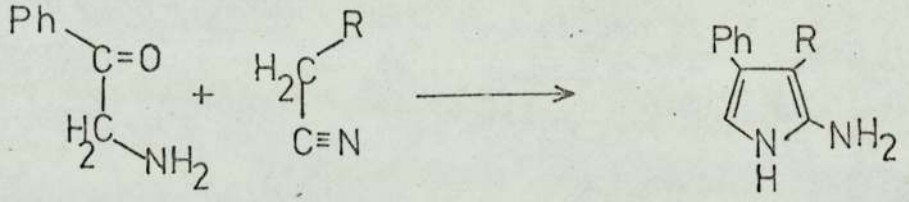
(150) (151)

(i) Synthesis of 2-aminopyrroles

2-Aminopyrrole itself is unknown and 2-aminopyrroles, in general, are unstable compounds, the most stable being those substituted derivatives containing electron-withdrawing groups, especially the di- and tri-phenyl compounds. The few 2-aminopyrroles that are known have been prepared by treatment of 5-pyrrolecarboxylic acid azides with hot 50% acetic acid[98,99], or by catalytic reduction of nitroso-[100], or nitro-[102] pyrroles.

Gewald[101], however, has reported a one-step synthesis of substituted 2-aminopyrroles by reaction of an ω-aminoketone

with malononitrile (153) in the presence of base, and this was repeated, using ω-aminoacetophenone (152) to afford 2-amino-3-cyano-4-phenylpyrrole (155). In order to provide a variety of 2-aminopyrrole precursors, benzyl cyanide, acetonitrile and ethyl cyanoacetate were used in this reaction, but only benzyl cyanide (154), which afforded 2-amino-3,4-diphenylpyrrole (156), reacted. The other nitriles yielded only 3,6-diphenyl-1,4-dihydropyrazine, formed by self-condensation of ω-aminoacetophenone.



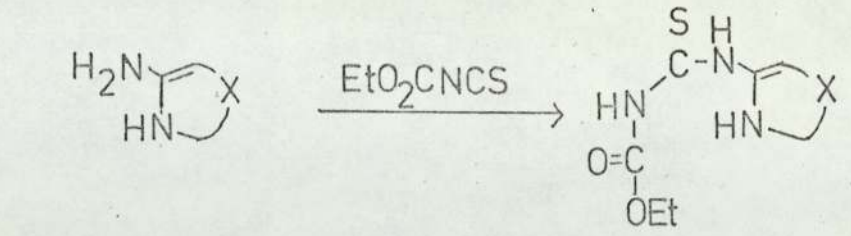
(153) R=CN
(154) R=Ph

(155) R=CN
(156) R=Ph

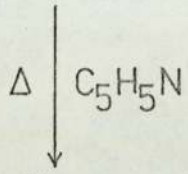
The 2-aminopyrroles (155-156) are stable when dry but decompose in warm organic solvents.

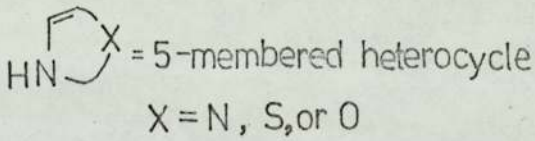
(ii) Reaction of 2-aminopyrroles with isocyanates

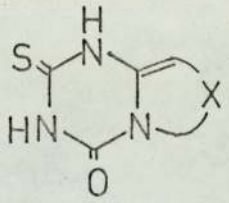
Isothiocyanates react with 2-aminopyrazoles, 2-aminotriazoles, 2-aminothiazoles and 2-aminooxazoles to give the 1,3-disubstituted ureas (157), which on heating with pyridine or triethylamine afford the corresponding bicyclic systems containing a triazine ring and a bridgehead nitrogen atom (158)[103]. 2-Aminobenzimidazole (159) and benzoyl isothiocyanate gave the benzimidazolotriazine (160).



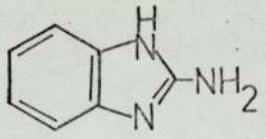
(157)



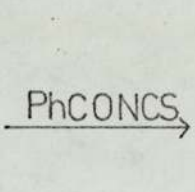


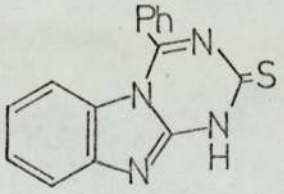


(158)



(159)





(160)

The reaction has not been reported to occur with 2-amino-pyrroles.

The final step of this reaction involves cyclisation to a ring nitrogen atom and thus involves the prior formation of the heterocyclic anion. In the pyrrole series this step will be much more difficult than the corresponding step in the five-membered di- or tri-azaaminoheterocycles since the extra-ring heteroatom will exert inductive and mesomeric

effects and thus make proton removal easier. This, plus the fact that 2-amino-4-ethyl-3,5-dimethylpyrrole and 2-amino-3,4-diethyl-5-methylpyrrole could not be acetylated, benzoylated or diazotised[98] (although it is not clear whether these failures were due to an inability to react or to instability) suggests that an analogous reaction with 2-aminopyrroles may present difficulties.

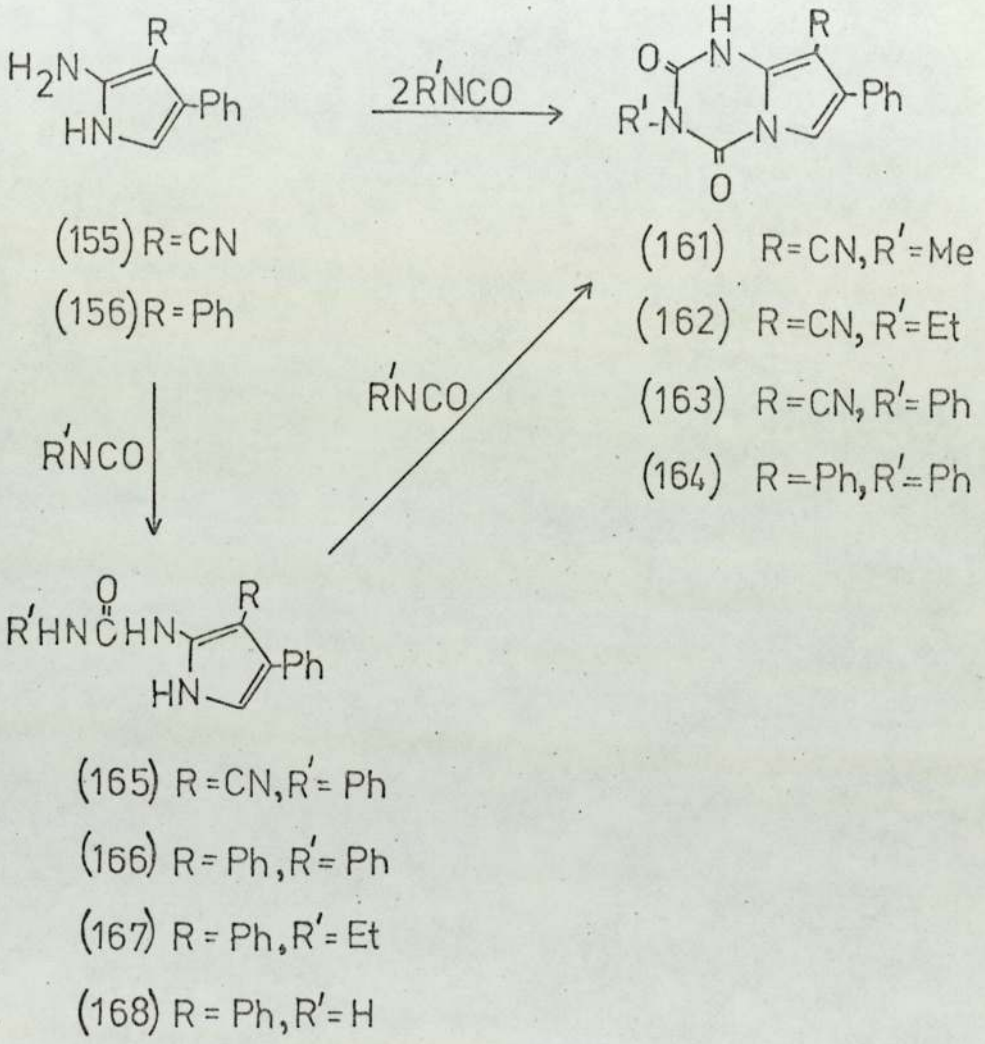
Reaction of 2-amino-3-cyano-4-phenylpyrrole (155) with methyl, or ethyl isocyanate in dry, refluxing pyridine afforded the corresponding 3-alkyl-8-cyano-7-phenylpyrrolo[1,2-a][1,3,5]triazines (161-162).

The yields were low (ca:20%) and much tarry material, from the decomposition of the aminopyrrole, was obtained. N,N'-dialkylureas, formed by the action of water on the isocyanates, were also isolated even when dry, freshly distilled solvents were used.

Reaction of 2-amino-3-cyano-4-phenylpyrrole (155) and 2-amino-3,4-diphenylpyrrole (156) with phenyl isocyanate afforded the corresponding pyrrolotriazines (163-164) in low yield (ca:10%).

1-Phenyl-3-(3-cyano-4-phenylpyrrol-2-yl)urea (165) was prepared by reaction of 2-amino-3-cyano-4-phenylpyrrole and phenyl isocyanate in benzene. When heated under reflux with phenyl isocyanate in dry pyridine this afforded 3,7-diphenylpyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione (163), and thus it is probable that such pyrrolylureas are intermediates in

the one-stage synthesis of pyrrolotriazines from 2-amino-pyrroles.



1-Phenyl-3(3,4-diphenylpyrrol-2-yl)urea (166), could not be induced to react with phenyl isocyanate in refluxing pyridine. 1-Ethyl-3-(3-cyano-4-phenylpyrrol-2-yl)urea could not be obtained, the reaction of ethyl isocyanate with the corresponding pyrrole giving only an intractable tar. Ethyl isocyanate and 2-amino-3,4-diphenylpyrrole in benzene afforded an unidentified mixture of compounds ($\underline{M}^+$, 319.169030,

$C_{20}H_{21}N_3O$;$\underline{M}^+$ 319.132921, $C_{19}H_{17}N_3O_2$) the infra-red spectra of which showed no C=O absorption. However, an attempted synthesis of 3-ethyl-7,8-diphenylpyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione by reaction of 2-amino-3,4-diphenylpyrrole in refluxing pyridine afforded a low yield of 1-ethyl-3-(3,4-diphenylpyrrol-2-yl)urea (167), together with the above unidentified mixture of compounds, but none of the required pyrrolotriazine.

Reaction of 2-amino-3,4-diphenylpyrrole (156) with potassium cyanate afforded 3-(3,4-diphenylpyrrol-2-yl)urea (168).

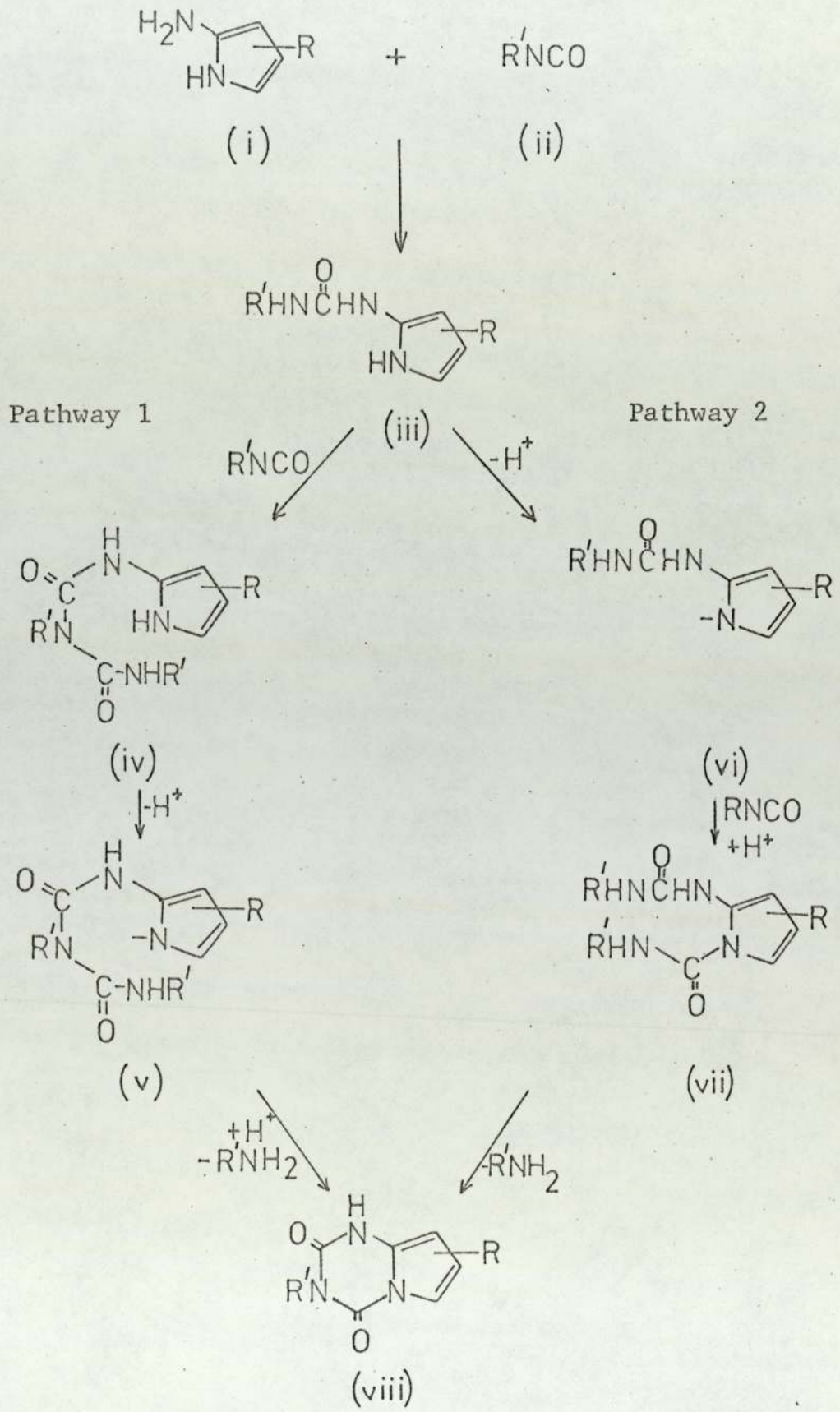
The mechanism outlined in scheme 7 is postulated for the synthesis of pyrrolo[1,2-a][1,3,5]triazindiones from 2-aminopyrroles.

The reaction can proceed via pathways 1 or 2 both of which involve the removal of a pyrrolyl N-H proton by the pyridine solvent, to give the reactive anions (v or vi). This step in the reaction sequence will be aided by the electron-withdrawing substituents on the pyrrole nucleus.

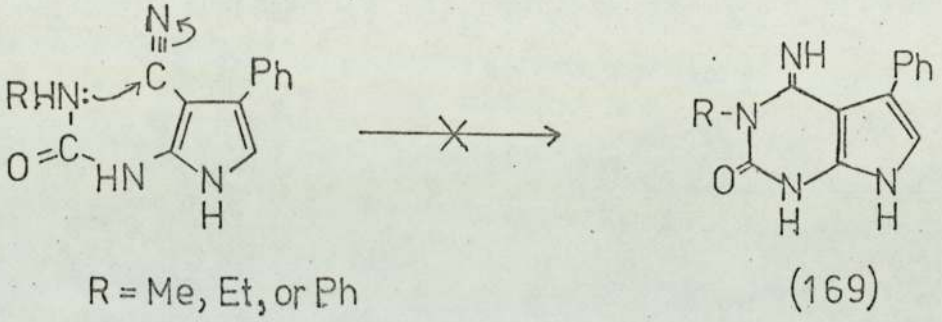
The steps (iii⟶ iv) and (vii⟶ viii) will depend upon the nucleophilicity of the attacking amide nitrogen atom, and thus this would explain the lower yields obtained when phenyl, rather than ethyl, or methyl, isocyanate is used, since this amide nitrogen atom will be less reactive in the phenyl substituted compounds than the alkyl substituted compounds.

No pyrrolopyrimidines of type (169) are isolated in the

Scheme 7

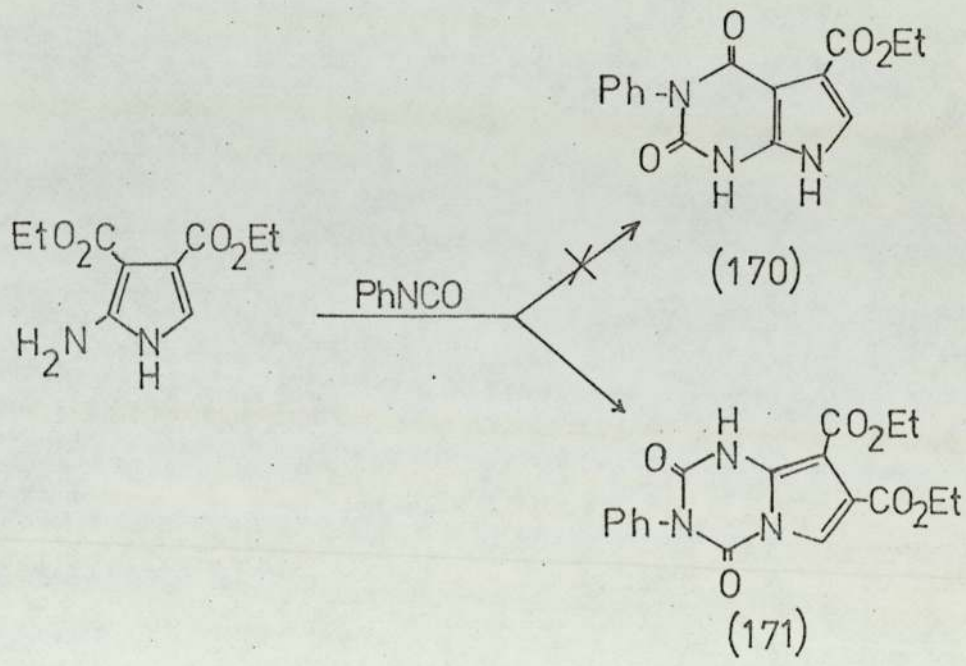


reaction of 2-amino-3-cyano-4-phenylpyrrole (155) with isocyanates, and in the attempted synthesis in these laboratories of the pyrrolopyrimidine (170), the pyrrolotriazine (171) was formed [104]. It is possible that the pyrrolopyrimidines could be formed by an intramolecular cyclisation of the pyrrolylurea intermediates as indicated below.



R = Me, Et, or Ph

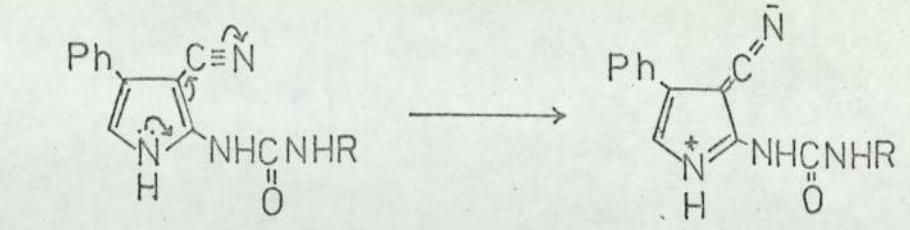
(169)



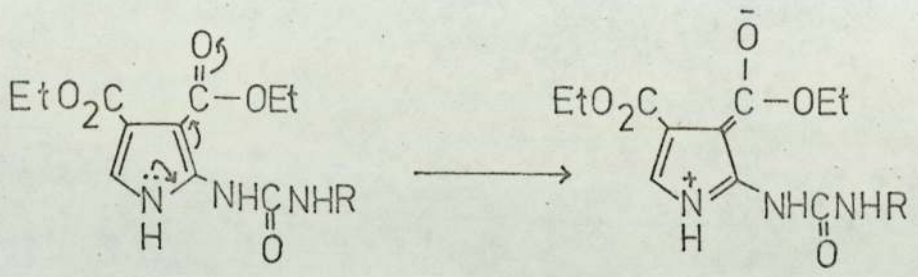
(170)

(171)

These findings suggest a deactivation of the reactive groups at the 3 position of the pyrrole ring which may possibly be attributed to the contributing forms (172) and (173) in the hybrid structures of the corresponding pyrroles.



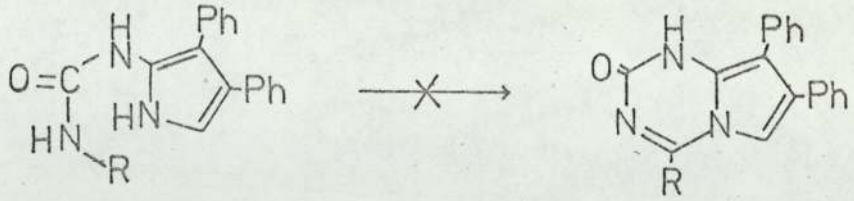
(172)



(173)

Reaction of 2-amino-3,4-diphenylpyrrole (156) with N-acetylurea, or p-nitrobenzoylurea, afforded the corresponding pyrrolylurea derivatives (174-175) but no evidence of the pyrrolotriazines (176-177). A similar reaction between 2-amino-3-cyano-4-phenylpyrrole (155) and acetylurea afforded a quantitative recovery of the acetylurea and a purple oil, suggesting the decomposition of the pyrrole occured faster than reaction with the urea.

1-(4-Nitrobenzoyl)-3-(3,4-diphenylpyrrol-2-yl)urea also failed to cyclise on treatment with triethylamine, diethylaniline or polyphosphoric acid, although treatment with triethylamine in acetic anhydride afforded 1-acetyl-2-acetylamino-3,4-diphenylpyrrole (178).

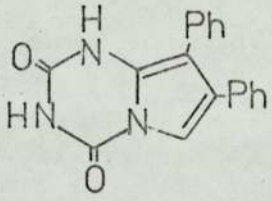


(174) R=COMe

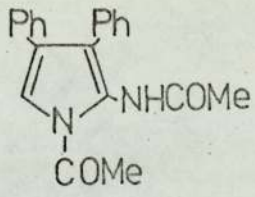
(175) R=COPhNO$_2$(p)

(176) R=Me

(177) R=PhNO$_2$(p)



(179)



(178)

The failure of these pyrrolylurea derivatives to cyclise may be due to the difficulty of anion formation, or to the lack of reactivity of the formed pyrrole anion. Cyclisation would involve an intramolecular nucleophilic attack by the pyrrolyl anion and the subsequent loss of water. However, the cyclisation step in the formation of the pyrrolotriazindiones from 2-aminopyrroles and isocyanates involves the loss of an amine (NH_2R) (page 74), which being a better leaving group than water will make cyclisation easier. The fact that reaction of 2-amino-3,4-diphenylpyrrole (156) with biuret in pyridine afforded an impure compound, the spectra of which were consistent with the pyrrolotriazine

structure (179), affords further evidence for this. As discussed in the introduction (page 10) pyrrole-2-carboxaldehyde formylhydrazones have been cyclised, by base-catalysed dehydration to give pyrrolo[1,2-d][1,2,4]triazines. The pyrroles used, however, contained no electron-withdrawing groups and their anions would therefore be more reactive than the pyrrolyl anions under consideration here.

The above facts indicate that it is anion reactivity which is the most important factor in cyclisations of this type, although ease of anion formation must also be involved.

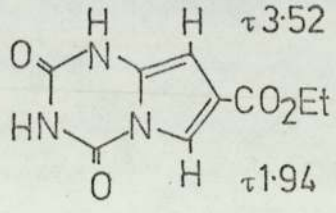
Other attempted preparations of pyrrolo[1,2-a][1,3,5] triazines from 2-aminopyrroles were treatment of 2-acetylamino-3-cyano-4-phenylpyrrole with formamide, and reaction of 2-amino-3,4-diphenylpyrrole with dicyandiamide. In all cases the starting material was recovered unchanged.

SPECTROSCOPIC PROPERTIES OF THE PYRROLO[1,2-a][1,3,5]TRIAZIN-2,4(1H,3H)-DIONES

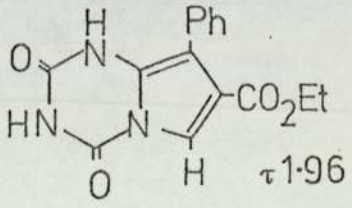
(i) Nuclear magnetic resonance spectroscopy

The 60MHz spectrum of ethyl 1,3-dimethylpyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-6-carboxylate (114) in $CDCl_3$, is given in figure 3 (page 80).

The pyrrole protons at positions 6 and 8 of 7-substituted pyrrolo[1,2-a][1,3,5]triazindiones occur as two doublets at approximately τ2.0 and τ4.0, although these occur at more deshielded positions (ca. τ 1.95 and τ 3.5 respectively) in trifloroacetic acid. The lower of these two resonances is attributed to the 6-H proton because of the deshielding effect of the adjacent pyrrolic nitrogen, and an examination of the spectra of ethyl 8-phenylpyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylate (102) and ethyl pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylate (101) confirms this assignment (values determined in CF_3COOH).



(101)



(102)

The coupling constant between the 6-H and 8-H protons is 2Hz (see figure 3), which is larger than the expected coupling

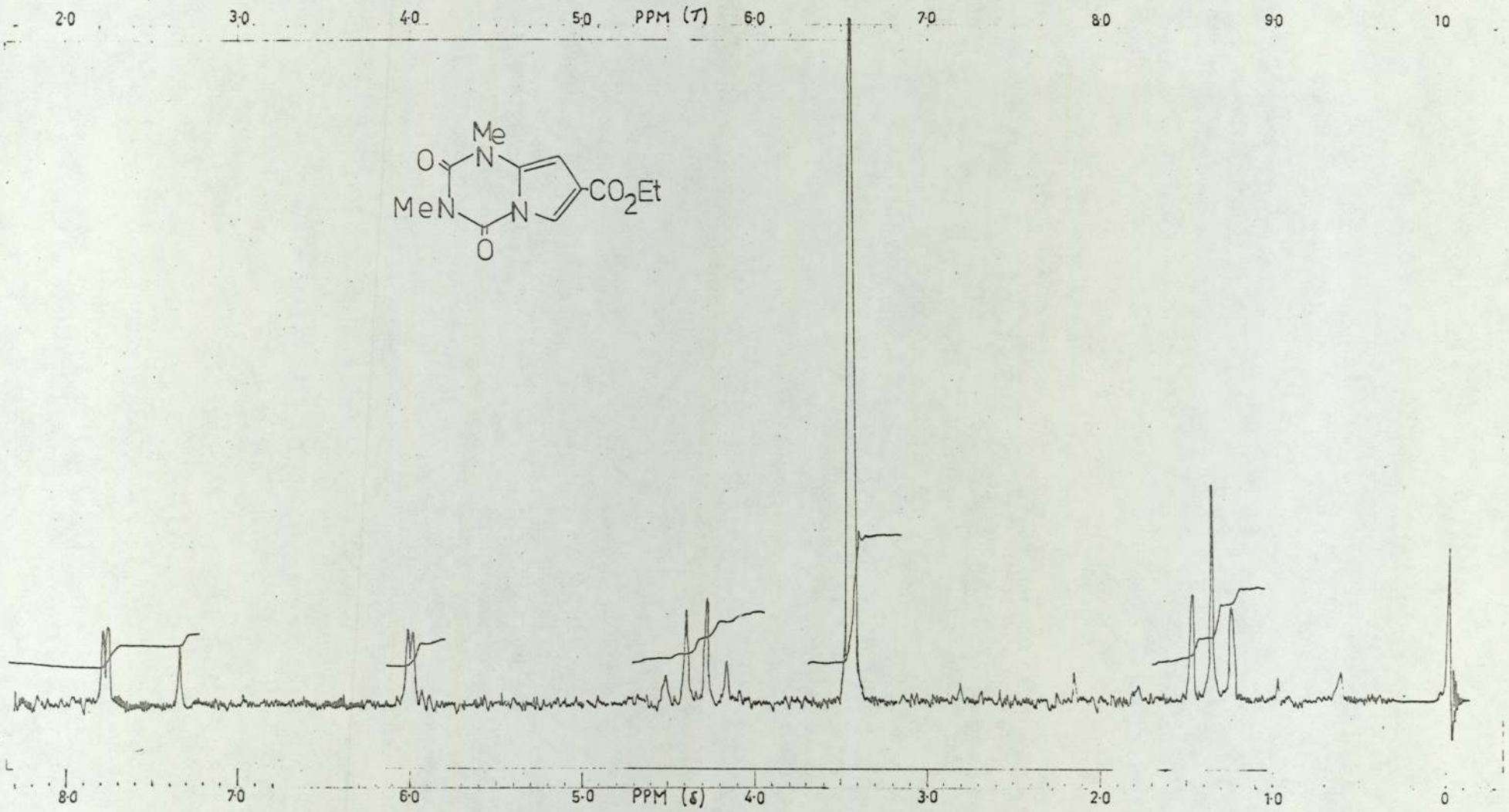

2·0
3·0
4·0
5·0
PPM (τ)
6·0
7·0
8·0
9·0
10
Me
N
O
MeN
N
O
CO2Et
8·0
7·0
6·0
5·0
PPM (δ)
4·0
3·0
2·0
1·0
0

Figure 3

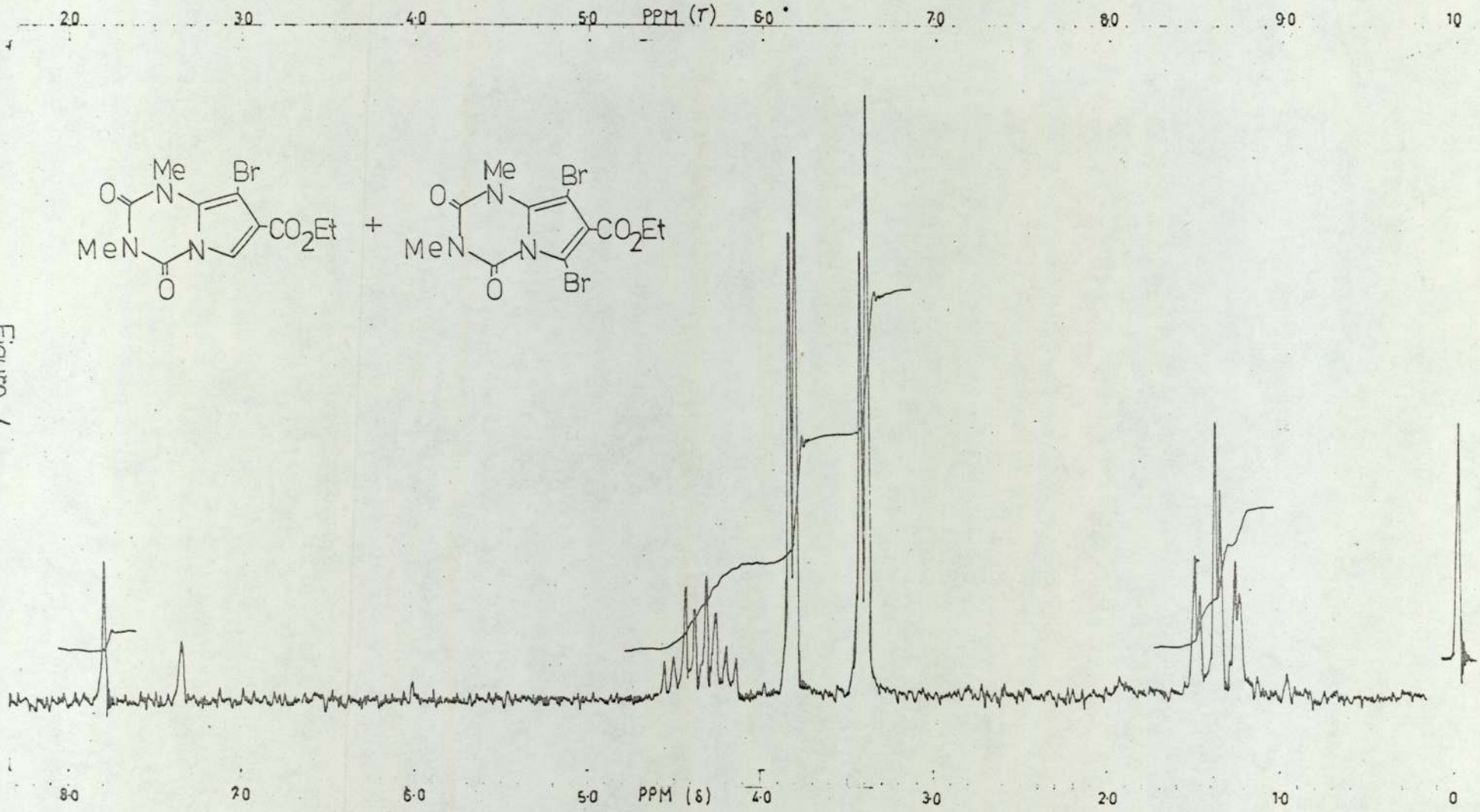
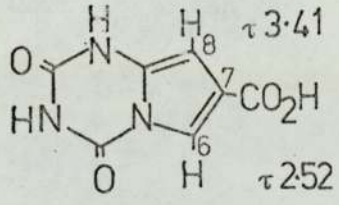

2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
Me
Br
O
N
MeN
N
O
CO2Et
+
Me
Br
O
N
MeN
N
O
Br
CO2Et
8·0
7·0
6·0
5·0
PPM (δ)
4·0
3·0
2·0
1·0
0

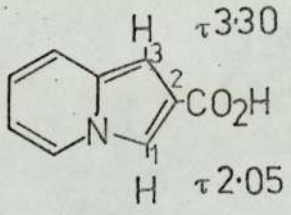
Figure 4

constant of the αβ' protons of pyrroles which lie within the range 1.35-1.5Hz. A comparison of the n.m.r. spectra of pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylic acid (111), indolizine-2-carboxylic acid (180), and 3-ethoxycarbonylpyrrole (181) shows differences in both the coupling constants of the relevant protons, and the chemical shift positions of these protons. These effects can be explained by the differing degrees of electron delocalisation in the various heterocycles, and previous workers have stated that it is not possible to predict coupling constants between ring hydrogen nuclei in condensed pyrroles from a knowledge of analogous values in pyrroles[106].



