Triazines and Related Products. Part 26.[1] Synthesis and Chemistry of Bicyclic Analogues of the Antitumour Drug 2,4,6-Tris(dimethylamino)-1,3,5-triazine (Hexamethylmelamine)

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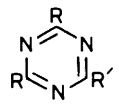
Interaction of 2,4-bis(dimethylamino)-6-hydrazino-1,3,5-triazine (**1c**) with aryl aldehydes yields a series of aryl hydrazones (**4**) which cyclise to 3-aryl-5,7-bis(dimethylamino)-1,2,4-triazolo[4,3-*a*]-[1,3,5]triazines (**6**) with lead(IV) acetate in dichloromethane. Rearrangement of these bicycles in methanolic sodium hydroxide affords stable isomeric 2-aryl-5,7-bis(dimethylamino)[1,2,4]triazolo-[1,5-*a*][1,3,5]triazines (**7**). Selected examples from both series of triazolotriazines were screened against the mouse M5076 reticulum cell sarcoma and P388 leukaemia *in vivo* but proved to have no antitumour activity.

One approach to the design of a potential second-generation analogue of the antitumour agent hexamethylmelamine (**1a**)[2,3] has been to attach sugar residues at the 6-position of the cytotoxic 2,4-bis(dimethylamino)-1,3,5-triazinyl fragment.[1] However, such compounds, although possessing desirable water solubility, have no activity against the murine M5076 ovarian sarcoma, a tumour sensitive to hexamethylmelamine.[4] In this paper we describe the synthesis of bicyclic modifications of hexamethylmelamine where the 1,3,5-triazine nucleus is conjoined to a 1,2,4-triazole ring and two dimethylamino groups are retained attached to the π-deficient ring.

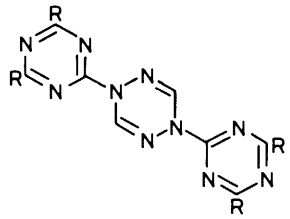


(**1**)

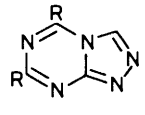
	R	R′
a;	NMe_2	NMe_2
b;	NMe_2	N_3
c;	NMe_2	$NHNH_2$
d;	NMe_2	NHNHCHO
e;	NMe_2	NHNHAc
f;	NMe_2	NH_2
g;	NMe_2	$N{=}CHNMe_2$
h;	NMe_2	$NHN{=}CHNMe_2$
i;	morpholino	NH_2
j;	morpholino	$N{=}CHNMe_2$
k;	morpholino	$NHNH_2$
l;	morpholino	$NHN{=}CHNMe_2$

Previous experience indicated that difficulties were likely to be encountered when appropriately substituted 1,3,5-triazines were subjected to conventional ring-closure processes. For example, the azidotriazine (**1b**) failed to cyclise to a tetrazolo-[1,5-*a*]triazine in a range of solvents.[1]

The hydrazinotriazine (**1c**) has been shown to afford the acyclic hydrazides (**1d**) and (**1e**) with formic acid and acetic acid respectively.[5] Interaction of the aminotriazines (**1f**) and (**1i**) with dimethylformamide dimethyl acetal yielded the formamidine derivatives (**1g**) and (**1j**) respectively. The former amidine hydrolysed to regenerate the amine (**1f**) in boiling aqueous ethanol. The corresponding dimethyl amidrazones (**1h**) and (**1l**), formed from hydrazines (**1c**) and (**1k**) and dimethylformamide dimethyl acetal, respectively, melted with concomitant liberation of dimethylamine, followed by resolidification. However, mass spectral analysis of the products confirmed them to be the 1,4-disubstituted-1,2,4,5-tetrazines (**2a**) and (**2b**) rather than the bicyclic triazolo[4,3-*a*][1,3,5]triazines (**3a**) and (**3b**) of identical elemental analytical constitution. The tetrazine (**2a**) was also formed in very low yield from hydrazinotriazine (**1c**) and refluxing triethyl orthoformate. In contrast, the formylhydrazinotriazine (**1d**) underwent cyclo-dehydration in phosphorus trichloride oxide at 95 °C to afford a poor yield of the triazolo[4,3-*a*][1,3,5]triazine (**3a**). This conversion has been accomplished more efficiently by employing phosphorus pentaoxide in boiling xylene as the dehydrating agent.[5]



