# Triazines and Related Products. Part 30.[1] Cationic Analogues of the Antitumour Drug 2,4,6-Tris(dimethylamino)-1,3,5-triazine (Hexamethylmelamine)

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Chloro-1,3,5-triazines react with trimethylamine in ether to afford water-soluble quaternary salts. 2,4,6-Tris(dimethylamino)-1,3,5-oxadiazinium chloride (10) is formed when dimethylcyanamide and dimethylcarbamoyl chloride are heated at 170 °C. The oxadiazinium chloride reacts with ammonia to afford 2,4-bis(dimethylamino)-1,3,5-triazin-6(1H)-one by an ANRORC reaction, with primary amines to afford amine-adducts (15) of the 1,3,5-oxadiazine or, under forcing conditions, 1,2,4-trisubstituted-1,3,5-triazin-6(1H)-ones (20), (21) or (22). None of the cationic salts displayed antitumour activity *in vivo* in tumour-bearing mice and they were poor substrates for oxidative metabolism *in vitro*.

The antitumour drug 2,4,6-tris(dimethylamino)-1,3,5-triazine (hexamethylmelamine; HMM) (1) is a conundrum in that its chemical simplicity is not paralleled by any great biochemical understanding of its mode of action. There is evidence to suggest that metabolic activation to N-hydroxymethyl metabolites is a prerequisite for the expression of antitumour activity:[2–4] the tris(hydroxymethyl) derivative (2) has been developed for clinical trial as a second-generation drug to obviate the need for a metabolic activation step.[5]
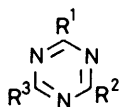
| | R[1] | R[2] | R[3] | |
|---|---|---|---|---|
| (1) | NMe$_2$ | NMe$_2$ | NMe$_2$ | |
| (2) | N(Me)CH$_2$OH | N(Me)CH$_2$OH | N(Me)CH$_2$OH | |
| (3) | Cl | NMe$_2$ | NMe$_2$ | |
| (4) | $\overset{+}{\text{N}}$Me$_3$ | NMe$_2$ | NMe$_2$ | (Cl$^-$) |
| (5) | $\overset{+}{\text{N}}$(Me)$_2$Et | NMe$_2$ | NMe$_2$ | (Cl$^-$) |
| (6) | $\overset{+}{\text{N}}$(Me)Et$_2$ | NMe$_2$ | NMe$_2$ | (Cl$^-$) |
| (7) | $\overset{+}{\text{N}}$Et$_3$ | NMe$_2$ | NMe$_2$ | (Cl$^-$) |
| (8) | $\overset{+}{\text{N}}$Me$_3$ | $\overset{+}{\text{N}}$Me$_3$ | NMe$_2$ | (2Cl$^-$) |
| (9) | $\overset{+}{\text{N}}$Me$_3$ | $\overset{+}{\text{N}}$Me$_3$ | $\overset{+}{\text{N}}$Me$_3$ | (3Cl$^-$) |

Our efforts to bypass the pharmaceutical problems engendered by the insolubility of HMM have taken the form of synthetic efforts to develop active, but more water-soluble, analogues. In previous parts of this series we have described monocyclic melamines bearing solubilising carbohydrate moieties[6] and bicyclic modifications where the bis(dimethylamino)-1,3,5-triazine nucleus is conjoined to a 1,2,4-triazole ring[7] but these efforts have not been rewarded by biological breakthroughs. This paper reports on the synthesis and properties of monocycles bearing onium groups of two types: 1,3,5-triazines with an exocyclic trialkylammonium group (4)—(9) and a 1,3,5-oxadiazinium salt (10) which is isoelectronic with HMM.

*Melamine Quaternary Salts.*—Earlier attempts to quaternise HMM under a range of conditions were thwarted by its chemical resilience.[6] Russian workers have shown that the chlorotriazine (3) reacts with trimethylamine in cold ether to afford the quaternary salt (4) in near quantitative yield.[8] Extending this synthesis to bulkier amines in the present work led to the formation of a low yield of the salt (5) but with