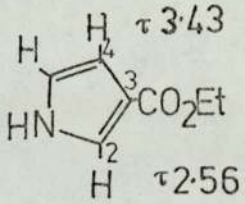
$J_{6,8}$ = 2Hz

(111)[a]



$J_{1,3}$ = 1Hz

(180)[a,c]



$J_{2,4}$ = 1·4 Hz

(181)[b,d]

(a) Values determined in $[(CD_3)_2SO]$

(b) Values determined in 26% solution in dioxan.

(c) Reference 107

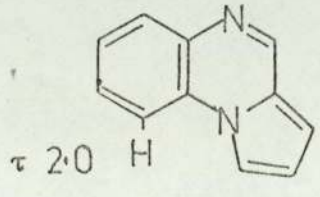
(d) Reference 108

The n.m.r. spectrum of a mixture of mono- and dibrominated products produced by treatment of ethyl 1,3-dimethylpyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylate (114) with N-bromosuccinimide in chloroform for 1h is given in figure 4. The presence of a resonance at τ 2.19, now

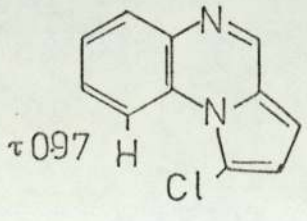
uncoupled, attributed to the 6-H proton and the absence of the 8-H proton which absorbs at τ 4.0 in the unbrominated compound indicates that the mixture is composed of ethyl 8-bromo-1,3-dimethylpyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylate (115) and ethyl 6,8-dibromo-1,3-dimethyl-pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylate (116).

The methyl protons at position 1 of the unbrominated pyrrolotriazindione occur as a singlet at τ 6.54 but are deshielded by the presence of a bromo-group at position 8 and in ethyl 8-bromo-1,3-dimethylpyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylate (115) absorb at τ 6.16. The methyl protons at the 3- position are unaffected. The introduction of a second bromo-group, into the 6 position, causes a small downfield shift, of 1.5Hz, of both the N-1 and N-3 methyl protons.

A similar deshielding effect has been observed in the pyrroloquinoxaline series[109]. The 9-H proton of the unsubstituted compound (182) is deshielded by the presence of a chloro substituent (183) at position 1.



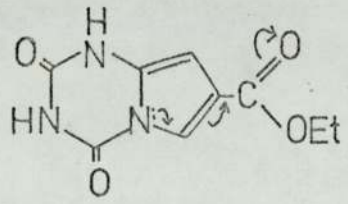
(182)



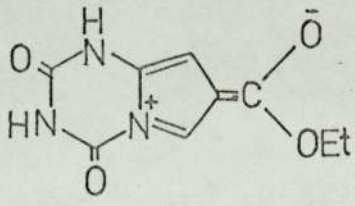
(183)

(ii) Infra-red spectroscopy

The infra-red spectra, in the region 1600-1800cm^{-1}, of the pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-diones, containing a carbonyl function in the 7- position show a broad, ill-defined, carbonyl stretching band at 1690-1730cm^{-1}. No carbonyl absorbances as high as those of the 1,3,5-triazin-2,4(1H,3H)-diones (page 30) are exhibited. The ester carbonyl stretching vibration which absorbs at ca. 1690cm^{-1}, this value being obtained by comparison with the spectrum of pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione (109), cannot be distinguished from the amide C=O stretches. The low frequency of this absorption can be explained by the presence of contributing forms such as (184) in the hybrid structure.



(101)



(184)

Similar observations have been made in the pyrrole series[110]. The 3-alkyl(aryl)-8-cyano-7-phenylpyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-diones exhibit two carbonyl stretching bands at ca. 1740cm^{-1} and 1690cm^{-1}. The lower of the two bands is the most intense, as in the 3-substituted-1,3,5-triazin-2,4(1H,3H)-diones (page 31).

Ethyl 1,3-dimethylpyrrolo[1,2-a][1,3,5]triazin-2,4

(1H,3H)-dione-7-carboxylate (114) also exhibits two carbonyl bands at 1735cm^{-1} and 1710cm^{-1}. The higher, less intense, band is associated with an amide C=O stretch, and the lower band consists of both ester C=O and amide C=O stretches.

The pyrrolotriazindiones also exhibit bands which may be attributed to pyrrole-ring stretching vibrations. Thus the pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-diones containing an acid or an ester function at position -7 show bands at ca. 1550cm^{-1} and 1500cm^{-1}. Previous workers[110] have reported that pyrrole esters show ring vibration bands at ca. 1565 and 1550cm^{-1}. Pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione (109) exhibits two bands, in the region 1500-1600cm^{-1}, at 1560cm^{-1} and 1525cm^{-1}. The remaining pyrrolotriazines studied, containing phenyl- or cyanosubstituents in the pyrrole ring, exhibit small bands at 1580cm^{-1} and 1560cm^{-1}, and a larger band at ca. 1510cm^{-1}.

(iii) Ultra-violet spectroscopy

The u.v. spectra of some pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-diones are given in Table 4.

All the compounds show an intense absorption band at ca. 220-240nm., which is unaffected by the addition of acid, but shows a slight bathochromic shift (2-3nm) on addition of base in all but the N,N'-dimethyl compound. This absorption is attributed to the pyrrole moiety. Pyrroles containing carbonyl groups at the 3 position show a bathochromic shift of the pyrrole absoprtion of ca. 30-50nm (from 208nm) with

the appearance of a second intense absorption band in the region 240-280nm[111], which shifts to longer wavelengths with increasing conjugative power of the substituent.

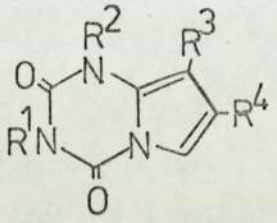


Table 4

Compound	$\lambda_{max.}$ (nm)	ε	$\lambda_{max.}$ (nm)	ε
(102) R^1=R^2=H, R^3=Ph, R^4=CO_2Et	227	5,517	267	1,430
(112) R^1=R^2=R^3=H, R^4=CO_2Me	219	4,056	288.5	367
(114) R^1=R^2=Me, R^3=H, R^4=CO_2Et	221	8,638	284	1,000
(162) R^1=Et, R^2=H, R^3=CN, R^4=Ph	237	8,035	279	2,679
(185)* R^1=Ph, R^2=H, R^3=R^4=CO_2Et	222	8,194	267	2,783

* For preparation of this compound see Ref. 104.

The pyrrolotriazines show a small band at ca. 250-260nm which appears as a shoulder of the larger absorption. This band is most obvious in the N,N'-dimethyl compound (114).

Addition of base causes a large bathochromic shift (ca. 15-25nm), accompanied by an increase in intensity, of the

longer wavelength, less intense band, for all but the N,N'-dimethyl compound , thus indicating this band to be associated with the triazine ring amide groups. In the presence of acid the longer wavelength band is shifted slightly to shorter wavelengths (2-3nm) with an increase in intensity for those compounds having N-alkyl substituents (i.e. compounds 114, 162, and 185).

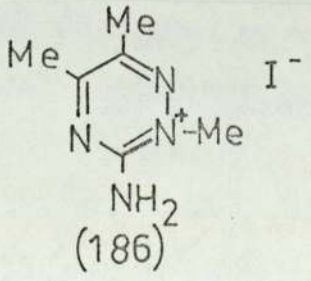
The mass spectra of the pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-diones are discussed elsewhere (page 109).

ATTEMPTED SYNTHESIS OF PYRROLO[2,1-f][1,2,4]TRIAZINES FROM ASSYMETRICAL TRIAZINE PRECURSORS

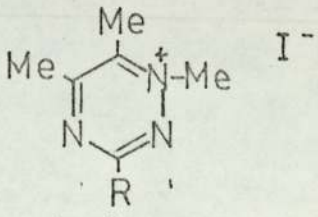
Several alkylaryl-1,2,4-triazines have been quaternised[112] and it was intended to extend the scope of these reactions to include quaternisation by α-halogeno-ketones. Subsequent cyclisation of the products to pyrrolo[2,1-f][1,2,4]triazines, by an extension of the Tschitschibabin indolizine synthesis[34,35,36], was envisaged.

(i) Quaternisation of 1,2,4-triazines with alkyl halides

Reaction of 3-amino-5,6-dimethyl-1,2,4-triazine with methyl iodide, in refluxing methanol, afforded a low yield (13%) of a yellow quaternary salt (186), and much dark green, unidentified material. Milder conditions resulted in the recovery of the starting material. Previous workers[113] have shown that 1,2,4-triazines, with a 3-amino function form N-2-oxides, and thus it is suggested that quaternisation will also occur at N-2. Later work, describing the synthesis of the imidazo[1,2-b][1,2,4]triazines (page 91), showed that quaternisation with phenacyl bromide occurs at N-2.



(186)



(187) R = SMe
(188) R = Ph

The quaternary salts (187-188) were obtained in good yields as red-bronze coloured compounds by the action of

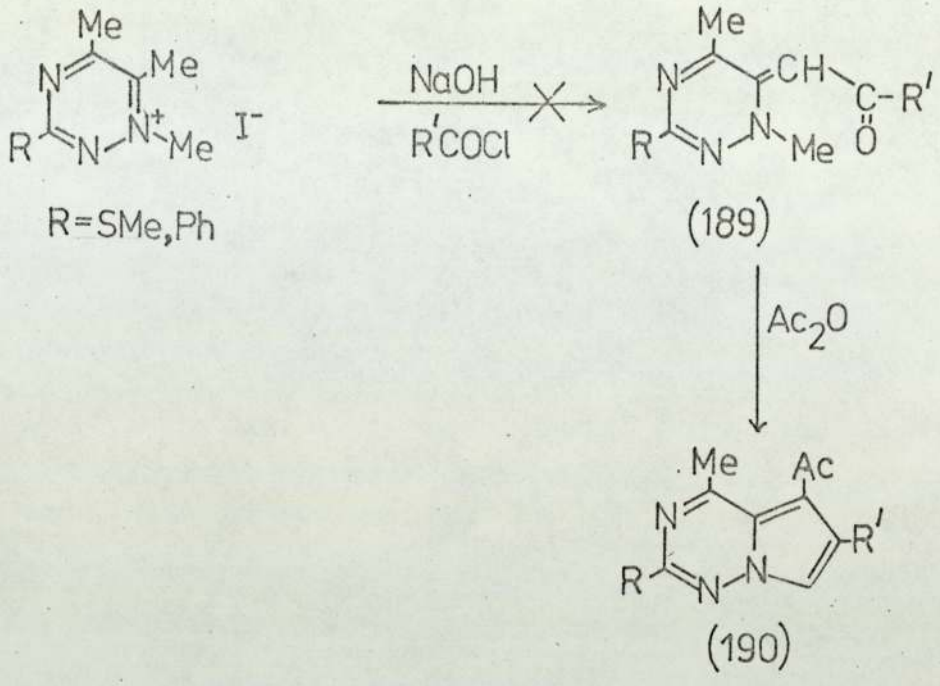
methyl iodide on 5,6-dimethyl-3-methylthio- and 5,6-dimethyl-3-phenyl-1,2,4-triazine, respectively. N-oxidation of 3-unsubstituted- and 3-methoxy-1,2,4-triazines occurs at position 1[113], and thus the quaternary salts were assumed to have the respective formulae (187-188).

Atkinson and Cossey[112], working on the quaternisation of 1,2,4-triazines containing alkyl and aryl substituents, made the observation that compounds quaternised at N-2 are colourless, whilst the corresponding N-1 substituted isomers are red compounds. Their attempts to confirm this hypothesis were inconclusive, though the results would seem to agree with the findings of the present work.

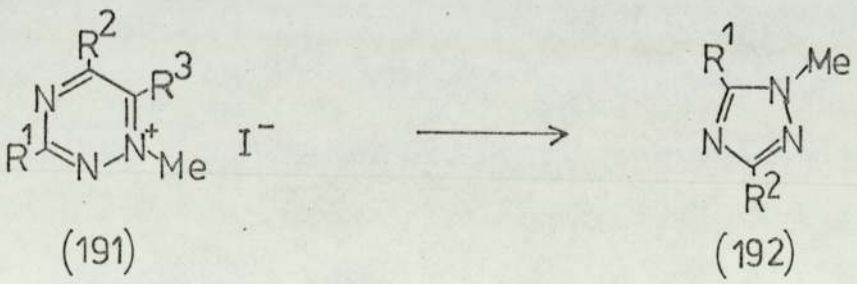
The reaction conditions for the synthesis of the quaternary salts (187-188) are critical since, in the presence of air, organic solvents, or heat, the reaction mixtures rapidly darkened and became oily.

The triazinylmethiodides (187-188) whilst being fairly stable crystalline solids, decomposed in warm organic solvents, but even in the crystalline state 1,5,6-trimethyl-3-methylthio-1,2,4-triazinium iodide (187) smelt strongly of methyl mercaptan.

Melton and Wibberley[114] have shown that indolizines can be prepared by an intramolecular aldol-type condensation of a suitably substituted acyl- or ethoxycarbonyl-methine. It was thus hoped that this method could be extended to the synthesis of the pyrrolo[2,1-*f*][1,2,4]triazine ring system (190).



No methines of type (189) could be isolated by the action of base on the quaternary salts. However, a recent publication, giving no experimental details, claims that the triazoles (192), are formed by the action of base on the quaternary salts (191)[115].



(191) (192)

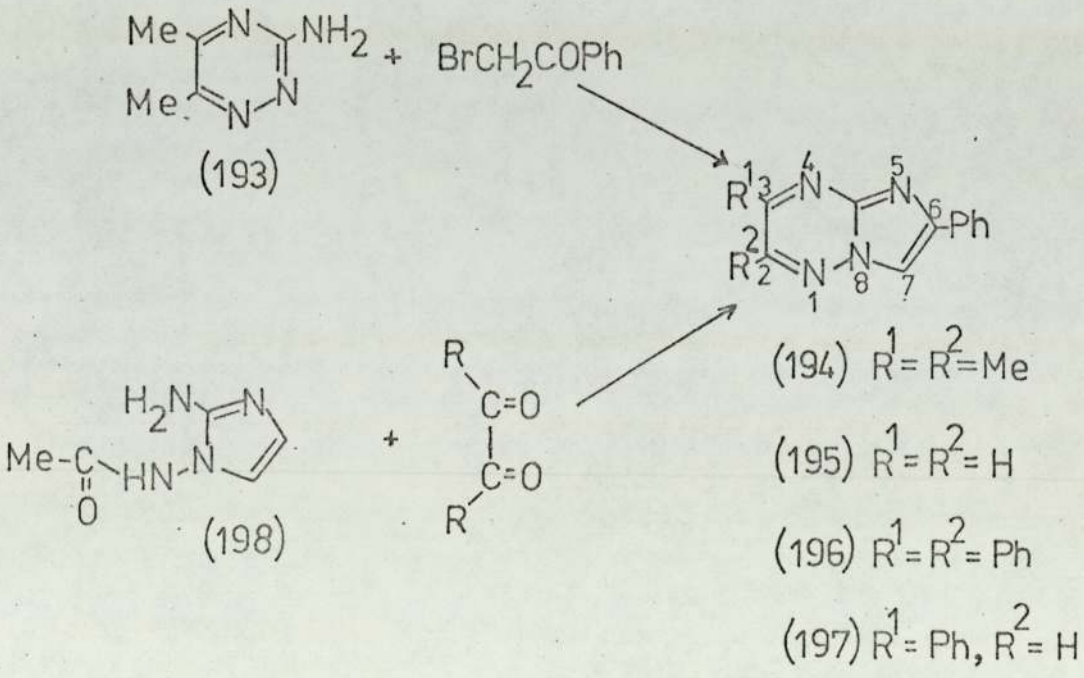
R^1 = OMe, SMe, H
R^2 = H, Me, Ph
R^3 = H, Me, Ph

6-Methyl-1,2,4-triazin-3,5(2H,4H)-dione failed to react with methyl iodide in dimethylformamide, or with

phenacyl bromide, or ethyl bromopyruvate in refluxing alcoholic solvents.

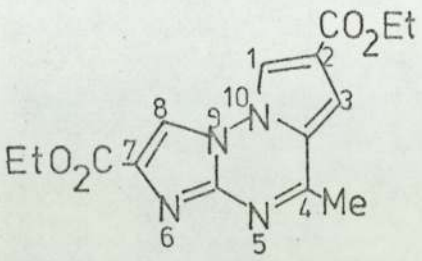
(ii) Reaction of 1,2,4-triazines with α-halogeno-ketones

3-Amino-5,6-dimethyl-1,2,4-triazine (193) and phenacyl bromide, in the presence of base ($NaHCO_3$), afforded 2,3-dimethyl-6-phenyl imidazo[1,2-b][1,2,4]triazine (194). In the absence of base the imidazotriazine hydrobromide was obtained. This reaction has been well investigated and the imidazo[1,2-b][1,2,4]triazines are the subject of many papers[116-117] and patents[118-121]. An independant synthesis of the system from 2-amino-1-acetamido-4-phenylimidazole (198) confirmed the structure of the compounds[116].

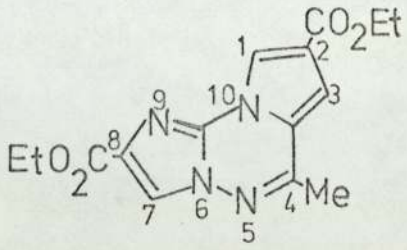


Reaction of 3-amino-5,6-dimethyl-1,2,4-triazine (193) with ethyl bromopyruvate, however, gave a tricyclic product which was identified on the basis of its infra-red, mass

and n.m.r. spectra, and analytical data, as a pyrroloimidazotriazine of structure (199) or (200).



(199)



(200)

The n.m.r. spectrum of the tricyclic product (199) or (200) is given in figure 5.

It is interesting to compare the coupling constant of the 1-, and 3-protons (J=1.2Hz), which is in the accepted range for the coupling constant of the equivalent protons of pyrroles[106], with that of the 6-, and 8-protons of the pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-diones (J=2Hz) (page 79). Whether isomer (199) or (200) is produced in the reaction cannot, however, be determined by the information gained from the n.m.r. spectrum.

The reaction is vigorous and occurs at room temperature in organic solvents, accompanied by the production of intractable material. In the absence of solvent, deep blue, presumably polymeric, oils are obtained.

When two equivalents of ethyl bromopyruvate were used in an attempt to improve the yields less of the tricyclic

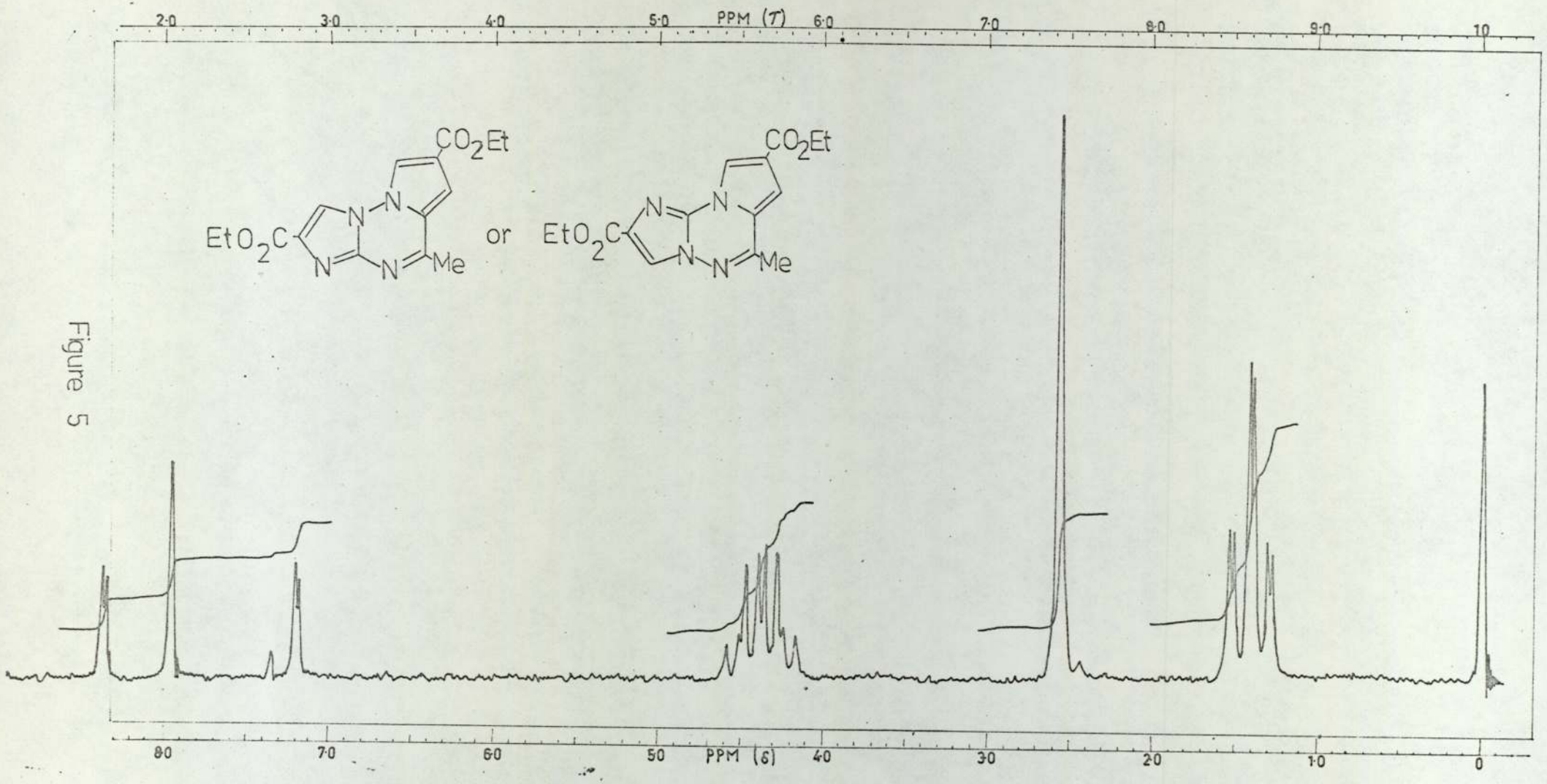

2·0
3·0
4·0
5·0
PPM (τ)
6·0
7·0
8·0
9·0
10
CO2Et
EtO2C
N
N
N
N
Me
or
CO2Et
EtO2C
N
N
N
N
Me
8·0
7·0
6·0
5·0
PPM (δ)
4·0
3·0
2·0
1·0
0

Figure 5

product was obtained, and no other identifiable products were isolated. In the presence of sodium bicarbonate none of the pyrroloimidazotriazine was isolated.

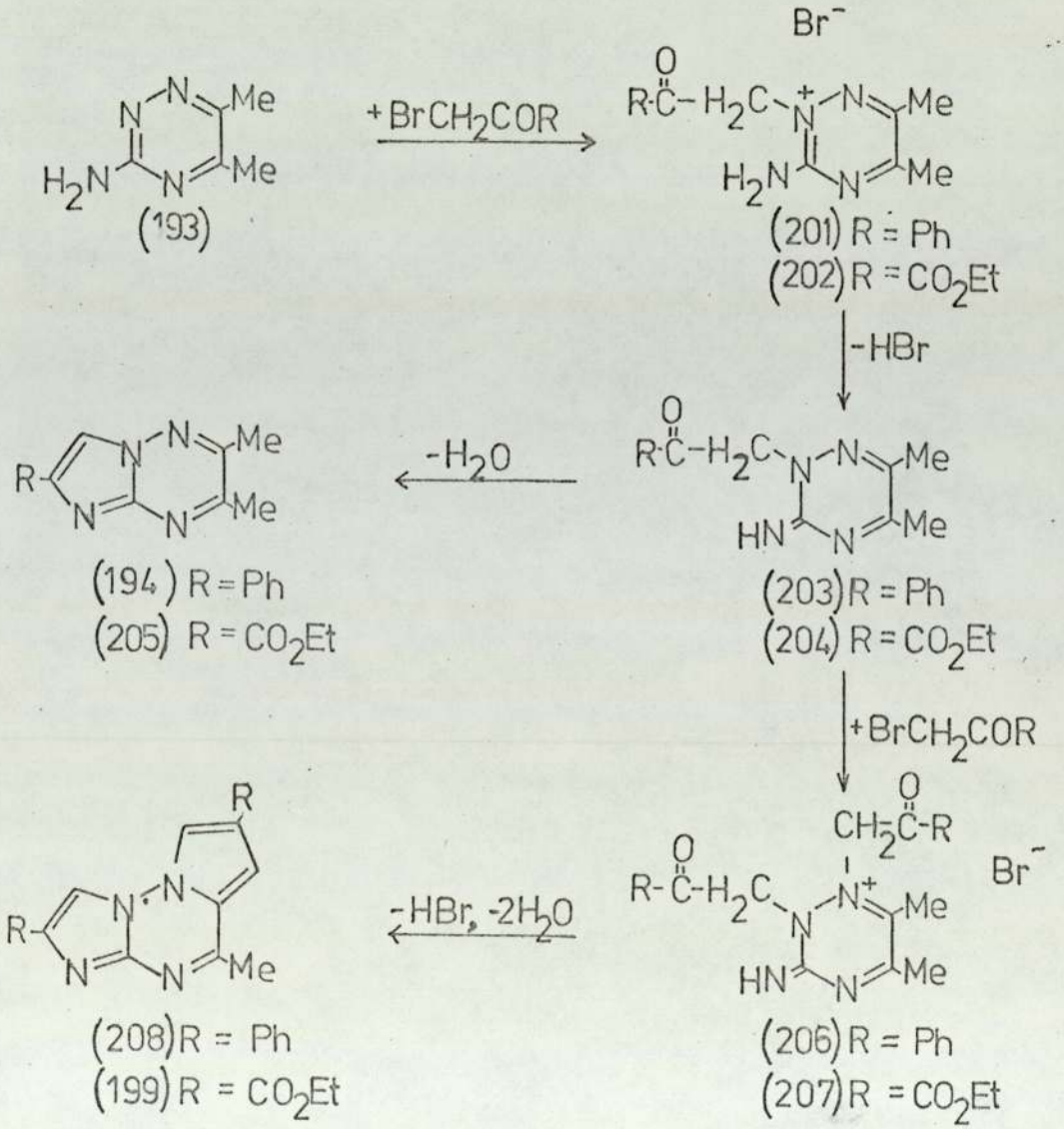
2-Amino-5,6-dimethyl-1,2,4-triazine and two equivalents of phenacyl bromide afforded only the imidazotriazine (194) and the reaction of the aminotriazine and ethyl bromopyruvate became even more intriguing with the discovery that 2,3-dimethyl-6-phenylimidazo[1,2-b][1,2,4]triazine (194) did not react with ethyl bromopyruvate in refluxing organic solvents. 2,3-Dimethyl-6-phenylimidazo[1,2-b][1,2,4]triazine (194) was however quaternised, in low yield (10%), with methyl iodide in refluxing methanol, though it was not possible to show the position of substitution.

No products could be isolated from the reaction of bromoacetaldehyde with 3-amino-5,6-dimethyl-1,2,4-triazine.

It has been suggested[117-119] that quaternisation of the imidazotriazine system occurs at position 1, and that styrylation of the methyl group at position 2 is possible. These facts would support the structure (199) for the tricycle, although the absence of any bicyclic products in the reaction, and the rapidity of the reaction compared to the difficulty of quaternisation of the imidazotriazines, suggest that prior formation of a bicyclic intermediate is unlikely.

A more reasonable explanation can be envisaged by a consideration of the possible intermediate (203-204),

formed by the removal of HBr from the quaternary salt (201-202). A second molecule of the triazine will help by acting as a catalyst for this, but the attempted use of sodium bicarbonate as a catalyst resulted in the recovery of the starting material, presumably since this base reacted preferentially with ethyl bromopyruvate. Such an intermediate could cyclise to give (194-205), or react with a second molecule of α-halogeno-ketone to give the quaternary salts (206-207).

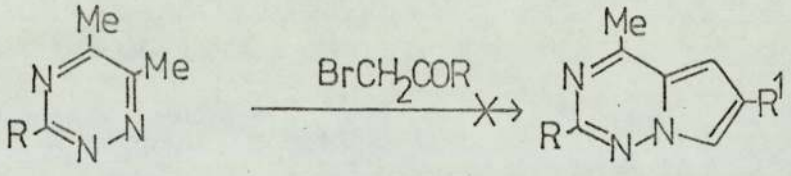


Cyclisation of (203) to 2,3-dimethyl-6-phenylimidazo [1,2-b][1,2,4]triazine (194) is the faster reaction, but in view of the greater reactivity of ethyl bromopyruvate both cyclisation of (204) and further quaternisation of (204) will be faster than the comparable reactions with phenacyl bromide. It is also possible that quaternisation to give (207) may occur more rapidly than cyclisation, thus resulting in a tricyclic product (199).

The site of quaternisation of the N-pyruvyl- compound (204) must decide the final structure of the compound. The intermediate (204) has a fixed bond structure and the relative basicities of the N-1 and N-4 atoms will depend on the inductive effects of the various substituents. It may be supposed that the inductive effect of the C=N moiety will render the nitrogen atom at position 4 the least basic, and thus quaternisation may be predicted to occur at N-1 to give diethyl 4-methylpyrrolo[2,1-f]imidazo[1',2'-b][1,2,4] triazine-2,7-dicarboxylate, (199) rather than the isomeric diethyl 4-methylpyrrolo[1,2-d]imidazo[1',2'-b][1,2,4]triazine-2,8-dicarboxylate (200).

