222. *Potential Tumour-inhibitors based on Diazomethane.*

By J. A. HENDRY, F. L. ROSE, and A. L. WALPOLE.

Cyanuric chloride reacts readily in the cold with diazomethane to yield the corresponding dichlorodiazomethyl-1 : 3 : 5-triazine. The remaining chlorine atoms have been replaced by a variety of amine residues,* including ethyleneimine. Only one or two of the products exhibit tumour-inhibitory activity. An alternative route involved condensation of diguanides with oxalic acid esters.

THE occurrence of a diazomethyl residue in " azaserine "[1] (I), an antibiotic substance having tumour-growth inhibitory properties, prompted the synthesis of a number of other substances containing the same reactive grouping for evaluation as anti-tumour agents.

Two lines of study were proposed. The first envisaged combination within the same molecule of the diazomethyl group with various amino-acid residues, and the second the preparation of polyfunctional derivatives analogous with the polyalkylating tumour-inhibitors, many of which were initially prepared in these laboratories, typified by the triaziridyltriazine (II). It then seemed evident that the simplest way in which to accomplish the first objective would be to employ the 1 : 3 : 5-triazine ring to provide also the conjunctive group linking the diazomethyl and amino-acid residues. For both

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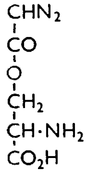
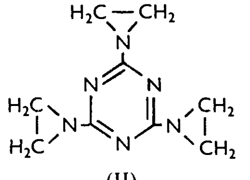
* Cf. B.P. 769,722.

[1] Stock, Reilly, Buckley, Clarke, and Rhoads, *Nature*, 1954, **173**, 71.

purposes, general methods were developed for the preparation of diazomethyl-1 : 3 : 5-triazines of type (III). While this work was being written up for publication, the synthesis of certain compounds related to (III) was described by Grundmann and Kober,[2] but in only one or two instances have the same compounds been prepared.



(I)



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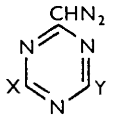

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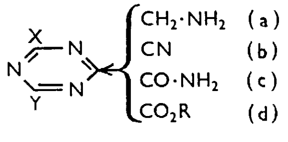

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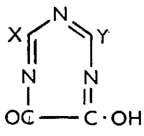

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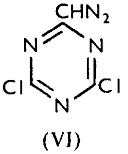

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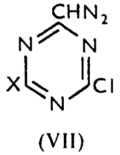
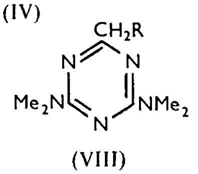


(VII)



(VIII)

It was reasonable to suppose that the diazomethyl group in the triazines (III) would be comparatively unstable, and for this reason the first methods investigated aimed at the introduction of the X and Y substituents at early stages of the syntheses, leaving the diazomethyl group to be formed in the final step, for example by the action of nitrous acid on the corresponding aminomethyltriazine (IVa) or a derivative thereof such as the urea or toluene-*p*-sulphonamide. The most direct route to compounds (IV) appeared to be through the nitriles (IVb), formed in turn from the amides (IVc) and triazine esters (IVd). Since it was initially intended that X and Y should be amino-groups, the esters would be derived from oxalguanamines. Some attention has already been paid to the action of oxalic esters on diguanides. Overberger and Shapiro,[3] and Ridi and Checchi,[4] have shown that phenyldiguanide and diethyl oxalate react in cold methanolic solution with the rapid formation, not of the expected triazine ester, but, through the elimination of two molecules of ethanol, of a yellow product $C_{10}H_9O_2N_5$. Both sets of authors speculate on the structure of this substance which might contain the seven-membered ring (V; X = Ph·NH, Y = NH_2) (a triazatropolone structure), or one of several possible five-membered cyclic systems. We have effected similar condensations with *N*¹-*p*-chlorophenyl-*N*⁵-dimethyldiguanide and *N*¹*N*¹*N*⁵-trimethyl-*N*⁵-phenyldiguanide. In the former instance the sparingly soluble colourless product gave analyses as for (V; X = *p*-Cl·C_6H_4·NH, Y = NMe_2), while the latter formed the triazine ester (IVd; X = NPhMe, Y = NMe_2, R = Et) freely soluble in organic solvents. Contact of these products with aqueous ammonia in dimethylformamide and methanol, respectively, gave the corresponding triazine amides (IVc), or alternatively from the former compound an isomer such as that derived from (V). These substances in turn gave the nitriles (IVb) with phosphoryl chloride, and ultimately the aminomethyltriazines by reduction with hydrogen in the presence of palladium. The conversion of the aminomethyl derivatives into the diazomethyl compounds was under investigation when the much simpler route starting with cyanuric chloride was discovered, and proceeded no further than the isolation of a very small yield of the compound (III; X = *p*-Cl·C_6H_4·NH, Y = NMe_2) by the action of nitrous acid in a mixture of acetic acid and benzene.