diethylmethylamine and triethylamine neither of the required salts (6) and (7) were formed. Increasing the reaction time and/or temperature was of no benefit and when dimethylformamide was employed as the solvent the only product isolated was HMM (1). (Interaction of reactive chloroarenes with amines in dimethylformamide often leads to the replacement of chloro by dimethylamino groups and the reaction has preparative significance).[9] The trimethylammonium salt (4) has been employed successfully as a 'pseudo' reactive halide for the attachment of sugar residues to a bis(dimethylamino)-1,3,5-triazine nucleus.[6] However, reaction of (4) with hot triethylamine led to the recovery of unchanged starting material and HMM presumably by a Hofmann-type elimination (Scheme 1).
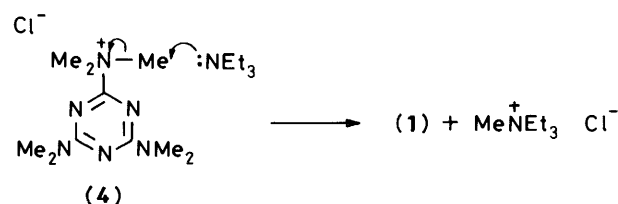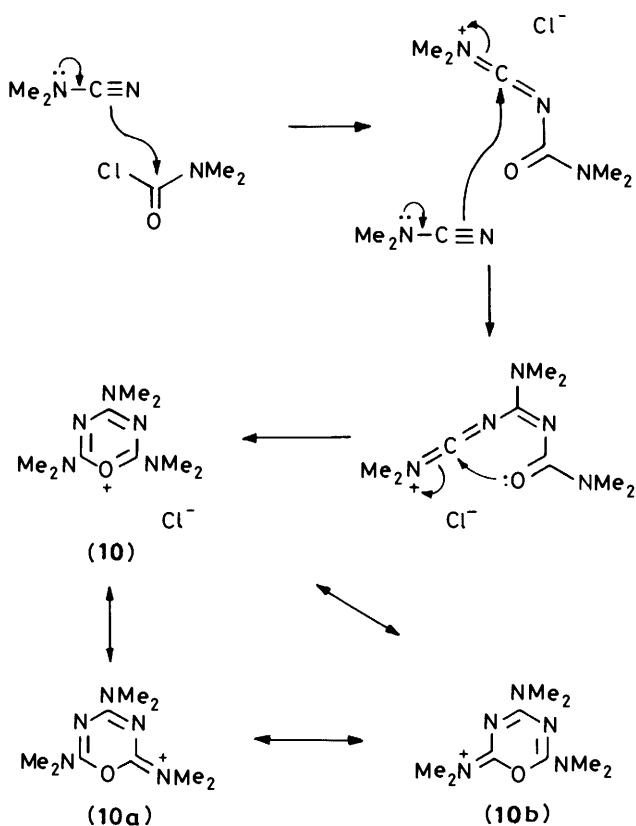
**Scheme 1.**

The mass spectrum of (4) gave a base peak at $m/z$ 210 corresponding to HMM, presumably by a similar loss of methyl chloride. The dimethylethylammonium analogue (5) gave prominent peaks at $m/z$ 210 and 224 by losses of ethyl chloride and methyl chloride respectively, from the molecular ion.

The deliquescent bis- and tris-onium compounds (8) and (9) were formed from an excess of trimethylamine and 2,4-dichloro-6-dimethylamino-1,3,5-triazine and cyanuric chloride, respectively, in cold ether.

*Synthesis and Physical Properties of 2,4,6-Tris(dimethylamino)-1,3,5-oxadiazinium Chloride.*—When dimethylcyanamide and dimethylcarbamoyl chloride in a 2:1 molar ratio were heated to 170 °C for 30 min the reaction mixture darkened. On cooling to 120 °C the melt solidified. The recrystallised material had m.p. 123 °C which was reduced to 103 °C as the highly deliquescent solid absorbed moisture. An analysis of the hydrated product was consistent with the molecular formula C$_9$H$_{18}$ClN$_5$O·1.25 H$_2$O. Two structures can be considered for this compound: the 1,3,5-oxadiazinium salt (10), and the acyclic imidoyl chloride (11). The extreme water solubility of the product and a molecular ion at $m/z$ 212 (C$_9$H$_{18}$N$_5$O) in its mass spectrum pointed to structure (10) whereas the presence of a

strong band at 1 720 cm⁻¹ in the i.r. spectrum suggested the isomer (11). An X-ray crystal structure determination eventually confirmed the 1,3,5-oxadiazinium structure (10).[10] Although conveniently written with a formal positive charge on the ring oxygen, there is considerable delocalisation of charge, an effect favoured by the near coplanarity of the dimethylamino (dimethyliminium) substituents. The C–O bond distances (1.366 and 1.386 Å) exceed by 0.02 Å those of a typical flavylium salt (12)[11] with charge localised on oxygen and are comparable with those of furan (1.368 Å).[12] The anomalous i.r. band at 1 720 cm⁻¹ is assigned to the C=$\overset{+}{N}$Me₂ stretching frequency; the model compound dichloromethylenedimethylammonium chloride (13) has an i.r. band at 1 720 cm⁻¹.

A mechanism to explain the formation of (10) is summarised in Scheme 2. The reactions of dialkylcyanamides with phosgene



Scheme 2.

and benzoyl chloride[13] have been studied but only in the latter case was an oxadiazinium salt (14) isolated, albeit in low yield (16%). This salt underwent thermal decomposition to yield benzonitrile, dimethylcyanamide and dimethylcarbamoyl chloride. The high yield (70%) of the oxadiazinium salt (10) formed in the present work is presumably attributable to the fact that thermal fragmentation in this case will regenerate the starting materials, and the overall yield of the cyclic species will depend on its thermodynamic stability. In fact, if the reactants used in the synthesis of (10) are heated at > 180 °C a vigorous exothermic reaction ensues and dimethylcarbamoyl chloride is evolved from the system. The only product isolated is HMM (1); presumably this is formed by trimerisation of dimethylcyanamide. Attempted syntheses of the known 2,4,6-tris(dimethylamino)-1,3,5-thiadiazinium chloride (10; S instead of O),[14] either by heating dimethylcyanamide with dimethylthiocarbamoyl chloride or by treating the oxadiazinium salt (10) with sodium sulphide, were unsuccessful.

It is interesting to compare the spectral properties of the oxadiazinium salt (10) with those of HMM. The salt had $\lambda_{max.}$ 247 nm (cf. 228 nm for HMM).[15] The mass spectrum of the salt showed major ions corresponding to losses of 15 (Me), 29 (CH₂=NH), 43 (CH₂=NMe) and 70 (Me₂NC≡N); similar fragmentations have been reported for HMM.[15] In fact a small peak at m/z 210 (C₉H₁₈N₆) is always observed in the mass spectrum of (10), presumably from the pyrolytic trimerisation of dimethylcyanamide.

