SYNTHESIS AND REACTIONS OF WATER-SOLUBLE CONGENERS OF HEXAMETHYLMELAMINE

by

Philip Rushton

A thesis submitted for the degree of

Doctor of Philosophy

in the

University of Aston in Birmingham

February 1984

Department of Pharmacy

University of Aston in Birmingham

Birmingham B4 7ET

To My Parents And Sister

Synthesis And Reactions Of Water-Soluble Congeners Of Hexamethylmelamine

by Philip Rushton

Submitted for the degree of Doctor of Philosophy, 1984, in the University of Aston in Birmingham

The pharmacological and chemical properties of hexamethylmelamine are reviewed and, in particular, attention is focussed upon its antitumour properties. These antitumour properties, although far from ideal, were attributed to the N-methyl groups present in the molecule and various workers were motivated to prepare analogues with enhanced water-solubility. The syntheses of some of these analogues are described together with the reduced antitumour properties observed for these compounds. Most of these analogues bore four or less N-methyl groups and it was proposed that six N-methyl groups were necessary for optimal activity. The quaternary salt, heptamethylmelamine chloride, was screened for antitumour activity which was found to be absent and the compound was found to be extremely toxic to mice. This toxicity was believed to be due to the presence of the trimethylammonium moiety which is present also in acetylcholine and may impart cholinergic properties to this quaternary salt of hexamethylmelamine.

These observations founded the basis of this thesis and initially, attempts were made to prepare higher homologues of heptamethylmelamine chloride with larger groups on the ammonium moiety in order to suppress the possible cholinergic activity. The synthesis of these homologues proved to be impossible for all but the lowest homologues and this result coupled with the surprisingly higher toxicity of hexamethylethylmelamine chloride led to loss of interest in this series of analogues.

The philosophy was extended to other congeners of hexamethylmelamine with a complement of six N-methyl groups but with enhanced water-solubility.

The first successfully prepared analogue was 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium chloride which, although isoelectronic with hexamethylmelamine, was extremely water-soluble. The structure of this analogue was not immediately obvious but it was confirmed as 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium chloride by X-ray crystallography. Unfortunately, this modification sacrificed the antitumour properties and the compound was found to be extremely toxic.

This oxadiazinium salt, however, is a pyrylium-type system and it was decided to compare and contrast its reactions with other pyrylium systems in their reactions with nucleophiles. It rapidly became apparent that oxadiazinium salt underwent the predicted reaction with the nucleophile but the products obtained were not those expected and several novel heterocyclic compounds were isolated. Reaction with ammonia gave a triazin-2-one, with primary amines an oxadiazine or one of two possible triazin-2-ones, with hydrazine to give a 1,2,4-triazole and with hydroxylamine to give a 1,2,4-oxadiazole. Reaction with phenylhydrazine gave a 1,2,4-triazole but it was not the expected phenyl homologue of the product obtained with hydrazine. The crystal structure of this product was determined because the product could not be characterised by any other means.

Some of these products had modest water-solubility and were screened for antitumour properties but were devoid of favourable activity.

Finally, various, novel triazolotriazines with amino or dimethylamino substituents were successfully prepared but their antitumour properties have not as yet been evaluated.

KEYWORDS: Hexamethylmelamine, Oxadiazinium Salt, Oxadiazine, Triazin-2-one, Triazolotriazine.

ACKNOWLEDGEMENTS

I would like to acknowledge all of my colleagues in the Department of Pharmacy at the University of Aston for their friendship, advice and support during the work I have undertaken.

In particular I would like to thank Professor M.F.G. Stevens, Dr. M.D. Threadgill, Dr. C.H. Schwalbe and Dr. W.J. Irwin for invaluable advice and discussions.

Finally, I acknowledge and thank the Science and Engineering Research Council for their financial support for this project.

CONTENTS

LIST OF SCHEMES

LIST OF TABLES

LIST OF FIGURES

LIST OF PLATES

ABBREVIATIONS

ANRORC	Addition-Nucleophilic-Ring-Opening-Ring-Closure With Ring Retention
$ANRORC_c$	Addition-Nucleophilic-Ring-Opening-Ring-Closure With Ring Contraction
$ANRORC_e$	Addition-Nucleophilic-Ring-Opening-Ring-Closure With Ring Expansion
br	broad (n.m.r. peak)
d	doublet (n.m.r. peak)
DMF	dimethylformamide
HMM	hexamethylmelamine
i.r.	infra-red
m	multiplet (n.m.r. peak)
m.p.	melting point
M.S.	mass spectroscopy
m.w.	molecular weight
n.m.r.	nuclear magnetic resonance
PMM	pentamethylmelamine
q	quartet (n.m.r. peak)
s	singlet (n.m.r. peak)
t	triplet (n.m.r. peak)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
t.l.c.	thin-layer chromatography
as-TMM	2-dimethylamino-4,6-bis(methylamino)-1,3,5-triazine
s-TMM	2-amino-4,6-bis(dimethylamino)-1,3,5-triazine
u.v.	ultra-violet

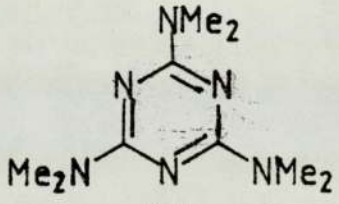
INTRODUCTION

1 HEXAMETHYLMELAMINE

1.1 Pharmacology Of Hexamethylmelamine

Hexamethylmelamine [2,4,6-tris(dimethylamino)-1,3,5-triazine] [HMM] (1) made its pharmacological debut as an insect chemosterilant. Borkovec and De Milo prepared various 1,3,5-triazines and reported that HMM was one of the most effective chemosterilants against male house-flies[1].

Later, it was discovered that HMM also had significant antitumour activity against a wide range of solid-tumour cell-lines; including small (oat) cell lung carcinoma[2,3], ovarian carcinomas[4,5] and breast tumours[6-8]. Favourable activity has also been observed against Bilharzial bladder cancer[9,10], cervical cancer[11] and lymphomas[6,11,12]. This wide spectrum of antitumour activity coupled with the relatively easy and inexpensive production of HMM made it an appealing candidate for clinical studies with human tumours.



(1)

1.2 Formulation And Clinical Effects Of Hexamethylmelamine

HMM is almost totally insoluble in water and this prevents its formulation in a suitable physiological solution. Consequently, parenteral administration was not possible and oral administration had to be employed. Even so, large, oral doses needed to be given to patients to ensure sufficient alimentary absorption, but this was still very poor and variable[13]. Dire nausea and gastrointestinal toxicity were observed[14] and much of the HMM was regurgitated. The antiperistaltic activity was thought to be a direct consequence of the gastrointestinal irritation.

HMM appeared to be only modestly effective as a single,

chemotherapeutic agent although in combination with cyclophosphamide, methotrexate and 5-fluorouracil (as Hexa-CAF[15-19]) and with cyclophosphamide, adriamycin and *cis*-dichlorodiammineplatinum (II) (as CHAP[20-22]), it was found that excellent, clinical activity against ovarian tumours resulted.

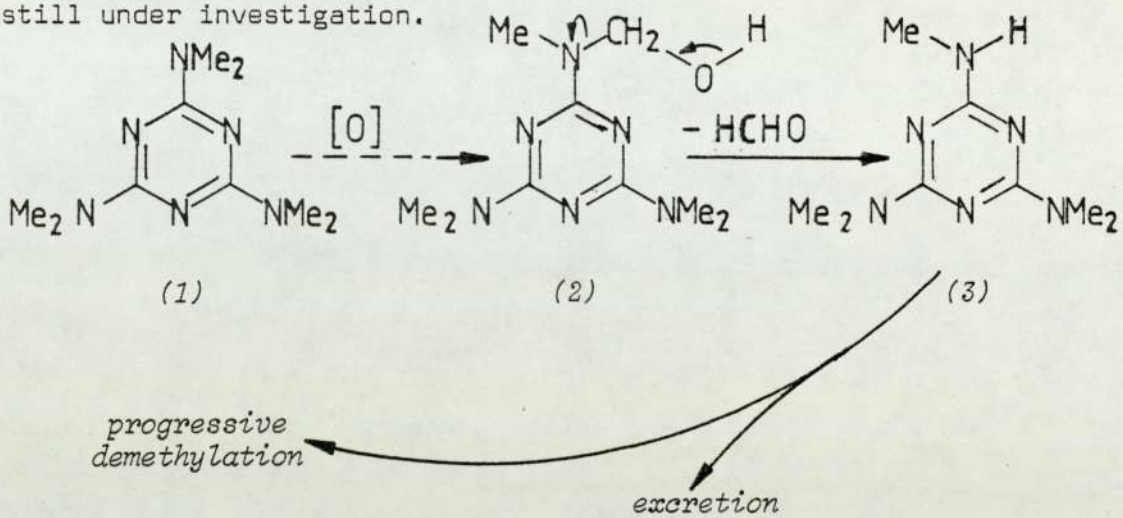
1.3 Mode Of Antitumour Action Of Hexamethylmelamine

The absolute mode of action of virtually any drug is subject to conjecture and HMM is no exception. Two putative hypotheses are under investigation to elucidate the mode of antitumour action of HMM.

The favoured theory concerns metabolic activation of the drug[23-27] and this belief derives from the observation of N-demethylated bioproducts, which have been isolated and identified[23,24]. The proposed metabolic pathway is illustrated in Scheme 1. The oxidation stage(s) was originally thought to occur within the liver microsomes[25] but recent evidence has disclosed that certain tumour cells also have this capacity[26]. Incubation of HMM with liver microsomes, *in vitro*, yields formaldehyde, which can be detected by the Nash colour test[28]. The formaldehyde is released by the breakdown of an N-hydroxymethyl intermediate (2), which has been isolated and characterised[27]. Further evidence for the presence of this intermediate (2), during metabolism, is revealed by a "differential Nash test"[29]. Briefly: the drug is incubated with liver microsomes and then treated with cytosolic cell fractions, which contain the relevant enzymes to convert any free formaldehyde into formic acid; the Nash test then only reveals the formaldehyde released by the intermediate (2). The N-demethylated product, pentamethylmelamine [2-methylamino-4,6-bis(dimethylamino)-1,3,5-triazine] [PMM] (3) is then either excreted or further demethylated by a similar process.

It is uncertain whether the antitumour activity is a consequence

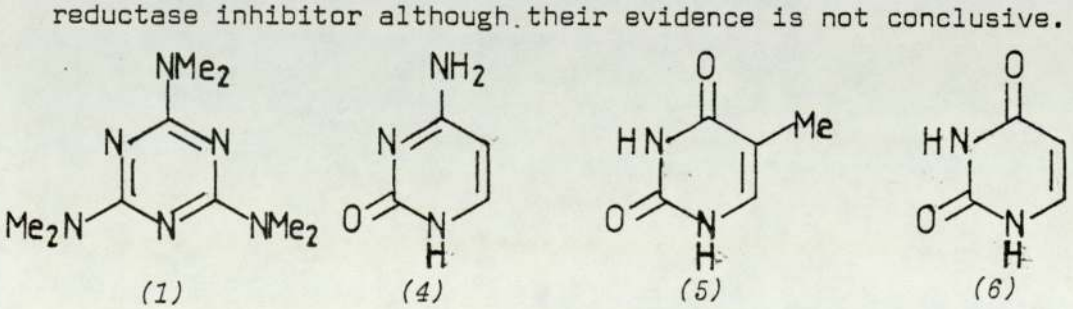
of the production of free formaldehyde or due to the actual intermediate (2) or a bioconjugate of this intermediate (2). This is still under investigation.



Scheme 1: Proposed Metabolism of Hexamethylmelamine

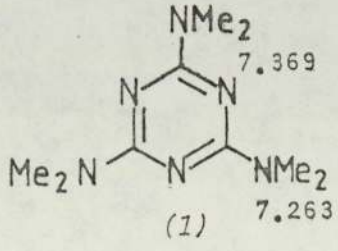
The alternative possibility is that HMM acts as an antimetabolite. No strong supportive evidence exists to corroborate this theory but no firm contradictory evidence has been discovered. The 1,3,5-triazine ring in HMM is structurally similar to the pyrimidine ring in cytosine (4), thymine (5) and uracil (6), which are the naturally occurring pyrimidine bases in nucleic acids. HMM may be recognised by a specific pyrimidine receptor(s) and block the normal biochemical processes which follow recognition and receptor/substrate interaction.

Various workers have claimed that HMM is not a dihydrofolate reductase inhibitor although their evidence is not conclusive.

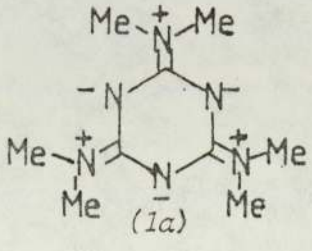


1.4 Physical And Chemical Properties Of Hexamethylmelamine

HMM is a white, crystalline solid which is virtually insoluble in water although it is more soluble in all other polar and non-polar solvents[30]. Various melting point ranges have been reported[30] which are centered around 173°C for HMM. The drug possesses the three, characteristic, i.r. bands displayed by all 1,3,5-triazines[31]. Strong bands at 1530 and 1390 cm^{-1} reflect the triazine, in-plane, ring vibrations and a weaker band at 800 cm^{-1} corresponds to the out-of-plane, ring vibration. The u.v. spectrum is consistent with a conjugated system (λ_{max}=228nm)[30]. The ^{1}H n.m.r. spectrum in deuterochloroform contains a singlet (δ=3.07)[30] indicative of six, equivalent N-methyl groups connected to an aromatic nucleus. The ^{13}C n.m.r. spectrum contains a downfield singlet (165.75 ppm) corresponding to the three, equivalent, sp^2, ^{13}C-centres within the triazine ring and an upfield singlet (35.62 ppm) corresponding to the six, equivalent, sp^3, ^{13}C-centres of the N-methyl groups[30]. The mass spectrum contains the expected parent, M^+ ion (m/z=210), which fragments *via* several discrete pathways: losses of 15($CH_3^{\cdot}$), 27(HCN), 29(CH_2=NH) and 70(Me_2NCN) are predominantly observed[30]. Simmonds and Stevens[32] determined the pK_a of HMM, spectroscopically, as 4.88 ±0.8. The electron density calculations indicate that the most basic N-centres are those within the triazine ring, which leads to the major resonance hybrid (1a) for HMM[33].



(1)



(1a)

Chemically[32], HMM is relatively inert and can be recovered unchanged from boiling 2M-hydrochloric acid or 2M-sodium hydroxide. HMM resists hydrazinolysis, photolysis, oxidation (with 86% hydrogen peroxide in acetic/sulphuric acids mixture) and methylation (with iodomethane in

methanol or dimethyl sulphate in hot, 2M-sodium hydroxide).

1.5 Analogues Of Hexamethylmelamine

Various workers have prepared compounds, which are structurally related to HMM, in an attempt to produce water soluble compounds and to obtain a structure/antitumour activity correlation for the N-methyl group.

The synthesis of HMM and these analogues is described in the next chapter whereas the antitumour and structure/activity results are presented in Chapter 3.

2 SYNTHESIS OF HEXAMETHYLMELAMINE AND ITS WATER-SOLUBLE ANALOGUES

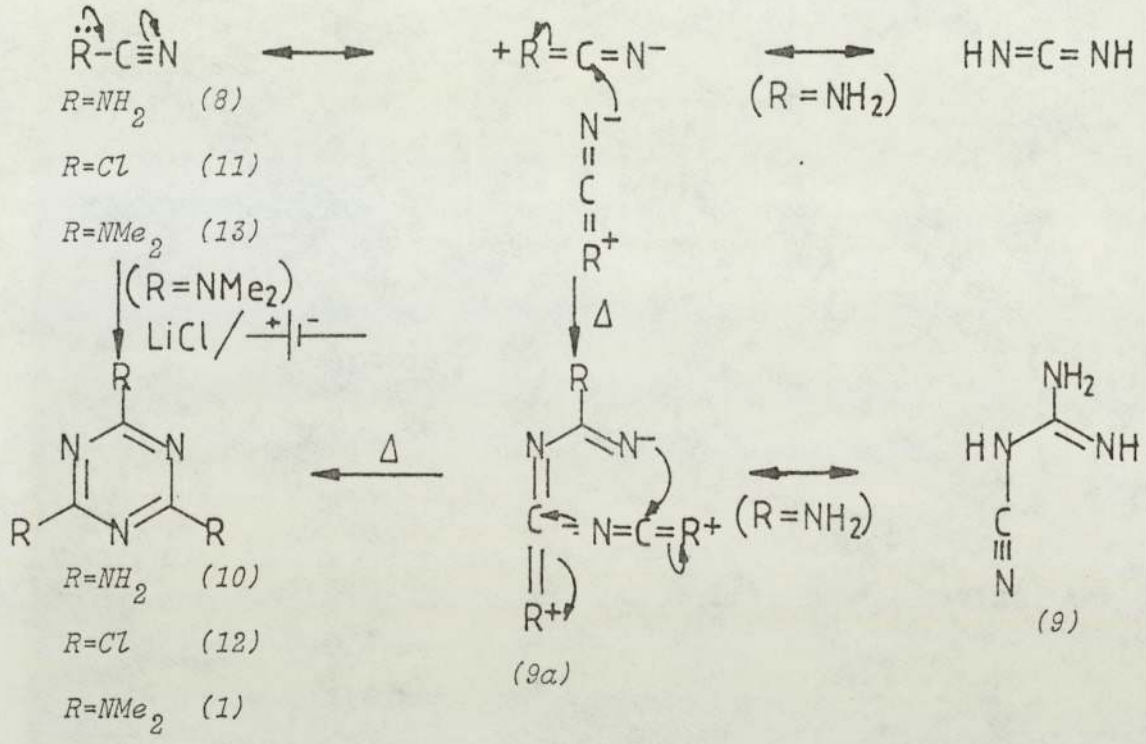
2.1 General Aspects Of Melamine Synthesis

It is well established that cyanamide (8) undergoes stepwise, thermal trimerisation[34-41]. When cyanamide is heated to its melting point, reaction occurs and its dimer, dicyandiamide [N-cyanoguanidine] (9) is formed. If cyanamide (8) or its dimer (9) is heated to higher temperatures then trimerisation occurs and melamine [2,4,6-triamino-1,3,5-triazine] (10) is obtained (Scheme 2).

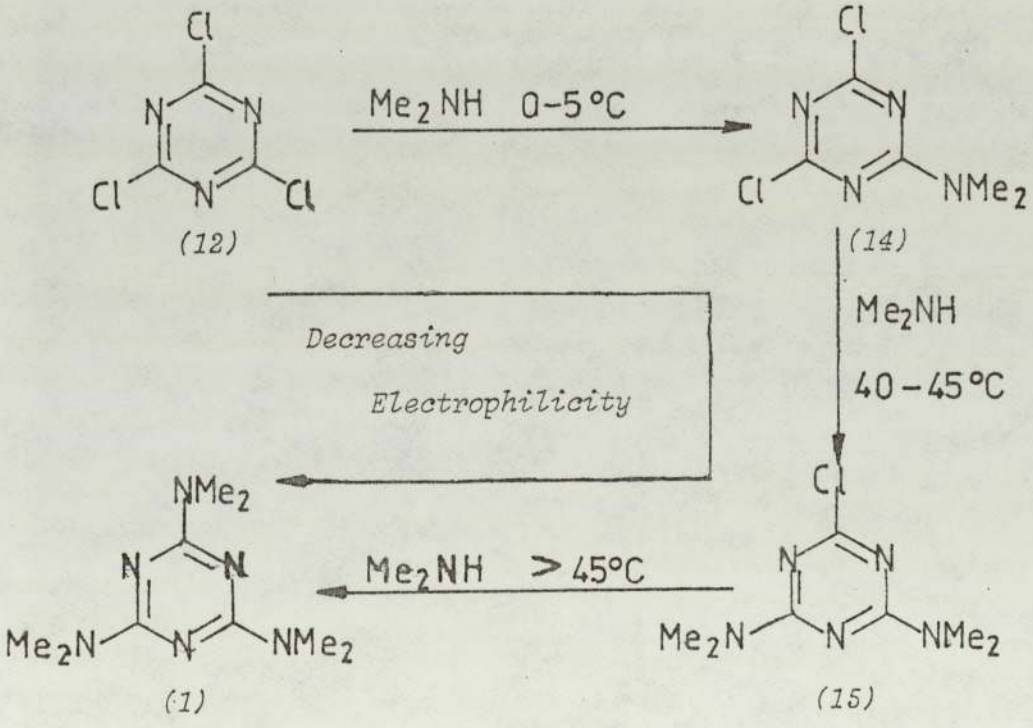
A similar reaction occurs with cyanogen chloride (11) to form cyanuric chloride [2,4,6-trichloro-1,3,5-triazine] (12)[42,43] although the dipolar dimer (9a; R=Cl) is not isolable (Scheme 2).

It would be expected that N,N-dimethylcyanamide (13) should undergo a similar reaction to form HMM (1) and that the dipolar dimer (9a; R=NMe_2) would not be isolable. The thermal trimerisation, however, has not been reported and the only recorded case cited, for the trimerisation of dimethylcyanamide (13), is the electrolysis of dimethylcyanamide (13) saturated with lithium chloride whereupon HMM (1) is formed at the cathode[44] (Scheme 2).

The most convenient starting material from which to prepare melamines is cyanuric chloride (12), which is susceptible to nucleophilic attack. It has been reported that cyanuric chloride (12) can be reacted with amines under controlled reaction conditions to favour, exclusively, mono-, di- or trisubstituted products[45,46]. Cyanuric chloride (12) reacts at 0-5^{o}C with one molar equivalent of dimethylamine to yield 2,4-dichloro-6-dimethylamino-1,3,5-triazine (14) whereas two molar equivalents of dimethylamine at 40-45^{o}C yields 2-chloro-4,6-bis(dimethylamino)-1,3,5-triazine (15). Excess dimethylamine at higher temperatures results in trisubstitution of cyanuric chloride (12) and HMM (1) is obtained (Scheme 3).



Scheme 2: Trimerisation Of Cyanamides And Cyanogen Chloride

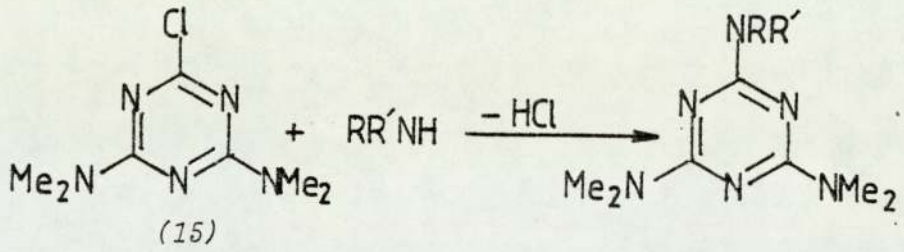


Scheme 3: Progressive Dimethylamino Substitution Of Cyanuric Chloride

This substitution selectivity arises from the activating effect of the chloro group versus the deactivating effect of the dimethylamino group towards nucleophilic substitution. The 1,3,5-triazine ring is highly π-electron deficient and in cyanuric chloride (12) the three chloro substituents serve to reduce further the electron density at carbon; the molecule is electrophilic as a result. Replacement of one chloro group in cyanuric chloride (12) by a dimethylamino substituent converts a formerly activated site into a deactivated site and increases the net electron density within the heterocycle. This trend extends throughout the transition from cyanuric chloride (12) to HMM (1), which is insensitive to nucleophilic attack. As the most electrophilic species present in the reaction mixture is always the most chloro substituted derivative, then, providing that the temperature and molar ratios of reactants are enforced, the reaction will proceed specifically, to produce mainly one product from nucleophilic substitution.

2.2 Preparation Of Specific Melamines

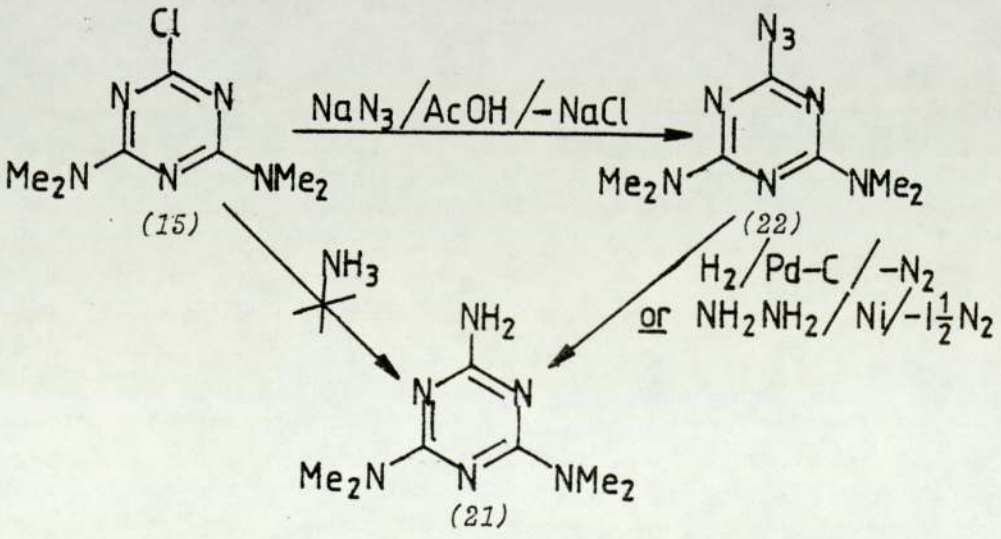
Cumber and Ross[47] prepared various melamines, bearing at least four N-methyl groups, in an attempt to obtain water-soluble compounds with antitumour activity. In general, all the compounds were prepared from the 2-chloro derivative (15) and the requisite amine under aqueous, reflux conditions. Reaction of the 2-chloro derivative (15) with dimethylamine, methylamine, diethylamine, N-methylethanolamine, diethanolamine, N-methylhydroxylamine and sarcosine yielded HMM (1), PMM (3) and products (16-20).



(15)

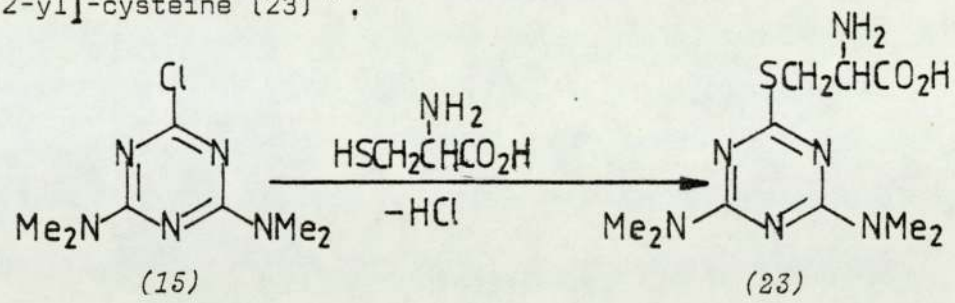
R	R'	
Me	Me	(1)
Me	H	(3)
Et	Et	(16)
Me	CH_2CH_2OH	(17)
CH_2CH_2OH	CH_2CH_2OH	(18)
Me	OH	(19)
Me	CH_2CO_2H	(20)

Hot, concentrated, aqueous ammonia solution is not sufficiently nucleophilic to displace the chloro substituent in the 2-chloro derivative (15) and 2-amino-4,6-bis(dimethylamino)-1,3,5-triazine (21) cannot be prepared by this route. The 2-chloro derivative reacts readily with sodium azide in glacial acetic acid to form the 2-azido derivative (22)[48], which is readily reduced by catalytic hydrogenation[32] or hydrazine hydrate and Raney nickel[32] to the desired 2-amino derivative (21).



(21)

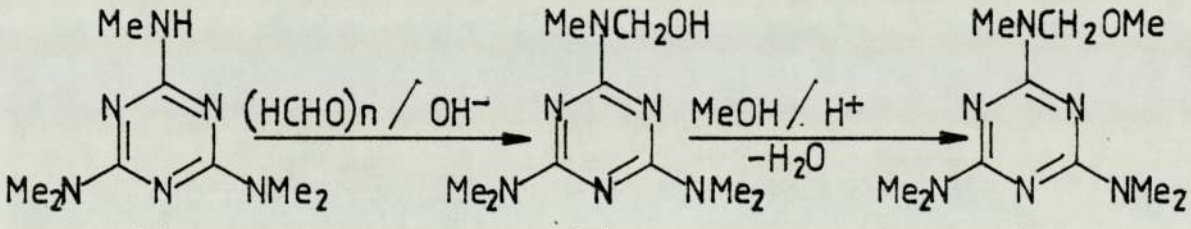
Cysteine reacts with the 2-chloro derivative (15) under aqueous reflux conditions to produce S-[4,6-bis(dimethylamino)-1,3,5-triazin-2-yl]-cysteine (23)[47].



(15) (23)

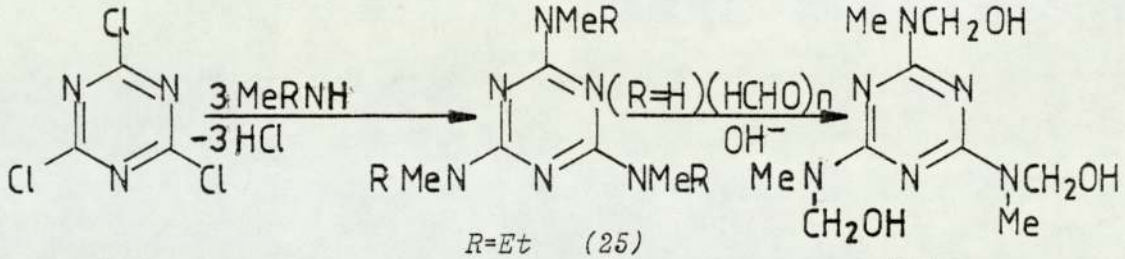
Besides the simple N-alkylmelamines, Cumber and Ross[47] prepared some N-hydroxymethylmelamines, which are the putative metabolic intermediates during, *in vitro* and *in vivo*, demethylation (Section 1.3).

If PMM (3) is treated with paraformaldehyde under aqueous, alkaline conditions then 2-N-hydroxymethylmethylamino-4,6-bis(dimethylamino)-1,3,5-triazine (2) is obtained, which can be converted into its methyl ether (24) on treatment with acidic methanol.



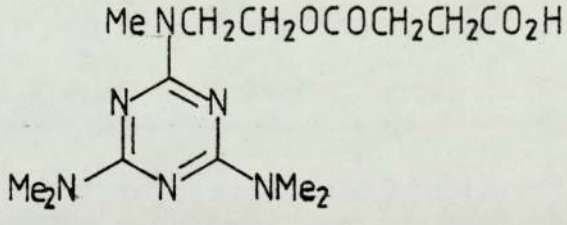
(3) (2) (24)

The same authors[47] prepared two symmetrical trimethylmelamines by reacting cyanuric chloride (12) with ethylmethylamine to obtain 2,4,6-tris(ethylmethylamino)-1,3,5-triazine (25) and with methylamine to obtain the intermediate, trimethylmelamine, which was converted, with alkaline paraformaldehyde, into 2,4,6-tris(N-hydroxymethylmethylamino)-1,3,5-triazine (27).



(12) *R=Et (25)* *R=H (26)* *(27)*

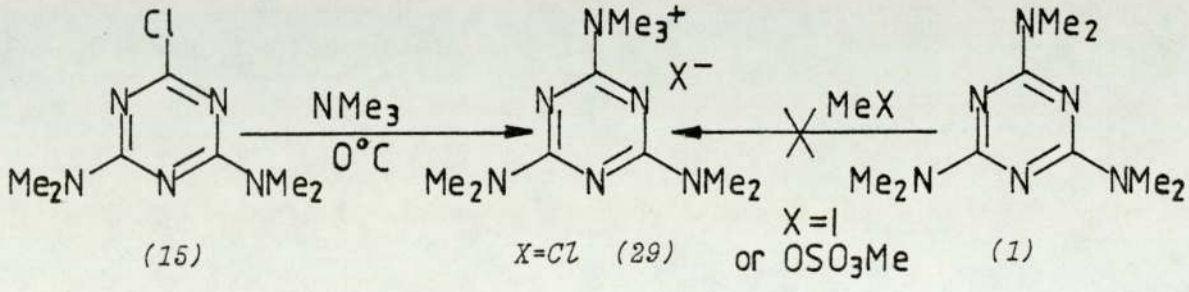
The antitumour activity of all of these compounds (plus the hemisuccinate (28) of compound (17), which was prepared by treating compound (17) with succinic anhydride) was evaluated. The results for the activity are presented in the next chapter. Various other workers have prepared other water-soluble analogues which are described below.



(28)

2.3 Quaternary Salts Of Hexamethylmelamine

Previously (Section 1.4), it was stated that HMM resists quaternisation with standard methylating agents. Two Russian workers, however, have prepared the quaternary salt, N-[4,6-bis(dimethylamino)-1,3,5-triazin-2-yl]trimethylammonium chloride (29) by the interaction between the 2-chloro derivative (15) and trimethylamine in ether[49,50].

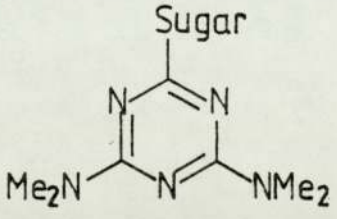


(15) *X=Cl (29)* *(1)*

No other quaternary salts of HMM are quoted in the literature.

2.4 Carbohydrate-Linked Melamines

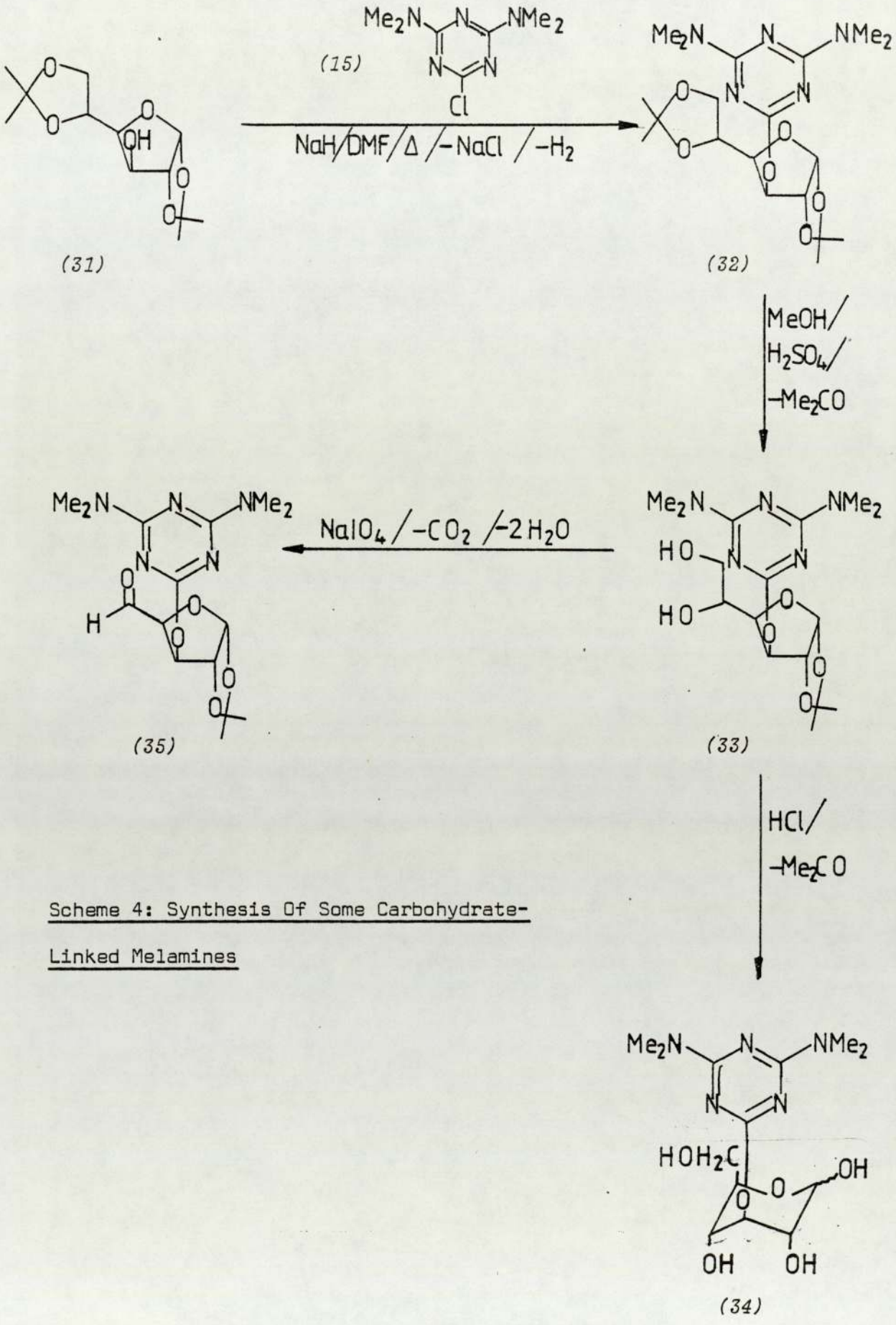
Simmonds and Stevens[32] investigated the synthetic possibilities of connecting various carbohydrate residues onto the triazine nucleus. The compounds, which they prepared, were of the general structure (30); in order to maintain a minimum of four N-methyl groups.



(30)

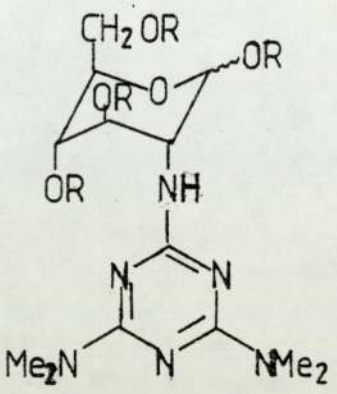
In their early experiments, they employed a partially protected sugar residue in order to minimise the possible side-reactions. Prolonged interaction between the 2-chloro derivative (15) and 1,2;5,6-di-O-isopropylidene-α-D-glucofuranose (31) in DMF in the presence of sodium hydride at 130°C yielded the 3-O-substituted-glucofuranose (32), which could be specifically hydrolysed with cold, methanolic sulphuric acid to yield the diol (33) by removal of the 5,6-isopropylidene group. Further hydrolysis, with 0.4M-hydrochloric acid, removed the 1,2-isopropylidene group to form the glucopyranose (34). The glucofuranose (33) was susceptible to slow oxidation with sodium metaperiodate to yield the aldehyde (35) (Scheme 4).

Neither the 2-chloro derivative (15) nor the 2-azido derivative (22) could be condensed with the amino function of glucosamine or its methylglycoside without substantial decomposition of the carbohydrate residue. The quaternary salt (29), however, has the excellent, volatile, leaving-group, trimethylamine and the salt (29) readily reacts with glucosamine in aqueous potassium hydoxide to form the N-triazinyl-glucosamine (36), which can be converted readily into its tetra-O-acetate (37) with acetic anhydride in pyridine. Furthermore, the



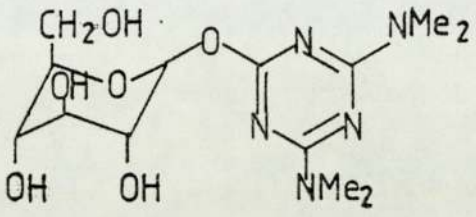
Scheme 4: Synthesis Of Some Carbohydrate-Linked Melamines

salt (29) reacts with the protected sugar (31) in cold, aqueous sodium hydroxide to yield the glucofuranose (32). Similarly, D-glucose itself reacts with the salt (29) under mildly basic conditions to form the β-D-glycoside (38).



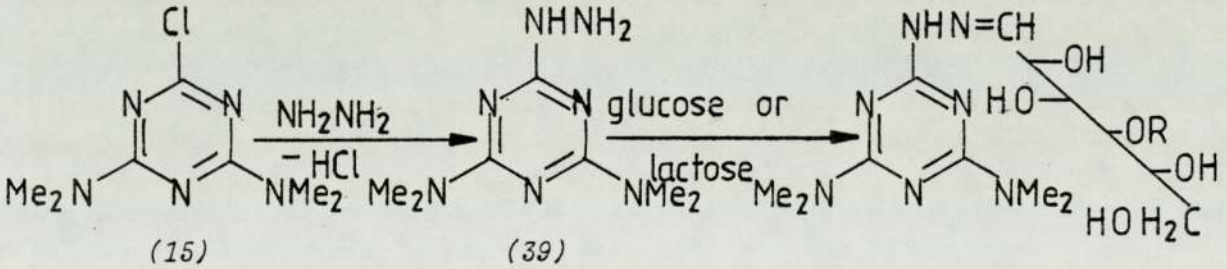
R=H (36)

R=Ac (37)



(38)

The 2-chloro derivative (15) reacts readily with hydrazine in ethanol to yield 2-hydrazino-4,6-bis(dimethylamino)-1,3,5-triazine (39), which condenses with the reducing sugars, glucose and lactose, to produce the corresponding hydrazones (40) and (41) respectively.



(15) *(39)*

R=H (40)

R=β-D-galactopyranosyl (41)

Hence, many and varied modifications have been made to the drug HMM (1) in an attempt to obtain water soluble derivatives, which will have antitumour activity. The effects of these modifications on the antitumour activity of these compounds is described in the next chapter.

3 ANTITUMOUR ACTIVITY OF WATER-SOLUBLE ANALOGUES OF HEXAMETHYLMELAMINE

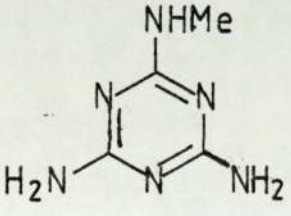
3.1 Pentamethylmelamine

PMM (3) is the first, stable metabolite of HMM (1) (Section 1.3) and was subjected to clinical trial as an alternative to HMM on the basis that it was more water soluble and formed a stable hydrochloride salt to enable its formulation in physiological saline. It was hoped that the unpleasant, antiperistaltic activity caused by HMM would be circumvented by the direct injection of PMM into the bloodstream.

Phase I, clinical trials[51-56], however, revealed that the same degree of nausea was experienced by patients and the original belief that this effect was caused by gastrointestinal irritation by HMM was no longer the sole, contributory factor. It is now believed that PMM has a central nervous action and probably stimulates the vomiting centre in the brain[14].

3.2 Comparative Antitumour Activity Of Hexamethylmelamine And Its Desmethyl Analogues

In 1975, Lake *et al*[57] demonstrated the importance of the N-methyl group for antitumour activity using murine Sarcoma 180 and Lewis lung carcinoma. Melamine (10) had no antitumour activity and the increase in antitumour activity from monomethylmelamine (42) up to HMM was directly paralleled by a rise in the toxicity of the compounds, imparting a fairly constant therapeutic-index to the series.



(42)

In 1977, Rutty *et al*[24] extended the structure/antitumour activity correlation. They found that, *in vitro*, cytotoxic (antitumour) activity was lost when fewer than four N-methyl groups were present in the melamine drugs.

3.3 Antitumour Activity Of Alkylmelamines With Four Or Less N-Methyl Groups

The compounds, prepared by Cumber and Ross[47], together with their relative water solubilities and antitumour activity, *in vivo*, are summarised in Table 1. Most of these compounds were also tested, *in vitro*, by Rutty and Connors[58] for antitumour activity against ADJ PC6A plasma cytoma cells. Clearly, it can be seen that the only compounds, which exhibit ubiquitous antitumour activity are HMM (1), PMM (3), the N-hydroxymethyl intermediate (2) and its methyl ether (24), together with the tris(N-hydroxymethylmethylamino)- derivative (27).

The tetramethylmelamine (21) and the diethyltetramethylmelamine (16) had only *in vitro* activity against the PC6A tumour cells.

All the other modifications had generally dyschemotherapeutic effects even though the compounds contained the four N-methyl groups postulated as being required by Rutty *et al*[24] for antitumour activity.

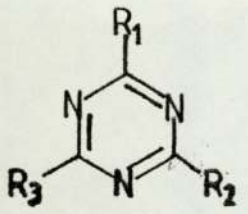
3.4 Antitumour Activity Of Carbohydrate-Linked Melamines

The compounds, prepared by Simmonds and Stevens[32], were found to be totally inactive against M 5076 reticulum cell sarcoma[59] and P 388 lymphocytic leukaemia[60] even though the postulated four N-methyl groups are present in all of these compounds.

3.5 Antitumour Activity Of The Quaternary Salt (29)

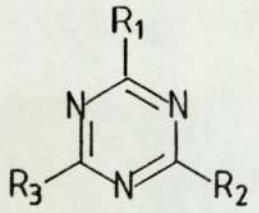
The quaternary salt (29) is exceptionally water-soluble and was tested against the ADJ PC6A plasma cytoma[61], *in vitro*, and no

Table 1: Comparison Of Water Solubilities And Antitumour Activity Of Hexamethylmelamine And Its Water Soluble Analogues



	R_1	R_2	R_3	Relative H_2O Solubility (HMM=1)	Antitumour Activity Against Human Lung Xenograft
21	NH_2	NMe_2	NMe_2	4.1	Inactive[a]
3	NHMe	NMe_2	NMe_2	23.7	Active
1	NMe_2	NMe_2	NMe_2	1	Active
16	NEt_2	NMe_2	NMe_2	0.74	Marginal[a]
2	$NMe(CH_2OH)$	NMe_2	NMe_2	(∿10)[b]	Active
24	$NMe(CH_2OMe)$	NMe_2	NMe_2	(∿16.5)[b]	Active
17	$NMe(CH_2CH_2OH)$	NMe_2	NMe_2	35.4	Inactive
28	$NMe(CH_2CH_2OCOCH_2CH_2CO_2H)$	NMe_2	NMe_2	2800	Marginal
18	$N(CH_2CH_2OH)_2$	NMe_2	NMe_2	90.7	Inactive
19	NMe(OH)	NMe_2	NMe_2	9.94	c

Table 1 *(continued)*



	R_1	R_2	R_3	Relative H_2O Solubility (HMM=1)	Antitumour Activity Against Human Lung Xenograft
20	$NMe(CH_2CO_2H)$	NMe_2	NMe_2	2200	Inactive
15	Cl	NMe_2	NMe_2	6.7	Inactive
23	$SCH_2CH(NH_2)CO_2H$	NMe_2	NMe_2	24.6	Inactive
25	NMeEt	NMeEt	NMeEt	0.55	*c*
27	$NMe(CH_2OH)$	$NMe(CH_2OH)$	$NMe(CH_2OH)$	99.3	Active

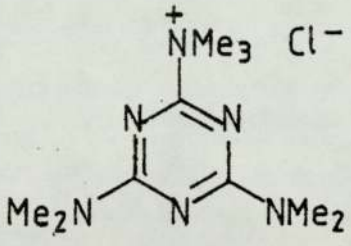
a Active against PC6A cells, *in vitro*, only

b Compound decomposed on contact with water

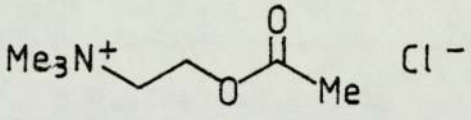
c Result not indicated by author(s)

antitumour activity was observed. *In vivo*, doses in excess of 40 $mgkg^{-1}$ were found to be fatally toxic (LD_{50} ~28 $mgkg^{-1}$) to mice and lower doses had no apparent antitumour effect against the ADJ PC6A plasma cytoma[62].

The toxicity was thought to be attributable to the quaternary, trimethylammonium "head" in the molecule (29), which is identical to that present in acetylcholine (43), and could impart cholinergic activity to this salt (29). *In vitro*, studies with the salt (29) on the frog rectus and rat diaphragm/phrenic nerve preparations[63] indicated that the salt (29) competitively blocked the post-junctional site of the neuromuscular junction at dose levels of 20 μgml^{-1}. It was calculated that the LD_{50} dose (28 $mgkg^{-1}$) could easily produce this concentration (20 μgml^{-1}), if not more, at the neuromuscular junction[63].



(29)



(43)

3.6 Conclusion And Objectives

It is apparent, from the results presented in this chapter, that the modifications which were made to the drug HMM (1), resulted in a general reduction or loss of antitumour activity. The quaternary salt (29) was apparently inactive although its high toxicity prevented any higher dosage antitumour effects.

The initial task presented, at the outset of this work, was to prepare various other quaternary salts of HMM with larger alkyl substituents on the cationic "head" in order to try to eliminate any cholinergic activity. The synthesis of these salts is described in the following chapter. Subsequent chapters will discuss alternative methods for the introduction of a water-solubilising entity into

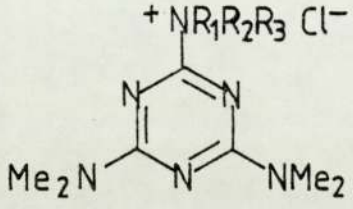
the HMM nucleus and the chemical properties of these derivatives are described. The final chapter will present some of the pharmacological findings for some of the compounds prepared, together with an *in vitro/in vivo* correlation of the protocols used.

RESULTS AND DISCUSSION

4 QUATERNARY AMMONIUM SALTS RELATED TO HEXAMETHYLMELAMINE

4.1 Synthesis Of Monocationic Salts

It was hoped that the reaction between 2-chloro-4,6-bis(dimethylamino)-1,3,5-triazine (15) and trimethylamine to form the heptamethyl salt (29) could be extended to other tertiary amines as a synthetic route to novel higher homologues (44) in this series.

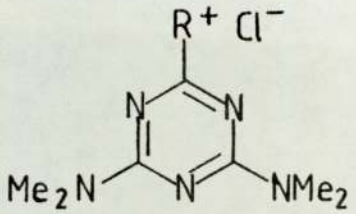


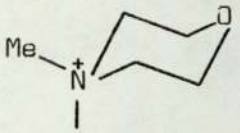
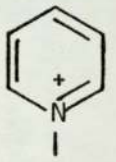
(44)

The reaction between the 2-chloro derivative (15) and various tertiary amines was investigated primarily in dry ether solution at $0^{o}C$, ambient temperature or in some instances at reflux. The amines investigated together with the reaction conditions and yields of products are presented in Table 2.

The considerable variation in product yield for the various amines can be rationalised in terms of steric hindrance and effective lone pair donation by nitrogen. If the simple trialkylamine series is segregated, it can be seen that the yield of product decreases as the molecular weight and bulk of the alkyl chains on the amines increases. The larger alkyl groups prevent effective collisions between the reactants conducive to reaction as the effeciency of the lone pair donation of the amine to the electrophilic carbon centre in the 2-chloro derivative (15) is reduced. This explanation is further supported by the inclusion of N-methylmorpholine. Although N-methylmorpholine has a similar molecular weight to diethylmethylamine, the cyclic arrangement of the ethyl groups reduces the steric bulk of the amine and the reaction is more effecient than with the acyclic

Table 2: Reaction Conditions And Yields Of Quaternary Ammonium Salts Related To Hexamethylmelamine



	R	%Yield	Reaction Conditions
29	$-\overset{+}{N}Me_3$	80-90	2 days at 0°C
45	$-\overset{+}{N}Me_2Et$	40	4 days at 20°C
46	$-\overset{+}{N}MeEt_2$	Minimal	6 days at 20°C then 2 days at reflux
47	$-\overset{+}{N}Et_3$	Nil	7 days at 20°C then 2 days at reflux
48	$-\overset{+}{N}Me_2CH_2CH_2OH$	a	2 days at 20°C
49		20	3 days at 20°C
50		Minimal	7 days at 20°C then 2 days at reflux

a Product was too deliquescent to isolate

diethylmethylamine.