(**2**)



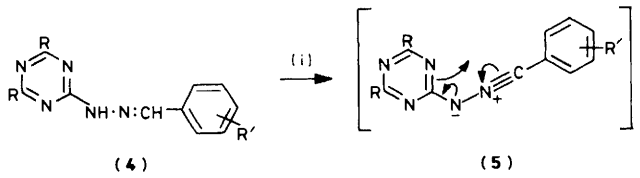
(**3**)

a; R = NMe_2
b; R = morpholino

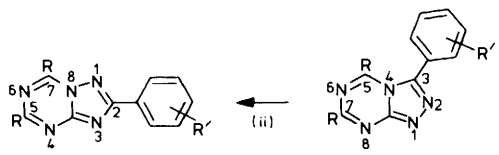
Oxidation of benzylidene derivatives of hydrazino-1,3,5-triazines with lead(IV) acetate has been employed to achieve entry into the 1,2,4-triazolo[4,3-*a*][1,3,5]triazine series.[6] We have adapted this route to prepare bicyclic systems bearing the required two dimethylamino substituents.[1]

A series of hydrazones (**4a**—**h**) was prepared from the hydrazinotriazine (**1c**) and benzaldehyde or nitro- and chlorobenzaldehydes in boiling ethanol. Similarly the hydrazinomorpholinotriazine (**1k**) reacted with 2- and 4-nitrobenzaldehyde to yield the hydrazones (**4m**) and (**4n**) respectively.

The hydrazone (**4a**), when oxidised with lead(IV) acetate in dichloromethane, afforded the 3-phenyl-1,2,4-triazolo[4,3-*a*]-[1,3,5]triazine (**6a**) which was isolated as an acetic acid solvate. The solvate crystallised unchanged from ethanol and exhibited a high-frequency carbonyl absorption (1 725 cm^{-1}) normally associated with ester functions. Despite this puzzling feature the adduct is evidently not a covalent solvate (**8a**) since its mass



(4) (5)

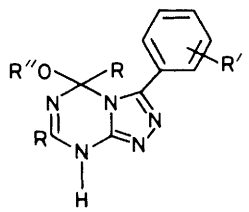


(7) (6)

R	R′	R	R′
a; NMe_2	H	**h**; NMe_2	2,4-$(NO_2)_2$
b; NMe_2	2-NO_2	**i**; NMe_2	3,5-$(NO_2)_2$
c; NMe_2	3-NO_2	**j**; NMe_2	2-NH_2
d; NMe_2	4-NO_2	**k**; NMe_2	2-NHAc
e; NMe_2	2-Cl	**l**; NMe_2	2-N_3
f; NMe_2	3-Cl	**m**; morpholino	2-NO_2
g; NMe_2	4-Cl	**n**; morpholino	4-NO_2

Scheme 1. *Reagents:* (i) Lead(IV) acetate–dichloromethane; (ii) 10% sodium hydroxide–boiling methanol

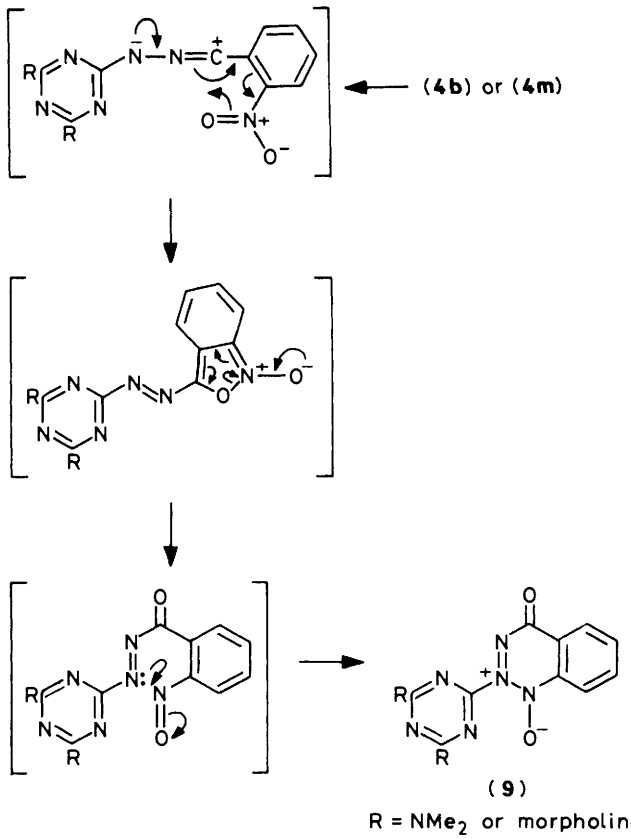
spectrum exhibited a molecular ion at *m/z* 283 ($C_{14}H_{17}N_7$) (Table 1) and the acetic acid could be totally removed from the solvate by brief treatment with aqueous sodium hydrogencarbonate. Moreover the chemical shifts of the 5- and 7-NMe_2 protons were uninfluenced by solvation with acetic acid (Table 1).