The alternative route followed from the observation that cyanuric chloride with two molecular proportions of diazomethane in ether gave the primary condensation product (VI) in good yield, the second molecule of diazomethane acting as an acid-binding agent

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[2] Grundmann and Kober, *J. Amer. Chem. Soc.*, 1957, **79**, 944.
[3] Overberger and Shapiro, *ibid.*, 1954, **76**, 93.
[4] Ridi and Checchi, *Ann. Chim.* (*Italy*), 1953, **43**, 807.

giving nitrogen and (presumably) methyl chloride in the manner demonstrated by Bradley and Robinson [5] for the reaction of this substance with benzoyl chloride. The remaining chloride atoms in this product (VI) retained their reactivity and were replaced in subsequent experiments either with the same, or serially with different, substituents. For this purpose it was more convenient to use a benzene solution obtained after removal of the ether from the initial condensation, which step also discarded small quantities of unwanted by-products. Replacement of the first chlorine atom, for example by amines, was usually smooth and complete at temperatures up to 30°. The second chlorine substituent needed rather higher temperatures, but even in conditions requiring the use of boiling ethanol the diazomethyl group remained intact provided that the environment was kept alkaline. In this manner, the monochloro-derivatives (VII) were first made carrying substituents (X) = NH_2, NHMe, NMe_2, $NH{\cdot}C_6H_4Cl$-*p*, $NH{\cdot}CH_2{\cdot}CO_2Et$, and $NH{\cdot}C_6H_4{\cdot}CO_2Na$-*o*), and the fully substituted compounds listed in the Table were prepared from them by further reaction as already indicated or, where the final product was the symmetrical one with X = Y, by the direct action of the appropriate reagents on the dichloro-compound (VI) without isolation of the intermediate monochlorotriazines. Attempts to hydrolyse the ester group of compound (III; X = NMe_2, Y = $NH{\cdot}CH_2{\cdot}CO_2Et$) led to extensive breakdown.

	Compound (III)		Significant inhibition of: *	
Code no.	X	Y	Walker tumour	sarcoma 180
19,530	NH_2	NMe_2	—	—
19,911	NH_2	NEt_2	—	—
19,395	NHMe	NMe_2	±	Nt
18,488	NHMe	$NH{\cdot}[CH_2]_3{\cdot}NEt_2$	±	Nt
18,937	NMe_2	NMe_2	+	+
20,522	NMe_2	$NH{\cdot}CH_2{\cdot}CO_2Et$	—	Nt
21,274	Morpholino	Morpholino	±	—
21,275	$N{<}C_5H_{10}$	$N{<}C_5H_{10}$	—	—
18,584	$NH{\cdot}[CH_2]_3{\cdot}NEt_2$	$NH{\cdot}C_6H_4Cl$-*p*	—	—
19,190	$N{<}[CH_2]_2$	$N{<}[CH_2]_2$	+	+
18,394	NHMe	Cl	—	—
18,936	$NH{\cdot}C_6H_4Cl$-*p*	Cl	—	—
20,290	$NH{\cdot}CH_2{\cdot}CO_2Et$	Cl	—	—

* Compounds in which X = NH_2, Y = $NH{\cdot}[CH_2]_3{\cdot}NEt_2$, OMe, and SEt, and (no. 19,394) X = NMe_2, Y = $NH{\cdot}C_6H_4Cl$-*p*, were not subjected to either test. Nt = not tested.

All of the above triazines carrying the diazomethyl group were sensitive to acids, decomposing with vigorous evolution of nitrogen. The chemical nature of the decomposition products was examined in some detail in the case of compound (III; X = Y = NMe_2). After decomposition in hot dilute sulphuric acid, the hydroxymethyltriazine (VIII; R = OH) was finally isolated, but the alkali-solubility of the reaction product at the earlier stages of the decomposition suggested that the sulphuric ester might have been an intermediate. Hot dilute hydrochloric acid gave a high yield of the chloromethyl product (VIII; R = Cl), while cold glacial acetic acid formed the acetoxy-derivative (VIII; R = OAc). Similarly, 3 : 4 : 5-trimethoxybenzoic acid in boiling benzene gave the acyloxymethyltriazine, and the same reaction effected in boiling methanol gave the methoxymethyltriazine as a by-product in substantial amount.