It must be noted that no tricyclic products have been reported in the synthesis of imidazo[1,2-b]pyridazines from 3-amino-6-methylpyridazine and α-halogeno-ketones or bromoacetaldehyde[123]. Ethyl bromopyruvate has not been used in this synthesis, but this may suggest that the quaternisation of the imino compound (204) occurs at N-4.

5,6-Dimethyl-3-methylthio-1,2,4-triazine (209) and phenacyl bromide did not react when stirred in ether at room temperature, but when stirred in the absence of solvent the starting material (30%) was recovered and much polymeric material was formed. All other attempts to prepare 1-methyl-3-methylthio-7-phenylpyrrolo[2,1-f][1,2,4]triazine (211) by the above reaction, or the 7-carbethoxy-derivative (212), resulted in the formation of intractable oils.

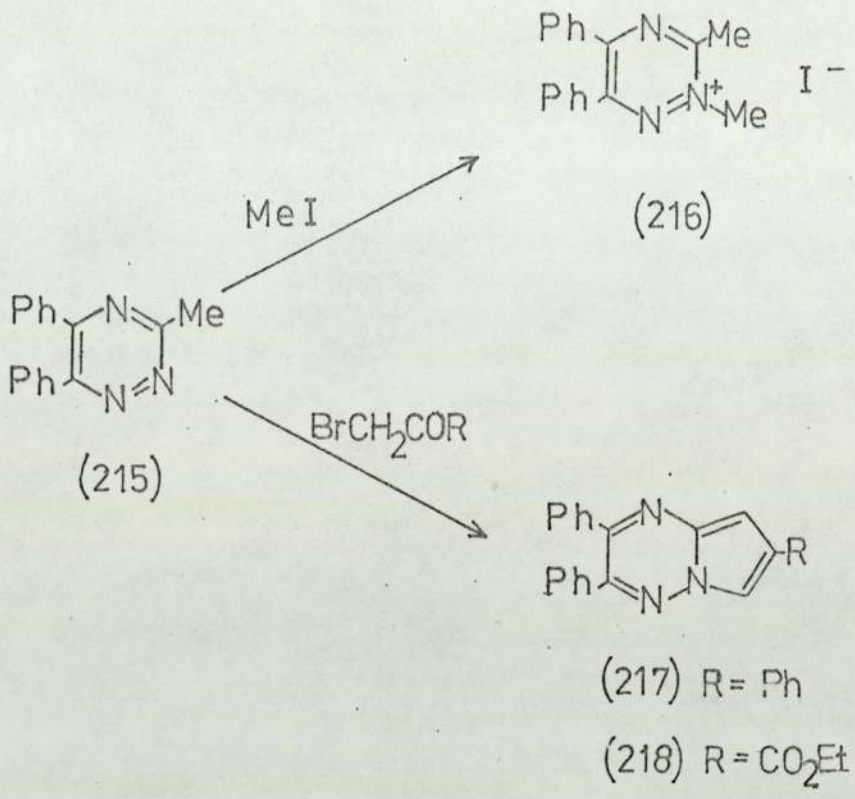


(209) R = SMe
(210) R = Ph

(211) R = SMe, R = Ph
(212) R = SMe, R = CO_2Et
(213) R = R = Ph
(214) R = Ph, R = CO_2Et

The reaction of 5,6-dimethyl-3-phenyl-1,2,4-triazine (210) with ethyl bromopyruvate or phenacyl bromide similarly gave none of the required pyrrolotriazines (213-214). The starting materials (209-210) were recovered, or when stronger reaction conditions were used, intractable oils.

Atkinson and Cossey[112] have shown that 3-methyl-5,6-diphenyl-1,2,4-triazine (215) undergoes quaternisation with methyl iodide to give 2,3-dimethyl-5,6-diphenyl-1,2,4-triazine (216) as a stable colourless compound.



Reaction of the triazine (215) with ethyl bromopyruvate or phenacyl bromide might thus be expected to give the 7-substituted pyrrolo[1,2-b][1,2,4]triazines (217-218). Phenacyl bromide and 3-methyl-5,6-diphenyl-1,2,4-triazine, however, afforded a mixture of the unreacted triazine, its hydrobromide salt, phenacyl bromide, and an unidentified red oil, the infra-red spectrum of which indicated the presence of a C≡N grouping and a carbonyl function. In the presence of sodium bicarbonate the starting material was recovered in quantitative yield. The attempted synthesis of the pyrrolotriazine (218) also afforded a mixture of the starting material and its hydrobromide salt, although an n.m.r. spectrum of the remaining brown mother liquors, though poorly

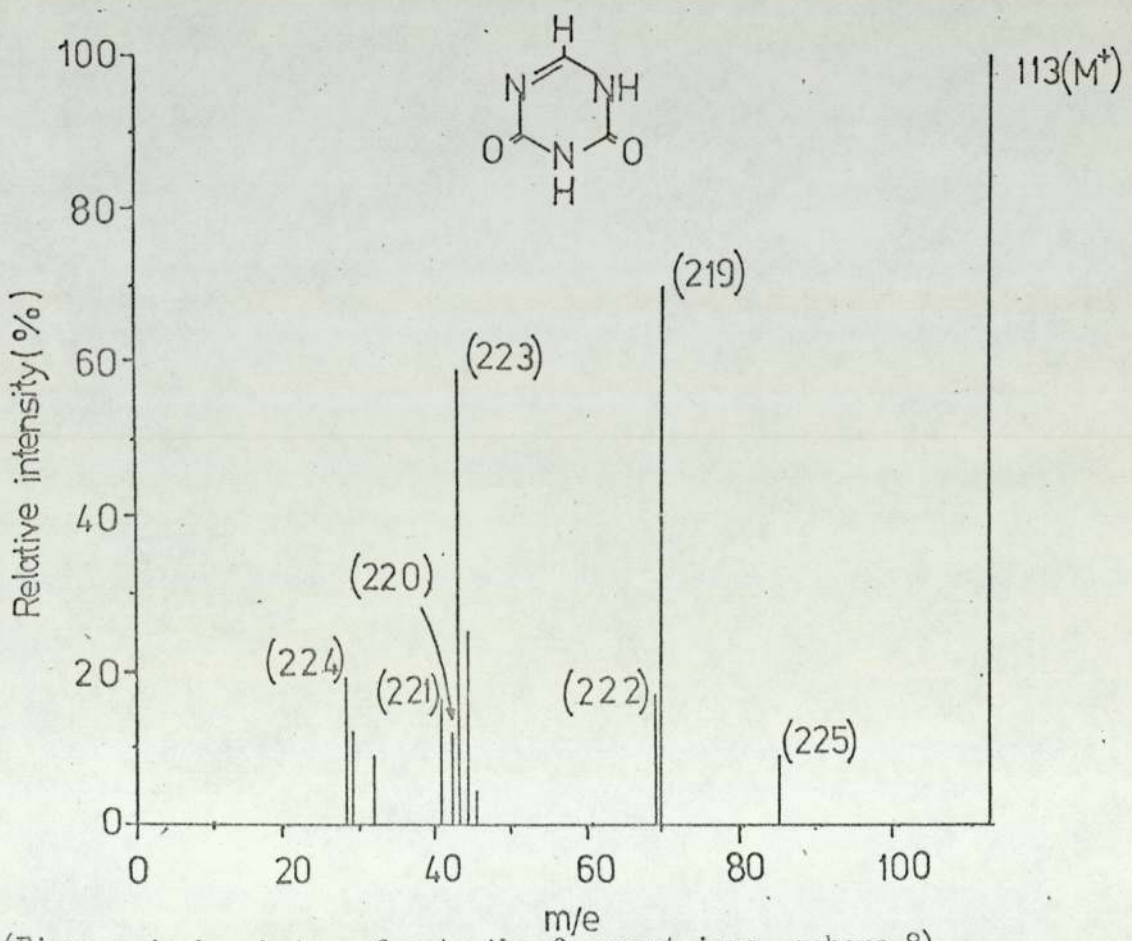
resolved, indicated the presence of ester protons and aromatic protons, but no resonance attributable to the 3-methyl protons of the starting material was observed.

MASS SPECTRA

The mass spectra of several 1,3,5-triazines, pyrrolyl-ureas, pyrrolo[1,2-a][1,3,5]triazines, and 1,2,4-triazines and their derivatives are recorded and an attempt is made to show possible common pathways of fragmentation for all these classes of compounds. Postulation of fragmentation patterns is in several cases based upon ion source determinations and accurate mass measurements.

Relative abundances are quoted to 3 % of the base peak unless ions of less than that intensity are important in the fragmentation. Transitions supported by metastable peaks are denoted by an asterisk.

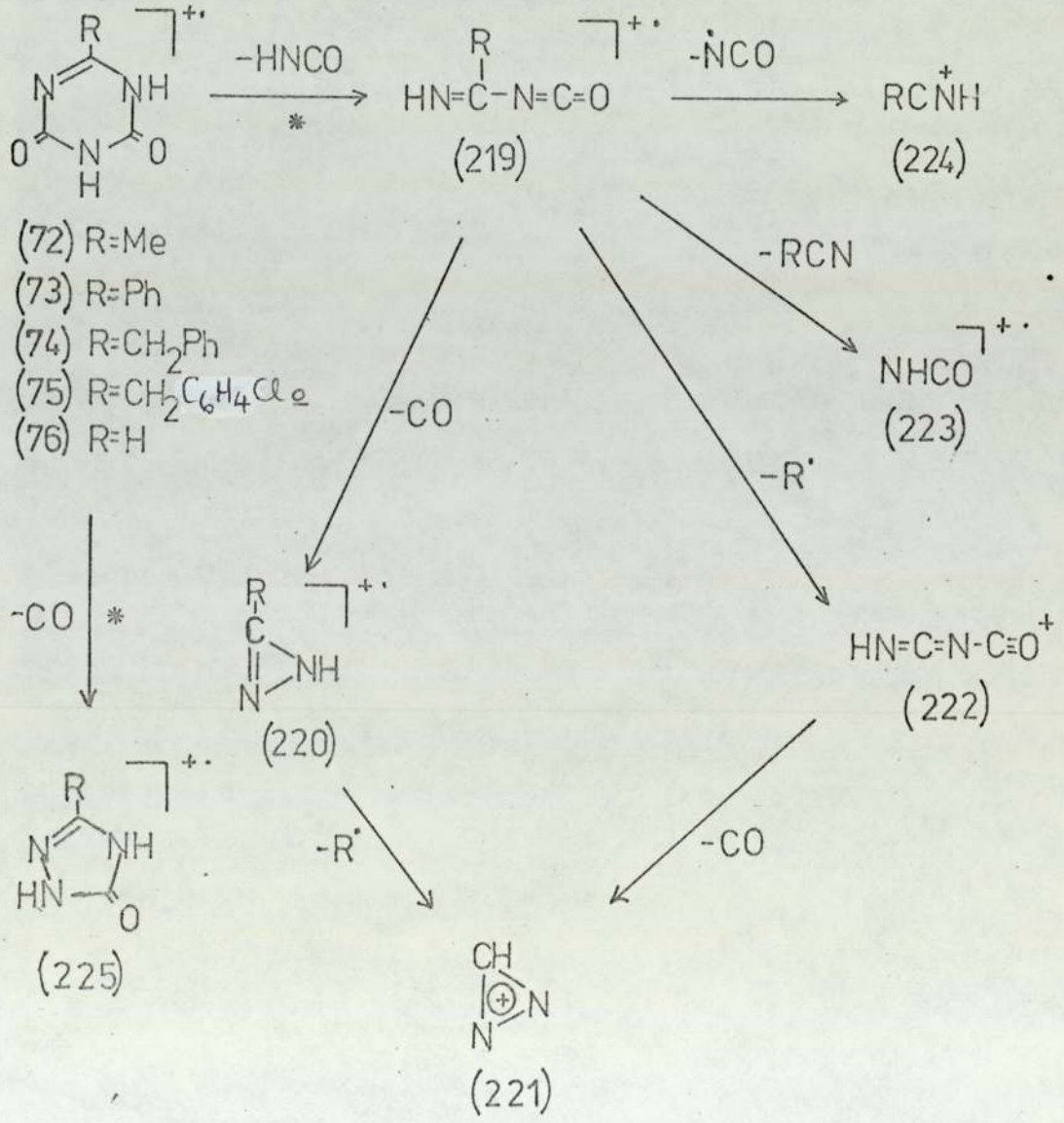
(i) 1,3,5-Triazin-2,4(1H,3H)-diones and related compounds



(Figures in brackets refer to the fragment ions, scheme 8)

1,3,5-Triazin-2,4(1H,3H)-dione (76) (fig 6) decomposes via a retro-Diels-Alder reaction with the expulsion of neutral isocyanate to give the ion radical (219,R=H), see scheme 8 , which may lose carbon monoxide and a hydrogen atom in the sequence (219)→ (220)→ (221) or (219)→ (222)→ (221) (R=H). Species (219)(R=H) can also decompose by ejection of HCN to give the ionised isocyanate (223), or by loss of the ·NCO radical and formation of the protonated nitrile (224,R=H).

Scheme 8



A minor loss of carbon monoxide from the parent gives a small peak (10%) at m/e 85, corresponding to the ion radical (225,R=H).

The triazindiones (72-75) also show a similar fragmentation pattern, although the relative intensities of the fragment ions vary.

Table 5 gives the relative intensities of the ions (219-224) for various triazindiones and differences in the fragmentation patterns of these compounds, compared to 1,3,5-triazin-2,4(1H,3H)-dione, are discussed.

Table 5

Fragment ion	Relative Intensity (%)				
	R				
	H	Me	Ph	CH_2Ph*	$CH_2PhCl(o)^{\ddagger}$
M^+	100	51	70	38	-
219	70	41	23	3	4
220	13	6	4	25	-
221	17	16	-	7	5
222	17	40	15	25	10
223	59	22	29	18	31
224	19	100	100	10	-

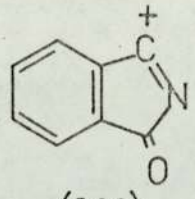
* M-1 is the base peak.

‡ m/e 125 is the base peak.

The individual variations shown in the table result according to the nature of the R group, thus the major

pathway when R=Me or Ph is a retro-Diels-Alder reaction to give (219,R=Me or Ph), followed by ejection of ·NCO to give the protonated nitrile (224,R=Me or Ph).

6-Phenyl-1,3,5-triazin-2,4(1H,3H)-dione (73) shows a peak at m/e 130 (53 % of the base peak), corresponding to the isoindolone structure (226) formed by ejection of $\cdot NH_2$ from the ion radical (219,R=Ph), the mechanism presumably involving a hydrogen transfer from the phenyl substituent.



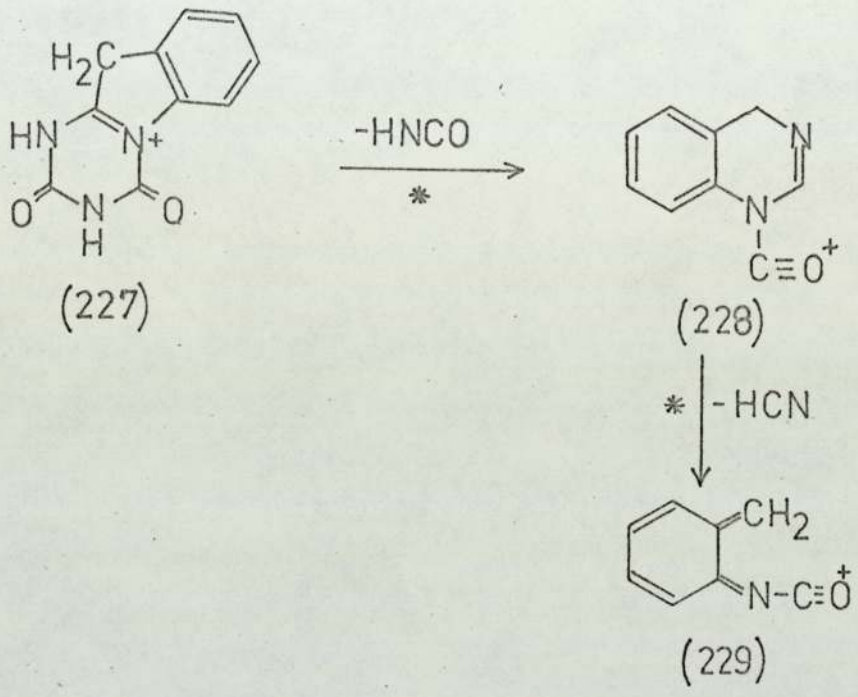
(226)

6-Benzyl-(74) and 6-(2-chlorobenzyl)-(75)1,3,5-triazin-2,4(1H,3H)-dione both show significantly different spectra from the other derivatives, and this can be attributed to the favourable geometry of the compounds, which allows for interation between a nitrogen atom of the triazine ring and the benzyl substituent. Thus the base peak in the spectrum of 6-benzyl-1,3,5-triazin-2,4(1H,3H)-dione (74) is the M-1 peak for which the structure (227) is proposed.

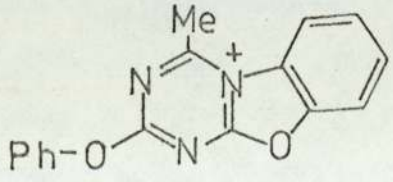
This fragments to give peaks at m/e 159 (228) and m/e 132 (229).

6-(2-Chlorobenzyl)-1,3,5-triazin-2,4(1H,3H)-dione (75) shows no molecular ion, but a peak at m/e 202, corresponding to the triazinoindole ion (227). The base peak is the protonated o-chlorobenzylcyanide ion and the peak at m/e 134

has been shown by accurate mass measurements to have the formula C_8H_8NO; an ion source determination has shown this to arise from the ion (227).



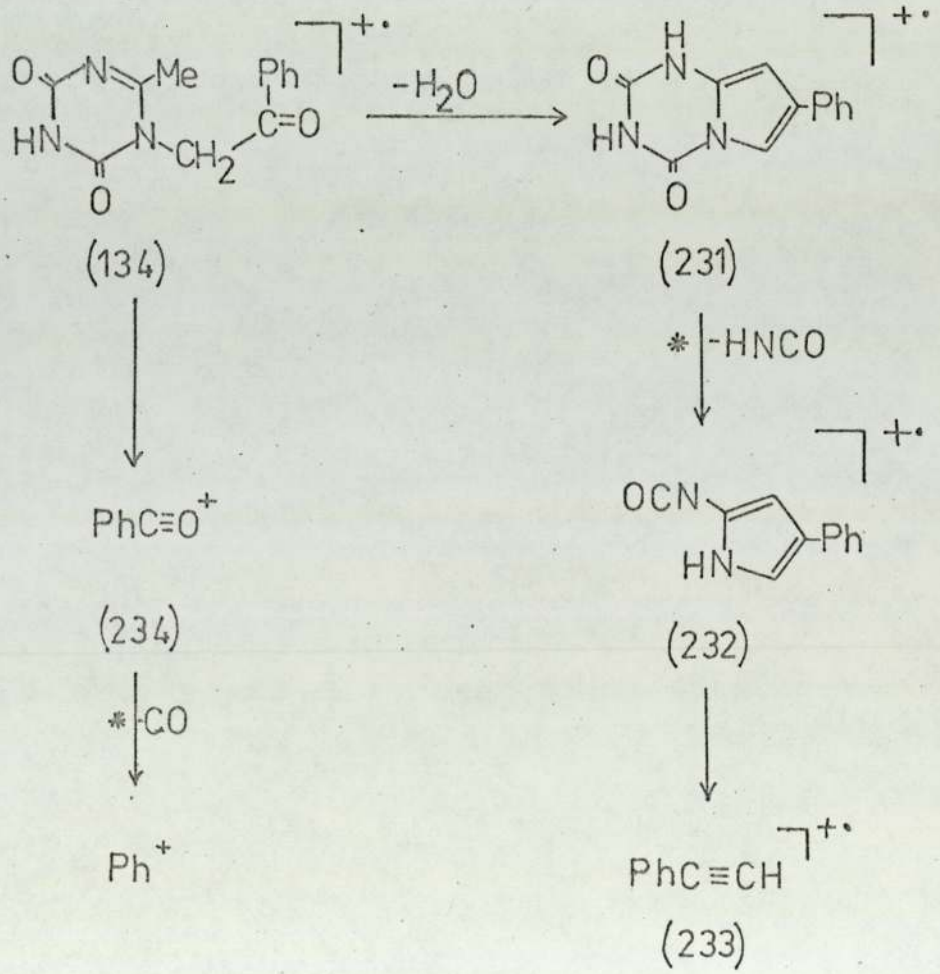
6-Methyl-2,4-diphenoxy-1,3,5-triazine (124) also shows a similar intramolecular interaction, this time between a ring nitrogen atom and an -OPh substituent, and loss of ·H affords the tricyclic ion (230). Similarly many 6-substituted-2,4-diamino (or substituted amino)-1,3,5-triazines exhibit an interaction between a suitably placed substituent and a nitrogen atom of the heteroring[124,125].



(230)

1,3,5-Triazin-2,4,6(1H,3H,5H)-trione (cyanuric acid) shows a breakdown pattern similar to that of the triazindiones, although it differs from the spectrum of barbituric acid in exhibiting a peak at m/e 44, corresponding to protonated isocyanate; barbituric acid shows no equivalent peak[126].

6-Methyl-1-phenacyl-1,3,5-triazin-2,4(1H,3H)-dione hydrobromide (134·HBr) shows a very small molecular ion at m/e 245 (7%), which, by loss of water, gives the pyrrolo-triazindione (231).

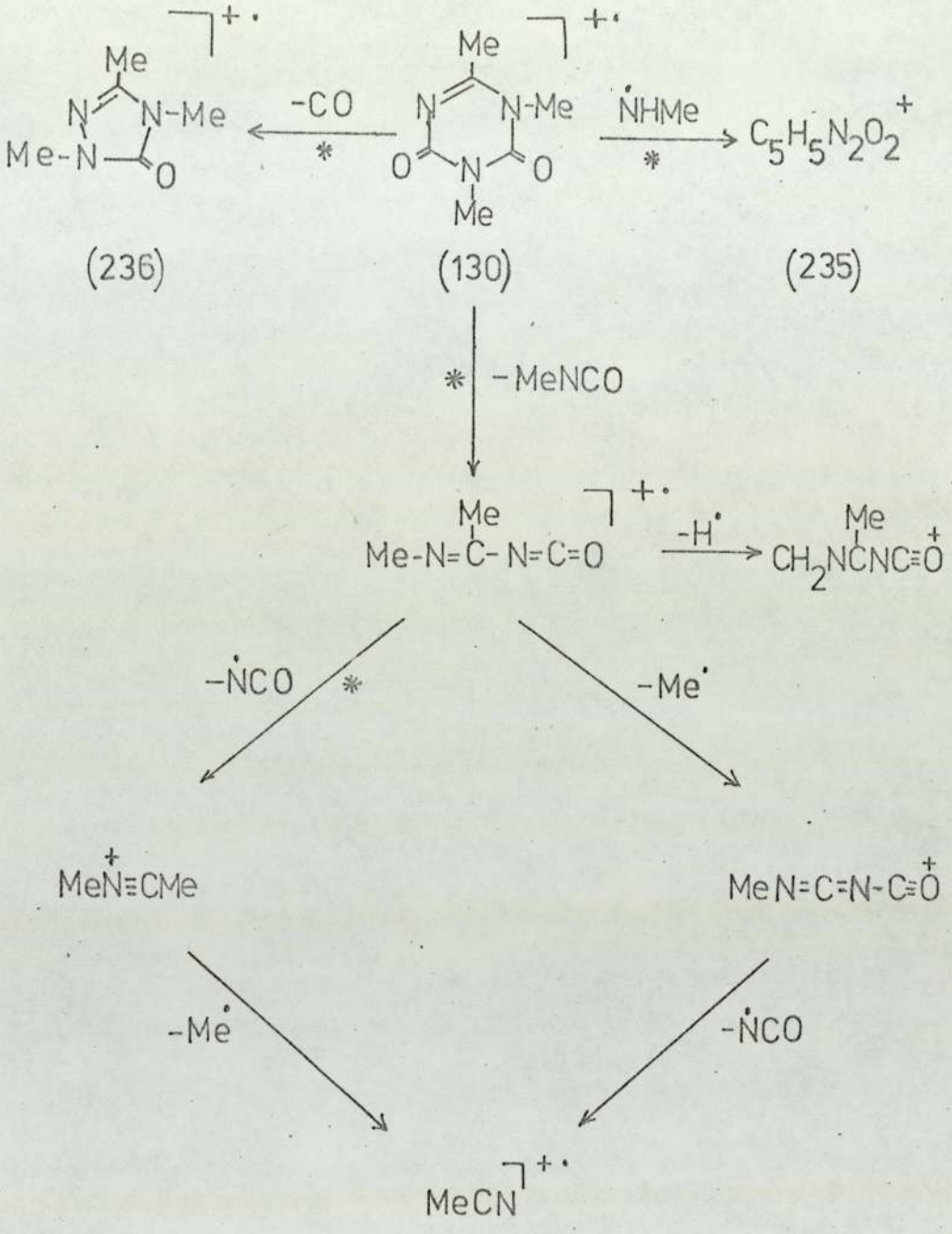


Evidence for the pyrrolotriazindione structure (231) is afforded by the presence of a peak at m/e 102 (233), since phenylacetylene (233) is present as a fragment ion in the spectra of 2-aminopyrrole derivatives containing a phenyl substituent. The base peak of the spectrum is given by the benzoyl ion (234).

The mass spectrum of 6-methyl-1,3-diphenacyl-1,3,5-triazin-2,4(1H,3H)-dione (135) is dominated by the benzoyl ion, but does again show peaks corresponding to pyrrolotriazine structures. Loss of 18 mass units from the molecular ion affords the 3-phenacyl-7-phenylpyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione radical ion, which fragments further to give the pyrrolotriazine (231).

1,3,6-Trimethyl-1,3,5-triazin-2,4(1H,3H)-dione (130) fragments in the expected manner (scheme 9). The losses of CO and ·NHMe from the molecular ion give the ions (235) and (236) respectively. The low relative intensities of these ions and the large metastable peaks shown for these losses, confirm that they require a high activation energy. The mechanism of ejection of ·NHMe is obscure, but must presumably require initial ring opening, followed by proton transfer. Loss of carbon monoxide, accompanied by ring contraction, is more obvious.

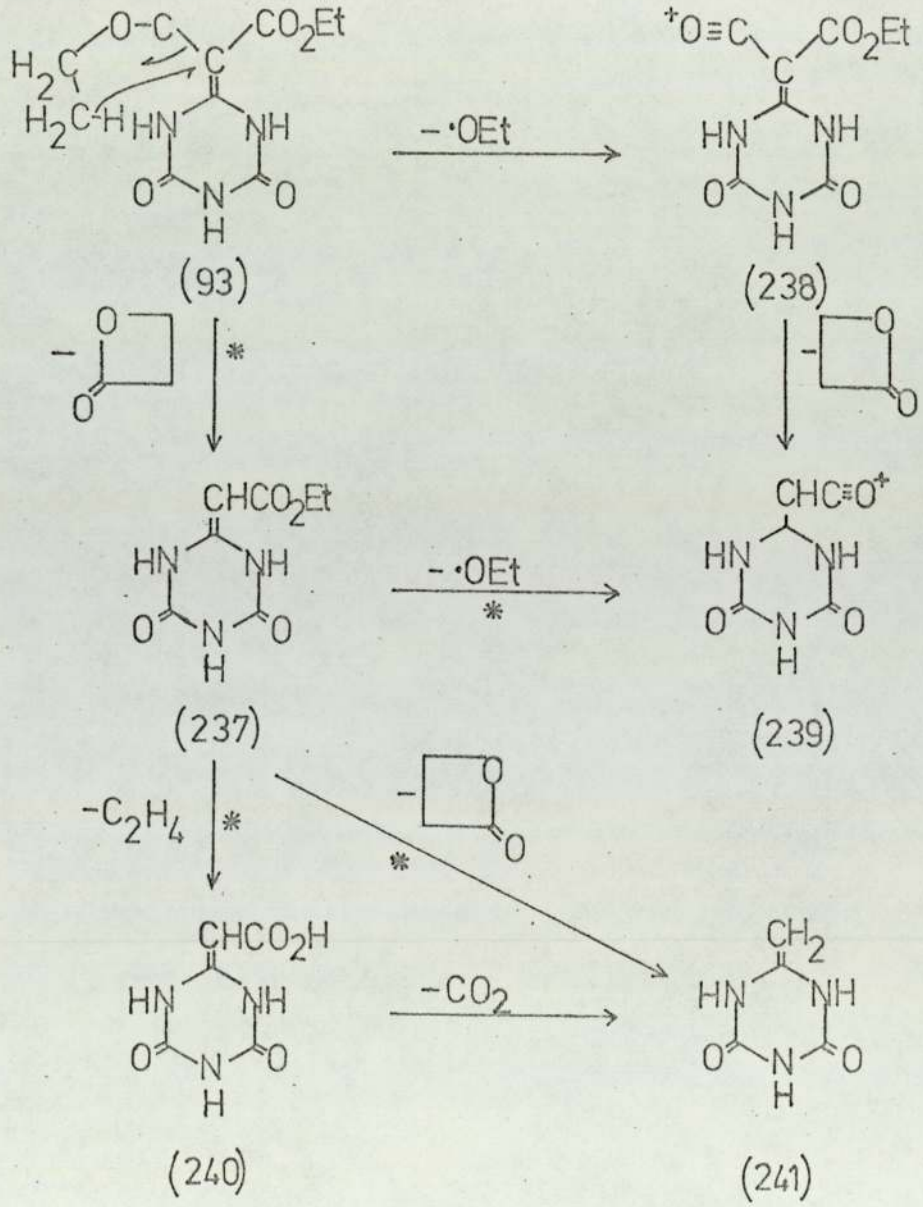
Scheme 9



The spectra of the dicarbethoxymethylene-1,3,5-triazines show no fragments corresponding to the breakdown of the triazine ring, or to the loss of a malonyl grouping.

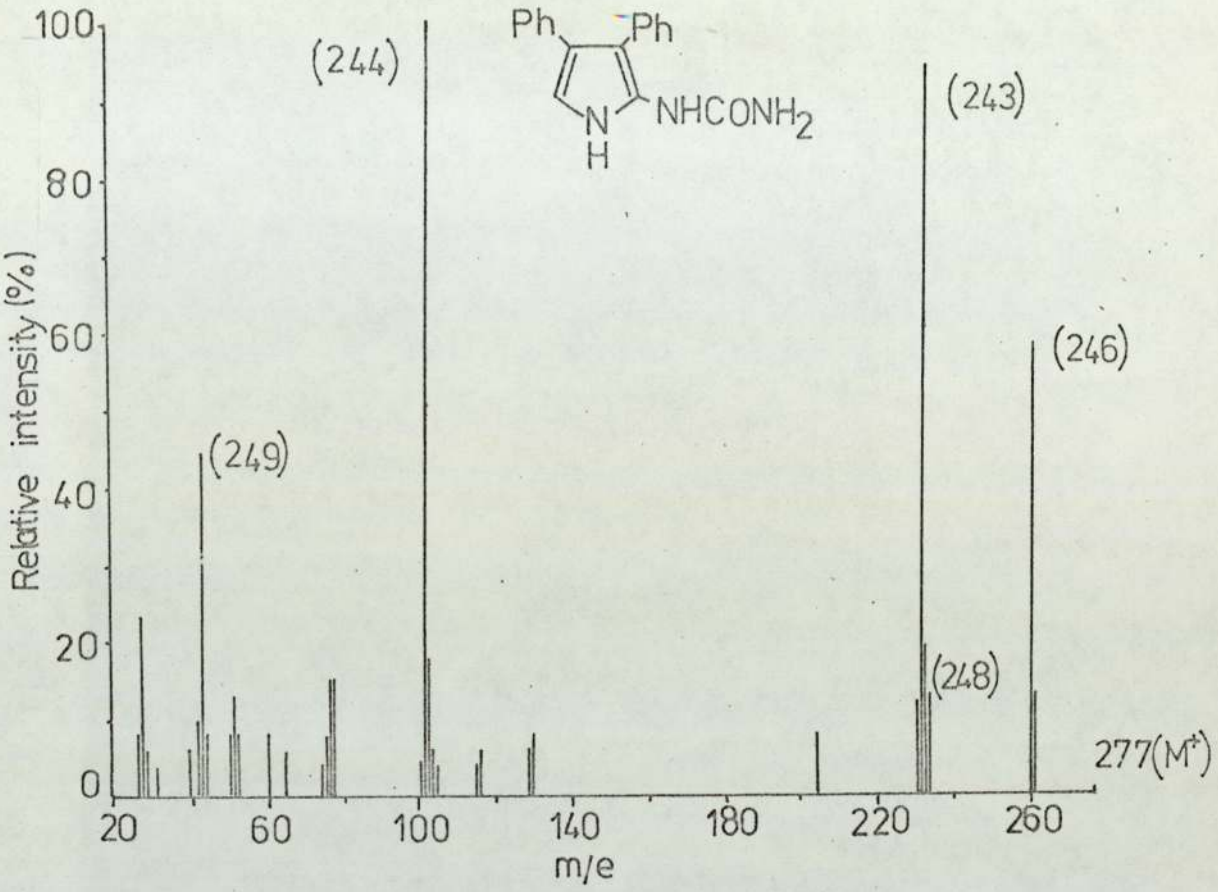
6(1H)-Dicarbethoxymethylene-1,3,5-triazin-2,4(3H,5H)-dione (93) shows no ejection of HNCO from the molecular ion, as might be expected on comparison with the other triazindiones.