(8)

R	R′	R″
a; NMe_2	H	Ac
b; morpholino	2-NO_2	H
c; morpholino	4-NO_2	H

The mechanism of this type of cyclisation is considered[6] to involve a reactive nitrilium species (**5**) in which the electrophilic carbon atom is intercepted by the azine ring nitrogen (Scheme 1). We were interested to observe the outcome when the nitrilium species was offered a choice of *two* nucleophilic sites at which to cyclise. Thus on the basis of precedents established in the oxidative cyclisation of simple arylhydrazones of 2-nitrobenzaldehyde,[7,8] interception of the nitrilium intermediate generated from the nitro-derivatives (**4b** and **m**) might be expected to furnish 2-triazinyl-1,2,3-benzotriazinium oxides (**9**; R = NMe_2 or morpholino) (Scheme 2). However, the absence of carbonyl absorptions in the products isolated from these hydrazones excluded the *ortho*-nitro interaction possibility: in fact the products formed in high yield from the lead(IV) acetate oxidation of dimethyl-substituted triazinylhydrazones (**4b**—**g**) were the unsolvated triazolo[4,3-*a*][1,3,5]triazines (**6b**—**g**)



(**4b**) or (**4m**)

(**9**)

R = NMe_2 or morpholino

Scheme 2.

respectively. In contrast, the morpholino-substituted hydrazones (**4m** and **n**) under similar conditions afforded products tentatively identified as the covalent hydrates (**8b** and **c**) respectively. Although no satisfactory microanalyses could be obtained to support this assignment their mass spectra showed molecular ions at *m/z* 430 (Table 1), indicative of covalent incorporation of water into the expected molecular formula $C_{18}H_{20}N_8O_4$ (*m/z* 412). Alternative ring-opened structures are excluded by the absence of carbonyl absorptions in the i.r. spectra of the water adducts. Presumably the bulky morpholino substituents can be accommodated more comfortably if C-5 adopts a tetrahedral geometry similar to the structures of comparable covalent adducts in the [1,2,4]triazolo[5,1-*c*]-[1,2,4]triazine field.[9] In fact, such adducts as observed in this work could be considered as 'Dimroth intermediates' along the reaction pathway (**6**) ⟶ (**7**) and the triazolo[4,3-*a*]triazines (**6a**—**g**), although stable in polar and non-polar solvents, underwent rapid rearrangement in 10% methanolic sodium hydroxide to give the corresponding [1,5-*a*] isomers (**7a**—**g**). When these reactions were monitored by t.l.c. (silica gel; chloroform–methanol as developing solvent) the [1,5-*a*] series were the faster moving isomers in each case and in boiling methanol the reaction went to completion within 1 h.

In the series of hydrazones (**4**) the *N*-methyl resonance absorbed at δ 3.11—3.20. The pairs of isomeric compounds (**6**) and (**7**) could be recognised easily by the chemical shift of their *N*-methyl groups (Table 1). Thus the 5-dimethylamino protons are shielded by the 3-aryl group (Figure) in the [4,3-*a*] series and appear about 1 p.p.m. upfield of the corresponding protons in the [1,5-*a*] series: the 7-dimethylamino protons ([4,3-*a*] series) are uninfluenced by the disposition of the aryl substituent and absorb at δ 3.22 (±0.05) in both isomeric series.