The ¹H n.m.r. spectrum of the salt in D₂O displays a broad singlet (δ 3.3) whereas in CDCl₃ three sharp absorptions appear. The 4-dimethylamino group gives a singlet (δ 3.4) and



(11)

(12)



(13)

(14)
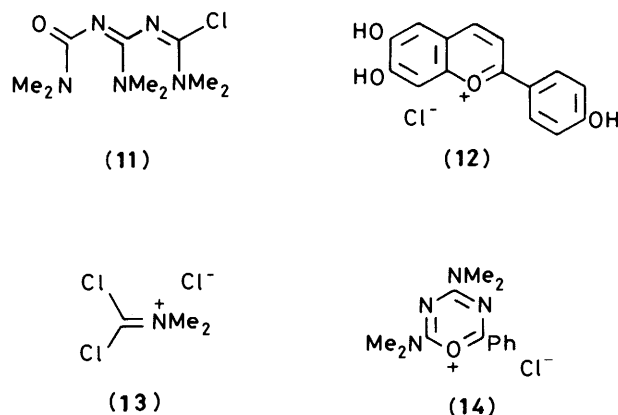
the 2- and 6-dimethylamino groups, which are equivalent, appear as a doublet at δ 3.3 due to amidic type restricted rotation of the ring carbon-exocyclic nitrogen bond similar to that observed in dimethylformamide. This assignment is supported by the crystal structure analysis which indicates that the 4-dimethylamino group is comparatively free to rotate whereas the 2- and 6-substituents are constrained in trigonal geometry[10] with mesomers (10a) and (10b) being the principal contributors. HMM in contrast gives only a sharp singlet at δ 3.07 in CDCl₃.[15]

The upfield signals in the ¹³C n.m.r. spectrum have an identical profile to the ¹H n.m.r. spectrum. The singlet at 37.808 p.p.m. is assigned to the 4-dimethylamino group and the close doublet at 37.282 and 37.150 p.p.m. to the 2-and 6-dimethylamino groups. The lowfield signals at 155.638 and 159.584 p.p.m. are assigned to C-2 plus C-6, and C-4 respectively.

Reactions of 2,4,6-Tris(dimethylamino)-1,3,5-oxadiazinium Chloride with Ammonia and Primary Amines.—When the oxadiazinium salt (10) was heated with concentrated aqueous ammonia the product was the 1,3,5-triazin-6(1H)-one (20; R=H). This triazinone was identical with an authentic specimen prepared by 2M-hydrochloric acid hydrolysis of 2-chloro-4,6-bis(dimethylamino)-1,3,5-triazine (3). (The same compound is also formed, surprisingly, when tetramethylguanidine is heated in boiling benzyl alcohol).[16] The mechanism for the ammonia reaction follows the ANRORC pathway[17] with the salt (10) behaving like a diazapyrylium system and undergoing initial addition of ammonia at C-2 to give the adduct (15; R=H). Electrocyclic ring-opening to the dimethylcarbamoyl biguanide (17; R=H) followed by recyclisation via the carbinolamine (19; R=H) affords the triazinone following loss of volatile dimethylamine. The alternative aromatisation by loss of water to yield HMM was not observed.

The reaction between the salt (10) and primary amines was complex and three different types of product were obtained, only two of which were characterised completely: the adducts (15) and the triazinones (20). Under more forcing conditions

**Table 1.** 1,3,5-Oxadiazines and 1,3,5-triazines formed from the reaction of 2,4,6-tris(dimethylamino)-1,3,5-oxadiazinium chloride (10) with ammonia and amines

| Substituent R [in initial amine and product(s)] | Reaction conditions | Product yields (%)[a] | | |
|---|---|---|---|---|
| | | (15) | (20) | (21) or (22) |
| H | A | | 63[b] | |
| H | B | | 80[b] | |
| Me[c] | C | 56 | | |
| Me[d] | C | 60 | | |
| Et[e] | C | 70 | | |
| Pr | C | 67 | | |
| Pr | D[f] | 22 | | |
| Pr[i] | C | 72 | | |
| Bu | C | 77 | | |
| Bu[s] | C | 63 | | |
| Bu[t] | C | 26 | | |
| Cyclohexyl | C | 60 | | |
| Cyclohexyl | D | | | 12 |
| Cyclohexyl | E | | 87 | |
| Cyclohexyl | F | | 37 | |
| Cyclohexyl | G | | | 63 |
| Cyclohexyl | H | | | 44 |
| PhCH$_2$ | C | 69 | | |
| PhCH$_2$ | D[g] | | | 42 |
| PhCH$_2$CH$_2$ | C | 78 | | |
| PhCH$_2$CH$_2$ | D[g] | | | 39 |
| Ph | C | | 7 | |
| Ph | I[g] | | 71 | |
| Ph | J | | 55 | 6 |
| $p$-MeC$_6$H$_4$ | D | | 31 | |
| $p$-MeC$_6$H$_4$ | I | | 64 | |
| $p$-MeC$_6$H$_4$ | J | | 55 | 2 |
| $p$-MeOC$_6$H$_4$ | D | | 59 | |
| $p$-MeOC$_6$H$_4$ | I | | 67 | |
| $p$-MeOC$_6$H$_4$ | J | | 53 | 17 |
| $p$-ClC$_6$H$_4$ | D | | 41 | |
| $p$-ClC$_6$H$_4$ | I | | 89 | |
| $p$-ClC$_6$H$_4$ | J | | 58 | |
| $p$-BrC$_6$H$_4$ | D | | 47 | |
| $p$-BrC$_6$H$_4$ | I | | 72 | |
| $p$-NO$_2$C$_6$H$_4$ | J | | 78 | |

[a] Yields recorded are for recrystallised products: see Table 2 for physical data. [b] Contaminated with a trace of (10). [c] Methylamine (33% w/v) in ethanol used. [d] Methylamine (40% w/v) in water used. [e] Ethylamine (71% w/w) in water used. [f] Reflux time 15 min. [g] Reflux time 30 min.