The molecular ion fragments by loss of $\overline{CH_2CH_2COO}$, or ejection of $\cdot OEt_3$, and the ion (239) can thus be formed by routes (93)→ (237)→ (239) or (93)→ (238)→ (239). Loss of ethylene from (237) by a McLafferty rearrangement affords the acid (240) which decarboxylates to give the triazindione (241) which can also be formed by a second $\overline{CH_2CH_2COO}$ loss from (237).



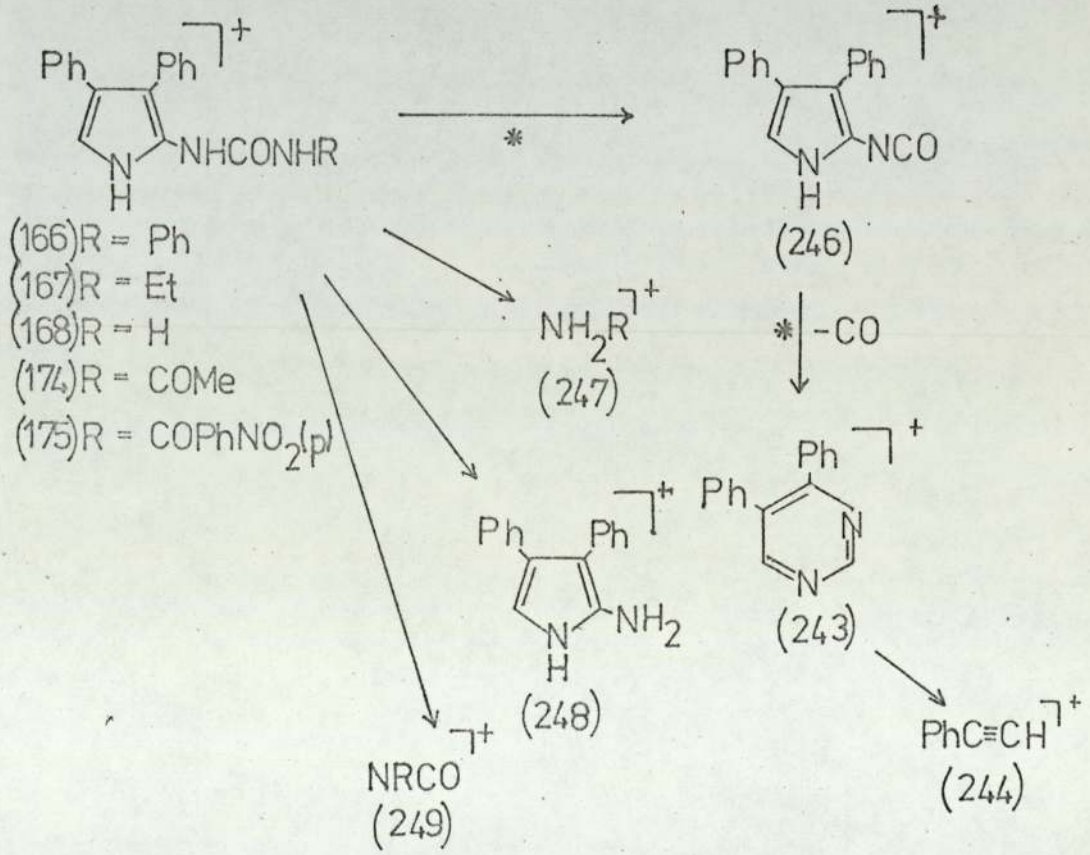
The major peaks in the spectrum of 2,4,6(1H,3H,5H)-tris(dicarbethoxymethylene)-1,3,5-triazine (94) are similarly

Fig. 7



(Figures in brackets refer to the fragment ions, scheme 10)

Scheme 10



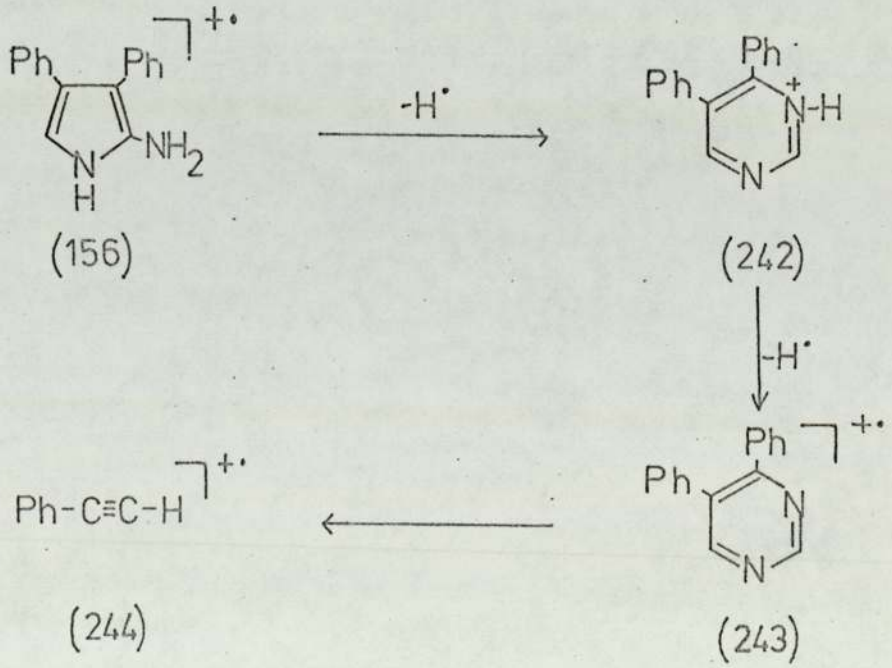
due to fragmentations involving the ester moieties.

The spectrum of 3-benzyl-6(1H)-dicarbethoxymethylene-1,3,5-triazin-2,4(3H,5H)-dione (95) exhibits a large peak at m/e 91 (tropylium ion).

(ii) Pyrrole derivatives

The mass spectrum of 2-amino-3,4-diphenylpyrrole (156) shows a large molecular ion (base peak). The stability of this species can be explained by stabilisation of the radical through the conjugated aromatic system.

The molecular ion shows an M-1 peak (242) (20%) and a large M-2 peak due to the species (243) (58%).



Phenylacetylene (244) is the only other peak of significant intensity in the spectrum.

The mass spectrum of 3-(2-amino-3,4-diphenylpyrrol-2-yl) urea (156) is given in figure 7.

The pyrrolylureas all show a small molecular ion, which fragments as shown in scheme 10, although the relative intensities of the various fragment ions differ (table 6).

Loss of an amine radical to afford the isocyanate (246) can involve fransfer of a hydrogen atom from either the pyrrolyl nitrogen atom, or the amide nitrogen atom.

Table 6

Fragment ion	Relative Intensity (%)				
	R=H	R=Ph	R=Et‡	R=$COCH_3$	R=$COPhNO_2$(p)
M^+	0.6	7	18	8	-
246	59	8	52	100	100
243	95	-	-	9	7
244	100	7	30	28	30
247	-	100	24	22	35
248	13	16	6	76	9
249	44	25	4	6	-

‡ The base peak of this compound is m/e 30.

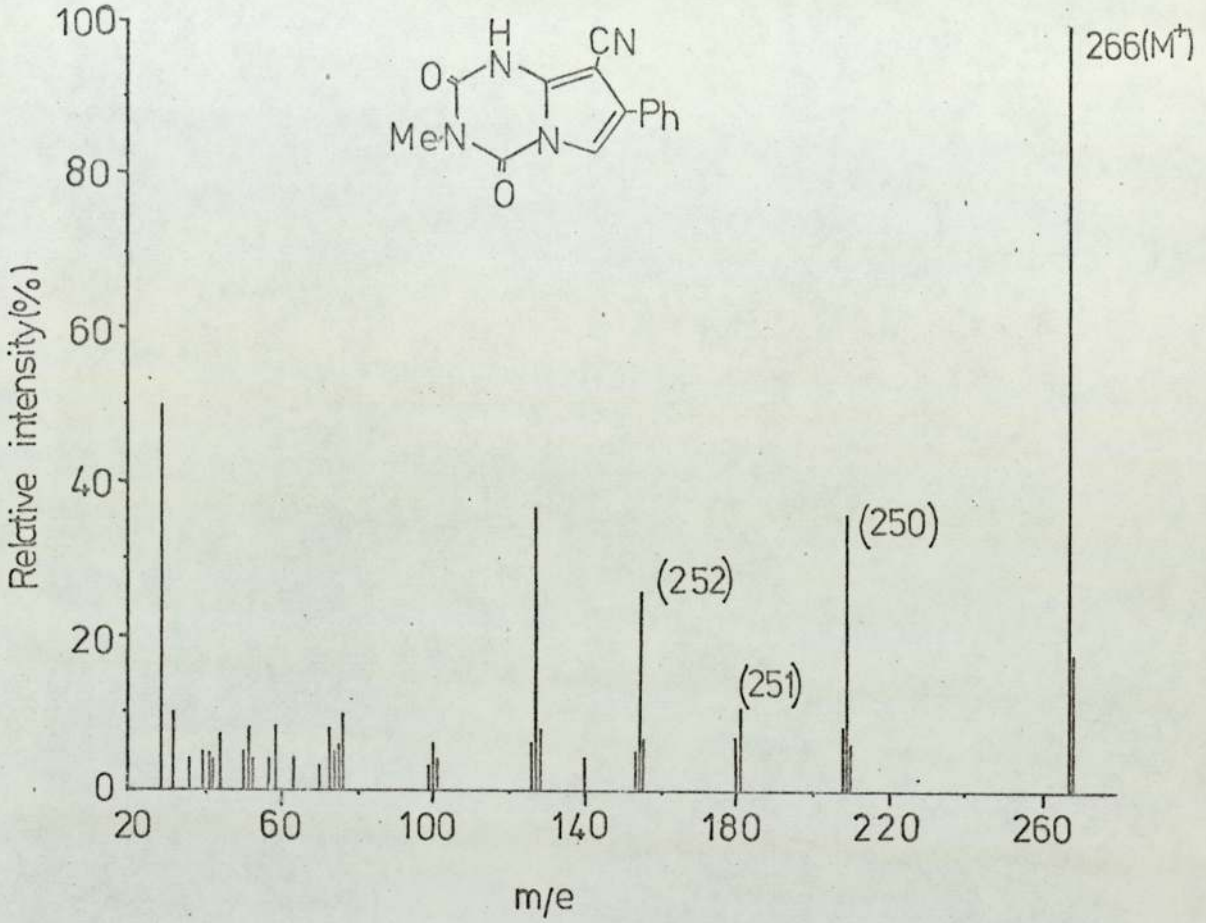
1-Phenyl-3-(2-amino-3-cyano-4-phenylpyrrol-2-yl)urea (155) shows a similar decomposition to the 3-phenyl analogue.

(iii) Pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-diones

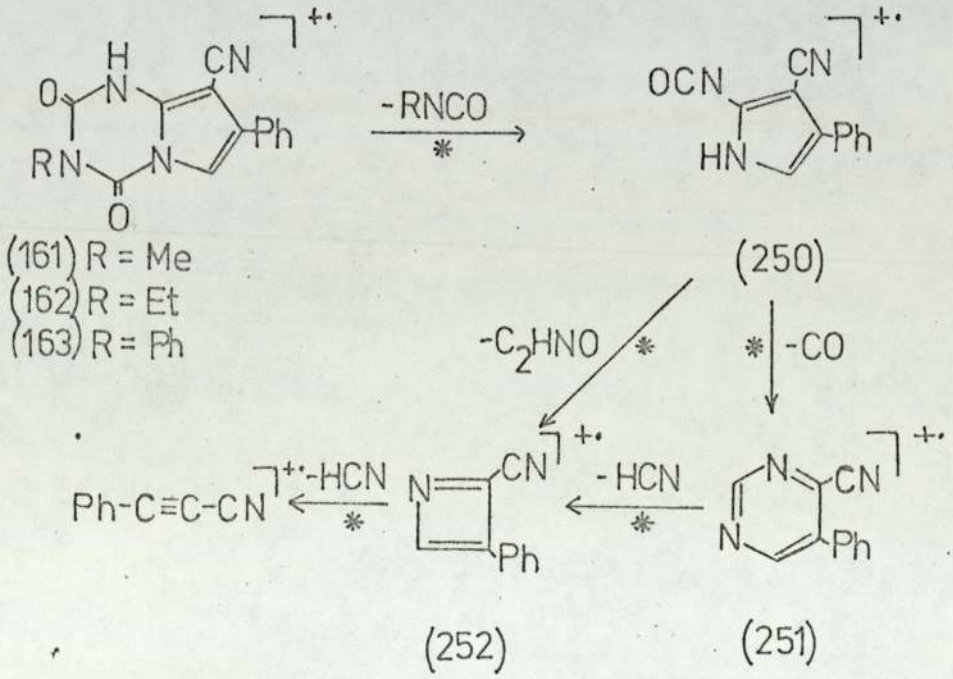
The mass spectrum of 7-cyano-3-methyl-6-phenylpyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione (161) is given in figure 8 . The 3-ethyl derivative shows a similar spectrum.

The compounds exhibit a large molecular ion (base peak), which decomposes by loss of RNCO to give (250).

Fig. 8



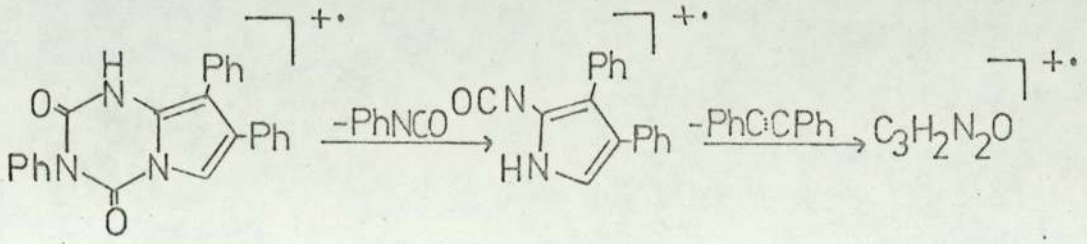
(Figures in brackets refer to fragment ions, below)



The lack of any double bond in the 'triazindione moiety' of the pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-diones will block decomposition by a retro-Diels-Alder reaction and would thus account for the stability of the molecular ion. The ion (250) further fragments by loss of carbon monoxide (251) then ejection of two molecules of HCN. An ion source determination confirmed that (252) also arises directly from (250).

The spectrum of the 3-phenyl derivative (R=Ph) (163) shows the same corresponding peaks but the molecular ion is much smaller (only 14% of the base peak) and the base peak is the ion (252). This must be due to the easier loss of PhNCO from the molecular ion as compared to loss of Alkyl isocyanate. An additional peak at m/e 164 (30%) has not been identified but its formation must involve a complex mechanism.

3,7,8-Triphenylpyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione (164) shows no visible molecular ion. The base peak of the spectrum m/e 83 (254), must presumably arise by loss of diphenylacetylene from (253).



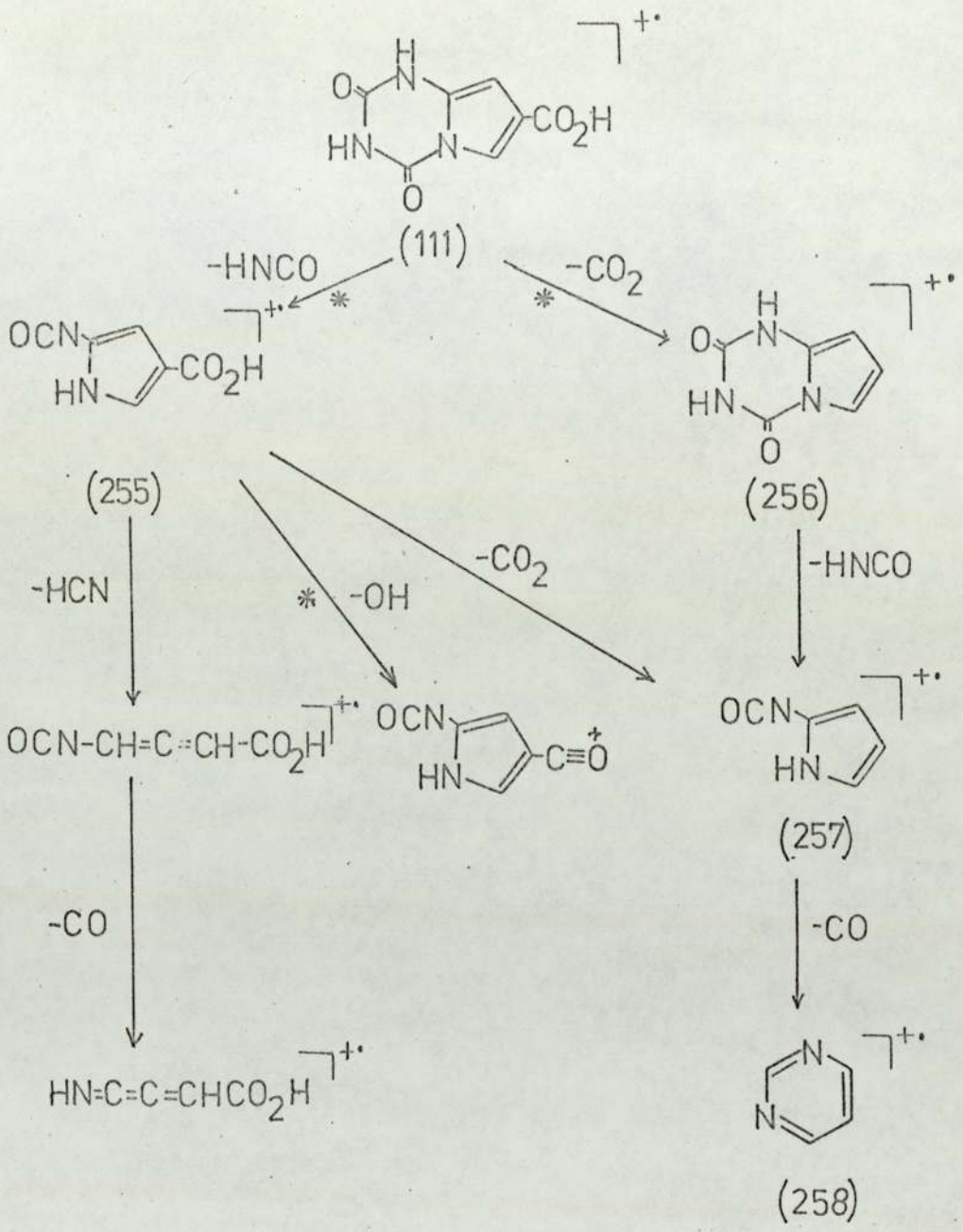
(164) (253) (254)

The base peak of the spectrum of 3-phenacyl-7-phenyl-pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione (140) is due to the 7-phenylpyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione radical ion (231) (page 104).

The spectrum of pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylic acid (111) exhibits a large molecular ion. This ion is very stable and none of the other peaks in the spectrum are of any significant size. The stability of this compound to fragmentation can be explained by a consideration of two factors: lack of a double bond in the triazindione moiety, which is necessary to initiate ejection of HNCO, and the fragmentation mechanism of pyrrole-carboxylic acids. No information is available for pyrrole-3-carboxylic acids, but pyrrole-2-acids fragment mainly by loss of ·OH, H_2O or H_2O+CO_2, all of which require participation by the pyrrolyl N-H[122], and it is thus likely that pyrrole-3-carboxylic acids and the pyrrolotriazindione-7-carboxylic acid will be stable to electron impact.

The molecular ion ejects HNCO and CO_2 to give the ions (255) and (256), loss of HNCO being the most favourable.

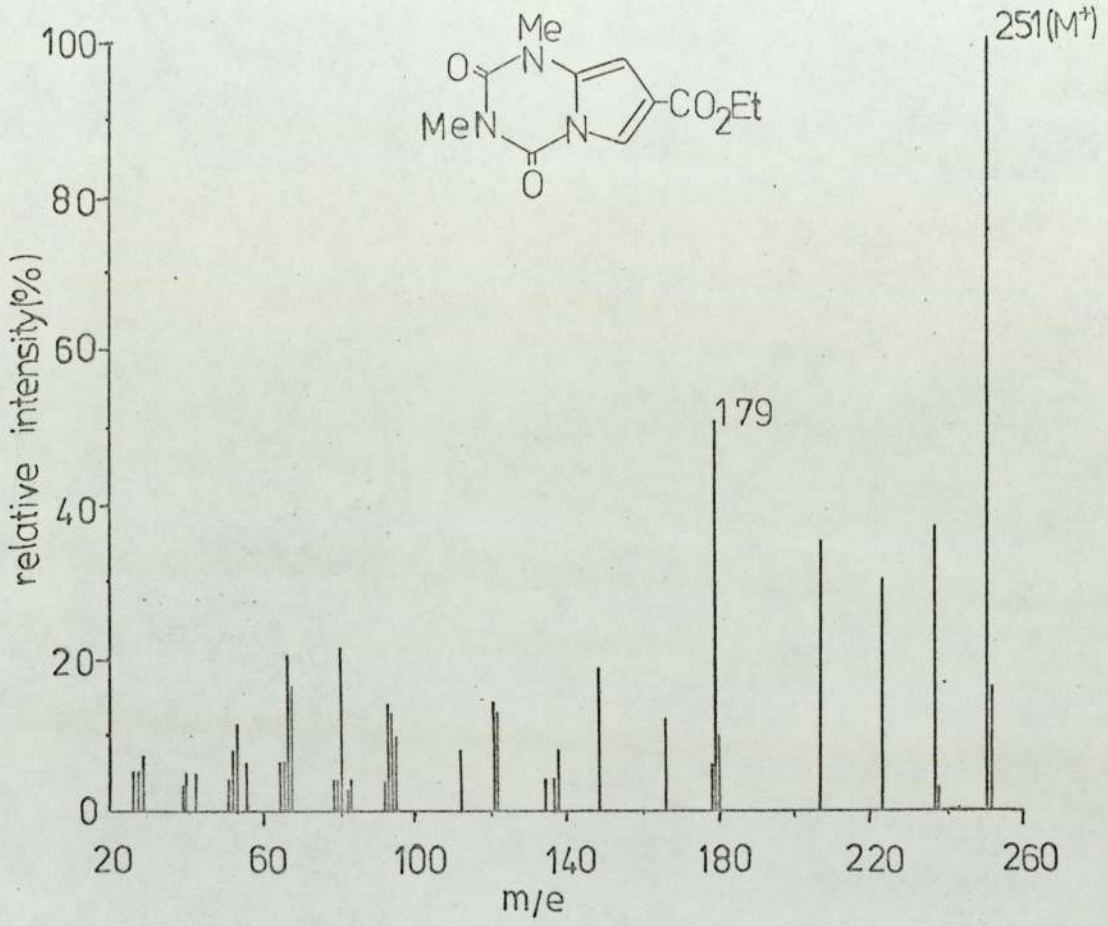
The ion (257), which ejects CO to give (258), can be formed by either route (111)→ (255)→ (257) or (111)→ (256)→ (257). The radical ion (255) also fragments by loss of ·OH and HCN as indicated.



The mass spectrum of ethyl 1,3-dimethylpyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylate (114) is given in figure 9 . The molecular ions of all the esters are the base peaks, and the major fragmentations involve the ester grouping. In the ethyl esters peaks are seen at M-28, loss of C_2H_4, presumably by McLafferty rearrangement, and at

M-45, loss of ·OEt. The spectrum of methyl pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylate (112) shows a peak at m/e 178 (loss of ·OMe).

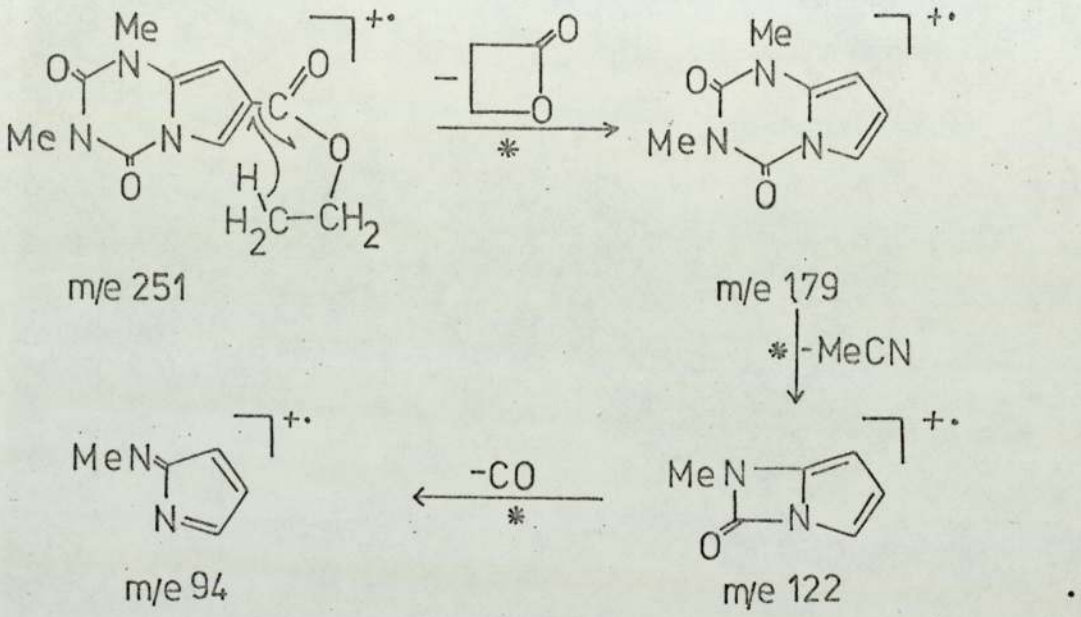
Fig. 9



The most interesting feature of the above spectrum is the ion at m/e 179. All the esters in fact exhibit a peak of relatively large intensity, corresponding to a loss of $\overline{(CH_2)_n COO}$ from the molecular ion, comfirmed by metastable peaks, accurate mass and ion source determinations. Pyrrole-carboxylic acid esters do not show this loss[122], although Jones and Stanyer[127] noticed a similar loss in the spectra of ethyl indolizine-3-carboxylates and ethyl indolizine-4-carboxylates, and since this was not shown by ethyl indolizine-6-carboxylates suggested that initial transfer

of H to the peri position took place. Such a transfer, however, cannot occur in the ethyl pyrrolo[1,2-a][1,3,5] triazindione-7-carboxylates and thus $\overline{CH_2CH_2COO}$ must be ejected by a cyclic mechanism as indicated (scheme 11).

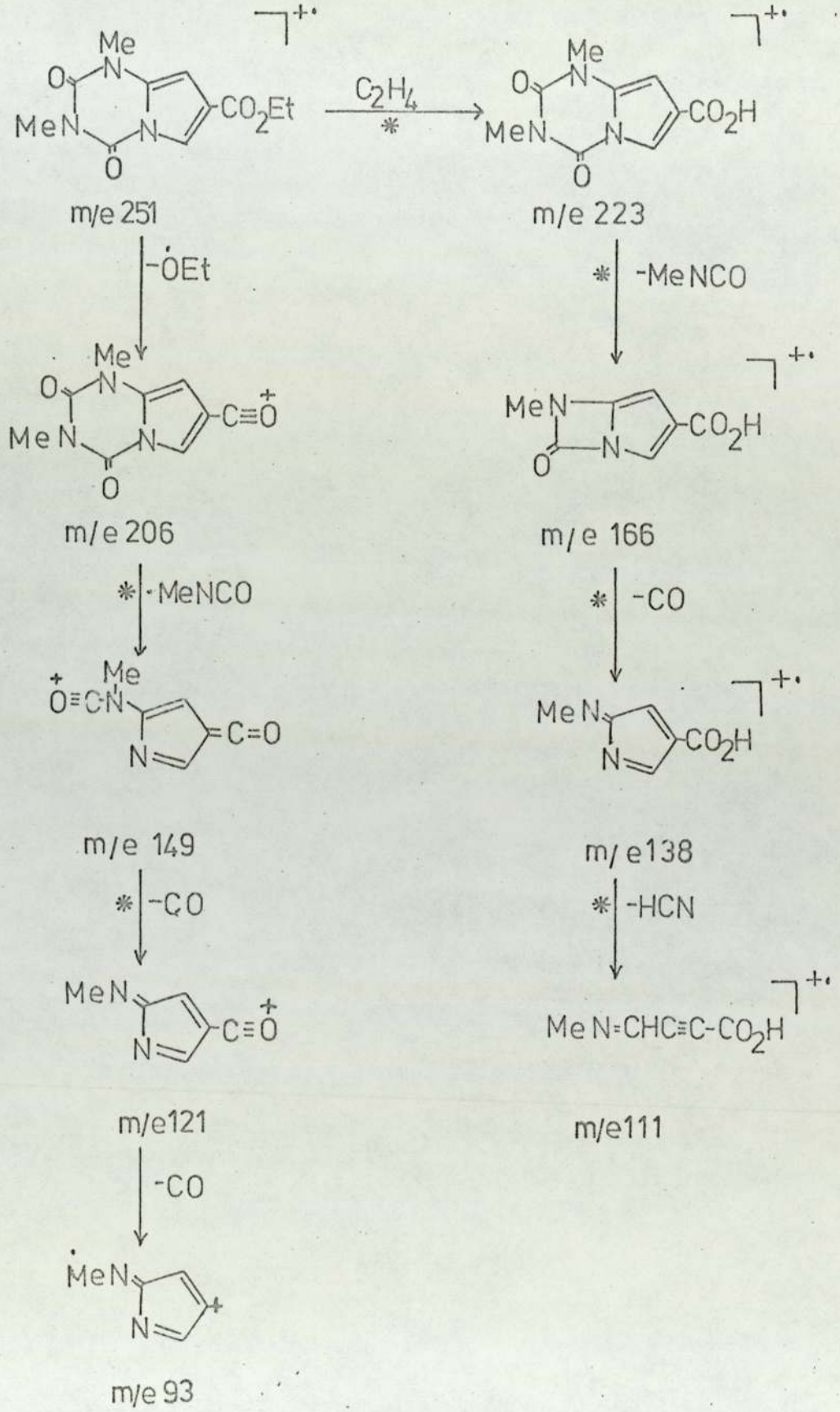
Scheme 11



The M-$\overline{CH_2COO}$ ion of methyl pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylate (112), however, is much reduced (7% of base peak) and this would be expected if a cyclic mechanism similar to that shown above is involved. An accurate mass determination on the peak at m/e 151 in the spectrum of the methyl ester in fact showed it to consist of two ions, one of which had arisen by loss of $\overline{CH_2COO}$ from the molecular ion, and the other from the M-OMe ion.