If pyridine is now included, it would be predicted that it should have less steric bulk than triethylamine and possibly even diethylmethylamine; the product (50), however, was not obtained. The steric hindrance theory alone cannot accommodate this observation. In all the other tertiary amines investigated the central N-atom is in sp^3 hybridisation and the quaternary derivatives of these amines are tetrahedral. In pyridine, the N-atom is in sp^2 hybridisation in order to maintain ring-planarity. Quaternisation of pyridine results in a trigonal quaternary salt where lone pair orbital overlap is poorer and in this case barely occurs to form the desired product (50).

Thus, a reactivity sequence can be drawn for the tertiary amines, although it is not certain exactly where to place pyridine (Figure 1).

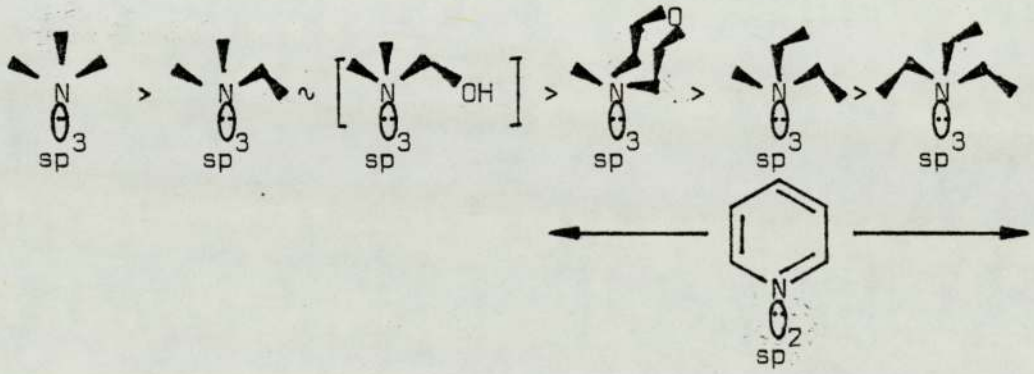


Figure 1: Reactivity Of Tertiary Amines Towards 2-chloro-4,6-bis(dimethylamino)-1,3,5-triazine (15)

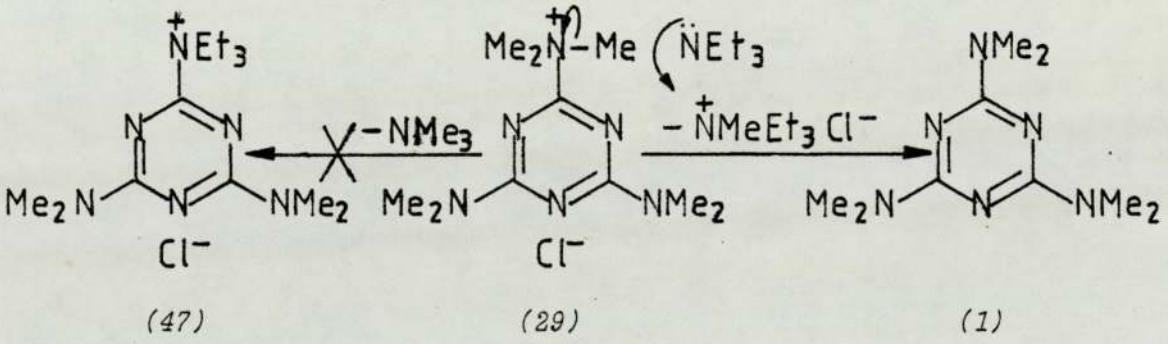
Various, futile attempts were made to overcome the steric barrier to reaction by increasing the solvent polarity and the temperature and pressure of the reaction.

It appeared that the simple quaternisation of tertiary amines with the 2-chloro derivative (15) was of little synthetic value except for the lowest homologues.

A second approach, which was considered, was to replace the

2-chloro derivative (15) with the heptamethyl salt (29) as the substrate in the reactions with tertiary amines. The aim was that the volatile, leaving-group trimethylamine would be expelled from the system on heating with a less volatile tertiary amine and even if the equilibrium was predominantly towards the reactants the loss of trimethylamine would become the driving force to push the reaction to near completion.

The heptamethyl salt (29) was heated to reflux in neat triethylamine but the only products which could be isolated were the unreacted salt (29) and HMM (1). The only reasonable explanation of this peculiar result is that a "transquaternisation" reaction had occurred (Scheme 5). It has already been stated (Section 1.4) that HMM is an extremely stable chemical entity and its formation in this reaction could bely the thermodynamic factors for this reaction to occur.



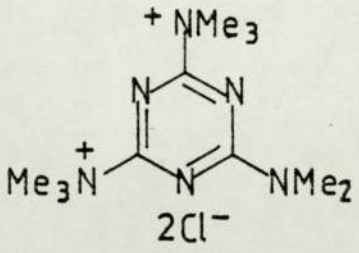
(47) *(29)* *(1)*

Scheme 5: Dequaternisation Of The Heptamethyl Salt (29) By Triethylamine

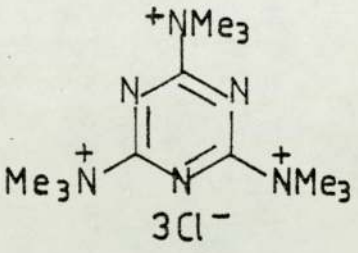
No further synthetic routes to the higher homologues could be devised.

4.2 Synthesis Of Polycationic Salts

Two further novel salts were proposed for direct comparison with the parent heptamethyl salt (29). These compounds were the dicationic, octamethyl salt (51) and the tricationic, nonamethyl salt (52) which could be theoretically prepared from the 2,4-dichloro derivative (14) and cyanuric chloride (12) respectively on treatment with excess trimethylamine.



(51)



(52)

The reactions were investigated in dry ether solution. The 2,4-dichloro derivative (14) gave a 90% yield of product after 1 day at $0^{o}C$ with trimethylamine. Cyanuric chloride (12) is only sparingly soluble in ether so the reaction was conducted at $20^{o}C$ for 1 hour whereupon a yield of 95% of product was obtained after 1 hour with trimethylamine (*c.f.* 80-90% yield of the heptamethyl salt (29) after 2 days at $0^{o}C$ for the interaction of the 2-chloro derivative (15) with trimethylamine).

The increased yield observed for the heptamethyl salt (29) compared with the nonamethyl salt (52) is explicable synonymously with the progressive dimethylamine substitution of cyanuric chloride (12) (Section 2.1). In summary, the reactivity of the chloro substituents decreases with increasing dimethylamino substitution. The trimethylammonium substituents, however, still activate the triazine nucleus to nucleophilic substitution since the lone-pair of electrons on the N-centre is no longer available to donate to the heterocycle.

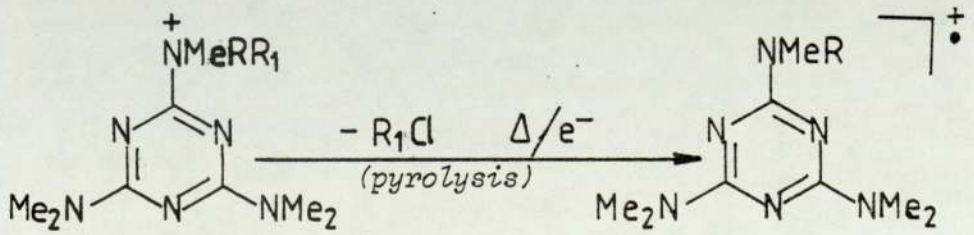
4.3 Physical And Spectroscopic Properties For The Quaternary Salts Related To Hexamethylmelamine

All the quaternary salts, which were successfully isolated, were highly deliquescent white solids with extreme water solubility and moderate solubility in partially chlorinated hydrocarbons. Some of the homologues were too deliquescent to be subjected to elemental analysis and in some cases, the melting points and mass spectra could not be determined.

The i.r. spectra displayed the characteristic triazine in-plane and out-of-plane ring vibrations (Table 3).

The ^{1}H n.m.r. spectra indicated that the positive charge was not delocalised because the alkyl substituent protons on the "onium head" resonate at discernably lower field than the dimethylamino group protons (Table 3). These observations are consistent with the general structure proposed (44) (Section 4.1).

The mass spectra are somewhat unusual in that the cationic parent ions are not observed (Table 3). The heptamethyl salt (29) appears to lose chloromethane on pyrolysis and the only observed parent M^{+} ion is that of HMM (1) (m/z=210). A similar dequaternisation reaction occurs for the hexamethylethyl salt (45) which also exhibits a peak corresponding to HMM (1) (m/z=210) by loss of chloroethane but a further peak corresponding to pentamethylethylmelamine (53) (m/z=224) is also observed by loss of chloromethane.



Not Observed

R=R'=Me (29) (m/z=225)

R=Me;R'=Et(45) (m/z=239)

Observed

R=Me (1) (m/z=210)

R=Et (53)(m/z=224)

Table 3: Spectroscopic Data Obtained For The Successfully Prepared Quaternary Salts Related To Hexamethylmelamine

	i.r. ν cm^{-1}			^1H n.m.r.			Mass Spectrometric Parent Ions (m/z)
	a	b	c	δ		Inference	
29	1620	1415	820	3.2	*(s)* (12H)	N-C$\underline{H}_3$	210
				3.7	*(s)* (9H)	$\overset{+}{N}$-C$\underline{H}_3$	
45	1620	1420	820	1.5	*(t)* (3H)	$CH_2C\underline{H}_3$	224 and 210
				2.9	*(s)* (12H)	N-C$\underline{H}_3$	
				3.5	*(s)* (6H)	$\overset{+}{N}$-C$\underline{H}_3$	
				3.7	*(q)* (2H)	$\overset{+}{N}$-C$\underline{H}_2CH_3$	
49	1640	1420	820	3.3	*(s)* (12H)	N-C$\underline{H}_3$	d
				3.7	*(s)* (3H)	$\overset{+}{N}$-C$\underline{H}_3$	
				4.0	*(dxq)* (8H)	$\overset{+}{N}$-C$\underline{H}_2C\underline{H}_2$-O	
51	1620	1390	830	3.2	*(s)* (6H)	N-C$\underline{H}_3$	d
				3.8	*(s)* (18H)	$\overset{+}{N}$-C$\underline{H}_3$	
52	1620	1390	830	3.9	*(s)* (27H)	$\overset{+}{N}$-C$\underline{H}_3$	d

a,b triazine in-plane ring vibrations c triazine out-of-plane ring vibration d unobtainable

(d) doublet *(s)* singlet *(t)* triplet *(q)* quartet *(dxq)* doublet of quartets

The remainder of the fragmentation pattern observed is identical to that of HMM(1) for the heptamethyl salt (29) and homologous for the hexamethylethyl salt (45).

4.4 The Extended Philosophy

The hexamethylethyl salt (45) was screened for antitumour properties, *in vivo*, which were found to absent. Furthermore, the salt (45) appeared to be, anomalously, even more toxic than the heptamethyl homologue (29). These results coupled with the lack of synthetic routes to the higher homologues led to loss of interest in this series of compounds.

It was decided to investigate other heterocyclic systems related to 1,3,5-triazines and HMM (1) but bearing a charged ring heteroatom which would enable delocalisation of this charge and perhaps remove any cholinergic side-effects attributable to the localised charge of the trimethylammonium moiety. This approach also allows the sextet of N-methyl groups to be retained.

The following chapter will describe these systems and the chemical properties of the compounds successfully prepared will be reviewed in subsequent chapters.

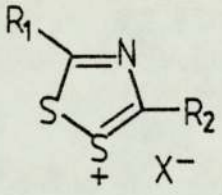
A later chapter will review some selected bicyclic systems related to HMM (1) which may have possible antitumour properties.

5 THIADIAZINIUM AND OXADIAZINIUM SALTS RELATED TO HEXAMETHYLMELAMINE

5.1 Synthesis Of Thiadiazinium Salts

In the search for new insect chemosterilants, Oliver *et al*[64] investigated various cationically charged heterocyclic systems bearing various substituted amino functional groups.

One such system they investigated was the 1,2,4-dithiazolium system (54): various amino groups in the 3 and 5 positions gave rise to compounds which, in some instances, had favourable insect chemosterilizing activity. Not surprisingly, one of the most effective chemosterilants was 3,5-bis(dimethylamino)-1,2,4-dithiazolium bromide (55).



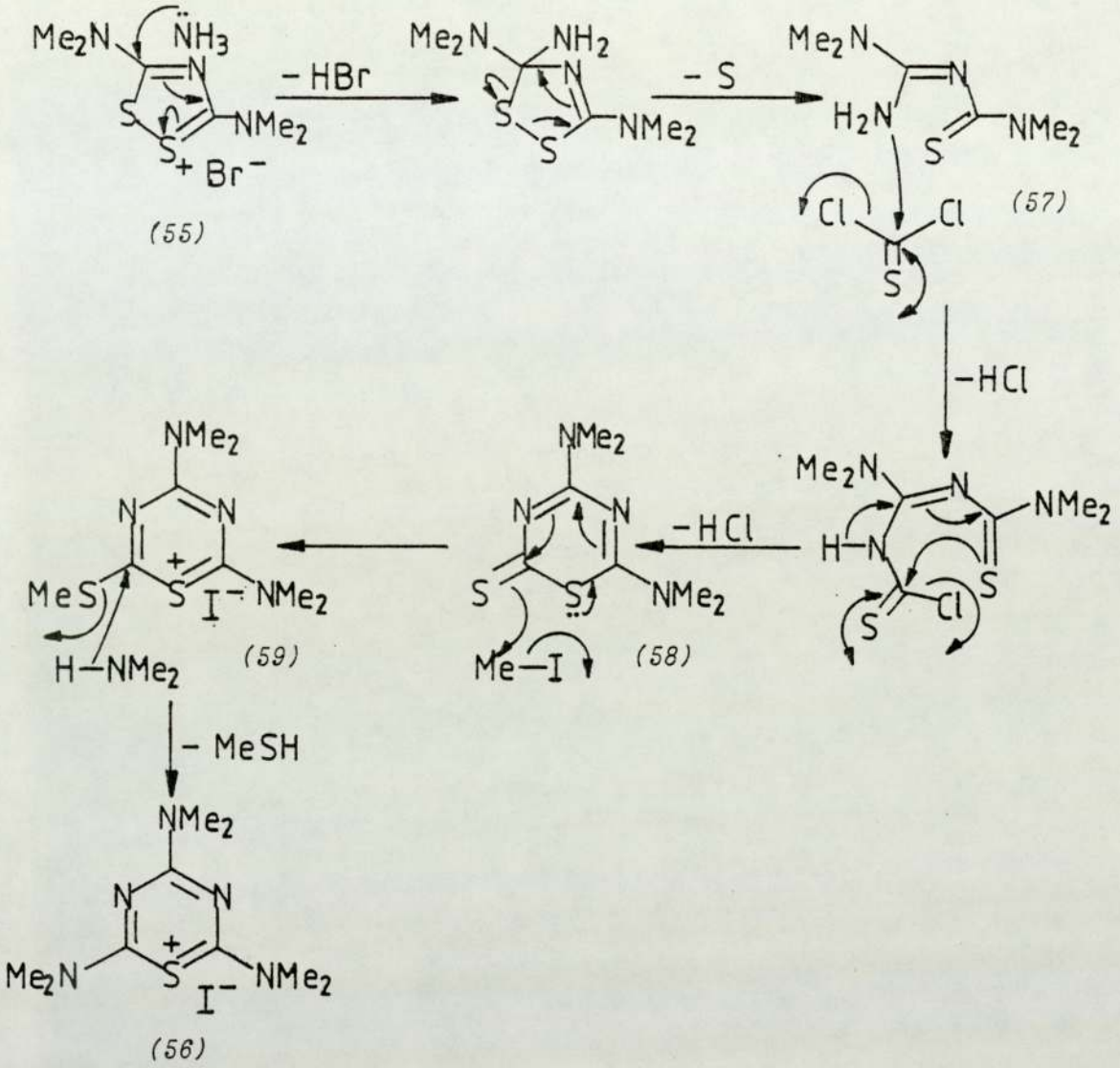
(54)

R_1=R_2=NMe_2;X=Br *(55)*

The heterocyclic nucleus is substantially different to that in HMM (1) and Oliver and De Milo[65] investigated other systems more closely related to HMM (1).

They devised an elaborate synthesis of the hitherto unknown heterocycle, 2,4,6-tris(dimethylamino)-1,3,5-thiadiazinium iodide (56) from the dithiazolium bromide synthon (55). Treatment of the dithiazolium salt (55) with ammonia caused ring opening with extrusion of atomic sulphur to yield the dimethylthiocarbamoyldimethylguanidine (57) which could be recyclised with thiophosgene to the 1,3,5-thiadiazin-2-thione (58). Addition of iodomethane resulted in the aromatic 1,3,5-thiadiazinium salt (59) which could be readily converted to the desired product (56) on treatment with anhydrous dimethylamine (Scheme 6).

The corresponding oxygen analogues *viz* 3,5-bis(dimethylamino)-1,2,4-dioxazolium salts (60) and 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium

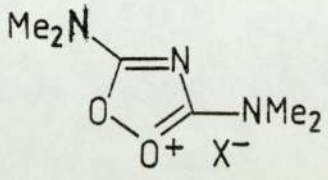


Scheme 6: Conversion Of The 1,2,4-dithiazolium System Into The 1,3,5-thiadiazinium System

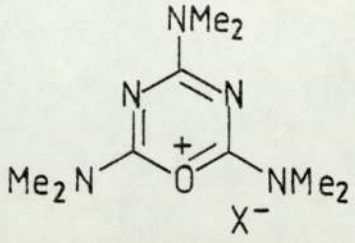
salts (61) have not been reported. It would be unlikely that the dioxazolium system (60) would be stable due to the presence of a peroxy bond in conjunction with a positive charge and an attempt to prepare this compound could be hazardous.

The oxadiazinium salt (61) was selected as the next target molecule to be investigated: the sextet of N-methyl groups is present in the

oxadiazinium salt (61) and the heterocyclic nucleus is isoelectronic with the 1,3,5-triazine nucleus in HMM (1). These factors may be conducive to produce comparable biological properties to HMM (1).



(60)

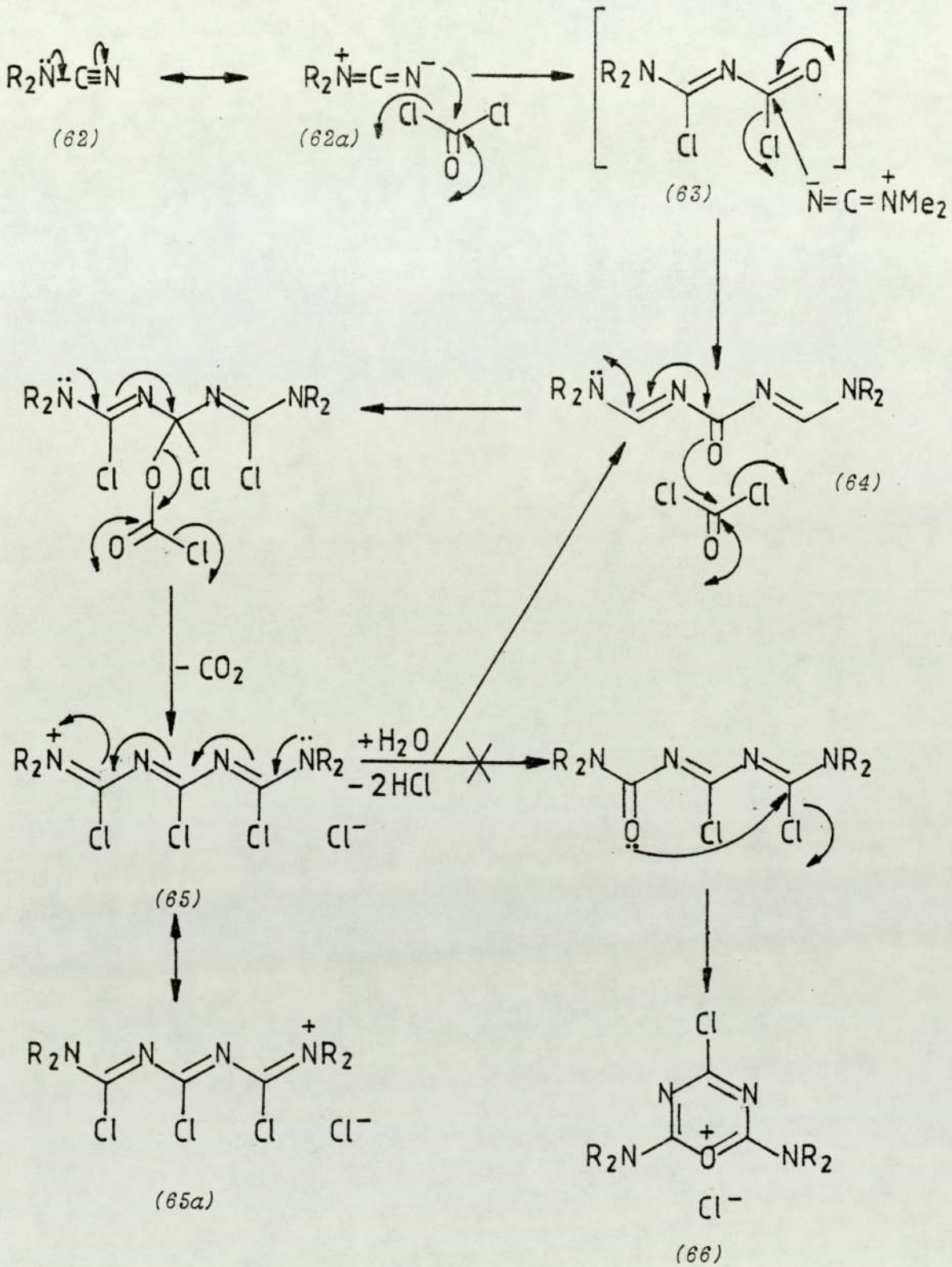


(61)

5.2 Synthesis Of Oxadiazinium Salts

The reaction between N,N-dialkylcyanamides (62) and phosgene has been studied extensively[66-69]. Dialkylcyanamides (62) are superficially 1,3-dipoles and the major resonance hybrid (62a) can be drawn to explain their chemical properties. The nucleophilic nitrogen centre of the dialkylcyanamide (62) attacks phosgene but the 1:1 adduct (63) is transient and has never been isolated, whatever the molar ratios of the reactants. Instead, the bifunctional phosgene reacts further with the dialkylcyanamide (62) and 1,5-bis(dialkylamino)-1,5-dichloro-2,4-diazapenta-1,4-diene (64) is isolated. If the phosgene is in excess, however, then a further reaction occurs with this product (64) with expulsion of carbon dioxide to form N-[5-dialkylamino-1,3,5-trichloro-2,4-diazapenta-1,4-dienylidene]-dialkylammonium chloride (65). Theoretical hydrolysis of this product (65) could feasibly yield the oxadiazinium salt (66) but in practice the precursor (64) is reobtained (Scheme 7).

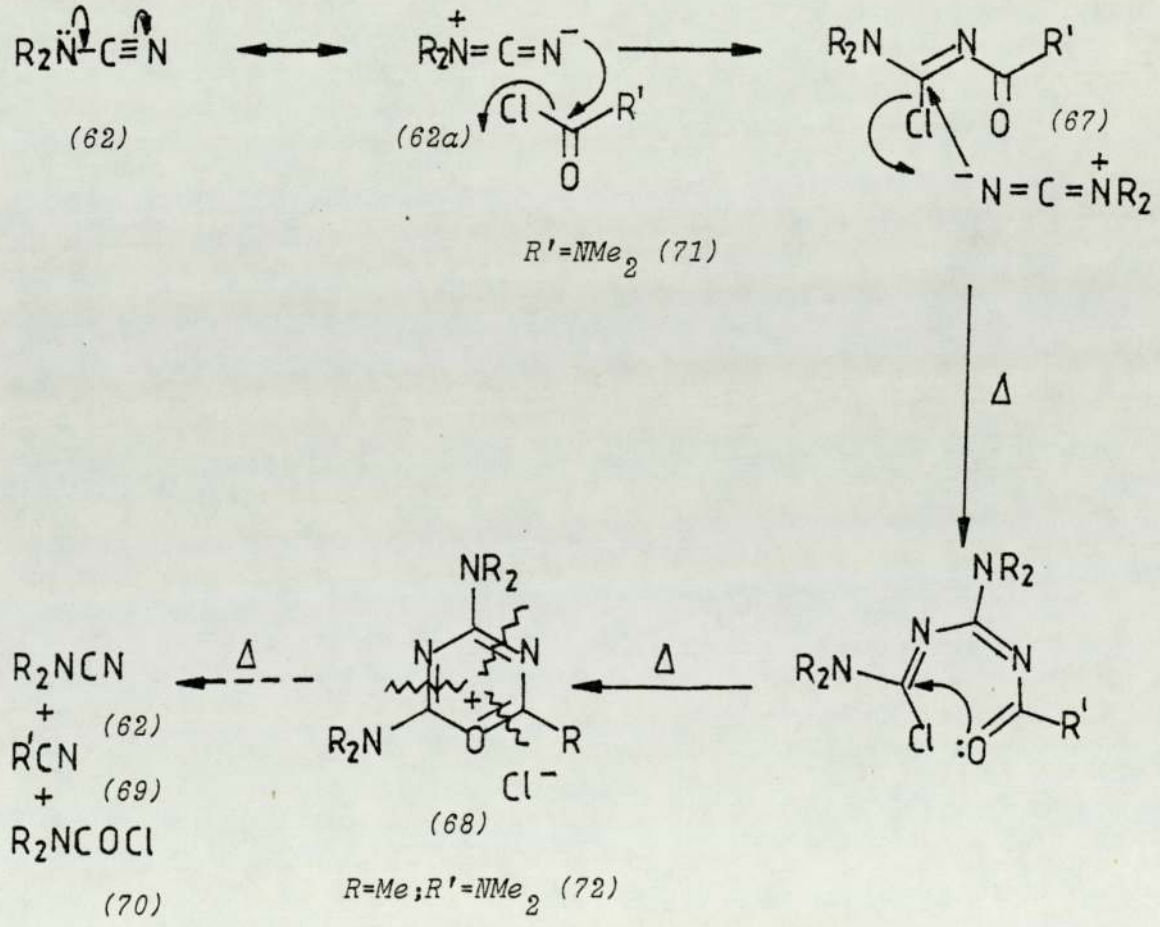
The reaction of N,N-dialkylcyanamides (62) with monofunctional acid chlorides to yield acylchloroformamidines (67) has also been investigated by Bredereck and Richter[70]. They also discovered that if the chloroformamidine (67) was heated with a further equivalent of the dialkylcyanamide (62), small quantities of trisubstituted oxadiazinium chlorides (68) could be obtained.



Scheme 7: Reactions Of Dialkylcyanamides With Phosgene

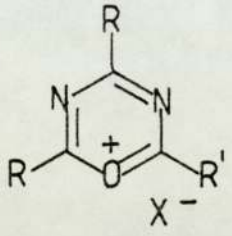
Unfortunately, the oxadiazinium chlorides (68) thermally generated were almost as equally thermally labile and "thermal depolymerisation" occurred to generate an unreactive nitrile (69), an N,N-dialkylcarbamoyl chloride (70) and N,N-dialkylcyanamide (62) (Scheme 8).

If the acid chloride employed were N,N-dimethylcarbamoyl chloride (71) and the dialkylcyanamide were N,N-dimethylcyanamide (13) then the product expected would be the desired oxadiazinium chloride (72). Furthermore, the thermolysis of this salt (72) would generate only the same reactants. This result could produce a theoretically larger yield of the product (72) than the previous salts (68) but, ultimately, the overall yield would depend upon the thermodynamic stability of the cyclic species (72).



Scheme 8: Reactions Of Dialkylcyanamides With Acid Chlorides And Formation Of 1,3,5-oxadiazinium Chlorides

It has also been reported[71-73] that the thermally refractive alkyl and aryl nitriles (69) may be conjugated with acid halides to form oxadiazinium salts (73) in the presence of a Lewis acid at room temperature. These salts (73), however, are much less stable than the salts (68 and 72) mentioned previously.



R/R'=aryl or alkyl

(73)

5.3 Reaction Between N,N-Dimethylcyanamide And N,N-Dimethylcarbamoyl Chloride

Dimethylcyanamide (13) and dimethylcarbamoyl chloride (71) were heated together in a 2:1 molar ratio. The colourless solution underwent a gradual darkening in colour from yellow through orange and red to a greenish brown liquid at reflux (~175°C). If reflux is maintained until the reactants have been in contact for a full 30 minutes and then allowed to cool, the whole mixture crystallises and a white solid can be obtained on recrystallisation from dichloromethane and ether. If the reaction mixture is not allowed to cool after 30 minutes contact, a very vigorous exothermic reaction occurs and dimethylcarbamoyl chloride (71) is expelled from the system and the major product isolated is HMM (1). This result is probably due to the catalytic action of the acid chloride (71) on the thermal trimerisation of dimethylcyanamide (13).

The white solid obtained from the controlled reaction was found to be extremely soluble in water; soluble in partially chlorinated hydrocarbons, dimethylformamide, acetonitrile, alcohols; sparingly soluble in acetone and tetrahydrofuran; virtually insoluble in ether and totally insoluble in carbon tetrachloride and hydrocarbons.

The white solid rapidly darkens on exposure to moisture and the melting point is lowered from 123°C to 102-103°C. The spectroscopic features of "dry" and "damp" samples are virtually identical indicating that the material is not hydrolysed on exposure to moisture. The low melting point of older samples is probably due to dissolution of the compound in its water of crystallisation rather than true fusion.

The compound was subjected to elemental analysis and the results obtained appeared initially to contradict a constitution of dimethylcyanamide (13) and dimethylcarbamoyl chloride (71) in 2:1 molar ratio (Table 4). Closer inspection of the figures, however, reveals that the percentages of carbon, nitrogen and chlorine are lower than the calculated amounts whereas oxygen and hydrogen are higher; furthermore, the %C/%N ratio for both the calculated (1.543) and observed (1.540/1.545) figures are in close agreement. It would appear that the compound is hydrated and the empirical formula obtained correlates well with $C_9H_{18}N_5O^+Cl^-.1.25H_2O$.

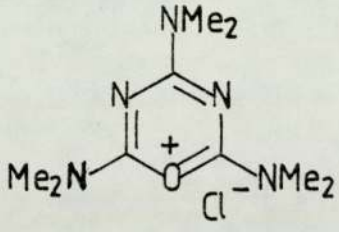
	%C	%H	%N	%Cl	(%O)	%C/%N
Calculated	43.64	7.27	28.28	14.34	6.47	1.543
Found I	39.65	8.01	25.75	14.21	12.38	1.540
Found II	39.36	7.96	25.48	14.21	12.99	1.545

Table 4: Microanalytical Data For The Product Obtained From Dimethylcyanamide And Dimethylcarbamoyl Chloride

The u.v. spectrum observed for the compound in water was consistent with a conjugated structure (λ_{max}=247nm) and the position of the main absorption band was found to be intermediate between HMM (1) (λ_{max}=228nm) and benzene (λ_{max}=254nm).

The compound showed negligible decomposition in aqueous solution and on addition of acid but basification resulted in an almost instantaneous loss of the u.v. chromophore. The rate of decomposition in Earl's physiological buffer (pH=7.4) was found to be negligible over 3 hours by u.v. absorption but further basification (>pH=8) resulted again in instantaneous decomposition.

The data so far presented is in agreement with the proposed structure (72):



(72)

5.4 Spectroscopic Properties Of 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium Chloride

The spectroscopic properties of the oxadiazinium salt (72), which follow, were not entirely consistent with the proposed structure and certain anomalous observations resulted in the absolute structure being determined by X-ray crystallography (Section 5.5). The structure (72) was found to be essentially correct.

The solid-state i.r. spectrum (KBr disc) observed showed four, very strong, mid-range bands (ν=1720,1600,1490 and 1400cm^{-1}). The anomalous band (ν=1720cm^{-1}) appeared to contradict the cyclic structure (72) and was thought to be due to the carbonyl stretching frequency of the acyclic isomer (74):

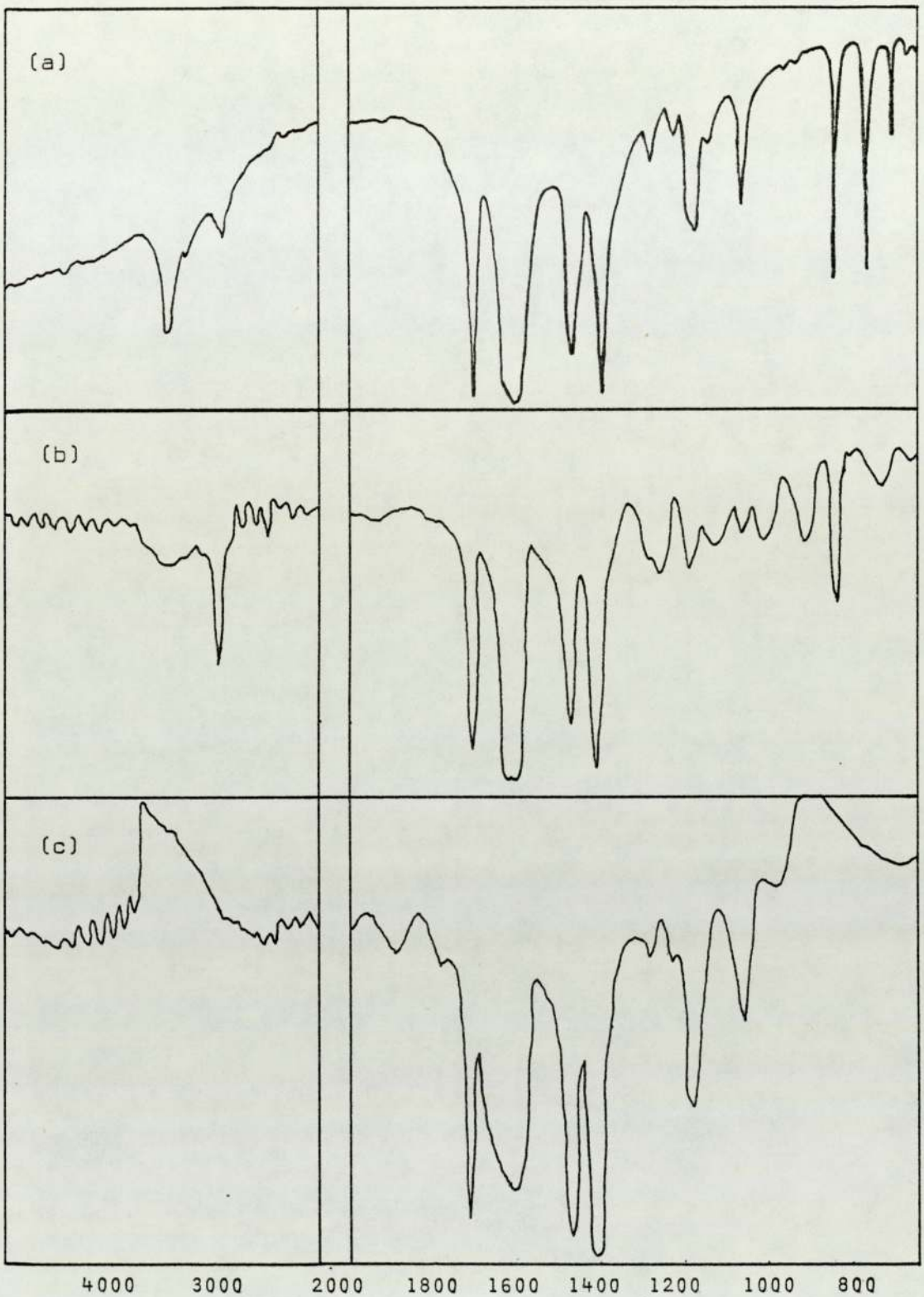
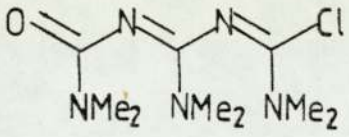


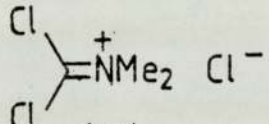
Figure 2: I.r. Spectra For 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium Chloride As a) KBr Disc, b) Solution In Chloroform In Irtran II Cells And c) Aqueous Solution In Irtran II Cells At 4E



(74)

The salient features of the solid-state i.r. spectrum are extended to the spectra observed for solutions of the compound in chloroform and water. This evidence supports the stability of the compound in solution and that the nature of the compound in the solid-state is retained on dissolution (Figure 2).

The acyclic isomer (74) is an imino-chloride and this class of compounds is known to be fairly readily hydrolysed. Indeed, it was found later that the anomalous i.r. band (ν=1720cm^{-1}) was due to the >C=$\overset{+}{N}$Me$_2$ bond stretching frequency and this was confirmed by using phosgenedimethyliminium chloride (75) as a model compound (ν=1720cm^{-1}):



(75)

The ^{1}H n.m.r. spectra for the compound were determined in deuterium oxide and deuterochloroform solutions. The deuteroaqueous solution displays a broad singlet (δ=3.3) whereas the deuterochloroform solution exhibits three, sharp, closely-centred singlets (δ=3.3). Furthermore, if the organic solution is shaken with excess deuterium oxide the spectrum is found to be virtually unaltered indicating that the compound is not chemically altered on contact with water (Figure 3). The difference between the organic and aqueous solution spectra is probably due to solvent effects. In aqueous solution, the ions are randomly dispersed and hydrated causing band-broadening whereas in the organic solution the material is probably dissolved as an ion-pair and the solvation is possibly much less.

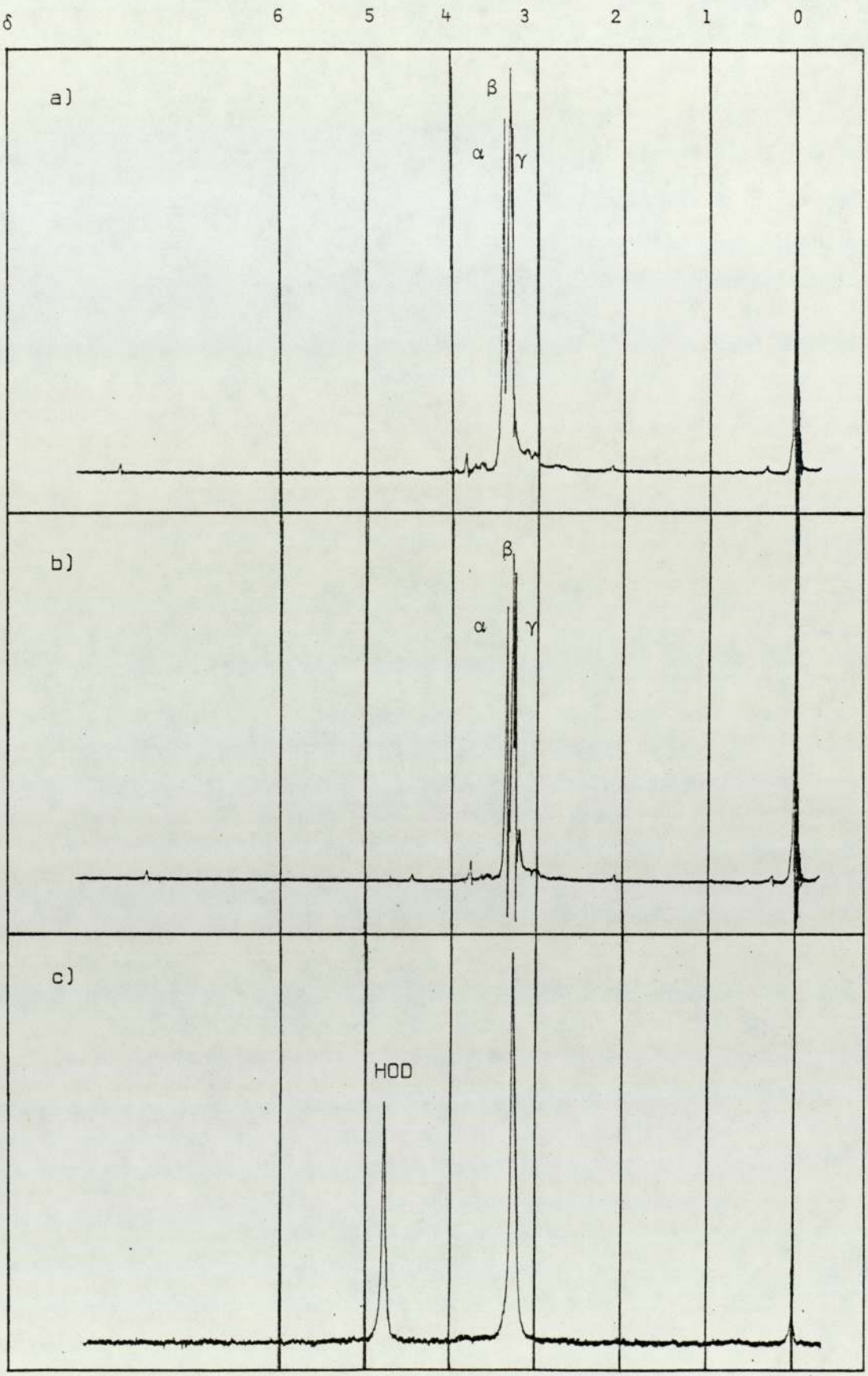
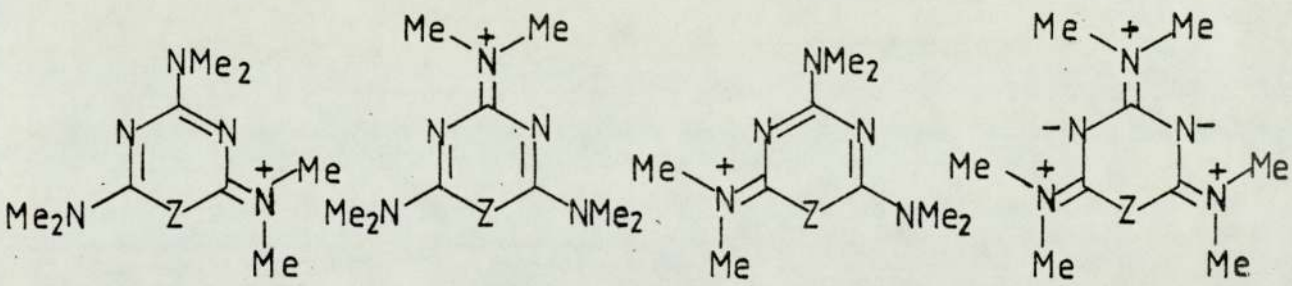


Figure 3: ^{1}H n.m.r. Spectra For 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium Chloride In a) Deuterochloroform, b) Deuterochloroform After Shaking With Excess Deuterium Oxide And c) Deuterium Oxide Solutions

Oliver and De Milo[65] observed similar results for the thiadiazinium salt (56): the deuterochloroform solution gave rise to two singlets at δ=3.37 and δ=3.49 which integrated for 6 and 12 protons respectively. The solution in hexafluoroacetone deuterate, however, gave a singlet at δ=3.32 corresponding to 6 protons and a doublet centred at δ=3.30 corresponding to 12 protons. Three major iminium-type resonance hybrids may be drawn for the oxadiazinium salt (72a, 72b, 72c) and the thiadiazinium salt (56a, 56b, 56c) and in both cases the three hybrids can be combined to give the composite hybrids (72d) and (56d) respectively.



Z=S	*(56a)*	*(56b)*	*(56c)*	*(56d)*
Z=O	*(72a)*	*(72b)*	*(72c)*	*(72d)*

The symmetry of the molecules results in the 2 and 6 positions being equivalent and restricted rotation is inherent at these positions which causes the exocyclic N-centres to be in nearly sp^2 hybridisation. The dimethylamino group at the 4 position will give rise to a singlet whether or not the N-centre is predominantly sp^2 or sp^3 hybridised since the two proximate ring N-atoms are equivalent. In the case of the oxadiazinium salt this has been assigned to peak α (Figure 3a). The dimethylamino groups at the 2 and 6 positions give rise to a doublet due to the proximate ring atoms being different. One methyl group is in the proximity of the O-centre whereas the other resides near the N-centre. This amidic type splitting of the ^1H n.m.r. signals is similar to that observed for N,N-dimethylformamide. This assignment of signals is supported by the crystal structure (Section 5.5)

which indicates that the 4-dimethylamino substituent is comparatively free to rotate whereas the 2 and 6 substituents are constrained in trigonal geometry.

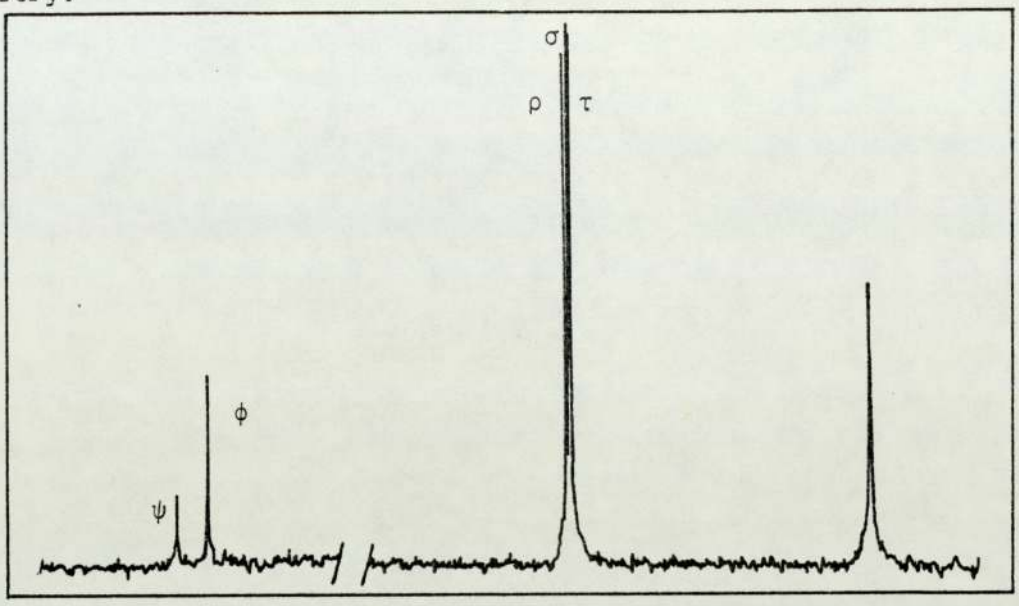


Figure 4: ^{13}C n.m.r. Spectrum For 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium Chloride

The ^{13}C n.m.r. spectrum (Figure 4) obtained in deuterochloroform is explicable in similar terms to the proton assignments. The upfield signals τ (37.150ppm), σ (37.282ppm) and ρ (37.808ppm) have an identical profile to the ^{1}H n.m.r. spectrum. The close doublet (τ+σ) and singlet (ρ) can be assigned to the 2+6 and 4 dimethylamino ^{13}C-centres respectively in an analogous manner to the dimethylamino proton assignments. The low-field signals ϕ (155.638ppm) and ψ (159.584ppm) can be assigned to the ring ^{13}C-centres. The absolute assignment of these singlets is uncertain although they correspond to the two different types of sp^2 ^{13}C-centres present in the molecule. Using the profile observed for the sp^3 ^{13}C-centres, it is probable that the lowest field singlet (ψ) corresponds to the 4-position carbon whereas the higher field singlet (ϕ) accounts for the 2 and 6 positional carbon atoms.

The mass spectrum is consistent with the structure (72) proposed in that the parent M^+ ion observed (m/z=212) corresponds to the cationic, heterocyclic fragment of the salt (72). The fragmentation pattern followed similar pathways to HMM (1) and similar fragments are extruded from the daughter ions: 15($CH_3^{\bullet}$), 29(CH_2=NH), 43(MeN=CH_2) and 70(Me_2NCN). A small peak is also observed for HMM (1) (m/z=210) which is probably formed by the pyrolysis of the oxadiazinium salt (72).

5.5 X-Ray Crystal Structure Determination Of 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium Chloride

5.5.1 Data Collection

The absolute structure for the oxadiazinium salt (72) was determined to support the spectroscopic evidence beyond doubt and the result has been published recently[74]. Crystals of the salt (72) were obtained from its solution in dichloromethane containing a trace of dry ether as florets of needles up to 3mm long. A specimen of 1.0x0.5x0.1mm was selected and mounted on a glass fibre. The radiation enclosure was used as a dry box by placing within it a large evaporating basin of anhydrous calcium chloride. The unit cell dimensions were determined by least-squares analysis of setting-angles of 25 reflections on an Enraf-Nonius CAD-4 diffractometer using a graphite monochromated MoK_α source. The data was collected by ω-2θ scans with a scan range in θ of $1.00+0.35\tan\theta^{o}$ at a scan rate of $0.5\text{-}5.0^{o}min^{-1}$ dependant upon the intensity. Two intensity standards were measured every 2 hours and showed an initial increase of $\sim$20% in the first 8-10 hours, attributable to recrystallisation of the material from the liquid film present on the crystal. A negligible decrease in intensity followed and separate correction functions (linear with time) were applied to the intensities measured during these two phases. 2656 reflections were measured with $2\lesssim\theta\lesssim25^{o}$ of which 2403 were unique (R_{int}=0.042) and 1156 of these were classified as observed ($F>3\sigma$). Standard

deviations were assigned on the basis of counting statistics and instrument instability and corrections were made for Lorentz-polarisation effect but not for absorption. Molecular drawings of the molecule and its unit-cell were obtained with the PLUTO program developed by Motherwell[75].

5.5.2 Solution Of Structure

The structure was solved by direct phasing with SHELX[76]. For the initial least-squares refinement of non-hydrogen atom positions and isotropic temperature factors, the ring system was treated as a 1,3,5-triazine. An abnormally low temperature factor and a positive peak on a difference electron density map enabled the ring oxygen atom to be distinguished. Two water molecules were also identified. The hydrogen atoms were entered into their calculated positions (assuming minimum steric hindrance for methyl groups and linear hydrogen bonds for water molecules) and then allowed to refine. In the final least-squares refinement the coordinates and anisotropic thermal parameters of all non-hydrogen atoms were adjusted together with the coordinates and isotropic temperature factors of all hydrogen atoms except the protons connected to the water molecule oxygen O3. This water molecule may not occupy all available sites in view of the higher temperature factor found for O3 compared with O2 and is supported by the microanalytical data (Section 5.2) which indicates ∿1.25 molecules of water of crystallisation. The magnitudes of the observed factors (F_o) were weighted by

$$w=1/[\sigma^2(F_o)+0.00239F_o^2]$$

and a small empirical extinction correction was applied. The final discrepancy indices were R=0.057; R_w=0.052 for observed data and a goodness-of-fit ratio (S=1.06) was obtained. No feature on a final difference electron density map exceeded $0.26eÅ^{-3}$.

5.5.3 Structural Features Observed For 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium Chloride

The monoclinic crystals had unit-cell dimensions of $\underline{a}$=7.608(4)Å, $\underline{b}$=16.099(7)Å, $\underline{c}$=12.127(8)Å and β=99.82(5)°. The calculated unit-cell volume is 1463.7Å^3 which gives rise to a calculated density of 1.29Mgm^{-3} (m.w.=283.75).

The molecule and its numbering scheme are illustrated in Plate 1. The atomic coordinates are shown in Table 5, the bond distances in Table 6 and the bond angles in Table 7.

The cyclic structure including the three exocyclic nitrogen centres has C-N bonds within a 0.07Å range indicating extensive delocalisation of the positive charge (Figure 5).