*Reaction Conditions:* A See Experimental section. B Compound (10) (5.0 g) in dichloromethane (25 ml) was emulsified with concentrated aqueous ammonia (10 ml) for 15 min. The organic phase was separated, dried (anhydrous calcium chloride) and filtered. Evaporation of solvent yielded product. C The amine (20 mmol) was added to a solution of (10) (5.0 g) in dichloromethane (25 ml). When the exothermic reaction had subsided triethylamine (2 ml) was added and the solution was stirred for 30 min. The mixture was shaken with 20% aqueous potassium carbonate and the dried (potassium carbonate) organic layer was evaporated and the residue crystallised. For crystallisation solvent see Table 2. D A mixture of compound (10) (5.0 g), the amine (20 mmol) and pyridine (5 ml) was boiled for either 15 or 30 min. Water was added and the crystallised product was collected. Alternatively, the product was extracted into chloroform and the dried (potassium carbonate) layer was evaporated to dryness. E The oxadiazinium salt (5.0 g) was heated with cyclohexylamine (20 mmol) and triethylamine (2 ml) in carbon tetrachloride (25 ml) for 1 h. The cooled suspension was filtered, the filtrate treated with excess light petroleum and the product collected. F As E but using water as solvent (10 ml) and a reflux time of 16 h. G The oxadiazinium salt (5.0 g) and cyclohexylamine (50 mmol) were boiled in carbon tetrachloride (50 ml) for 20 min. The mixture was filtered, the filtrate diluted with excess light petroleum and the product collected. H As G but using dioxan (15 ml) as solvent. The hot solution was poured on to crushed ice (50 g) and the product collected. I The oxadiazinium salt (5.0 g), the arylamine (20 mmol) and dimethylformamide (5 ml) were boiled together (1 h). The mixture was cooled, diluted with water (50 ml) and the products extracted into dichloromethane. The dried (potassium carbonate) organic layer was evaporated and the product crystallised (for solvents see Table 2). J Oxadiazinium salt (5.0 g), arylamine (20 mmol) and toluene (10 ml) were heated to reflux for 15 or 30 min. Triethylamine (2 ml) was added and the mixture shaken with dichloromethane (25 ml) and water (10 ml). The product was obtained by evaporation of the dried (potassium carbonate) organic layer.

another series of products was obtained where one of the dimethylamino groups of the triazinones (20) was replaced by a further molecule of amine. This third category of product probably has structure (21) or (22). In general, under mildly basic conditions the products obtained from aliphatic amines are the adducts (15) (see Table 1): the aromatic amines under similar conditions give the triazinones (20). If the reaction is conducted under forcing basic conditions, or in a heterogeneous medium, a mixture of the triazinones (20) and products (21) or

(22) are formed (Scheme 3). In the cases where mixtures were produced the components were characterised by t.l.c. and ¹H n.m.r. and mass spectroscopy (Table 2).

In the series of adducts the lower homologues (15; R=Me, Et) were water-soluble and deliquescent whereas the higher homologues were insoluble in water but soluble in organic solvents. All compounds in the series were stable in cold neutral or basic conditions but decomposed at their melting-points liberating dimethylamine. When the adduct (15; R = cyclohexyl) was

thermolysed at 150 °C or heated in 1M-hydrochloric acid a mixture of starting material and triazinone (20; R = cyclohexyl) was formed. In boiling cyclohexylamine the adduct was again completely consumed and the two triazinones (20) and (21) [or (22)] were detected in the product mixture (t.l.c. and m.s.).

Evidence to support the proposed structure (15) was forthcoming from the spectroscopic properties (Table 2). The absence of a carbonyl absorption excludes the acyclic isomeric structure (17). The sharp peak in the range 3 250—3 350 cm$^{-1}$ was not an OH absorption [thus excluding the dihydrotriazine (19) and the enol tautomer (18) of biguanide (17)] since the corresponding proton in the $^1$H n.m.r. spectrum of the ethylamine adduct (15; R = Et) at δ 4.80 was a triplet coupled to the adjacent prochiral methylene group which itself absorbed as a complex multiplet at δ 3.2. On deuteriation the triplet assigned to the NH proton of structure (15; R = Et) disappeared and the