Most of the compounds have been examined for inhibitory action upon the growth of the Walker carcinoma 256 in rats, or the Crocker sarcoma 180 in mice, or both. With the Walker tumour the procedure adopted was essentially similar to that already described.[6] With sarcoma 180 the method used was a modification of that described by Stock.[7] Several of the compounds, given by daily intraperitoneal injection in maximal sub-lethal doses to tumour-bearing rats, caused a marked fall in the gross weight of the tumour-bearing animals. Only two inhibited tumour-growth to an extent which was clearly greater than could be accounted for by their general " toxic " effect, indicated by the

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[5] Bradley and Robinson, *J.*, 1928, **1310**.

[6] Walpole, *Brit. J. Pharmacol.*, 1951, **6**, 135; Hendry, Rose, and Walpole, *ibid.*, p. 201.

[7] Stock, *Amer. J. Med.*, 1950, **8**, 658.

fall in gross weight referred to. The activity of one of these (18,937) recalls that of tris(dimethylamino)triazine,[8] than which it is in fact more active. Further tests however, showed that 18,937 is almost inactive when given by mouth and unsuitable for parenteral administration in man. The other active compound (19,190) is inferior in activity to other polyfunctional ethyleneimines.

EXPERIMENTAL

Reaction of Diguanides with Oxalic Esters.—(a) N^1-p-*Chlorophenyl*-N^5-*dimethyldiguanide*. Dimethyl oxalate (22 g.) in methanol (50 c.c.) was added to a stirred solution of the diguanide (25 g.) in methanol (400 c.c.) initially at 30°. The heavy crystalline deposit that was rapidly formed was collected, washed with methanol, and used without further purification for conversion into the amide (below). A specimen of the *product* crystallised from dimethylformamide in colourless needles, m. p. 310° (decomp.) (Found: C, 48·7; H, 4·3; N, 22·9. $C_{12}H_{12}O_2N_5Cl$ requires C, 49·05; H, 4·1; N, 23·85. The triazine ester requires C, 50·74; H, 4·55; N, 22·75%).

(b) N^1-*Phenyldiguanide*. Similarly prepared from the diguanide (20 g.) and dimethyl oxalate (20 g.), the reaction mixture being set aside for 2 hr., the *product* formed pale yellow leaflets [19·2 g.; m. p. 218° (decomp.)]. Overberger and Shapiro[3] give m. p. 222—225° (decomp.).

(c) $N^1N^1N^5$-*Trimethyl*-N^5-*phenyldiguanide*. The diguanide (5·5 g.) and diethyl oxalate (4·4 g.) were heated together on the steam-bath for 1 hr., after which the excess of ester was removed under reduced pressure. The residual oily *product* (Found: C, 59·4; H, 6·8; N, 24·3. $C_{15}H_{19}O_2N_5$ requires C, 59·8; H, 6·3; N, 23·3%) was freely soluble in organic solvents, but attempts to isolate it by distillation led to decomposition. It was used directly for conversion into the amide.

2-*Carbamoyl*-4-p-*chloroanilino*-6-*dimethylamino*-1 : 3 : 5-*triazine*.—The crude moist product from (a) above was shaken for 20 hr. with aqueous ammonia (200 c.c.; *d* 0·88) and dimethylformamide (100 c.c.). The colourless *amide* that resulted (18 g.; m. p. 289—291°) was filtered off. If formed colourless prisms (from dimethylformamide), m. p. 301—302° (Found: C, 49·2; H, 4·8; N, 29·0. $C_{12}H_{13}ON_6Cl$ requires C, 49·2; H, 4·4; N, 28·7%).

2-p-*Chloroanilino*-4-*cyano*-6-*dimethylamino*-1 : 3 : 5-*triazine*.—The clear solution formed when the above crude amide (150 g.) and phosphoryl chloride (700 c.c.) were refluxed for 3 hr. was distilled under reduced pressure to remove excess of the latter (400 c.c.) and then decomposed in ice-water. The *nitrile* (93 g.; m. p. 198—200°) was obtained sensibly pure by lixiviation in water (5 l.) at 40° and crystallisation (charcoal) from acetic acid. It formed colourless needles (from toluene), m. p. 200° (Found: C, 52·5; H, 4·1; N, 31·0; Cl, 13·3. $C_{12}H_{11}N_6Cl$ requires C, 52·5; H, 4·0; N, 30·6; Cl, 12·9%).