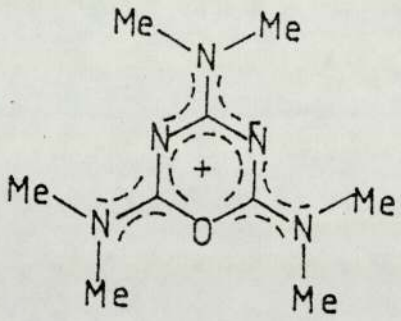


Figure 5: Delocalisation Of The Positive Charge In 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium Chloride

This effect is favoured by the near coplanarity of the N-methyl substituents with the ring. The heterocyclic nucleus exhibits partial double bonds and the positive charge is not localised on the oxygen centre. Indeed, multiple bonding to oxygen is relatively minor and the C-O distances of 1.366(6) and 1.386(5)Å exceed by 0.02Å those in 4',6,7-trihydroxyflavylium chloride hydrate (76)[77] and are comparable to those in furan (77)[78] with C-O bonds of 1.368(6)Å.

The D_{3h} symmetry observed within experimental error for crystalline HMM (1)[79] collapses to a crude C_{2v} symmetry for the oxadiazinium salt (72) with related bond distances differing by 0.03Å or less. A comparison of the

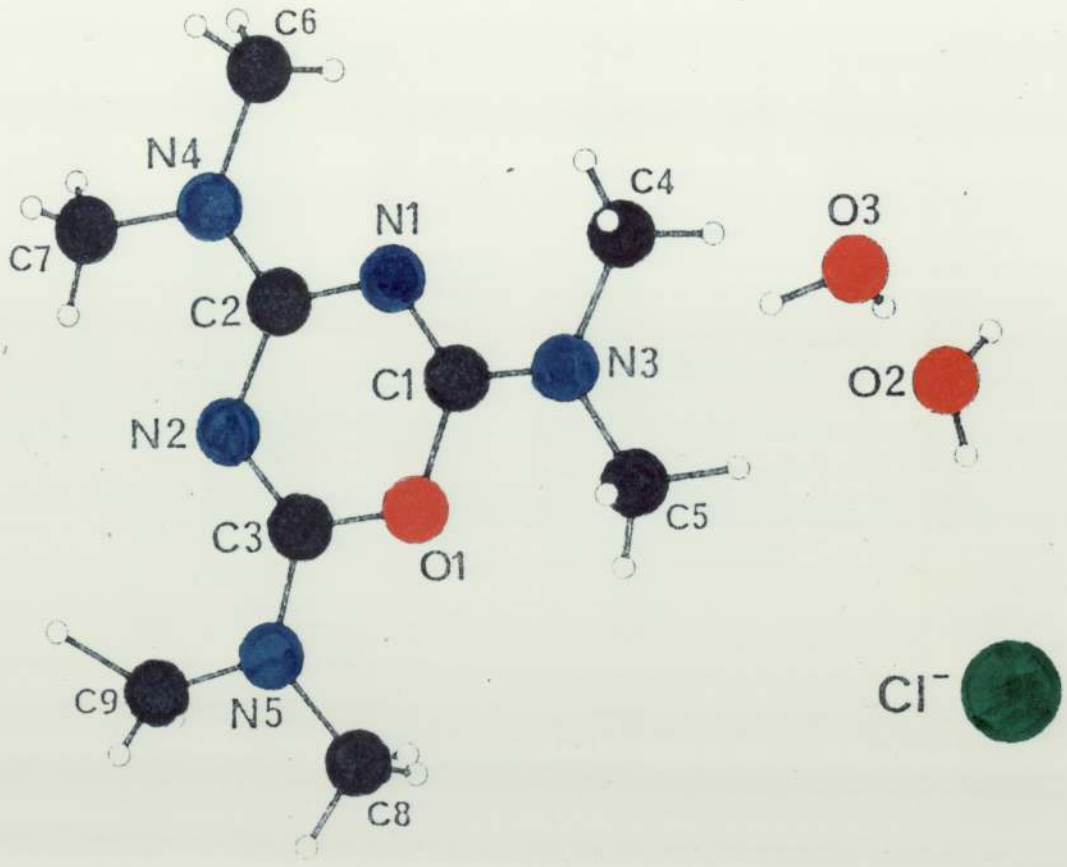


Plate 1: PLUTO Drawing Of 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium Chloride In Projection Onto Its Least-Squares Plane Showing The Atom Numbering Scheme

Table 5: Fractional Atomic Coordinates ($x10^4$, $x10^3$ For H) And Isotropic Temperature Factors ($Å^2 x10^3$) With Estimated Standard Deviations In Parentheses

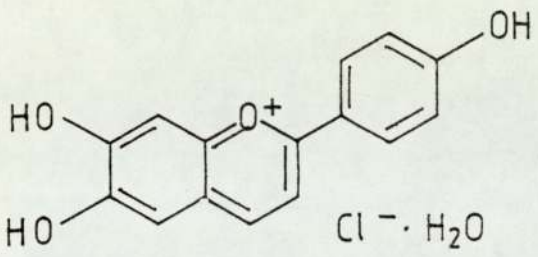
$$U_{eq} = \frac{1}{3}(U_{11} + U_{22} + U_{33} + 2U_{13}\cos\beta)$$

Atom	x	y	z	U_{eq}/U_{iso}
C1	1620(3)	-1207(1)	-5664(2)	75(<1)
O1	7139(5)	-537(2)	-997(3)	39(1)
O2	2102(6)	722(3)	-4953(4)	57(2)
O3	4548(7)	1879(3)	-5662(4)	92(3)
N1	6688(6)	741(3)	-142(3)	34(2)
N2	8508(8)	-321(3)	874(3)	36(2)
N3	5614(6)	475(3)	-1998(3)	37(2)
N4	8020(6)	922(3)	1678(4)	41(2)
N5	8671(2)	-1569(3)	-53(4)	37(2)
C1	6472(7)	265(3)	-1021(5)	31(2)
C2	7722(7)	445(3)	774(4)	34(2)
C3	8122(7)	-790(3)	-5(5)	34(2)
C4	4900(10)	1327(4)	-2172(6)	55(4)
C5	5428(9)	-73(4)	-2981(5)	46(3)
C6	7169(11)	1747(4)	1688(6)	60(4)
C7	9229(9)	659(5)	2700(5)	56(4)
C8	8116(10)	-2109(4)	-1013(6)	53(4)
C9	9668(10)	-1949(4)	954(6)	61(4)
H21	199(7)	14(4)	-525(5)	150(54)
H22	108(6)	87(3)	-474(4)	58(29)

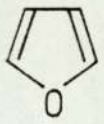
Table 5 *(continued)*

Atom	x	y	z	U_{eq}/U_{iso}
H31[a]	378	150	-544	105(42)
H32[a]	562	168	-529	105(44)
H41	373(6)	130(3)	-243(4)	64(31)
H42	539(7)	154(4)	-280(5)	139(50)
H43	498(6)	165(4)	-150(4)	95(38)
H51	417(7)	6(4)	-352(5)	131(50)
H52	537(6)	-68(4)	-278(5)	107(41)
H53	623(6)	4(4)	-338(5)	120(46)
H61	673(6)	182(4)	241(5)	114(42)
H62	665(6)	182(4)	100(5)	96(40)
H63	819(6)	211(3)	180(4)	81(34)
H71	875(6)	74(4)	328(5)	101(40)
H72	1038(7)	90(5)	275(6)	212(75)
H73	944(7)	2(4)	279(5)	138(47)
H81	907(6)	-254(4)	-102(5)	117(43)
H82	807(6)	-188(3)	-173(4)	67(31)
H83	689(7)	-236(4)	-96(5)	152(52)
H91	1048(6)	-222(4)	81(5)	86(38)
H92	881(7)	-231(4)	136(5)	140(48)
H93	1010(6)	-156(3)	160(4)	80(33)

a Positional parameters were not refined for these atoms



(76)



(77)

Table 6: Bond Distances (Å) With Estimated Standard Deviations In Parentheses

For All Non-Hydrogen Atoms

O1 - C1	1.386(5)	N3 - C5	1.470(7)
O1 - C3	1.366(6)	N4 - C2	1.326(6)
N1 - C1	1.300(6)	N4 - C6	1.479(7)
N1 - C2	1.335(6)	N4 - C7	1.474(7)
N2 - C2	1.367(6)	N5 - C3	1.326(6)
N2 - C3	1.298(6)	N5 - C8	1.457(7)
N3 - C1	1.296(6)	N5 - C9	1.458(7)
N3 - C4	1.477(7)		

Table 7: Bond Angles (°) With Estimated Standard Deviations In Parentheses

For All Non-Hydrogen Atoms

C1 - O1 - C3	116.1(4)	C2 - N4 - C7	121.5(5)	N1 - C1 - N3	124.7(7)
C1 - N1 - C2	116.5(5)	C6 - N4 - C7	117.5(5)	N1 - C2 - N2	125.6(5)
C2 - N2 - C3	114.7(5)	C3 - N5 - C8	123.3(5)	N1 - C2 - N4	118.3(5)
C1 - N3 - C4	119.2(5)	C3 - N5 - C9	118.9(5)	N2 - C2 - N4	116.0(5)
C1 - N3 - C5	123.3(5)	C8 - N5 - C9	117.2(5)	O1 - C3 - N2	124.3(5)
C4 - N3 - C5	117.3(5)	O1 - C1 - N1	122.5(5)	O1 - C3 - N5	111.9(5)
C2 - N4 - C6	120.9(5)	O1 - C1 - N3	112.8(5)	N2 - C3 - N5	123.9(5)

distances and angles between HMM (1) and the oxadiazinium salt (72), averaged over the approximate symmetry, reveals considerably shorter (>6σ) ring C-N bonds adjacent to the oxygen atom in the oxadiazinium salt (72); little difference in other C-N ring bonds; shorter (>5σ) exocyclic C_{ring}-N distances in the oxadiazinium salt (72) and no clear trend in N-methyl distances. These observations are consistent with the enhanced electron donation from the dimethylamino groups of the oxadiazinium salt (72) in response to the positive charge created by replacing a ring N-atom in HMM (1) with an O-atom to form the oxadiazinium salt (72).

Bond angles within the oxadiazinium ring (72) are increased from 120° at carbon and decreased at nitrogen but not to the same degree as in HMM (1) in which the mean N-C-N and C-N-C angles are 127.3(5) and 112.7(5)° respectively.

Steric hindrance between the N-methyl groups is relieved by a small movement (up to ±0.2Å) out of the plane of the heterocycle but not by the obvious mechanism whereby a concerted series of twists about exocyclic C_{ring}-N bonds causes the dimethylamino groups to "propellor".

This twist does occur about C2-N4 which depresses C6 and elevates C7 relative to the plane of the ring. The entire dimethylamino group connected to C1 is elevated and the entire dimethylamino group at C3 is depressed. The sum of the bong angles at each of the dimethylamino N-centres is very close to 360° indicating substantial sp^2 hybridisation of these N-centres. Efficient π-overlap with the ring is also encouraged by this lack of twisting.

The spatial arrangement of the atoms in the oxadiazinium salt (72) is illustrated in Plate 2.

Plate 3 illustrates the arrangement of ions and solvent molecules in the unit-cell and how they are held together by hydrogen bonding and stacking.

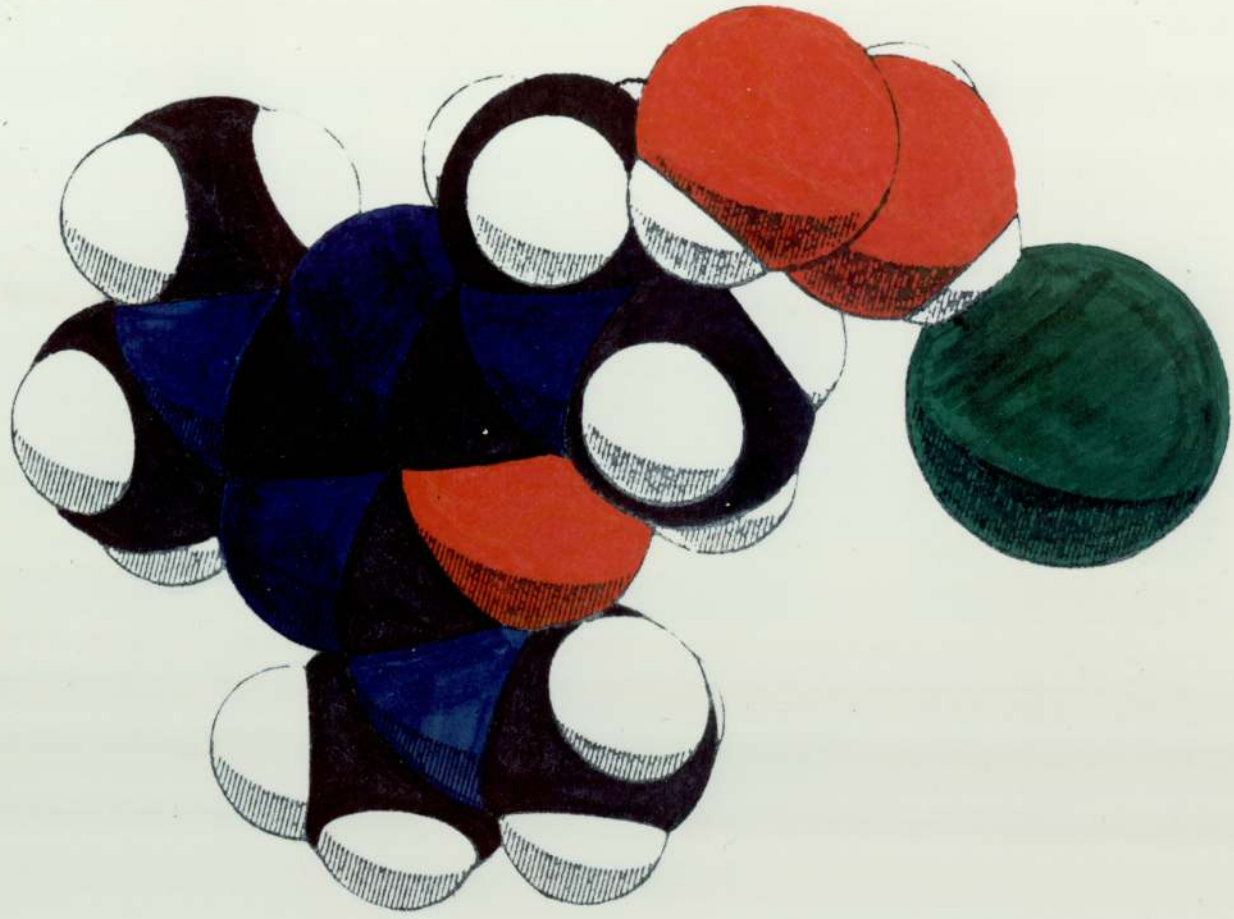


Plate 2: PLUTO Space-Filling Diagram Of 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium Chloride

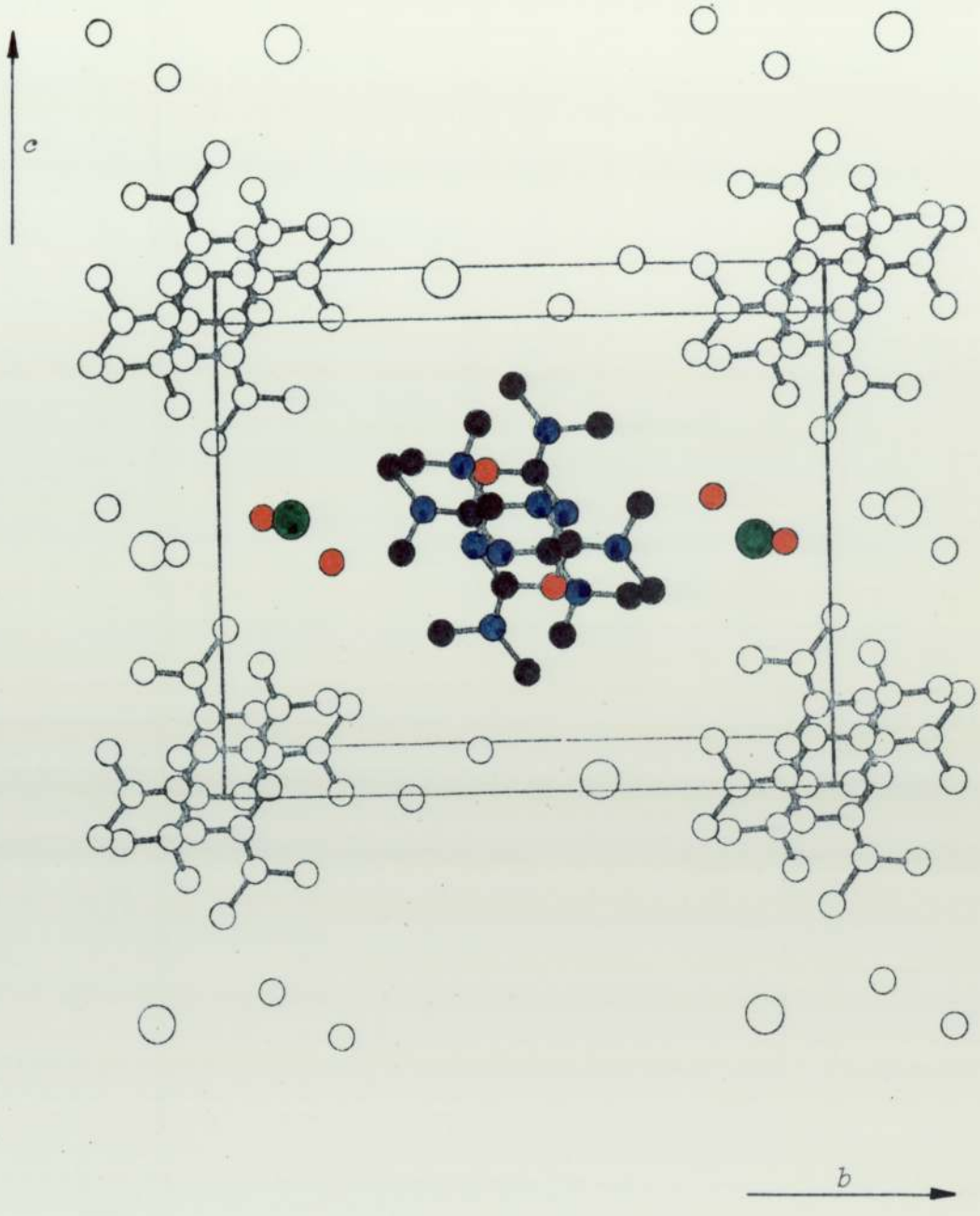
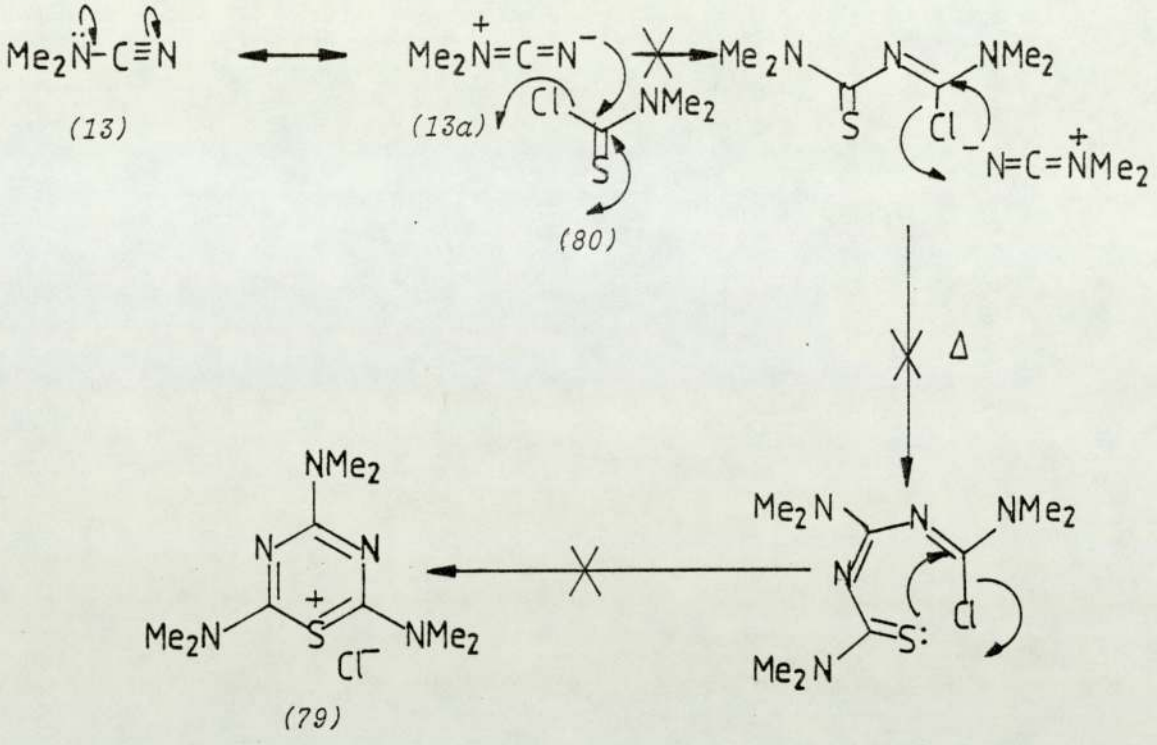


Plate 3: PLUTO Drawing Of The Unit-Cell Contents For 2,4,6-tris (dimethylamino)-1,3,5-oxadiazinium Chloride Viewed Down *a*

The chloride anion accepts hydrogen bonds from two symmetry-related O2 water molecules and one O3 water molecule with O...Cl distances of 3.227(5), 3.148(5) and 3.264(5)Å. The remaining water hydrogen atom connected to O3 forms a hydrogen bond to the other water molecule oxygen O2 atom with an O...O distance of 2.867(5)Å. The heterocyclic cations form stacks in the *a* direction by the action of centres of symmetry. This packing mode enables the dimethylamino groups on successive molecules within the stack to interleave. The closest interaction between molecules is between C1 and N1 of adjacent rings at 3.398(6)Å. The crystallographic data would therefore suggest that the resonance hybrids (72a, 72b and 72c) are probably reflections of the true structure and that the predominant species present are the iminium salts (72a and 72c). For the sake of convenience the salt (72) will be drawn and treated as the oxadiazinium system with the charge situated on the oxygen atom and as such, ought to mimic the reactions of other pyrylium type systems. Pyrylium salts (78) are well known for their reactions with nucleophiles[80-81] and accordingly much work has been carried out with nitrogen nucleophiles. The reactions of the oxadiazinium salt (72) with various amines will be compared with other pyrylium systems in the following two chapters.

5.6 Alternative Synthetic Routes To 2,4,6-tris(dimethylamino)-thiadiazinium Salts

It was thought that the synthetic route to the oxadiazium salt (72) could be extended to the thiadiazinium chloride (79) by reacting dimethylcyanamide (13) with N,N-dimethylthiocarbamoyl chloride (80) (Scheme 9). The reaction was conducted under similar conditions that of the oxadiazium salt (72) preparation but the reaction mixture charred and the product obtained was an unidentifiable tar.

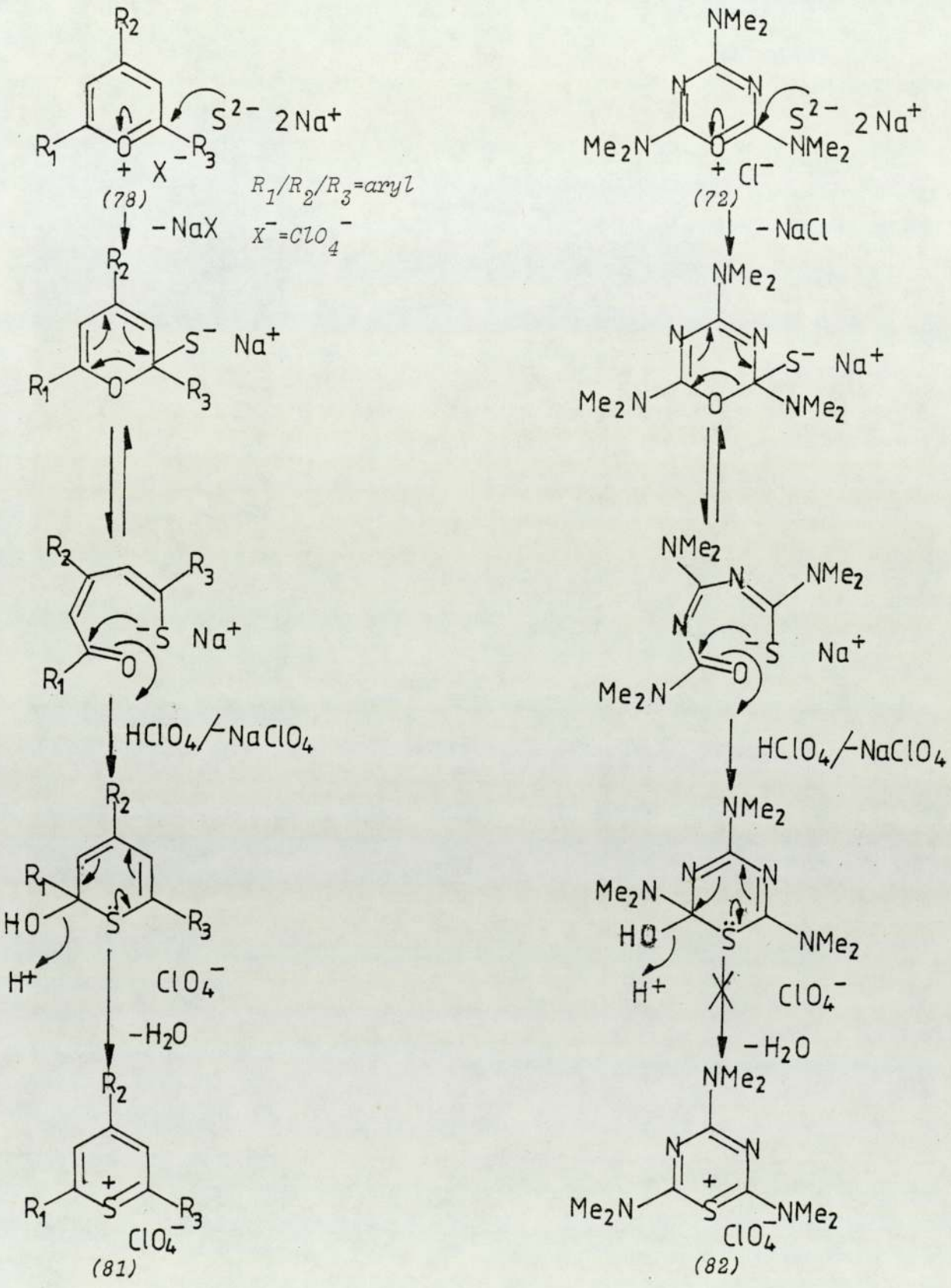


Scheme 9: Theoretical Synthetic Route To 2,4,6-tris(dimethylamino)-1,3,5-thiadiazinium Chloride

Pyrylium salts (78) are known to react with sodium sulphide to form thiapyrylium salts (81) (Scheme 10)[82]. An attempt to convert the oxadiazinium salt (72) into the thiadiazinium salt (82) with sodium sulphide under analogous conditions was not successful. A very small yield of a highly insoluble, resinous semisolid was obtained which was impossible to analyse.

5.7 Pharmacological Properties Of 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium Chloride

The oxadiazinium salt (72) was screened for antitumour properties and it was found that the compound was exceedingly toxic. Doses greater than 100mgkg^{-1} resulted in murine fatalities within 5 minutes of injection. Doses between 25 and 100mgkg^{-1} resulted in death within 24 hours of administration. Very low doses ($\sim$0.25mgkg^{-1}) were not found to be toxic but no apparent antitumour activity was observed against the M5076



Scheme 10: Conversion Of Pyrylium Salts Into Thiapyrylium Salts With Sodium Sulphide And Its Theoretical Application To The Conversion Of Oxadiazinium Salts Into Thiadiazinium Salts

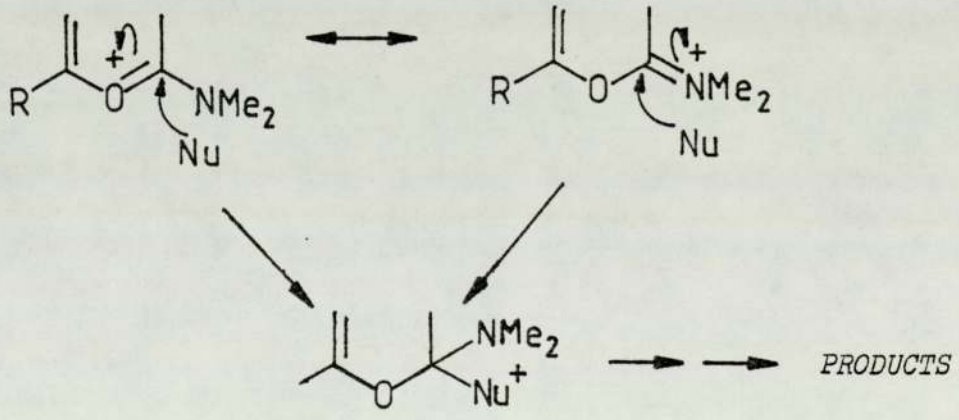
reticulum cell sarcoma.

It is suspected that the high toxicity of the compound may be attributable to cholinergic activity and that the dimethyliminium groups at the 2 and 6 positions of the oxadiazinium salt (72a and 72c) may be sufficiciently similar to acetylcholine (43) to exhibit cholinergomimetic activity. This explanation is purely theoretical and no substantiating evidence has been purported.

6 REACTIONS OF PYRYLIUM SYSTEMS WITH NITROGEN NUCLEOPHILES

6.1 Classification Of 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium Chloride As A Pyrylium System

Although it was found that the oxadiazinium salt (72) had relatively little multiple bonding to the oxygen centre (Section 5.4.3) and that the dimethylamino contributors (72a and 72c) were strong reflections of the true structure, the reaction pathways of the oxadiazinium salt (72) with nucleophiles ought to resemble those of other pyrylium systems: pyrylium systems are non-classical carbenium ions and are susceptible to nucleophilic attack. This first step involves addition of the nucleophile to the potential carbenium ion of the pyrylium system which relieves the charge located on the oxygen heteroatom by relocalisation of the lone-pair of electrons by a π-bond shift. This bond shift is essentially equivalent if the charge is relieved from a dimethyliminium group and the resultant heterocycle is identical:



This provides a logical assignment of the oxadiazinium salt (72) into the pyrylium system classification.

The reaction pathway which follows the nucleophilic addition usually involves ring-opening followed by ring-closure and has been termed the ANRORC (Addition-Nucleophilic-Ring-Opening-Ring-Closure) mechanism.

It will become apparent that three possible ANRORC reactions can occur dependant upon the nucleophile and the differences are manifest in the final ring-closure step. The new heterocycle formed may be with ring retention (ANRORC), ring contraction ($ANRORC_c$) or ring expansion ($ANRORC_e$).

6.2 Reactions Of Pyrylium Salts With Nucleophiles

6.2.1 Reactions With Ammonia And Primary Amines

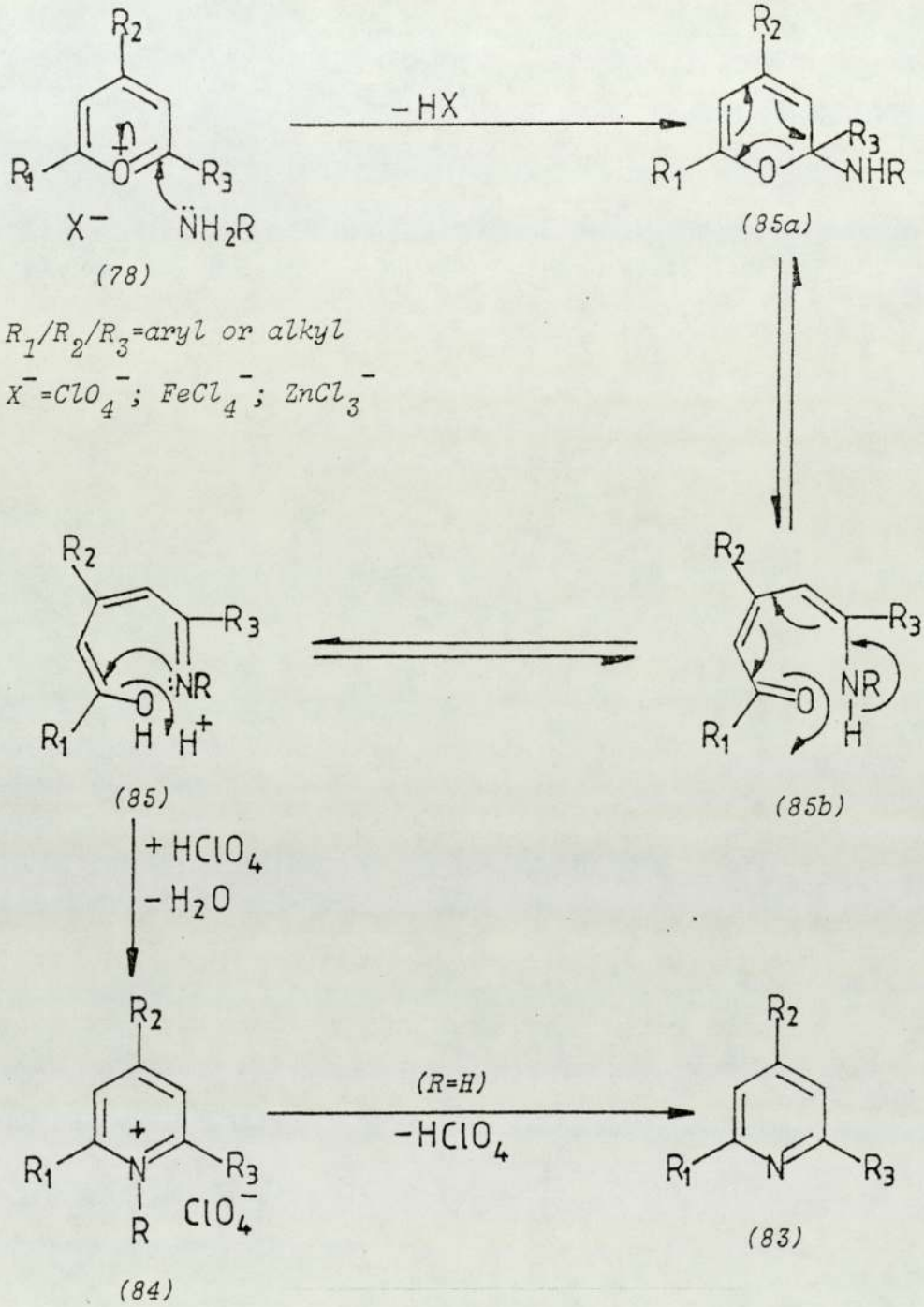
Pyrylium salts (78) undergo ANRORC reactions with ammonia and primary amines to form pyridines (83)[83,84] and pyridinium salts (84)[83,85] respectively (Scheme 11). The nucleophilic amine attacks the 2 or 6 positions which are equivalent in symmetrically substituted pyrylium salts (78; $R_1=R_3$) and in the case of asymmetrically substituted pyrylium salts (78; $R_1\neq R_3$) the addition occurs at the least sterically-hindered centre. Evidence for the acyclic species (85) has been propounded by Balaban and Toma[85,86] who have successfully isolated some of the intermediate imino-enols (85) thereby supporting the ANRORC mechanism. Ring-closure occurs under the influence of acid to form a new heterocycle with retention of the ring.

This reaction has proved to be of enormous synthetic value as it provides a means of obtaining pyridines which cannot be prepared by more conventional routes.

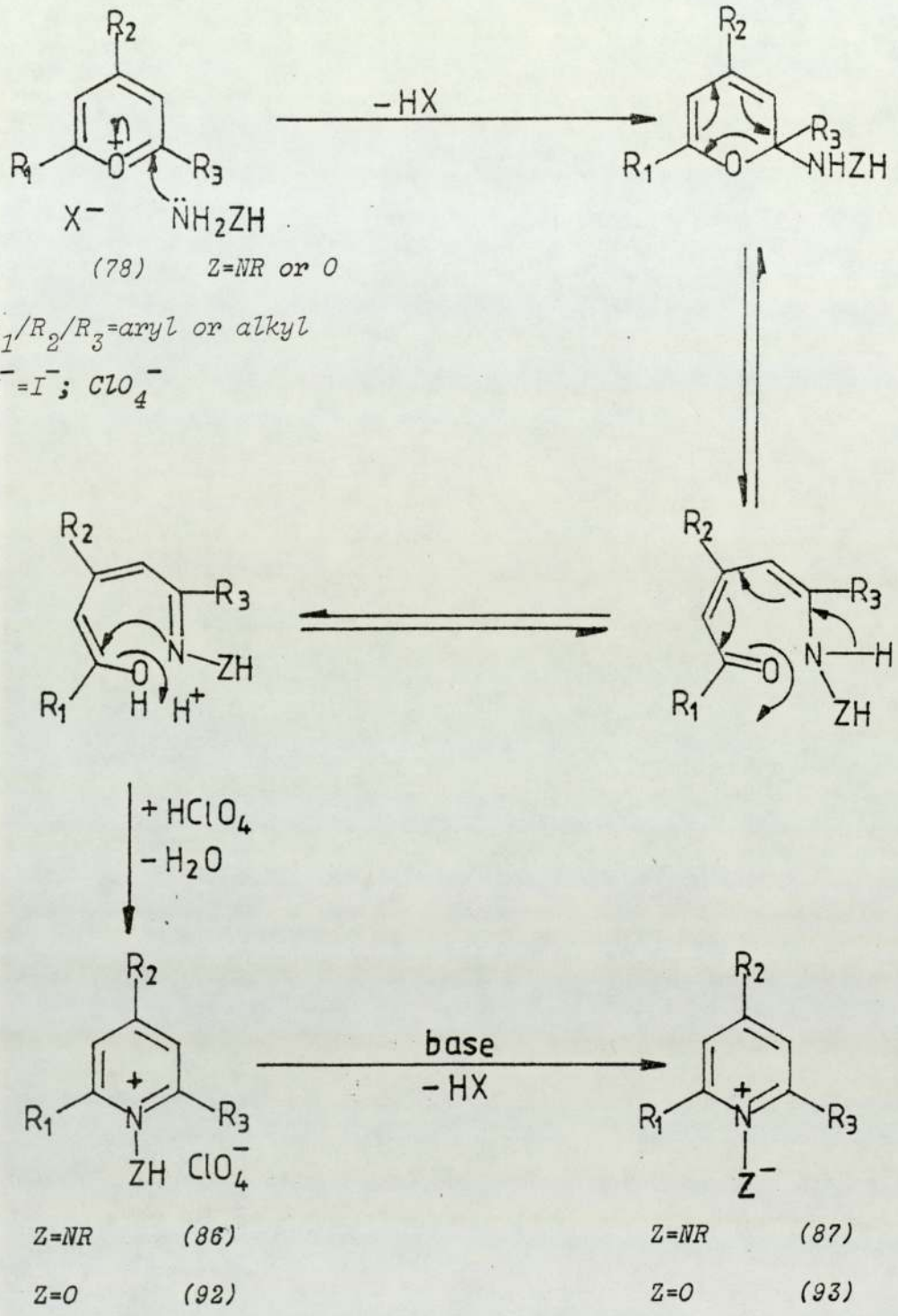
6.2.2 Reaction With Hydrazine And Its Monosubstituted Derivatives

Pyrylium salts (78) can be reacted with hydrazines to obtain three different products dependant upon the reaction conditions.

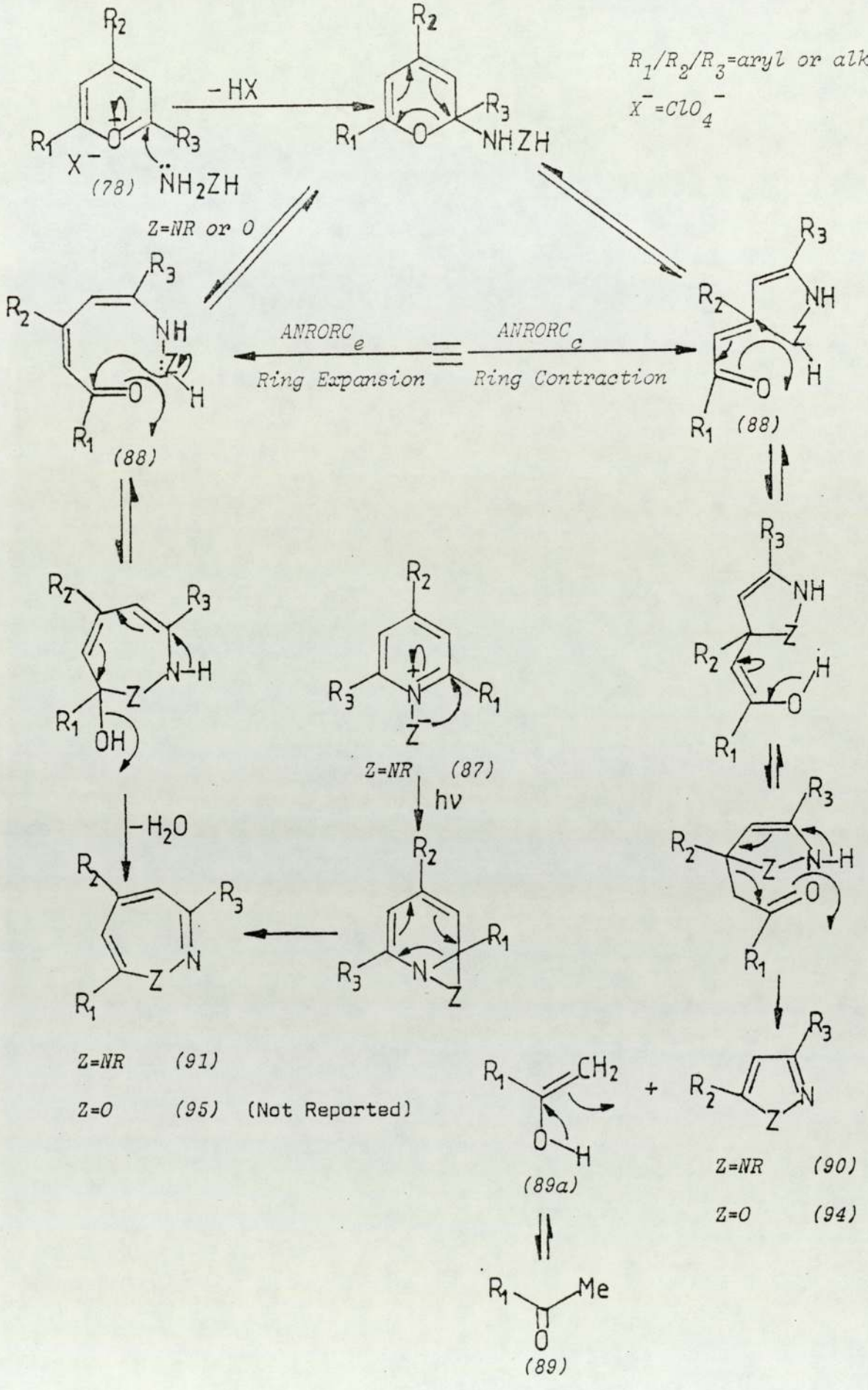
If the hydrazine is in equimolar ratio with the pyrylium salt (78) then the product obtained is with ring-retention (ANRORC) and an



Scheme 11: Formation Of Pyridines And Pyridinium Salts From The Reaction Of Pyrylium Salts With Ammonia And Primary Amines Respectively



Scheme 12: Reactions Of Pyrylium Salts With Hydrazines And Hydroxylamine To Form Products With Ring-Retention (ANRORC)



Scheme 13: Reactions Of Pyrylium Salts With Hydrazines And Hydroxylamine To Form Ring-Expanded (ANRORC$_e$) And Ring-Contracted (ANRORC$_c$) Products

N-amino(substitutedamino)pyridinium salt (86)[87,88] is formed in an analogous manner to the pyridinium salts (84) (Section 6.2.1) (Scheme 12; Z=NR). Treatment of the N-substitutedaminopyridinium salts (86) with base causes deprotonation to the corresponding, highly coloured N^+-N^- betaines or ylides (87)[89,90] (Scheme 12; Z=NR).

The hydrazines, however, may also act as bidentate nucleophiles and if the hydrazine is in twofold excess with the pyrylium salt (78), the ring-contracted ($ANRORC_c$) product (90) is obtained. The ring-closure involves attack of the terminal hydrazine nitrogen centre on the 4 position of the pyrylium salt intermediate (88) and subsequent tautomerism with extrusion of a methyl ketone (89) to yield a pyrazole (90)[91] Scheme 13; Z=NR).

Under certain reaction conditions, the terminal hydrazine nitrogen centre may also attack the 6 position of the intermediate (88) to form the ring-expanded ($ANRORC_e$) 1,2-diazepine (91) albeit in low yield[91,92] (Scheme 13; Z=NR). Streith and Cassal[93] found that u.v. irradiation of some of the N^+-N^- betaines (87) also resulted in 1,2-diazepine (91) formation in good yield.

6.2.3 Reaction With Hydroxylamine

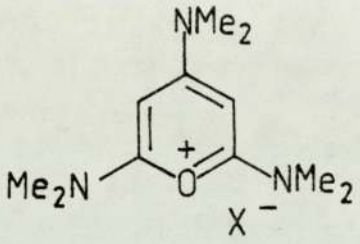
Hydroxylamine reacts with pyrylium salts (78) to form N-hydroxypyridinium salts (92) which are not normally isolated but are converted *in situ* to their respective pyridine-N-oxides (93) on basification[94] (Scheme 12; Z=O).

Like the hydrazines, hydroxylamine can also react as a bidentate nucleophile and the ring contracted 1,2-oxazoles (94) have been obtained from pyrylium salts (78) and hydroxylamine with extrusion of a methyl ketone (89)[91] (Scheme 13; Z=O). Theoretically, the hydroxylamine ought to form the ring-expanded 1,2-oxazepine (95) although this reaction nor the

photolysis of the N-oxides (93) (*c.f.* hydrazines Section 6.2.2) have been reported.

6.2.4 2,4,6-tris(dimethylamino)-pyrylium Salts

2,4,6-tris(dimethylamino)-pyrylium salts (96) would be ideal comparative models for the ANRORC reactions which could be expected from the oxadiazinium salt (72), unfortunately, the compound is unknown.



(96)

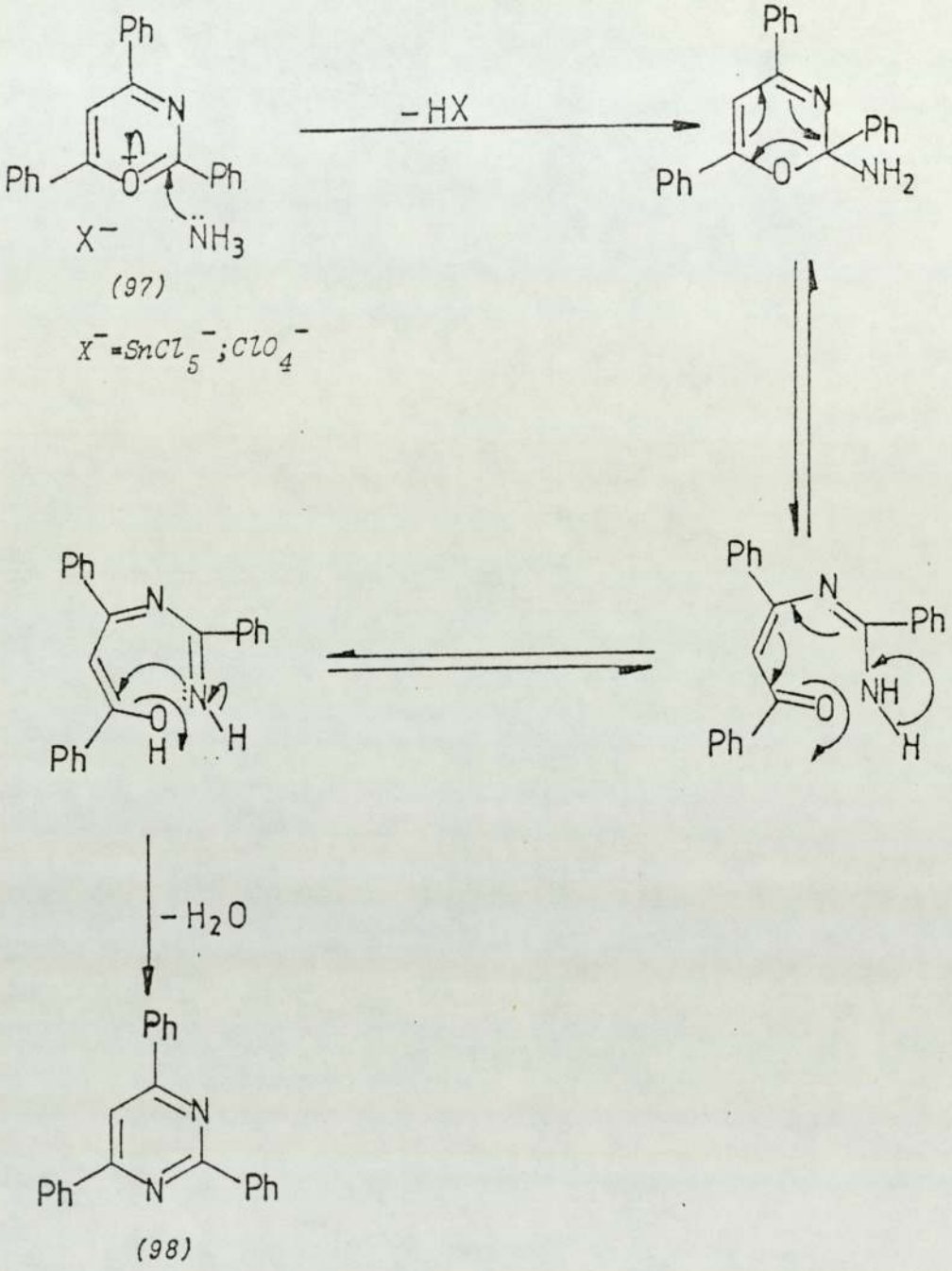
6.3 Reactions Of 1,3-oxazinium Salts With Nucleophiles

6.3.1 Reaction With Ammonia And Primary Amines

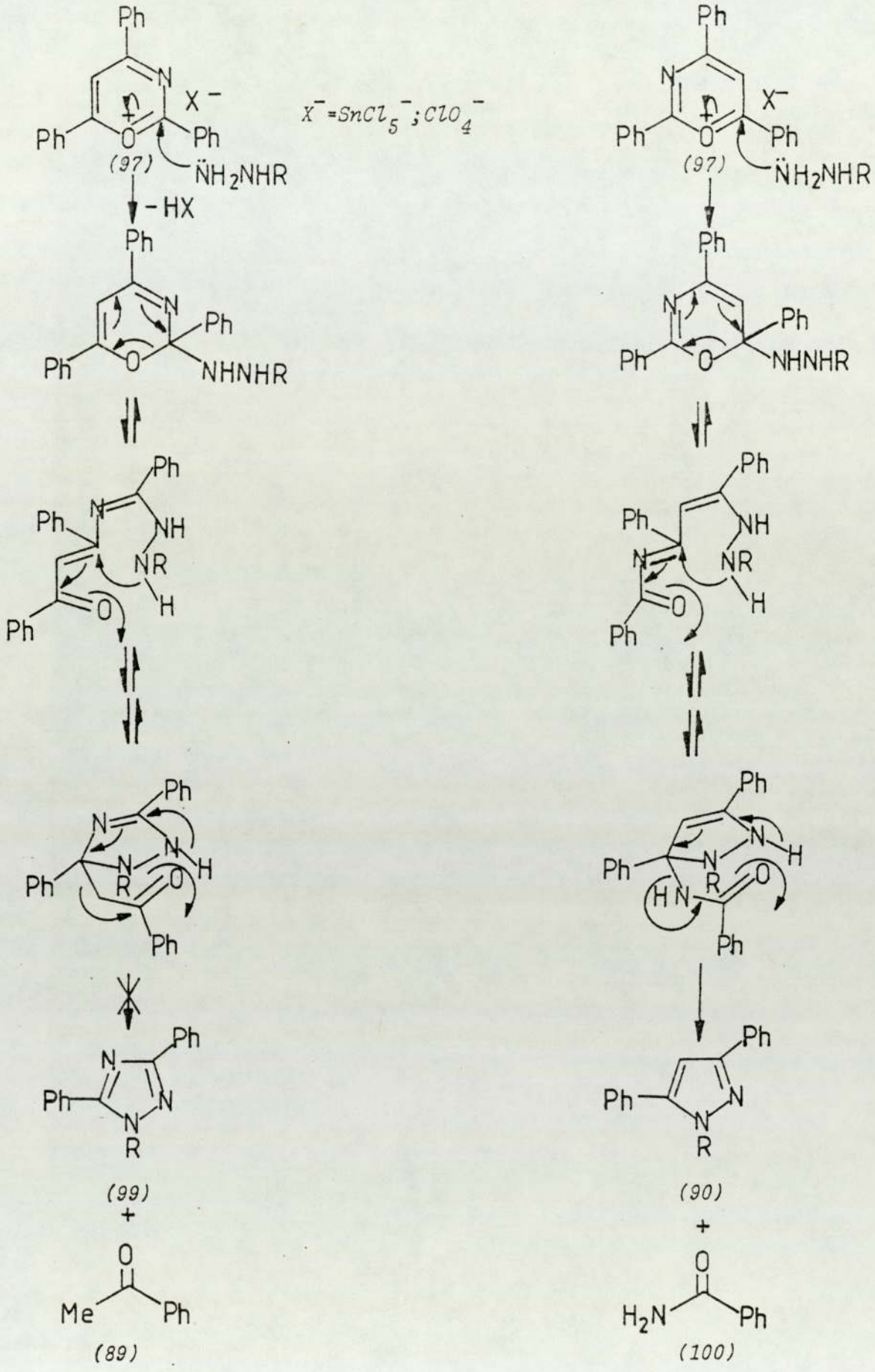
Schmidt[71] prepared 2,4,6-triphenyl-1,3-oxazinium salts (97) and reported that their reaction with ammonia led to the expected triphenyl-pyrimidine (98)[71] (Scheme 14) by analogy to the pyrylium salts (78) (Section 6.2.1). The reaction with primary amines has not been reported.