**Table 2.** Physical data and spectral characteristics of 1,3,5-oxadiazines and 1,3,5-triazin-6(1H)-ones

| Compd. R | | M.p. (°C) | Molecular formula (M$^+$)$^a$ | Microanalytical data | | | | Spectroscopic data | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Found C | (Required) H | N | $\nu_{max.}$ $^b$ (cm$^{-1}$) | δ values$^c$ | | RNCO$^{+\cdot}$ |
| (15) | Me | 124$^d$ | C$_{10}$H$_{22}$N$_6$O (242) | 49.1 (49.6)* | 9.4 (9.1) | 35.3 (34.7)* | 3 000(NH) | 2.90 (3 H, d, NHMe) 2.95 (6 H, s, NMe$_2$) 3.00 (6 H, s, NMe$_2$) 3.05 (6 H, s, NMe$_2$) 5.10 (1 H, br, NH) | | 57 |
| (15) | Et | 131$^d$ | C$_{11}$H$_{24}$N$_6$O (256) | 51.5 (51.5) | 9.7 (9.4) | 33.1 (32.8) | 3 000(NH) | 1.20 (3 H, t, CH$_2$Me) 2.90 (6 H, s, NMe$_2$) 3.00 (6 H, s, NMe$_2$) 3.05 (6 H, s, NMe$_2$) 3.20 (2 H, m, CH$_2$Me) 4.80 (1 H, br, NH) | | 71 |
| (15) | Pr | 96 | C$_{12}$H$_{26}$N$_6$O (270) | 53.2 (53.3) | 9.9 (9.7) | 31.2 (31.1) | 3 250(NH) | 0.85 (3 H, t, CH$_2$Me) 1.50 (2 H, m, CH$_2$CH$_2$Me) 2.80 (6 H, s, NMe$_2$) 2.90 (6 H, s, NMe$_2$) 2.95 (6 H, s, NMe$_2$) 3.20 (2 H, m, NCH$_2$CH$_2$Me) 4.90 (1 H, br, NH) | | 85 |
| (15) | Pr$^i$ | 151$^d$ | C$_{12}$H$_{26}$N$_6$O (270) | 53.2 (53.3) | 9.9 (9.7) | 31.1 (31.1) | 3 250(NH) | 1.20 (6 H, d, CHMe$_2$) 2.85 (6 H, s, NMe$_2$) 3.00 (6 H, s, NMe$_2$) 3.05 (6 H, s, NMe$_2$) 3.20 (1 H, sept, CH(Me)$_2$) 4.90 (1 H, br, NH) | | 85 |
| (15) | Bu | 74$^e$ | C$_{13}$H$_{28}$N$_6$O (284) | 51.7 (51.7)† | 10.2 (9.9)† | 28.3 (27.8)† | 3 350(NH) | 0.80 (3 H, t, CH$_2$Me) 1.30 (4 H, br, (CH$_2$)$_2$Me) 2.75 (6 H, s, NMe$_2$) 2.85 (6 H, s, NMe$_2$) 2.90 (6 H, s, NMe$_2$) 3.00 (2 H, m, NCH$_2$(CH$_2$)$_2$Me) 4.80 (1 H, br, NH) | | 99 |
| (15) | Bu$^s$ | 128$^e$ | C$_{13}$H$_{28}$N$_6$O (284) | 54.5 (54.9) | 10.0 (9.9) | 29.6 (29.6) | 3 300(NH) | 1.10 (8 H, br, MeCHCH$_2$Me) 2.90 (6 H, s, NMe$_2$) 3.00 (6 H, s, NMe$_2$) 3.05 (6 H, s, NMe$_2$) 3.10 (1 H, m, CH) 4.80 (1 H, br, NH) | | 99 |
| (15) | Bu$^t$ | 126$^d$ | C$_{13}$H$_{28}$N$_6$O (284) | 54.4 (54.9) | 10.0 (9.9) | 29.5 (29.6) | 3 250(NH) | 1.40 (9 H, d, (Me)$_3$) 2.80 (6 H, s, NMe$_2$) 3.05 (6 H, s, NMe$_2$) 3.10 (6 H, s, NMe$_2$) 4.20 (1 H, br, NH) | | 99 |
| (15) | Cyclohexyl | 166$^f$ | C$_{15}$H$_{30}$N$_6$O | 58.4 (58.1) | 10.0 (9.8) | 27.6 (27.1) | 3 250(NH) | 1.50 (10 H, br, C$_5$H$_{10}$) 2.90 (6 H, s, NMe$_2$) 3.10 (6 H, s, NMe$_2$) 3.15 (6 H, s, NMe$_2$) 3.20 (1 H, m, CHC$_5$H$_{10}$) 4.85 (1 H, br, NH) | | 125 |
| (15) | PhCH$_2$ | 76$^d$ | C$_{16}$H$_{26}$N$_6$O | 60.1 (60.4) | 8.5 (8.2) | 26.2 (26.4) | 3 300(NH) | 2.90 (6 H, s, NMe$_2$) 2.95 (12 H, s, 2 × NMe$_2$) 4.40 (2 H, br, CH$_2$) 7.35 (5 H, s, Ph) | | 133 |
| (20) | p-NO$_2$C$_6$H$_4$ | 202$^k$ | C$_{13}$H$_{16}$N$_6$O$_3$ | 50.9 (51.3) | 5.5 (5.3) | 28.0 (27.6) | 1 700(CO) | 3.20‡ (12 H, s, 2 × NMe$_2$) 7.90 (2 H, d, Ar, 2 × CH) 8.50 (2 H, d, Ar, 2 × CH) | | |
| (21) or (22) | Pr | 176$^l$ | C$_{11}$H$_{21}$N$_5$O | 53.2 (53.0) | 8.3 (8.4) | 28.4 (28.1) | 3 300(NH) 1 660(CO) | 1.05 (12 H, m, aliphatic CH) 3.10 (6 H, s, NMe$_2$) 3.35 (2 H, m, NHCH$_2$) | | |