Table 1. Spectral characteristics of 1,2,4-triazolo[4,3-*a*][1,3,5]triazines (**6**) and [1,2,4]triazolo[1,5-*a*][1,3,5]triazines (**7**) and (**8**)

Compound	^{1}H N.m.r. spectra [a] (δ)		Mass spectra [b] (*m*/*z*) (% intensity)
(**6a**)	2.67[c]	3.23[c]	283(100), 268(31), 254(14), 240(16), 214(10), 213(9), 180(8), 170(13), 137(23), 103(16), 96(19), 82(43), 67(62)
(**6a**)·acetic acid solvate	2.68[d]	3.24[d]	283(100), 268(40), 254(12), 240(15), 214(10), 213(8), 170(18), 137(30), 109(8), 103(12), 96(20), 85(25), 82(50), 72(13), 69(13), 67(25)
(**6b**)	2.55	3.27	328(22), 298(10), 296(6), 253(37), 238(27), 210(22), 182(22), 166(30), 134(24), 96(100)
(**6c**)	2.78	3.26	328(14), 313(7), 298(20), 283(8), 193(40), 167(60), 151(30), 150(50), 137(100), 121(60), 120(50), 105(30), 104(40)
(**6d**)	2.55	3.26	328(19), 318(8), 298(46), 283(11), 238(14), 185(14), 176(27), 129(30), 111(38), 109(30), 98(49), 97(68), 96(51), 95(51), 85(49), 83(89), 82(57), 81(62), 73(51), 71(78), 69(100)
(**6e**)	2.60	3.23	319(30), 317(100), 304(8), 302(23), 290(3), 288(8), 282(15), 276(3), 274(8), 250(3), 248(8), 137(25), 96(22), 82(45), 67(56)
(**6f**)	2.73	3.23	319(28), 317(100), 304(12), 302(38), 290(6), 288(18), 276(6), 274(18), 250(3), 248(12), 137(68), 96(44), 82(97), 69(38), 67(100)
(**6g**)	2.73	3.25	
(**7a**)	3.53[e]	3.19[e]	283(100), 268(13), 254(30), 240(26), 214(22), 200(13), 199(13), 180(17), 169(15), 144(13), 137(39), 110(26), 96(35), 77(24), 71(28), 69(24), 67(48)
(**7b**)	3.47	3.20	328(100), 313(38), 311(36), 298(36), 285(16), 283(13), 180(56), 137(51), 96(73), 71(36), 69(33), 67(60)
(**7c**)	3.57	3.20	328(90), 313(39), 299(50), 298(100), 283(45), 269(21), 255(18), 180(21), 138(33), 137(30), 96(45), 71(36), 69(30), 67(45)
(**7d**)	3.55	3.28	328(100), 315(29), 313(51), 299(51), 298(80), 285(24), 283(29), 185(7), 180(22), 176(54), 149(20), 138(29), 137(44), 130(22), 119(17), 118(32), 110(12), 109(22), 96(44), 82(24), 71(37), 69(27), 67(54)
(**7e**)	3.55	3.20	319(36), 317(100), 304(19), 302(56), 290(11), 288(31), 276(8), 274(28), 250(11), 248(31), 180(42), 137(61), 109(36), 96(64), 71(42), 67(61)
(**7f**)	3.48	3.17	319(36), 317(100), 304(21), 302(61), 290(9), 288(30), 276(9), 274(27), 250(6), 248(21), 180(24), 137(61), 109(30), 96(52), 71(36), 67(58)
(**7g**)	3.53	3.20	319(34), 317(100), 304(21), 302(55), 290(11), 288(32), 276(10), 274(27), 250(6), 248(21), 180(24), 137(47), 109(26), 96(44), 71(29), 67(47)
(**7j**)	3.43	3.17	298(100), 283(22), 268(16), 254(16), 184(18), 180(19), 138(24), 137(27), 113(21), 96(21), 83(55), 71(21), 69(18), 67(37)
(**7k**)	3.53[f]	3.20	340(25), 326(20), 325(100), 298(10), 256(10), 255(50), 240(15), 185(7), 184(5), 180(8), 157(8), 144(10), 118(10), 96(30), 83(11), 71(18), 67(23)
(**7l**)	3.53	3.20	324(9), 298(54), 283(37), 268(15), 255(10), 254(11), 240(10), 166(41), 149(47), 96(100), 71(51), 69(38), 67(24)
(**7m**)			412(2), 383(7), 337(21), 336(85), 335(24), 307(24), 306(100), 305(40), 293(37), 291(27), 279(80), 276(42), 275(37), 261(57), 249(50), 221(30), 219(24), 153(26), 138(40), 113(17), 94(27), 82(22), 69(28), 68(27)
(**8b**)			430(1), 337(19), 336(83), 335(26), 307(26), 306(100), 305(42), 293(40), 291(28), 279(79), 276(44), 275(40), 263(63), 249(49), 221(28), 219(26), 153(20), 138(44), 105(37), 96(12), 94(30), 91(30), 71(21), 69(44)
(**8c**)			430(36), 413(14), 412(54), 400(16), 383(27), 382(100), 381(32), 355(29), 351(29), 337(23), 325(43), 236(25), 235(29), 221(20), 209(18), 280(18), 150(16), 138(18), 120(68), 118(59), 83(43), 69(34), 66(29)