2-*Aminomethyl*-4-p-*chloroanilino*-6-*dimethylamino*-1 : 3 : 5-*triazine*.—The above nitrile (14 g.), suspended in methanol (125 c.c.) and concentrated hydrochloric acid (5 c.c.), was reduced with hydrogen at room temperature and pressure over palladium chloride (0·2 g.). The methanolic filtrate after removal of the catalyst was evaporated to dryness, the residue digested in boiling 0·25N-hydrochloric acid (300 c.c.) (charcoal) and filtered, and concentrated hydrochloric acid (100 c.c.) added. The *dihydrochloride* crystallised in colourless needles, m. p. 298° (decomp.) (Found: C, 39·8; H, 5·0; N, 23·3; Cl, 19·7. $C_{12}H_{15}N_6Cl,2HCl,\frac{1}{2}H_2O$ requires C, 39·9; H, 5·0; N, 23·3; Cl, 19·6%).

2-p-*Chloroanilino*-4-*diazomethyl*-6-*dimethylamino*-1 : 3 : 5-*triazine*.—Sodium nitrite (0·5 g.) was added to a mixture of the above aminomethyltriazine (0·5 g. of base, prepared by the addition of sodium hydroxide to an aqueous solution of the dihydrochloride), glacial acetic acid (5 c.c.), and benzene (5 c.c.) and shaken for 5 min. at 10—20°. Water was added and the yellow benzene layer was washed with dilute aqueous sodium carbonate and water and dried (K_2CO_3). The solution was applied to an alumina column and eluted with 1 : 19 methanol–benzene. The light yellow band was collected in an eluate which was evaporated. The residue was digested with light petroleum (b. p. 80—100°) and filtered. The solid left after evaporation of the petroleum recrystallised from methanol, affording the bright yellow *diazomethyl derivative* (20 mg.), m. p. 153°; mixed m. p. with material prepared as described below, 142—153°.

Treatment of a solution at 50° of the aminomethyltriazine in dilute hydrochloric acid with

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[8] Buckley, Stock, Crossley, and Rhoads, *Cancer Res.*, 1950, **10**, 208; Hendry, Homer, Rose, and Walpole, *Brit. J. Pharmacol.*, 1951, **6**, 357.

sodium nitrite gave a colourless crystalline precipitate of the hydrochloride of 2-p-*chloroanilino*-4-*dimethylamino*-6-*hydroxymethyl*-1 : 3 : 5-*triazine* which was shaken with dilute sodium carbonate and extracted by ethyl acetate, recovered, and recrystallised from toluene, affording colourless prisms, m. p. 183—184° (Found: C, 51·0; H, 4·9; N, 24·1. $C_{12}H_{14}ON_5Cl$ requires C, 51·5; H, 5·0; N, 24·9%).

2-*Carbamoyl*-4-*dimethylamino*-6-N-*methylanilino*-1 : 3 : 5-*triazine*.—The oily ester from (c) above was shaken in methanol (10 c.c.) for 2 hr. with aqueous ammonia (50 c.c.; *d* 0·88). The precipitate of crude *amide* (2·85 g.; m. p. 112°) afforded colourless rosettes (from benzene), m. p. 125° (Found: C, 57·6; H, 6·1; N, 30·3. $C_{13}H_{16}ON_6$ requires C, 57·3; H, 5·9; N, 30·8%).

2-*Cyano*-4-*dimethylamino*-6-N-*methylanilino*-1 : 3 : 5-*triazine*, prepared as described above from the amide (6·7 g.) and phosphoryl chloride (30 c.c.), afforded colourless needles (3·7 g.), m. p. 120°, from light petroleum (b. p. 100—120°) (Found: C, 61·3; H, 5·8; N, 33·5. $C_{13}H_{14}N_6$ requires C, 61·4; H, 5·5; N, 33·1%).

Reduction of the nitrile (1·4 g.) in methanol (50 c.c.) containing concentrated hydrochloric acid (0·55 c.c.) with hydrogen (240 c.c.; theor. 246 c.c.) over palladium chloride (0·1 g.), filtration and evaporation to small bulk gave colourless 2-*aminomethyl*-4-*dimethylamino*-6-N-*methylanilino*-1 : 3 : 5-*triazine hydrochloride*, m. p. 252—253° (Found: C, 49·9; H, 6·7; N, 26·8; Cl, 16·6. $C_{13}H_{18}N_6,1\frac{1}{2}HCl$ requires C, 49·9; H, 6·2; N, 26·9; Cl, 17·0%).