**Table 2** (continued)

| Compd. R | | M.p. (°C) | Molecular formula (M⁺)ᵃ | Microanalytical data | | | Spectroscopic data | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Found | (Required) | | $v_{max.}$ᵇ (cm⁻¹) | δ valuesᶜ | RNCO⁺· |
| | | | | C | H | N | | | |
| (21) or (22) | Cyclohexyl | 201ⁱ | $C_{17}H_{29}N_5O$ | 63.9 (64.0) | 9.3 (9.1) | 21.8 (22.0) | 3 300(NH) 1 710(CO) | 1.50 (21 H, m, aliphatic CH) 3.10 (6 H, s, NMe₂) 3.45 (1 H, m, CH) | |
| (21) or (22) | PhCH₂ | 203ⁱ | $C_{19}H_{21}N_5O$ | 67.9 (68.1) | 6.5 (6.3) | 20.8 (20.9) | 3 250(NH) 1 660(CO) | 3.20§ (6 H, s, NMe₂) 4.50 (2 H, s, NHCH₂) 5.30 (2 H, s, NCH₂) 7.25 (5 H, s, Ph) 7.30 (5 H, s, Ph) | |
| (21) or (22) | PhCH₂CH₂ | 205ⁱ | $C_{21}H_{25}N_5O$ | 69.0 (69.4) | 7.1 (6.9) | 19.0 (19.3) | 3 250(NH) 1 660(CO) | 3.10§ (6 H, s, NMe₂) 3.40 (4 H, br, NHCH₂ and NCH₂) 4.00 (4 H, m, NHCH₂CH₂ and NCH₂CH₂) 7.20 (10 H, s, 2 × Ph) | |

*Instruments:* ᵃ Recorded on a VG Micromass 12 instrument at 70 eV; source temperature 200—300 °C. ᵇ I.r. spectra were measured on a Pye-Unicam SP200 spectrometer as KBr discs. ᶜ Recorded on a Varian EM 360A spectrometer in $CDCl_3$ (exceptions: see footnotes ‡§); *Recrystallisation solvents:* ᵈ Acetone–ether. ᵉ Ether. ᶠ Acetone. ᵍ Chloroform–light petroleum. ʰ Ethyl acetate–ether. ⁱ Toluene–ether. ʲ Aqueous ethanol. ᵏ Aqueous methanol. ⁱ Ethanol–pyridine. * Unsatisfactory microanalysis may be attributable to the deliquescent nature of the compound. † Required for *hydrate* of (15; R' = Bu). ‡ In trifluorocacetic acid. § In $CDCl_3$–[(CD₃)₂SO] (1:1).
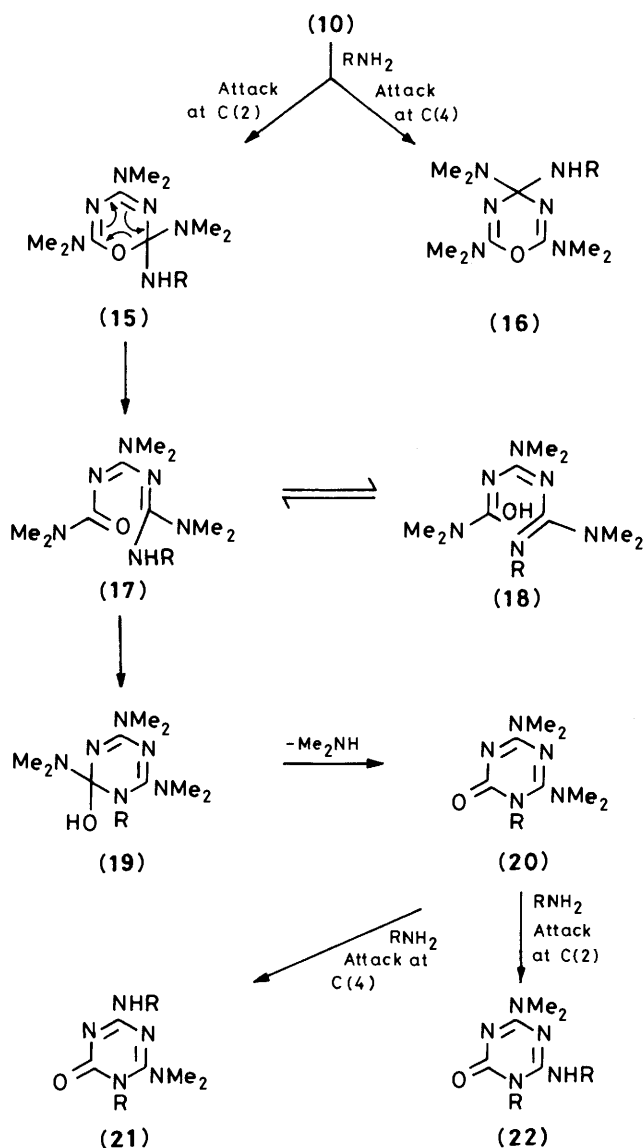


**Scheme 3.**

methylene multiplet collapsed to a quartet. The dimethylamino groups absorbed as three singlets in the range δ 2.9—3.1.