6.3.2 Reaction With Hydrazine And Its Monosubstituted Derivatives

The reaction between 1,3-oxazinium salts (97) and hydrazine itself has been investigated by Schmidt[71], who found that only the ring-contracted (ANRORC$_C$) pyrazole (90) could be obtained (Scheme 15). This result poses an interesting chemical problem: theoretically, it can be seen that two possible products could be obtained *viz* a pyrazole (90) or a 1,2,4-triazole (99). The latter product is not obtained which indicates that the nucleophilic attack may occur selectively as far away from the heteroatoms as possible *i.e.* exclusively at the 6 position. Alternatively,



Scheme 14: Formation Of 2,4,6-triphenylpyrimidine From 2,4,6-triphenyl 1,3-oxazinium Salts And Ammonia

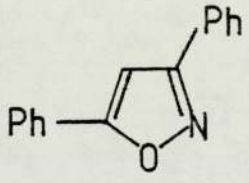


Scheme 15: Production Of Pyrazoles Versus 1,2,4-triazoles From The Reaction Between 1,3-oxazinium Salts And Hydrazines (ANRORC)

the nucleophilic attack stage may be reversible. In any event, the pyrazole (90) is encountered exclusively by virtue of the amide (100) being the preferential leaving-group.

6.3.3 Reaction With Hydroxylamine

This reaction has not been investigated although by analogy to the reaction of 1,3-oxazinium salts (97) with hydrazines (Section 6.3.2) it could be envisaged that only the 1,2-oxazole (101) would be obtained by a similar mechanism.



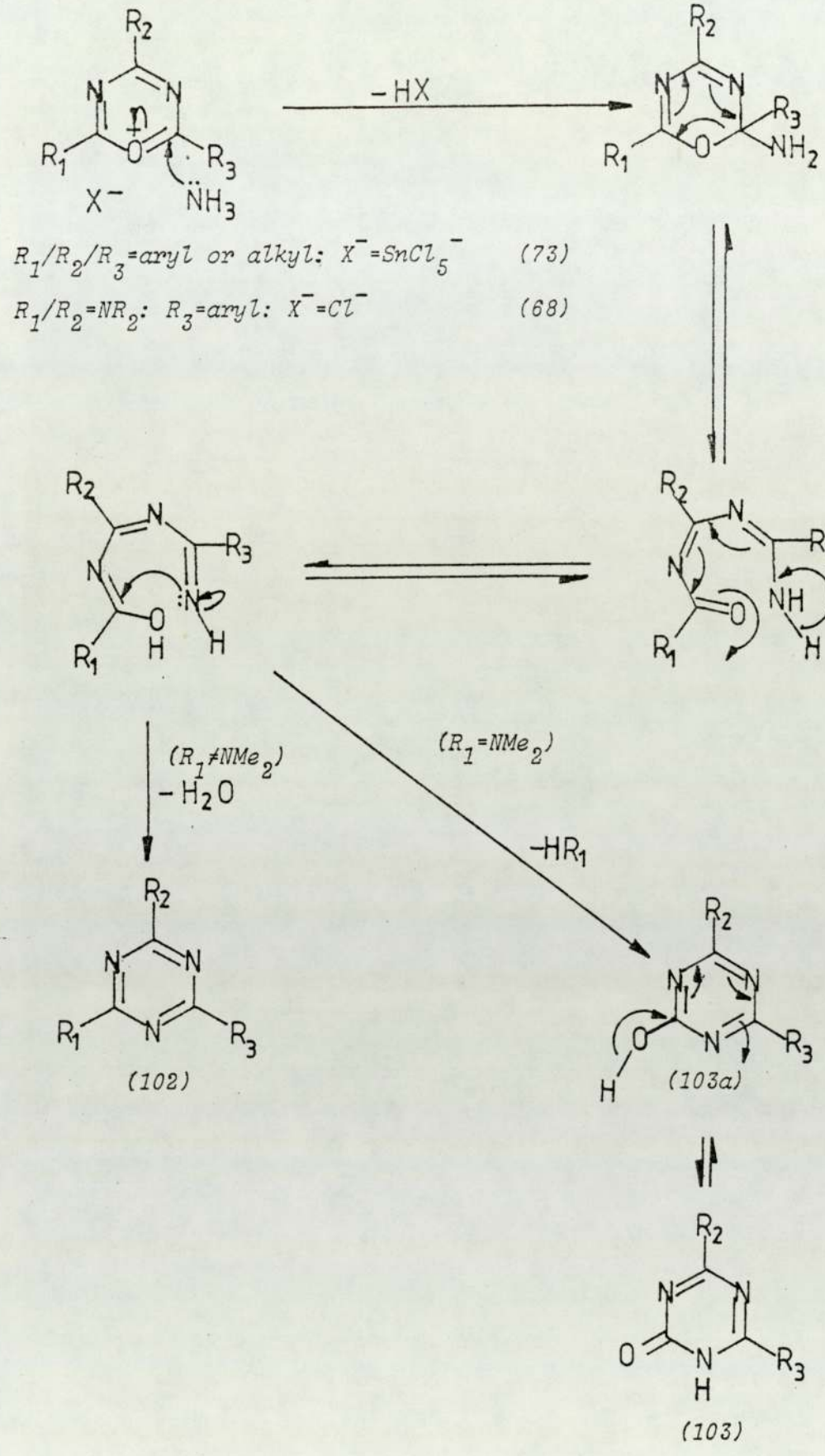
(101)

6.4 Reactions Of 1,3,5-oxadiazinium Salts With Nucleophiles

6.4.1 Reaction With Ammonia And Primary Amines

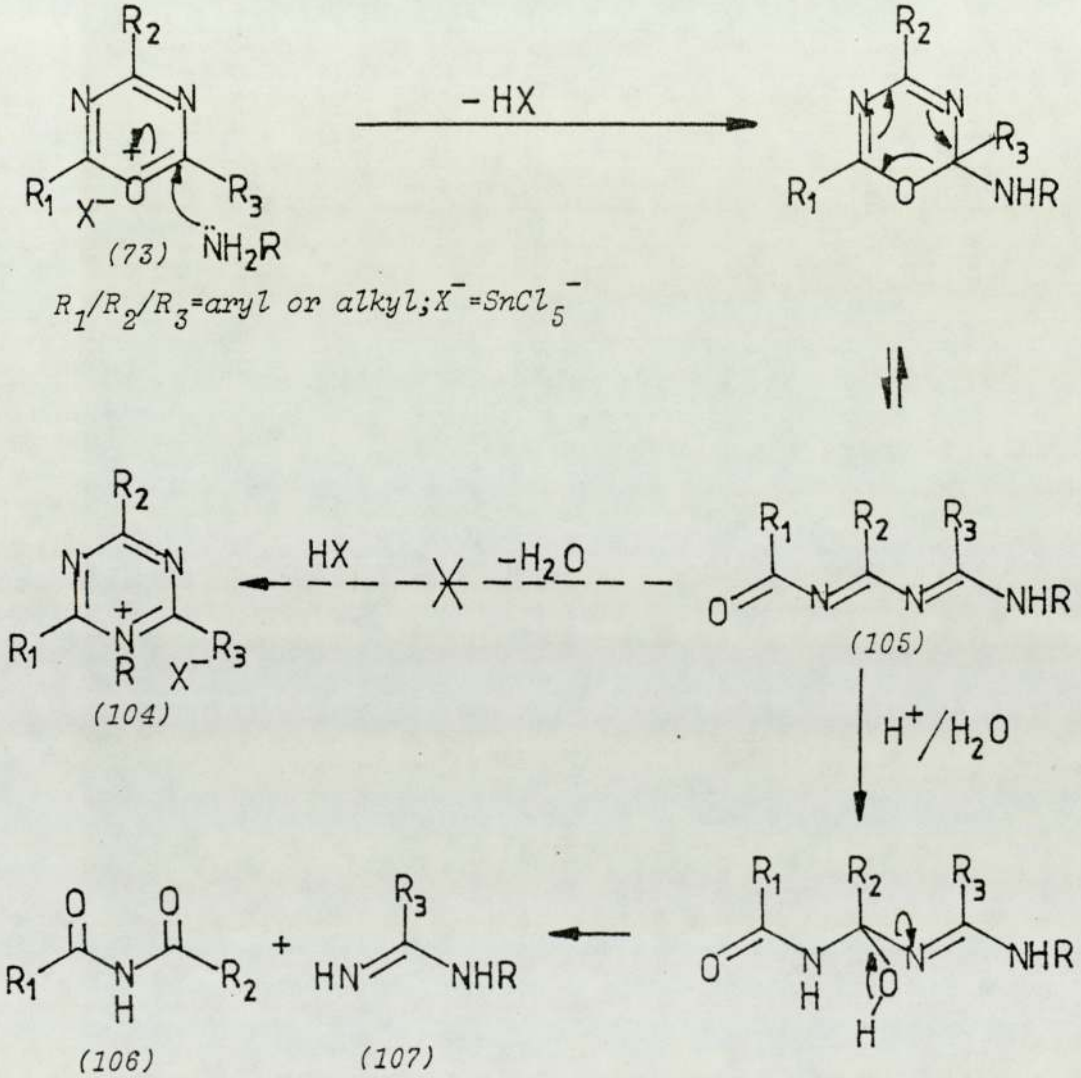
The 1,3,5-oxadiazinium salts (68 and 73) have been investigated in their reactions with ammonia and the salts (73) yield the expected 1,3,5-triazine (102)[71] by the usual ANRORC mechanism (Scheme 16). A dichotomy exists with the oxadiazinium salts (68), however, in that if the dialkylamino substituents are not dimethylamino groups then the expected 1,3,5-triazine (102) is obtained[70]. In the dimethylamino substituted salts (68; R_1=R_2=NMe_2) the ring-closure step involves loss of dimethylamine due to its excellent leaving group abilities and a triazin-2-one (103) is obtained[70] (Scheme 16).

The reaction with primary amines has only been reported for the oxadiazinium salts (73)[95] and the product obtained was found not to be the expected 1,3,5-triazinium salt (104). Under mild and basic conditions, the acyclic intermediates (105) are obtained and are found to be quite stable



Scheme 16: Reaction Of Known 1,3,5-oxadiazinium Salts With Ammonia

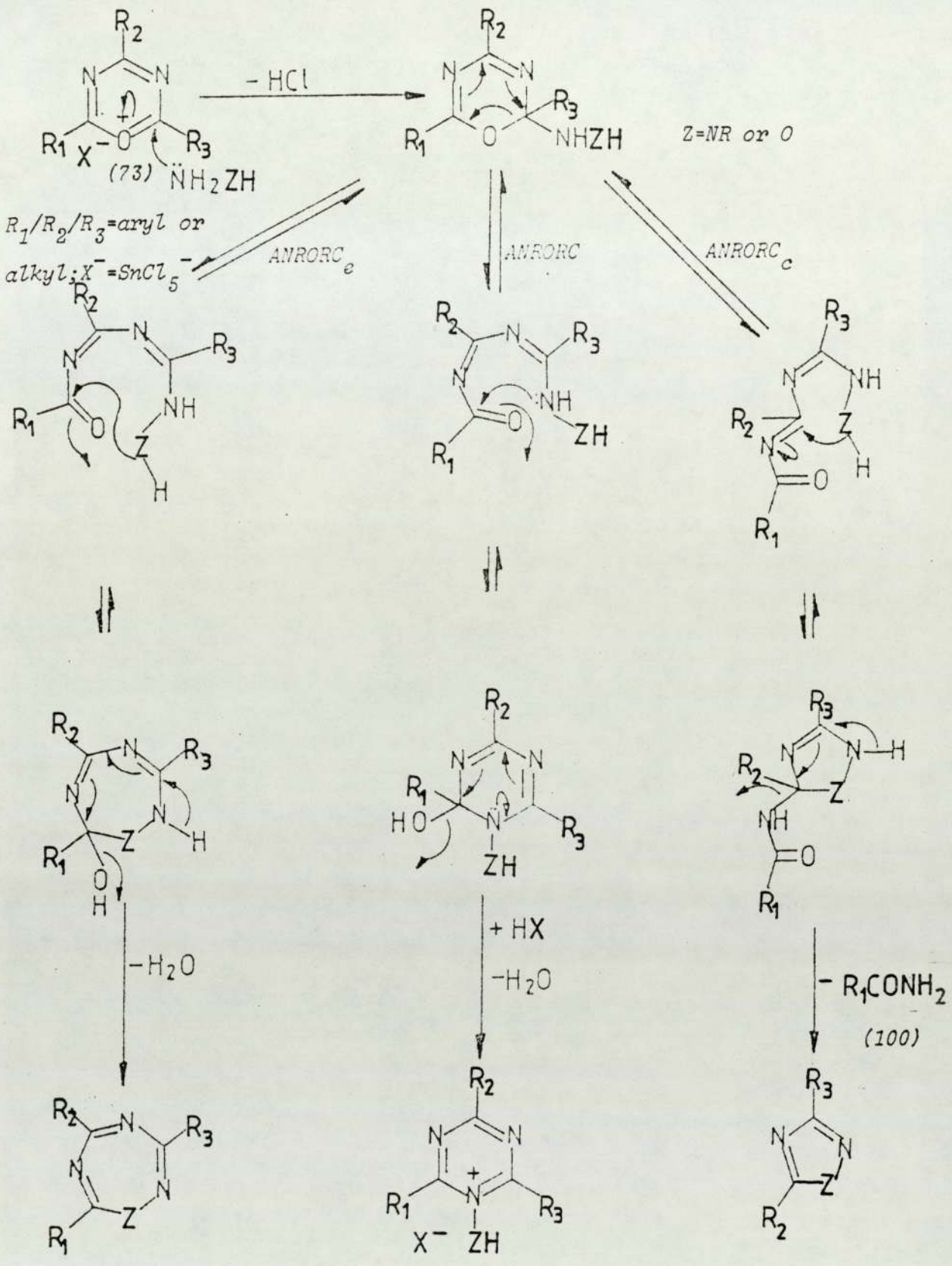
in the solid-state and in neutral or basic solutions. Acidification, however, results in decomposition and a mixture of a diacylamine (106) and an amidine (107) is obtained by the acid catalysed hydrolysis of the intermediate (105) (Scheme 17).



Scheme 17: Reaction Of Triaryl(alkyl)oxadiazinium Salts With Primary Amines

6.4.2 Reaction With Hydrazine And Its Monosubstituted Derivatives

The oxadiazinium salts (73) react with hydrazines to yield the ring-contracted (ANRORC$_c$) 1,2,4-triazoles (108) with expulsion of an amide (100) (Scheme 18; Z=NR)[71]. The products obtained from ANRORC (109) and ANRORC$_e$ (110)



Z=NR	(110)	(Not Reported)	Z=NR	(109)	(Not Reported)	Z=NR	(108)	
Z=O	(113)	(Not Reported)	Z=O	(112)	(Not Reported)	Z=O	(111)	

Scheme 18: Reaction Of Triaryl(alkyl)oxadiazinium Salts With Hydrazines And Hydroxylamine

pathways have not been isolated. The reactions of oxadiazinium salts (68) with hydrazines have not been investigated.

6.4.3 Reaction With Hydroxylamine

The oxadiazinium salts (73) yield the ring-contracted 1,2,4-oxadiazole (111) on reaction with hydroxylamine ($ANRORC_c$) (Scheme 18; Z=O)[71] but the ANRORC (112) and $ANRORC_e$ (113) products have not been isolated. The oxadiazinium salts (68) have not been investigated in their reactions with hydroxylamine.

6.5 Conclusion

Although all the pyrylium systems undergo similar ANRORC reactions with nucleophiles, the actual products obtained seem to depend on both the number of ring-heteroatoms and the nature of the ring-substituents.

Thus, if the ring substituents are viable leaving-groups and more effective than OH^-, then the ring-substituent is lost on recyclisation and the original ring oxygen atom becomes a carbonyl group.

As the number of ring-heteroatoms is increased, it appears that the reactions of the pyrylium systems with bidentate nucleophiles are dominated by $ANRORC_c$ products and the ANRORC and $ANRORC_e$ products are not encountered.

The next chapter will describe and discuss the products obtained from the oxadiazinium salt (72) with similar nucleophiles.

7 REACTIONS OF 2,4,6-TRIS(DIMETHYLAMINO)-1,3,5-OXADIAZINIUM CHLORIDE

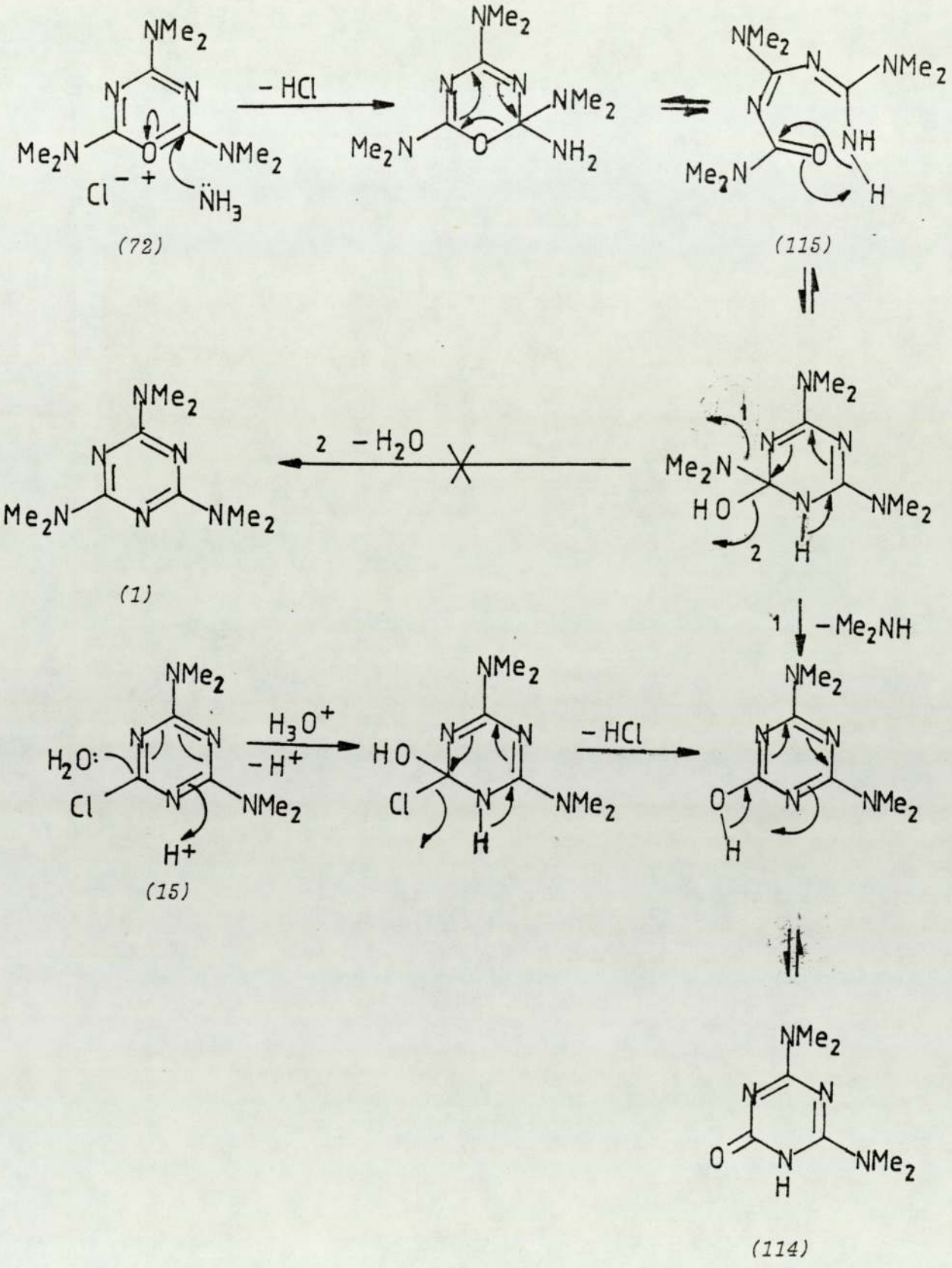
7.1 Reaction With Ammonia

Two possible products may be predicted for the reaction of the oxadiazinium salt (72) with ammonia. If the oxadiazinium system (72) behaves like a typical pyrylium (78), 1,3-oxazinium (97) or oxadiazinium (73) salt (Sections 6.2.1, 6.3.1 and 6.4.1) then the ANRORC reaction ought to produce HMM (1). On the other hand, it was found that the dimethylamino substituted oxadiazinium salts (68; R_1=R_2=NMe_2) (Section 6.4.1) preferentially recyclised with loss of dimethylamine and in this situation the oxadiazinium salt (72) would be expected to form the 4,6-bis(dimethylamino)-1,3,5-triazin-2(1H)-one (114) on reaction with ammonia. It is possible that the inherent thermodynamic stability of HMM (1) may provide the driving force for the former reaction to proceed.

The product obtained from the oxadiazinium salt (72) after boiling with concentrated aqueous ammonia was found not to be HMM (1). The spectroscopic properties of the product obtained indicated the presence of a characteristic i.r. C=O band (ν=1680 cm^{-1}), only two dimethylamino groups (δ=3.3 and 3.4) as determined by ^1H n.m.r. in deuterochloroform (containing trifluoroacetic acid) solution and the mass spectrum produced a parent ion (M^+=183) which corresponded to the triazin-2-one (114).

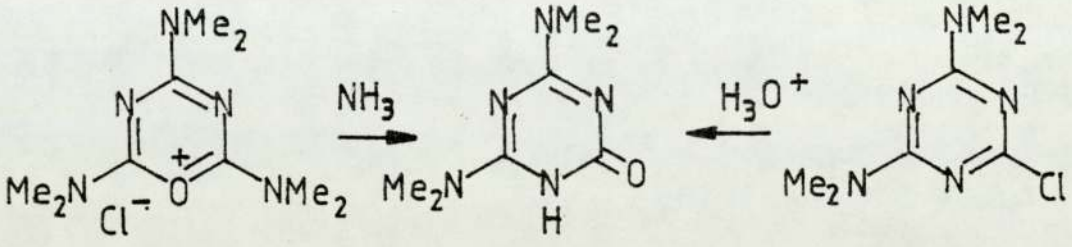
Furthermore, the triazin-2-one (114) obtained from the oxadiazinium salt (72) was found to be identical to an authentic specimen prepared by the acid-catalysed hydrolysis of 2-chloro-4,6-bis(dimethylamino)-1,3,5-triazine (15)[30] (Scheme 19) (Table 8).

The splitting of the ^1H n.m.r. dimethylamino signals for the triazin-2-one (114) is interesting. The compound (114) is not sufficiently soluble in deuterochloroform to obtain a ^1H n.m.r. spectrum but the



Scheme 19: Formation Of 4,6-bis(dimethylamino)-1,3,5-triazin-2(1H)-one From The Interaction Of The Oxadiazinium Salt (72) With Ammonia And The Acid Hydrolysis Of 2-chloro-4,6-bis(dimethylamino)-1,3,5-triazine

Table 8: Comparison Of Some Of The Features Of The Triazin-2-ones (114) Obtained From The Oxadiazinium Salt (72) And Ammonia And The Acid-Hydrolysis Of The 2-chloro-triazine (15)

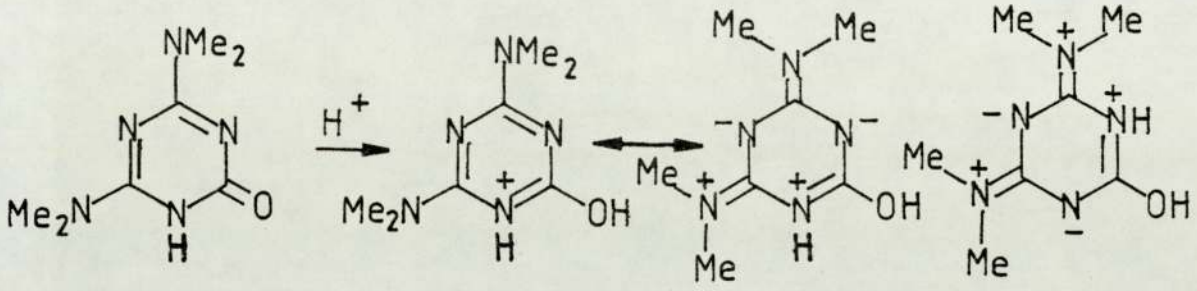


(72) *(114)* *(15)*

Feature	Triazin-2-one (114)	
	From Oxadiazinium Salt (72)	From 2-chloro-triazine (15)
m.p. ^{o}C	292	292
i.r. C=O ν cm^{-1}	1680	1680
^{1}H n.m.r.	δ=3.3 (6H) N-C$\underline{H}_3$	δ=3.3 (6H) N-C$\underline{H}_3$
	δ=3.4 (6H) N-C$\underline{H}_3$	δ=3.4 (6H) N-C$\underline{H}_3$
M.S. M^{+}=	183	183

addition of a little trifluoroacetic acid caused dissolution. The triazin-2-one (114) is a basic compound as indicated by its insolubility in water but greatly enhanced solubility in acid. The protonation will occur at oxygen to form an aromatic heterocycle (114a) and this species (114a) is present in the deuterochloroform/trifluoroacetic acid solution. The dimethylamino groups will suffer restricted rotation and this is represented by the resonance hybrids (115b and 115c). On the basis of these hybrids it can be seen that two equivalent pairs of N-methyl groups are present (α and β). The α-methyl group protons experience a similar field environment to those in HMM (1) and these groups would be expected

to display a similar chemical shift to those in HMM (1) (δ=2.9), allowing for the overall charge on the molecule which lowers the observed chemical shift (δ=3.3). The β methyl protons are in the proximity of two electron deficient nitrogen centres and appear downfield (δ=3.4).



(114) *(114a)* *(114b)* *(114c)*

An attempt was made to isolate the intermediate species (115) by briefly intermixing a dichloromethane solution of the oxadiazinium salt (72) and aqueous ammonia. Treatment of the dried organic phase with excess ether yielded a product which was found to be a mixture of the triazin-2-one (114) and another product.

It is believed that the contaminant is in fact the unreacted oxadiazinium salt (72) because i) t.l.c. of the mixture gave two spots one of which corresponded to the triazin-2-one (114) and one which remained on the origin suggesting that this contaminant is very polar; and ii) the mass spectrum of the mixture gave the parent ion for the triazin-2-one (114) (M^+=183) but no peak corresponding to the intermediate (115) (M^+=228) was observed. A peak corresponding to the oxadiazinium salt (72) (M^+=212) was observed although this peak may also arise from the intermediate (115) by loss of 16 ($\dot{N}H_2$). The fact that the material is not t.l.c. motile would tend to suggest that this peak truly represents the unreacted oxadiazinium salt (72).

7.2 Reactions With Primary Amines

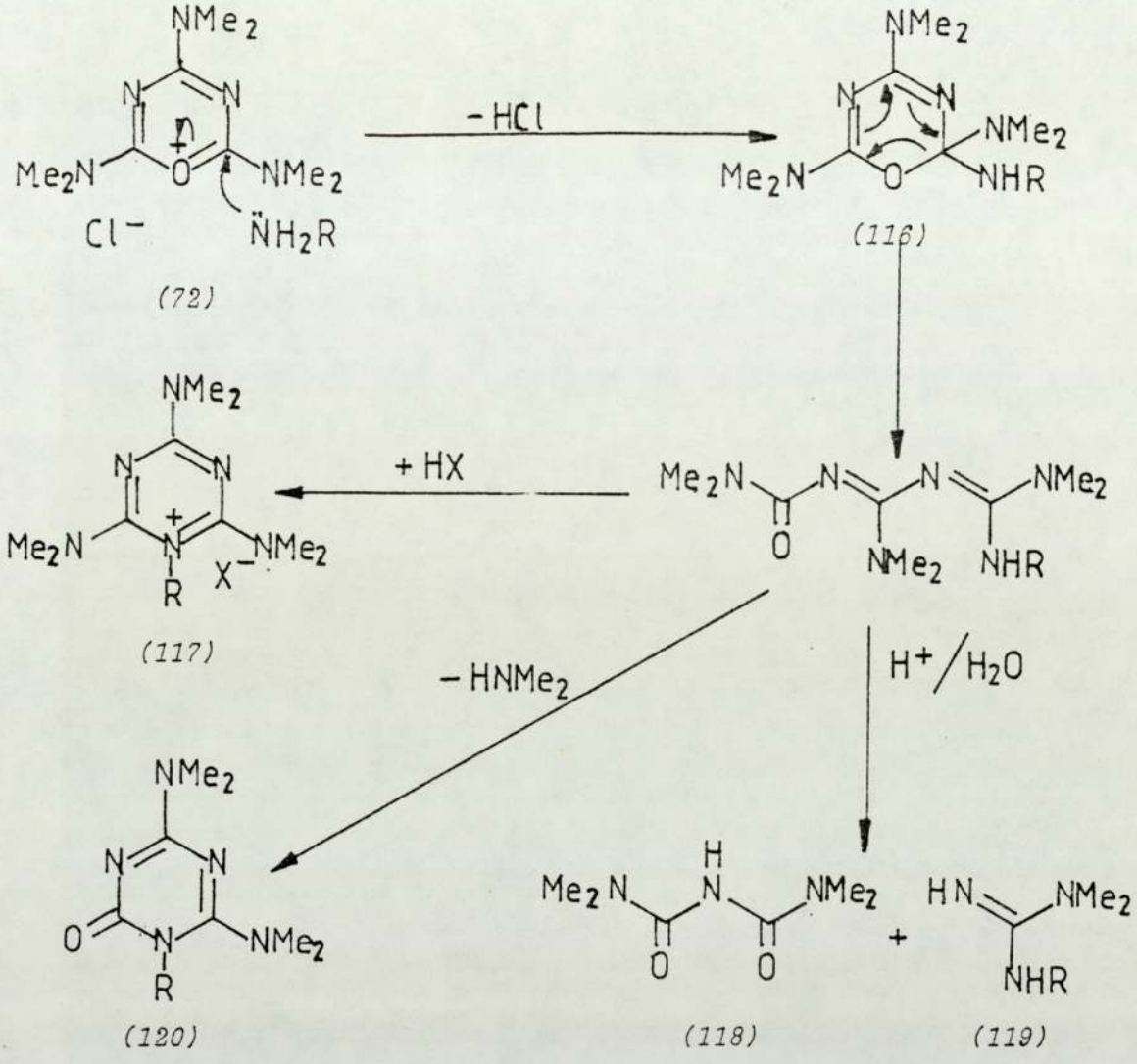
The oxadiazinium salt (72) ought to react with primary amines to form the intermediate species (116) which would probably acyclise (116b) by analogy to the pyrylium (78) and oxadiazinium (73) salts (Sections 6.2.1 and 6.4.1). It would also be predicted that the intermediates (116) would react further on acidification although it is unlikely that a triazinium salt (117) would be formed. The two possible reactions which may occur are the hydrolysis to a mixture of tetramethylbiuret (118) and N-substituteddimethylguanidine (119) by analogy to the oxadiazinium salts (73) (Section 6.4.1) or, alternatively, a 1,3,5-triazin-2-one (120) may be formed by analogy to the reaction of the oxadiazinium salt (72) with ammonia (Section 7.1) (Scheme 20).

Many experiments were conducted to evaluate the reaction of the oxadiazinium salt (72) with various primary amines and it was found that three possible products could be obtained dependant upon the amine selected and the reaction conditions.

Under very mild and basic conditions, the product obtained from the oxadiazinium salt (72) was a 1:1 adduct ($C_9H_{19}N_6OR$) of the salt (72) with the primary amine with loss of hydrogen chloride:

$$\underset{(72)}{C_9H_{18}N_5O^+Cl^-} + \underset{R=alkyl}{RNH_2} \xrightarrow{-HCl} C_9H_{19}N_6OR$$

The aromatic amines, however, under similar reaction conditions gave a mixture of a second product ($C_7H_{12}N_5OR$) corresponding to the adduct ($C_9H_{19}N_6OR$) with loss of dimethylamine and the unreacted oxadiazinium salt (72). Under no conditions could the adducts ($C_9H_{19}N_6OR$) be isolated for the aromatic amines.



Scheme 20: Putative Reaction Pathways And Products Which Could Result From The Reaction Of The Oxadiazinium Salt (72) On Treatment With Primary Amines

$$C_9H_{18}N_5O^+Cl^- \underset{(72)}{} + \underset{R=aryl}{RNH_2} \xrightarrow{-HCl} \underset{Not\ Isolable}{[C_9H_{19}N_6OR]} \xrightarrow{-Me_2NH} C_7H_{12}N_5OR$$

Under more rigorous and neutral or acidic conditions, both the aliphatic and aromatic amines gave rise to this second product ($C_7H_{12}N_5OR$).

If the reaction is conducted under rigorous and basic conditions or in a solvent in which the oxadiazinium salt (72) is barely soluble or in an excess of primary amine, the product obtained was either a mixture of the second product ($C_7H_{12}N_5OR$) plus a small amount of a third product ($C_5H_7N_5OR_2$) or the third product ($C_5H_7N_5OR_2$) exclusively:

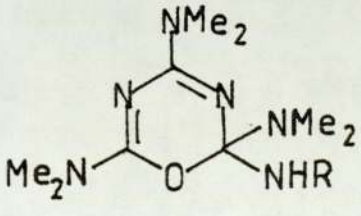
$$\underset{(72)}{C_9H_{18}N_5O^+Cl^-} + 2RNH_2 \xrightarrow{\Delta\ -HCl\ -(1+x)Me_2NH} C_7H_{12}N_5OR + xC_5H_7N_5OR_2 + (1-x)Me_2NH$$

R=alkyl or aryl

In general, it was found that the heterogeneous or basic reaction conditions tended to favour the mixture ($C_7H_{12}N_5OR$ + $C_5H_7N_5OR_2$) whereas a twofold excess of the amine favoured exclusively the third product ($C_5H_7N_5OR_2$).

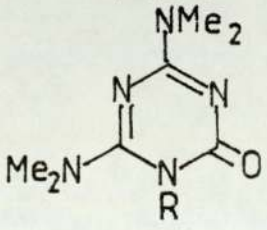
The structures of these three products proved to be extremely difficult to determine beyond doubt although it is believed that the structures (116, 120 and 121) represent the products and are in agreement with the spectroscopic data observed.

$C_9H_{19}N_6OR$



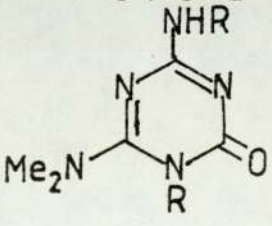
(116)

$C_7H_{12}N_5OR$



(120)

$C_5H_7N_5OR_2$

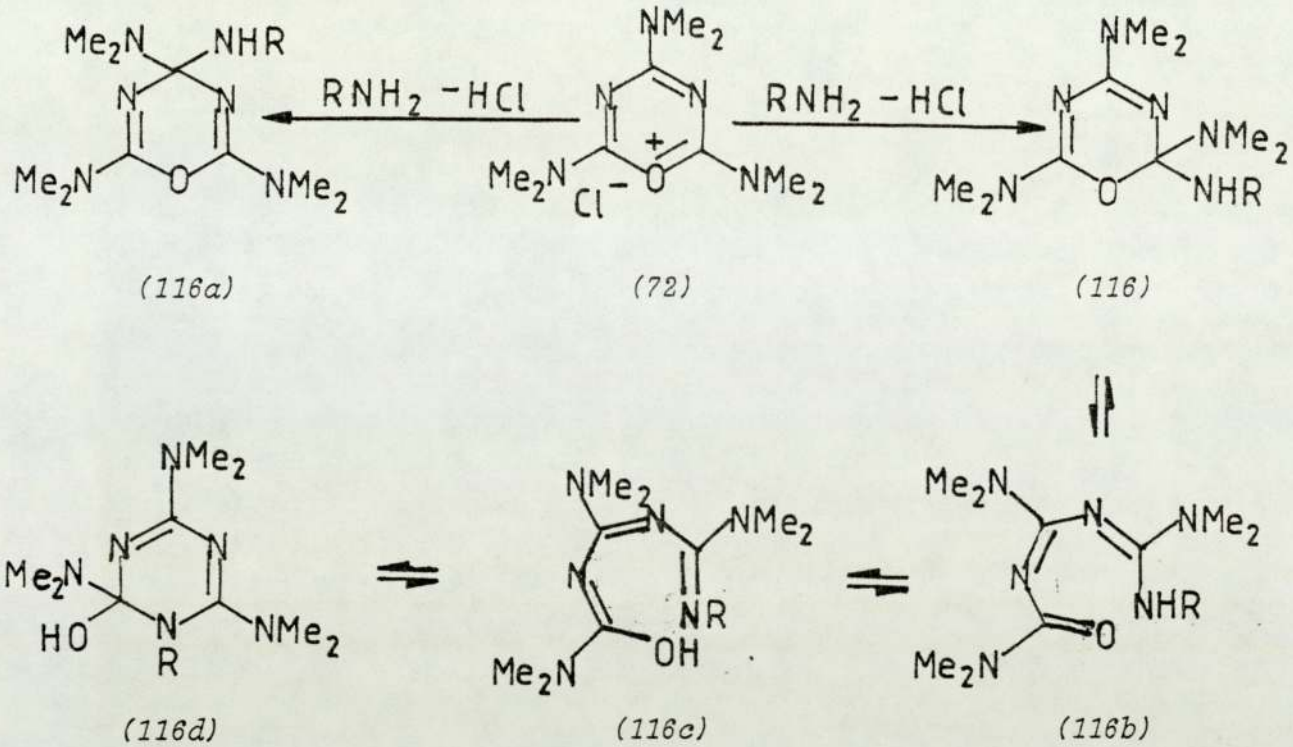


(121)

The assignment of these structures together with the spectroscopic data obtained can be rationalised as follows:

7.2.1 The Intermediate Adducts ($C_9H_{19}N_6OR$) (116)

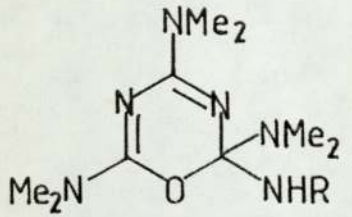
The aliphatic amines react readily with the oxadiazinium salt (72) in dichloromethane solution in the presence of triethylamine to yield the corresponding 1:1 adducts (116) with loss of hydrogen chloride. These adducts (116) were found to be difficult to crystallise but carefully controlled precipitation of the adducts (116) from their solutions yielded solid products. The adducts (116) were found to be stable in the solid-state and in cold neutral or basic solutions. The lower homologues (116) were found to be reasonably water-soluble but the solubility rapidly decreased as the R group became more hydrophobic. Thus, adduct (116; R=Me) is extremely water soluble and deliquescent whereas the adduct (116; R= cyclohexyl) is nearly insoluble. All the adducts (116) had relatively low melting points and all decomposed at or slightly above their melting temperatures with evolution of an alkaline gas. If the neutral aqueous solutions or suspensions of the adducts (116) was heated to reflux or treated with acid and then rebasified, the product obtained appeared to be a mixture of the unchanged adduct (116) plus the product (120) corresponding to loss of dimethylamine from the adduct (116). The question posed by this reaction is whether the amine attacks the equivalent 2 or 6 positions or the 4 position of the oxadiazinium salt (72). Scheme 21 illustrates both of these alternatives and all of the possible structures for these adducts (116). Clearly, it can be seen that aatack of the amine at the 4-position of the salt (72) leads to a 4-substitutedamino-2,4,6-tris(dimethylamino)-1,3,5-oxadiazine (116a). attack of the amine at the 2 or 6 positions of the salt (72) leads to the isomeric 2-substitutedamino-2,4,6-tris(dimethylamino)-1,3,5-oxadiazine (116) which can electrocyclically



Scheme 21: Possible Structures For The Adducts Arising From Attack Of Primary Amines On The (2 or 6) Or 4 Positions Of The Oxadiazinium Salt (72)

ring open to form the amino-ketone (116b) which can tautomerise to the imino-enol (116c) or ring close to 2-hydroxy-2,4,6-tris(dimethylamino)-1,3,5-triazine (116d). The adducts (116) were found to be chromatographically pure which suggested that only one of these species is present. Earlier, it was stated (Section 6.4.1) that the triary(alkyl)oxadiazinium salts (73) gave rise to the acyclic intermediates (105) *via* attack at the 2 or 6 positions of the salts (73) by the amine. The evidence for this structure (105) derived from the observation of characteristic i.r. N-H and C=O bands although the latter band was peculiarly low ($\nu\sim1630cm^{-1}$)[95]. The i.r. spectra for the adducts (116) both in the solid-state (KBr disc) and in solution (CCl_4) displayed a sharp band attributable to an N-H or O-H group (ν=3250-3350cm^{-1}) (Table 9) but in all cases no band was observed in the range ν=1600-1800cm^{-1}. This observation suggested that the adducts (116) were not

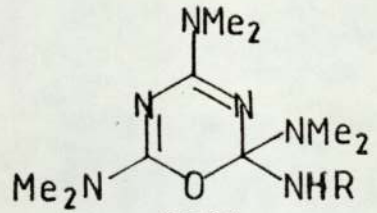
Table 9: Physical And Spectroscopic Features Exhibited By The Intermediate Adducts ($C_{18}H_{19}N_6OR$) And The Assignment Of The Features To The 2-substitutedamino-2,4,6-tris-(dimethylamino)-1,3,5-oxadiazine (116) Structure



(116)

R=	m.p. (°C dec.)	i.r. N-H ν cm^{-1}	^{1}H n.m.r. δ=			Inference	M.S. M$^+$	M$^+$-44	M$^+$-45	RNCO$^+$
Me	124	3300	2.90	*(d)*	(3H)	N-C$\underline{H}_3$	242	198	197	57
			2.95	*(s)*	(6H)	N-C$\underline{H}_3$				
			3.00	*(s)*	(6H)	N-C$\underline{H}_3$				
			3.05	*(s)*	(6H)	N-C$\underline{H}_3$				
			5.10	*(br)*	(1H)	N-$\underline{H}$				
Et	131	3300	1.20	*(t)*	(3H)	CH_2-C$\underline{H}_3$	256	212	211	71
			2.90	*(s)*	(6H)	N-C$\underline{H}_3$				
			3.00	*(s)*	(6H)	N-C$\underline{H}_3$				
			3.05	*(s)*	(6H)	N-C$\underline{H}_3$				

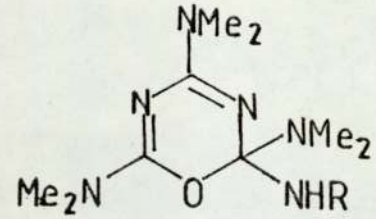
Table 9 *(continued)*



(116)

R=	m.p. (°C dec.)	i.r. N-H ν cm^{-1}	^{1}H n.m.r. δ=			Inference	M.S. M$^+$	M$^+$-44	M$^+$-45	RNCO$^+$
Et			3.20	*(m)*	(2H)	N-C$\underline{H}_2$CH$_3$				
			4.80	*(br)*	(1H)	N-$\underline{H}$				
Pr	96	3250	0.85	*(t)*	(3H)	CH$_2$C$\underline{H}_3$	270	226	225	85
			1.50	*(dxq)*	(2H)	CH$_2$C$\underline{H}_2$CH$_3$				
			2.80	*(s)*	(6H)	N-C$\underline{H}_3$				
			2.90	*(s)*	(6H)	N-C$\underline{H}_3$				
			2.95	*(s)*	(6H)	N-C$\underline{H}_3$				
			3.20	*(m)*	(2H)	N-C$\underline{H}_2$CH$_2$				
			4.90	*(br)*	(1H)	N-$\underline{H}$				
Me$_2$CH-	151	3250	1.20	*(d)*	(6H)	CH(C$\underline{H}_3$)$_2$	270	226	225	85
			2.85	*(s)*	(6H)	N-C$\underline{H}_3$				
			3.00	*(s)*	(6H)	N-C$\underline{H}_3$				
			3.05	*(s)*	(6H)	N-C$\underline{H}_3$				

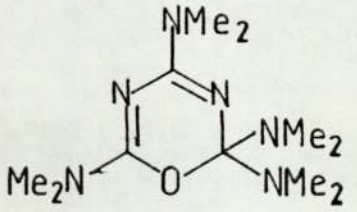
Table 9 *(continued)*



(116)

R=	m.p. (°C dec.)	i.r. N-H ν cm^{-1}	^{1}H n.m.r. δ=			Inference	M.S. M$^+$	M$^+$-44	M$^+$-45	RNCO$^+$
Me_2CH-			3.20	*(dxd)*	(1H)	N-C$\underline{H}$$(CH_3)_2$				
			4.90	*(br)*	(1H)	N-$\underline{H}$				
Bu	74	3350	0.80	*(t)*	(3H)	$CH_2C\underline{H}_3$	284	240	239	99
			1.30	*(br)*	(4H)	$CH_2(C\underline{H}_2)_2CH_3$				
			2.75	*(s)*	(6H)	N-C$\underline{H}_3$				
			2.85	*(s)*	(6H)	N-C$\underline{H}_3$				
			2.90	*(s)*	(6H)	N-C$\underline{H}_3$				
			3.00	*(m)*	(2H)	N-C$\underline{H}_2CH_2$				
			4.80	*(br)*	(1H)	N-$\underline{H}$				
MeEtCH-	128	3300	1.10	*(br)*	(8H)	$C\underline{H}_3CHC\underline{H}_2C\underline{H}_3$	284	240	239	99
			2.90	*(s)*	(6H)	N-C$\underline{H}_3$				
			3.00	*(s)*	(6H)	N-C$\underline{H}_3$				
			3.05	*(s)*	(6H)	N-C$\underline{H}_3$				

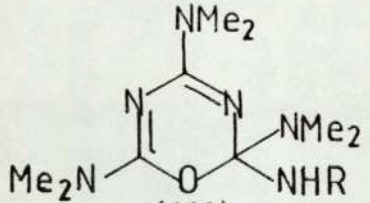
Table 9 *(continued)*



(116)

R=	m.p. (°C dec.)	i.r. N-H ν cm^{-1}	^{1}H n.m.r. δ=			Inference	M.S. M$^+$	M$^+$-44	M$^+$-45	RNCO$^+$
MeEtCH-			3.10	*(m)*	(1H)	N-C$\underline{H}$(CH$_3$)CH$_2$CH$_3$				
			4.80	*(br)*	(1H)	N-$\underline{H}$				
Me$_3$C-	126	3250	1.40	*(d)*	(9H)	CH(C$\underline{H}_3$)$_3$	284	240	239	99
			2.80	*(s)*	(6H)	N-C$\underline{H}_3$				
			3.05	*(s)*	(6H)	N-C$\underline{H}_3$				
			3.10	*(s)*	(6H)	N-C$\underline{H}_3$				
			3.35	*(m)*	(1H)	N-C$\underline{H}$(CH$_3$)$_3$				
			4.20	*(br)*	(1H)	N-$\underline{H}$				
*cyclo*C$_6$H$_{11}$	166	3250	1.50	*(br)*	(10H)	CHC$_5\underline{H}_{10}$	310	266	265	125
			2.90	*(s)*	(6H)	N-C$\underline{H}_3$				
			3.10	*(s)*	(6H)	N-C$\underline{H}_3$				
			3.15	*(s)*	(6H)	N-C$\underline{H}_3$				
			3.20	*(m)*	(1H)	N-C$\underline{H}$C$_5$H$_{10}$				
			4.85	*(br)*	(1H)	N-$\underline{H}$				

Table 9 *(continued)*



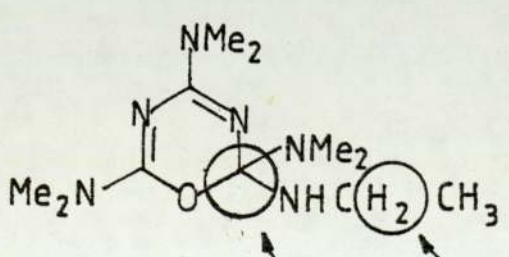
(116)

R=	m.p. (°C dec.)	i.r. N-H ν cm^{-1}	^{1}H n.m.r. δ=			Inference	M.S. M$^+$	M$^+$-44	M$^+$-45	RNCO$^+$
$PhCH_2$-	76	3300	2.90	*(s)*	(6H)	N-C$\underline{H}_3$	318	274	273	133
			2.95	*(s)*	(12H)	N-C$\underline{H}_3$				
			4.40	*(br)*	(2H)	N-C$\underline{H}_2$Ph				
			7.35	*(s)*	(5H)	C$_6\underline{H}_5$				
$PhCH_2CH_2$-	123	3300	2.80	*(s)*	(6H)	N-C$\underline{H}_3$	332	288	287	147
			2.90	*(s)*	(6H)	N-C$\underline{H}_3$				
			3.00	*(s)*	(6H)	N-C$\underline{H}_3$				
			3.40	*(m)*	(4H)	N-C$\underline{H}_2$C$\underline{H}_2$Ph				
			4.70	*(br)*	(1H)	N-$\underline{H}$				
			7.30	*(s)*	(5H)	C$_6\underline{H}_5$				

br=broad *d*=doublet *dxd*=doublet of doublets *dxq*=doublet of quartets *m*=multiplet *q*=quartet

s=singlet *t*=triplet

the amino-ketones (116b). The imino-enol (116c) structure would also be expected to show an i.r. C=N band within this region. The ^{1}H n.m.r. spectra (60MHz) (Table 9) of these adducts (116) all displayed three, closely-centered singlets (δ∿2.9-3.1) which integrated for three dimethylamino groups (6:6:6) and a broad peak (δ∿5) corresponding to the N-H or O-H group. The ^{1}H n.m.r. spectrum (220MHz) determined for the ethylaminoadduct (116; R=Et) (Figure 6) clearly indicated that the broad peak (δ=4.8) is actually a triplet and disappears on exchanging the proton with deuterium oxide. Similarly, the CH_2 fragment (δ=3.37) of the ethyl residue appears as a complex multiplet which collapses to a broad quartet after treatment with deuterium oxide. This evidence establishes beyond doubt that the proton at low-field is indeed connected to the nitrogen centre of the N-ethyl group and not the oxygen centre. Unfortunately, the coupling constant for these observed peaks is very small and an accurate value can not be determined. Analysis of the complex multiplet observed for the CH_2 fragment suggests that the N-ethyl fragment resonances are not a straightforward doublet of quartets but rather that the methylene protons appear to be prochiral. The outcome of this observation is that the methylene proton host carbon centre must be in close proximity with a chiral centre. This evidence again supports the 2-substitutedoxadiazine structure (116; R=Et) as the ring sp^3 carbon centre is chiral.