Preparations involving the Use of Diazomethane. (a) *Intermediates.*—2 : 4-*Dichloro*-6-*diazomethyl*-1 : 3 : 5-*triazine*. Cyanuric chloride (25 g.) was added during 25 min. to a stirred solution of diazomethane (13·3 g.) in ether (700 c.c.) at 7—10°. Evolution of nitrogen was complete after 1 hr., then the solvent was removed under reduced pressure. The residue was dissolved in benzene (170 c.c.) and the solution, after being dried ($CaCl_2$) and clarified with charcoal, was used without further treatment in the preparations described immediately below. The solid left by removal of the solvent from a small volume of the solution afforded the dichlorodiazomethyltriazine as yellow needles [from light petroleum (b. p. 60—80°)], m. p. 115—118° (Found: C, 25·5; H, 0·5; N, 36·1; Cl, 37·3. Calc. for $C_4HN_5Cl_2$: C, 25·25; H, 0·5; N, 36·8%; Cl, 37·35%). Grundmann and Kober [2] give m. p. 111·5—112·5°.

2-*Amino*-4-*chloro*-6-*diazomethyl*-1 : 3 : 5-*triazine*. A benzene solution of dichlorodiazomethyltriazine (prepared as above from 31·8 g. of cyanuric chloride) was added during 10 min. to a stirred mixture of concentrated aqueous ammonia (88 c.c.) and water (88 c.c.) kept at 10—15°. After 1¼ hr. the crude aminotriazine [33 g.; m. p. 168° (decomp.)] was filtered off, washed with water, dried, and used without further purification in subsequent preparations. A small sample gave pale yellow crystals, m. p. 180—181° (decomp.), from much benzene (Found: C, 28·5; H, 2·2; N, 47·8. Calc. for $C_4H_3N_6Cl$: C, 28·15; H, 1·75; N, 49·2%). Grundmann and Kober [2] give m. p. 186° (decomp.).

2-*Chloro*-4-*diazomethyl*-6-*methylamino*-1 : 3 : 5-*triazine*. 30% Aqueous methylamine (30 c.c.) was added slowly to a stirred solution of the above dichlorodiazomethyltriazine (from 9·2 g. of cyanuric chloride) in benzene at $<40°$. The crude precipitated *methylaminotriazine* (6 g.; (decomp. 190°) recrystallised from dimethylformamide as pale yellow plates, decomp. 210° (Found: C, 32·8; H, 3·0; N, 44·4; Cl, 20·3. $C_5H_5N_6Cl$ requires C, 32·5; H, 2·7; N, 45·5; Cl, 19·25%).

2-*Chloro*-4-*diazomethyl*-6-*dimethylamino*-1 : 3 : 5-*triazine*. This was similarly prepared from the dichlorodiazomethyltriazine (from 10 g. of cyanuric chloride) and 29·4% aqueous dimethylamine (20 c.c.) at 5—10°. The benzene layer was dried ($CaCl_2$) and the solvent removed below 40°. The residue, recrystallised from light petroleum, then ethanol, gave the pale yellow *dimethylaminotriazine*, m. p. 102—103° (Found: C, 36·3; H, 3·6; N, 39·3; Cl, 18·3. $C_6H_7N_6Cl$ requires C, 36·25; H, 3·5; N, 42·3; Cl, 17·9%).

2-*Chloro*-4-p-*chloroanilino*-6-*diazomethyl*-1 : 3 : 5-*triazine*. A solution of *p*-chloroaniline (7·05 g.) in benzene (45 c.c.) was stirred in a mixture of the dichlorodiazomethyltriazine (from 9 g. of cyanuric chloride) in benzene, and potassium carbonate (13·8 g.) in water (90 c.c.) for 2 hr. at 35—40°. The crude p-*chloroanilinotriazine* [8·4 g.; m. p. 188° (decomp.)] obtained on filtration was sufficiently pure for further use, but a little, recrystallised from methanol, gave pale yellow needles, m. p. 193° (Found: C, 43·0; H, 1·8. $C_{10}H_6N_6Cl_2$ requires C, 42·7; H, 2·1%).