[a] Recorded on a Varian EM 360A spectrometer in deuteriochloroform solution. [b] Recorded on a V.G. Micromass 12 instrument at 70 eV; source temperature 250—300 °C. [c] Lit. values (ref. 5) δ 2.7 (5-NMe_2) and 3.22 (7-NMe_2). [d] Also shows absorptions at δ 2.12 (3 H, s, CH_3CO_2H) and 12.2 (1 H, s, CH_3CO_2H). [e] Lit. values (ref. 5) δ 3.52 (7-NMe_2) and 3.2 (5-NMe_2). [f] Also shows an absorption at δ 2.25 (3 H, s, CH_3CO).

Steric crowding between the 3- and 5-substituents in the unstable [4,3-*a*] series may offer a partial explanation for the ease with which these compounds rearrange to the [1,5-*a*] isomers. The Dimroth rearrangement is initiated by nucleophilic attack at the electrophilic carbon atom (C-5) of the azine ring.[10] Electron-deficiency at this centre is enhanced by polyaza-substitution in the azine ring, but in the present cases is countered by the mesomeric effect of the 5-dimethylamino-substituents. The principal driving force for rearrangement in 1,2,4-triazoloazines, in general,[11] originates from electronic interactions between the sp^2 lone-pair orbitals on the adjacent triazole ring nitrogens. This effect and the aforementioned *peri*-interaction between the 3- and 5-substituents in the [4,3-*a*] series can be relieved by rearrangement to the thermodynamically preferred [1,5-*a*] isomers (Figure).

The u.v. spectra of the hydrazones (**4**) exhibit two bands; the major peak occurs at 227—229 nm and a minor peak at 305—317 nm. Addition of acid increases the intensity of the minor peak relative to the major with a concurrent hypsochromic shift (3—10 nm). The triazolo[4,3-*a*]triazines (**6**) similarly have two bands in their u.v. spectra at 228—238 nm (major) and 260—275 nm (minor). Addition of acid elicits a hyperchromic and hypsochromic effect (1—10 nm) on the minor peak. The triazolo[1,5-*a*]triazines (**7**) show only one major peak (227—244 nm) with a second peak (253—335 nm) which is generally only manifested as a shoulder, or, if significantly shifted, observed as a minor feature only. Addition of acid has no effect on the spectra in this series. Addition of base to ethanolic solutions of the hydrazones (**4**) and the bicyclic compounds (**6**) and (**7**) had no effect on the positions or intensities of the main absorption bands.