(116; R=Et)

chiral *prochiral protons*

sp^3 carbon

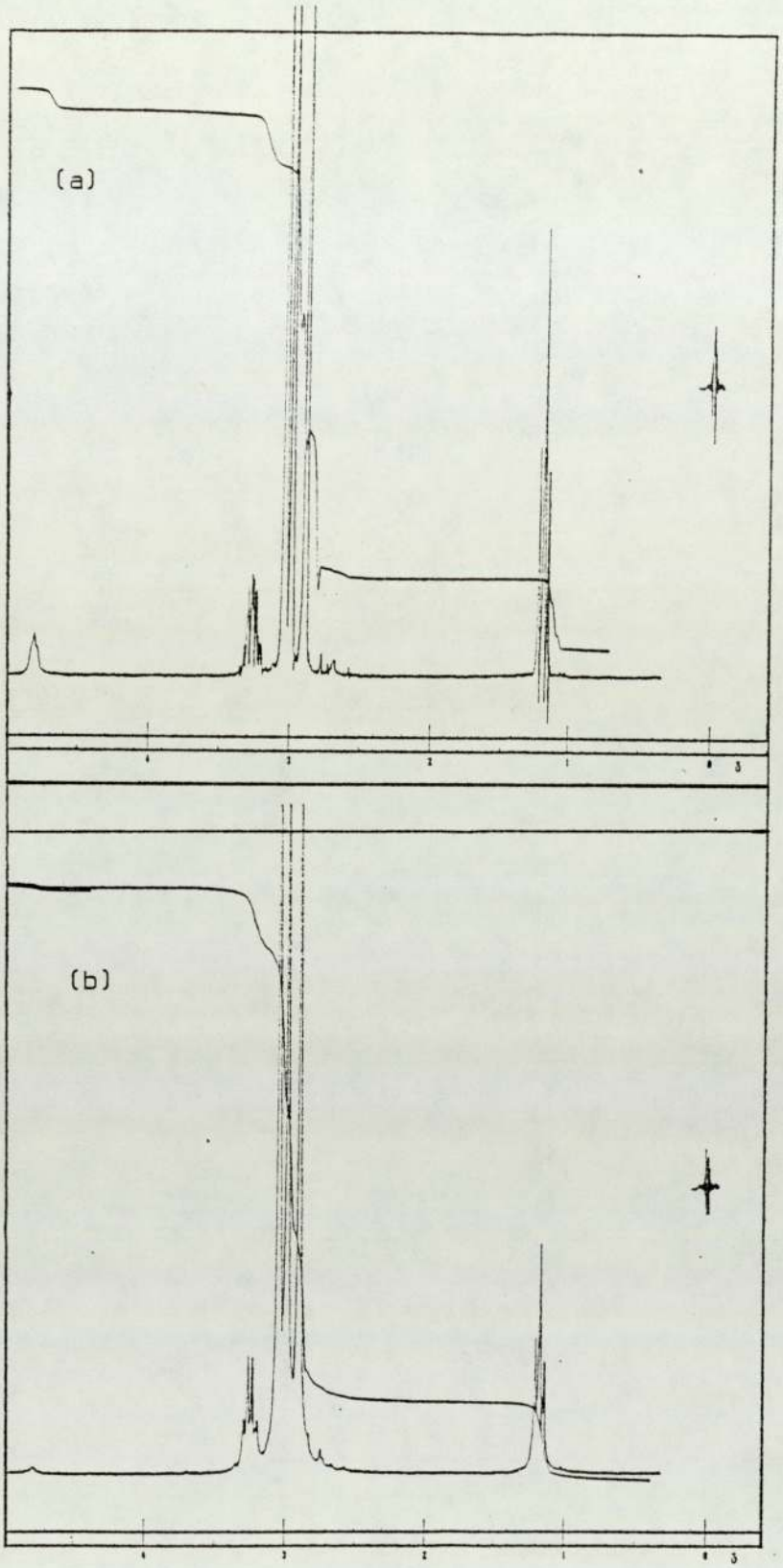


Figure 6: ^{1}H n.m.r. (220MHz) Spectrum Obtained For 2-ethylamino-2,4,6-tris(dimethylamino)-1,3,5-oxadiazine In a) Deuterochloroform And b) Deuterochloroform After Shaking With Deuterium Oxide

This rationalisation coupled with the low melting points recorded for the adducts (116) would tend to suggest that they are in fact racemic mixtures which neatly explains the difficulty encountered in crystallisation of these intermediates (116).

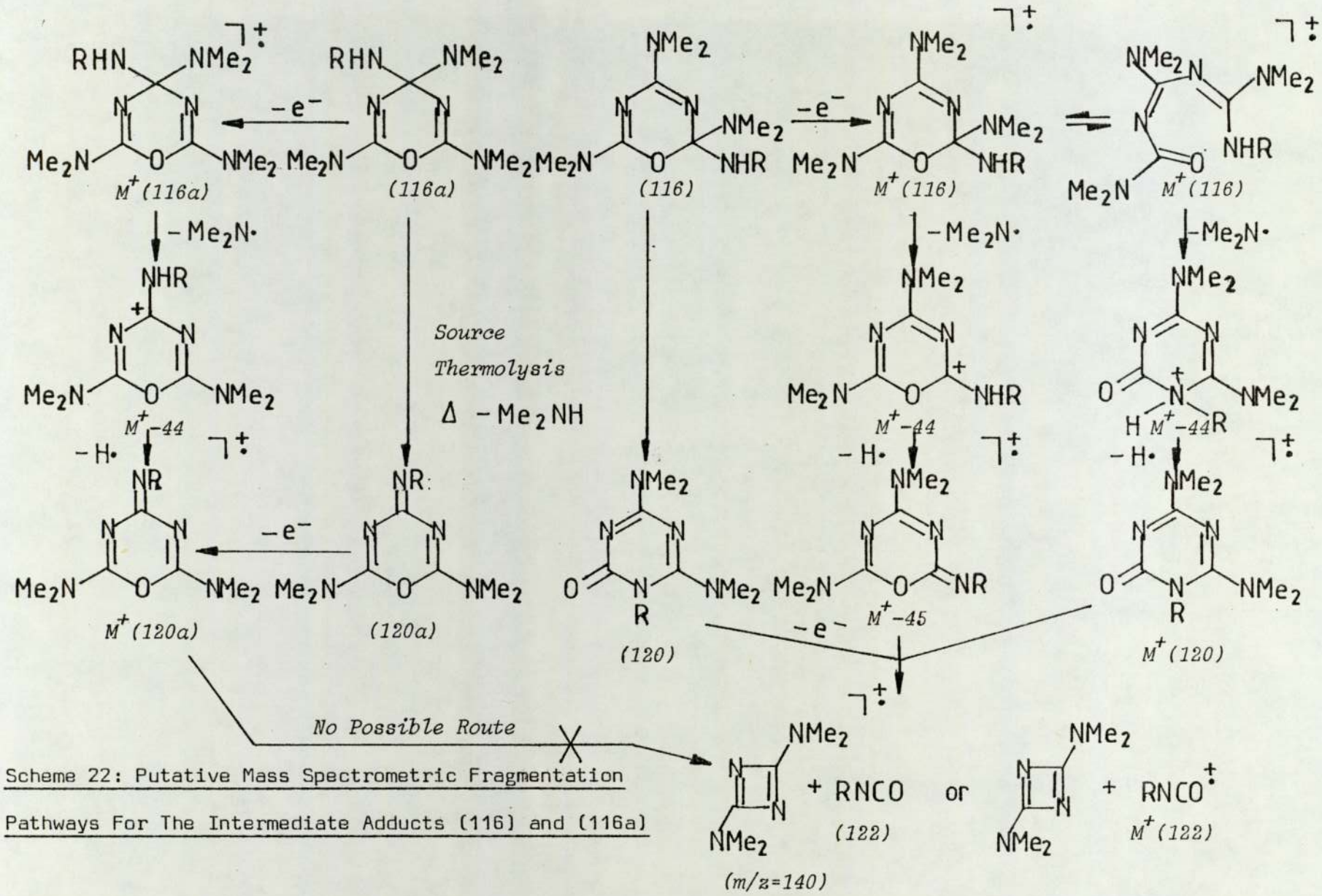
Coalescence of the i.r. and ^{1}H n.m.r. spectra certainly seems to indicate the oxadiazine structure (116) as the adduct, although none of the observations can completely eliminate the 4-isomer (116a).

The ^{13}C n.m.r. spectra for the intermediates (116) were extremely complex and could not be satisfactorily explained.

The mass spectra for the adducts (116) revealed the requisite parent M^{+} ions in all cases (Table 9) and the first observed daughter ion resulted from loss of the dimethylamino radical ($Me_2N^{\cdot}$) followed by loss of a hydrogen radical ($H^{\cdot}$). The resulting product (120) arising from these losses could feasibly arise from source thermolysis of the adducts (116) as these are known to evolve an alaline gas on fusion. The same daughter ion (120) is observed for the product obtained when the oxadiazinium salt (72) is treated with the primary amine at higher temperatures (See Section 7.2.2) although, under the spectrometer conditions this can neither be assigned to the structure (120) nor the structure (120a). The further fragmentation pattern observed for both the adducts (116) and their proposed products (120) is very similar.

Scheme 22, illustrates the possible fragmentation patterns for the two isomeric adducts (116 and 116a) and it can clearly be seen that either isomer can feasibly lose dimethylamine by source pyrolysis or by stepwise radical elimination to form the isomeric structures (120 and 120a).

However, the observation of peaks corresponding to the alkyl isocyanate (122) can only be derived from fragmentation of the 2-isomer (116) and this finally allows structure (116a) to be elimated from the list of possibilities.



Scheme 22: Putative Mass Spectrometric Fragmentation Pathways For The Intermediate Adducts (116) and (116a)

The chemical ionisation mass spectrum for the cyclohexyl intermediate (116; R=cyclohexyl) (Figure 7) was found to give the expected M+1 parent ion (m/z=311) which exhibited a similar fragmentation pattern to that observed in the electron impact mass spectrum.

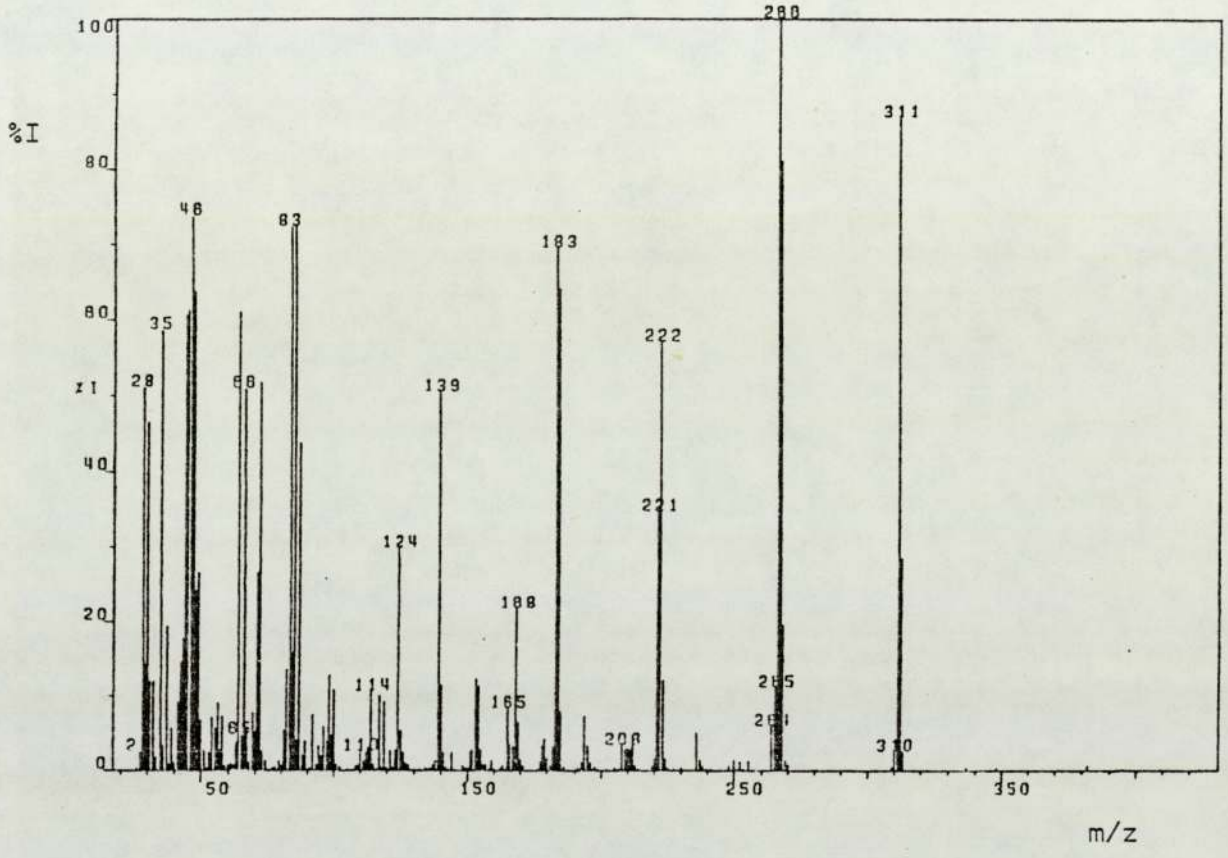
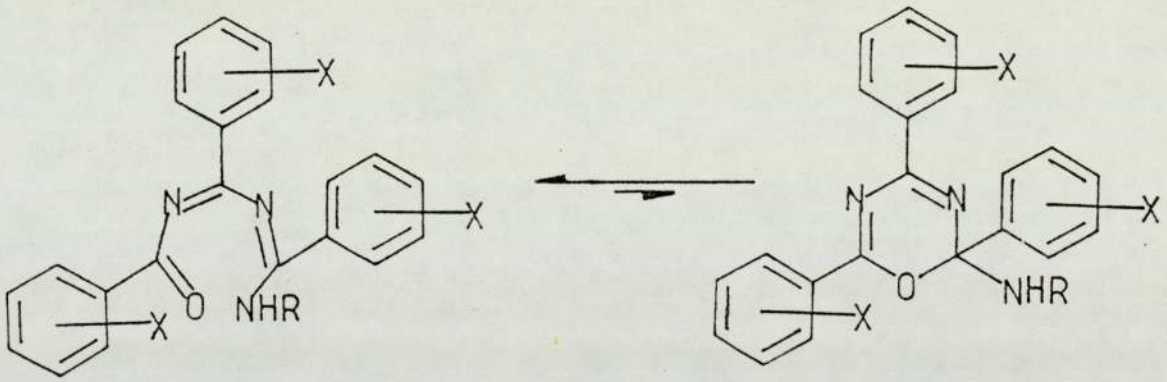


Figure 7: Chemical Ionisation Mass Spectrum Obtained For 2-cyclohexylamino-2,4,6-tris(dimethylamino)-1,3,5-oxadiazine (116; R=cyclohexyl)

An attemp was made to prove the oxadiazine (116) structure by X-ray crystallography but efforts to determine the unit-cell dimensions resulted in inconsistent and grossly exaggerated values. It was thought that this may be due to radiation-induced decomposition of the crystal to form a mixture of the adduct (116) and the product (120) by loss of dimethylamine.

In the absence of crystallographic proof of the structure (116), it is believed that this structure (116) is indeed correct as it seems to be

uniformly consistent with all the spectroscopic features observed. This structure (116) is, however, divergent with the adducts obtained from the oxadiazinium salts (73) which were acyclic (105) isomers. A possible explanation for this difference could arise from the nature of the ring-substituents. If the cyclic (105a) and acyclic (105) forms of the adducts obtained from the oxadiazinium salts (73) are compared, it can be seen that the acyclic isomer (105) is completely conjugated whereas the cyclic (105a) species is not conjugated throughout the whole molecule. This probably provides the thermodynamic factors for the cyclic (105a) to ring open to the completely conjugated structure (105).



(105) *(105a)*

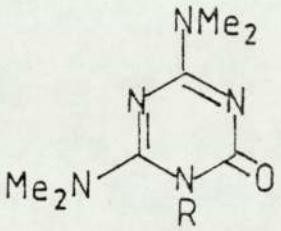
X=Cl;Me;MeO;NO_2

7.2.2 The Triazin-2-ones ($C_7H_{12}N_5OR$) (120)

Thermolysis of the 2-alkylaminooxadiazines (116) resulted in the evolution of an alkaline gas and the product obtained on cooling was a glassy solid which was found to be impossible to recrystallise. The product was found to be a mixture of the unchanged adduct (116) and the triazin-2-one (120). A similar mixture of products was obtained when the intermediates (116) were treated with acid and then rebasified. Under certain reaction conditions, some of the alkylamines reacted with the oxadiazinium salt (72) to form the triazin-2-one (120) exclusively but these were exceptions rather than the rule.

Table 10: Selected Spectroscopic Features

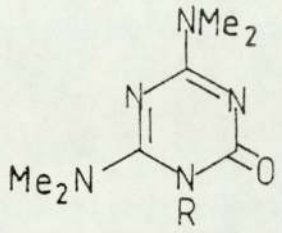
For The 1-aryltriazin-2-ones (120)



(120)

R=	i.r. C=O	^{1}H n.m.r.[a]				M.S.	
	ν cm^{-1}	δ=			Inference	M^+	$RNCO^+$
C_6H_5	1680	2.70	*(s)*	(6H)	N-C$\underline{H}_3$	259	119
		3.20	*(s)*	(6H)	N-C$\underline{H}_3$		
		7.40	*(s)*	(5H)	N-C$_6\underline{H}_5$		
$4MeOC_6H_4$	1680	2.70	*(s)*	(6H)	N-C$\underline{H}_3$	289	149
		3.20	*(s)*	(6H)	N-C$\underline{H}_3$		
		3.80	*(s)*	(3H)	O-C$\underline{H}_3$		
		6.90	*(d)*	(2H)	N-C(C$\underline{H}$)$_2$(CH)$_2$C-O		
		7.25	*(d)*	(2H)	N-C(CH)$_2$(C$\underline{H}$)$_2$C-O		
$4MeC_6H_4$	1680	2.30	*(s)*	(3H)	-C$_6$H$_4$-C$\underline{H}_3$	273	133
		2.80	*(s)*	(6H)	N-C$\underline{H}_3$		
		3.20	*(s)*	(6H)	N-C$\underline{H}_3$		
		7.20	*(s)*	(4H)	N-C$_6\underline{H}_4$-		
$4ClC_6H_4$	1680	2.70	*(s)*	(6H)	N-C$\underline{H}_3$	295/	155/
		3.20	*(s)*	(6H)	N-C$\underline{H}_3$	293	153
		7.35	*(d)*	(2H)	N-C(C$\underline{H}$)$_2$(CH)$_2$C-Cl	(1:3)	(1:3)
		7.40	*(d)*	(2H)	N-C(CH)$_2$(C$\underline{H}$)$_2$C-Cl		
$4BrC_6H_4$	1680	2.80	*(s)*	(6H)	N-C$\underline{H}_3$	339/	199/
		3.20	*(s)*	(6H)	N-C$\underline{H}_3$	337	197
		7.20	*(d)*	(2H)	N-C(C$\underline{H}$)$_2$(CH)$_2$C-Br	(1:1)	(1:1)
		7.60	*(d)*	(2H)	N-C(CH)$_2$(C$\underline{H}$)$_2$C-Br		

Table 10 *(continued)*



(120)

R=	i.r. C=O ν cm^{-1}	^{1}H n.m.r. δ= Inference	M.S. M^+	$RNCO^{+\cdot}$
$4NO_2C_6H_4$	1700	3.30[b] *(s)* (12H) N-C$\underline{H}_3$ 7.90 *(d)* (2H) N-C(C$\underline{H}$)$_2$(CH)$_2$C-NO_2 8.50 *(d)* (2H) N-C(CH)$_2$(C$\underline{H}$)$_2$C-NO_2	304	164

a determined in deuterochloroform

b determined in trifluoroacetic acid

d=doublet

s=singlet

The aromatic primary amines reacted with the oxadiazinium salt (72) under controlled conditions to form the triazin-2-ones (120) exclusively.

The i.r. spectra of the products (120) exhibited strong, characteristic C=O bands (ν=1680-1700cm^{-1}) and an absence of N-H bands (Table 10). This evidence supports the triazin-2-one (120) structure and further supports the existence of the intermediate 2-subsituted oxadiazines (116) which can readily form the triazin-2-one (120) and further opposes the 4-isomer (116a) which can not feasibly form the triazin-2-one (120).

The ^{1}H n.m.r. spectra for the triazin-2-ones (120) revealed the presence of two dimethylamino groups (two singlets) in deuterochloroform solution

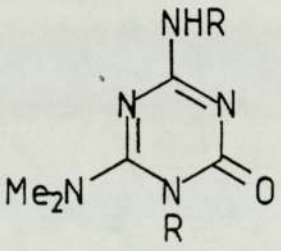
(Table 10). It is likely that the highest field singlet corresponds to the 4-dimethylamino group protons as this group is in a similar environment to those in HMM (1) and the 6-dimethylamino group protons resonate at lower field.

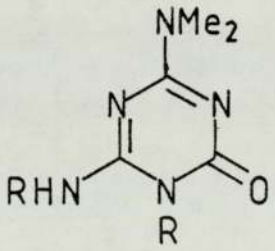
The mass spectra (Table 10) for the triazin-2-ones (120) gave the expected parent M^+ ions and in all cases the isocyanate peak (122) was observed as with the corresponding adducts (116) (Section 7.2.1; Scheme 22).

The spectroscopic observations appear to conclusively support the triazin-2-one (120) structure.

7.2.3 The Triazin-2-ones ($C_5H_7N_5OR_2$) (121)

The product (121) obviously consists of the original oxadiazinium salt (72) plus two equivalents of the primary amine with loss of hydrogen chloride and two equivalents of dimethylamine. Two possible isomeric structures (121 and 121a) can be drawn for this product:

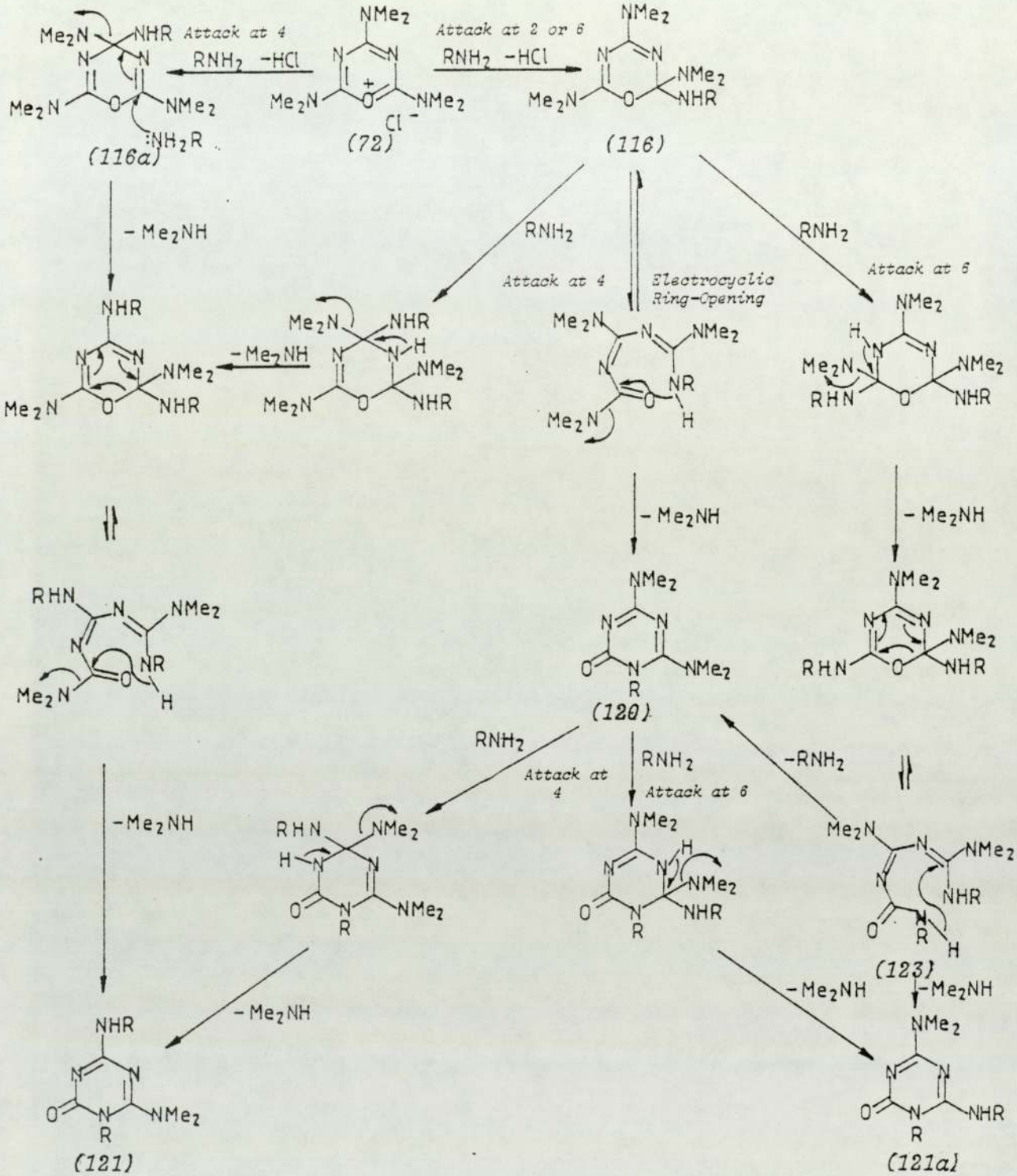




It has already been mentioned (Section 7.2) that the reaction to form these products (121) is favoured by basic and/or heterogeneous conditions. This would tend to suggest that the attack of the second amine equivalent occurs before ring closure which is acid-catalysed. Furthermore, the adducts (116) are much more soluble in less polar solvents than the oxadiazinium salt (72) and would more likely undergo a homogeneous reaction with the dissolved amine.

Alternatively, the fact that mixtures of both the triazin-2-ones (120 and 121) are commonly obtained may suggest that the product (121) arises from the triazin-2-one (120) on reaction with the primary amine. These theories were investigated by heating either the intermediate adduct (116) or the triazin-2-one (120) with an excess of the primary amine but in both cases the product was a mixture of the triazin-2-ones (120 and 121) and in the former case a substantial amount of the unchanged adduct (116) was also present. The most reasonable explanation of these observations is that, paradoxically, the reaction is acid catalysed i.e. the hydrogen chloride liberated by the oxadiazinium salt (72) after treatment with the primary amine is trapped in the reaction mixture by the basic solvent and provides sufficient acidity for the ring-closure and second equivalent of primary amine substitution to occur. Scheme 23 illustrates the major theoretical routes to both of the triazin-2-one (121 and 121a) isomers resulting from substitution of the adducts (116) or the triazin-2-ones (120).

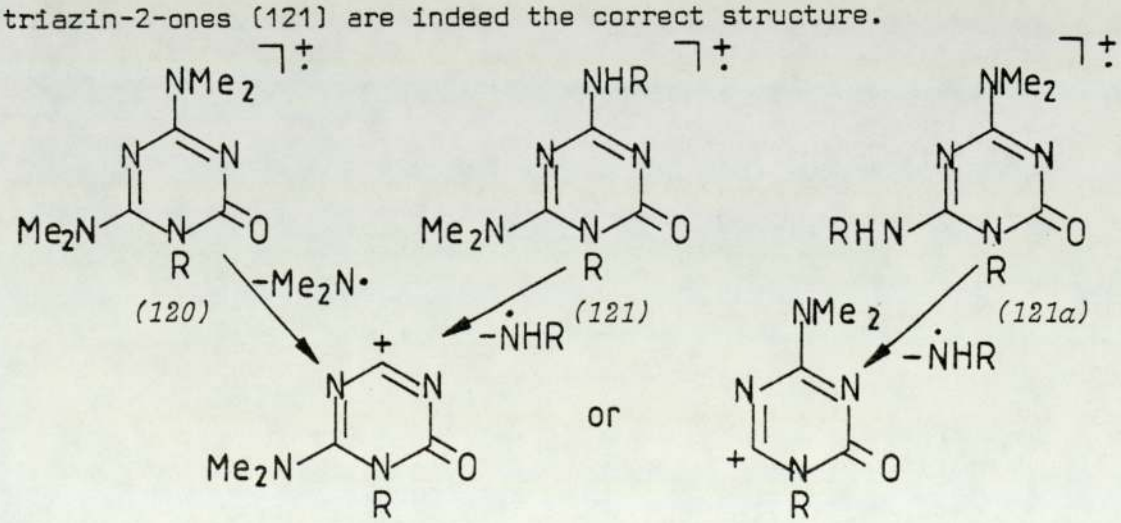
It is almost impossible to distinguish the two isomers (121 and 121a) by standard spectroscopic means without authentic samples and the only supportive structural evidence for the 4-substituted isomer (121) derives from the ^{1}H n.m.r. spectra. However, it is believed that the substitution by the second amine equivalent at whatever stage it occurs would probably occur as far away as possible from the other N-R group i.e. at the 4-position due to steric crowding. Furthermore, if attack did occur at the 6-position of the intermediate (116) the recyclisation of the intermediate (123) would probably entail the loss of primary amine instead of dimethylamine due to steric crowding and the normal triazin-2-one (120) would be formed. This could explain why mixtures of the triazin-2-ones (120 and 121) are encountered wherby the only viable route to the product (121) exclusively is by attack at the 4-position.



Scheme 23: Possible Reaction Mechanisms Which Result In The Formation Of The Two Isomeric Triazin-2-ones (121) and (121a)

On the basis of the dimethylamino assignments for the triazin-2-ones (120) the ^{1}H n.m.r. spectra for the pure triazin-2-ones (121) and the mixtures (120 + 121) would tend to suggest that the 4-isomer (121) is the actual product. In the mixtures (120 + 121), the high field singlet is slightly deficient indicating that in some molecules the 4-position is no longer dimethylamino substituted and the pure triazin-2-ones (121) only exhibit the lower field singlet.

In the majority of cases only the mixtures (120 + 121) were obtained and these were characterised by t.l.c., ^{1}H n.m.r. and mass spectroscopy. The mass spectra for these mixtures (120 + 121) showed the usual parent M^+ ions corresponding to the triazin-2-ones (120) but larger parent M^+ ions corrsponding to the triazin-2-ones (121) were also observed. No apparent intermediate fragmentation between these two parent ions was observed and the whole of the alkylamino group must be lost from the parent ion for the triazin-2-ones (121) (Scheme 24). Apart from the appearance of the larger (M^+) parent ion for the triazin-2-ones (121), the mass spectra for the two triazin-2-ones (120 and 121) are indistinguishable. In the absence of irrevocable structural evidence it is believed that the 4-substitued triazin-2-ones (121) are indeed the correct structure.



Scheme 24: Mass Spectral Fragmentation Of The Parent Triazin-2-ones (120 and 121) M^+ Ions

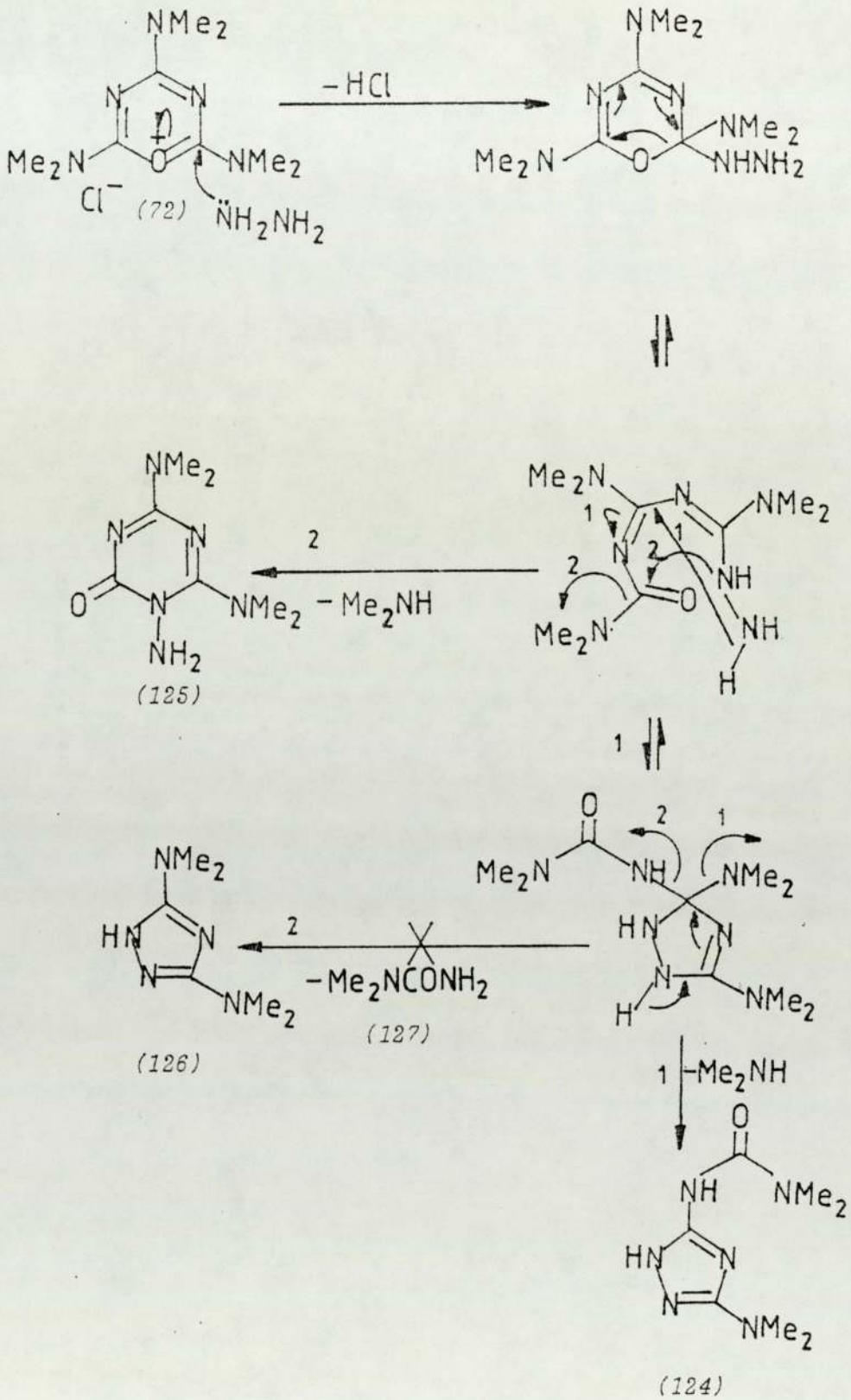
7.3 Reactions With Hydrazine And Its Monosubstituted Derivatives

7.3.1 Hydrazine

It was concluded (Section 6.5) that pyrylium systems containing other heteroatoms formed exclusively ring-contracted products on reaction with hydrazines. The oxadiazinium salt (72) would be expected to follow a similar pathway and form an $ANRORC_c$ product although the outcome is not straightforward. It has been observed already that ANRORC reactions of the oxadiazinium salt (72) with ammonia and primary amines proceeded with loss of dimethylamine on recyclisation (Sections 7.1 and 7.2) and the $ANRORC_c$ ring-closure step with hydrazine would be expected also to involve loss of dimethylamine.

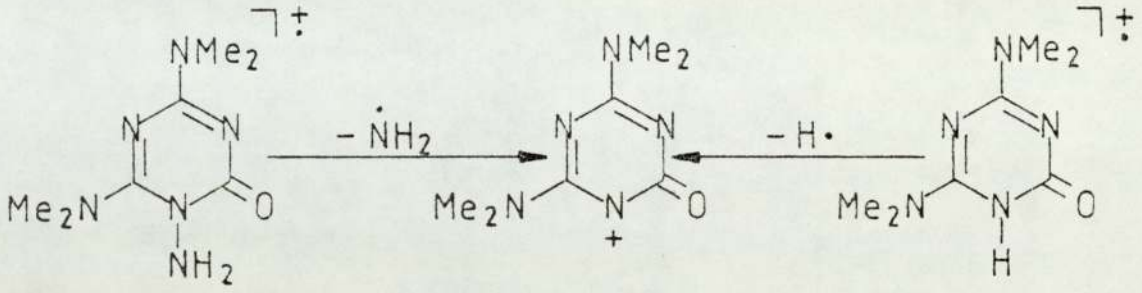
Initial analysis of the spectroscopic data obtained for the product isolated from the oxadiazinium salt (72) on reaction with hydrazine did not immediately indicate whether the product was ring-contracted (124) or not (125). Scheme 25 illustrates the routes to both of these products (124 and 125) and furthermore, the product (126) formed by loss of N,N-dimethyl-urea (127) on ring-closure ($ANRORC_c$) was not obtained by analogy to the oxadiazinium salts (73) (Section 6.4.2). It can be seen that the triazole (124) and the N-amino-triazin-2-one (125) are isomers and the spectroscopic features of both the compounds (124 and 125) will be very similar and difficult to distinguish without authentic specimens.

It was concluded, however, that the $ANRORC_c$ triazole (124) was indeed the correct structure on the basis that i) the product did not give a characteristic mauve colour on treatment with ninhydrin indicative of free $-NH_2$ groups and ii) the mass spectrum fragmentation pattern for the parent M^+ ion (m/z=198) ought to show a loss of 16($H_2N^\bullet$) for the triazin-2-one (125) which would form the same daughter ion as the loss of a hydrogen radical from the triazin-2-one (114). The mass spectral fragmentation



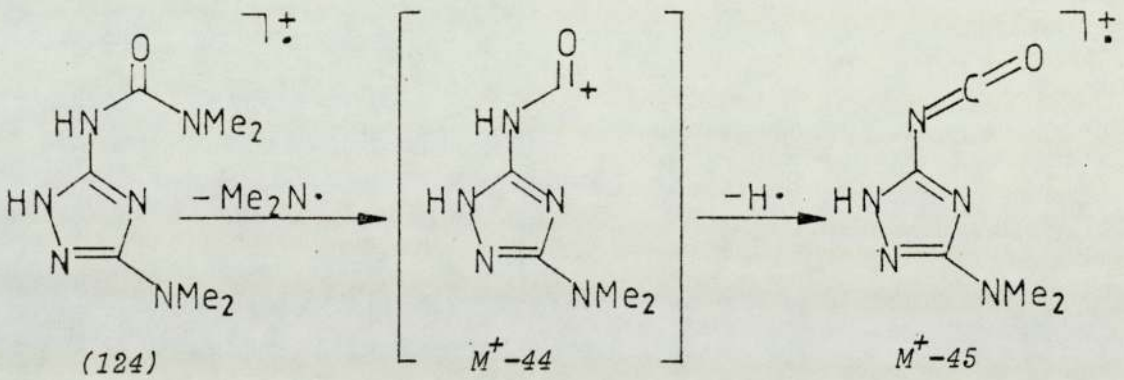
Scheme 25: Reaction Of The Oxadiazinium Salt (72) With Hydrazine To Produce Either A 1,2,4-triazole (124)(ANRORC) Or An N-amino-1,3,5-triazin-2-one (125) (ANRORC)

patterns should be very similar if structure (125) was the correct assignment.



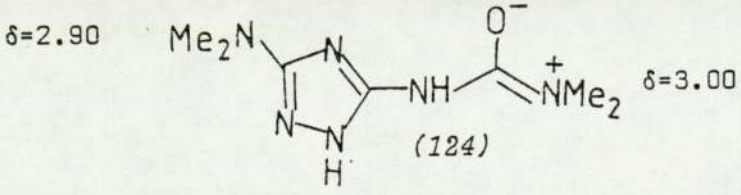
(125) m/z=182 (114)

The spectra were considerably different and the first observed daughter ion corresponds to the loss of dimethylamine:



(124) M^+-44 M^+-45

The i.r. spectrum for the triazole (124) displayed a characteristic C=O band (ν=1660cm^{-1}) and a complex N-H pattern (ν=3250-3100cm^{-1}). The ^{1}H n.m.r. spectrum determined in a mixture of deuterochloroform and hexadeutero-dimethylsuphoxide revealed the presence of two dimethylamino groups as two singlets (δ=2.90 and 3.00) which can be assigned on the basis that the dimethylamino substituent on the urea residue probably resonates at lower field due to its proximity to a carbonyl group which effectively deshields the dimethylamino protons by amidic resonance:



δ=2.90 δ=3.00

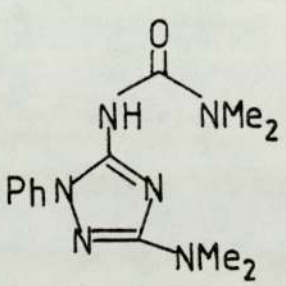
(124)

The two exchangeable protons could not be detected and are probably very broad.

An attempt to isolate an intermediate species in the reaction between the oxadiazinium salt (72) and hydrazine failed and the triazole (124) was isolated. Furthermore, the triazole (124) was found to be the only product formed whatever the molar ratios of reactants.

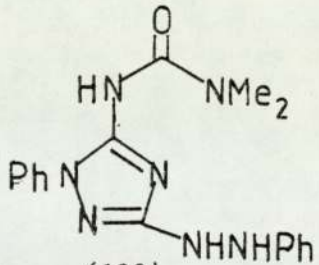
7.3.2 Phenylhydrazine

The reaction of the oxadiazinium salt (72) with phenylhydrazine gave only one product irrespective of the reaction conditions. It was immediately apparent, however, that the product obtained was not the expected N-phenyl homologue (128) of the triazole (124) which was obtained with hydrazine (Section 7.3.1).



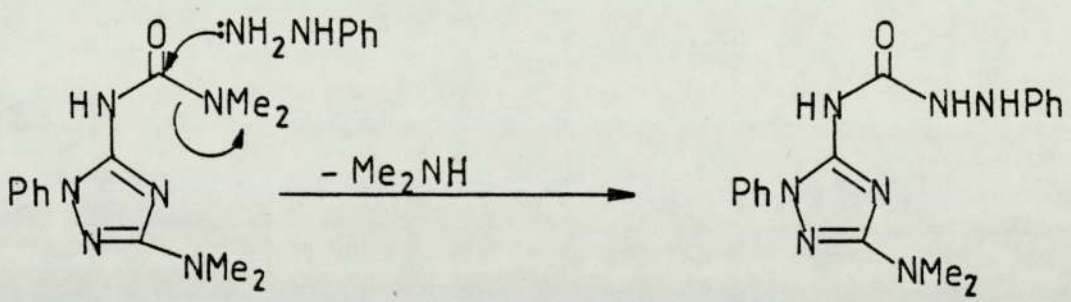
(128)

The product obtained was found to bear only one dimethylamino residue and invariably contained two phenylhydrazine residues. This reaction is analogous to the reaction of the oxadiazinium salt (72) with primary amines under rigorous basic or heterogeneous conditions to produce the triazin-2-ones (121) (Section 7.2.3) whereupon two equivalents of the primary amine were incorporated into the product (121). It was originally thought that the second phenylhydrazine moiety replaced the ring dimethylamino substituent to form the triazole (129) although it was found by X-ray crystallography that this structure (129) was incorrect (See Section 7.4).



(129)

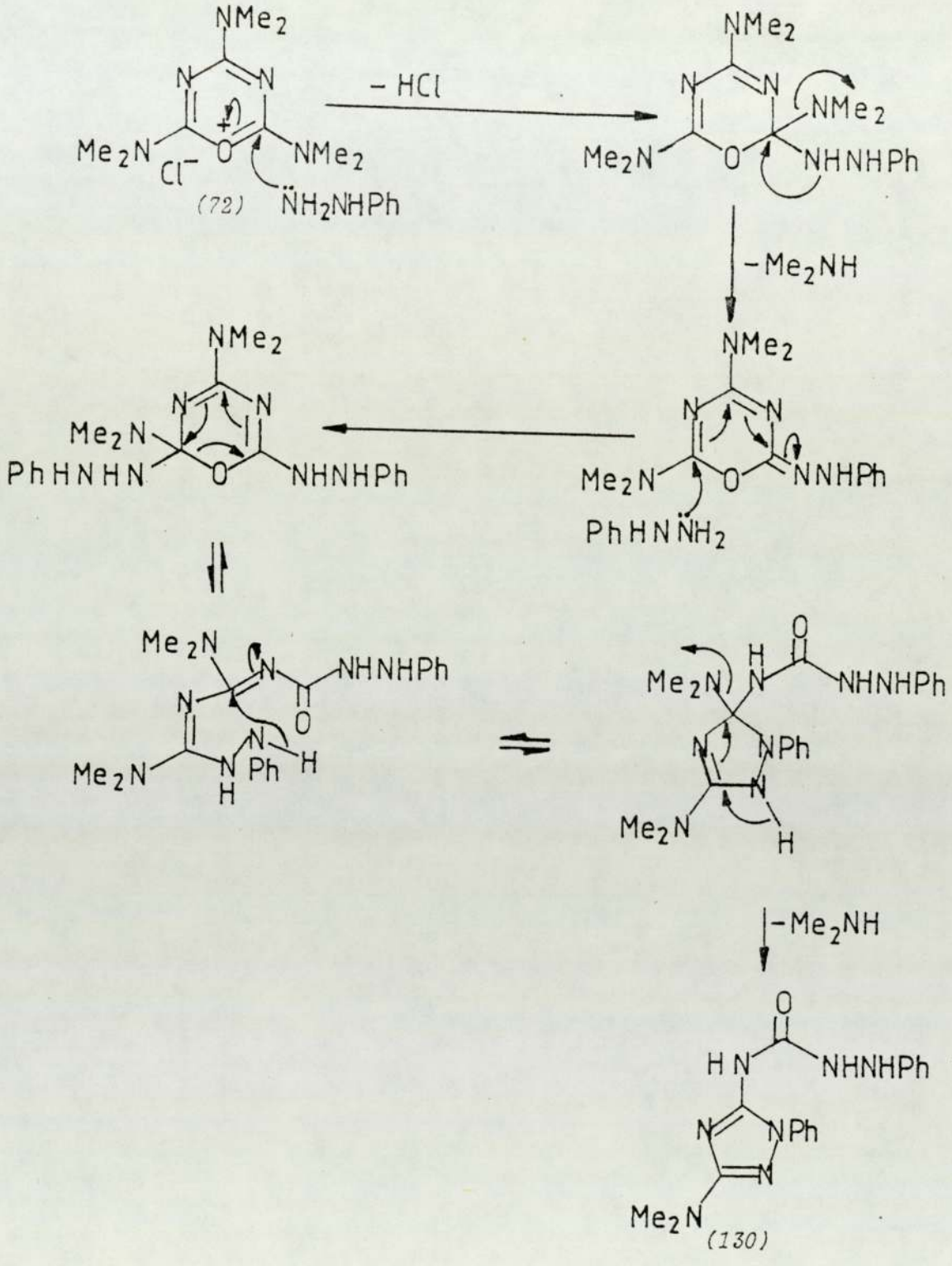
The actual product obtained was the triazole (130) which presents some interesting mechanistic arguments. It would be expected that if product (130) was formed from the triazole (128) by phenylhydrazine substitution of the urea residue, then under the mildest possible conditions either partial or no substitution of this type would be expected to occur and both products (128 and 130) ought to be isolable.



(128) *(130)*

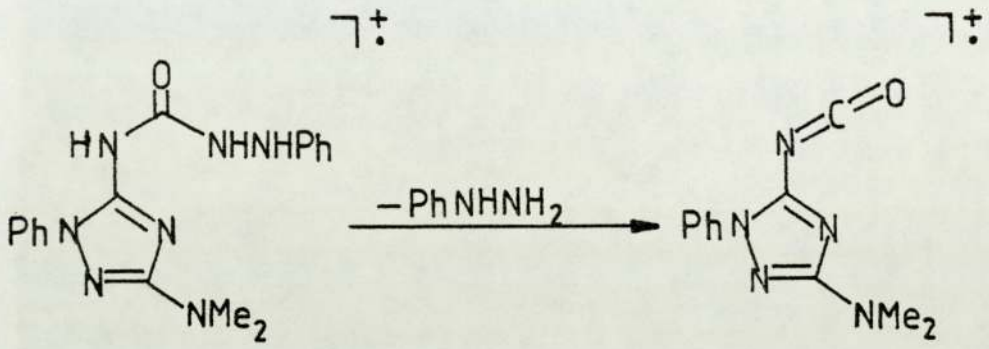
It was noticed, however, that the product invariably contained two phenylhydrazine residues. If the phenylhydrazine was in equimolar ratio with the oxadiazinium salt (72) then less than 50% yield of product was isolated. If the phenylhydrazine was in twofold or more excess then excellent yields of the triazole (130) were obtained. These observations would tend to suggest that the phenylhydrazine residue on the urea substituent is probably incorporated very early on in the reaction pathway and Scheme 26 is proposed to explain the ocurrence of the exclusively disubstituted triazole (130).

The i.r. spectrum of the triazole (130) contained a characteristic C=O band (ν=1680cm^{-1}) and an N-H band (ν=3200cm^{-1}). The ^{1}H n.m.r. spectrum obtained in deuterochloroform and hexadeuterodimethylsulphoxide revealed the presence of one dimethylamino group (δ=2.95), a complex aromatic multiplet



Scheme 26: Proposed Reaction Pathway For The Interaction Of The Oxadiazinium Salt (72) With Phenylhydrazine To Form The Triazole (130)

(δ=7.80-6.80) corresponding to the two phenyl residues and two N-H peaks (δ=8.80 and 9.20) corresponding to the hydrazo and N-H groups respectively. The mass spectrum showed the expected parent M^+ ion (m/z=337) which fragmented by loss of phenylhydrazine to give the daughter isocyanate (m/z=229):



(130) (m/z=337) *(m/z=229)*

7.4 X-Ray Crystal Structure Determination Of The Triazole (130)

7.4.1 Data Collection

Crystals of the triazole (130) were obtained from its solution in methanol containing a trace of ether as a granular mass of pale yellow crystals. A specimen of 0.92x0.40x0.28mm was selected and mounted on a glass fibre. The unit-cell dimensions were determined by least-squares analysis of setting-angles of 23 reflections on an Enraf-Nonius CAD-4 diffractometer using graphite monochromated MoK_α source. The data was collected by ω-2θ scans with a scan range in θ of $1.00+0.35\tan\theta^o$ at a scan rate of 0.7 - $3.3^o min^{-1}$ dependant upon the intensity. Two intensity standards were measured every two hours which remained constant over the data collection and the orientation of the crystal was checked every 200 reflections and no significant movement was observed. 3762 reflections were measured with $2 \leq \theta \leq 27^o$ of which 3735 were unique (R_{int}=0.074) and 2186 of these were classified as observed ($F>3\sigma$). Standard deviations were assigned on the basis of counting statistics and instrument instability and corrections were made for Lorentz-polarisation

but not for absorption. Molecular drawings of the molecule and its unit-cell were obtained with the PLUTO programme developed by Motherwell[75].