2-o-*Carboxyanilino*-4-*chloro*-6-*diazomethyl*-1 : 3 : 5-*triazine*. Similarly prepared from reaction of a solution of anthranilic acid (10 g.) in water (110 c.c.) and anhydrous sodium carbonate (15 g.), with the dichlorodiazomethyltriazine in benzene (from 9·2 g. of cyanuric chloride), this was isolated as the *sodium salt* by filtration and washing with 20% aqueous sodium acetate. The salt was purified (7·5 g.; pale yellow prisms) by reprecipitation from water (580 c.c.) with sodium acetate (250 g.), followed by crystallisation (charcoal) from methanol (250 c.c.) and water (sufficient to dissolve at the boil) (Found, after drying at 100°: C, 38·5; H, 2·8; N, 23·8; Cl, 10·9. $C_{11}H_6O_2N_6ClNa,2H_2O$ requires C, 37·9; H, 2·85; N, 24·1; Cl, 10·8%).

2-*Chloro*-4-*diazomethyl*-6-*ethoxycarbonylmethylamino*-1 : 3 : 5-*triazine*. Dichlorodiazomethyltriazine in benzene (from 22·4 g. of cyanuric chloride) was added during 10 min. to a stirred solution of glycine ethyl ester hydrochloride in N-sodium hydroxide (300 c.c.). After 2 hours' stirring at 35—40° the suspension was cooled to 10° and filtered. Recrystallisation of the crude *ester* (17·6 g.) from methanol gave pale yellow crystals, m. p. 153° (decomp.) (Found: C, 37·7; H, 3·1; N, 30·5. $C_8H_9O_2N_6Cl$ requires C, 37·4; H, 3·5; N, 32·75%).

(b) *Final Products containing Diazomethyl Residues*.—2-*Amino*-4-*diazomethyl*-6-*dimethylamino*-1 : 3 : 5-*triazine*. 2-Amino-4-chloro-6-diazomethyl-1 : 3 : 5-triazine (1 g.) was stirred in 20% aqueous dimethylamine (5 c.c.) for 15 min. at 40—45°. The crude *product* (m. p. 150°) gave pale yellow crystals, m. p. 152° (decomp.), from methanol (Found: C, 40·7; H, 5·5; N, 54·6. $C_6H_9N_7$ requires C, 40·2; H, 5·0; N, 54·7%).

2-*Amino*-4-*diazomethyl*-6-*diethylamino*-1 : 3 : 5-*triazine*. Similarly prepared from 2-amino-4-chloro-6-diazomethyl-1 : 3 : 5-triazine (11 g.), diethylamine (30 c.c.), and water (30 c.c.), the crude *product* had m. p. 137—140° and, after recrystallisation from ethanol, m. p. 146—148° (Found: C, 46·4; H, 6·7; N, 46·9. $C_8H_{13}N_7$ requires C, 46·35; H, 6·3; N, 47·35%).

2-*Amino*-4-*diazomethyl*-6-3′-(*diethylamino*)*propylamino*-1 : 3 : 5-*triazine*. 2-Amino-4-chloro-6-diazomethyl-1 : 3 : 5-triazine (1 g.) and diethylaminopropylamine (2 g.) were mixed and kept at 60—65° for 10 min. The solution obtained by adding water was extracted twice with benzene, and the benzene layer washed with water, dried (Na_2SO_4), and applied to an alumina column. Concentration of the eluate (1 : 49 methanol–benzene) gave a pale yellow *product*, m. p. 106—108° (Found: C, 50·1; H, 7·4; N, 42·1. $C_{11}H_{20}N_8$ requires C, 50·0; H, 7·6; N, 42·4%).

2-*Amino*-4-*diazomethyl*-6-*methoxy*-1 : 3 : 5-*triazine*. 2-Amino-4-chloro-6-diazomethyl-1 : 3 : 5-triazine (1·7 g.) and methanol (25 c.c.), in which sodium (0·46 g.) had previously been dissolved, were refluxed for 15 min. The cooled suspension was filtered, and the residue (m. p. 170°) left after evaporation of the filtrate crystallised from benzene. The *product* then had m. p. 182° (decomp.) (Found: C, 35·8; H, 3·9; N, 49·9. $C_5H_6ON_6$ requires C, 36·1; H, 3·6; N, 50·6%).

2-*Amino*-4-*diazomethyl*-6-*ethylthio*-1 : 3 : 5-*triazine*. A mixture of 2-amino-4-chloro-6-diazomethyl-1 : 3 : 5-triazine (1·7 g.), ethanethiol (1·5 c.c.), and methanol (25 c.c.), in which sodium (0·23 g.) had previously been dissolved, was refluxed for 15 min. The crude *product* obtained after cooling, filtration, and evaporation of the filtrate gave needles (from methanol), m. p. 204° (decomp.) (Found: C, 36·9; H, 5·3; N, 42·2; S, 15·6. $C_6H_8N_6S$ requires C, 36·75; H, 4·1; N, 42·85; S, 16·3%).