The mass spectra of typical examples of hydrazones (**4**) indicate that initial losses of imine molecules or methyl radicals from the dimethylamino groups occur to only a minor extent. The major fragmentation involves loss of an aryl cyanide and produces an ion at *m*/*z* 182 corresponding to the radical ion of 2-amino-4,6-bis(dimethylamino)-1,3,5-triazine (**1f**): subsequent losses are typically those characteristic of methylmelamines.[12] The mass spectra of both bicyclic series show molecular ions of high abundance and losses from the dimethylamino moieties represent major features: production of peaks at *m*/*z* 137, 96, 82, 71, 69, and 67 are common to all the analogues and represent

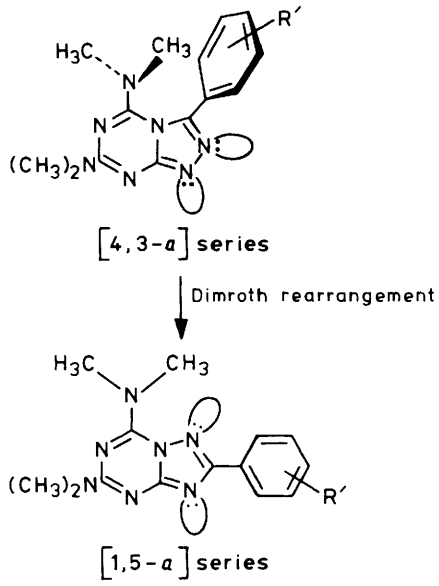


Figure. Steric and electronic interactions in isomeric triazolotriazines; for R′ see Scheme 1

fragments derived from the 1,3,5-triazine component of the bicycles.

Nitration of the 2-phenyltriazolotriazine (**7a**) at room temperature afforded an inseparable mixture of dinitrated products, probably (**7h**) and (**7i**). T.l.c. examination of the products confirmed the absence of the mononitrophenyl derivatives (**7b—d**). Reduction of the *o*-nitrophenyltriazolotriazine (**7b**) by hydrogen over a 5% palladium–charcoal catalyst, or by hydrazine and Raney nickel in ethanol, yielded the strongly fluorescent (under u.v. light) amine (**7j**) which gave an acetyl derivative (**7k**) in hot acetic anhydride and was smoothly converted into the azide (**7l**) by the diazotisation–azidation route. Results of our effort to effect de-oxidative cyclisation of the *o*-nitrophenyltriazolotriazines (**6b**) and (**7b**), oxidative cyclisation of the amine (**7j**), and thermal and photochemical cyclisation of the azide (**7l**) to tetracyclic heterocycles will be reported in a future paper in this series.

Certain of the mono- and bi-cyclic 1,3,5-triazines described in this paper were tested for inhibitory activity against the mouse M5076 reticulum cell sarcoma *in vivo* (Table 2). Only hexamethylmelamine (**1a**) and 2-amino-4,6-bis(dimethylamino)-1,3,5-triazine (**1f**) had any activity against this tumour.

The hydrazone (**4d**) and the triazolotriazines (**6b**), (**7b**), (**7d**), and (**7m**) had no inhibitory effect against the P388 lymphocytic leukaemia in mice *in vivo* at doses of 400 mg kg^{-1} on a 9-day dosage schedule. A correlation has been established between *in vivo* activity of methylmelamines against mouse tumours and plasma levels of formaldehyde precursors—presumably *N*-hydroxymethylmelamines[13]—formed by oxidative metabolism of the *N*-methyl group. The inactivity of the bicyclic analogues of hexamethylmelamine may be explained by their being poor substrates for oxidative demethylation. Thus, when incubated with mouse liver microsomes and appropriate cofactors, the bicycles (**6a**), (**6e**), (**7a**), and (**7e**) afforded only 18, 14, 35, and 16%, respectively, of the levels of demethylation achieved with the clinically active drug hexamethylmelamine (**1a**).[14] However, demethylation *in vitro* does not always reflect the *in vivo* oxidative process.[13] Thus while 2-amino-4,6-bis(dimethylamino)-1,3,5-triazine (**1f**) is only demethylated to the extent of 38% of that of hexamethylmelamine *in vitro*, it is demethylated almost as efficiently *in vivo* and has antitumour properties (Table 2).