7.4.2 Solution Of Structure

The structure was solved by direct phasing with SHELX[76]. The initial least-squares refinement enabled all the non-hydrogen atoms to be located and revealed the triazole (130) skeleton. The hydrogen atoms were entered into their calculated positions (assuming minimal steric hindrance for methyl groups and trigonal geometry for phenyl protons) and the common temperature factor for the methyl groups was allowed to refine but not the positional parameters. The phenyl protons were refined on the assumption that they ride on their host carbon atoms. The hydrazo and amidic hydrogen atoms were selected from the most likely remaining peaks on a difference electron density map and then allowed to refine. In the final least-squares refinement the coordinates and anisotropic thermal parameters for all non-hydrogen atoms were adjusted together with the coordinates and isotropic temperature factors for the hydrazo and amidic protons. The common temperature factor for the methyl groups was refined together with the separate isotropic thermal parameters for the phenyl protons. The magnitudes of the observed factors (F_o) were weighted by:

$$w=1/[\sigma^2(F_o) + 0.000694F_o^2]$$

and the final discrepancy indices were R=0.067, R_w=0.074 for observed data and a goodness-of-fit ratio (S=0.93) was obtained. No peak on a final difference electron density map exceeded 0.27eÅ^{-3}.

7.4.3 Structural Features Observed For The Triazole (130)

The monoclinic crystals had unit-cell dimensions of $\underline{a}$=10.874(2)Å, $\underline{b}$=6.716(5)Å, $\underline{c}$=23.798(4)Å and β=95.88(2)°. The calculated unit-cell volume is

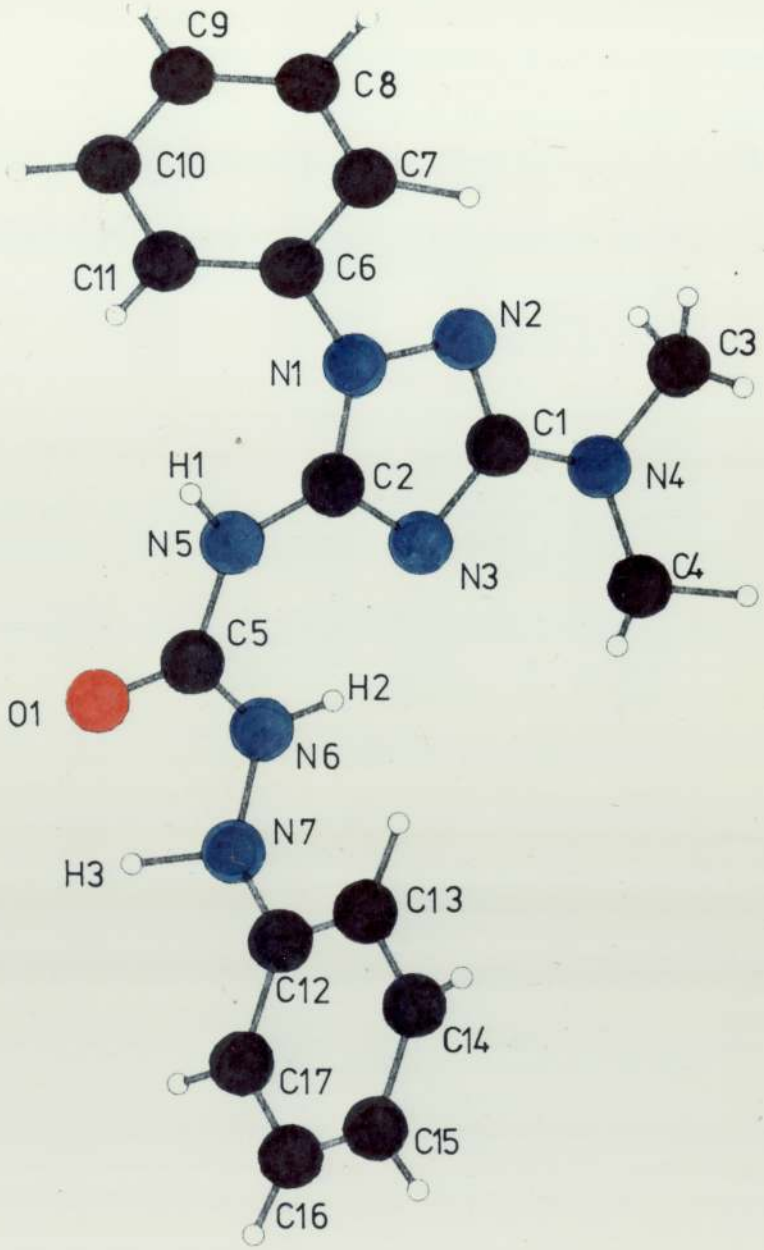


Plate 4: PLUTO Drawing Of 1-phenyl-4-(3'-dimethylamino-1'-phenyl-1',2',4'-triazol-5'-yl)semicarbazide (130) In Projection Onto Its Least-Squares Plane Showing The Atom Numbering Scheme

Table 11: Fractional Atomic Coordinates ($x10^4$) And Isotropic Temperature Factors ($Å^2 x10^3$, $x10^2$ For H) With Estimated Standard Deviations In Parentheses

$$U_{eq} = \frac{1}{3}(U_{11}+U_{22}+U_{33}+2U_{13}\cos\beta)$$

Atom	x	y	z	U_{eq}/U_{iso}
O1	2343(2)	2301(4)	2642(1)	50(1)
N1	5643(3)	5910(4)	3521(1)	48(2)
N2	6458(3)	5815(5)	4012(1)	61(2)
N3	5013(3)	3350(5)	3997(1)	57(2)
N4	6595(4)	3523(8)	4769(2)	104(3)
N5	3859(3)	4118(5)	3110(3)	49(2)
N6	3325(3)	1051(5)	3449(1)	51(2)
N7	2625(3)	-694(5)	3441(1)	52(2)
C1	6043(4)	4295(7)	4271(2)	65(2)
C2	4807(3)	4457(5)	3532(2)	46(2)
C3	7631(5)	4640(10)	5040(2)	101(4)
C4	6043(5)	2065(8)	5059(2)	94(4)
C5	3119(3)	2449(5)	3050(1)	41(2)
C6	5811(3)	7457(5)	3129(2)	45(2)
C7	5622(3)	7160(6)	2560(2)	57(2)
C8	5856(4)	8686(8)	2200(2)	72(3)
C9	6303(4)	10526(8)	2426(1)	76(3)
C10	6497(4)	10782(7)	2991(2)	73(3)
C11	6253(3)	9253(6)	3349(2)	61(2)

Table 11 *(continued)*

Atom	x	y	z	U_{eq}/U_{iso}
C12	1496(3)	-530(6)	3690(1)	55(2)
C13	709(4)	-2163(8)	3630(2)	72(3)
C14	-373(5)	-2152(11)	3892(2)	100(4)
C15	-662(5)	-562(14)	4209(2)	123(5)
C16	131(6)	1111(12)	4266(2)	115(5)
C17	1206(5)	1097(8)	4005(2)	78(3)
H1	3713(44)	5302(73)	2842(21)	93(15)
H2	3838(40)	1408(66)	3746(18)	75(13)
H3	2607(34)	-1617(62)	3031(17)	64(11)
H31	7716	4565	5414	171(13)
H32	8205	5131	4824	171(13)
H33	7173	5458	5195	171(13)
H41	6260	1030	5011	171(13)
H42	6066	2255	5464	171(13)
H43	5157	1896	5040	171(13)
H71	5287	5746	2391	52(10)
H81	5690	8494	1748	90(14)
H91	6500	11724	2146	84(13)
H101	6845	12188	3161	83(14)
H111	6400	9467	3801	122(20)
H131	936	-3435	3383	102(17)
H141	-991	-3413	3848	102(16)
H151	-1508	-556	4410	129(20)
H161	-88	2372	4520	84(14)
H171	1818	2368	4044	75(13)

Table 12: Bond Distances (Å) With Estimated Standard Deviations In Parentheses For All Non-Hydrogen Atoms

O1 - C5	1.224(4)	N4 - C4	1.371(6)	C8 - C9	1.414(7)
N1 - N2	1.395(4)	N5- C2	1.382(4)	C9 - C10	1.350(7)
N1 - C2	1.336(4)	N5 - C5	1.378(4)	C10 - C11	1.377(6)
N1 - C6	1.420(4)	N6 - C5	1.337(4)	C12 - C13	1.390(5)
N2 - C1	1.297(5)	N6 - N7	1.396(4)	C12 - C17	1.379(6)
N3 - C1	1.390(4)	N7 - C12	1.422(5)	C13 - C14	1.386(8)
N3 - C2	1.333(5)	C6 - C7	1.364(5)	C14 - C15	1.362(9)
N4 - C1	1.373(5)	C6 - C11	1.381(5)	C15 - C16	1.414(10)
N4 - C3	1.449(5)	C7 - C8	1.376(6)	C16 - C17	1.380(7)

Table 13: Bond Angles (°) With Estimated Standard Deviations In Parentheses For All Non-Hydrogen Atoms

N2-N1-C2	109.0(3)	N2-C1-N4	124.3(3)	C7-C8-C9	119.5(4)
N2-N1-C6	118.1(6)	N3-C1-N4	119.5(4)	C8-C9-C10	120.2(4)
C2-N1-C6	132.9(3)	N1-C2-N3	111.5(3)	C9-C10-C11	120.0(4)
N1-N2-C1	102.2(3)	N1-C2-N5	124.4(3)	C10-C11-C6	119.9(4)
C1-N3-C2	101.2(3)	N3-C2-N5	124.1(3)	N7-C12-C13	116.4(4)
C1-N4-C3	116.1(4)	O1-C5-N5	119.7(3)	N7-C12-C17	122.9(4)
C1-N4-C4	121.9(4)	O1-C5-N6	123.9(3)	C13-C12-C17	120.6(4)
C3-N4-C4	120.3(4)	N5-C5-N6	116.3(3)	C12-C13-C14	119.5(5)
C2-N5-C5	126.4(3)	N1-C6-C7	121.9(3)	C13-C14-C15	120.5(5)
C5-N6-N7	122.0(3)	N1-C6-C11	116.9(3)	C14-C15-C16	120.3(5)
N6-N7-C12	115.0(3)	C7-C6-C11	121.0(4)	C15-C16-C17	119.1(6)
N2-C1-N3	116.1(3)	C6-C7-C8	119.4(4)	C16-C17-C12	120.1(5)

1738.0Å^3 which gives rise to a calculated density of 1.29 Mgm^{-3} (m.w.=337.38). The molecule and its numbering scheme are illustrated in Plate 4. The atomic coordinates are shown in Table 11, the bond distances in Table 12 and the bond angles in Table 13. The whole of the molecule (130) is not planar but the phenyl substituent at N1 is twisted out of the plane of the triazole ring, together with the dimethylamino substituent at C1 to relieve steric crowding. The N-phenylsemicarbazido side-chain at C2 is interesting in that it appears to direct the terminal phenyl residue as far away as possible from the phenyl residue at N1. This is achieved by a cisoid geometry between the bonds connecting N3, C2, N5, C5, N6 and H2 and is facilitated by a hydrogen bond from H2 to N3 (1.880Å) to form a six-membered ring (Figure 8). The remainder of the side-chain adopts transoid geometry between the bonds connecting C5, N6, N7 and C12 and appears to be partially facilitated by a weak hydrogen bond from H3 to O1 (2.795Å) to form a five-membered ring (Figure 8). An examination of the relative bond lengths (Table 12) suggests that some delocalisation does exist and the extent is illustrated in Figure 9. Ultimately, the geometry of the various bonds leads to a very compact molecule as can be seen from the space-filling representation of the molecule (Plate 5) and it can be seen that the perimeter of the molecule has the lipophilic phenyl and dimethylamino groups exposed which probably explains the total lack of water-solubility of the triazole (130).

The hydrogen bonding is not limited to intramolecular bonds and it can be seen from the orientation of the molecules within the unit-cell (Plate 6) that the mode of stacking is facilated by symchemical intermolecular hydrogen bonding from O1 to H1 (2.523Å) (Figure 8) and the centre of symmetry occurs at the intersection of the lines bisecting the dimethylamino and carbonyl groups of adjacent molecules.

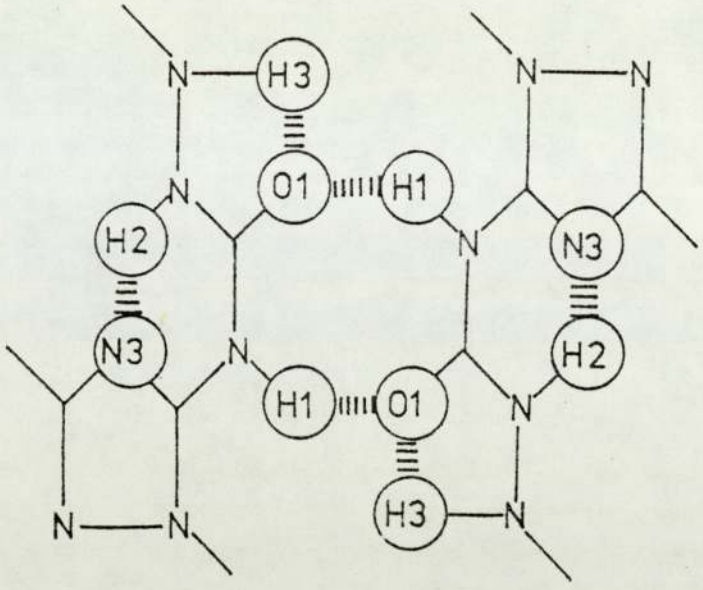


Figure 8: Intermolecular And Intramolecular Hydrogen Bonding In The Triazole (130)

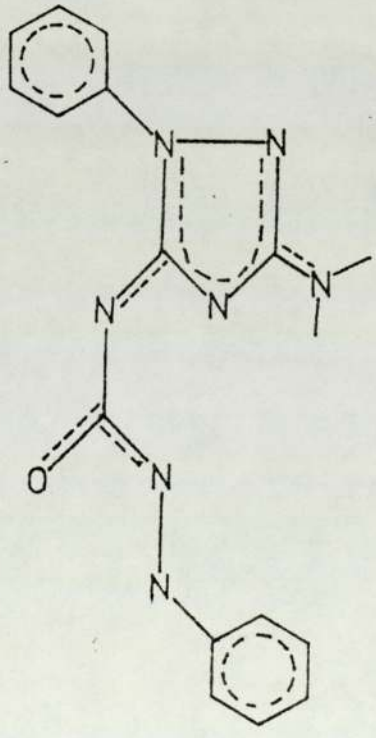


Figure 9: Delocalisation Within The Triazole (130)

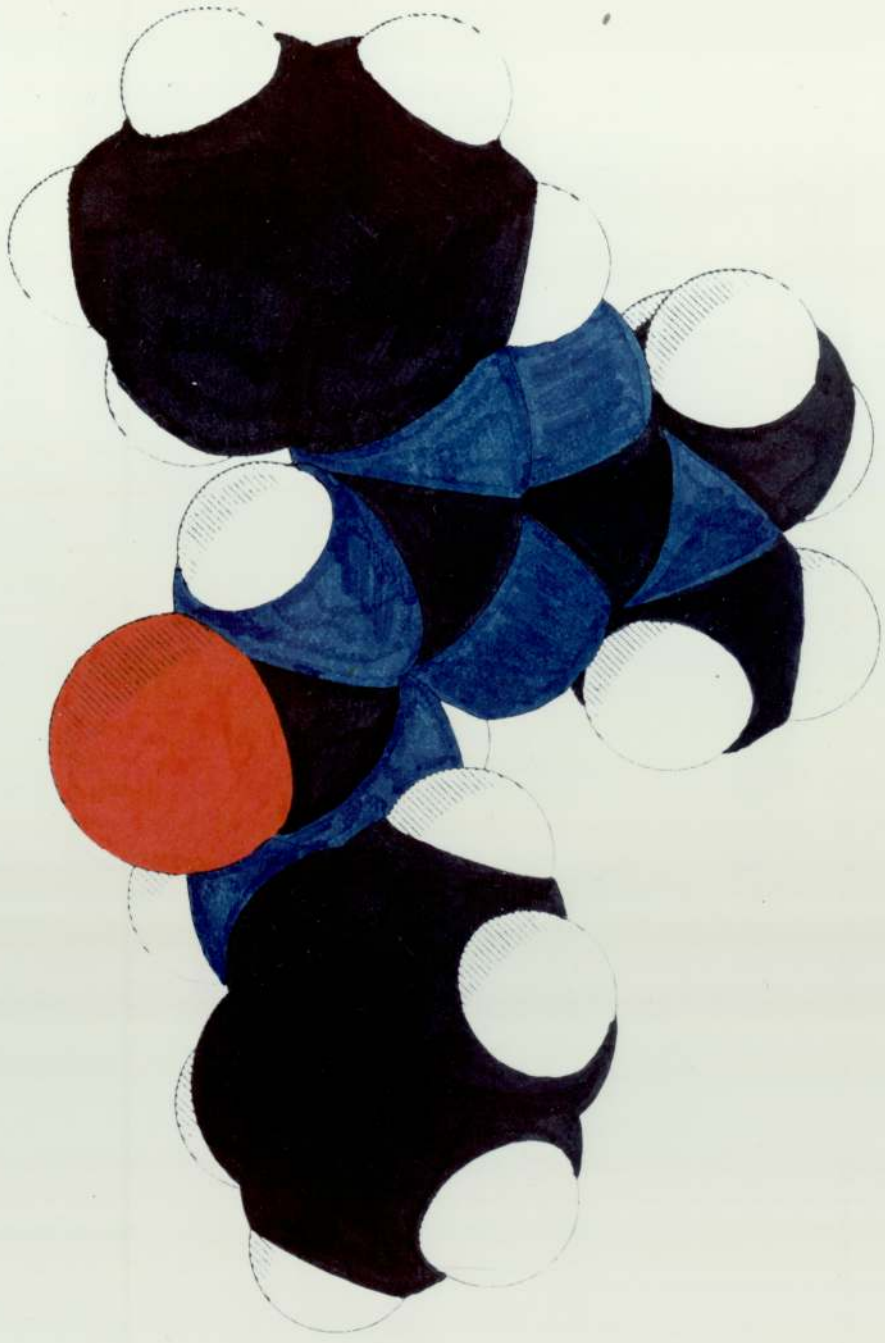


Plate 5: PLUTO Space-Filling Diagram Of 1-phenyl-4-(3'-dimethylamino-1'-phenyl-1',2',4'-triazol-5'-yl)semicarbazide (130)

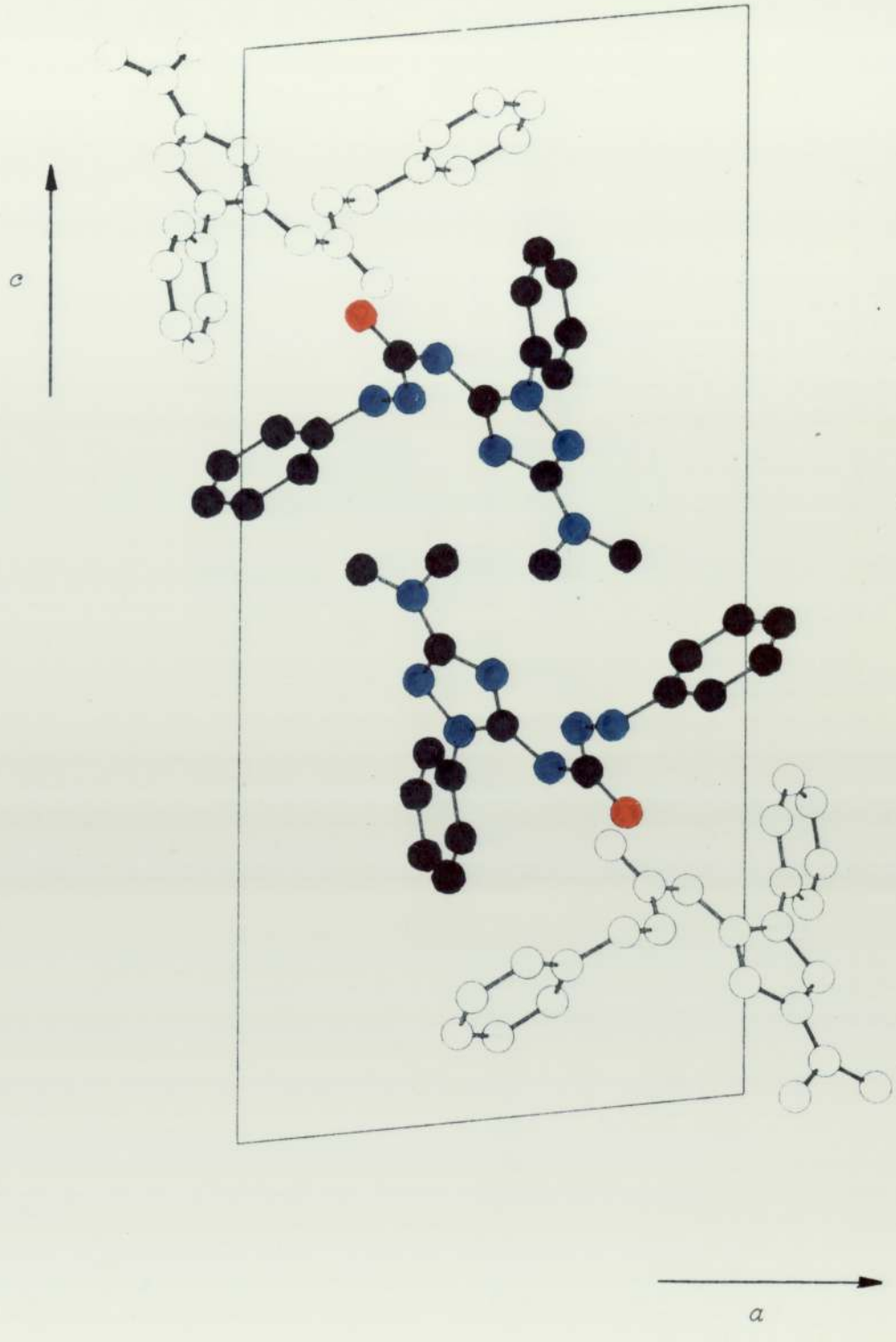
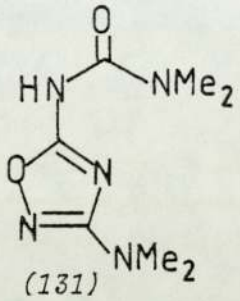


Plate 6: PLUTO Drawing Of The Unit-Cell Contents For 1-phenyl-4-(3'-dimethyl-amino-1'-phenyl-1',2',4'-triazol-5'-yl)semicarbazide (130) Viewed Along *b*

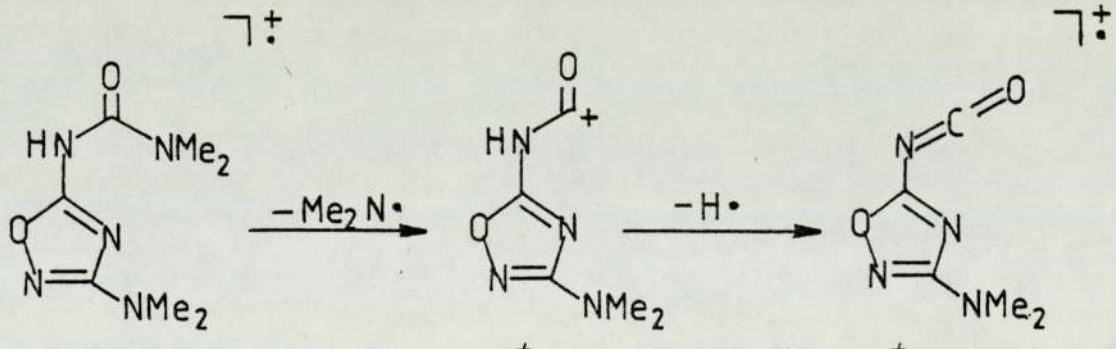
7.5 Reaction With Hydroxylamine

By analogous arguments to the reaction of the oxadiazinium salt (72) with hydrazine (Section 7.3.1) it is believed that the ring-contracted 1,2,4-oxadiazole (131) is formed from the oxadiazinium salt (72) when reacted with hydroxylamine.



(131)

The compound (131) displays characteristic C=O (ν=1660cm^{-1}) and N-H (ν=3400cm^{-1}) bands in the i.r. spectrum. The ^{1}H n.m.r. spectrum reveals the two dimethylamino groups (δ=3.00 and 3.15) attributable to the ring and urea dimethylamino groups respectively. The N-H group is not visible and is probably very broad. The mass spectrum gives the expected parent M^{+} ion (m/z=199) which loses dimethylamino and hydrogen radicals successively to form the daughter isocyanate (m/z=154):



(131) *M^{+}-44* *M^{+}-45*

7.6 Conclusion

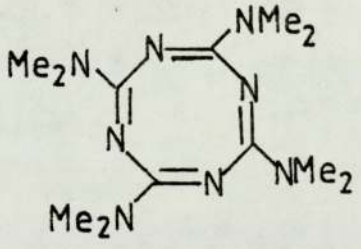
It appears that the oxadiazinium salt (72) behaves in a similar fashion to other known pyrylium systems (Chapter 6) in its initial reaction with nucleophiles although the products obtained are considerably different due to the excellent leaving-group properties of the dimethylamino group which appears to control the reaction pathways open to the various intermediate species.

8 HEXAMETHYLMELAMINE AND SOME OF ITS BICYCLIC MODIFICATIONS

8.1 Hexamethylmelamine

Although HMM (1) is the trimer of dimethylcyanamide (13), it was mentioned earlier (Section 2.1) that the thermally initiated trimerisation of dimethylcyanamide (13) appeared to be unknown.

In the investigation of the formation of the oxadiazinium salt (72) from dimethylcyanamide (13) and dimethylcarbamoyl chloride (71) it was noted that excessive heating of these two components led to respectable yields of HMM (1) plus a very small amount of another contaminant which may be the cyclic tetramer (132) of dimethylcyanamide (13):



(132)

This tetramer (132) has not been isolated although the mass spectrum of the pyrolysed oxadiazinium salt (72) shows a small peak (m/z=280) which could feasibly be assigned to this tetramer (132). Furthermore, there is no intermediate fragmentation between this ion (m/z=280) and that corresponding to HMM (1) (m/z=210). This would suggest that dimethylcyanamide (13) is readily lost from the tetramer (132) to form HMM (1).

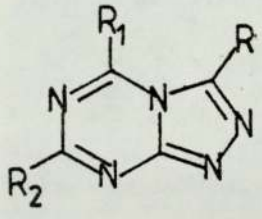
It was decided to investigate the thermal polymerisation of dimethylcyanamide (13) and it was found that heating the pure material (13) for several hours did not produce any detectable polymerisation products (t.l.c.). An attempt to catalyse the polymerisation with aluminium chloride at room temperature proceeded with explosive violence and the reaction was abandoned. It has been reported[96] that alkyl and aryl cyanides when treated with strong acids (e.g. triflic acid) readily trimerise and the corresponding 1,3,5-triazines have been isolated. Two attempts were made to trimerise

dimethylcyanamide (13) with trifluoroacetic acid but both resulted in severe explosions and were abandoned.

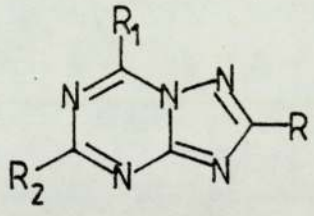
It appears that the formation of HMM (1) from the pyrolysis of the oxadiazinium salt (72) is an exceptional reaction which proceeds smoothly but not quantitatively and no further investigations on the thermal trimerisation of dimethylcyanamide (13) were conducted.

8.2 Triazolotriazines

The isomeric 1,2,4-triazolo[4,3-a]-1,3,5-triazine (133) and 1,2,4-triazolo[1,5-a]-1,3,5-triazine (134) systems have received much attention and various workers have devised routes to these compounds:



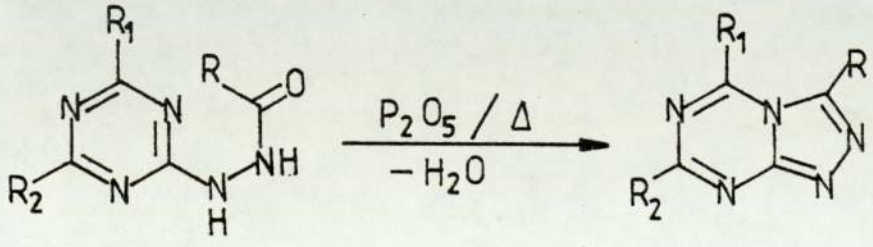
(133)



(134)

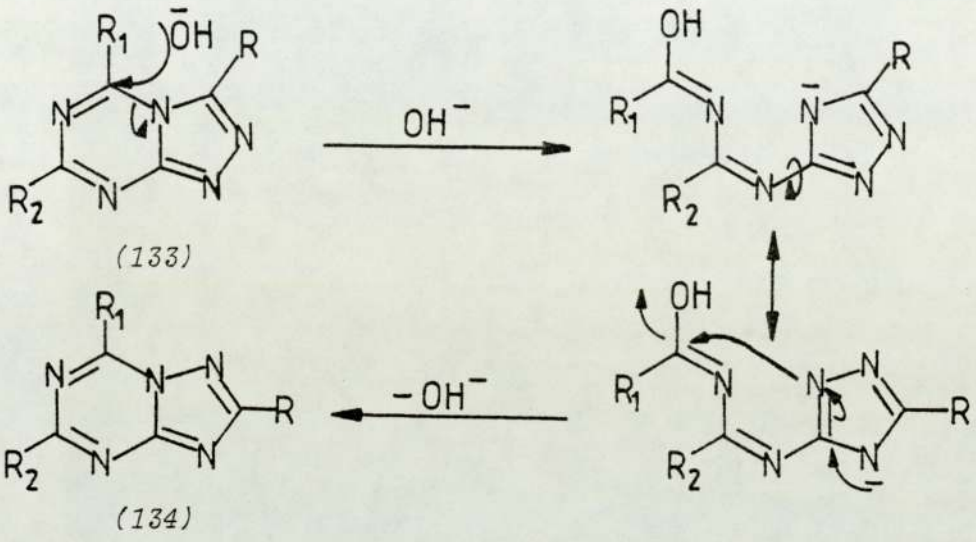
8.3 Synthetic Routes To Triazolotriazines

In general, the bicycles (133 and 134) are prepared from suitable triazines onto which the triazole fragment is fused. A popular route to the triazolotriazines (133) involved dehydration of acyltriazin-2-yl-hydrazides (135) with phosphorus pentoxide[97].



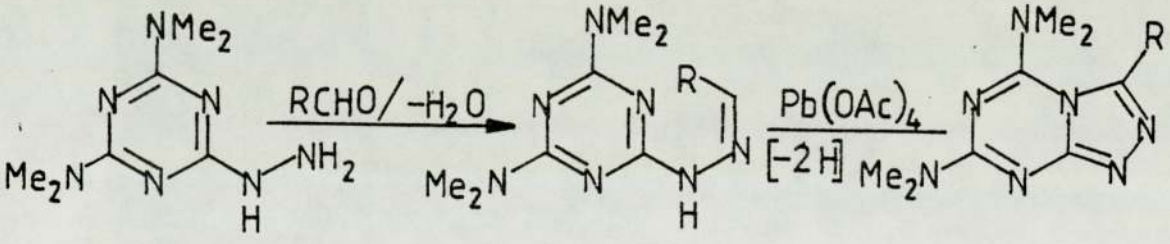
(135) *(133)*

The isomeric triazolotriazines (134) can be obtained from these triazolotriazines (133) upon treatment with base which causes a Dimroth-type[98] skeletal rearrangement:



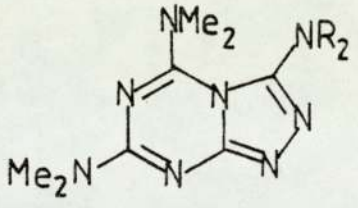
(133) *(134)*

More recently, Langdon *et al*[99] investigated the oxidation of various amidrazones (136) with lead tetraacetate to form the triazolotriazines (133; R_1=R_2=NMe_2). The amidrazones (136) themselves were readily obtained from the condensation of the hydrazinotriazine (39) with aldehydes:



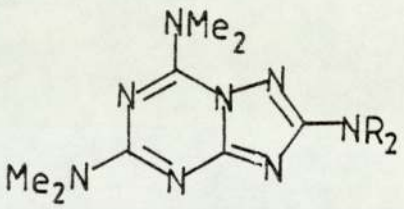
(39) *(136)* *(133; R_1=R_2=NMe_2)*

These methods work extremely effectively for reactions where the triazole substituent (R) is H, alkyl or aryl. The compounds of interest, however, were the triazolotriazines (137, 138, 139 and 140) where the triazole substituent is amino or dimethylamino which may possess similar antitumour properties to HMM (1).



R=H (137)

R=Me (139)



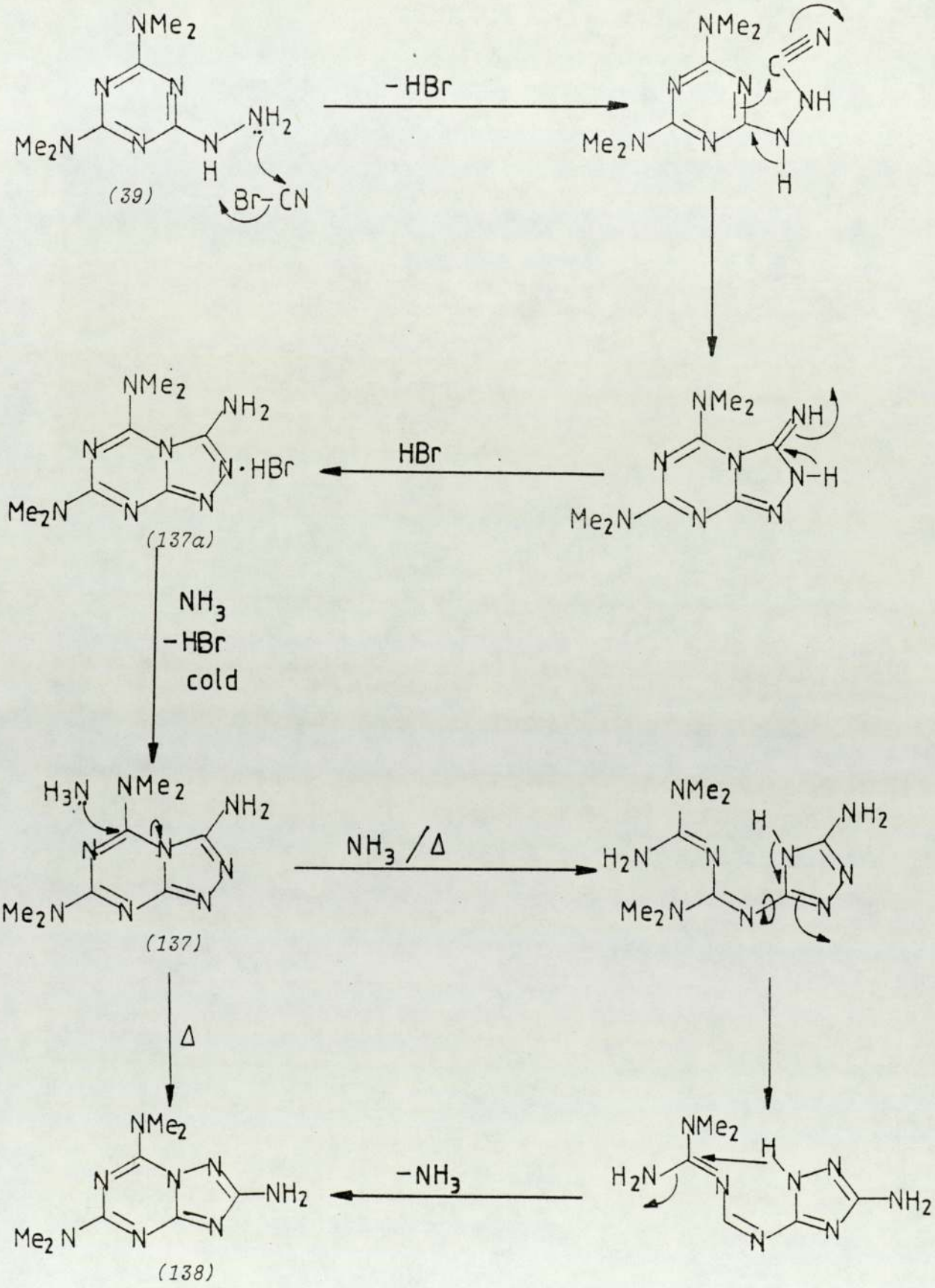
R=H (138)

R=Me (140)

It was not envisaged that these compounds (137, 138, 139 and 140) could be readily obtained by the above methods and alternative synthetic routes were devised.

8.4 Synthesis Of Aminotriazolotriazines (137 and 138)

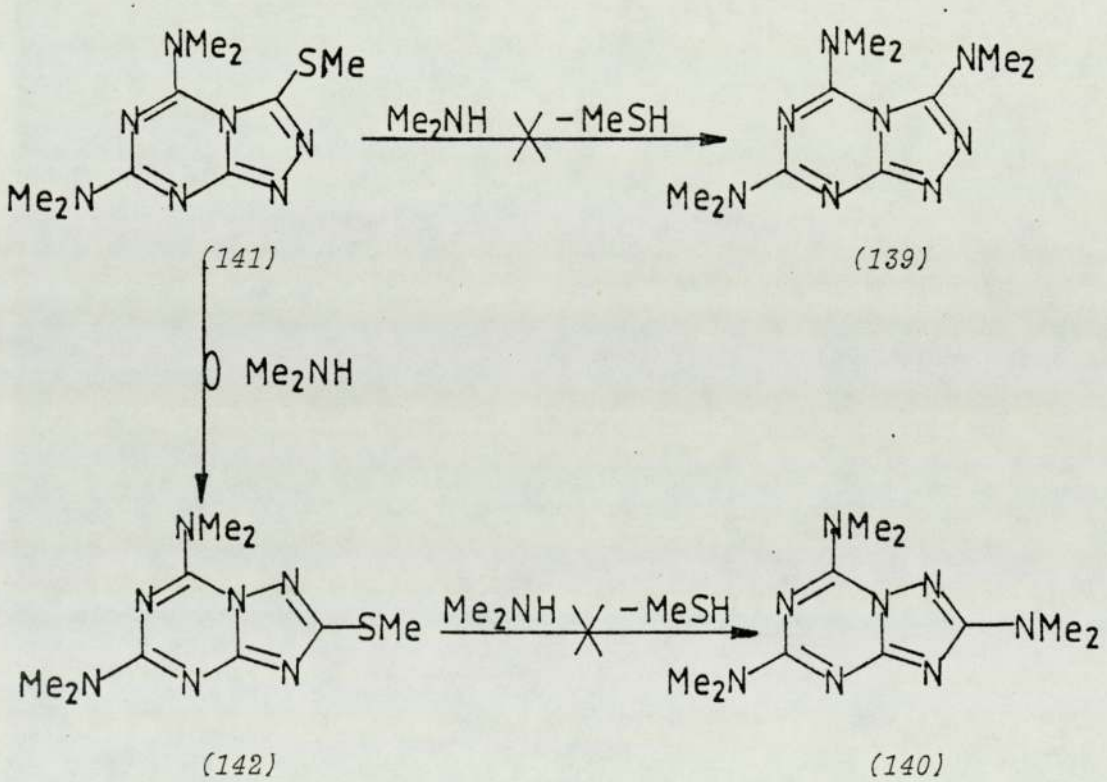
An interesting synthetic route to the aminotriazolotriazine (137), which was investigated, was the addition of cyanogen bromide to the hydrazinotriazine (39). The product obtained was found to be the hydrobromide salt (137a) of the triazolotriazine (137) and was in excellent yield (Scheme 27). The free base (137) was easily obtained from the salt (137a) by treatment with cold aqueous ammonia whereupon a yellow precipitate (137) was formed. The free base (137) was found to be poorly soluble in all common solvents but soluble in acidic media. When heated to its melting point, the free base (137) resolidifies and finally remelts at a higher temperature. This phenomenon is believed to be a thermally initiated Dimroth-type[98] rearrangement of the free base (137) to the isomeric aminotriazolotriazine (138). If an ammoniacal aqueous suspension of the aminotriazolotriazine (137) is heated to reflux, a transient intense red colour appears which when discharged leaves a white product which was found to be the isomeric aminotriazolotriazine (138) (Scheme 27).



Scheme 27: Possible Reaction Network For The Aminotriazolotriazines (137 and 138)

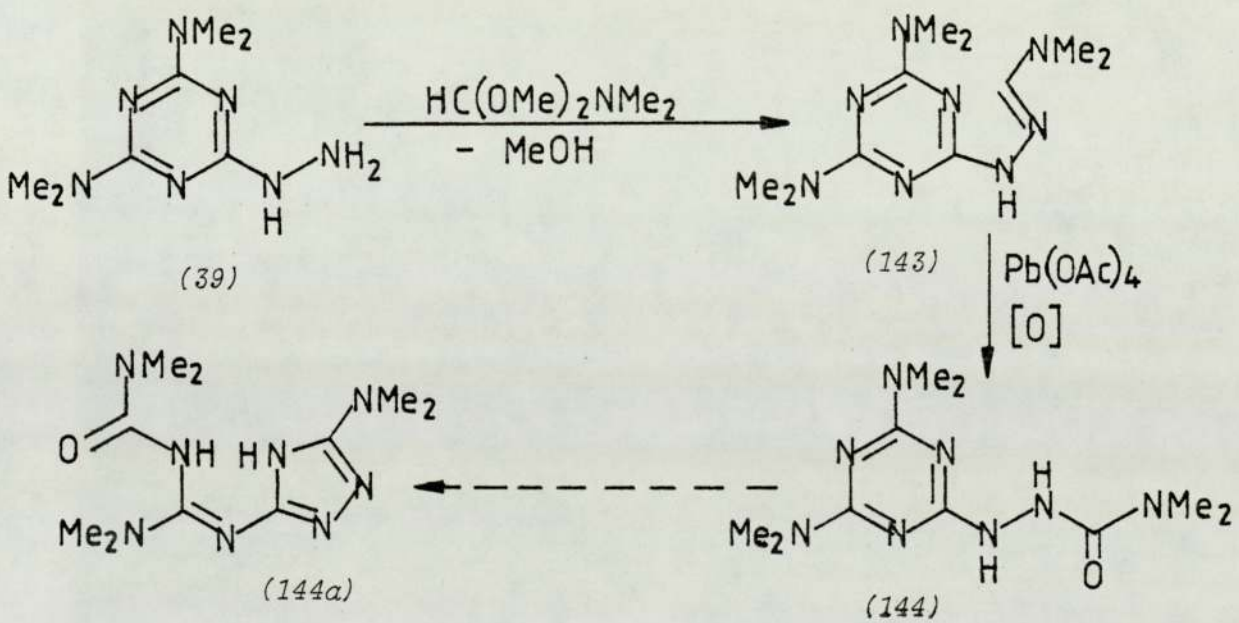
8.5 Dimethylaminotriazolotriazines (139 and 140)

Not surprisingly, workers in the search for insect chemosterilants have also sought the dimethylaminotriazolotriazines (139 and 140)[100]. They attempted to prepare the dimethylaminotriazolotriazine (139) by dimethylamine substitution of the S-methyltriazolotriazine (141). Instead of replacing the S-methyl group, the action of anhydrous dimethylamine upon the S-methyltriazolotriazine (141) effected its Dimroth-type[98] rearrangement to the isomeric S-methyltriazolotriazine (142) (Scheme 28).



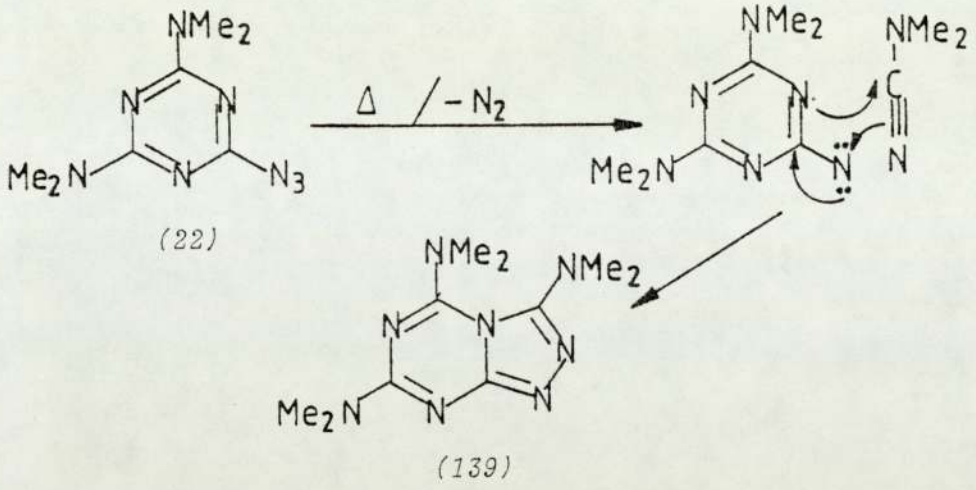
Scheme 28: Reactions Of The S-methyltriazolotriazines (141 and 142) With Anhydrous Dimethylamine

Langdon *et al*[99] investigated the possible oxidation of the amidrazone (143) (formed from the hydrazinotriazine (39) on condensation with dimethylformamide dimethylacetal) with lead tetraacetate but the small yield of product isolated appeared not to be the desired product (139). The oxidation product appeared to be some covalent hydrate of the dimethyltriazolotriazine (139) and displayed a characteristic C=O band in its i.r. spectrum together with an appropriate parent M^+ ion in its mass spectrum. The actual structure of this product is subject to conjecture but structures (144 and 144a) are reasonable candidates:



It was decided to investigate the insertion of the thermally generated nitrene (145) from the azidotriazine (22) into dimethylcyanamide (13) which may produce the desired dimethylaminotriazolotriazine (139) (Scheme 29). The product isolated, however, from the reaction mixture appeared to be the unreacted azidotriazine (22).

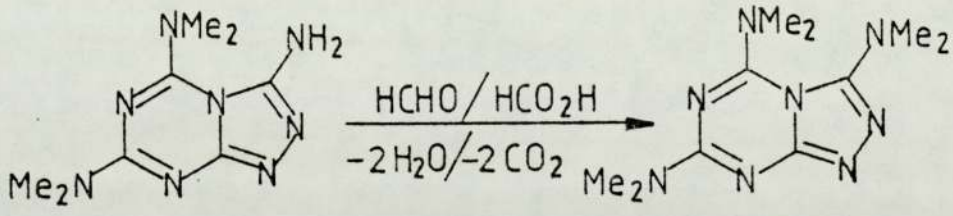
An alternative route to the dimethylaminotriazolotriazines (139 and 140) which was considered was an Eshweiler-Clark[101] methylation of the aminotriazolotriazines (137 and 138) with formic acid and formaldehyde. An attempt to convert the aminotriazolotriazine (137) into the dimethylaminotriazolo-



(22) (139)

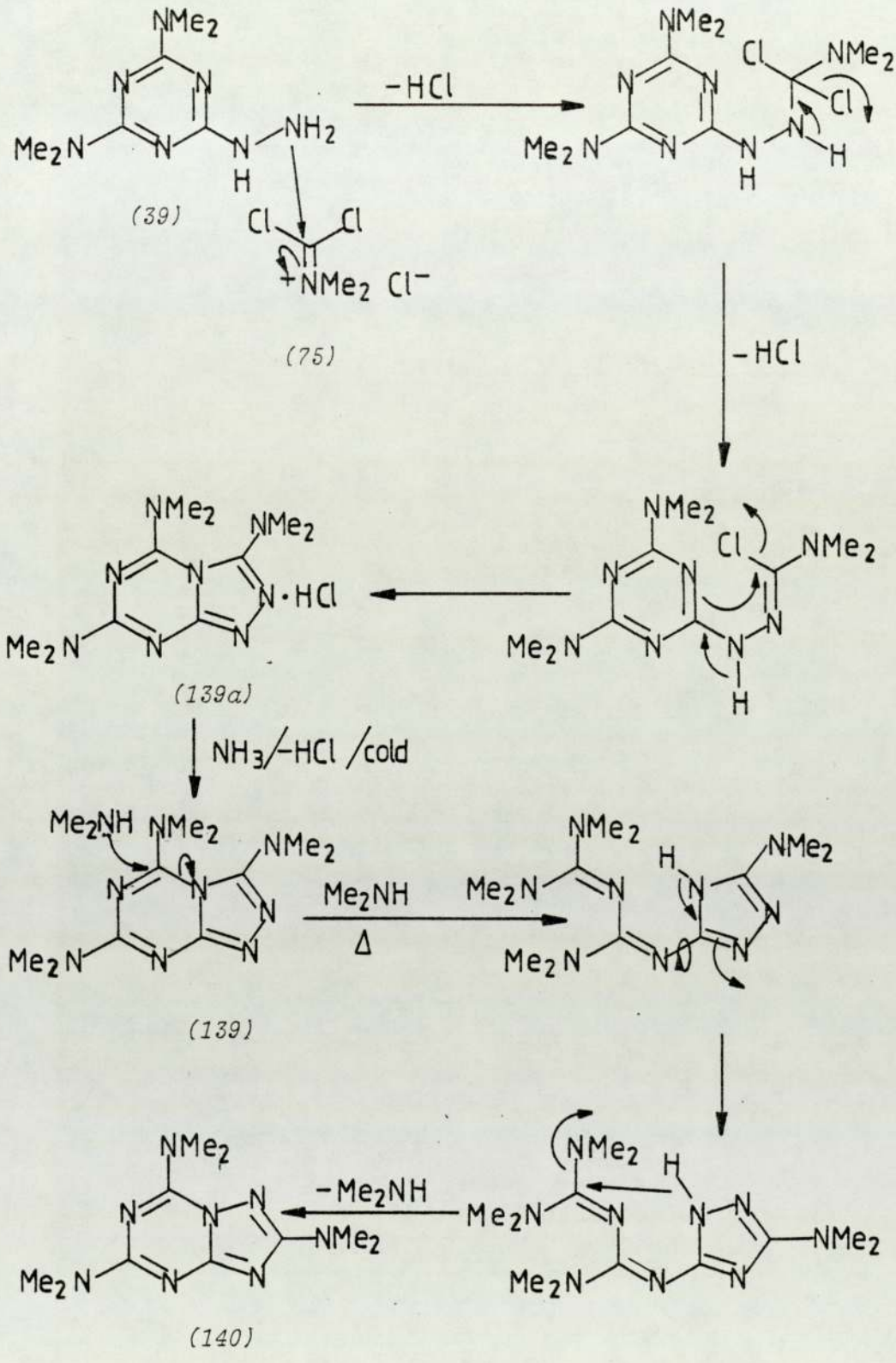
Scheme 29: Theoretical Formation Of The Dimethylaminotriazolotriazine (139) From The Azidotriazine (22)

triazine (139) failed and the reaction mixture charred:



(137) (139)

Phosgeneiminium chloride [dichloromethylenedimethyliminium chloride] (75) is an extremely reactive electrophile and is in the correct oxidation state to form the dimethylaminotriazolotriazine (139) with the hydrazinotriazine (39). The reaction was investigated and was found to work moderately efficiently in anhydrous chlorobenzene to produce the hydrochloride salt (139a) of the desired dimethylaminotriazolotriazine (139) in modest yields. The reaction proceeds with the formation of an extremely intense transient yellow colour which becomes an orange colour as the reaction reaches completion. The putative reaction pathway is illustrated in Scheme 30. Basification of the salt (139a) with cold aqueous ammonia yielded the free base (139). If the dimethylaminotriazolotriazine (139) is heated to reflux in aqueous dimethylamine, the product undergoes the expected Dimroth-type[98] rearrangement to the

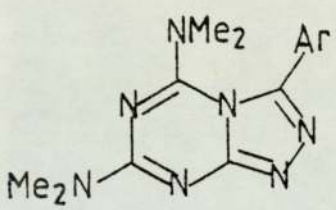


Scheme 30: Possible Reaction Network For The Dimethylaminotriazolotriazines (139 and 140)

isomeric dimethylaminotriazolotriazine (140) (Scheme 30).