The remaining fragmentations of ethyl 1,3-dimethyl-pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylate are outlined below (scheme 12).

Scheme 12



(iv) 1,2,4-Triazines and related compounds

6-Methyl-1,2,4-triazin-3,5(2H,4H)-dione (6-azauracil) (81) decomposes by loss of HNCO in a similar manner to its 1,3,5-triazindione isomer (72). The molecular ion of the 1,2,4-triazindione is much more stable to fragmentation, however, and forms the base peak of the spectrum.

The remaining 1,2,4-triazines for which mass spectra have been determined follow straightforward fragmentation pathways as described in the literature[128].

The mass spectrum of 2,3-dimethyl-6-phenylimidazo[1,2-b][1,2,4]triazine (194) affords evidence for its assigned structure, since, unlike the 1,2,4-triazines it does not show a loss of N_2, confirming the nitrogen atom at position 4 to be the bridgehead atom.

The tricyclic diethyl 4-methylpyrrolo[2,1-f]imidazo[1',2'-b][1,2,4]triazine-2,7-dicarboxylate (199) or its isomer (200) gives a mass spectrum, the main peaks in which are due to fragmentations of the ester groupings. Loss of $\overline{CH_2CH_2COO}$ is again exhibited and ejection of this from the molecular ion affords the base peak. This loss may well occur from the imidazoyl ester and the greater importance of the loss may be due to the involvement of the adjacent imidazoyl nitrogen atom.

EXPERIMENTAL

Infra-red spectra were determined, unless otherwise stated, as Nujol mulls, with a Unicam SP 200 spectrophotometer.

Nuclear magnetic resonance spectra were measured, unless otherwise stated, with tetramethyl-silane as internal standard, on a Varian A60-A spectrometer. All the peaks are assigned in terms of τ values. Abbreviations used in the interpretation of n.m.r. spectra are:
s = singlet; d = doublet; t = triplet; q = quartet;
m = multiplet; J = coupling constant; a = removed on deuteration.

Mass spectra were determined on an A.E.I. MS9 spectrometer, operating at 100 μa and 70 eV. $\underline{M}^+$ signifies the molecular ion peak. Abbreviations used in the results of ion source determinations are v = very; s = small; m = medium; l = large to describe the size of the deflection of the collector meter. The figures refer to the value of the scan kV.

Melting points are uncorrected. Reaction temperatures are those of an external oil bath.

Light petroleum refers to the fraction boiling at 60° - 80°, unless otherwise stated.

2,4-Diamino-6-methyl-1,3,5-triazine (60)

This was prepared by the method of American Cyanamid Co.[55] colourless needles, m.p. 272-274° (lit., 271-273°) (from methanol).

$\nu_{max.}$ 3500, 3400, 3340 and 3150(N-H)cm^{-1}.

$\tau(CF_3COOH)$ 7.25(3H,s,CH_3), 2.17(2H,broad s,NH_2).

2,4-Diamino-6-cyanomethyl-1,3,5-triazine (61)

This was prepared by the method of Hickmott[56], colourless needles, m.p. 276-278° (lit., 275-277°) (from methanol).

$\nu_{max.}$ 3480, 3360 and 3150(N-H), 2300(C≡N)cm^{-1}.

$\tau(CF_3COOH)$ 6.24(2H,s,CH_2CN), 2.82(4H,broad s,2- and 4-NH_2).

Reaction of 2,4-diamino-6-methyl-1,3,5-triazine with various α-halogeno-ketones

(i) With phenacyl bromide:

(a) The diaminotriazine (2g) and phenacyl bromide (3.2g) were heated under reflux in ethanol for 66h to afford a quantitative yield of the starting material.

(b) Phenacyl bromide (4g) and the diaminotriazine (1.3g) when heated at 80°, in the absence of solvent, afforded 2,4-diamino-6-methyl-1,3,5-triazine hydrobromide, m.p. 315° decomp.

(ii) With ethyl bromopyruvate:

The diaminotriazine (1.25g) and ethyl bromopyruvate (0.98g) were heated under reflux in ethanol for 40h to give

the starting material in quantitative yield.

(iii) With bromoacetaldehyde:

A mixture of bromoacetaldehyde diethyl acetal (0.5g), hydrobromic acid ($1.0cm^3$, d = 1.38) and water ($1cm^3$) was heated under reflux for 0.5h. Ethanol ($20cm^3$) was added to the cooled mixture which was then neutralised with sodium bicarbonate. The precipitated salt was removed by filtration and the filtrate, diluted to $100cm^3$ with ethanol, was heated under reflux with 2,4-diamino-6-methyl-1,3,5-triazine (2.5g). After 24h the insoluble material (0.43g) was collected and shown to consist mainly of 2,4-diamino-6-methyl-1,3,5-triazine hydrobromide. The mass spectrum of this crude material showed the presence of a peak at m/e 143; however this was a very minor component of the mixture and could not be separated.

The remaining ethanolic mother liquors were evaporated to dryness to give a dark brown solid (2.6g) which could not be decolourised by heating under reflux in methanol containing animal charcoal. Thin layer chromatographic analysis of this product [Silica with propanol-ethanol (4:1) mixed solvent; Alumina with ethanol containing 5% acetic acid] showed the presence of four (or possibly five) very closely running components. No pure compounds could be isolated from this mixture.

Attempted reaction of 2,4-diamino-6-cyanomethyl-1,3,5-triazine with phenacyl bromide

(i) The diaminotriazine (0.5g) and phenacyl bromide (0.35g) were heated under reflux in ethanol ($30cm^3$) for 20h to give starting material only.

(ii) The above reaction was repeated, using dimethylformamide as the solvent and a refluxing time of 0.5h. Starting material only was isolated but intractable oily material was also produced.

2-Amino-4,6-dimorpholino-1,3,5-triazine (70)

This was prepared by the method of Kaiser et al[57], colourless needles, m.p. 174-175° (lit., 170-172°) (from ethanol).

$\nu_{max.}$	3400, 3300 and 3200(N-H)cm^{-1}.
$\tau(CDCl_3)$	6.28(16H,s,4- and 6-$\overline{NCH_2CH_2OCH_2CH_2}$),
	4.89(2H, broad s, 2-NH_2)[a].

4,6-Dichloro-2-methyl-1,3,5-triazine

This was prepared by the method of Hirt, Nidecker and Birchtold[129], colourless plates, m.p. 97-98° (lit., 98°) (from light petroleum b.p. 60-80°).

2-Methyl-4,6-dimorpholino-1,3,5-triazine (69)

A slurry of 2-methyl-4,6-dichloro-1,3,5-triazine (1.1g) in water ($10cm^3$) was added to morpholine (1.2g) and the

resulting mixture refluxed for 2h, during which time one equivalent of aqueous sodium hydroxide was added to keep the mixture just alkaline to phenolphthalein. After cooling the mixture the deposited 2-methyl-4,6-dimorpholino-1,3,5-triazine (1.65g, 93%) was collected, colourless needles, m.p. 137-138° (lit., 143-145°) [130] (from ethanol).

$\tau(CDCl_3)$ 7.73(3H,s,CH_3), 6.26(16H,s,2- and 4-$\overline{NCH_2CH_2OCH_2CH_2}$)

Reaction of 2-methyl-4,6-dimorpholino-1,3,5-triazine with various α-halogeno-ketones

(i) With ethyl bromopyruvate

The 1,3,5-triazine (0.7g) and ethyl bromopyruvate(0.25g) were heated under reflux in methanol (or acetone) for 40h. Removal of the solvent afforded a quantitative recovery of triazine.

(ii) With bromoacetaldehyde:

2-Methyl-4,6-dimorpholino-1,3,5-triazine (1.3g) and bromoacetaldehyde (from 1.3g bromoacetaldehyde diethyl acetal) were heated under reflux in ethanol for 8h. The cooled mixture was concentrated to $3cm^3$ and diluted with water ($15cm^3$) then neutralised with sodium bicarbonate, and extracted with chloroform. Removal of the chloroform, after drying, gave the starting material.

(iii) With phenacyl bromide:

2-Methyl-4,6-dimorpholino-1,3,5-triazine (0.28g) and phenacyl bromide (0.1g) in acetone ($10cm^3$) were heated under

reflux for 70h to give a quantitative recovery of the starting material.

5,7-Dimorpholino-imidazo[1,2-a][1,3,5]triazine (71)

This was prepared by the method of Kobe, Stanovnick and Tisler[58], m.p. 230° (lit., 234-236°) (from water).

The n.m.r. spectrum of 5,7-dimorpholino-imidazo[1,2-a][1,3,5] triazine has been recorded elsewhere[58].

Reaction of 2-amino-4,6-dimorpholino-1,3,5-triazine with various α-bromo-ketones

(i) With phenacyl bromide:

(a) The aminotriazine and phenacyl bromide heated under reflux in ethanol for 68h did not react.

(b) Phenacyl bromide and 2-amino-4,6-dimorpholino-1,3,5-triazine heated at 80° in the absence of solvent gave the triazinylhydrobromide (81%), m.p. 202-206° decomp. Basification of this with aqueous sodium bicarbonate gave the free base.

(ii) With ethyl bromopyruvate

The triazine and ethyl bromopyruvate were heated under reflux in acetone for 43h and, after removal of the solvent, gave a yellow oily solid. Trituration of this with water gave the triazinylhydrobromide (41%). No further products could be extracted from the aqueous solution.

6-Methyl-1,3,5-triazin-2,4(1H,3H)-dione (72)

This was prepared by the method of Necki[59].

2,4-diamino-6-methyl-1,3,5-triazine (30g) was added slowly to a mixture of concentrated sulphuric acid ($134cm^3$) and water ($40cm^3$) so that the temperature remained below 30^o. The mixture was then heated at 150^o for 2h with stirring, cooled, poured into water and neutralised with calcium carbonate. After removal of the precipitated calcium sulphate the aqueous filtrate was taken to dryness to give a colourless solid, which was extracted with hot methanol. The extract was evaporated to dryness and the residue re-extracted with methanol. This procedure was repeated several times until all of the inorganic material had been removed. The final methanolic extract gave the triazine (60%), colourless needles, m.p. 273-275° decomp. (lit., 276-277°) (from methanol).

$\nu_{max.}$ 1760 and 1705(C=O), 1600(C=N)cm^{-1}.

$\tau(CF_3COOH)$ 7.10(3H,s,CH_3).

$\tau\left[(CD_3)_2SO\right]$ (dimethylsulphoxide, τ 7.38, internal standard).

7.75(3H,s,CH_3), -1.85(2H,broad s,1- and 3-NH)[a].

Potassium salt of 6-methyl-1,3,5-triazin-2,4(1H,3H)-dione

Potassium hydroxide (0.23g), in the minimum of ethanol, was added to a solution of the triazindione (0.51g) in ethanol ($50cm^3$). The colourless precipitate was collected and dried in vacuo to give the potassium salt (0.56g, 85%).

$\nu_{max.}$ 3180(N-H), 1660 and 1640(C=O)cm^{-1}.

6-Methyl-1,3,5-triazin-2,4(1H,3H)-dione hydrochloride

This was prepared by the method of Ostrogovich[77], colourless needles, m.p. 280-281° decomp. (lit., 276-277°)(from water).

$\nu_{max.}$ 1780 and 1725(C=O), 1600(C=N)cm^{-1}.

1,3,5-Triazin-2,4(1H,3H)-dione (76)

This was prepared by the method of Piskala and Gut[64], colourless prisms, m.p. 280° (from water)

The infra-red spectrum of this compound is recorded elsewhere[63].

6-Phenyl-1,3,5-triazin-2,4(1H,3H)-dione (73)

This was prepared by the method of Ostrogovich and Tanislav[61], colourless needles, m.p. 293-294° decomp. (from water).

$\nu_{max.}$ 1740 and 1690(C=O)cm^{-1}.

6-Benzyl-1,3,5-triazin-2,4(1H,3H)-dione (74)

This was prepared by the method of Ostrogovich and Tanislav[61], lustrous plates, m.p. 254-255° (lit., 251-252°) (from ethanol).

(Found: M^+, 203.069202. $C_{10}H_9N_3O_2$

requires M, 203.069472).

$\nu_{max.}$ 1750 and 1670(C=O), 1605(C=N)cm^{-1}.

$\tau(CF_3COOH)$ 5.58(2H,s,$C_6H_5CH_2$), 2.54(5H,s,$C_6H_5CH_2$).

1-(2 -Chlorobenzyl)-1,3,5-triazin-2,4(1H,3H)-dione (75)

o-Chlorophenylacetylchloride (1.9g) and biuret (0.7g) were heated slowly to 140° and this temperature was maintained for 1h. The mixture was then cooled and washed with ethanol to give 1-(2 -chlorophenyl) acetylbiuret (1.2g, 69%), colourless solid, m.p. 228-232°.

The crude biuret was added to an aqueous potassium hydroxide solution (25cm^3, containing 0.8g KOH) and the mixture stirred for 6h. Acetic acid was then added to precipitate the triazindione (0.5g, 45%), colourless needles, m.p. 268-269° decomp.

(Found: C,50.3; H,3.4; N,17.7. $C_{10}H_8ClN_3O_2$
requires C,50.5; H,3.4; N,17.7%).

$\nu_{max.}$ 3120(N-H), 1750 and 1670(C=O)cm^{-1}.

τ (CF_3COOH) 5.43(2H,s,$ClC_6H_4CH_2$), 2.51(4H,s,$ClC_6H_4CH_2$).

Attempted reaction of 6-methyl-1,3,5-triazin-2,4(1H,3H)-dione with phenacyl bromide

(i) Methyl-1,3,5-triazin-2,4(1H,3H)-dione (1.27g) and phenacyl bromide (2.0g) were heated under reflux in methanol (100cm^3) for 2 weeks. The triazine was recovered unchanged.

(ii) Methyltriazindione (1.3g) and phenacyl bromide (2.0g) were heated together, in the absence of solvent, for 17h at 80°. The resulting oil was triturated with acetone to give the triazindione hydrobromide (1.5g, 72%) as a pale yellow solid, m.p. 280-283°.

$\nu_{max.}$ 1780 and 1725(C=O)cm^{-1}.

None of the required pyrrolotriazine could be gained from the mother liquors.

(iii) The 1,3,5-triazindione (2.6g) and phenacyl bromide (2.2g) were heated under reflux in 2-ethoxyethanol for 45h. Removal of the solvent under reduced pressure gave a black tar from which only phenacyl bromide could be recovered.

(iv) 6-Methyl-1,3,5-triazin-2,4(1H,3H)-dione (0.7g) and phenacyl bromide (0.6g) were refluxed in dimethylformamide ($5cm^3$). After 8h removal of the solvent, under reduced pressure, gave a dark brown oil, which on trituration with 2N hydrochloric acid afforded a dark brown solid. This was washed with ether and treated with animal charcoal in refluxing methanol to give 3-phenacyl-7-phenylpyrrolo[1,2-a][1,3,5] triazin-2,4(1H,3H)-dione* as a mauve-brown powder, m.p. decomp. slowly above 300°.

An analytically pure sample could not be obtained.

(Found: M^+, 345. $C_{20}H_{15}N_3O_3$ requires M, 345).

$\nu_{max.}$ 1750 and 1690(C=O), 1620(C=C)cm^{-1}.

$\tau(CF_3COOH)$. 4.28(2H,s,3-$CH_2COC_6H_5$), 2.30(12H,m,3-$CH_2COC_6H_5$, 7-C_6H_5 and 6- and 8-H).

* Or the isomeric 1-phenacyl-7-phenylpyrrolo[1,2-a][1,3,5] triazin-2,4(1H,3H)-dione.

Attempted synthesis of 7,8-diphenylpyrrolo[1,2-a][1,3,5] triazin-2,4(1H,3H)-dione

6-Benzyl-1,3,5-triazin-2,4(1H,3H)-dione (2.0g) and phenacyl bromide (1.0g) were heated under reflux in 1,2-dimethoxyethane (100cm^3). After 24h removal of the solvent gave a quantitative recovery of the starting material.

Ethyl pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylate (101)

6-Methyl-1,3,5-triazin-2,4(1H,3H)-dione (1.3g) was heated under reflux with ethyl bromopyruvate (0.9g) and ethanol (100cm^3) for 70h. Removal of the solvent under reduced pressure gave a yellow solid which was washed with 2N hydrochloric acid to yield the pyrrolotriazine. Extraction of the acidic washings with ether yielded a further quantity of the pyrrolotriazine, total yield (0.5g, 48%), fawn needles, m.p. 260-1° decomp. (from ethanol).

(Found: C,48.6; H,4.2; N,18.7%; M^+, 223.059300. $C_9H_9N_3O_4$ requires C,48.4; H,4.1; N,18.8%; M, 223.059071).

$\nu_{max.}$ 3450 and 3250(N-H), 1740 and 1700(C=O), 1630(C=C), 1230(C-O)cm^{-1}.

τ(CF_3COOH) 8.53(3H,t,J=6Hz,$COOCH_2\underline{CH}_3$), 5.48(2H,q,J=6Hz, $COO\underline{CH}_2CH_3$), 3.52(1H,d,J=2Hz,8-H), 1.94(1H,d,J=2Hz,5-H)

Ethyl 8-phenylpyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylate (102)

6-Benzyl-1,3,5-triazin-2,4(1H,3H)-dione (2.03g), ethyl bromopyruvate(1.95g) and 1,2-dimethoxyethane ($50cm^3$) were refluxed together for 24h. Removal of the solvent under reduced pressure gave a brown residue which was washed with a little methanol to give the pyrrolotriazine (1.4g, 47%), colourless needles, m.p. 277-278° decomp. (from methanol).

(Found: C,60.1; H,4.2; N,13.8%; M^+, 299.091534.

$C_{15}H_{13}N_3O_4$

requires C,60.2; H,4.3; N,14.1%; M, 299.090598).

$\nu_{max.}$ 3200 and 3100(N-H), 1745 and 1720(C=O), 1620(C=C), 1200(C-O)cm^{-1}.

$\tau(CF_3COOH)$ 8.73(3H,t,H=7Hz,$COOCH_2\underline{CH_3}$), 5.62(2H,q, J=7Hz,$COO\underline{CH_2}CH_3$), 2.60(5H,s,8-$C_6\underline{H_5}$), 1.96(1H,s,6-H).

Attempted synthesis of pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione from 6-methyl-1,3,5-triazin-2,4(1H,3H)-dione

Bromoacetaldehyde, from 1.3g bromoacetaldehyde diethyl acetal, and 6-methyl-1,3,5-triazin-2,4(1H,3H)-dione (0.64g) were heated under reflux in ethanol for 30h. Removal of the solvent afforded a quantitative yield of the triazindione starting material.

8-Phenylpyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione (110)

6-Benzyl-1,3,5-triazin-2,4(1H,3H)-dione (1.0g), bromoacetaldehyde (from 1.5g bromoacetaldehyde diethyl acetal) and 1,2-dimethoxyethane (60cm^3) were heated under reflux for 5h. Removal of the solvent under reduced pressure gave a purple oily solid which on trituration with ethanol afforded the pyrrolotriazine as a purple-brown solid (0.65g, 58%), m.p. slowly decomp. above 300°.

On standing the compound quickly changed colour to a deep red-purple and an analytically pure sample could not be obtained.

(Found: M^+, 227.068941. $C_{12}H_9N_3O_2$ requires M, 227.069472).

$\nu_{max.}$ 3400 and 3200(N-H), 1735-1680(C=O), 1630(C=C)cm^{-1}.

No suitable solvent was available for the determination of an n.m.r. spectrum.

Pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylic acid (111)

Ethyl pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylate (0.1g) was warmed with 2N hydrochloric acid (5cm^3) on a steam bath for 2h. The carboxylic acid separated from the hot solution as colourless needles (0.06g, 69%), m.p. 289-291° decomp.

The acid was washed with water and cleaned by dissolution in sodium hydroxide followed by precipitation with hydrochloric

acid, but no suitable solvent could be found for recrystallisation.

(Found: $\underline{M}^+$, 195.028001. $C_7H_5N_3O_4$
requires $\underline{M}$, 195.026674).

$\nu_{max.}$ 3300(bonded OH), 3150(N-H),1725 and 1700(C=O), 1630(C=C)cm^{-1}.

$\tau[(CD_3)_2SO]$ 4.25(1H,d,J=2Hz,8H),3.41(2H,broad,s,1- and 3-NH)[a], 2.52(1H,d,J=2Hz,6-H).

Pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione (109)

Pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylic acid (0.1g) and copper bronze (0.05g) were intimately mixed and heated to 280° in a closed flask fitted with a cold finger. The flask was then evacuated (1mm Hg) and the pyrrolotriazine collected on the cold finger (0.04g, 52%), colourless powder, m.p. 208-210° decomp.

The pyrrolotriazine rapidly decomposed on contact with air or organic solvents.

(Found: $\underline{M}^+$, 151.038092. $C_6H_5N_3O_2$
requires $\underline{M}$, 151.038173).

$\nu_{max.}$ 1710(C=O), 1630(C=C)cm^{-1}.

Methyl pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylate (112)

The pyrrolotriazine-7-carboxylic acid (0.2g) was heated in refluxing methanol containing a little concentrated sulphuric acid for 16h. Concentration of the solvent to $10cm^3$

gave a brown solid which was refluxed with methanol and animal charcoal to give the methyl ester (0.17g, 79%), colourless plates, m.p. 288° decomp. (from methanol).

(Found: C,45.9; H,3.7; N,20.1%; M^+,209. $C_8H_7N_3O_4$ requires C,45.9; H,3.4; N,20.1%; M, 209).

$\nu_{max.}$ 3200 and 3100(N-H), 1740, 1720, and 1700 (C=O), 1630(C=C), 1220(C-O)cm^{-1}

$\tau[(CD_3)_2SO]$ (dimethylsulphoxide, τ7.38, internal standard) 6.15(3H,s,$COOCH_3$), 4.20(1H,d,J=2Hz,8-H) 2.42(1H,d,J=2Hz,6-H).

Ethyl 1,3-dimethylpyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylate (114)

To a solution of the ethyl pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylate (0.5g) in ethanol ($20cm^3$) was added potassium hydroxide (0.2g) in the minimum of ethanol and the dipotassium salt which rapidly separated was collected and dried in vacuo (0.5g, 75%). The potassio derivative was then stirred with methyl iodide (0.5g) in dimethylformamide ($5cm^3$) for 21h and the mixture poured onto water ($20cm^3$) to yield the dimethylpyrrolotriazindione (0.5g, 83%), colourless needles, m.p. 178-178.5° (from ethanol).

(Found: C,52.6; H,5.2; N,16.7%; M^+,251. $C_{11}H_{13}N_3O_4$ requires C,52.3; H,5.2; N,17.0%; M,251).

$\nu_{max.}$ 1735 and 1700(C=O), 1620(C=C), 1200(C-O)cm^{-1}.

$\tau(CDCl_3)$ 8.63(3H,t,J=7Hz,$COOCH_2\underline{CH}_3$), 6.55(6H,s,1-and 3-CH_3), 5.65(2H,q,J=7Hz,$COO\underline{CH}_2CH_3$), 4.00(1H,d, J=2Hz,8-H), 2.24(1H,d,J=2Hz,6-H).

Attempted synthesis of Ethyl 2,4-dichloropyrrolo[1,2-a][1,3,5]triazine-7-carboxylate (121)

(i) The following methods all gave intractable oils or tars:

(a) Ethyl pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylate (0.3g) and phosphorus oxychloride were heated under reflux for 3h.

(b) To a suspension of ethyl pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylate (0.34g) in chloroform was added thionyl chloride (1.14g) and dimethylformamide ($0.2cm^3$) and the mixture heated at 80^o for 1h.

(c) Ethyl pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylate (0.2g), phosphorus oxychloride ($12cm^3$) and dimethylaniline (0.4g) were heated at 120^o for 6h.

(ii) The following methods, outlined below, gave the starting material as the sole product:

(a) Ethyl pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylate and thionyl chloride (50% excess) were heated together at 80^o for 1.5h.

(b) Ethyl pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylate (0.3g) and phosphorus oxychloride ($1cm^3$) were heated under reflux for 1h.

(c) Ethyl pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-

7-carboxylate (0.28g), phosphorus oxychloride and phosphorus pentachloride were heated at 120° for 5h.

Bromination of Ethyl 1,3-dimethylpyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylate

The pyrrolotriazine (0.26g) and N-bromosuccinimide (0.18g) were heated under reflux in chloroform ($4cm^3$) for 10min. The cooled mixture was filtered, washed with sodium hydroxide solution (10%) and water and dried ($MgSO_4$). The resulting solution was concentrated and applied to a 20cm preparative t.l.c. plate (0.1cm silica gel with $CaSO_4$ binder) and the chromatogram was developed with benzene containing 10% ethylacetate. Under u.v. light two bands were visible, these were removed and extracted with chloroform. The fastest running fraction was ethyl 8-bromo-1,3-dimethylpyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylate (115) (0.06g, 17.5%), colourless needles, m.p. 169-170° (from ethanol).

[Found: C,39.8; H,3.7; N,12.6%; M^+ (^{79}Br isotope),329.

$C_{11}H_{12}N_3O_4Br$

requires C,40.0; H,3.6; N,12.7%; M(^{79}Br isotope),329].

The second fraction was ethyl 6,8-dibromo-1,3-dimethylpyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylate (116) (0.02g, 5%), colourless needles, m.p. 115° (from ethanol).

[Found: $\underline{M}^+$(^{79}Br isotope), 406.911491. $C_{11}H_{11}N_3O_4Br_2$
requires $\underline{M}$(^{79}Br isotope), 406.911729].

A similar reaction using 0.36g of N-bromosuccinimide and a refluxing time of 1h gave approximately equal amounts of the mono- and di-brominated products as shown by the n.m.r. spectrum of the crude mixture.

$\tau(CDCl_3)$ 8.62(3H,t,J=7Hz,$COOCH_2C\underline{H}_3$)*,
8.59(3H,t,J=7Hz,$COOCH_2C\underline{H}_3$)‡,
6.57(3H,s,3-CH_3)*, 6.55(3H,s,3-CH_3)‡,
6.16(3H,s,1-CH_3)*, 6.14(3H,s,1-CH_3)‡,
5.66(2H,q,J=7Hz,$COOC\underline{H}_2CH_3$)*,
5.60(2H,q,J=7Hz,$COOC\underline{H}_2CH_3$)‡,
2.19(1H,s,6-$\underline{H}$)*.

* Protons assigned to the 8-bromoderivative,

‡ Protons assigned to the 6,8-dibromoderivative.

2-Methyl-4,6-diphenoxy-1,3,5-triazine (124)

This was prepared by the method of Forbes and Gould[131], fawn needles, m.p. 79-80° (from the minimum of methanol).

(Found: $\underline{M}^+$, 279. $C_{16}H_{13}N_3O_2$
requires $\underline{M}$, 279).

$\nu_{max.}$ 1580 (skeletal vibration), 1220(C-O-Ph)cm^{-1}.

$\tau(CDCl_3)$ 7.51(3H,s,CH_3), 2.83(10H,m,2- and 4-OC_6H_5).

2,4-Dimethoxy-6-methyl-1,3,5-triazine (123)

This was prepared by the method of Grundmann and Mini[132] colourless needles, m.p. 67° (from petroleum ether b.p. 40-60°) (lit., 67-69°).

(Found: M^+, 155. $C_6H_9N_3O_2$
requires M, 155).

$\nu_{max.}$ 1580 (skeletal vibration), 1210(C-O-CH_3)cm^{-1}.

τ (CCl_4) 7.65(3H,s,CH_3), 6.07(6H,s,2- and 4-OCH_3).

Reaction of 2,4-dimethoxy-6-methyl-1,3,5-triazine with ethyl bromopyruvate

(i) The triazine (0.31g) and ethyl bromopyruvate (0.2g) were heated under reflux in absolute ethanol ($15cm^3$) for 68h. After removal of the solvent the remaining oily solid was triturated with dilute hydrochloric acid to give ethyl pyrrolo [1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylate (0.05g, 11%), identical to an authentic sample. A chloroform extract of the aqueous washings was dried ($MgSO_4$) and the solvent removed to afford a brown oil, the n.m.r. spectrum of which showed the presence of ethyl protons, and a small amount of starting material, but no evidence of any pyrrolotriazine. The aqueous mother liquors were taken to dryness to give 6-methyl-1,3,5-triazin-2,4(1H,3H)-dione hydrobromide (0.1g, 25%) as a fawn solid.

(ii) The above reaction was repeated using 1,2-dimethoxyethane as the refluxing solvent. After 68h removal of the solvent

gave a brown oil which was taken up in chloroform and the insoluble ethyl pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-6-carboxylate collected (0.015g, 3.5%). After being dried, ($MgSO_4$), the chloroform extract was taken to dryness to yield a brown oil. N.m.r. spectroscopic and chromatographic analysis of this material showed it to consist entirely of the starting materials.

Reaction of 2-methyl-4,6-diphenoxy-1,3,5-triazine with ethyl bromopyruvate

Ethyl bromopyruvate(0.2g), diphenoxytriazine (0.56g) and ethanol ($10cm^3$) were refluxed for 76h. Removal of the solvent under reduced pressure gave an orange oil, which on trituration with methanol yielded ethyl pyrrolo[1,2-a][1,3,5] triazin-2,4(1H,3H)-dione-7-carboxylate , identical to the authentic sample.

1,3,5-Trimethyl-1,3,5-triazin-2,4(1H,3H)-dione (130)

An ethereal solution of diazomethane (containing approximately 6g of diazomethane, 3.5 fold excess) was added dropwise to a stirred suspension of 6-methyl-1,3,5-triazin-2,4(1H,3H)-dione (2.54g) in dioxan ($100cm^3$) and the mixture was stirred for a further 48h. After removal of the small amount of insoluble material the solvents were distilled off under reduced pressure to give a yellow oil which was washed with light petrol and recrystallised from carbon tetrachloride

to give the trimethyltriazindione (2.8g, 90%), pale yellow prisms, m.p. 89-91°.

Chromatographic analysis of the crude yellow oil showed no evidence of any other products.

(Found: C,46.2; H,5.8; N,27.1%; M^+,155.069085. $C_6H_9N_3O_2$ requires C,46.5; H,5.8; N,27.4%; M,155.069472).

$\nu_{max.}$ 1720 and 1670(C=O), 1600(C=N)cm^{-1}

$\tau(CDCl_3)$ 7.55(3H,s,6-CH_3), 6.68(3H,s,1-CH_3), 6.55(3H,s,3-CH_3).

When ether was used as the sole solvent for the above reaction a much poorer yield (22%) of the dimethylated producted was obtained and in this case chromatographic analysis of the crude oil showed the presence of a small amount of a second component. The peak at m/e 169 in the mass spectrum of the crude oil showed that this minor component was probably 6-ethyl-1,3-dimethyl-1,3,5-triazin-2,4(1H,3H)-dione.

Reaction of the potassium salt of 6-methyl-1,3,5-triazin-2,4(1H,3H)-dione with methyl iodide

The potassium salt of the triazindione (0.1g) and methyl iodide were heated under reflux in methanol ($10cm^3$) for 2h and the solvent was then removed to give a yellow oil. This oil was dissolved in water and the resulting solution extracted with chloroform and the extract dried ($MgSO_4$) and concentrated to yield a pale yellow oil, the n.m.r. spectrum

of which was identical to that of 1,3,6-trimethyl-1,3,5-triazin-2,4(1H,3H)-dione.

The aqueous solution was taken to dryness and the resulting oil triturated with acetone. The precipitated potassium iodide was separated and the acetone soluble fraction evaporated to dryness to give a pale yellow oily solid, the n.m.r. spectrum of which indicated a mixture of 6-methyl-1,3,5-triazin-2,4(1H,3H)-dione and 1,6-dimethyl-1,3,5-triazin-2,4(1H,3H)-dione in a 1:1 ratio.