2-*Diazomethyl*-4-*dimethylamino*-6-*methylamino*-1 : 3 : 5-*triazine*. The above 2-chloro-4-diazomethyl-6-methylamino-1 : 3 : 5-triazine (9·2 g.) was stirred into 20% aqueous dimethylamine (45 c.c.) initially at 45°. A period of complete solution was followed rapidly by crystallisation of the *product* (7·2 g.), which had m. p. 118—120° when recrystallised from ethanol (Found: C, 43·9; H, 5·8; N, 48·8. $C_7H_{11}N_7$ requires C, 43·5; H, 5·7; N, 50·8%).

2-*Diazomethyl*-4-*diethylaminopropylamino*-6-*methylamino*-1 : 3 : 5-*triazine*. Prepared and purified as described above for 2-amino-4-diazomethyl-6-3′-(diethylamino)propylamino-1 : 3 : 5-triazine, from 2-chloro-4-diazomethyl-6-methylamino-1 : 3 : 5-triazine (6·6 g.) and diethylaminopropylamine (15 g.), the *product* (6 g.) had m. p. 50—51° (Found: C, 51·6; H, 8·1; N, 40·8. $C_{12}H_{22}N_8$ requires C, 51·8; H, 7·9; N, 40·3%).

2 : 4-*Diaziridyl*-6-*diazomethyl*-1 : 3 : 5-*triazine*. Dichlorodiazomethyltriazine (from 8·6 g. of cyanuric chloride) in benzene was added to a solution of ethyleneimine (6·9 g.) and triethylamine (16·5 g.) in benzene (50 c.c.) stirred at 10°. After 3 hr. the suspension was filtered and the filtrate evaporated under reduced pressure. The residue (7·2 g.) was continuously extracted with boiling light petroleum (b. p. 40—60°). The extracted product recrystallised from light petroleum–ethyl acetate as pale yellow felted prismatic needles, decomp. 120° without melting (Found: C, 47·5; H, 4·2; N, 48·0. Calc. for $C_8H_9N_7$: C, 47·3; H, 4·4; N, 48·3%). Grundmann and Kober [2] give decomp. 108° without melting.

2-*Diazomethyl*-4 : 6-*dimorpholino*-1 : 3 : 5-*triazine*. Dichlorodiazomethyltriazine (from 10·4 g. of cyanuric chloride) in benzene was added dropwise to morpholine (21·8 g.) and water

(60 c.c.) kept at 40°. After 2 hr. at 35—40°, the precipitate (9·4 g.) which was formed was collected, washed with water and benzene, and dried *in vacuo*. The *product* formed pale yellow microcrystals, m. p. 198°, from benzene (Found: C, 49·6; H, 5·8; N, 33·4. $C_{12}H_{17}O_2N_7$ requires C, 49·5; H, 5·85; N, 33·7%).

2-*Diazomethyl*-4 : 6-*dipiperidino*-1 : 3 : 5-*triazine*. Similarly prepared from the dichlorotriazine (from 10·4 g. of cyanuric chloride) in benzene, piperidine (21·2 g.), and water (60 c.c.), the *product* remained dissolved in the benzene layer and was obtained by separation and evaporation of the solvent, followed by recrystallisation from light petroleum (b. p. 80—100°); it had m. p. 107° (Found: C, 58·9; H, 6·9; N, 28·8. $C_{14}H_{21}N_7$ requires C, 58·5; H, 7·3; N, 34·1%).

2-*Diazomethyl*-4 : 6-*bisdimethylamino*-1 : 3 : 5-*triazine*. Similarly prepared from the dichlorotriazine (from 10·4 g. of cyanuric chloride) in benzene and 30% aqueous dimethylamine (37 g.), the *product* likewise remained dissolved in the benzene layer. It finally recrystallised from light petroleum (b. p. 80—100°) as yellow rosettes, m. p. 94° (Found: C, 46·2; H, 6·0; N, 47·3. $C_{18}H_{13}N_7$ requires C, 46·4; H, 6·3; N, 47·3%).

2-*Diazomethyl*-4-*dimethylamino*-6-*ethoxycarbonylmethylamino*-1 : 3 : 5-*triazine*. Powdered 2-chloro-4-diazomethyl-6-ethoxycarbonylmethylamino-1 : 3 : 5-triazine (10 g.) was stirred into 30% aqueous dimethylamine (50 c.c.) at 20°. The crystalline product (m. p. 129°) which was precipitated from the initially complete solution was collected and recrystallised from methanol; it had m. p. 138° (Found: C, 44·7; H, 5·4; N, 36·3. $C_{10}H_{15}O_2N_7$ requires C, 45·2; H, 5·6; N, 37·0%).