However, all the foregoing features do not exclude another possibility, *i.e.* structure (16), the adduct formed by attack of amine at C-4 in the oxadiazinium salt]. Crucially, the mass spectra of all the adducts show initial losses of a dimethyl radical followed by a hydrogen radical and prominent radical ion peaks corresponding to the alkyl isocyanates (Table 2 and Scheme 4):
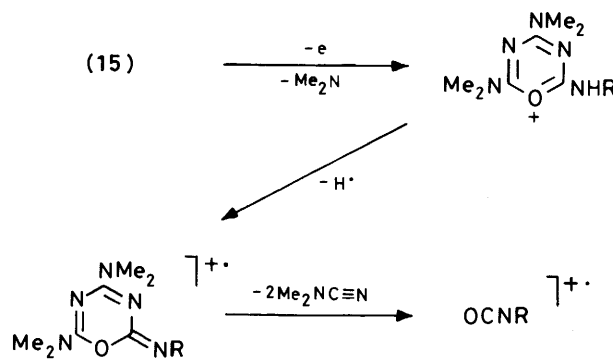


**Scheme 4.**

this fragmentation pathway is only possible in the C-2 adducts, *i.e.* structure (15).

The triazinones (20) formed by loss of dimethylamine from the adducts (15) showed two dimethylamino singlets in their ¹H n.m.r. spectra, a carbonyl band (1 680—1 700 cm⁻¹) but no NH absorptions in their i.r. spectra, and prominent isocyanate radical ion peaks (Table 2).

The products formed (formally) from the original oxadiazinium salt plus two moles of amine with loss of hydrogen chloride and two moles of dimethylamine were isolated in the pure state only with certain of the aliphatic amines; their spectroscopic characteristics (Table 2) were consistent with structures (21) [or (22)] but it was not possible to distinguish between these isomers with the available information. The corresponding products from aromatic amines were formed in admixture with triazinones (20) and other by-products and were not isolated pure. Their presence in the mixtures could be adduced only by analysis of the ¹H n.m.r. spectra of the mixtures. Attempts to prepare the product (21; R = cyclohexyl) [or isomer (22;

R = cyclohexyl)] in practicable yields by treating its presumed precursor, the adduct (15; R = cyclohexyl), with an excess of cyclohexylamine was not successful; only mixtures were formed and we are unable to pinpoint the timing of the dimethylamine displacement steps in the overall reaction (10) → (21) [or (22)].

*Biological Properties of Melamine Quaternary Salts and* 1,3,5-*Oxadiazines.*—The heptamethylmelamine salt (4) had no anti-tumour activity against the P388 leukaemia and ADJ/PC6A plasmacytoma *in vivo* in mice. Single doses of 40 mg kg⁻¹ proved to be rapidly fatal possibly because of cholinergic activity since the salt competitively blocked the post-junctional site of the neuromuscular junction of the frog rectus and rat diaphragm-phrenic nerve preparations at doses of 20 μg ml⁻¹.[18] The hexamethylethylmelamine salt (5) was, surprisingly, more toxic than the congener (4) even though it would be predicted to have less cholinergic activity due to its larger onium head. Dis-appointingly, the target compound, the oxadiazinium salt (10), had no antitumour activity against the P388 leukaemia and M5076 reticulum cell sarcoma in mice; the latter tumour is sensitive to HMM.[19] There is a strong correlation between *in vivo* antitumour activity of methylmelamines and plasma levels of *N*-hydroxymethyl species formed by oxidative metabolism of the *N*-methyl groups.[4] The inactivity of the cationic hetero-cycles described here can be attributed probably to their being poor substrates for oxidative demethylation. Thus, when the salts (4), (8), (9), and (10) were incubated with mouse liver microsomes and cofactors, the levels of demethylation achieved were 2, 2.6, 0, and 6.5%, respectively, the levels achieved with the clinically-active drug HMM.

Representatives of the 1,3,5-oxadiazinium salt-amine adducts (15; R = Et, Pr, Bu, Buᵗ, cyclohexyl, PhCH₂, PhCH₂CH₂) were screened against the P388 leukaemia in mice. At doses of 100 mg kg⁻¹ (daily × 5) the compounds were inactive and at 200 mg kg⁻¹ were toxic, producing premature deaths in all cases.

## Experimental
Details of spectroscopic equipment and procedures are given in the footnotes to Table 2. Light petroleum refers to that fraction of b.p. 60—80 °C. Ether refers to diethyl ether.

N-[4,6-*Bis(dimethylamino)*-1,3,5-*triazin-2-yl*] *trimethyl-ammonium Chloride* (4).—2-Chloro-4,6-bis(dimethylamino)-1,3,5-triazine (3.0 g) in dry ether (30 ml) and trimethylamine (6 ml) was stirred at 25 °C for 2 days. The precipitated salt was collected, washed with ether and had m.p. 169 °C (lit.,[8] m.p. 168—170 °C); *m/z* 210 (*M*⁺ − MeCl).

N-[4,6-*Bis(dimethylamino)*-1,3,5-*triazin-2-yl*]*ethyldimethyl-ammonium Chloride* (5).—This *salt* (40%) was obtained as above employing ethyldimethylamine as reactant and was a white deliquescent solid, m.p. 119 °C (decomp.) (Found: C, 48.0; H, 8.5; N, 30.5. C₁₁H₂₃ClN₆ requires C, 48.1; H, 8.4; N, 30.6%); λ_max. (KBr) 1 620, 1 420, and 820 cm⁻¹; δ (CDCl₃) 1.5 (3 H, t, CH₂*Me*), 2.9 (12 H, s, 2 × NMe₂), 3.5 (6 H, s, N-Me), and 3.7 (2 H, q, CH₂Me); *m/z* 224 (*M*⁺ − MeCl) and *m/z* 210 (*M*⁺ − EtCl).