$\tau\left[(CD_3)_2SO\right]$ (dimethylsulphoxide, τ7.38, internal standard).

7.72(3H,s,CH_3)*, 7.50(3H,s,6-CH_3)‡,

6.60(3H,s,1-CH_3)‡, 4.40(3H,broad s,N-H)a*‡.

* Protons assigned to 6-methyl-1,3,5-triazin-2,4(1H,3H)-dione.

‡ Protons assigned to 1,6-dimethyl-1,3,5-triazin-2,4(1H,3H)-dione.

Reaction of the potassium salt of 6-methyl-1,3,5-triazin-2,4(1H,3H)-dione with phenacyl bromide

The potassium salt of the triazindione (0.56g) and phenacyl bromide (0.7g) were stirred at room temperature in dimethylformamide (10cm^3) for 15h. The mixture was then poured into water to give 6-methyl-1,3-diphenacyl-1,3,5-triazin-2,4(1H,3H)-dione (0.4g, 32.5%), colourless prisms, m.p. 103-105° efferves. (from carbon tetrachloride-chloroform).

[Found: C,60.7; H,4.7; N,10.23%; $\underline{M}^+(-2H_2O)$, 363.

$C_{20}H_{17}N_3O_4.2H_2O$

requires: C,60.15; H,5.3; N,10.5%; $\underline{M}(-2H_2O)$, 363].

$\nu_{max.}$ 1740, 1690, and 1680(C=O)cm^{-1}.

$\tau(CDCl_3)$ 7.69(3H,s,CH_3), 5.03(2H,s,1-$C\underline{H}_2COC_6H_5$),

4.60(2H,s,3-$C\underline{H}_2COC_6H_5$),

2.52(6H,m,1- and 3-$CH_2CO\underline{Ph}$,m, and p protons),

2.05(4H,m,1- and 3-$CH_2CO\underline{Ph}$,o protons).

On standing the aqueous mother liquors afforded an unidentified compound (0.07g), colourless prisms, m.p. 234.5-235.5° decomp. (from aqueous dimethylsulphoxide).

(Found: C,54.1; H,4.9; N,15.5%).

$\nu_{max.}$ 1695(C=O)cm^{-1}.

$\tau[(CD_3)SO]$ (dimethylsulphoxide, τ7.38, internal standard).

7.75(3H,s), 6.58(3H,s), 5.15(1H,s), 5.08(1H,s),

2.28(3H,m), 1.90(2H,m).

Evaporation of the remaining mother liquors to dryness gave 6-methyl-1,3,5-triazin-2,4(1H,3H)-dione (0.32g, 74%), identical to an authentic sample.

Reaction of the potassium salt of 6-methyl-1,3,5-triazin-2,4(1H,3H)-dione with two moles of phenacyl bromide

The potassium salt of 6-methyl-1,3,5-triazin-2,4(1H,3H)-dione (3.3g) and phenacyl bromide (8g) were stirred in dimethylformamide (30cm^3) for 96h and the mixture then poured into water. Extraction of the aqueous solution with

chloroform gave a yellow oil, which after being triturated with the minimum of chloroform gave 6-methyl-1-phenacyl-1,3,5-triazin-2,4(1H,3H)-dione hydrobromide (0.08g, 1.6%), pale yellow solid, m.p. 281-283° decomp.

[Found: $\underline{M}^+$ 245, $\underline{M}^+(-H_2O)$, 227.068941. $C_{12}H_{11}N_3O_3.H_2O$ requires $\underline{M}$ 245, $\underline{M}(-H_2O)$, 227.069472].

$\nu_{max.}$ 1780 and 1700(C=O), 1600(C=N)cm^{-1}.

τ (CF_3COOH) 7.02(3H,s,CH_3), 4.12(2H,s,1-$C\underline{H}_2COPh$), 2.33(3H,$CH_2COP\underline{h}$,$\underline{m}$ and $\underline{p}$ protons), 1.92(2H, $CH_2COP\underline{h}$,$\underline{o}$ protons).

The chloroform washings, after removal of the solvent, yielded 6-methyl-1,3-diphenacyl-1,3,5-triazin-2,4(1$\underline{H}$,3$\underline{H}$)-dione (0.62g, 8.6%), identical to the previous sample.

3-Phenacyl-7-phenylpyrrolo[1,2-a][1,3,5]triazin-2,4(1$\underline{H}$,3$\underline{H}$)-dione (140)

6-Methyl-1,3-diphenacyl-1,3,5-triazin-2,4(1$\underline{H}$,3$\underline{H}$)-dione (0.1g) and acetic acid ($5cm^3$) were refluxed for 15h and then cooled to yield the pyrrolotriazine (0.25g, 26.5%), fawn needles, m.p. 280° (from aqueous dimethylformamide).

[Found: C,67.7; H,4.9; N,11.6%; $\underline{M}^+(-\frac{1}{2}H_2O)$, 345.111598. $C_{20}H_{15}N_3O_3.\frac{1}{2}H_2O$

requires C,68.1; H,4.6; N,11.9%; $\underline{M}(-\frac{1}{2}H_2O)$, 345.111334].

$\nu_{max.}$ 1740 and 1685(C=O), 1640(C=C)cm^{-1}.

6(1H)-Dicarbethoxymethylene-1,3,5-triazin-2,4(3H,5H)-dione(93)

A solution of sodium diethylmalonate in ethanol, prepared from sodium (2.3g) and diethyl malonate(16g), was added dropwise to a suspension of cyanuric chloride (18.4g) stirring in ether. After the addition was completed the mixture was heated on a water-bath for 0.5h and then filtered hot. The filtrate was evaporated to dryness and the residue extracted with acetone. Removal of the acetone gave the triazindione (16.5g, 61%), colourless needles, m.p. 181-182° (lit., 181°)[85] (from ethanol).

(Found: M^+, 271.079377. $C_{10}H_{13}N_3O_6$ requires M^+, 271.080427).

$\nu_{max.}$ 1760(C=O, amide), 1720(C=O , ester), 1640(C=C)cm^{-1}

$\tau(CDCl_3)$ 8.70[6H,t,J=7Hz,$(COOCH_2\underline{CH_3})_2$], 5.75[4H,q, J=7Hz,$(COO\underline{CH_2}CH_3)_2$], 1.18(1H, broad s,3-NH)[a], -2.22(2H, broad s, 1- and 5-NH)[a].

Attempted Synthesis of 6-carboxymethyl-1,3,5-triazin-2,4(1H,3H)-dione (89)

(i)6-Dicarbethoxymethylene-1,3,5-triazin-2,4(1H,3H)-dione (1.4g) and concentrated hydrochloric acid were heated at 130° for 4h to give a quantitative yield of 6-methyl-1,3,5-triazin-2,4(1H,3H)-dione hydrochloride.

(ii) Use of 8N hydrochloric acid in the above reaction gave the triazinyl hydrochloride as above.

(iii)6-Dicarbethoxymethylene-1,3,5-triazin-2,4(1H,3H)-dione (1.4g) and 2N (or 4N) hydrochloric acid were heated at 130° for 15h. A quantitative recovery of the starting material was obtained.

3-Benzyl-6(1H)-dicarbethoxymethylene-1,3,5-triazin-2,4(3H,5H)-dione (95)

Potassium hydroxide (0.28g), in the minimum of ethanol, was added to a solution of 6-carbethoxymethylene-1,3,5-triazin-2,4(1H,3H)-dione (1.36g) in ethanol. The precipitated potassium salt was collected, and dried in vacuo, then stirred with benzyl bromide (0.86g) in dimethylformamide ($25cm^3$). After 12h the mixture was poured into water ($100cm^3$) to yield the N-benzyltriazindione (1.8g, 99%), colourless needles, m.p. 135-136° (from ethanol).

(Found: C,56.2; H,5.3; N,11.7%; M^+, 361.129259.

$C_{17}H_{19}N_3O_6$

requires C,56.5; H,5.3; N,11.6%; M, 361.127375).

$\nu_{max.}$ 1745(C=O, amide) 1705(C=O, ester), 1645(C=C)cm^{-1}.

τ ($CDCl_3$) 8.70[6H,t,J=7Hz,$(COOCH_2CH_3)_2$], 5.76[4H,q,J=7Hz,$(COOCH_2CH_3)_2$], 5.03(2H,s 3-$CH_2C_6H_5$), 2.68(5H,m,3-$CH_2C_6H_5$) -2.26(2H, broad s, 1- and 3-NH)[a].

Attempted synthesis of 1,3-dibenzyl-6(1H)-dicarbethoxymethylene-1,3,5-triazin-2,4(3H,5H)-dione

The potassium salt of 3-benzyl-6-dicarbethoxymethylene-1,3,5-triazin-2,4(1H,3H)-dione, obtained as a colourless solid by the addition of an ethanolic solution of potassium hydroxide to a solution of the 3-benzyltriazindione in ethanol, was stirred with benzyl bromide in dimethylformamide for 15h but, on pouring into water, afforded 3-benzyl-6-dicarbethoxymethylene-1,3,5-triazin-2,4(1H,3H)-dione as the sole product.

2,4,6(1H,3H,5H)-tris(dicarbethoxymethylene)-1,3,5-triazine (94)

This was prepared, using three equivalents of sodium diethyl malonate, by the method used for the preparation of 6(1H)-dicarbethoxymethylene-1,3,5-triazin-2,4(3H,5H)-dione, colourless needles, m.p. 182-183° (from ethanol).

$\nu_{max.}$ 1680(C=O), 1605(C=C)cm^{-1}.

$\tau(CDCl_3)$ 8.63[18H,t,J=7Hz,$(COOCH_2CH_3)_3$],
5.66[12H,q,J=7Hz,$(COOCH_2CH_3)_3$],
-3.83(3H,broad s,1-,3-, and 5-NH)[a].

The potassium salt of this compound when stirred with benzyl bromide in dimethylformamide for 15h afforded only 2,4,6(1H,3H,5H)-tris(dicarbethoxymethylene)-1,3,5-triazine.

Attempted synthesis of 2,6(1H,3H)-bis(dicarbethoxymethylene)-1,3,5-triazin-4(5H)-one

Attempts to prepare this by the method used for the preparation of 6(1H)-dicarbethoxymethylene-1,3,5-triazin-2,4-dione, but using two equivalents of sodium diethyl malonate, or by the method of Reynolds, Berner & Boutwell[87] gave the tris(dicarbethoxymethylene)-derivative only.

3-(2,4-diamino-1,3,5-triazin-6-yl)propionic acid(142)

This was prepared by the method of Nagy[133], colourless solid, infusible.

$\nu_{max.}$ 3350 and 3160(N-H), 1700(C=O)cm^{-1}.

$\tau(CF_3COOH)$ 6.86(4H,s,CH_2CH_2OH), 2.5(2H,broad s,NH_2).

3-(2,4-diamino-1,3,5-triazin-6-yl)propionitrile (141)

This was prepared by the method of American Cyanamid Co.[55], colourless needles, m.p. 246-248° (lit., 247-248°) (from methanol).

$\nu_{max.}$ 3500, 3400, 3350, and 3100(N-H), 2250(C≡N)cm^{-1}.

$\tau(CF_3COOH)$ 6.88(4H,m,CH_2CH_2CN), 2.50(2H,broad s,NH_2).

3-(2,4-diamino-1,3,5-triazin-6-yl)propan-2-one (143)

This was prepared by the method of Thurston[134], colourless plates, m.p. 185-186° (lit., 184-185°) (from ethanol).

$\nu_{max.}$ 3350 and 3150(N-H), 1710(C=O)cm^{-1}.

τ (CF_3COOH) 7.56(3H,s,-$CH_2CH_2COC\underline{H}_3$), 6.79(4H,m,-$C\underline{H}_2C\underline{H}_2COCH_3$), 2.25(4H,broad s,2- and 4-NH_2).

Attempted synthesis of 2,4-diaminopyrrolo[1,2-a][1,3,5]triazin-6(7H)-one (145)

(i) 3-(2,4-diamino-1,3,5-triazin-6-yl) propionic acid (0.5g) and phorphorus oxychloride (10cm^3) were heated under reflux for 5h. Removal of the excess of phorphorus oxychloride under reduced pressure gave a dark tarry solid which was poured into ice water and neutralised with sodium carbonate. No organic material could be extracted from the aqueous solution.

(ii) 3-(2,4-diamino-1,3,5-triazin-6-yl) propionic acid (0.5g), acetic anhydride (40cm^3) and a little concentrated sulphuric acid were heated at 70° for 0.5h. The mixture was concentrated under reduced pressure and neutralised with aqueous potassium hydroxide (10%). Further concentration of the mixture gave a crystalline mass, which, when washed with the minimum of water, afforded the starting material. No further products could be isolated.

(iii) 3-(2,4-diamino-1,3,5-triazin-6-yl) propionic acid (0.5g) and polyphosphoric acid (5g) were heated at 100° for 4h. No identifiable products could be isolated from the resultant mixture.

Attempted synthesis of 2,4,6-triaminopyrrolo[1,2-a][1,3,5] triazine (144)

2-(2,4-diamino-1,3,5-triazin-6-yl) propionitrile (0.5g) and acetic anhydride ($5cm^3$) were refluxed for 1h to yield 2-(2,4-diacetamido-1,3,5-triazin-6-yl) propionitrile, (0.7g, 94%), colourless needles, m.p. 214-216° (from methanol).

$\nu_{max.}$ 3400 and 3330(N-H), 2250(C≡N) cm^{-1}

$\tau(CF_3COOH)$ 7.45(6H,s,2- and 4-$NHCOCH_3$),

6.6(2H,m,6-CH_2CH_2CN), 6.9(2H,m,6-CH_2CH_2CN).

The same product was obtained when the refluxing time was extended to 60h.

Attempted synthesis of 2,4-diamino-6-methylpyrrolo[1,2-a][1,3,5]triazine (146)

(i) 2-(2,4-diamino-1,3,5-triazin-6-yl)propan-2-one (0.15g) and polyphosphoric acid (1.5g) were stirred at 100° for 20min. The mixture was then cooled, poured into ice-water and the resultant solution neutralised. No organic material could be obtained from this aqueous solution.

(ii) The above reaction was repeated with ethyl polyphosphoric acid but afforded no identifiable products.

(iii) 2-(2,4-diamino-1,3,5-triazin-6-yl)propan-2-one (0.5g) and acetic anhydride ($25cm^3$) were heated under reflux for 12h. No identified products were isolated.

2-Amino-3,4-diphenylpyrrole (156)

ω-Aminoacetophenone hydrochloride (2.57g) in ethanol (70%, 30cm^3) was added dropwise over 15 min to a mixture of benzylcyanide (2.34g) and sodium hydroxide (1.1g) which was stirred and vigorously refluxed in ethanol (70%, 50cm^3). The mixture was refluxed for a further 0.5h after the addition was completed then quickly cooled and poured onto crushed ice. The precipitate was filtered and washed well with water to yield the aminopyrrole (1.45g 42%), colourless plates, m.p. 279-280° (from methanol).

(Found: C,81.8; H,12.1; N,6.0%; $\underline{M}^+$ 234.114782 $C_{16}H_{14}N_2$

requires C,82.1; H,12.0; N,6.0%; $\underline{M}$ 234.115693).

$\nu_{max.}$ 3420 and 3220(N-H), 1605(C=C)cm^{-1}.

2-Amino-3-cyano-4-phenylpyrrole (155)

This was prepared by the above method from ω-amino acetophenone hydrochloride and malononitrile, (58%), grey plates m.p. 175° (from benzene, sublimation) (Gerwald [101] quotes m.p. 172-174°).

$\nu_{max.}$ 3380 and 3250(N-H), 2200(C≡N), 1640(C=C), 1600(C=C)cm^{-1}.

Attempted synthesis of 2-amino-4-phenylpyrrole

An adaptation of the previous method using ω-amino-acetophenone hydrochloride and acetonitrile yielded 2,5-diphenyl-1,4-dihydropyrazine as the sole product.

Attempted synthesis of 2-amino-3-ethoxycarbonyl-4-phenyl pyrrole

The procedure was repeated with ω-aminoacetophenone hydrochloride and ethylcyanoacetate. 2,5-Diphenyl-1,4-dihydropyrazine was the only product isolated.

8-Cyano-3-methyl-7-phenylpyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione (161)

2-Amino-3-cyano-4-phenylpyrrole (1.83g), methyl isocyanate (1.2g), and dry pyridine (15cm^3) were refluxed with stirring for 5h. Removal of the pyridine under reduced pressure gave a dark brown oil, which on trituration with chloroform yielded the pyrrolotriazine (0.58g, 22%), colourless needles, m.p. 338-340° decomp. (from dimethylformamide).

(Found: C,62.5; H,4.2; N,21.0%; M^+ 266.079989.

$C_{14}H_{10}N_4O_2$

requires C,63.2; H,3.8; N,21.1%; M 266.080370).

$\nu_{max.}$ 3400(N-H), 2250(C≡N), 1740 and 1680(C=O), 1640(C=C)cm^{-1}.

No suitable solvent was available for the determination of a n.m.r. spectrum.

The chloroform filtrate was chromatographed on a neutral alumina column and the eluate decolourised with animal charcoal to yield dimethylurea, colourless needles, m.p. 107° (from light petroleum).

8-Cyano-3-ethyl-7-phenylpyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)- dione (162)

Ethyl isocyanate (1.5g), 2-amino-3-cyano-4-phenylpyrrole (1.83g), and dry pyridine ($10cm^3$) were refluxed together for 15h. Removal of the pyridine under reduced pressure and trituration of the resulting oil with chloroform gave the pyrrolotriazine (0.4g, 14.5%). Recrystallisation from methanol gave green needles (0.25g, 9%), m.p. 292-294°, concentration of the solution afforded a second crop of colourless needles (0.15g, 5.5%), m.p. 291-293°.

Both sets of crystals gave similar spectra and analytical results and a mixed melting point determination was undepressed.

Found:(green needles) C,64.0; H,4.5; N,19.8%; M^+,280.095719.

(colourless needles) C,64.0; H,4.5; N,20.1%; M,280.095167.

$C_{15}H_{12}N_4O_2$

requires C,64.0; H,4.3; N,20.0%; M,380.096019 .

$\nu_{max.}$ (green needles) 3140(N-H), 2225(C≡N),1755 and 1710(C=O), 1640(C=C)cm^{-1}.

(colourless needles) 3130(N-H), 2250(C≡N), 1740 and 1695(C=O), 1630(C=C)cm^{-1}.

$\tau[(CD_3)_2SO]$ (dimethylsulphoxide,τ7.38, internal standard).

8.70(3H,t,J=7Hz,3-CH_2CH_3),

6.02(2H,q,J=7Hz,3-CH_2CH_3),

2.53(5H,s,8-C_6H_5), 2.32(1H,s,6-H).

8-Cyano-3,7-diphenylpyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione (163)

2-Amino-3-cyano-4-phenylpyrrole (0.58g) and phenyl isocyanate (1.0g), in dry pyridine ($10cm^3$), were heated under reflux for 3h. Removal of the pyridine under reduced pressure and trituration of the oily brown solid obtained with chloroform yielded diphenylurea (0.6g), as colourless needles, m.p. 242-243° (from ethanol). Evaporation of the filtrate to dryness and trituration of the resulting oil with ethanol gave a fawn powder (0.35g) which after being sublimed and crystallised from ethanol and acetone mixture gave the pyrrolotriazine (0.08g, 8%), pale yellow plates, m.p. 305° decomp. (from ethanol-acetone).

[Found: C,66.1; H,3.7; N,16.2%; $M^+(-H_2O)$, 328.09471.
$C_{19}H_{12}N_4O_2.H_2O$
requires C,66.0; H,4.0; N,16.2%; $M(-H_2O)$, 328.096019].

$\nu_{max.}$ 3400(N-H), 2250(C≡N), 1745 and 1690(C=O), 1640(C=C)cm^{-1}.

3,7,8-Triphenylpyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione (164)

2-Amino-3,4-diphenylpyrrole (0.47g) and phenyl isocyanate (0.96g) were refluxed in dry pyridine solution ($10cm^3$) for 3h. Removal of the pyridine under reduced pressure gave a brown oil which yielded diphenylurea, colourless needles, m.p. 242-243° (from ethanol) (lit., 237-237.5°)[135] on trituration with chloroform. The chloroform

washings were taken to dryness and the resulting orange oil triturated with ethanol, whilst cooling in a solid carbon dioxide and acetone bath, to give the pyrrolotriazine (0.08g, 10.5%), colourless solid, m.p. 210-212°.

[Found: $\underline{M}^+$, 379. $\underline{M}^+$(-PhNCO), 260.095294. $C_{24}H_{17}N_3O_2$. requires $\underline{M}$, 379. $\underline{M}$(-PhNCO), 260.094958].

$\nu_{max.}$ 3350(N-H), 1700 and 1660(C=O), 1595(C=C)cm^{-1}.

The n.m.r. spectrum was poorly resolved and the pyrrole proton could not be distinguished in the aromatic multiplet.

$\tau(CDCl_3)$ 3.0[m,$(C_6H_5)_3$,pyrrolic-H].

1-Phenyl-3-(3-cyano-4-phenyl pyrrol-2-yl)urea (165)

2-Amino-3-cyano-4-phenyl pyrrole (0.28g), phenyl isocyanate (0.18g), and dry benzene (10cm^3) were refluxed together for 0.5h and the mixture was then cooled and filtered to give the pyrrolylurea (0.23g, 50%), mauve needles, m.p. 269-271° decomp. (from dimethylformamide).

(Found: C,71.5; H,4.8; N,18.5%; $\underline{M}^+$, 302. $C_{18}H_{14}N_4O$ requires C,71.5; H,4.6; N,18.5%; $\underline{M}$, 302).

$\nu_{max.}$ 3400(N-H), 2250(C≡N), 1700(C=O), 1640(C=C)cm^{-1}.

1-Phenyl-3-(3,4-diphenyl pyrrol-2-yl)urea (166)

2-Amino-3,4-diphenylpyrrole (0.23g), phenyl isocyanate (0.13g) and dry benzene (10cm^3) were heated together under reflux for 5min to yield the urea (0.32g, 92%), colourless needles, m.p. 204-205° (from ethanol).

[Found: C,76.3; H,5.8; N,11.2%; $\underline{M}^+(-H_2O)$, 353.153147.
$C_{23}H_{19}N_3O.\frac{1}{2}H_2O$
requires C,76.2; H,5.5; N,11.6%; $\underline{M}$ $(-H_2O)$, 353.152804].
$\nu_{max.}$ 3300(N-H), 1660(C=O)cm^{-1}.

1-(3,4-Diphenylpyrrol-2-yl)urea (168)

2-Amino-3,4-diphenylpyrrole (0.23g) in a little ethanol was added to water ($2cm^3$) containing potassium cyanate (0.08g) and concentrated hydrochloric acid ($0.1cm^3$) and the resultant mixture stirred for 2h at room temperature to yield the pyrrolylurea, m.p. 149-151°, colourless needles, (from ethanol).

(Found: $\underline{M}^+$, 277.121682. $C_{17}H_{15}N_3O$
requires $\underline{M}$, 277.121505).
$\nu_{max.}$ 3450,3400 and 3220(N-H), 1660(C=O)cm^{-1}.

Synthesis of 8-cyano-3,7-diphenylpyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione (163) from 1-phenyl-3-(3-cyano-4-phenylpyrrol-2-yl)urea (165)

The pyrrolylurea (0.6g), phenyl isocyanate (0.25g), and dry pyridine ($10cm^3$) were heated together under reflux for 15h. Removal of the pyridine under reduced pressure gave a dark brown oily solid which on trituration with chloroform yielded the starting material (0.35g, 58%). The chloroform washings were evaporated to dryness to give a dark green solid (0.2g) which could not be decolourised by boiling with

ethanol containing animal charcoal. Thin layer chromatographic examination of this material (alumina with acetic acid, or silica with ethanol) showed the presence of two components; the pyrrolylurea as a minor component, and a component with the same R_F. value as the authentic pyrrolotriazine as the major component. Repeated recrystallisation of the green solid from the minimum of ethanol gave the pyrrolotriazine (0.03g, 4.5%) as off-white plates with identical m.p., i.r. spectrum, and R_F. value to the authentic sample.

A third product (0.005g), which formed as a colourless sublimate in the condenser during the course of the reaction, was shown to be diphenylurea.

Attempted synthesis of 3,7,8-triphenylpyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione from the corresponding pyrrolylurea

1-Phenyl-3-(3,4-diphenylpyrrol-2-yl)urea (0.53g), phenyl isocyanate (0.18g), and dry pyridine ($10cm^3$) were heated under reflux for 15h. Removal of the pyridine under reduced pressure gave an oily brown solid which on trituration with chloroform yielded diphenylurea (0.06g, 18.7%). The chloroform washings, after removal of the solvent, gave a brown oil from which was obtained the unchanged pyrrolylurea (0.47g, 89%) on trituration with light petroleum.

Attempted synthesis of 1-ethyl-3-(3-cyano-4-phenylpyrrol-2-yl) urea

(i) 2-Amino-3-cyano-4-phenylpyrrole (0.92g) and ethyl isocyanate (0.35g) were refluxed in dry benzene ($20cm^3$) (or petroleum ether). After 4h a quantitative yield of the starting material was recovered.

(ii) 2-Amino-3-cyano-4-phenylpyrrole (0.58g), ethyl isocyanate (0.22g) and pyridine ($10cm^3$) were heated under reflux for 10h. Removal of the pyridine under reduced pressure gave a dark brown intractable tar.

(iii) 2-Amino-3-cyano-4-phenylpyrrole (0.58g), ethyl isocyanate (0.22g), and pyridine ($10cm^3$) were heated under reflux for 2h. Removal of the pyridine under reduced pressure gave a brown tar which, after being triturated with chloroform, afforded diethylurea (0.12g, 67%), colourless needles, m.p. 216-218° (from methanol).

No further identifiable products could be obtained from the mother liquors.

Attempted Synthesis of 3-ethyl-7,8-diphenylpyrrolo[1,2-a][1,3,5] triazin-2,4(1H,3H)-dione

2-Amino-3,4-diphenylpyrrole (1.17g), ethyl isocyanate (0.89g), and dry pyridine ($15cm^3$) were refluxed for 16h, then cooled to yield 1-ethyl-3-(3,4-diphenylpyrrol-2-yl)urea (0.1g, 6.5%), colourless needles, m.p. 328-330° (from ethanol).

(Found: $\underline{M}^+$, 305.153371. $C_{19}H_{19}N_3O$

requires $\underline{M}$, 305.152804).

$\nu_{max.}$ 1660(C=O)cm^{-1}.

Removal of the pyridine under reduced pressure and trituration of the resulting oil with ether gave an unidentified mixture of compounds, (0.44g), colourless needles, m.p. 198-200° (from methanol).

(Found: $\underline{M}^+$, 319.169030. $C_{20}H_{21}N_3O$

requires $\underline{M}$, 319.168453.

Found: $\underline{M}^+$, 319.132921. $C_{19}H_{17}N_3O_2$

requires $\underline{M}$, 319.132069).

These compounds were not separated.

The n.m.r. spectrum of the mixture was only poorly resolved but indicated the presence of an ethyl grouping and two phenyl moieties.

An identical mixture of compounds was obtained from an attempted preparation of 1-ethyl-3-(3,4-diphenylpyrrol-2-yl) urea by reaction of 2-amino-3,4-diphenylpyrrole with ethyl isocyanate in benzene.

The ethereal washings were taken to dryness and chromatographed on a neutral alumina column with chloroform as eluting solvent to give a pale yellow oil. This was washed with petrol to give a small amount of an unidentified pale yellow solid, m.p. 60° efferves.

$\nu_{max.}$ 3300(N-H), 1695(C=O)cm^{-1}.

1-Acetyl-3-(3,4-diphenylpyrrol-2-yl)urea (174)

2-Amino-3,4-diphenylpyrrole (0.48g), pyridine ($5cm^3$), and acetylurea (0.21g) were refluxed for 2h. After removal of the solvent under reduced pressure the remaining oily brown solid was washed with chloroform to give the pyrrolylurea (0.43g, 66%), colourless needles, m.p. 248-249° decomp. (from methanol).

(Found: C,71.1; H,5.3; N,13.2%; M^+ 319. $C_{19}H_{17}N_3O_2$ requires C,71.5; H,5.3; N,13.2%; M 319).

$\nu_{max.}$ 3300(N-H), 1710 and 1670(C=O)cm^{-1}.

Attempted synthesis of 1-acetyl-3-(3-cyano-4-phenylpyrrol-2-yl)urea

2-Amino-3-cyano-4-phenylpyrrole (1.22g), acetylurea (0.68g), and pyridine ($10cm^3$) were refluxed together for 3h. The deep purple solid, obtained after removal of the pyridine, was washed with chloroform to give a quantitative recovery of N-acetylurea. No unchanged pyrrole could be recovered from the chloroform washings.

1-(4-Nitrobenzoyl)-3-(3,4-diphenylpyrrol-2-yl)urea (175)

2-Amino-3,4-diphenylpyrrole (0.88g), p-nitrobenzoylurea (1.0g), and pyridine ($10cm^3$) were refluxed together for 16h. Removal of the solvent under reduced pressure gave a brown solid which was washed with chloroform to yield the pyrrolylurea, (1.48g, 96%), orange needles,

m.p. 230-231° (from dimethylformamide).

(Found: C,65.9; H,4.5; N,12.9. $C_{24}H_{18}N_4O_4 \cdot \frac{1}{2}H_2O$ requires C,66.2; H,4.4; N,12.9%).

$\nu_{max.}$ 3400 and 3300 (N-H), 1695 and 1660 (C=O), 1530 and 1350(NO_2)cm^{-1}.

Attempted ring closure of 1-(4-nitrobenzoyl)-3-(3,4-diphenylpyrrol-2-yl)urea

The following methods gave only unchanged starting material:

(i) The pyrrole (0.19g) was stirred in dichloromethane ($10cm^3$) with triethylamine (0.05g) for 20h.

(ii) The pyrrolylurea (0.21g), diethylaniline (0.075g), and xylene ($5cm^3$) were refluxed together for 3.5h.

(iii) Polyphosphoric acid and the pyrrolylurea were stirred together for several hours.

1-Acetyl-2-acetylamino-3,4-diphenylpyrrole (178)

1-(4-Nitrobenzoyl)-3-(3,4-diphenylpyrrol-2-yl)urea (0.1g) and triethylamine (0.04g) were heated together for 0.5h in acetic anhydride ($5cm^3$) on a steam bath, and the mixture then refluxed for 1h. The cooled mixture was triturated with aqueous ethanol to yield the pyrrole (0.07g, 98%), mauve needles, m.p. 196-198° (from methanol).

The compound was unstable and darkened on contact with warm organic solvents.

(Found: C,74.6; H,5.8; N,8.7%; $\underline{M}^+$, 318.136820

$C_{20}H_{18}N_2O_3$

requires C,75.5; H,5.7; N,8.8%; $\underline{M}$, 318.136023).

$\nu_{max.}$ 3300(N-H), 1725 and 1705(C=O)cm^{-1}.

$\tau\left[(CD_3)_2SO\right]$ 6.23$\left[6H,s,(OCH_3)_2\right]$, 2.24(11H,m,3- and 4-$C_6H_5$, and 6-H).

Synthesis of 7,8-diphenylpyrrolo$\left[1,2\text{-}a\right]\left[1,3,5\right]$triazin-2,4(1H,3H)-dione (179)

2-Amino-3,4-diphenylpyrrole (0.47g), biuret (0.21g), and pyridine ($5cm^3$) were heated under reflux for 15h. Removal of the pyridine under reduced pressure gave a fawn solid which was washed with water, ethanol, and acetone to give the pyrrolotriazine, colourless solid (0.57g, 94%), m.p. 303-305° decomp.

No suitable solvent was available for recrystallisation of the product.