Comparison of the ^1H n.m.r. spectra for the aryl substituted triazolotriazines (133; R=aryl; $R_1=R_2=NMe_2$ and 134; R=aryl; $R_1=R_2=NMe_2$) with the dimethylaminotriazolotriazines (139 and 140) would suggest that the following assignments (δ) are probable:

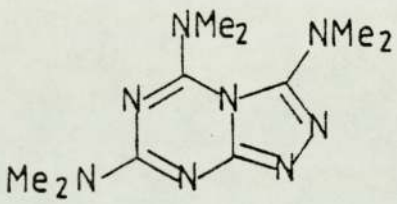
δ=2.55-2.73



δ=3.17-3.20

(133; R=aryl; $R_1=R_2=NMe_2$)

δ=3.00

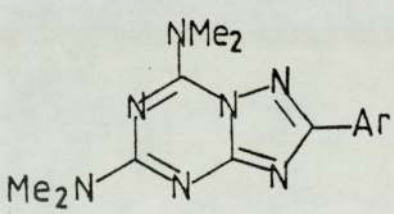


δ=3.30

δ=3.25

(139)

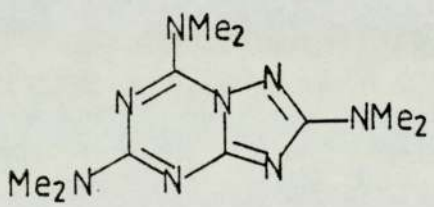
δ=3.43-3.55



δ=3.20

(134; R=aryl; $R_1=R_2=NMe_2$)

δ=3.45



δ=3.20

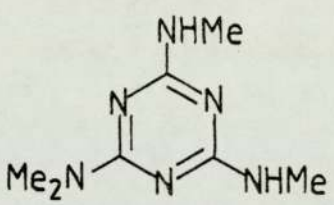
δ=3.10

(140)

9 PHARMACOLOGICAL PROPERTIES OF COMPOUNDS BEARING N-METHYL GROUPS

9.1 Comparative *In Vitro* N-demethylation

The results for the *in vitro* N-demethylation test described earlier (Section 1.3) for various melamines and related compounds are illustrated in Figure 10 and Table 14. It can be seen that the compounds which N-demethylate the most efficiently also have antitumour properties with the exception of the 2-chlorotriazine (15) which actually N-demethylates more efficiently than HMM (1) *in vitro* but has no *in vivo* antitumour activity. Furthermore, it can be seen that the symmetrical tetramethylmelamine (*s*-TMM) (21) demethylates nearly twice as efficiently as its asymmetric isomer (*as*-TMM) (145), *in vitro*.



(145)

9.2 *In Vivo* Antitumour Properties Of Water-Souble Congeners Of Hexamethylmelamine

Table 15 summarises the compounds and antitumour properties which have been examined so far against the P 388 leukaemia. It can be seen that all of the compounds are inactive and in many cases rather toxic. The oxadiazinium salt (72) was also screened against the M 5076 reticulum cell sarcoma and was found to have comparable inactivity and toxicity. Surprisingly, the hexamethylethyl salt (45) is even more toxic than the heptamethyl salt (29) even though it would be predicted to have less cholinergic activity due to the larger ethyl group present. All of the oxadiazines (116) obtained from the oxadiazinium salt (72) and primary amines had no apparent antitumour activity and were fairly toxic materials.

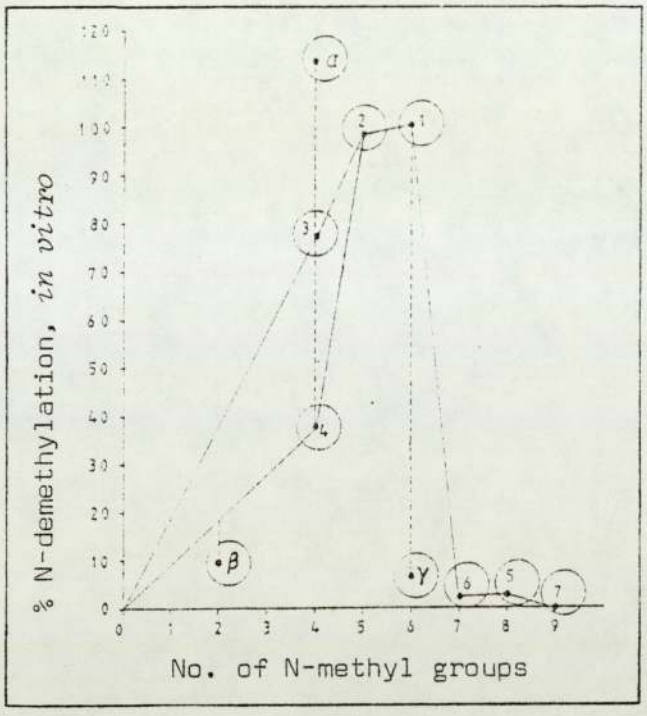


Figure 10: Graph Illustrating The Relative % N-demethylation Of Poly-N-methylmelamines And Related Compounds, *In Vitro*, As A Function Of The Number Of N-methyl Groups Present In The Compound

Table 14: % N-demethylation For Poly-N-methylmelamines And Related Compounds, *In Vitro*

Compound		Graph Point[a]	% N-demethylation[b]
2-chlorotriazine	(15)	α	113.2
HMM	(1)	1	100.0
PMM	(3)	2	98.0
s-TMM	(21)	3	77.0
as-TMM	(145)	4	37.5
dimethylcyanamide	(13)	β	9.5
oxadiazinium salt	(72)	γ	6.5
octamethyl salt	(51)	5	2.6
heptamethyl salt	(29)	6	2.0
nonamethyl salt	(52)	7	0

a Figure 10 b HMM=100%

Table 15: *In Vivo*, Antitumour Activity For Water-Soluble Congeners Of Hexamethylmelamine Against The P 388 Leukaemia

Compound	Dose[a]	T/Cx100%[b]	Comments
heptamethyl salt (29)	200.00	TOX	Toxic
	100.00	TOX	
	50.00	TOX	
	25.00	111	Inactive
	12.00	108	
	6.00	99	
hexamethylethyl salt (45)	200.00	TOX	Toxic
	100.00	TOX	
	50.00	TOX	
	25.00	TOX	
	12.00	TOX	
	6.00	108	Inactive
oxadiazinium salt (72)	200.00	TOX	Toxic
	100.00	TOX	
	50.00	TOX	
	25.00	113	Inactive
	12.50	103	
	6.25	106	
ethyloxadiazine	200.00	TOX	Toxic
(116; R=Et-)	100.00	96	Inactive
	50.00	96	
propyloxadiazine	200.00	TOX	Toxic
(116; R=$CH_3(CH_2)_2$-)	100.00	95	Inactive
	50.00	102	

Table 15 *(continued)*

Compound	Dose[a]	T/Cx100%[b]	Comments
butyloxadiazine	200.00	95	Inactive
(116; R=$CH_3(CH_2)_3$-)	100.00	89	
	50.00	88	
t-butyloxadiazine	200.00	TOX	Toxic
(116; R=$(CH_3)_3C$-)	100.00	104	Inactive
	50.00	100	
	25.00	100	
cyclohexyloxadiazine	200.00	TOX	Toxic
(116; R=cyclo-C_6H_{11}-)	100.00	100	Inactive
	50.00	96	
	25.00	105	
benzyloxadiazine	200.00	TOX	Toxic
(116; R=$PhCH_2$-)	100.00	TOX	Inactive
	50.00	96	Inactive
	25.00	107	
2-phenylethyloxadiazine	200.00	TOX	Toxic
(116; R=$PhCH_2CH_2$-)	100.00	100	Inactive
	50.00	107	
	25.00	100	

a mg kg^{-1} day^{-1} for first 5 days

b survival time of treated/survival time of untreatedx100%

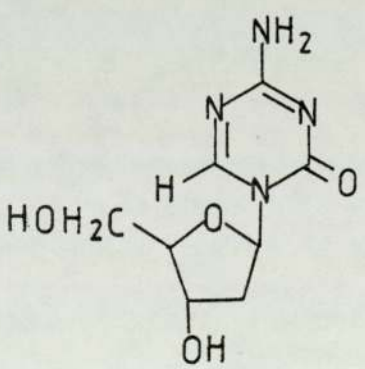
$\sim$125 for antitumour activity

<<100=TOX

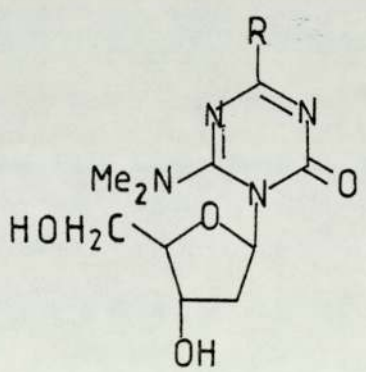
9.3 Epilogue

None of the triazin-2-ones (120 and 121) nor the amino (137 and 138) or dimethylamino (139 and 140) triazolotriazines have been screened for antitumour properties yet.

Interestingly, another known antitumour agent - 5-aza-2'-deoxycytidine (146)[102], which is extremely expensive and difficult to prepare, has a similar heterocyclic nucleus to the triazin-2-ones (120 and 121). Furthermore, 5-aza-2'-deoxycytidine (146) is not stable in acid solution whereas the triazin-2-ones (120 and 121) are. If the triazin-2-ones (120 and 121) where R=alkyl or aryl were found to be devoid of antitumour properties, it would probably be worthwhile preparing suitable analogues (147 and 148) where R=sugar residue. The synthesis of these analogues could be readily accomplished by reaction of the oxadiazinium salt (72) with an appropriate aminosugar. These analogues (147 and 148) would be much closer relatives of 5-aza-2'-deoxycytidine (146) and may bear the desirable oncological properties. This is speculation but it provides a future for the work undertaken and described within this thesis.



(146)



R=NMe$_2$ *(147)*

R=2-deoxyribofuranosamino- *(148)*

EXPERIMENTAL

10 EXPERIMENTAL

10.1 Notes On Instrumentation And Compound Analysis

1. All melting points are reported uncorrected.

2. Infra-red spectra were recorded on a Pye-Unicam SP200 spectrophotometer and, unless otherwise stated, as KBr discs.

3. Ultra-violet spectra were recorded on a Pye-Unicam SP8000 spectrophotometer.

4. ^{1}H n.m.r. (60MHz) spectra were recorded on a Varian EM360A spectrometer in suitable solvents using tetramethylsilane as an internal standard. The signals were assigned in δ ppm downfield from tetramethylsilane.

5. ^{1}H n.m.r. (220MHz) and ^{13}C n.m.r. spectra were conducted by Physico-Chemical Measurements Unit, Harwell in suitable solvents using tetramethylsilane as an internal standard.

6. Mass spectra were recorded on a Micromass 128 single-focussing mass spectrometer.

7. Elemental analyses were carried out at Elemental Microanalyses Limited and in the Department Of Chemistry, University Of Aston.

8. X-ray crystallography was conducted on an Enraf-Nonius four-circle CAD 4 diffractometer.

9. Ethanol refers to 95% ethanol and petrol refers to the petroleum fraction with the boiling range 60-80^{o}C.

10.2 Preparation Of Known Compounds

The following compounds were synthesised using similar methods to those published and all compounds were confirmed by i.r., ^{1}H n.m.r. and mass spectroscopy:

2-chloro-4,6-bis(dimethylamino)-1,3,5-triazine (15) m.p. 69^{o}C (lit.[45,46], m.p. 66-68^{o}C)

2,4-dichloro-6-dimethylamino-1,3,5-triazine (14) m.p. 121°C (lit.[45,46], m.p. 122.5-123.5)

2-azido-4,6-bis(dimethylamino)-1,3,5-triazine (22) m.p. 106°C (lit.[46], m.p. 104-106°C)

2-hydrazino-4,6-bis(dimethylamino)-1,3,5-triazine (39) m.p. 149°C (lit.[32], 148.5-152.5°C)

N-[4,6-bis(dimethylamino)-1,3,5-triazin-2-yl]trimethylammonium chloride (29) m.p. 169°C (lit.[49], m.p. 168-170°C)

4,6-bis(dimethylamino)-1,3,5-triazin-2-one (114) m.p. 292°C (lit.[32], m.p. 292°C)

10.3 Synthesis Of Quaternary Ammonium Salts Related To Hexamethylmelamine

10.3.1 Monocationic Salts

2-chloro-4,6-bis(dimethylamino)-1,3,5-triazine (15) (3.00g; 15mmol) was dissolved in dry ether (30ml) and the requisite tertiary amine (30mmol) was added. After allowing the solution to stand at ambient temperature (in some cases the solution was then heated to reflux and allowed to cool) the product which precipitated out was filtered off, washed well with dry ether and dried at ambient temperature *in vacuo* (See Table 2).

N-[4,6-bis(dimethylamino)-1,3,5-triazin-2-yl]ethyldimethylammonium chloride (45) was obtained from ethyldimethylamine as a white deliquescent solid (40%) m.p. 119°C with decomposition; ν_{max} = 1620, 1420, 820 cm^{-1}; $\delta(CDCl_3)$ 1.5 (3 H, $CH_2C\underline{H}_3$), 2.9 (12 H, *s*, N-C$\underline{H}_3$), 3.5 (6 H, *s*, $\overset{+}{N}$-C$\underline{H}_3$), 3.7 (2 H, *q*, $\overset{+}{N}$-C$\underline{H}_2CH_3$); m/ 224 and 210. Found C, 48.0; H, 8.50; N, 30.5. Calculated for $C_{11}H_{23}N_6Cl$

C, 48.1; H, 8.4; N, 30.6.

N-[4,6-bis(dimethylamino)-1,3,5-triazin-2-yl]methylmorpholinium chloride (49) was obtained from methylmorpholine as a white deliquescent solid (20%) m.p. ~103°C; ν_{max} = 1640, 1420, 820 cm^{-1}; δ($CDCl_3$) 3.3 (12 H, *s*, N-C$\underline{H}_3$), 3.7 (3 H, *s*, $\overset{+}{N}$-C$\underline{H}_3$), 4.0 (8 H, *dxq*, $\overset{+}{N}$-C$\underline{H}_2$C$\underline{H}_2$-O). Material was too deliquescent to be subjected to mass spectroscopy and elemental analysis.

Attempts To Prepare N-[4,6-bis(dimethylamino)-1,3,5-triazin-2-yl]diethylmethylammonium chloride (46)

1. 2-chloro-4,6-bis(dimethylamino)-1,3,5-triazine (15) (3.00g; 15mmol) was heated to reflux in diethylmethylamine (10ml) for 24 hours. Dry ether (50ml) was added to the cool solution but no precipitation occurred. The solution was concentrated under reduced pressure to dryness and the residue was shown to be the unreacted 2-chloro-4,6-bis(dimethylamino)-1,3,5-triazine (15).

2. 2-chloro-4,6-bis(dimethylamino]-1,3,5-triazine (15) (3.00g; 15mmol) and diethylmethylamine (30ml) were heated in a sealed Curtius tube for 24 hours at 150-200°C in a sand bath. The mixture was triturated with a little dry acetone and ether. The solid was found to be predominantly the unreacted 2-chloro-4,6-bis(dimethylamino)-1,3,5-triazine (15).

Attempts To Prepare N-[4,6-bis(dimethylamino]-1,3,5-triazin-2-yl]triethylammonium chloride (47]

1. 2-chloro-4,6-bis(dimethylamino)-1,3,5-triazine (15) (3.00g; 15mmol) and triethylamine (3.00g; 30mmol) were heated to reflux in dry THF (30ml) for 2 days. On cooling, minimal product crystallised out.

2. As in 1 using dry toluene (30ml). On cooling, minimal product crystallised out.

3. As in 1 using dry DMF (30ml). On cooling and addition of excess dry ether minimal product crystallised out.

4. As in 1 using dry acetonitrile (30ml). On cooling and addition of excess dry ether minimal product crystallised out.

5. 2-chloro-4,6-bis(dimethylamino)-1,3,5-triazine (15) (3.00g; 15mmol) was heated to reflux in dry triethylamine (30ml) for 24 hours. On cooling and addition of excess dry ether, minimal crystallisation occurred.

6. N-[4,6-bis(dimethylamino)-1,3,5-triazin-2-yl]trimethylammonium chloride (29) (5.20g; 20mmol) was heated to reflux in triethylamine (50ml) for 4 hours. The cooled suspension was filtered and the solid was shown to be the unreacted N-[4,6-bis(dimethylamino)-1,3,5-triazin-2-yl]trimethylammonium chloride (29). The filtrate was concentrated under reduced pressure to dryness and the residue was shown to be hexamethylmelamine (1).

10.3.2 Polycationic Salts

N,N'-(6-dimethylamino-1,3,5-triazin-2,4-yl)bis(trimethylammonium Dichloride (51)

2,4-dichloro-6-dimethylamino-1,3,5-triazine (14) (1.95g; 10mmol) was dissolved in dry ether (50ml) and excess trimethylamine was added. After allowing the solution to stand at 0°C for 1 day, the product was filtered off, washed well with dry ether and dried at ambient temperature *in vacuo*. N,N'-(6-dimethylamino-1,3,5-triazin-2,4-yl)bis(trimethylammonium) dichloride (51) was obtained as a white, extremely deliquescent solid (90%) and its melting point could not be determined; ν_{max} = 1620, 1390, 830 cm^{-1}; $\delta(CDCl_3)$ 3.2 (6 H, *s*, N-C$\underline{H}_3$), 3.8 (18 H, *s*, $\overset{+}{N}$-C$\underline{H}_3$). Material was too deliquescent to be subjected to mass spectroscopy and elemental analysis.

N,N',N"-1,3,5-triazin-2,4,6-yl-tris(trimethylammonium) Trichloride (52)

Cyanuric chloride (12) (1.85g; 10mmol) was dissolved in dry ether (50ml) and excess trimethylamine was added. After allowing the solution to stand at ambient temperature for 1 hour, the product was filtered off, washed well with dry ether and dried at ambient temperature *in vacuo*. N,N',N"-1,3,5-triazin-2,4,6-yl-tris(trimethylammonium trichloride (52) was obtained as a sticky, extremely deliquescent white solid (95%) and its melting point could not be determined; ν_{max} = 1620, 1390, 830 cm^{-1}; $\delta(CDCl_3)$ 3.9 (27 H, *s*, $\overset{+}{N}$-C$\underline{H}_3$). Material was too deliquescent to be subjected to mass spectroscopy and elemental analysis.

10.4 Synthesis Of 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium Chloride (72)

1. Dimethylcyanamide (13) (7.00g; 0.1mol) and dimethylcarbamoyl chloride (71) (5.40g; 0.05mol) were heated on an oil bath at 170°C for 30 minutes. On cooling the reaction mixture in ice for 15 minutes, crystallisation occurred and the solid was filtered off and recrystallised from dry chloroform and ether. 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium chloride (72) was obtained as a

pale orange deliquescent solid (25%) m.p. 103°C; ν_{max} = 1720, 1600, 1490, 1400 cm^{-1}; δ($CDCl_3$) 3.3 (3 closely centred singlets) (3x6 H, 3x*s*, N-C$\underline{H}_3$); m/z=212. Material was not subjected to elemental analysis.

2. As in 1 except heated for 45 minutes at 170°C. 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium chloride (72) was obtained as a pale orange deliquescent solid (44%) m.p. 103°C; ν_{max} = 1720, 1600, 1490, 1400 cm^{-1}; δ($CDCl_3$) 3.3 (3 closely centred singlets) (3x6 H, 3x*s*, N-C$\underline{H}_3$); m/z=212. Material was not subjected to elemental analysis.

3. Dimethylcyanamide (13) (140g; 2mol) and dimethylcarbamoyl chloride (71) (107.5g; 1mol) were heated together for approximately 30 minutes. The following changes were observed:

Temperature °C	Colour	Comments
25-120	Straw	Mixture commences "to bubble" at 120°C.
154-155	Straw	Mixture commences to reflux.
155-162	Pale Yellow	Rapid temperature rise.
162-172	Yellow	Gradual temperature rise.
172-177	Transient Orange To Dark Brown	Temperature rise takes approximately 20 minutes.

{N.B. If the temperature is allowed to exceed 180°C, then an extremely vigorously exothermic reaction occurs and the temperature rapidly and uncontrollably rises to 220+°C with evolution of a lachrymatory vapour (dimethylcarbamoyl chloride) (71) and the chief product isolated is hexamethylmelamine (1).}

On allowing the reaction mixture to cool naturally, the liquid completely crystallised at ~120°C. The solid was triturated with dry ether and recrystallised from dry dichloromethane and THF. The product was filtered off, washed well with dry ether and dried at 80°C *in vacuo* over phosphorus pentoxide.

2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium chloride (72) was obtained as a cream, highly deliquescent solid (70%) m.p. 123°C. On exposure to moisture, the material rapidly turned pale brown and the melting point was lowered to 103°C.

ν_{max} = 1720, 1600, 1490, 1400 cm^{-1}; $\delta(CDCl_3)$ 3.3 (3 closely centred singlets) (3x6 H, 3x*s*, N-CH_3); m/z=212. Found C, 39.7; H, 8.0; N, 25.8. Calculated for $C_9H_{18}N_5O^+Cl^-.1.25H_2O$ C, 40.0; H, 7.6; N, 25.9.

10.5 Attempted Syntheses Of 2,4,6-tris(dimethylamino)-1,3,5-thiadiazinium Salts (79 and 82)

2,4,6-tris(dimethylamino)-1,3,5-thiadiazinium Chloride (79)

1. Dimethylcyanamide (13) (7.00g; 0.1mol) and dimethylthiocarbamoyl chloride (80) (6.20g; 0.05mol) were heated to dissolution and then to reflux for 30 minutes. The mixture charred and the resultant tar could not be characterised.

2. As in 1 except heated at 110°C for 2 hours. The tarry black residue which was obtained could not be characterised.

2,4,6-tris(dimethylamino)-1,3,5-thiadiazinium Perchlorate (82)

A solution of sodium sulphide nonahydrate (2.00g; 8mmol) in water (20ml) was added to a solution of 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium chloride (72) (1.00g; 4mmol) in acetone (80ml). The solution was agitated for 30 minutes then treated with a solution of perchloric acid (71%w/w; 4ml) made up to solution (20ml) with water. Water (40ml) was then added and the solution cooled in ice for several hours. Filtration of the cloudy solution yielded a very small amount of a very viscous, yellow, foul-smelling grease which was found to be insoluble in all common solvents and the product could not be characterised.

10.6 Reactions Of 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium Chloride (72)

10.6.1 With Ammonia

1. 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium chloride (72) (5.00g; 20mmol) and concentrated aqueous ammonia (10ml) were heated to reflux for 15 minutes. Ethanol was added to the hot suspension to dissolution and the product which crystallised out on cooling was filtered off, washed with water and dried at 100°C *in vacuo*. 4,6-bis(dimethylamino)-1,3,5-triazin-2(1H)-one (114) was obtained as a white solid (63%) m.p. 292°C and was found to be identical in every respect to the product obtained by the acid hydrolysis of 2-chloro-4,6-bis(dimethylamino)-1,3,5-triazine (15) (Section 10.2) m.p. 292°C. Mixed m.p. 292°C.

2. A solution of 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium chloride (72) (5.00g; 20mmol) in dichloromethane (25ml) was thoroughly intermixed

with concentrated aqueous ammonia (10ml) for several minutes. The phases were separated and the organic phase dried over anhydrous calcium chloride. The mixture was refiltered and the filtrate concentrated under reduced pressure at room temperature to dryness. The residue was recrystallised from chloroform and ether and was found not to be the expected intermediate (115) and 4,6-bis(dimethylamino)-1,3,5-triazin-2(1H)-one (114) was obtained as a white solid (∿80%) contaminated with a small amount of unreacted 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium chloride (72) m.p. 286-288°C. Mixed m.p. 289-291°C.

10.6.2 With Primary Amines

The reactions between 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium chloride (72) and various primary amines were investigated under a variety of reaction conditions. The major experimental difficulty encountered was the isolation of pure compounds because in many cases the products obtained were mixtures and contained unreacted amine and had similar solubilty characteristics resulting in poor separation by recrystallisation.

The major reaction conditions investigated are as follows:

1. The primary amine (20mmol) was added to a solution of 2,4,6-tris-(dimethylamino)-1,3,5-oxadiazinium chloride (72) (5.00g;20mmol) in dichloromethane (25ml) whereupon a vigorous exothermic reaction occurred. On subsidence of the exotherm, triethylamine (2ml) was added and the solution was stirred for 30 minutes. The solution was washed with 20% aqueous potassium carbonate solution and the phases were separated. The aqueous phase was exhaustively extracted with dichloromethane and the combined organic phases were dried (K_2CO_3), filtered and the filtrate concentrated under reduced pressure. The residual oils or solids were recrystallised from suitable solvents and dried at ambient temperature

in vacuo.

Methylamine (as 33%w/v solution in alcohol) gave 2-methylamino-2,4,6-tris(dimethylamino)-1,3,5-oxadiazine (116; R=Me) as a white deliquescent solid (acetone/ether; 56%) m.p. 124°C with decomposition; ν_{max}= 3300 cm^{-1}; $\delta(CDCl_3)$ 2.90 (3 H, *d*, N-C$\underline{H}_3$), 2.95 (6 H, *s*, N-C$\underline{H}_3$), 3.00 (6 H, *s*, N-C$\underline{H}_3$), 3.05 (6 H, *s*, N-C$\underline{H}_3$), 5.10 (1 H, *br*, N-$\underline{H}$); m/z=242. Found C, 49.1; H, 9.4; N, 35.3. Calculated for $C_{10}H_{22}N_6O$ C, 49.6; H, 9.1; N, 34.7.

Methylamine (as 40%w/w aqueous solution) gave 2-methylamino-2,4,6-tris-(dimethylamino)-1,3,5-oxadiazine (116; R=Me) as a white deliquescent solid (acetone/ether; 60%) m.p. 123°C with decomposition; ν_{max}= 3300 cm^{-1}; $\delta(CDCl_3)$ 2.90 (3 H, *d*, N-C$\underline{H}_3$), 2.95 (6 H, *s*, N-C$\underline{H}_3$), 3.00 (6 H, *s*, N-C$\underline{H}_3$), 3.05 (6 H, *s*, N-C$\underline{H}_3$), 5.10 (1 H, *br*, N-$\underline{H}$); m/z=242.

Ethylamine (as 71%w/w aqueous solution) gave 2-ethylamino-2,4,6-tris-(dimethylamino)-1,3,5-oxadiazine (116; R=Et) as a white solid (acetone/ether; 70%) m.p. 131°C with decomposition; ν_{max}= 3300 cm^{-1}; $\delta(CDCl_3)$ 1.20 (3 H, *t*, $CH_2C\underline{H}_3$), 2.90 (6 H, *s*, N-C$\underline{H}_3$), 3.00 (6 H, *s*, N-C$\underline{H}_3$), 3.05 (6 H, *s*, N-C$\underline{H}_3$), 3.25 (2 H, *m*, N-C$\underline{H}_2CH_3$), 4.80 (1 H, *br*, N-$\underline{H}$); m/z=256. Found C, 51.5; H, 9.7; N, 33.1. Calculated for $C_{11}H_{24}N_6O$ C, 51.5; H, 9.4; N, 32.8.

Propylamine gave 2-propylamino-2,4,6-tris(dimethylamino)-1,3,5-oxadiazine (116; R=$CH_3(CH_2)_2$-) as a white solid (ether; 67%) m.p. 96°C with decomposition; ν_{max}= 3250 cm^{-1}; $\delta(CDCl_3)$ 0.85 (3 H, *t*, $CH_2C\underline{H}_3$), 1.50 (2 H, *dxq*, $CH_2C\underline{H}_2CH_3$), 2.80 (6 H, *s*, N-C$\underline{H}_3$), 2.90 (6 H, *s*, N-C$\underline{H}_3$), 2.95 (6 H, *s*, N-C$\underline{H}_3$), 3.20 (2 H,

m, N-C$\underline{H}_2$CH$_2$], 4.90 (1 H, *br*, N-$\underline{H}$); m/z=270. Found C, 53.6; H, 9.9; N, 31.3. Calculated for $C_{12}H_{26}N_6O$ C, 53.3; H, 9.7; N, 31.1.

Isopropylamine gave <u>2-isopropylamino-2,4,6-tris(dimethylamino)-1,3,5-oxadiazine</u> (116; R=(CH$_3$)$_2$CH-) as a white solid (acetone/ether; 72%) m.p. 151°C with decomposition; ν_{max}= 3250 cm^{-1}; δ(CDCl$_3$) 1.20 (6 H, *d*, CH(C$\underline{H}_3$)$_2$), 2.85 (6 H, *s*, N-C$\underline{H}_3$), 3.00 (6 H, *s*, N-C$\underline{H}_3$), 3.05 (6 H, *s*, N-C$\underline{H}_3$), 3.20 (1 H, *dxd*, N-C$\underline{H}$(CH$_3$)$_2$), 4.90 (1 H, *br*, N-$\underline{H}$); m/z=270. Found C, 53.2; H, 9.9; N, 31.2. Calculated for $C_{12}H_{26}N_6O$ C, 53.3; H, 9.7; N, 31.1.

Butylamine gave <u>2-butylamino-2,4,6-tris(dimethylamino)-1,3,5-oxadiazine</u> (116; R= CH$_3$(CH$_2$)$_3$-) as a white hygroscopic solid (ether; 77%) m.p. 74°C with decomposition; ν_{max}= 3350 cm^{-1}; δ(CDCl$_3$) 0.80 (3 H, *t*, CH$_2$C$\underline{H}_3$), 1.30 (4 H, *br*, CH$_2$(C$\underline{H}_2$)$_2$CH$_3$), 2.75 (6 H, *s*, N-C$\underline{H}_3$), 2.85 (6 H, *s*, N-C$\underline{H}_3$), 2.90 (6 H, *s*, N-C$\underline{H}_3$), 3.00 (2 H, *m*, N-C$\underline{H}_2$CH$_2$-), 4.80 (1 H, *br*, N-$\underline{H}$); m/z=284. Found C, 51.7; H, 10.2; N, 28.3. Calculated for $C_{13}H_{28}N_6O.H_2O$ C, 51.7; H, 9.9; N, 27.8.

sec-Butylamine gave <u>2-sec-butylamino-2,4,6-tris(dimethylamino)-1,3,5-oxadiazine</u> (116; R=CH$_3$CH$_2$CH(CH$_3$)-) as a white solid (ether; 63%) m.p. 128°C with decomposition; ν_{max}= 3300 cm^{-1}; δ(CDCl$_3$) 1.10 (8 H, *br*, C$\underline{H}_3$C$\underline{H}_2$CH(C$\underline{H}_3$)), 2.90 (6 H, *s*, N-C$\underline{H}_3$), 3.00 (6 H, *s*, N-C$\underline{H}_3$), 3.05 (6 H, *s*, N-C$\underline{H}_3$), 3.10 (1 H, *m*, N-C$\underline{H}$(CH$_3$)CH$_2$CH$_3$), 4.80, *br*, N-$\underline{H}$); m/z=284. Found C, 54.5; H, 10.0; N, 29.6. Calculated for $C_{13}H_{28}N_6O$ C, 54.9; H, 9.9; N, 29.6.

tert-Butylamine gave <u>2-tert-butylamino-2,4,6-tris(dimethylamino)-1,3,5-oxadiazine</u> (116; R=(CH$_3$)$_3$C-) as a white solid (acetone/ether; 26%) m.p. 126°C with decomposition; ν_{max}= 3250 cm^{-1}; δ(CDCl$_3$) 1.40 (9 H, *d*, CH(C$\underline{H}_3$)$_3$),

2.80 (6 H, *s*, N-C$\underline{H}_3$), 3.05 (6 H, *s*, N-C$\underline{H}_3$), 3.10 (6 H, *s*, N-C$\underline{H}_3$), 3.35 (1 H, *m*, N-C$\underline{H}$(CH$_3$)$_3$), 4.20 (1 H, *br*, N-$\underline{H}$); m/z=284. Found C, 54.4; H, 10.0; N, 29.5. Calculated for $C_{13}H_{28}N_6O$ C, 54.9; H, 9.9; N, 29.6.

Cyclohexylamine gave 2-cyclohexylamino-2,4,6-tris(dimethylamino)-1,3,5-oxadiazine (116; R=cycloC_6H_{11}-) as a white solid (acetone; 60%) m.p. 166°C with decomposition; ν_{max}= 3250 cm^{-1}; δ(CDCl$_3$) 1.50 (10 H, *br*, CHC$_5\underline{H}_{10}$), 2.90 (6 H, *s*, N-C$\underline{H}_3$), 3.10 (6 H, *s*, N-C$\underline{H}_3$), 3.15 (6 H, *s*, N-C$\underline{H}_3$), 3.20 (1 H, *m*, N-C$\underline{H}$C$_5$H$_{10}$), 4.85 (1 H, *br*, N-$\underline{H}$); m/z=310. Found C, 58.4; H, 10.0; N, 27.3. Calculated for $C_{15}H_{30}N_6O$ C, 58.1; H, 9.8; N, 27.1.

Benzylamine gave 2-benzylamino-2,4,6-tris(dimethylamino)-1,3,5-oxadiazine (116; R=PhCH$_2$-) as a white solid (acetone/ether; 69%) m.p. 76°C with decomposition; ν_{max}= 3300 cm^{-1}; δ(CDCl$_3$) 2.90 (6 H, *s*, N-C$\underline{H}_3$), 2.95 (12 H, *s*, N-C$\underline{H}_3$), 4.40 (2 H, *br*, N-C$\underline{H}_2$Ph), 7.35 (5 H, *s*, C$_6\underline{H}_5$); m/z=318. Found C, 60.1; H, 8.5; N, 26.2. Calculated for $C_{16}H_{26}N_6O$ C, 60.4; H, 8.2; N, 26.4.

2-Phenylethylamine gave 2-(2'-phenyl)ethylamino-2,4,6-tris(dimethylamino)-1,3,5,oxadiazine (116; R=PhCH$_2$CH$_2$-) as a white solid (acetone/ether; 78%) m.p. 123°C with decomposition; ν_{max}= 3300 cm^{-1}; δ(CDCl$_3$) 2.80 (6 H, *s*, N-C$\underline{H}_3$), 2.90 (6 H, *s*, N-C$\underline{H}_3$), 3.00 (6 H, *s*, N-C$\underline{H}_3$), 3.40 (4 H, *m*, N-C$\underline{H}_2$C$\underline{H}_2$-), 4.70 (1 H, *br*, N-$\underline{H}$), 7.30 (5 H, *s*, C$_6\underline{H}_5$); m/z=332. Found C, 61.6; H, 8.7; N, 25.5. Calculated for $C_{17}H_{28}N_6O$ C, 61.5; H, 8.4; N, 25.3.

Aniline gave 1-phenyl-4,6-bis(dimethylamino)-1,3,5-triazin-2-one (120; R=Ph) as a white solid (acetone/ether; 7%) m.p. 151°C; ν_{max}= 1680 cm^{-1}; δ(CDCl$_3$) 2.70 (6 H, *s*, N-C$\underline{H}_3$), 3.20 (6 H, *s*, N-C$\underline{H}_3$), 7.40 (5 H, *s*, N-C$_6\underline{H}_5$);

m/z=259. Found C, 59.8; H, 6.7; N, 27.3. Calculated for $C_{13}H_{17}N_5O$ C, 60.2; H, 6.6; N, 27.0.

2. 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium chloride (72) (5.00g; 20mmol), the primary amine (20mmol) and DMF (5ml) were heated together to reflux. After maintaining reflux for a suitable time period the reaction mixture was treated with water (50ml) and allowed to cool. The solution or suspension was exhaustively extracted with dichloromethane and the combined organic extracts dried (K_2CO_3), filtered and concentrated under reduced pressure. The residual oils or solids were then recrystallised from suitable solvents and dried at 80°C *in vacuo*.

Aniline gave 1-phenyl-4,6-bis(dimethylamino)-1,3,5-triazin-2-one (120; R=Ph) as a white solid (ethyl acetate/ether; 71%) m.p. 164°C; ν_{max}= 1680 cm^{-1}; δ($CDCl_3$) 2.70 (6 H, *s*, N-C$\underline{H}_3$), 3.20 (6 H, *s*, N-C$\underline{H}_3$), 7.40 (5 H, *s*, N-C$_6\underline{H}_5$); m/z=259. Found C, 60.1; H, 6.7; N, 26.9. Calculated for $C_{13}H_{17}N_5O$ C, 60.2; H, 6.6; N, 27.0. (30 minutes reflux).

p-Toluidine gave 1-(4'-methyl)phenyl-4,6-bis(dimethylamino)-1,3,5-triazin-2-one (120; R=4MeC_6H_4-) as a white solid (toluene/ether; 64%) m.p. 201°C; ν_{max}= 1680 cm^{-1}; δ($CDCl_3$) 2.30 (3 H, *s*, -C$\underline{H}_3$), 2.80 (6 H, *s*, N-C$\underline{H}_3$), 3.20 (6 H, *s*, N-C$\underline{H}_3$), 7.20 (4 H, *s*, N-C$_6\underline{H}_4$-); m/z=273. Found C, 61.4; H, 7.1; N, 25.8. Calculated for $C_{14}H_{19}N_5O$ C, 61.5; H, 7.0; N, 25.6. (30 minutes reflux).

p-Anisidine gave 1-(4'-methoxy)phenyl-4,6-bis(dimethylamino)-1,3,5-triazin-2-one (120; R=4MeOC_6H_4-) as a white solid (acetone/ether; 67%) m.p. 159°C; ν_{max}=1680 cm^{-1}; δ($CDCl_3$) 2.70 (6 H, *s*, N-C$\underline{H}_3$), 3.20 (6 H, *s*, N-C$\underline{H}_3$), 3.80 (3 H, *s*, O-C$\underline{H}_3$), 6.90 (2 H, *d*, N-C(C$\underline{H}$)$_2$(CH)$_2$C-O), 7.25 (2 H, *d*, N-C(CH)$_2$(C$\underline{H}$)$_2$C-O); m/z=289. Found C, 58.2; H, 6.8; N, 24.5. Calculated for

$C_{14}H_{19}N_5O_2$ C, 58.1; H, 6.6; N, 24.2. (30 minutes reflux).

p-Chloroaniline gave 1-(4'-chloro)phenyl-4,6-bis(dimethylamino)-1,3,5-triazin-2-one (120; R=4ClC$_6$H$_4$-) as a white solid (aqueous ethanol; 89%) m.p. 184°C; ν_{max}= 1680 cm^{-1}; δ($CDCl_3$) 2.70 (6 H, *s*, N-C$\underline{H}_3$), 3.20 (6 H, *s*, N-C$\underline{H}_3$), 7.35 (2 H, *d*, N-C(C$\underline{H}$)$_2$(CH)$_2$C-Cl), 7.40 (2 H, *d*, N-C(CH)$_2$(C$\underline{H}$)$_2$C-Cl); m/z=295/293 (1:3). Found C, 53.0; H, 5.5; N, 23.9. Calculated for $C_{13}H_{16}N_5OCl$ C, 53.2; H, 5.5; N, 23.9. (1 hour reflux).

p-Bromoaniline gave 1-(4'-bromo)phenyl-4,6-bis(dimethylamino)-1,3,5-triazin-2-one (120; R=4BrC$_6$H$_4$-) as a cream solid (aqueous ethanol; 72%) m.p. 197°C; ν_{max}= 1680 cm^{-1}; δ($CDCl_3$) 2.80 (6 H, *s*, N-C$\underline{H}_3$), 3.20 (6 H, *s*, N-C$\underline{H}_3$), 7.20 (2 H, *d*, N-C(C$\underline{H}$)$_2$(CH)$_2$C-Br), 7.60 (2 H, *d*, N-C(CH)$_2$(C$\underline{H}$)$_2$C-Br); m/z=339/337 (1:1). Found C, 46.1; H, 4.9; N, 20.9. Calculated for $C_{13}H_{16}N_5OBr$ C, 46.2; H, 4.7; N, 20.7. (1 hour reflux).

3. A mixture of 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium chloride (72) (5.00g; 20mmol) and the primary amine (20mmol) in pyridine (5ml) was heated to reflux. After maintaining reflux for a suitable time period, excess water was added and the suspension reheated to reflux. Ethanol was added (if necessary) to clarify the suspension and the product which crystallised out on cooling was filtered off, washed with water and dried at 80°C *in vacuo*.

Propylamine gave 1-propyl-4-propylamino-6-dimethylamino-1,3,5-triazin-2-one (121; R=CH$_3$(CH$_2$)$_2$-) as a cream solid (aqueous ethanol/pyridine; 22%) m.p. 176°C; ν_{max}= 3300, 1660 cm^{-1}; δ($CDCl_3$) 1.05 (12 H, *br*, N-(C$\underline{H}_2$)$_2$C$\underline{H}_3$ + NH-CH$_2$C$\underline{H}_2$C$\underline{H}_3$), 3.10 (6 H, *s*, N-C$\underline{H}_3$), 3.35 (2 H, *m*, NH-C$\underline{H}_2$-); m/z=249. Found C, 53.2; H, 8.3; N, 28.4. Calculated for $C_{11}H_{21}N_5O$ C, 53.0; H, 8.4; N, 28.1. (15 minutes reflux).

Cyclohexylamine gave 1-cyclohexyl-4-cyclohexylamino-6-dimethylamino-1,3,5-triazin-2-one (121; R=cycloC_6H_{11}-) as a cream solid (aqueous ethanol/pyridine; 12%) m.p. 201°C; ν_{max}= 3300, 1710 cm^{-1}; δ($CDCl_3$) 1.50 (21 H, *br*, N-cyclo$C_6\underline{H}_{11}$- + NH-cycloCH$C_5\underline{H}_{10}$), 3.10 (6 H, *s*, N-C$\underline{H}_3$), 3.45 (1 H, *m*, NH-cyclo$C\underline{H}C_5H_{10}$); m/z= 319. Found C, 63.9; H, 9.3; N, 21.8. Calculated for $C_{17}H_{29}N_5O$ C, 64.0; H, 9.1; N, 22.0. (15 minutes reflux).

Benzylamine gave 1-benzyl-4-benzylamino-6-dimethylamino-1,3,5-triazin-2-one (121; R=$PhCH_2$-) as a cream solid (aqueous ethanol/pyridine; 42%) m.p. 203°C; ν_{max}= 3250, 1660 cm^{-1}; δ($CDCl_3/CD_3SOCD_3$) 3.20 (6 H, *s*, N-C$\underline{H}_3$), 4.50 (2 H, *d*, NH-C$\underline{H}_2$-), 5.30 (2 H, *s*, N-C$\underline{H}_2$-), 7.25 (5 H, *s*, $C_6\underline{H}_5$-), 7.30 (5 H, *s*, $C_6\underline{H}_5$-); m/z=335. Found C, 67.9; H, 6.5; N, 20.8. Calculated for $C_{19}H_{21}N_5O$ C, 68.1; H, 6.3; N, 20.9. (30 minutes reflux).

2-Phenylethylamine gave 1-(2'-phenyl)ethyl-4(2'-phenyl)ethylamino-6-dimethylamino-1,3,5-triazin-2-one (121; R=$PhCH_2CH_2$-) as a cream solid (aqueous ethanol/pyridine; 39%) m.p. 205°C; ν_{max}= 3250, 1660 cm^{-1}; δ($CDCl_3/CD_3SOCD_3$) 3.10 (6 H, *s*, N-C$\underline{H}_3$), 3.40 (4 H, *br*, N-C$\underline{H}_2CH_2$- + NH-C$\underline{H}_2CH_2$-), 4.00 (4 H, *m*, N-$CH_2C\underline{H}_2$- + NH-$CH_2C\underline{H}_2$-), 7.20 (10 H, *s*, 2x$C_6\underline{H}_5$-); m/z=363. Found C, 69.0; H, 7.1; N, 19.0. Calculated for $C_{21}H_{25}N_5O$ C, 67.4; H, 6.9; N, 19.3. (30 minutes reflux).

4. A mixture of 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium chloride (72), (5.00g; 20mmol) and the primary amine (20mmol) in pyridine (5ml) was heated to reflux. After maintaining reflux for a suitable time period, water (10ml) was added and the mixture exhaustively extracted with chloroform. The combined organic phases were dried (K_2CO_3), filtered and the filtrate was concentrated under reduced pressure to dryness. The residue was recrystallised and dried at 80-100°C *in vacuo*.

Benzylamine gave a mixture (1:1) of 1-benzyl-4,6-bis(dimethylamino)-1,3,5-triazin-2-one (120; R=$PhCH_2$-) and 1-benzyl-4-benzylamino)-6-dimethylamino-1,3,5-triazin-2-one (121; R=$PhCH_2$-) as a cream solid (chloroform/cyclohexane; ∿13% (120) and ∿16% (121)) m.p. 208°C; ν_{max}= 3200, 1660 cm^{-1}; δ($CDCl_3$/CD_3SOCD_3) 2.70 (6 H, *s*, N-C$\underline{H}_3$), 3.10 (6 H + 6 H, *s*, N-C$\underline{H}_3$), 4.50 (2 H, *d*, NH-C$\underline{H}_2$-), 5.20 (2 H + 2 H, *s*, 2xN-C$\underline{H}_2$-), 7.20 (5 H + 5 H + 5 H, *m*, 3x$C_6\underline{H}_5$-); m/z=335 (121) and 273 (120). Mixture not subjected to elemental analysis. (30 minutes reflux).

p-Toluidine gave 1-(4'-methyl)phenyl-4,6-bis(dimethylamino)-1,3,5-triazin-2-one (120; R=4MeC_6H_4-) as a cream solid (chloroform/cyclohexane; 31%) m.p. 200°C; ν_{max}= 1680 cm^{-1}; δ($CDCl_3$) 2.30 (3 H, *s*, -C$\underline{H}_3$), 2.80 (6 H, *s*, N-C$\underline{H}_3$), 3.20 (6 H, *s*, N-C$\underline{H}_3$), 7.20 (4 H, *s*, N-$C_6\underline{H}_4$-); m/z=273. (30 minutes reflux). Identical to sample prepared in method 2.

p-Anisidine gave 1-(4'-methoxy)phenyl-4,6-bis(dimethylamino)-1,3,5-triazin-2-one (120; R=4MeOC_6H_4-) as a cream solid (chloroform/petrol; 59%) m.p. 158°C; ν_{max}= 1680 cm^{-1}; δ($CDCl_3$) 2.70 (6 H, *s*, N-C$\underline{H}_3$), 3.20 (6 H, *s*, N-C$\underline{H}_3$), 3.80 (3 H, *s*, O-C$\underline{H}_3$), 6.90 (2 H, *d*, N-C(C$\underline{H}$)$_2$(CH)$_2$C-O), 7.25 (2 H, *d*, N-C(CH)$_2$(C$\underline{H}$)$_2$C-O m/z=289. (10 minutes reflux). Identical to sample prepared in method 2.

p-Chloroaniline gave 1-(4'-chloro)phenyl-4,6-bis(dimethylamino)-1,3,5-triazin-2-one (120; R=4ClC_6H_4-) as a white solid (aqueous ethanol; 41%) m.p. 184°C; ν_{max}= 1680 cm^{-1}; δ($CDCl_3$) 2.70 (6 H, *s*, N-C$\underline{H}_3$), 3.20 (6 H, *s*, N-C$\underline{H}_3$), 7.35 (2 H, *d*, N-C(C$\underline{H}$)$_2$(CH)$_2$C-Cl), 7.40 (2 H, *d*, N-C(CH)$_2$(C$\underline{H}$)$_2$C-Cl); m/z=295/293 (1:3) (1 hour reflux). Identical to sample prepared in method 2.

p-Bromoaniline gave 1-(4'-bromo)phenyl-4,6-bis(dimethylamino)-1,3,5-triazin-

2-one (120; R=4BrC_6H_4-) as a cream solid (aqueous ethanol; 47%) m.p. 197°C; ν_{max}= 1680 cm^{-1}; $\delta(CDCl_3)$ 2.80 (6 H, *s*, N-C$\underline{H}_3$), 3.20 (6 H, *s*, N-C$\underline{H}_3$), 7.20 (2 H, *d*, N-C(C$\underline{H}$)$_2$(CH)$_2$C-Br), 7.60 (2 H, *d*, N-C(CH)$_2$(C$\underline{H}$)$_2$C-Br); m/z=339/337 (1:1). (1 hour reflux). Identical to sample prepared in method 2.

p-Nitroaniline was chiefly recovered contaminated with a very small amount of 1-(4'-nitro)phenyl-4,6-bis(dimethylamino)-1,3,5-triazin-2-one (120; R= 4$NO_2C_6H_4$-) as a dark yellow solid (aqueous ethanol) m.p. 142-144°C; ν_{max}= 1640 cm^{-1}; m/z=304.

5. A mixture of 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium chloride (72) (5.00g; 20mmol) and the primary amine (20mmol) in toluene (10ml) was heated to reflux. After maintaining reflux for a suitable time period, triethylamine (2ml) was added and the cooled mixture diluted with dichloromethane (25ml). The solution was washed with water (10ml) and the aqueous phase exhaustively extracted with dichloromethane. The combined organic phases were dried (K_2CO_3), filtered and the filtrate concentrated under reduced pressure to dryness. The residue was recrystallised and dried at 50-80°C *in vacuo*.