2-p-*Chloroanilino*-4-*diazomethyl*-6-*dimethylamino*-1 : 3 : 5-*triazine*. Similarly prepared from 2-chloro-4-*p*-chlorophenylamino-6-diazomethyl-1 : 3 : 5-triazine (7·7 g.) and 30% aqueous dimethylamine (75 c.c.), the yellow *product*, m. p. 153°, recrystallised from methanol (Found: C, 49·8; H, 5·0; N, 34·3. $C_{12}H_{12}N_7Cl$ requires C, 49·75; H, 4·15; N, 33·85%).

2-p-*Chloroanilino*-4-*diazomethyl*-6-*diethylaminopropylamino*-1 : 3 : 5-*triazine*. Prepared and purified as described above for the corresponding 2-aminotriazine, from 2-chloro-4-*p*-chlorophenylamino-6-diazomethyl-1 : 3 : 5-triazine (1·7 g.) and diethylaminopropylamine (2 g.), the *product* formed a colourless crystalline powder, m. p. 86—87° (Found : C, 54·2; H, 5·8; N, 29·9; Cl, 9·7. $C_{17}H_{23}N_8Cl$ requires C, 54·45; H, 6·15; N, 29·9; Cl, 9·5%).

2 : 4-*Bisdimethylamino*-6-*hydroxymethyl*-1 : 3 : 5-*triazine and esters therefrom*. The above diazomethyl-bisdimethylaminotriazine (10 g.) was added portionwise to cooled 2N-sulphuric acid (50 c.c.) and stirred until evolution of nitrogen had ceased. The resultant solution was gently boiled for 10 min., basified while still hot with dilute aqueous sodium hydroxide, cooled to 55° (the slight precipitate being discarded), then kept at room temperature overnight. The *product* crystallised in pale cream rhombs, m. p. 67—68° (Found: C, 48·6; H, 7·1; N, 33·0. $C_8H_{15}ON_5$ requires C, 48·7; H, 7·6; N, 35·5%).

A similar decomposition (8 g.) in 2N-hydrochloric acid led to an immediate oily precipitate (6 g.) on hot basification which when recrystallised twice from methanol gave 2-*chloromethyl*-4 : 6-*bisdimethylamino*-1 : 3 : 5-*triazine*, m. p. 78—80° (Found: C, 44·9; H, 6·7; N, 32·2. $C_8H_{14}N_5Cl$ requires C, 44·6; H, 6·5; N, 32·5%). The hydroxymethyl derivative (0·75 g.; m. p. 67—68°) was recovered from the cooled aqueous mother-liquors.

2-*Acetoxymethyl*-4 : 6-*bisdimethylamino*-1 : 3 : 5-*triazine* (2·3 g.) was likewise obtained as colourless prismatic needles, m. p. 68—70° (Found: C, 49·9; H, 7·6; N, 28·0. $C_{10}H_{17}O_2N_5$ requires C, 50·2; H, 7·1; N, 29·3%), when water (50 c.c.) was added to the diazomethyltriazine (5 g.) in cooled glacial acetic acid (10 c.c.).

2 : 4-*Bisdimethylamino*-6-(3 : 4 : 5-*trimethoxybenzoyloxymethyl*)-1 : 3 : 5-*triazine*, colourless plates (2·5 g.), m. p. 129—130° (Found: N, 17·8. $C_{18}H_{25}O_5N_5$ requires N, 17·9%), was obtained by recrystallisation from light petroleum (b. p. 80—100°) of the product from the diazomethyltriazine (2·4 g.) and 3 : 4 : 5-trimethoxybenzoic acid (3·1 g.) in dry refluxing benzene (50 c.c.) (2 hr.). An attempt to effect the same reaction in methanol gave 30% of a by-product, 2 : 4-*bisdimethylamino*-6-*methoxymethyl*-1 : 3 : 5-*triazine*, m. p. 49—51°, separated by dissolution in dilute hydrochloric acid and reprecipitation with sodium hydroxide, and recrystallised from light petroleum (b. p. 40—60°) (Found: C, 51·3; H, 8·1; N, 33·7. $C_9H_{17}ON_5$ requires C, 51·2; H, 8·05; N, 33·2%).

Research Department,
Imperial Chemical Industries Limited, Pharmaceuticals Division,
Alderley Park, Macclesfield, Cheshire.

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