Spectroscopic evidence showed this compound to be impure.

(Found: $\underline{M}^+$, 303.101349, $C_{18}H_{13}N_3O_2$

requires $\underline{M}$, 303.100770).

$\nu_{max.}$ 3400, 3300 and 3230(N-H), 1700-1680(C=O)cm^{-1}.

2-Acetamido-3-cyano-4-phenylpyrrole

2-Amino-3-cyano-4-phenylpyrrole (0.5g) in acetic anhydride ($2.5cm^3$) was warmed on a steam bath for 0.5h and the solution cooled to yeild the pyrrolylamide, (0.32g, 52%),

pale grey plates, m.p. 286-288° (lit., 290°)[104], (from methanol).

$\nu_{max.}$ 3320(N-H), 2250(C≡N), 1670(C=O), 1620(C=C)cm^{-1}.

The pyrrolylamide was recovered unchanged after being heated with formamide in refluxing pyridine for periods of up to 24h.

1,5,6-Trimethyl-3-methylthio-1,2,4-triazinium iodide (187)

5,6-Dimethyl-3-methylthio-1,2,4-triazine (1.55g) and methyl iodide (7.6g) were shaken in a sealed flask* for 16h. Addition of ether to the mixture gave the quaternary iodide (2.2g, 74%), copper plates, m.p. 199-200° decomp. (from ethanol).

The product decomposed rapidly on contact with warm organic solvents to give dark green/red florescent solutions accompanied by release of methyl mercaptan. Concentration of these solutions gave only dark green intractable tars.

(Found: C,28.5; H,4.1; N,13.9. $C_7H_{12}N_3S$

requires C,28.3; H,4.0; N,14.1%).

$\tau(D_2O)$ 7.33(3H,s,5-CH_3), 7.16(3H,s,6-CH_3), 7.10(3H,s,SCH_3), 5.58(3H,s,2-CH_3).

* The reaction mixture immediately turned dark green on contact with air.

When acetone or dimethylformamide was used as a solvent for the above reaction poorer yields (4%-24%) were obtained, accompanied by the formation of much florescent, probably

polymeric material.

Under refluxing conditions, using methanol as the solvent, the reaction afforded a black intractable tar.

Reaction of 5,6-dimethyl-3-methylthio-1,2,4-triazine with dimethylsulphate, under a variety of conditions, in an attempt to form the quaternary methyl compound, afforded only intractable tars.

1,5,6-Trimethyl-3-phenyl-1,2,4-triazinium iodide (188)

5,6-Dimethyl-3-phenyl-1,2,4-triazine (0.93g) was shaken with excess methyl iodide (2.16g) for 15h in a closed flask. The solid was then collected and washed with ether to yield the triazinium iodide (0.93g, 57%), red-bronze needles, m.p. 195-197° decomp. (from ethanol).

(Found: C,44.1; H,4.4; N,12.7. $C_{12}H_{14}IN_3$ requires C,44.0; H,4.3; N,12.8%).

No suitable solvent was available for the determination of an n.m.r. spectrum.

The ethereal washings, on concentration, afforded the triazinyl starting material (0.36g, 39%).

3-Amino-2,5,6-trimethyl-1,2,4-triazinium iodide (186)

3-Amino-5,6-dimethyl-1,2,4-triazine (0.62g) and methyl iodide (1.3g) were heated under reflux in methanol ($60cm^3$) for 15h. Concentration of the methanolic solution gave the quaternary methiodide (0.17g, 13%), yellow needles,

m.p. 224-225.5° (from ethanol).

(Found: C,27.3; H,4.2; N,21.0. $C_6H_{11}IN_4$ requires C,27.1; H,4.1; N,21.1%).

$\nu_{max.}$ 3300, 3200(N-H)cm^{-1}.

$\tau(D_2O)$ 7.32(6H,s,3- and 4-CH_3), 5.78(3H,s,1-CH_3).

Further concentration of the methanolic solution afforded a dark orange oil, which, on standing, decomposed to give an oil which exhibited a green-red florescence in solution.

The starting material was recovered, in a quantitative yield, when the aminotriazine and excess methyl iodide were refluxed in absence of solvent for 15h. When the above reaction was carried out in dimethylformamide at room temperature, only a dark green intractable oil, which showed a green-red florescence in solution in both organic and aqueous solvents, was obtained.

Attempted synthesis of 1, 5 — dimethyl-6-methylene-3-methylthio-1,2,4-triazine

To 1,5,6-trimethyl-3-methylthio-1,2,4-triazinium iodide (0.2g) in a vigorously stirred mixture of water and carbon tetrachloride, was added 0.1N NaOH ($7cm^3$). The carbon tetrachloride layer was separated but rapidly became dark red, and no identifiable products could be isolated.

Attempted synthesis of 1,5-dimethyl-6-methylene-3-phenyl-1,2,4-triazine

The above method was repeated, but afforded only a dark brown solid, from which no identifiable products could be isolated.

Attempted synthesis of 6-benzoylmethylene-1,5-dimethyl-3-methylthio-1,2,4-triazine

1,5,6-trimethyl-3-methylthio-1,2,4-triazinium iodide (0.3g), water ($3cm^3$), carbon tetrachloride ($10cm^3$), and benzoyl chloride (0.17g) were vigorously stirred under an atmosphere of nitrogen whilst 0.1N NaOH ($10cm^3$) was added. The carbon tetrachloride layer was separated and taken to dryness to give a dark intractable oil.

6-Methyl-1,2,4-triazin-3,5(2H,4H)-dione (81)

This was prepared by the method of Gut[136] colourless needles, m.p. 210° (lit., 212°).

$\nu_{max.}$ 1720 and 1675 (C=O)cm^{-1}.

Attempted reaction of 6-methyl-1,2,4-triazin-3,5(2H,4H)-dione with:

(i) Methyl iodide

6-Methyl-1,2,4-triazin-3,5(2H,4H)-dione (0.38g) and methyl iodide (0.65g) were stirred in dimethylformamide ($5cm^3$)

for 24h. The solvent was removed under reduced pressure and the resulting gum triturated with light petroleum to afford a quantitative recovery of the starting material.

(ii) Phenacyl bromide

The 1,2,4-triazindione (0.64g) and phenacyl bromide (1.0g) were heated under reflux in methanol ($60cm^3$) for 72h. Starting materials were recovered in quantitative yield.

(iii) Ethyl bromopyruvate

6-Methyl-1,2,4-triazindione (0.76g), ethyl bromopyruvate (0.6g) and ethanol ($80cm^3$) were heated under reflux for 50h. Concentration of the mixture afforded a quantitative recovery of the starting material.

2,3-Dimethyl-6-phenylimidazo[1,2-b][1,2,4]triazine (194)

3-Amino-5,6-dimethyl-1,2,4-triazine (1g), phenacyl bromide (1.6g), and sodium bicarbonate (1.0g) were heated under reflux in methanol ($40cm^3$) for 1h. The mixture was then concentrated and the yellow precipitate collected, digested with a mixture of ethanol and ether (1:1) and the insoluble inorganic material removed by filtration. Removal of the solvent gave the imidazotriazine (1.62g, 90%), yellow needles, m.p. 215-216° (lit., 213)

(Found: C,69.4; H,5.5; N,24.8%; M^+, 224. $C_{13}H_{12}N_4$ requires C,69.6; H,5.4; N,25.0%; M,224).

$\tau(CDCl_3)$ 7.50(3H,s,2-CH_3), 7.44(3H,s,3-CH_3), 2.67(3H,m,6-Ph,m-and p-protons),

2.01(2H,m,6-Ph,o-protons), 2.02(1H,s,7-H).

The above reaction, in the absence of sodium bicarbonate, afforded the imidazotriazine hydrobromide (85%), m.p. 300-303° decomp. An aqueous solution of the hydrobromide was basified and extracted with ether, dried ($MgSO_4$) and the solvent removed to give the free base.

Diethyl-4-methylimidazo[1,2-b]pyrrolo[2',1'-f][1,2,4]triazine-2,7-dicarboxylate (199), or isomer (200).

3-Amino-5,6-dimethyl-1,2,4-triazine (0.5g) and ethyl bromopyruvate (0.8g) were heated under reflux in ethanol ($50cm^3$) for 1h. Removal of the solvent gave a dark brown oily solid which was triturated with ether to yield the imidazopyrrolotriazine hydrobromide (0.82g,51%). An aqueous solution of the hydrobromide was basified with 2-N sodium hydroxide and then extracted with ether and the ethereal solution dried ($MgSO_4$). Removal of the solvent gave the pyrroloimidazotriazine, colourless needles, m.p. 199-200° (from ethanol).

(Found: C,56.7; H,5.1; N,17.7%; M^+, 316.117146. $C_{15}H_{16}N_4O_4$ requires C,56.9; H,5.1; N,17.7%; M, 316.117106).

$\nu_{max.}$ 1710(C=O), 1615(C=N), 1575(C=C)cm^{-1}

$\tau(CDCl_3)$ 8.60(3H,t,J=7Hz,2-$COOCH_2\underline{CH_3}$), 8.58(3H,t,J=7Hz,7-$COOCH_2\underline{CH_3}$), 7.43(3H,s,4-CH_3), 5.64(2H,q,J=7Hz,2-$COO\underline{CH_2}CH_3$), 5.57(2H,q,J=7Hz,7-$COO\underline{CH_2}CH_3$), 2.8(1H,d,J=1.2Hz,

1-H), 2.03(1H,s,8-H), 1.65(1H,d,J=1.2Hz, 7-H).

The above reaction was repeated with twice the amount of ethyl bromopyruvate to give the pyrroloimidazotriazine (15.8%). No hydrobromide of the product was isolated, nor could any identifiable products be obtained from the dark red oily mother liquors.

To the aminotriazine (0.31g) in ethanol (20cm^3) at room temperature was added ethyl bromopyruvate (1g). Fumes of HBr were immediately produced. After stirring for 12h the precipitated tricycle was separated by filtration (0.12g, 15.2%).

1,2,3-Trimethyl-6-phenylimidazo[1,2-b][1,2,4]triazinium iodide

6-Phenyl-2,3-dimethylimidazo[1,2,4]triazine (0.12g) and methyl iodide (0.4g) were heated under reflux for 20h. Concentration of the mixture afforded the starting material (0.08g, 67%) and addition of ether to the mother liquors gave the methiodide, (0.02g, 10%), yellow needles, m.p. 250-251° decomp.(from methanol-ether).

(Found: C,44.9; H,4.5; N,14.7. $C_{14}H_{15}IN_4 \cdot \frac{1}{2}H_2O$ requires C,44.8; H,4.4; N,14.9%).

Attempted synthesis of 4-methyl-2,7-diphenylpyrrolo[2,1-f]imidazo[1',2'-b][1,2,4]triazine(208)

3-Amino-5,6-dimethyl-1,2,4-triazine (1g), phenacyl bromide (3g), sodium bicarbonate (2g), and methanol (50cm^3)

were heated under reflux for 1.5h. The inorganic material was separated and the mixture concentrated to afford 2,3-dimethyl-6-phenylimidazo[1,2-b][1,2,4]triazine (0.83g, 46%). The remaining oil was shown, by spectroscopic and chromatographic evidence, to consist of a mixture of the imidazotriazine and the starting material.

Attempted reaction of 2,3-dimethyl-6-phenylimidazo[1,2-b][1,2,4]triazine with ethyl bromopyruvate

(i) The imidazotriazine (0.45g), ethyl bromopyruvate (0.4g), and ethanol were heated under reflux for 6h and the mixture cooled to afford 2,3-dimethyl-6-phenylimidazo[1,2-b][1,2,4]triazine hydrobromide (0.07g, 11.5%), identical with an authentic sample. Concentration of the remaining mixture gave the unreacted imidazotriazine.

(ii) The above reaction, was repeated in the presence of sodium bicarbonate to afford a quantitative recovery of the starting material.

Reaction of 3-amino-5,6-dimethyl-1,2,4-triazine with bromoacetaldehyde

The aminotriazine (1.6g) and bromoacetaldehyde (from 6g bromoacetaldehyde diethyl acetal) were heated under reflux in ethanol ($50cm^3$) for 1h. Concentration of the mixture gave a dark brown solid which could not be further purified.

Reaction of 5,6-dimethyl-3-methylthio-1,2,4-triazine with α-halogeno-ketones

(i) With phenacyl bromide

(a) The 1,2,4-triazine (0.39g) and phenacyl bromide (0.5g) were stirred for 15h in ether at room temperature. No reaction occured.

The following methods all gave dark oils from which no identifiable products could be gained.

(b) The reaction (a), above, gently heated on a steam bath.

(c) 5,6-Dimethyl-5-methylthio-1,2,4-triazine (1.55g) and phenacyl bromide (1.99g) were heated under reflux in acetone 15h.

(d) The triazine (0.78g) and phenacyl bromide (1g) were stirred at room temperature for 1.5h. Starting material (0.23g, 30%) was recovered from this reaction.

(e) 5,6-Dimethyl-3-methylthio-1,2,4-triazine (0.47g), phenacyl bromide (0.6g) and dimethylformamide were stirred at room temperature.

(ii) With ethyl bromopyruvate

No identifiable products were isolated from the following reactions.

(a) 5,6-Dimethyl-6-methylthio-1,2,4-triazine (0.62g) in acetone ($20cm^3$) was heated under reflux with ethyl bromopyruvate (0.4g).

(b) The triazine and ethyl bromopyruvate were stirred

at room temperature in the absence of any solvent.

(c) 5,6-Dimethyl-6-methylthio-1,2,4-triazine and the α-halogeno-ketone were shaken, at room temperature, in ether.

Attempted synthesis of ethyl 1-methyl-3-phenylpyrrolo[2,1-f][1,2,4]triazine-7-carboxylate (210)

(i) 5,6-Dimethyl-3-phenyl-1,2,4-triazine (0.56g), ethyl bromopyruvate (0.3g) and acetone were heated under reflux for 18h. Concentration of the resultant solution afforded a dark brom tar, which on being washed with ethanol and ether, gave the hydrobromide of the starting material as a deliquescent grey solid (0.6g, 89%). Treatment of this with sodium bicarbonate in 50% ethanol gave the free base.

The original ether and ethanol washings were taken to dryness to give the starting material.

(ii) Ethyl bromopyruvate (0.8g) and 5,6-dimethyl-3-phenyl-1,2,4-triazine (0.38g) were shaken for 1h to give a deep blue oil, from which no identifiable products were obtained.

(iii) 5,6-Dimethyl-3-phenyl-1,2,4-triazine (0.37g), ethyl bromopyruvate (0.4g), sodium bicarbonate (0.5g) and ethanol ($30cm^3$) were heated under reflux for 12h. Removal of the solvent gave a quantitative recovery of the starting material.

(iv) The above reaction was repeated, using proton sponge in place of sodium bicarbonate. Starting material (55%) was the only identifiable product obtained.

Attempted synthesis of 1,3-dimethyl-7-phenylpyrrolo[2,1-f][1,2,4]triazine (213)

(i) 5,6-Dimethyl-3-phenyl-1,2,4-triazine (0.18g) and phenacyl iodide (0.25g) were refluxed in acetone ($10cm^3$) for several hours. No reaction occured.

(ii) The above reaction was repeated, using methanol as the solvent, to afford a dark intractable oil.

(iii) 5,6-Dimethyl-3-phenyl-1,2,4-triazine (0.18g) and phenacyl iodide (0.25g) were warmed together on a steam bath for several hours. No identifiable products could be isolated from the reaction.

Attempted synthesis of ethyl 2,3-diphenylpyrrolo[1,2-b][1,2,4]triazine-6-carboxylate (218)

(i) 3-Methyl-5,6-diphenyl-1,2,4-triazine (0.25g), ethyl bromopyruvate (0.2g) and ethanol ($15cm^3$) were refluxed for 15h, and the solvent then removed. Trituration of the resultant oil with chloroform gave 3-methyl-5,6-diphenyl-1,2,4-triazine hydrobromide (0.12g, 36%). The chloroform washings afforded a brown oil from which no identifiable products could be obtained, although the poorly resolved n.m.r. spectrum indicated that the required pyrrolotriazine might be present.

$\tau(CDCl_3)$ 8.73(3H,m,$COOCH_2\underline{CH}_3$), 5.83(2H,m,$COO\underline{CH}_2CH_3$), 2.67(12H,m,2- and 3-C_6H_5 and pyrrolic-H's).

The reaction was repeated using two molecules of the

base to one of the α-halogeno-ketone, but afforded only the starting material and its hydrobromide.

(ii) Reaction (i) above, was repeated, with a reflux period of 45h to give the triazinyl hydrobromide (0.2g, 30%). Concentration of the mother liquors, and trituration of the resulting oil with light petroleum, gave a dark brown solid (0.65g). When chromatographed on a column of neutral alumina with carbon tetrachloride as eluting solvent the only identifiable product obtained was 3-methyl-5,6-diphenyl-1,2,4-triazine.

Attempted synthesis of 2,3,7-triphenylpyrrolo[1,2-b][1,2,4]triazine (217)

(i) 3-Methyl-5,6-diphenyl-1,2,4-triazine (0.25g), phenacyl bromide, and methanol ($15cm^3$) were heated under reflux for 20h. Removal of the solvent gave a yellow oil, which, on trituration with ether afforded the hydrobromide of the starting material (0.04g). Thin layer chromatographic analysis (alumina with ether) of the remaining oil indicated the presence of 3-methyl-5,6-diphenyl-1,2,4-triazine and its hydrobromide. A fourth component (R_F. 0.65) was also present.

The oil was chromatographed on a column of neutral alumina, with chloroform as the eluting solvent, and the starting material collected as the first fraction. The second, dark red, fraction, afforded an oil, which was not

identified.

$\nu_{max.}$	2250(C≡N), 1695(C=O)cm^{-1}.
$\tau(CDCl_3)$	3.0(s), 2.8(d,J=2Hz), 2.65(d,J=2Hz), 2.5(s), 2.18(d,J=3Hz).

(ii) 3-Methyl-5,6-diphenyl-1,2,4-triazine (0.5g), phenacyl bromide (0.4g), sodium bicarbonate (0.2g), and methanol ($30cm^3$) were refluxed together for 15h. A quantitative recovery of the starting material was obtained.

MASS SPECTRAL TABLES

(i) 1,3,5-Triazin-2,4(1H,3H)-diones and related compounds

1,3,5-Triazin-2,4(1H,3H)-dione (76)

m/e	113(M^+)	85	70	69	45	44	43	42
I%	100	10	70	17	4	25	59	13
m/e	41	32	29	28				
I%	17	9	12	19				

m* 64(113 → 85).

Accurate mass measurement:

m/e	Found	Empirical Formula	Required
85	85.028001	$C_2H_3N_3O$	85.027610

6-Methyl-1,3,5-triazin-2,4(1H,3H)-dione (72)

m/e	128	127(M^+)	110	85	84	70	69	64
I%	6	51	6	4	41	8	40	4
m/e	63	56	55	54	53	44	43	42
I%	3	6	4	4	6	11	22	100
m/e	41	40	39	38	29	28	27	26
I%	16	14	6	4	6	11	7	4

m* 55.6(127 → 84).

6-Phenyl-1,3,5-triazin-2,4(1H,3H)-dione (73)

m/e	190	189(M^+)	188	147	146	131	130	118
I%	9	70	11	4	23	5	53	4
m/e	105	104	103	102	91	78	77	76
I%	9	100	49	5	3	8	67	38
m/e	75	74	70	69	64	63	62	52
I%	12	8	7	15	5	8	3	18
m/e	51	50	44	43	42	40	39	
I%	53	35	10	29	6	4	19	

m* 116(146 → 130), 112.5(189 → 146), 74(146 → 104), 57(104 → 77).

Accurate mass measurement:

m/e	Found	Empirical Formula	Required
130	130.029531	C_8H_4NO	130.029287

6-Benzyl-1,3,5-triazin-2,4(1H,3H)-dione (74)

m/e	204	203(M^+)	202	201	160	159	133	132	
I%	7	38	100	3	3	10	5	25	
m/e	131	129	118	117	116	92	91	90	
I%	5	20	10	38	12	15	43	18	
m/e	89	86	78	77	70	69	66	65	
I%	13	3	3	10	7	25	3	18	
m/e	64	63	62	52	51	50	44	43	
I%	5	10	5	5	12	7	12	18	
m/e	42	41	40	39	38	36	32	28	27
I%	3	7	3	15	3	12	8	30	7

m* 201(203→ 202), 125.1(202→ 159), 109.6(159→ 132).

Accurate mass measurements on selected ions:

m/e	Found	Empirical Formula	Required
203	203.069202	$C_{10}H_9N_3O_2$	203.69472
132(a)	132.045054	C_8H_6NO	132.044936
132(b)	132.068502	$C_8H_8N_2$	132.068745

The ratio of 132(a) to 132(b) is ca: 5:1

Ion source determination. Meta-stable scan at 4-8 kv.

m/e 132

159→ 132(0.206)

202→ 132(0.529)

6-(2-Chlorobenzyl)-1,3,5-triazin-2,4(1H,3H)-dione (75)

m/e	203	202	194	170	172	160	159	155
I%	3	19	4	8.5	3	11	3	8
m/e	154	153	152	151	135	134	133	132
I%	8	4	23	3	15	63	3	17
m/e	128	127	126	125	116	107	99	98
I%	7	33	23	100	10	3	11	3
m/e	92	91	90	89	88	87	86	83
I%	26	69	26	43	3	4	3	3
m/e	77	76	75	74	73	70	69	65
I%	5	3	6	3	6	5	10	7
m/e	64	63	62	61	56	55	51	50
I%	6	26	11	4	16	3	11	9
m/e	45	44	43	42	41	40	39	38
I%	5	37	31	8	5	3	31	5

m/e	36	32	29	28
I%	11	9	9	43

m* 89(202→ 134).

Accurate mass measurements on selected ions:

m/e	Found	Empirical Formula	Required
202	202.062538	$C_{10}H_8N_3O_2$	202.061647
134	134.060366	C_8H_8NO	134.060585

Ion source determination. Meta-stable scan at 4-8 kv.

m/e 134

201/202→ 134(m 0.504)

190→ 134(vw 0.415)

180→ 134(m 0.341)

161→ 134(w 0.199)

1,3,6-Trimethyl-1,3,5-triazin-2,4(1H,3H)-dione (130)

m/e	156	155(M^+)	99	98	97	83	70	58
I%	8	91	4	28	30	28	8	8
m/e	57	56	55	54	41	40	28	27
I%	7	100	11	5	28	11	32	11

m* 104.1(155→ 127), 100.9(155→ 125), 62(155→ 98), 32(98→ 56).

6-Methyl-1,— phenacyl-1,3,5-triazin-2,4(1H,3H)-dione (134)

m/e	245(M^+)	228	227	184	183	157	156	155
I%	7	8	51	8	5	8	4	9
m/e	130	129	128	106	105	103	102	101
I%	7	8	4	9	100	5	24	4
m/e	82	80	78	77	76	75	70	56
I%	4	5	5	37	5	4	4	11
m/e	51	50	43	42	39			
I%	16	7	4	4	4			

m* 149(227→ 184), 56.5(105→ 77).

Accurate mass measurement on selected ions:

m/e	Found	Empirical Formula	Required
227	227.068941	$C_{12}H_9N_3O_2$	227.069472

6-Methyl-1,3-diphenacyl-1,3,5-triazin-2,4(1H,3H)-dione (135)

m/e	363(M^+)	345	227	184	161	156	154	118
I%	50.5	3	16	4	3	3	4	4
m/e	106	105	102	78	77	56	51	44
I%	9	100	10	5	37	10	13	16
m/e	38	36	32	28				
I%	3	6	5	28				

m* 56.6(105→ 77), 149(227→ 184).

3-Phenacyl-7-phenylpyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione (140)

m/e	346	345	287	228	227	185	184	183
I%	6	18	6	16	100	4	14	10
m/e	181	169	157	156	155	152	150	130
I%	6	4	8	4	8	4	6	4
m/e	129	128	120	108	107	106	105	104
I%	6	4	6	6	4	10	66	4
m/e	103	102	91	78	77	51	50	44
I%	4	12	4	6	26	10	6	8
m/e	43	39	28					
I%	6	6	10					
m*	564(105→ 77)							

Accurate mass measurements on selected ions:

m/e	Found	Empirical Formula	Required
345	345.111598	$C_{20}H_{15}N_3O_3$	345.111334

1,3,5-Triazin-2,4,6(1H,3H,5H)-trione

m/e	130	129(M^+)	87	86	70	64	44	43
I%	3	96	3	23	13	8	96	100
m/e	42	39	38	36	31	30	29	28
I%	10	4	5	16	7	7	13	27
m*	57.3(129→ 86).							

6(1H)-Dicarbethoxymethylene-1,3,5-triazin-2,4(3H,5H)-dione(93)

m/e	272	271(M^+)	227	226	225	201	200	199
I%	4	38	4	26	8	4	34	8
m/e	182	181	180	171	155	154	153	129
I%	10	4	10	20	6	28	22	4
m/e	128	127	112	111	110	94	87	85
I%	6	44	8	6	18	4	6	6
m/e	70	69	68	67	65	55	54	53
I%	12	20	40	20	4	6	4	4
m/e	46	45	44	43	42	41	40	39
I%	12	34	24	24	12	8	12	8
m/e	31	30	29	28	27	26		
I%	54	4	100	40	48	8		

m* 146(271⟶ 199), 147(199⟶ 291), 80.9(199⟶ 127), 119.2(199⟶ 154).

Accurate mass measurement on selected ion:

m/e	Found	Empirical Formula	Required
271	271.079377	$C_{10}H_{13}N_3O_6$	271.080427

2,4,6(1H,3H,5H)-Tris(dicarbethoxymethylene)-1,3,5-triazin(94)

m/e	463	462	437	418	411	390	391	372
I%	3	4	4	7	3	6	13	6
m/e	365	346	345	320	293	274	273	247
I%	12	8	28	18	4	5	14	19
m/e	228	227	202	201	175	165	133	118
I%	3	4	4	10	4	6	3	3

m/e	112	105	94	93	78	69	68	63
I%	3	3	10	19	4	6	24	7
m/e	46	45	44	43	42	41	31	30
I%	19	54	26	13	5	3	100	7
m/e	29	28	27	26				
I%	18	11	39	10				

m* 330(463→391), 305(391→345), 262(391→320), 233(320→273), 216(345→273), 191(247→320), 148(273→201).

3-Benzyl-6(1H)-dicarbethoxymethylene-1,3,5-triazin-2,4(3H,5H)-dione (95)

m/e	362	361	317	316	270	243	240	183
I%	2	8	7	22	9	5	3	8
m/e	170	133	132	106	105	104	92	91
I%	3	8	12	3	4	4	6	64
m/e	78	77	70	69	68	67	65	51
I%	3	7	3	5	7	3	9	5
m/e	46	45	44	43	42	41	40	39
I%	7	20	8	8	3	4	3	5
m/e	31	30	29	28	27	26		
I%	100	3	28	16	16	3		

m* 276.2(361→316), 229(361→270), 230.5(316→270).

Accurate mass measurements on selected ions:

m/e	Found	Empirical Formula	Required
361	361.129259	$C_{17}H_{19}N_3O_6$	361.127375

2,4-Dimethoxy-6-methyl-1,3,5-triazine (123)

m/e	156	155(M^+)	154	141	126	125	111	110
I%	7	80	16	3	10	69	3	39
m/e	99	98	85	84	83	72	70	69
I%	4	3	3	29	8	4	18	94
m/e	68	67	66	58	57	56	55	54
I%	7	19	3	31	10	63	5	4
m/e	53	43	42	41	40	39	30	29
I%	5	5	100	13	13	4	5	4
m/e	28	27						
I%	22	8						

m* 100.8(155⟶ 125), 96.8(125⟶ 110), 56.5(125⟶ 84), 56.5(84⟶ 69), 25.1(125⟶ 56).

2-Methyl-4,6-diphenoxy-1,3,5-triazine (124)

m/e	279(M^+)	278	186	185	169	168	161	160
I%	6	11	8	60	8	6	8	36
m/e	145	119	118	117	111	105	95	94
I%	19	14	100	3	3	3	11	3
m/e	92	78	77	76	70	67	66	65
I%	4	8	93	4	8	11	4	21
m/e	64	63	59	57	56	52	51	50
I%	3	4	5	5	7	3	370	8
m/e	43	42	41	40	38	32	28	27
I%	7	9	7	5	4	6	31	8

m* 278(279→ 278), 113.6(185→ 145), 113(186→ 145),
91.8(279→ 160), 87(160→ 118), 50.3(118→ 77).

Accurate mass measurements on selected ions:

m/e	Found	Empirical Formula	Required
145	145.040609	$C_8H_5N_2O$	145.040185
169	169.089030	$C_{12}H_{11}N$	169.089145
118	118.065738	C_8H_8N	118.065671

Ion source determination. Meta-stable scan at 4-8 kv.

m/e 145

264 → 145(w 0.819)

238.5→ 145(vs 0.645)

186 → 145(vs 0.284)

(ii) 2-Aminopyrroles and derivatives

2-Amino-3,4-diphenylpyrrole (156)

m/e	235	234(M^+)	233	232	231	204	206	149
I%	19	100	20	58	5	5	5	10
m/e	131	130	129	128	117	116	104	103
I%	4	3	5	5	10	11	8	14
m/e	102	77	76	75	74	73	71	70
I%	65	14	12	4	4	7	5	3
m/e	69	64	60	57	56	55	52	51
I%	5	5	12	10	4	8	7	10
m/e	45	44	43	41	39	32	31	29
I%	5	11	11	8	7	10	8	7

m/e	28	27
I%	46	8

m* 230(234→ 232).

Accurate mass measurement on selected ion:

m/e	Found	Empirical Formula	Required
234	234.114551	$C_{16}H_{14}N_2$	234.115693

3-(3,4-Diphenylpyrrol-2-yl)urea (168)

m/e	277(M^+)	261	260	234	233	232	231	204
I%	0.6	13	59	13	19	95	11	8
m/e	130	129	116	115	105	104	103	102
I%	6	11	6	4	4	6	18	100
m/e	101	78	77	76	75	74	63	60
I%	4	4	15	15	8	4	6	8
m/e	52	51	50	44	43	42	39	32
I%	8	13	8	8	44	10	6	4
m/e	29	28	27					
I%	6	23	8					

m* 207(260→ 232).

Accurate mass measurement on selected ion:

m/e	Found	Empirical Formula	Required
277	277.121682	$C_{17}H_{15}N_3O$	277.121505

1-Phenyl-3-(3,4-diphenylpyrrol-2-yl)urea (166)

m/e	353(M^+)	260	235	234	233	130	120	119
I%	7	8	4	16	3	8	3	25
m/e	102	94	93	92	91	78	77	76
I%	7	7	100	14	19	6	11	5
m/e	67	66	65	64	63	62	61	60
I%	14	64	32	32	22	12	6	4
m/e	54	53	52	51	50	49	44	43
I%	19	5	14	18	12	5	16	4
m/e	42	41	40	39	38	37	28	27
I%	5	14	26	50	34	16	27	14

m* 155(353→ 234), 46.8(93→ 66).

Accurate mass measurement on selected ion:

m/e	Found	Empirical Formula	Required
353	353.153147	$C_{23}H_{19}N_3O$	353.152804

1-Ethyl-3-(3,4-diphenylpyrrol-2-yl)urea (167)

m/e	305(M^+)	261	260	235	234	204	130	129
I%	18	10	52	11	6	5	15	7
m/e	128	117	116	115	105	104	103	102
I%	3	3	5	4	3	7	8	30
m/e	78	77	76	71	63	56	52	51
I%	4	14	6	4	3	6	4	8
m/e	50	45	44	43	42	41	40	39
I%	4	24	28	5	10	6	5	5

m/e	31	30	29	28	27	26
I%	5	100	12	21	16	6

m* 179.5(305→ 234), 207(260→ 232).