When 2-chloro-4,6-bis(dimethylamino)-1,3,5-triazine (3.0 g) was refluxed in diethylmethylamine (10 ml) for 24 h, or heated in a sealed tube at 175 °C for 24 h, the residue, after removal of excess of diethylmethylamine, was shown to be unchanged chlorotriazine.

Mixtures of 2-chloro-4,6-bis(dimethylamino)-1,3,5-triazine (3.0 g) and triethylamine (3.0 g) were refluxed (2 days) in dry THF, toluene and acetonitrile, or in the absence of solvent. In each case unchanged chlorotriazine was recovered.

*N*-[4,6-Bis(dimethylamino)-1,3,5-triazin-2-yl]trimethyl-ammonium chloride (5.2 g) was refluxed in triethylamine (50 ml) for 4 h. The cooled suspension was filtered and the solid residue was unchanged starting material. The filtrate, con-centrated under reduced pressure, afforded hexamethyl-melamine (0.6 g).

2-*Dimethylamino*-4,6-*bis(trimethylammonium)*-1,3,5-*triazine Dichloride* (8).—2,4-Dichloro-6-dimethylamino-1,3,5-triazine (1.95 g) in dry ether (50 ml) was stirred with trimethylamine for 24 h. The white extremely deliquescent *dichloride salt* (90%) was washed with dry ether and had λ_max. (KBr) 1 620, 1 390, and 830 cm⁻¹; δ(CDCl₃) 3.2 (6 H, s, NMe₂) and 3.8 (18 H, s, 2 × N⁺Me₃).

Similarly prepared from 2,4,6-trichloro-1,3,5-triazine was the deliquescent 2,4,6-*tris(trimethylammonium)*-1,3,5-*triazine tri-chloride* (9) (95%); λ_max. (KBr) 1 620, 1 390, and 830 cm⁻¹; δ(CDCl₃) 3.9 (27 H, s, 3 × N⁺Me₃).

2,4,6-*Tris(dimethylamino)*-1,3,5-*oxadiazinium Chloride* (10). —Dimethylcyanamide (140 g) and dimethylcarbamoyl chloride (107 g) were heated to 170 °C for 20 mins. The melt darkened and when cooled solidified at 120 °C. The solid was triturated with dry ether and crystallised from dichloromethane-THF. The anhydrous material, formed when the product was dried *in vacuo* at 80 °C over phosphorus pentaoxide, had m.p. 123 °C. On exposure to moisture the melting point was lowered to 103 °C. The *oxadiazinium chloride hydrate* had λ_max. (KBr) 1 720, 1 600, 1 490, and 1 400 cm⁻¹; δ(CDCl₃) 3.3 (12 H, d, 2-NMe₂ and 6-NMe₂) and 3.4 (6 H, s, 4-NMe₂) (Found: C, 39.7; H, 8.0; N, 25.8. C₉H₁₈ClN₅O·1.25 H₂O requires C, 40.0; H, 7.6; N, 25.9%).

2,4-*Bis(dimethylamino)*-1,3,5-*triazin-6(1H)-one* (20; R = H). —(i) 2,4,6-Tris(dimethylamino)-1,3,5-oxadiazinium chloride (5.0 g) and concentrated aqueous ammonia (10 ml) were refluxed for 15 min. The product (63%) which crystallised was collected, washed with water, dried and the white triazinone had m.p. 292 °C (lit.,[16] m.p. 290—292 °C); λ_max. (KBr) 1 680 cm⁻¹. (ii) 2-Chloro-4,6-bis(dimethylamino)-1,3,5-triazine (3) (0.5 g) was boiled in 1M-hydrochloric acid (10 ml) for 3 h. The cooled solution was neutralised with sodium acetate and the product (0.4 g) was the same triazinone (m.p. and mixed m.p. 292 °C).

The reactions of 2,4,6-tris(dimethylamino)-1,3,5-oxadiazin-ium chloride with ammonia and amines are described in Table 1 and the physical data of the products are collated in Table 2.

*Reactions of* 2-*Cyclohexylamino*-2,4,6-*tris(dimethylamino)*-1,3,5-*oxadiazine* (15; R = cyclohexyl).—(i) The oxadiazine (1.0 g) was heated on an oil-bath at 150 °C for 1 h. Some dimethylamine was evolved and the product was shown (t.l.c., i.r. and ¹H n.m.r. spectroscopy) to be a mixture of starting material and 1-cyclohexyl-2,4-bis-(dimethylamino)-1,3,5-tria-zin-6(1*H*)-one (20; R = cyclohexyl).

(ii) The oxadiazine (1.0 g) in 1M-hydrochloric acid (5 ml) was refluxed (0.5 h), cooled and basified with aqueous sodium carbonate. The precipitated product was a mixture (t.l.c.) of the starting material and the triazinone (20; R = cyclohexyl).

(iii) Oxadiazine (1.55 g) was boiled in cyclohexylamine (5 ml) for 1 h. T.l.c. examination of the mixture revealed the presence of starting material, the triazinone (20; R = cyclohexyl) and product (21; R = cyclohexyl) [or isomer (22; R = cyclohexyl)].

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