Aniline gave a mixture (23:2) of 1-phenyl-4,6-bis(dimethylamino)-1,3,5-triazin-2-one (120; R=C_6H_5-) and 1-phenyl-4-phenylamino-6-dimethylamino-1,3,5-triazin-2-one (121; R=C_6H_5-) as a cream solid (acetone/ether; ∿55% (120) + ∿6% (121)) m.p. 155-157°C; ν_{max}= 3300, 1680 cm^{-1}; $\delta(CDCl_3)$ 2.75 (5.5 H, *s*, N-C$\underline{H}_3$), 3.20 (6 H, *s*, N-C$\underline{H}_3$), 7.35 (5.4 H, *s*, $C_6\underline{H}_5$-); m/z=307 (121) and 259 (120). (30 minutes reflux).

p-Toluidine gave a mixture (24:1) of 1-(4'-methyl)phenyl-4,6-bis(dimethylamino)-

1,3,5-triazin-2-one (120; R=4MeC$_6$H$_4$-) and 1-(4'-methyl)phenyl-4-(4'-methyl)-phenylamino-6-dimethylamino-1,3,5-triazin-2-one (121; R=4MeC$_6$H$_4$-) as a cream solid (acetone/ether; ∿53% (120) + ∿2% (121)) m.p. 196-198°C; ν_{max} = 3400, 1680 cm^{-1}; δ(CDCl$_3$) 2.30 (3.2 H, *s*, -C$\underline{H}_3$), 2.70 (5.8 H, *s*, N-C$\underline{H}_3$), 3.20 (6 H, *s*, N-C$\underline{H}_3$), 7.20 (5.4 H, *s*, N-C$_6\underline{H}_4$-); m/z=335 (121) and 273 (120). (30 minutes reflux).

p-Anisidine gave a mixture (3:1) of 1-(4'-methoxy)phenyl-4,6-bis(dimethyl-amino)-1,3,5-triazin-2-one (120; R=4MeOC$_6$H$_4$-) and 1-(4'-methoxy)phenyl-4-(4'-methoxy)phenylamino-6-dimethylamino-1,3,5-triazin-2-one (121; R=4MeOC$_6$H$_4$-) as a cream solid (acetone/ether; ∿53% (120) + ∿17% (121)) m.p. 128-130°C; ν_{max}= 3250, 1680 cm^{-1}; δ(CDCl$_3$) 2.70 (4.5 H, *s*, N-C$\underline{H}_3$), 3.15 (6 H, *s*, N-C$\underline{H}_3$), 3.75 (4.9 H, *s*, O-C$\underline{H}_3$), ∿7 (8.3 H, *br-m*, N-C$_6\underline{H}_4$-); m/z=367 (121) and 289 (120). (30 minutes reflux).

p-Chloroaniline gave 1-(4'-chloro)phenyl-4,6-bis(dimethylamino)-1,3,5-triazin-2-one (120; R=4ClC$_6$H$_4$-) as a cream solid (acetone/ether; 58%) m.p. 184°C; ν_{max}= 1680 cm^{-1}; δ(CDCl$_3$) 2.70 (6 H, *s*, N-C$\underline{H}_3$), 3.20 (6 H, *s*, N-C$\underline{H}_3$), 7.35 (2 H, *d*, N-C(C$\underline{H}$)$_2$(CH)$_2$C-Cl), 7.40 (2 H, *d*, N-C(CH)$_2$(C$\underline{H}$)$_2$C-Cl); m/z=295/293 (1:3). (1 hour reflux). Identical to sample prepared in method 2.

p-Bromoaniline gave 1-(4'-bromo)phenyl-4,6-bis(dimethylamino)-1,3,5-triazin-2-one (120; R=4BrC$_6$H$_4$-) as a cream solid (acetone/ether; 59%) m.p. 197°C; ν_{max}= 1680 cm^{-1}; δ(CDCl$_3$) 2.80 (6 H, *s*, N-C$\underline{H}_3$), 3.20 (6 H, *s*, N-C$\underline{H}_3$), 7.20 (2 H, *d*, N-C(C$\underline{H}$)$_2$(CH)$_2$C-Br), 7.60 (2 H, *d*, N-C(CH)$_2$(C$\underline{H}$)$_2$C-Br); m/z=339/337 (1:1). (1 hour reflux). Identical to sample prepared in method 2.

p-Nitroaniline gave 1-(4'-nitro)phenyl-4,6-bis(dimethylamino)-1,3,5-triazin-2-one (120; R=4NO$_2$C$_6$H$_4$-) as a dark yellow solid (aqueous methanol; 78%) m.p.

202°C; ν_{max} = 1700 cm^{-1}; δ(TFA) 3.30 (12 H, *s*, N-C$\underline{H}_3$), 7.90 (2 H, *d*, N-C(C$\underline{H}$)$_2$(CH)$_2$C-NO_2), 8.50 (2 H, *d*, N-C(CH)$_2$(C$\underline{H}$)$_2$C-NO_2); m/z=304. Found C, 50.9; H, 5.5; N, 28.0. Calculated for $C_{13}H_{16}N_6O_3$ C, 51.3; H, 5.3; N, 27.6.

6. 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium chloride (72) (5.00g; 20mmol) and cyclohexylamine (50mmol) were heated to reflux in carbon tetrachloride (50ml) for 20 minutes. The cooled suspension was filtered and the filtrate treated with excess petrol. The product which precipitated out was filtered off and dried at 50°C *in vacuo*.

1-cyclohexyl-4-cyclohexylamino-6-dimethylamino-1,3,5-triazin-2-one (121; R=cycloC_6H_{11}-) was obtained as a white solid (carbon tetrachloride/petrol; 63%) m.p. 202°C; ν_{max} = 3300, 1710 cm^{-1}; δ($CDCl_3$) 1.50 (21 H, *br*, N-cyclo$C_6\underline{H}_{11}$- + NH-cycloCHC$_5\underline{H}_{10}$-), 3.10 (6 H, *s*, N-C$\underline{H}_3$), 3.45 (1 H, *m*, NH-cyclo$C\underline{H}C_5H_{10}$-); m/z =319. Identical to sample prepared in method 3.

7. 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium chloride (72) (5.00g; 20mmol), cyclohexylamine (20mmol) and triethylamine (2ml) were heated to reflux in carbon tetrachloride (25ml) for 1 hour. The cooled suspension was filtered and the filtrate treated with excess petrol. The product which precipitated out was filtered off and dried at 50°C *in vacuo*.

1-cyclohexyl-4,6-bis(dimethylamino)-1,3,5-triazin-2-one (120; R=cycloC_6H_{11}-) was obtained as a cream solid (carbon tetrachloride/petrol; 87%) m.p. 248°C with decomposition; ν_{max} = 1660 cm^{-1}; δ($CDCl_3$) 1.50 (11 H, *br*, N-cyclo$C_6\underline{H}_{11}$-), 2.85 (6 H, *s*, N-C$\underline{H}_3$), 3.10 (6 H, *s*, N-C$\underline{H}_3$); m/z=265. Found C, 59.0; H, 8.8; N, 26.7. Calculated for $C_{13}H_{23}N_5O$ C, 58.9; H, 8.7; N, 26.4.

8. A solution of 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium chloride (72)

(5.00g; 20mmol), cyclohexylamine (20mmol) and triethylamine (2ml) in water 15ml) was heated to reflux for 24 hours. Ethanol was added to dissolution and the product which crystallised out on cooling was filtered off and dried at 50°C *in vacuo*.

1-cyclohexyl-4,6-bis(dimethylamino)-1,3,5-triazin-2-one (120; R=cycloC_6H_{11}-) was obtained as a cream solid (aqueous ethanol; 21%) m.p. 247°C with decomposition; ν_{max}= 1660 cm^{-1}; $\delta(CDCl_3)$ 1.50 (11 H, *br*, N-cyclo$C_6\underline{H}_{11}$-), 2.85 (6 H, *s*, N-C$\underline{H}_3$), 3.10 (6 H, *s*, N-C$\underline{H}_3$); m/z=265. Identical to sample prepared in method 7.

9. A solution of 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium chloride (72) (5.00g; 20mmol) and cyclohexylamine (20mmol) in water (10ml) was heated to reflux for 16 hours. Propan-2-ol was added to dissolution and the product which crystallised out on cooling was filtered off and dried at 50°C *in vacuo*.

1-cyclohexyl-4,6-bis(dimethylamino)-1,3,5-triazin-2-one (120; R=cycloC_6H_{11}-) was obtained as a white solid (aqueous propan-2-ol; 37%) m.p. 248°C with decomposition; ν_{max}= 1660 cm^{-1}; $\delta(CDCl_3)$ 1.50 (11 H, *br*, N-cyclo$C_6\underline{H}_{11}$-), 2.85 (6 H, *s*, N-C$\underline{H}_3$), 3.10 (6 H, *s*, N-C$\underline{H}_3$); m/z=265. Identical to sample prepared in method 7.

10. 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium chloride (72) (5.00g; 20mmol) and cyclohexylamine (40mmol) were heated to reflux in dioxane (15ml) for 30 minutes. The hot solution was poured onto crushed ice (50g) and the product was filtered off, recrystallised and dried at 80°C *in vacuo*.

1-cyclohexyl-4-cyclohexylamino-6-dimethylamino-1,3,5-triazin-2-one (121; R=cycloC_6H_{11}-) was obtained as a cream solid (aqueous methanol; 44%) m.p. 202°C; ν_{max}= 3300 cm^{-1}; $\delta(CDCl_3)$ 1.50 (21 H, *br*, N-cyclo$C_6\underline{H}_{11}$- + NHcycloCHC$_5\underline{H}_{10}$-), 3.10 (6 H, *s*, N-C$\underline{H}_3$), 3.45 (1 H, *m*, NH-cyclo$\underline{H}$C$_5$H$_{10}$-);m/z=319. Identical to sample

prepared in method 3.

Attempted Conversions Of 2-cyclohexylamino-2,4,6-tris(dimethylamino)-1,3,5-oxadiazine (116; R=cycloC_6H_{11}-) Into 1-cyclohexyl-4,6-bis(dimethylamino)-1,3,5-triazin-2-one (120; R=cycloC_6H_{11}-)

1. 2-cyclohexylamino-2,4,6-tris(dimethylamino)-1,3,5-oxadiazine (116; R=cycloC_6H_{11}-) (1.00g; 3mmol) was heated on an oil bath at 150°C for 1 hour. An alkaline gas was evolved (dimethylamine?) and the cooled glassy residue was found to be a mixture of the starting material (116; R=cycloC_6H_{11}-) and the product (120; R=cycloC_6H_{11}-) by t.l.c.; ν_{max}= 3300, 1680 cm^{-1}; m/z=310 (116) and 265 (120).

2. 2-cyclohexylamino-2,4,6-tris(dimethylamino)-1,3,5-oxadiazine (116; R=cycloC_6H_{11}-) (1.00g; 3mmol) was suspended in water (5ml) and then acidified with drops of concentrated hydrochloric acid. The solution was heated to reflux for 30 minutes, cooled and basified with sodium carbonate. The product was filtered off and dried at 50°C *in vacuo*. The product was found to be a mixture of the starting material (116; R=cycloC_6H_{11}-) and the product (120; R=cyclo-C_6H_{11}-) by t.l.c.; ν_{max}= 3300, 1680 cm^{-1}; m/z=310 (116) and 265 (120).

Attempted Conversion Of 2-cyclohexylamino-2,4,6-tris(dimethylamino)-1,3,5-oxadiazine (116; R=cycloC_6H_{11}-) Into 1-cyclohexyl-4-cyclohexylamino-6-dimethylamino-1,3,5-triazin-2-one (121; R=cycloC_6H_{11}-)

A mixture of 2-cyclohexylamino-2,4,6-tris(dimethylamino)-1,3,5-oxadiazine (116; R=cycloC_6H_{11}-) (1.55g; 5mmol) and cyclohexylamine (5ml) was heated to reflux for 1 hour. T.l.c. of the cooled solution showed the presence of some unreacted starting material (116; R=cycloC_6H_{11}-) together with the product (121;

R=cycloC_6H_{11}-) and 1-cyclohexyl-4,6-bis(dimethylamino)-1,3,5-triazin-2-one (120; R=cycloC_6H_{11}-). Evaporation of a small aliquot of the solution to dryness gave a white solid m/z=319 (121), 310 (116) and 265 (120).

Attempted Conversion Of 1-(4'-methoxy)phenyl-4,6-bis(dimethylamino)-1,3,5-triazin-2-one (120; R=4MeOC_6H_4-) Into 1-(4'-methoxy)phenyl-4-(4'-methoxy)-phenyl-6-dimethylamino-1,3,5-triazin-2-one (121; R=4MeOC_6H_4-)

A mixture of 1-(4'-methoxy)phenyl-4,6-bis(dimethylamino)-1,3,5-triazin-2-one (120; R=4MeOC_6H_4-) (1.45g; 5mmol) and p-anisidine (0.70g; 6mmol) was heated to reflux in xylene (5ml) for 1 hour. T.l.c. of the cooled solution showed the presence of the unreacted starting material (120; R=4MeOC_6H_4-) together with the product (121; R=4MeOC_6H_4-). Evaporation of a small aliquot of the solution to dryness gave a cream solid m/z 367 (121) and 289 (120).

10.6.3 With Hydrazine

1. Hydrazine hydrate (1ml; 20mmol) was added to a solution of 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium chloride (72) (5.00g; 20mmol) in ethanol (10ml) whereupon a vigorously exothermic reaction occurred followed by gelatinisation. Triethylamine (2ml) was added followed by water (10ml) and the mixture heated to dissolution. The product which crystallised out on cooling was filtered off and dried at 100°C *in vacuo*.

N-(5-dimethylamino-1,2,4-triazol-3-yl)-N',N'-dimethylurea (124) was obtained as a white solid (aqueous ethanol; 82%) m.p. 217°C; ν_{max}= 3250, 1660 cm^{-1}; $\delta(CDCl_3/CD_3SOCD_3)$ 2.95 (6 H, *s*, N-C$\underline{H}_3$), 3.05 (6 H, *s*, N-C$\underline{H}_3$); m/z=198. Found C, 41.8; H, 7.2; N, 42.3. Calculated for $C_7H_{14}N_6O$ C, 42.4; H, 7.1; N, 42.4

2. Hydrazine hydrate (1ml; 20mmol) was added to a solution of 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium chloride (72) (5.00g; 20mmol) in dichloromethane (10ml). A vigorously exothermic reaction occurred followed by precipitation. The gel was suspended in petrol, filtered and the product dried at 80°C *in vacuo*.

N-(5-dimethylamino-1,2,4-triazol-3-yl)-N',N'-dimethylurea (124) was obtained as a white solid (78%) m.p. 216°C; ν_{max} = 3250, 1660 cm^{-1}; δ($CDCl_3$/CD_3SOCD_3) 2.95 (6 H, *s*, N-C$\underline{H}_3$), 3.05 (6 H, *s*, N-C$\underline{H}_3$); m/z=198. Sample identical to that prepared in method 1.

10.6.4 With Phenylhydrazine

1. A mixture of 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium chloride (72) (5.00g; 20mmol) and phenylhydrazine (4.40g; 40mmol) in dioxane (20ml) was heated to reflux for 5 minutes then concentrated under reduced pressure to dryness.

1-phenyl-4-(3'-dimethylamino-1'-phenyl-1',2',4'-triazol-5'-yl)semicarbazide (130) was obtained as a white solid (acetonitrile/absolute ethanol; 35%) m.p. 213°C; ν_{max} = 3200, 1680 cm^{-1}; δ($CDCl_3$/CD_3SOCD_3) 2.95 (6 H, *s*, N-C$\underline{H}_3$), 6.80-7.80 (10 H, *br-m*, 2xC$_6\underline{H}_5$-), 8.80 (2 H, *br*, -N$\underline{H}$-N$\underline{H}$-), 9.20 (1 H, *br*, N-$\underline{H}$); m/z=337. Found C, 60.4; H, 5.7; N, 29.1. Calculated for $C_{17}H_{19}N_7O$ C, 60.5; H, 5.7; N, 29.1.

2. A mixture of 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium chloride (72) (5.00g; 20mmol) and phenylhydrazine (2.20g; 20mmol) in pyridine (5ml) was heated to reflux for 30 minutes. The solvent was removed under reduced pressure and the residue recrystallised.

1-phenyl-4-(3'-dimethylamino-1'-phenyl-1',2',4'-triazol-5'-yl)semicarbazide (130) was obtained as a pale yellow solid (aqueous ethanol; 22%) m.p. 211°C;

ν_{max}= 3200, 1680 cm^{-1}; $\delta(CDCl_3/CD_3SOCD_3)$ 2.95 (6 H, *s*, N-C$\underline{H}_3$), 6.80-7.80 (10 H, *br-m*, 2x$C_6\underline{H}_5$-), 8.80 (2 H, *br*, -N$\underline{H}$-N$\underline{H}$-), 9.20 (1 H, *br*, N-$\underline{H}$); m/z=337. Identical to sample prepared in method 1.

3. A mixture of 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium chloride (72) 5.00g; 20 mmol) and phenylhydrazine (2.20g; 20mmol) in toluene (10ml) was heated. The mixture first dissolves then gelatinises. Triethylamine (2ml) was added and the mixture heated to reflux for 30 minutes. The solvent was removed under reduced pressure and the residue recrystallised.

1-phenyl-4-(3'-dimethylamino-1'-phenyl-1',2',4'-triazol-5'-yl)semicarbazide (130) was obtained as a pale yellow solid (aqueous methanol; 77%) m.p. 212°C; ν_{max}= 3200, 1680 cm^{-1}; $\delta(CDCl_3/CD_3SOCD_3)$ 2.95 (6 H, *s*, N-C$\underline{H}_3$), 6.80-7.80 (10 H, *br-m*, 2x$C_6\underline{H}_5$-), 8.80 (2 H, *br*, -N$\underline{H}$-N$\underline{H}$-), 9.20 (1 H, *br*, N-$\underline{H}$); m/z=337. Identical to sample prepared in method 1.

4. A mixture of 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium chloride (72) (5.00g; 20mmol) and phenylhydrazine (2.20g; 20mmol) in absolute ethanol (20ml) was heated to reflux for 1 hour. Water (10ml) was added and the cooled solution was filtered. The product was recrystallised.

1-phenyl-4-(3'-dimethylamino-1'-phenyl-1',2',4'-triazol-5'-yl)semicarbazide (130) was obtained as a white solid (methanol; 19%) m.p. 213°C; ν_{max}= 3200, 1680 cm^{-1}; $\delta(CDCl_3/CD_3SOCD_3)$ 2.95 (6 H, *s*, N-C$\underline{H}_3$), 6.80-7.80 (10 H, *br-m*, 2x $C_6\underline{H}_5$-), 8.80 (2 H, *br*, -N$\underline{H}$-N$\underline{H}$-), 9.20 (1 H, *br*, N-$\underline{H}$); m/z=337. Identical to sample prepared in method 1.

5. A mixture of 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium chloride (72) (5.00g; 20mmol), phenylhydrazine (4.40g; 40mmol) and triethylamine (2ml) in dichloromethane (20ml) was stirred to dissolution then heated to reflux for 15

minutes. The reaction mixture was poured into excess ether, filtered and the solid was recrystallised.

1-phenyl-4-(3'-dimethylamino-1'-phenyl-1',2',4'-triazol-5'-yl)semicarbazide (130) was obtained as a pale yellow solid (aqueous methanol; 34%) m.p. 212°C; ν_{max} = 3200, 1680 cm^{-1}; δ($CDCl_3/CD_3SOCD_3$) 2.95 (6 H, *s*, N-C$\underline{H}_3$), 6.80-7.80 (10 H, *br-m*, 2x$C_6\underline{H}_5$-), 8.80 (2 H, *br*, -N$\underline{H}$-N$\underline{H}$-), 9.20 (1 H, *br*, N-$\underline{H}$); m/z=337. Identical to sample prepared in method 1.

6. Phenylhydrazine (2.20g; 20mmol) Was added to a solution of 2,4,6-tris-dimethylamino)-1,3,5-oxadiazinium chloride (72) (5.00g; 20mmol) in dichloromethane (25ml) followed by triethylamine (2ml). After stirring the solution for 30 minutes at ambient temperature, the solution was washed with water (10ml) and the aqueous phase exhaustively extracted with dichloromethane. The combined organic phases were dried (K_2CO_3), filtered and the filtrate concentrated under reduced pressure to an oil which was recrystallised.

1-phenyl-4-(3'-dimethylamino-1'-phenyl-1',2',4'-triazol-5'-yl)semicarbazide (130) was obtained as a white solid (absolute ethanol/ether; 7%) m.p. 213°C; ν_{max} = 3200, 1680 cm^{-1}; δ($CDCl_3/CD_3SOCD_3$) 2.95 (6 H, *s*, N-C$\underline{H}_3$), 6.80-7.80 (10 H, *br-m*, 2x$C_6\underline{H}_5$-), 8.80 (2 H, *br*, -N$\underline{H}$-N$\underline{H}$-), 9.20 (1 H, *br*, N-$\underline{H}$); m/z=337. Identical to sample prepared in method 1.

7. A mixture of 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium chloride (72) and phenylhydrazine (4.40g; 40mmol) in pyridine (5ml) was heated to dissolution then reflux for 5-10 minutes. The mixture gelatinised and water (50ml) was added and the mixture reheated back to reflux for a further 10 minutes. The mixture was cooled in ice, filtered and the solid recrystallised.

1-phenyl-4-(3'-dimethylamino-1'-phenyl-1',2',4'-triazol-5'-yl)semicarbazide (130) was obtained as a white solid (dioxane/ether; 59%) m.p. 213°C; ν_{max} = 3200, 1680 cm^{-1}; δ($CDCl_3/CD_3SOCD_3$) 2.95 (6 H, *s*, N-C$\underline{H}_3$), 6.80-7.80 (10 H, *br-m*, 2x

$C_6\underline{H}_5$-), 8.80 (2 H, *br*, -N$\underline{H}$-N$\underline{H}$-), 9.20 (1 H, *br*, N-$\underline{H}$); m/z=337. Identical to sample prepared in method 1.

10.6.5 With Hydroxylamine

A solution of hydroxylamine hydrochloride (1.40g; 20mmol) and sodium hydroxide (0.80g; 20mmol) in water (5ml) was added to a solution of 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium chloride (72) (5.00g; 20mmol) in dichloromethane with stirring. Triethylamine (2ml) was added and after stirring, for 30 minutes, the emulsion was washed with water (5ml) and the aqueous phase was exhaustively extracted with dichloromethane. The combined organic extracts were dried (Na_2SO_4), filtered and the filtrate concentrated under reduced pressure to an oil which was recrystallised.

N-(5-dimethylamino-1,2,4-oxadiazol-3-yl)-N',N'-dimethylurea (131) was obtained as a cream, hygroscopic solid (acetone/ether; 35%) m.p. 72°C with decomposition; ν_{max}= 3400, 1660 cm^{-1}; $\delta(CDCl_3)$ 3.00 (6 H, *s*, N-C$\underline{H}_3$), 3.15 (6 H, *s*, N-C$\underline{H}_3$); m/z=199. Found C, 39.4; H, 7.2; N, 32.7. Calculated for $C_7H_{13}N_5O_2.0.75H_2O$ C, 39.5; H, 6.8; N, 32.9.

10.7 Attempted Polymerisations Of Dimethylcyanamide (13)

1. Dimethylcyanamide (13) (7.00g; 0.1mol) was heated to reflux for 4 hours. The temperature gradually rose from 165 to 250°C and the liquid darkened in colour. T.l.c. of the cooled liquid showed no spot corresponding to hexamethylmelamine (1) and the only observed spot was small, brown and at the origin.

2. Aluminium chloride (1.00g) was gradually added with stirring to dimethylcyanamide (13) (7.00g; 0.1mol) but after several minutes a violently explosive reaction occurred and the reaction mixture was expelled from the flask.

T.l.c. of the small amount of remaining liquid showed no trace of hexamethylmelamine (1).

3. Trifluoroacetic acid (10ml) was gradually added with stirring to dimethylcyanamide (13) (7.00g; 0.1mol). On complete addition and after a few minutes, a violently explosive reaction occurred which shattered the flask. The experiment was abandoned.

4. Trifluoroacetic acid (10ml) was gradually added with stirring to dimethylcyanamide (13) (7.00g; 0.1mol) maintained at 0-5°C in an ice bath. This temperature was maintained for a further 4 hours on complete addition and the mixture was then allowed to warm up slowly to ambient temperature. A violently explosive reaction occurred once again and the reaction mixture was expelled from the flask. T.l.c. of the small amount of residual liquid showed no hexamethylmelamine (1) present.

10.8 3-amino-5,7-bis(dimethylamino)-1,2,4-triazolo[4,3-a] and [2,3-a]-1,3,5-triazines (137 and 138)

3-amino-5,7-bis(dimethylamino)-1,2,4-triazolo[4,3-a]-1,3,5-triazine hydrobromide (137a) was obtained by heating a mixture of 2-hydrazino-4,6-bis-(dimethylamino)-1,3,5-triazine (39) (8.00g; 40mmol) and cyanogen bromide (4.50g; 42mmol) in absolute ethanol (50ml) to reflux for 2 hours. Further absolute ethanol was added to dissolution and the hot solution was filtered. The cool filtrate was treated with excess dry ether to precipitate out the product (137a) as a cream, hygroscopic solid (78%) m.p. 266°C with decomposition; ν_{max}= 3500, 1660, 1600 cm^{-1}; $\delta(CDCl_3/TFA)$ 3.35 (12 H, *s*, N-$C\underline{H}_3$); m/z=222. Found C, 31.9; H, 5.1; N, 37.4. Calculated for $C_8H_{14}N_8.HBr$ C, 31.7; H, 5.0; N, 37.0

3-amino-5,7-bis(dimethylamino)-1,2,4-triazolo[4,3-a]-1,3,5-triazine (137) was obtained by dissolving its hydrobromide salt (137a) (3.00g; 10mmol) in water (10ml) and adding concentrated aqueous ammonia (10ml). A yellow precipitate of the product (137) was formed which was filtered off and recrystallised from methanol/acetone as a yellow solid (92%); m.p. 113°C then resolidifies and remelts at 337°C; ν_{max} = 3300, 1600 cm^{-1}; δ($CDCl_3$/TFA) 3.35 (12 H, *s-br*, N-C$\underline{H}_3$); m/z=222. Found C, 40.6; H, 6.6; N, 46.6. Calculated for $C_8H_{14}N_8.H_2O$ C, 40.0; H, 6.7; N, 46.7.

3-amino-5,7-bis(dimethylamino)-1,2,4-triazolo[2,3-a]-1,3,5-triazine (138) was obtained by heating the hydrobromide salt (137a) (3.00g; 10mmol) with concentrated aqueous ammonia (10ml) to reflux for 30 minutes. Methanol was added to dissolution and the product which crystallised on cooling was filtered off and dried at 80°C *in vacuo*. The isomeric product (138) was obtained as a white solid (83%) m.p. 339°C; ν_{max} = 3300, 1600 cm^{-1}; δ($CDCl_3$/TFA) 3.30 (12 H, *s*, N-C$\underline{H}_3$); m/z=222. Material was pure by t.l.c. but gave unsatisfactory microanalytical results.

10.9 3,5,7-tris(dimethylamino)-1,2,4-triazolo[4,3-a] and [2,3-a]-1,3,5-triazines (139 and 140)

Attempted Syntheses Of 3,5,7-tris(dimethylamino)-1,2,4-triazolo[4,3-a]-1,3,5-triazine (139)

1. 2-azido-4,6-bis(dimethylamino)-1,3,5-triazine (22) (2.10g; 10mmol) was heated to reflux in dimethylcyanamide (13) (2ml) for 30 minutes. Water (10ml) was added to the cooled mixture then filtered. The residue was recrystallised from aqueous ethanol and the 2-azido-4,6-bis(dimethylamino)-1,3,5-triazine (22) was recovered (86%) unchanged.

2. A mixture of 3-amino-5,7-bis(dimethylamino)-1,2,4-triazolo[4,3-a]-1,3,5-triazine (137) (1.10g; 5mmol), aqueous formaldehyde (40%w/v; 2ml; 27mmol) and formic acid (0.60g; 13mmol) was heated to reflux for 30 minutes but the mixture rapidly charred and no characterisable product could be isolated.

3,5,7-tris(dimethylamino)-1,2,4-triazolo[4,3-a]-1,3,5-triazine hydrochloride (139a) was obtained by heating a mixture of 2-hydrazino-4,6-bis-(dimethylamino)-1,3,5-triazine (39) (4.00g; 20mmol) and phosgeneiminium chloride (75) (4.00g; 24mmol) in dry chlorobenzene (25ml) to reflux. A transient intense yellow colour appeared followed by dissolution, reprecipitation and redissolution with an accompanying orange colour. After 1 hour at reflux, the solvent was removed under reduced pressure and the residue recrystallised from prapan-2-ol/dry THF. The product (139a) was obtained as a white deliquescent solid (38%) m.p. 224°C; ν_{max} = 3500, 1680, 1600 cm^{-1}; $\delta(CDCl_3)$ 2.95 (6 H, *s*, N-C$\underline{H}_3$), 3.30 (6 H, *s*, N-C$\underline{H}_3$), 3.35 (6 H, *s*, N-C$\underline{H}_3$); m/z=250. Found C, 41.2; H, 6.7; N, 38.6. Calculated for $C_{10}H_{18}N_8.HCl.0.25H_2O$ C, 41.2; H, 6.7; N, 38.5.

3,5,7-tris(dimethylamino-1,2,4-triazolo[4,3-a]-1,3,5-triazine (139) was obtained by dissolving its hydrochloride salt (139a) (1.00g; 3mmol) in water (5ml) and adding concentrated aqueous ammonia (10ml). The suspension was exhaustively extracted with dichloromethane, the combined organic extracts dried, filtered and the solvent removed from the filtrate under reduced pressure. The residual oil was recrystallised from acetone/ether to yield the product (139) as a white solid (80%) m.p. 109°C; ν_{max} = 3500, 1600 cm^{-1}; $\delta(CDCl_3)$ 3.00 (6 H, *s*, N-C$\underline{H}_3$), 3.25 (6 H, *s*, N-C$\underline{H}_3$), 3.30 (6 H, *s*, N-C$\underline{H}_3$); m/z=250. Found C, 47.6; H, 7.2; N, 44.6. Calculated for $C_{10}H_{18}N_8$ C,48.0;

H, 7.2; N, 44.8.

3,5,7-tris(dimethylamino)-1,2,4-triazolo[2,3-a]-1,3,5-triazine (140) was obtained by heating the hydrochloride salt (139a) (3.00g; 10.5mmol) in aqueous dimethylamine (40%w/w; 20ml) for 30 minutes to reflux. Ethanol was added to dissolution and the product which crystallised out on cooling was filtered off and dried at 40°C *in vacuo*. The product (140) was obtained as a white solid (84%) m.p. 174°C; ν_{max} = 3500, 1600 cm^{-1}; $\delta(CDCl_3)$ 3.10 (6 H, *s*, N-C$\underline{H}_3$), 3.20 (6 H, *s*, N-C$\underline{H}_3$), 3.45 (6 H, *s*, N-C$\underline{H}_3$); m/z=250. Found C, 48.3; H, 7.4; N, 44.8. Calculated for $C_{10}H_{18}N_8$ C, 48.0; H, 7.2; N, 44.8.

REFERENCES

1. Borkovec A.B., De Milo A.B.: Insect chemosterilants. V Derivatives of melamine. J Med. Chem. *10*, 457-461 (1967).

2. Huang M.N., Takita H., Catane H., Yee Chen T.: Therapy of small cell carcinoma of the lung with hexamethylmelamine. Oncology *35*, 29-32 (1978).

3. De la Garza J.G., Carr D.T., Bise H.F.: Hexamethylmelamine (NSC-13875) in the treatment of primary cancer of the lung with metastases. Cancer *22*, 571-575 (1968).

4. Bonomi P., Morrin B., Wilbanks G., Slayton R.: Phase II trial of hexamethylmelamine (HMM) in ovarian carcinoma after alkylating-agent failure. Proc. Am. Assoc. Cancer Res. *19*, 335 (1978).

5. Johnson B.L., Fisher R.I., Bender R.A.: Hexamethylmelamine in alkylating-agent resistant ovarian carcinoma. Cancer *42*, 2157-2161 (1978).

6. Wilson W., Bisel H.F., Cole D., Rochlin D., Ramirez G., Madden R.: Prolonged low dose administration of hexamethylmelamine. Cancer *25*, 568-570 (1970).

7. Wilson W.L., Schroeder J.M., Bisel H.F., Mrazek R., Hummel R.P.: Phase II study of hexamethylmelamine (NSC-13875). Cancer *23*, 132-136 (1969).

8. Wampler G.L., Mellette S.J., Kuperminc M., Regelson W.: Hexamethylmelamine (NSC-13875) in the treatment of advanced cancer. Cancer Chemother. Rep. *56*, 505-514 (1972).

9. Gad-el-Mawla N., Muggia F.M., Hamza M.R.: Chemotherapeutic management of carcinoma of the Bilharzial bladder: A phase II trial with hexamethylmelamine and VM-26. Cancer Treat. Rep. *62*, 993-996 (1978).

10. Gad-el-Mawla N., Hamsa R., Chevlan E., Ziegler J.: Phase II chemotherapy trials in cancer of the Bilharzial bladder. Proc. Am. Assoc. Cancer Res. *19*, 393 (1978).

11. Legha S.S., Slavik M., Carter S.K.: Hexamethylmelamine, an evaluation of its role in the therapy of cancer. Cancer *38*, 27-35 (1976).

12. Borden E.C., Larsen P., Ansfield S.J.: Hexamethylmelamine treatment of sarcomas and lymphomas. Med. Pediatr. Oncol. *3*, 401-406 (1977).

13. D'Incalci M., Bolis G., Mangioni O., Morasca L., Garratini S.: Variable oral absorption of hexamethylmelamine in man. Cancer Treat. Rep. *62(12)*, 2117-2119 (1978).

14. Hahn D.A., Black C.: Hexamethylmelamine; a review. Drug Intell. and Clin. Pharmacy *14*, 591-598 (1980).

15. Young R.C., Chabner B.A., Hubbard S.P.: Advanced ovarian adenocarcinoma; melphalan (PAM) versus combination chemotherapy (Hexa-CAF). Proc. Am. Assoc. Cancer Res. *19*, 393 (1979).

16. Young R.C., Chabner B.A., Hubbard S.P.: Advanced ovarian adenocarcinoma: a prospective clinical trial of melphalan versus combination chemotherapy. N. Eng. J. Med. *299*, 1261-1266 (1978).

17. Smyth J.F. Advances In tumour prevention, detection and characterisation. Amsterdam.: Characterisation and treatment of human tumours. Excerpta Medica p. 332 (1978).

18. Ozols R.F., Garvin A.J., Costa J., Simon R.M., Young R.C.: Histologic grade in advanced ovarian cancer. Cancer Treat. Rep. *63*, 255-263 (1979).

19. Neijt J.P., van Lindert A.C.M., Vendrik C.P.J., Roozendaal K.J., Struyvenberg A., Pinedo H.M.: Treatment of advanced ovarian carcinoma with Hexa-CAF in patients with or without previous treatment. Cancer Treat. Rep. *64*, 323-326 (1980).

20. Kane R., Harvey H., Andrews T.: Phase II trial of CHAP in advanced ovarian carcinoma. Cancer Treat. Rep. *63*, 307-309 (1979).

21. Bruckner H.W., Wallach R.C., Kabakow B., Greenspan E.M., Gusberg S.B., Holland J.F.: Cis-platinum(DDP) for combination chemotherapy of ovarian carcinoma: improved response rates and survival. Proc. Am. Assoc. Cancer Res. *19*, 373 (1978).

22.Vogl S.E., Kaplan B.H., Moukhtar M., Berenzweig M.: The CHAP and HAD regiments in advanced ovarian cancer. Cancer Treat. Rep. *63*, 311-317 (1979).

23. Ames M.M., Powis G., Kovach J.S., Eagan R.T.: Disposition and metabolism of pentamethylmelamine and hexamethylmelamine in rabbits and humans. Cancer Res. *39*, 5016-5021 (1979).

24. Rutty C.J., Connors T.A., Nam N.H., Thang D.C., Hoellinger H.: In vivo studies with hexamethylmelamine. Europ. J. Cancer *14*, 713-720 (1977).

25. Ames M.M., Saunders M.E., Tiede W.S.: Metabolic activation of hexamethylmelamine and pentamethylmelamine by liver microsomal preparations. Life Sciences *29*, 1591-1598 (1981).

26. Begleiter A., Grover J., Goldenberg G.J.: Uptake and metabolism of hexamethylmelamine and pentamethylmelamine by L5178Y lymphoblasts in vitro. Cancer Res. *40*, 4489-4494 (1980).

27. Gescher A., D'Incalci M., Fanelli R., Farina P.: N-hydroxymethylpentamethylmelamine. A major in vitro metabolite of hexamethylmelamine. Life Sciences *26(2)*, 147-154 (1980).

28. Nash T.: The colorimetric estimation of formaldehyde by means of the Hantzsch reaction. Biochem. J. *55*, 416-421 (1953).

29. Gescher A., Hickman J.A., Stevens M.F.G.: Oxidative metabolism of some N-methyl containing xenobiotics can lead to stable progenitors of formaldehyde. Biochem. Pharmacol. *28*, 3235-3238 (1979).

30. Van De Vaart Van Zutphen H.P.C., Smulders C.F.A., Renema J., Hulshoff A.: Hexamethylmelamine and hexamethylmelamine hydrochloride. Pharmaceutisch Weekblad Sci. Edn. *4*, 25-31 (1982).

31. Padgett II W.M., Hamner W.F.: The infra-red spectra of some derivatives of 1,3,5-triazine. J. Am. Chem. Soc. *80*, 803-808 (1952).

32. Simmonds R.J., Stevens M.F.G.: Triazines and related products. Part 25. Methods for the attachment of sugar residues to cytotoxic 1,3,5-triazines. J. Chem. Soc. Perk. I. 1821-1825 (1982).

33. Ross D., Schwalbe C.H.: Electron density calculations for hexamethylmelamine. Aston University. (Not published).

34. Drechsel E.: Ueber Cyanamid. J. Prakt. Chem. *8*, 327-332 (1874).

35. Drechsel E.: Ueber Cyanamid. J. Prakt. Chem. *11*, 209-211 (1875).

36. Drechsel E.: Ueber das Verhalten des Cyanamids, Dicyandiamids und Melamins beim Erhitzen. J. Prakt. Chem. *13*, 330-333 (1876).

37. Franklin E.C.: The ammono carbonic acids. J. Am. Chem. Soc. *44*, 486-509 (1922).

38. Scholl W., Davis R., Brown O.E., Reid F.R.: Melamine of possible food value. Ind. Eng. Chem. *29*, 202-205 (1937).

39. Stollé R., Krauch K.: Über die Darstellung von Melamin und Ammelin aus Dicyandiamid, sowie Über Triamino-melamin und Diamino-ammelin. Ber. *46*, 2337-2339 (1913).

40. Davis T.L.: The action of ammonia water on dicyandiamide. J. Am. Chem. Soc. *43*, 2230-2233 (1921).

41. Cloez S., Cannizzaro S.: Untersuchungen über bei Amidartigen Verbindungen des Cyans. Ann. *78*, 228-231 (1851).

42. Oldham W.N.: Cyanuric chloride. U.S. 2,417,659 (1947) to American Cyanamid Co.

43. Thurston J.: Cyanuric chloride preparation. U.S. 2,416,656 (1947) to Am. Cyanamid Co.

44. Takenaka S., Sekina T.: Cathodic reaction of dimethylcyanamide. Denki Kagaku *36(5)*, 349-355 (1968).

45. Pearlman W.M., Banks C.K.: Substituted chlorodiamino-*s*-triazines. J. Am. Chem. Soc. *70*, 3726-3728 (1948).

46. Thurston J.T., Dudley J.R., Kaiser D.W., Hechenbleikner I., Schaefer F.C., Holm-Hansen D.: Cyanuric chloride derivatives I. Aminochloro-*s*-triazines. J. Am. Chem. Soc. *73(7)*, 2981-2983 (1951).

47. Cumber A.J., Ross W.C.J.: Analogues of hexamethylmelamine. The antineoplastic activity of derivatives with enhanced water solubility. Chem. Biol. Interactions *17(3)*, 349-357 (1977).

48. Kayama R., Hasunuma S., Sekiguchi S., Matsui K.: The thermal reactions of azido-1,3,5-triazines. Bull. Chem. Soc. Japan *47(11)*,2825-2829 (1974).

49. Dovlatyan V.V., Eliazyan K.A.: Synthesis of pesticides. 2-cyanomethyloxy-4,6-bis(alkyl(dialkyl)amino)-*s*-triazines and some of their reactions. Arm. Khim. Zh. *24(4)*, 354-361 (1971).

50. Dovlatyan V.V., Eliazyan K.A.: 2-cyanomethyloxy-4,6-bis(alkyl(dialkyl)-amino)-*s*-triazines and some of their reactions. Arm. Khim. Zh. *30(1)*, 66-69 (1977).

51. Goldberg R.S., Griffin J.P., McSherry J.W., Krakoff I.H.: Phase I study of pentamethylmelamine. Cancer Treat. Reps. *64*, 1319-1322 (1980).

52. Van Echo D.A., Chiuten D.F., Whitacre M., Aisner J., Lichtenfield J.L., Wiernik P.H.: Phase I trial of pentamethylmelamine in patients with previously treated malignancies. Cancer Treat. Reps. *64*, 1335-1339 (1980).

53. Eagan R.T., Creagan E.T., Rubin J., O'Connell M.J., Kovach J.S.: Early clinical trial of a 1 day intermittent schedule for pentamethylmelamine. Cancer Treat. Reps. *64*, 993-995 (1980).

54. Ihde D.C., Dutcher J.S., Young R.C., Cordes R.S., Barlock A.L., Hubbard S.M.,, Jones R.B., Boyd M.R.: Phase I trial of pentamethylmelamine: A clinical and pharmacologic study. Cancer Treat. Reps. *65*, 755-762 (1981).

55. Smith I.E., Muindi J.R.F., Newell D.R., Merai K., Rutty C.J., Wilman D.E.V., Taylor R.E.: Pentamethylmelamine (PMM): Phase I and pharmacokinetic studies. Proc. Am. Assoc. Cancer Res. *21*, 136 (1980).

56. Casper E.S., Gralla R.J., Lynch G.R., Jones B.R., Woodcock T.M., Gordon C., Kelsen D.P., Young C.W.: Phase I and pharmacological studies of pentamethylmelamine administered by 24 hour intravenous infusion. Cancer Res. *41*, 1402-1406 (1981).

57. Lake L.M., Grunden E.E., Johnson B.M.: Toxicity and antitumour activity of hexamethylmelamine and its N-demethylated metabolites in mice with transplantable tumours. Cancer Res. *35*,2858-2863 (1975).

58. Rutty C.J., Connors T.A.: In vitro studies with hexamethylmelamine. Biochem. Pharmacol. *26*, 2385-2391 (1977).

59. Langdon S.P., Simmonds R.J., Stevens M.F.G.: Carbohydrate linked melamine derivatives. BACR Conference (1981). Publ. Br. J. Cancer *44*, 290 (1981).

60. Langdon S.P.: Personal Communication (1983).

61. Rutty C.J., Abel G.: In vitro cytotoxicity of the methylmelamines. Chem. Biol. Interactions *29*, 235-246 (1980).

62. Harrap K.R.: Antitumour screening data for heptamethylmelamine chloride (CB 400-586). Chester Beatty Research (1977).

63. Moylam J.: The pharmacological properties of quaternary melamine derivatives. Third year project University of Aston (1978).

64. Oliver J.E., Chang S.C., Brown R.T., Stokes J.B., Borkovec A.B.: Insect chemosterilants 11. Substituted 3,5-diamino-1,2,4-dithiazolium salts and related compounds. J. Med. Chem. *15(3)*, 315-320 (1972).

65. Oliver J.E., De Milo A.B.: Substituted 2,4,6-tris(dimethylamino)-1,3,5-thiadiazinium salts. A new heteroaromatic system. J. Het. Chem. *8(6)*, 1087-1089 (1971).

66. Csűrös Z., Soós R., Antus-Ercsényi Á., Bitter I., Tamás J.: Acylation of disubstituted cyanamides with phosgene I. Acta Chim. Acad. Sci. Hung. *76(1)*, 81-94 (1973).

67. Csűrös Z., Soós R., Antus-Ercsényi Á., Bitter I.: Acylierung von disubstituierten Cyanamiden mit Phosgen II. Acta Chim. Acad. Sci. Hung. *77(4)*, 443-453 (1973).

68. Csűrös Z., Soós R., Antus-Ercsényi Á., Bitter I., Tamás J.: Acylation of disubstituted cyanamides with phosgene III. Acta Chim. Acad. Sci. Hung. *78(4)*, 409-417 (1973).

69. Csűrös Z., Soós R., Antus-Ercsényi Á., Bitter I., Tamás J.: Acylation of disubstituted cyanamides with phosgene IV. Acta Chim. Acad. Sci. Hung. *78(4)*, 419-430 (1973).

70. Bredereck K., Richter R.: Reaktionen mit Cyanamiden I. Umsetzungen von Dialkylcyanamiden mit Säurechloriden; Synthese von Dialkyl-[trichlor-dialkyl-amino-diazapentadienyliden]-ammonium chloriden. Ber. *99*, 2454-2460 (1966).

71. Schmidt R.R.: Activierung von Halogencarbonylverbindungen mit Lewis Säuren und ihre Umsetzung mit Mehrfachbindunssystemen. Ber. *98*, 334-351 (1965).

72. Martin D., Weise A.: Umsetzung elektrophiler Reagenzien mit Cyansäure-arylestern. Ber. *100*, 3736-3746 (1967).

73. Sumarokova T.N., Slavinskaya R.A., Litvyak I.G., Vykhrest N.Yu.: Structure and properties of 1,3,5-oxadiazin-1-ium salts. J. Gen. Chem. U.S.S.R. *50(10)*, 2331-2336 (1980).

74. Rushton P., Schwalbe C.H., Stevens M.F.G.: Structure of 2,4,6-tris(N,N-dimethylamino)-1,3,5-oxadiazinium chloride dihydrate, $C_9H_{18}N_5O^+Cl^-2H_2O$. Acta Cryst. *C39*, 476-478 (1983).

75. Motherwell W.D.S.: PLUTO. A program for plotting molecular and crystal structures. University of Cambridge, England. (1972).

76. Sheldrick G.M.: SHELX76. Program for crystal structure determination. University of Cambridge, England. (1976).

77. Ueno K., Saito N.: 4',6,7-trihydroxyflavylium chloride monohydrate; a synthetic anthocyanidin. Acta Cryst. *B33*, 111-113 (1977).

78. Fourme R.: Etude par diffraction X des structures cristallines du furanne à la pression atmosphérique. Acta Cryst. *B28*, 2984-2991 (1972).

79. Bullen G.J., Corney D.J., Stephens F.S.: Crystal and molecular structure of hexamethylmelamine [2,4,6-tris(dimethylamino)-1,3,5-triazine]. J. Chem. Soc. Perk. II. 642-646 (1972).

80. Dimroth K.: Neuere Methoden der präparativen organischen Chemie III. Aromatische Verbindungen aus Pyryliumsalzen. Angew. Chem. *72(10)*, 331-358 (1960).

81. Krivun S.V., Alfërova O.F., Sayapina S.V.: The reactions of certain aromatic cations. Russ. Chem. Revs. *43(10)*, 835-850 (1974).

82. Wizinger R., Ulrich P.: Zur Kenntnis der Thiopyryliumsalze. Helv. Chim. Acta *39*, 207-216 (1956).

83. Baeyer A., Piccard J.: Untersuchungen über das Dimethylpyron. Ann. *384*, 208-224 (1911).

84. Dilthey W.: Pyrylium compounds. J. Prakt. Chem. *94*, 53-76 (1916).

85. Toma C., Balaban A.T.: Reactions of pyrylium salts with nucleophiles V: Reaction of 2,4,6-trimethylpyrylium perchlorate with primary amines. Tetrahedron *22(Supp. 7)*, 9-25 (1966).

86. Balaban A.T., Toma C.: Reactions of pyrylium salts with nucleophiles IV: Isolation of an intermediate in the conversion of 2,4,6-triphenylpyrylium perchlorate into triphenylpyridine by ammonia. Tetrahedron *22 (Supp. 7)*, 1-8 (1966).

87. Schneider W., Seebach F.: Zur Kenntnis der Methyl-4-diaryl-2,6-pyryliumsalze und der Pyranhydrone. Ber. *54*, 2285-2298 (1921).

88. Schneider W., Riedel W.: Pyridin-arylimine III. Substituenteneinfluß und Konstituten der blauen Anhydrobasen. Ber. *74*, 1252-1278 (1941).

89. Balaban A.T., Frangopol P.T., Mateesco G., Nenitzesco C.D.: Structure et réactions des <<pyranol-hydrazides>>. Bull. Chim. Soc. France 298-302 (1962).

90. Dimroth K., Arnoldy G., von Eicken S., Schiffler G.: Untersuchungen über N+,N- betaine der Pyridinreihe. Ann *604*, 221-251 (1957).

91. Balaban A.T.: Reactions of pyrylium salts with nucleophiles VII: Conversion of 2,4,6-triphenylpyrylium into isoxazole or pyrazole derivatives by hydroxylamine or phenylhydrazine. Tetrahedron *24*, 5059-5065 (1968).

92. Buchardt O., Pederson C.L., Svanholm U.: Seven membered heterocyclic rings I: Formation of substituted 4H-1,2-diazepines from 2,4,6-triarylpyrylium salts and hydrazine.

93. Streith J., Cassal J.M.: Photochemical synthesis of ethyl-1H-diazepine-1-carboxylate. Angew. Chem. Int. Eng. Ed. *7(2)*, 129 (1968).

94. Schmitz E.: Isochinolin II. 3,4-dihydro-isochinolin-N-oxyd. Ber. *91*, 1488-1494 (1958).

95. Fuks R., Strebelle M., Wenders A.: Reaction of 1,3,5-oxadiazinium salts with amines; Formation of N-(N-benzoyliminobenzyl)-N'-substituted-benzamidines; a new class of compounds, azavinylogues of N-acylamidines. Synthesis *11*, 788-789 (1977).

96. Amer M.I., Booth B.L., Noori G.F.M., Proenca M.F.J.R.P.: The chemistry of nitrilium salts. Part 3. The importance of triazinium salts in Houben-Hoesch reactions catalysed by trifluoromethanesulphonic acid. J. Chem. Soc. Perkin Trans. I 1075-1082 (1983).

97. Deshpande R.J., Rama Rao A.V.: Synthesis of s-triazolo[4,3-a]-s-triazines and their isomerisation to s-triazolo[2,3-a]-s-triazines. Synthesis 863-865 (1974).

98. Guerret P., Jacquier R., Maury G.: An investigation of the minimal structural conditions for the Dimroth-type rearrangement in the polyaza-indolizine series. J. Het. Chem. *8*, 643-650 (1971).

99. Langdon S.P., Simmonds R.J., Stevens M.F.G.: Triazines and related product Part 26. Synthesis and chemistry of bicyclic analogues of the antitumour drug 2,4,6-tris(dimethylamino)-1,3,5-triazine (Hexamethylmelamine). J. Chem. Soc. Perkin Trans. I *In Press*.

100. De Milo A.B., Oliver J.E., Gilardi R.D.: The synthesis and Dimroth-type rearrangement of 5,7-bis(dimethylamino)-3-methylthio-s-triazolo[4,3-a]-s-triazine. J. Het. Chem. *10*, 231-233 (1973).

101. Clarke H.T., Gillespie H.B., Weisshaus S.Z.: Formaldehyde on amines and amino acids. J. Am. Chem. Soc. *55*, 4571-4587 (1933)

102. Momparler R.L., Gonzales F.A.: Effect of intravenous infusion of 5-aza-2'-deoxycytidine on survival time of mice with L 1210 leukaemia. Cancer Res. *38(9)*, 2673-2678 (1978).