Accurate mass measurement on selected ion:

m/e	Found	Empirical Formula	Required
305	305.153371	$C_{19}H_{19}N_3O$	305.152804

1-Acetyl-3-(3,4-diphenylpyrrol-2-yl)urea (174)

m/e	319(M^+)	261	260	235	234	233	232	231
I%	8	20	100	15	76	11	9	9
m/e	207	205	130	129	128	117	116	115
I%	5	8	20	9	6	6	6	5
m/e	104	103	102	85	77	76	70	59
I%	8	9	28	6	14	5	15	22
m/e	57	51	50	44	43	42	41	39
I%	6	6	6	20	55	12	5	5
m/e	28	27						
I%	9	5						

m* 212(319→ 260).

1-(4-Nitrobenzoyl)-3-(3,4-diphenylpyrrol-2-yl)urea (175)

m/e	261	260	234	232	231	204	167	166
I%	20	100	9	7	10	6	3	35
m/e	151	150	130	129	120	115	104	102
I%	4	50	9	9	3	4	19	30

m/e	92	77	76	75	65	63	52	51
I%	6	10	12	9	4	3	8	8
m/e	44	28						
I%	4	6						

m* 135.5(166→ 150).

Accurate mass measurement on selected ion:

m/e	Found	Empirical Formula	Required
260	260.095550	$C_{17}H_{12}N_2O$	260.094958

1-Phenyl-3-(3-cyano-4-phenylpyrrol-2-yl)urea (165)

m/e	302(M^+)	210	209	184	183	180	155	154
I%	2	6	39	3	18	4	10	10
m/e	127	120	119	102	94	93	92	91
I%	6	3	29	4	8	100	11	12
m/e	78	77	67	66	65	64	63	54
I%	9	7	4	28	17	9	7	4
m/e	52	51	50	46	44	41	40	39
I%	4	9	7	7	9	6	5	14
m/e	38	32	28					
I%	6	7	4					

m* 46.8(93→ 66).

1-Acetyl-2-acetylamino-3,4-diphenylpyrrole (178)

m/e	318	277	276	235	234	233	232	208
I%	8	3	13	5	24	7	7	12

m/e	207	192	191	180	179	167	151	150
I%	3	3	12	17	9	7	5	5
m/e	149	138	137	130	121	120	105	104
I%	3	3	4	3	3	5	3	24
m/e	103	102	92	77	76	75	74	65
I%	13	8	9	8	25	17	8	5
m/e	64	63	60	52	51	50	45	44
I%	4	4	3	3	8	22	5	6
m/e	43	42	39	30	28			
I%	100	9	3	5	6			

m* 239(318→ 276), 198(276→ 234), 55.5(104→ 76).

(iii) Pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-diones

8-Cyano-3-methyl-7-phenylpyrrolo 1,2-a 1,3,5 triazin-2,4 (1H,3H)-dione (161)

m/e	267	266(M^+)	210	209	208	181	180	155
I%	18	100	6	36	8	11	7	7
m/e	154	153	140	128	127	126	101	100
I%	26	5	4	8	33	6	3	6
m/e	99	77	76	75	73	70	68	58
I%	3	10	5	4	8	3	4	8
m/e	56	52	51	50	44	42	41	39
I%	4	4	8	5	7	4	3	5
m/e	36	32	28					
I%	4	10	50					

m* 164(266→ 209), 156.6(209→ 181), 131(181→ 154), 113.2(209→ 154), 104.5(154→ 127).

Accurate mass measurement on selected ions:

m/e	Found	Empirical Formula	Required
266	266.079989	$C_{14}H_{10}N_4O_2$	266.080370
154	154.052750	$C_{10}H_6N_2$	154.053096

Ion source determinations. Meta-stable scan 4-8 kv.

m/e 154

181→ 154(0.175vs)

209→ 154(0.356vs)

222.5→ 154(0.445vw)

265→ 154(0.721vw)

8-Cyano-3-ethyl-7-phenylpyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione (162)

m/e	281	280(M^+)	252	210	209	208	191	182
I%	19	100	5	9	47	9	4	7
m/e	181	180	177	175	155	154	153	148
I%	9	7	4	4	9	25	5	11
m/e	141	140	134	133	132	128	127	126
I%	9	5	5	4	4	9	40	5
m/e	103	100	93	77	76	75	72	70
I%	4	5	5	9	5	4	4	26
m/e	64	63	56	52	51	50	48	44
I%	7	5	5	4	7	4	4	5

m/e	43	42	41	39	36	32	31	29
I%	7	4	4	9	7	7	11	9
m/e	28	27						
I%	35	9						

m* 156.2(280→ 209), 156.6(209→ 181), 131(181→ 154), 104.5(154→ 127).

Accurate mass measurement on selected ion:

m/e	Found	Empirical Formula	Required
280	280.095167	$C_{15}H_{12}N_4O_2$	280.096019

8-Cyano-3,7-diphenylpyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione (163)

m/e	329	328(M^+)	210	209	182	181	180	167
I%	4	14	4	20	3	5	6	2
m/e	166	165	164	156	155	154	153	152
I%	6	14	30	5	35	100	14	4
m/e	140	128	127	120	119	105	91	77
I%	35	4	20	10	55	5	15	7
m/e	73	64	63	52	51	50	44	43
I%	9	8	5	3	6	4	12	7
m/e	41	39	38	32	28	18		
I%	3	5	3	5	27	30		

m* 156.7(209→ 181), 133.2(328→ 209), 69.2(119→ 91).

Accurate mass measurement on selected ion:

m/e	Found	Empirical Formula	Required
328	328.09471	$C_{19}H_{12}N_4O_2$	328.096019

3,6,7-Triphenylpyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione (164)

m/e	260	240	234	197	130	120	119	118
I%	4	3	4	3	3	5	41	4
m/e	117	106	105	103	94	93	92	91
I%	3	3	3	4	3	26	5	15
m/e	90	87	86	85	84	83	82	79
I%	3	13	3	67	4	100	5	3
m/e	78	77	76	66	65	64	63	62
I%	3	5	3	8	8	14	6.5	3
m/e	61	60	52	51	50	49	48	47
I%	3	5	5	6.5	5	10	14	26
m/e	46	45	44	43	41	40	39	38
I%	4	4	18	5	5	3	9	5
m/e	37	36	35	32	31	29	28	27
I%	3	6.5	9	9	5	5	42	5
m/e	26							
I%	3							

Accurate mass measurement on selected ion:

m/e	Found	Empirical Formula	Required
260	260.095294	$C_{24}H_{17}N_3O_2$	260.094958

Ethyl pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylate (101)

m/e	224	223(M^+)	208	207	197	196	195	180
I%	14	100	3	3	7	3	7	14
m/e	179	178	165	153	152	151	150	149
I%	12	57	3	3	14	33	7	5
m/e	136	135	134	125	124	123	120	119
I%	9	71	17	10	7	3	3	3
m/e	118	117	116	115	97	96	95	94
I%	16	19	10	3	5	7	3	3
m/e	91	85	84	83	81	79	78	77
I%	3	3	7	3	10	10	16	7
m/e	71	70	69	68	67	65	64	58
I%	3	16	7	7	3	7	7	7
m/e	57	56	55	54	53	52	51	50
I%	9	3	9	5	26	36	14	3
m/e	45	44	43	42	41	40	39	38
I%	10	57	48	5	8	3	8	8
m/e	37	36	35	32	31	29	28	27
I%	5	7	7	10	7	33	96	29
m/e	26							
I%	12							

m* 170(223→ 195), 143(223→ 178), 102.5(178→ 135), 102.2(223→ 151).

Accurate mass measurement on selected ions:

m/e	Found	Empirical Formula	Required
223	223.059071	$C_9H_9N_3O_4$	223.059300
151	151.038093	$C_6H_5N_3O_2$	151.038173
135	135.019097	$C_6H_3N_2O_2$	135.019450

Methyl pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylate (112)

m/e	211	210	209(M^+)	179	178	166	165	152
I%	3	11	100	4	29	4	4	3
m/e	157	150	139	138	136	135	134	123
I%	9	6	10	3	3	31	19	6
m/e	111	108	107	106	86	81	80	79
I%	4	6	10	9	3	6	19	7
m/e	78	77	70	69	68	64	59	58
I%	9	4	9	3	3	3	3	3
m/e	54	53	52	51	44	43	39	38
I%	3	14	16	9	3	4	3	3
m/e	31	29	28					
I%	3	4	3					

m* 151.5(209→178), 109(209→151), 102.5(178→135), 85(135→107).

Accurate mass measurement on selected ions:

m/e	Found	Empirical Formula	Required
151	151.037793	$C_6H_5N_3O_2$	151.038173
151	151.013794	$C_6H_3N_2O_3$	151.014364

Ion source determination. Meta-stable scan at 4-8 kv.

m/e 151 165→ 151(0.094s) 207→ 151(0.371vv1)

178→ 151(0.181v1) 220→ 151(0.460vs)

192→ 151(0.271vs)

Pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylic acid (111)

m/e	196	195(M^+)	152	135	134	125	124	110
I%	10	100	7	7	9	9	4	3
m/e	108	107	106	97	96	80	79	78
I%	6	8	10	9	6	15	4	8
m/e	77	70	69	68	53	52	51	45
I%	3	10	3	4	10	28	7	3
m/e	44	43	38	37	28	27		
I%	11	5	3	3	14	4		

m* 119.8(152→ 135), 118.8(195→ 152), 80(195→ 125).

Ethyl 1,3-dimethylpyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione-7-carboxylate (114)

m/e	252	251(M^+)	238	237	224	223	206	180
I%	16	100	3	23	4	30	35	10
m/e	179	178	166	149	138	137	134	122
I%	51	6	12	19	8	4	5	13
m/e	121	111	95	94	93	92	83	82
I%	14	8	10	13	14	4	4	3

m/e	80	79	78	67	66	65	64	56
I%	21	4	4	16	20	6	6	6
m/e	53	52	51	39	38	29	28	27
I%	11	8	4	5	5	4	7	5

m* 198.5(251→ 223), 170.9(251→ 207), 123.5(223→ 116), 127.5(251→ 179), 114.9(166→ 138), 107.9(206→ 149), 98.4(149→ 121), 89.3(138→ 111), 83(179→ 122), 72.3(122→ 94).

Pyrrolo[1,2-a][1,3,5]triazin-2,4(1H,3H)-dione (109)

m/e	152	151(M^+)	108	107	105	95	83	82
I%	5	16	6	5	9	4	3	5
m/e	81	80	79	77	73	71	70	69
I%	7	9	3	5	3	4	4	4
m/e	68	67	60	58	57	56	55	54
I%	3	3	12	4	5	3	7	5
m/e	53	52	51	45	44	43	42	41
I%	14	9	5	8	100	77	17	8
m/e	39	38	37	36	35	32	31	29
I%	5	27	5	77	15	4	6	18
m/e	28	27						
I%	29	9						

Accurate mass measurement on selected ion:

m/e	Found	Empirical Formula	Required
151	151.038092	$C_6H_5N_3O_2$	151.038173

Ethyl 8-bromo 1,3-dimethylpyrrolo[1,2-a][1,3,5] triazin-2,4 (1H,3H)-dione (115)

m/e	332	331	330	329	303	301	286	284
I%	8	98	13	100	15	16	13	13
m/e	259	257	229	227	206	201	199	193
I%	12	13	10	10	5	7	7	18
m/e	178	165	160	158	150	139	121	120
I%	5	26	5	5	5	10	5	5
m/e	110	92	91	90	80	77	66	64
I%	7	6	5	5	5	5	9	8
m/e	60	56	29	42				
I%	6	7	10	4				

m* 278(331→ 303), 275(329→ 301), 247(331→ 286), 245(329→ 284), 203(331→ 259), 200.5(329→ 257), 141(193→ 165).

(iv) 1,2,4-Triazine derivatives

6-Methyl-1,2,4(1H,3H)-triazin-3,5(2H,4H)-dione (81)

m/e	128	127	84	70	57	56	55	54
I%	6	100	10	4	3	73	8	3
m/e	52	44	43	42	41	40	39	29
I%	4	11	18	20	8	7	3	12
m/e	28	27	26					
I%	22	33	16					

m* 55.6(127→ 84), 58.2(84→ 70).

3-Amino-5,6-dimethyl-1,2,4-triazine (193)

m/e	125	124	96	55	54	53	52	51
I%	4	38	5	3	24	13	5	5
m/e	50	43	42	41	40	39	28	27
I%	3	100	14	8	6	28	12	15

m* 74.3(124→ 96), 28.2(54→ 39), 19.3(96→ 43).

5,6-Dimethyl-6-methylthio-1,2,4-triazine (209)

m/e	156	155	127	112	76	75	74	73
I%	6	53	12	3	5	4	100	6
m/e	72	58	55	54	53	52	51	50
I%	7	3	4	77	22	5	6	3
m/e	47	46	45	44	42	41	40	39
I%	7	7	10	3	4	7	7	41
m/e	28	27						
I%	12	21						

m* 104(155→ 127), 98.9(127→ 112), 28.2(54→ 39).

1,5,6-Trimethyl-3-phenyl-1,2,4-triazinium iodide (188)

m/e	200	199	198	186	172	157	128	127
I%	5	21	3	4	4	8	9	6
m/e	117	105	104	103	102	89	78	77
I%	7	7	75	29	3	3	5	26
m/e	76	75	74	64	63	56	55	54
I%	20	7	3	3	6	9	100	27

m/e	53	52	51	50	44	43	42	41
I%	42	16	26	17	4	6	6	7
m/e	40	39	38	36	35	30	29	28
I%	4	24	11	35	6	4	4	22
m/e	27							
I%	40							

Accurate mass measurement on selected ion:

m/e	Found	Empirical Formula	Required
199	199.110558	$C_{12}H_{13}N$	199.110942

2,3-Dimethyl-6-phenylimidazo[1,2-b][1,2,4]triazine (194)

m/e	225	224	223	197	196	184	183	182
I%	17	100	4	10	17	5	36	26
m/e	142	129	117	116	115	114	112	104
I%	4	8	4	17	18	8	6	18
m/e	103	102	94	93	92	90	89	88
I%	18	12	3	6	4	6	15	9
m/e	79	78	77	76	75	67	64	63
I%	4	6	12	10	5	6	5	11
m/e	62	54	53	52	51	50	43	42
I%	6	4	11	11	14	8	5	12
m/e	41	40	39	38	36	27		
I%	12	6	16	4	5	19		

Accurate mass measurement on selected ions:

m/e	Found	Empirical Formula	Required
224	224.106160	$C_{13}H_{12}N_4$	224.106191
196	196.087269	$C_{12}H_{10}N_3$	196.087468

Diethyl 4-methylpyrrolo[2,1-f]imidazo[1',2'-b][1,2,4]triazin-2,7-dicarboxylate (199) or isomer (200)

m/e	317	316	288	273	272	271	260	245
I%	18	88	10	3	13	74	3	16
m/e	244	243	225	216	215	214	211	199
I%	100	38	3	3	23	4	6	7
m/e	198	197	172	171	170	157	150	145
I%	10	3	10	23	15	3	4	3
m/e	144	143	142	133	130	129	120	119
I%	7	6	6	11	3	4	4	9
m/e	118	117	116	115	113	106	105	104
I%	22	6	7	4	18	4	6	6
m/e	103	102	100	93	92	91	90	89
I%	8	14	7	6	7	12	12	7
m/e	80	79	78	77	76	75	68	67
I%	4	5	9	23	17	9	3	9
m/e	66	65	64	63	62	57	55	53
I%	10	17	28	15	4	4	4	7
m/e	52	51	50	45	44	43	42	41
I%	6	11	12	6	9	6	5	5

m/e	40	39	38	36	32	29	28	27
I%	3	9	4	3	5	30	26	17
m/e	26							
I%	5							

m* 262.2(316→ 288), 232(316→ 271), 218(271→ 243), 196.5(243→ 171), 188.5(316→ 244), 121.2(244→ 172).

Accurate mass measurement on selected ion:

m/e	Found	Empirical Formula	Required
316	316.117106	$C_{15}H_{16}N_4O_4$	316.117146

BIBLIOGRAPHY

1. J. H. Bowie, A. W. Johnson, and G. Thomas, Tetrahedron Letters, 1964, 863.

2. J. R. Dyer, C. K. Kellogg, R. F. Nassar, and W. E. Streetman, Tetrahedron Letters, 1965, 585.

3. P. G. Caltrider, "Antibiotics", ed. D. Gottlieb and P. D. Shaw, Springer-Verlag, 1967, vol. 2, pp.677.

4. B. W. Bycroft, D. Cameron, L. R. Croft, A. W. Johnson, T. Webb, and P. Coggon, Tetrahedron Letters, 1968, 2925.

5. B. W. Bycroft, D. Cameron, L. R. Croft, A. Hassanali-Walji, A. W. Johnson, and T. Webb, Experentia, 1971, 27, 501.

6. B. W. Bycroft, Abstracts of Papers, The Chemical Society, Autumn meeting, Nottingham 1972.

7. B. W. Bycroft, D. Cameron, L. R. Croft, A. Hassanali-Walji, A. W. Johnson, and T. Webb, Tetrahedron Letters, 1968, 5901.

8. R. Richter, Chem. Ber., 1968, 101, 3002.

9. R Huisgen, K Herbig and M. Morikawa, Chem. Ber., 1967, 100, 1107.

10. V.A. Titkov, I. D. Pletner, L. V. Torocheshnikova, and T. F. Leina, Ger., 1221, 385/1966. Chem. Abs., 1967, 66, 19833h.

11. C. L. Dickinson Jr., W. J. Middleton, and V. A. Engelhardt, J. Org. Chem., 1962, 27, 2470.

12. E. Fanghaenel, K. Gewald, K. Peutsch, and K. Wagner, J. prackt. Chem., 1969, 311, 388.

13. M. Brugger, H. Wamloff, and F. Korte, Annalen, 1972, 755, 101.

14. H. Gross and J. Gloede, Angew. Chem. Internat. Edn., 1963, 2, 262.

15. G. W. H. Cheeseman, M. Rafiq, P. D. Roy, C. J. Turner, and G. V. Boyd, J. Chem. Soc. (C), 1971, 852

16. J. P. Cress and D. M. Forkey, Chem. Comm., 1973, 35.

17. C. Jaureguiberry and M. B. Roques, Comp. rend., 1972, 274, 1703.

18. P. Roy-Burnham, "Analogues of Nucleic Acid Components", Springer-Verlag, 1970, pp. 36-66.

19. G. M. Timmis and D. C. Williams, "Chemotherapy of Cancer", Butterworths, 1967, pp. 103-113.

20. J. Skoda "Progress in Nucleic Acid Research", ed. J. N. Davidson and W. E. Cohn, Academic Press, 1963, vol. 2, pp. 197.

21. G. M. Timmis and D. C. Williams, "Chemotherapy of Cancer", Butterworths, 1967, pp. 158.

22. J. Hill "Experimental Chemotherapy", ed. R. J. Schnitzer and F. Hawking, Academic Press, New York, 1963, vol.1, pp. 554.

23. M. I. S. Lomax and G. R. Greenberg, J. Biol. Chem., 1963 238, 367.

24. C. K. Mathews and S. S. Cohen, J. Biol. Chem., 1963, 238 367.

25. C. K. Mathews and S. S. Cohen, J. Biol. Chem., 1963, 238 853.

26. B. R. Baker, "The Design of Active-Site-Directed Irreversible Enzyme Inhibitors", Wiley, New York, 1967.

27. G. H. Hitchings, G. B. Elion, E. A. Falco, P. B. Russell, M. B. Sherwood, and H. Vanderwerff, J. Biol. Chem., 1950, 183, 1.

28. G. H. Hitchings, G. B. Elion, H. Vanderwerff, and E. A. Falco, J. Biol. Chem., 1948, 174, 765.

29. W. C. Bowman, M. J. Rand, and G. B. West, "Textbook of Pharmacology", Blackwell Scientific Publications, 1968, pp. 936.

30. H. C. Carrington, A. F. Crowther, D. G. Davey, A. A. Levi, and F. L. Rose, Nature, 1965, 168, 1080.

31. E. J. Modest, G. E. Foley, M. M. Pechet and S. S. Farber, J. Amer. Chem. Soc., 1952, 74, 855.

32. G. H. Hitchings, A. Maggiolo, P. B. Russell, H. Vanderwerff, and I. M. Rollo, J. Amer. Chem. Soc., 1952, 74, 3200.

33. G. H. Hitchings and J. J. Burchenal, Adv. Enzymol., 1965, 27, 417.

34. A. E. Tschitschibabin, Chem. Ber., 1927, 60, 1607.

35. A. E. Tschitschibabin, and F. Stepanow, Chem. Ber., 1927, 62, 1068.

36. A. E. Tschitschibabin, and F. Stepanow, Chem. Ber., 1930, 63, 470.

37. J. Taylor and D. G. Wibberley, J. Chem. Soc., 1968, 2693.

38. E. Ochiai and M. Yanai, J. Pharm. Soc. Japan, 1939, 59, 18.

39. R. L. Letsinger and R. Lasco, J. Org. Chem., 1956, 21, 765.

40. E. M. Smolin and L. Rapoport,"s-Triazines and Derivatives", Interscience Publisher's Inc., New York, 1959, pp. 145, and references cited therein.

41. F. C. Schaefer, and G. A. Peters, J. Org. Chem., 1961, 26, 2778.

42. F. C. Schaefer and G. A. Peters, J. Amer. Chem. Soc., 1959, 81, 1470.

43. F. C. Schaefer and G. A. Peters, J. Org. Chem., 1961, 26 2784.

44. H. Bredereck, F. Effenberger, A. Hofmann and M. Hajei, Angew. Chem. Internat. Edn., 1963, 2, 655.

45. F. C. Schaefer, J. Org. Chem., 1962, 27, 3608.

46. H. Bredereck, F. Effenberger, and A. Hofmann, Chem. Ber., 1963, 96, 3260.

47. A. Albert, R. Goldacre and J. Phillips, J. Chem. Soc., 1948, 2240.

48. A. Albert, "Heterocyclic Chemistry", 2nd edn. The Athlone Press, London, 1968, pp. 74.

49. J. T. Shaw, J. Org. Chem., 1962, 27, 3891.

50. G. F. Duffin, Adv. Heterocyclic Chem., 1964, 3, 2.

51. W. J. Irwin, Unpublished observations.

52. E. M. Smolin and L. Rapoport, "s-Triazines and Derivatives", Interscience Publisher's Inc., New York, 1959, pp. 222, and references cited therein.

53. B. Roth and J. Strelitz, J. Org. Chem., 1969, 34, 821.

54. J. Foucart, J. Nasielski and E. Van der Douckt, Bull. Soc. chim. belges, 1966, 75, 17.

55. American Cyanamid Co., B. P. 642,409/1950. Chem. Abs. 1952, 46, 146f.

56. P. W. Hicknott, J. Appl. Chem., 1966, 16, 227.

57. D. W. Kaiser, J. T. Thurston, J. R. Dudley, F. C. Schaefer, I. Hechenbliekner, and D. Holm-Hansen, J. Amer. Chem. Soc. 1951, 73, 2981.

58. J. Kobe, B. Stanovnick and M. Tisler, Monatsh., 1970, 101, 724.

59. M. Necki, Ber., 1874, 7, 755.

60. A. Ostrogovich and V. Stanciv, Gazz. Chim. Ital., 1935, 65, 229.

61. A. Ostrogovich and I. Tanislav, Gazz. Chim. Ital., 1934, 64, 824.

62. R. Zahradnik, J. Koutecky, J. Jonas, and J. Gut, Coll. Czech. Chem. Comm., 1963, 28, 882.

63. J. Skoda, "Progress in Nucleic Acid Research", ed. J. N. Davidson and W. E. Cohn, Academic Press, New York, 1965, vol. 2, pp. 197.

64. A. Piskala and J. Gut, "Synthetic Procedures in Nucleic Acid Chemistry", ed. W. W. Zorbach and R. S. Tipson, Wiley, London, 1968, vol. 1, pp. 105.

65. A. Ostrogovich and J. Cadariv, Gazz. Chim. Ital., 1940, 71, 505, 515, 524.

66. J. Jonas, M. Horak, A. Piskala, and J. Gut, Coll. Czech. Chem. Comm., 1962, 27, 2754.

67. M. Horak and J. Gut, Coll. Czech. Chem. Comm., 1961, 26, 1681.

68. A. Piskala, Coll. Czech. Chem. Comm., 1963, 28, 2365.

69. A. M. Randall, R. G. Fowler, N. Fuson, and J. R. Dangl, "Infra-red Determination of Organic Structures", D. Van Nostrand, New York, 1949.

70. H. W. Thompson and D. A. Jameson, Spectrochim. Acta., 1958, 13, 236.

71. A. Ostrogovich, Gazz. Chim. Ital., 1897, 27, 416.

72. J. Jonas and J. Gut, Coll. Czech. Chem. Comm., 1962, 27, 717.

73. E. Spinner, J. Chem. Soc., 1960, 1232.

74. J. Jonas and J. Gut, Coll. Czech. Chem. Comm., 1961, 26, 2155.

75. R.H.Johnson and F. Rohlich, Nature, 1959, 183, 244.

76. E. Spinner and J. C. B. White, J. Chem. Soc., (B), 1966, 996.

77. A. Ostrogovich, Gazz. Chim. Ital., 1914, 44, 562.

78. E. Spinner, J. Chem. Soc., 1960, 1226.

79. D. J. Brown, E. Hoerger, and S.Mason, J. Chem. Soc., 1955, 211.

80. E. N. Boitsov, A. I. Finkelshtein, Optika i Spectroskopiya, 1959, 7, 482.

81. D. Voet and A. Rich, "Progress in Nucleic Acid Research and Molecular Biology", ed. J. N. Davidson and W. E. Cohn, Academic Press, New York, 1970, vol. 10, pp. 183.

82. C. H. Schwalbe and W. Saenger, Acta.Cryst., 1973, B29, 61.

83. F. Jordan and B. Pullman, Theor. Chim. Acta., 1968, 9, 242.

84. C. H. Schwalbe, work in progress.

85. W. Kolb, J. prackt. Chem., 1894, 49, 90.

86. R. S. Rasmussen and R. R. Brattain, J. Amer. Chem. Soc., 1949, 71, 1073.

87. G. F. Reynolds, R. Berner and W. Boutwell, J. Heterocyclic Chem., 1972, 9, 1009.

88. N. V. Khronov-Borisov and E. V. Kisareva, Zhr. obshchei Khim., 1959, 29, 3010.

89. D. R. Bragg and D. G. Wibberley, J. Chem. Soc., 1963, 3277.

90. A. Albert, "Synthetic Procedures in Nucleic Acid Chemistry", ed. W. W. Zorbach and R. S. Tipson, Wiley, London, 1972, vol. 2, pp.1.

91. E. T. Burrows, D. D. Holland, and J. Kenyon, J. Chem. Soc., 1946, 1069.

92. D. G. Wibberley, unpublished observations.

93. A. J. Parker, Quat. Rev., 1962, 16, 163.

94. J. L. Wong and D. S. Fuchs, J. Org. Chem., 1971, 36, 848.

95. J. Gut, M. Prystas, J. Jonas and F. Sorm, Coll. Czech. Chem. Comm., 1961, 26, 974.

96. H. U. Blank and J. J. Fox, J. Heterocyclic Chem., 1970, 7, 735.

97. S. Mackenzie, Ph.D. Thesis, Heriot-Watt University, 1970.

98. H. Fischer, H. Gruggemos, A. Schafer, Annalen, 1939, 540, 30.

99. F. Endermann and H. Fischer, Annalen, 1939, 538, 172.

100. W. H. Davies and M. A. T. Rogers, J. Chem. Soc, 1944, 126.

101. K. Gewald, Z. Chem., 1961, 1, 349.

102.(a) J. Raines, Unpublished results.

(b) Reference 104.

103. L. Caprano and J. H. Schrepfer, Chem. Ber., 1971, 104, 3039.

104. T. D. Duffy, Ph. D. Thesis, University of Aston, 1973.

105. J. L. Wong, M. S. Brown and H. Rapoport, J. Org. Chem., 1965, 30, 2398.

106. J. W. Emsley, J. Feeney, and C. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy", Pergamon Press, 1966, vol. 2.

107. T. Kappe, Monatsh., 1967, 98, 1858.

108. S. Gronowitz, A. Homfeldt, B. Gestblom and R. A. Hoffman, Arkiv. Chim., 1961, 18, 133.

109. R. C. Fort, G. W. H. Cheeseman, and E. C. Taylor, J. Org. Chem., 1964, 29, 2440.

110. V. Eisner and R. L. Erskine, J. Chem. Soc., 1958, 971.

111. R. Alan Jones, Adv. Heterocyclic Chem., 1970, 11, 383.

112. C. M. Atkinson and H. D. Cossey, J. Chem. Soc., 1963, 1628.

113. W. W. Paudler and T. K. Chen, J. Org. Chem., 1971, 36, 787.

114. T. Melton and D. G. Wibberley, J. Chem. Soc. (C), 1967, 983.

115. J. Lee and W. W. Paudler, Chem. Comm., 1971, 1636.

116. A. Hertzheim, H. Pusch and H. Beyer, Chem. Ber., 1970, 103, 3537.

117. B. Mariani and R. Sgarbi, Chimica e Industria, 46, 630, 1964.

118. B. Mariani and R. Sgarbi, Ital. P. 752,234/1966, Chem. Abs., 1968, 69, 11415q.

119. Ferrania Societa per Azion, Belg. P. 657,084/1965, Chem. Abs., 1960, 54, 17760e.

120. (a) R. Fusco and S. Rossi, Ital. P. 536,121/1955, Chem. Abs., 1959, 53, 2264f.

(b) R. Rusco and S. Rossi, France P. 1,153,100/1960. Chem. Abs., 1962, 56, 9167.

(c) R. Fusco and S. Rossi, U. S. P. 2,837,520/1958, Chem. Abs., 1958, 52, 16388d.

(d) R. Fusco and S. Rossi, Ger. P. 1,026,321/1958, Chem. Abs., 1960, 54, 17434e.

121. Gevaert Photo-Production N. V. B. P. 1,001,064/1965.

122. H. Budzikiewicz, C. Djerassi, A. H. Jackson, G. W. Kenner, D. J. Newman, and J. M. Wilson, J. Chem. Soc., 1964, 1949.

123. A. Pollak, B. Stanovnick, and M. Tisler, Tetrahedron, 1968, 24, 2623.

124. J. Jorg, R. Houriet and G. Spiteller, Monatsh., 1966, 97, 1064.

125. P. N. Preston, W. Steedman, M. H. Palmer, S. M. Mackenzie, and M. F. G. Stevens, Org. Mass Spectrometry, 1970, 3, 863.

126. A. Costopanagiotis and H. Budzikiewicz, Monatsh., 1965, 96, 1800.

127. G. Jones and J. Stanyer, Org. Mass Spectrometry, 1970, 3, 1489.

128. W. W. Paudler and R. E. Herbener, J. Heterocyclic Chem., 1967, 4, 224.

129. R. Hirt, H. Nidecker, and R. Birchtold, Helv. Chim. Acta., 1950, 33, 1365.

130. T. Irikura, Y. Abe, K. Okamura, K. Higo, A. Maeda, F. Morinaga, G. Shirai, and S. Hatae, J. Medicin. Chem., 1970, 13, 1081.

131. A. D. Forbes and P. Gould, B. P. 1,107,987/1968, Chem. Abs., 1968, 69, 59291y.

132. C. Grundmann, and V. Mini, J. Org. Chem., 1964, 29, 678.

133. D. Nagy, U. S. P. 2,446,980/1948.

134. J. Thurston, U. S. P. 2,305,118/1943.

135."Handbook of Chemistry and Physics", 48th ed., The Chemical Rubber Co., Ohio, 1967, pp. C-591.

136. J. Gut, Coll. Czech. Chem. Comm., 1958, 23, 1588.

137. W. J. Irwin, D. G. Wibberley and (in part) G. Cooper, J.Chem.Soc., 1971, 3820.