Table 2. Activity of mono- and bi-cyclic melamines against the M5076 reticulum cell sarcoma *in vivo*[a]

Compound	Dose schedule[b]	Dose (mg kg^{-1})	% Inhibition of tumour volume[c]
(**1a**)	A	150[d]	70
(**1b**)	B	40[d]	0
(**1c**)	B	160[d]	22
(**1f**)	B	160[d]	92
(**4a**)	A	200	14
(**4b**)	A	200	12
(**4d**)	A	200	14
(**4f**)	A	200	14
(**4g**)	A	200	1
(**6a**)	A	200	14
(**6b**)	A	200[d]	6
(**6e**)	A	200	29
(**7a**)	A	200	4
(**7e**)	A	300[d]	26

[a] A suspension of 10^6 M5076 cells (from a routine passage grown as a solid subcutaneous tumour in BDF_1 mice) was injected intramuscularly into the left hind-leg of groups of ten female BDF_1 mice (18—23 g). Drugs were administered according to schedules A or B and mean tumour volumes measured by calipers every fourth day from day 12 until day 24. [b] A Animals dosed on days 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, and 21. B Animals dosed on days 1—17. [c] On day 24. [d] Approximate LD_{10} dose on a 2-day dosage schedule.

The low demethylation values allied with the lack of evidence of *in vivo* antitumour activity indicate that the bicyclic heterocycles prepared in the present work are unlikely candidates for clinical evaluation.

Experimental

Light petroleum refers to the fraction boiling in the range 60–80 °C.

N^2-[4,6-*Bis*(*dimethylamino*)-1,3,5-*triazin*-2-*yl*]-N′N′-*dimethylformamidine* (**1g**).—A solution of 2-amino-4,6-bis(dimethylamino)-1,3,5-triazine (**1f**) (2.0 g)[1] was refluxed in *NN*-dimethylformamide dimethyl acetal (2.0 g) for 3 h. The cooled solution deposited the *formamidine* (**1g**) (78%), m.p. 186—188 °C (from light petroleum–chloroform); $\delta_H(CDCl_3)$ 3.16 (18 H, s, 6 × CH_3) and 8.77 (1 H, s, CH) (Found: C, 50.5; H, 8.3; N, 41.6. $C_{10}H_{19}N_7$ requires C, 50.6; H, 8.1; N, 41.3%). Hydrolysis of the formamidine in boiling 10% aqueous ethanol for 2 h regenerated the starting amine (**1f**) in 54% yield. The hydrochloride salt of (**1g**), prepared by passing hydrogen chloride through a chloroform solution of the base, had m.p. 246—260 °C.

Similarly prepared from the aminotriazine (**1i**) and dimethylformamide dimethyl acetal was N^2-(4,6-*dimorpholino*-1,3,5-*triazin*-2-*yl*)-N′N′-*dimethylformamidine* (**1j**) in 70% yield, m.p. 190—192 °C (Found: C, 52.4; H, 7.4; N, 30.6. $C_{14}H_{23}N_7O_2$ requires C, 52.3; H, 7.6; N, 30.5%); $\delta_H(CDCl_3)$ 3.17 (6 H, s, 2 × CH_3), 3.78 (16 H, s, 8 × CH_2), and 8.70 (1 H, s, CH).

NN-*Dimethylformamide* N′-[4,6-*Bis*(*dimethylamino*)-1,3,5-*triazin*-4-*yl*]*hydrazone* (**1h**).—Interaction of 2,4-bis(dimethylamino)-6-hydrazino-1,3,5-triazine (**1c**) (2.0 g) in boiling *NN*-dimethylformamide dimethyl acetal (2.0 g) for 0.5 h afforded the *triazine* (**1h**) (59%) which crystallised from light petroleum–chloroform with m.p. 163—165 °C (resolidifies, then melts 320—325 °C) (Found: C, 47.5; H, 8.2; N, 44.2. $C_{10}H_{20}N_8$

requires C, 47.6; H, 8.0; N, 44.4%); $\delta_H(CDCl_3)$ 2.90 (6 H, s, 2 × CH_3), 3.11 (12 H, s, 4 × CH_3), and 7.70 (1 H, s, CH). The hydrochloride salt had m.p. 203—206 °C (resolidifies, then melts 280 °C).

Similarly prepared from the hydrazinotriazine (**1k**) and dimethylformamide dimethyl acetal was the *morpholinotriazine* (**1l**) (59%), m.p. 135—145 °C [resolidifies, then melts 335—340 °C (decomp.)] (Found: C, 50.0; H, 7.0; N, 33.1. $C_{14}H_{24}N_8O_2$ requires C, 50.0; H, 7.2; N, 33.1%); $\delta_H(CDCl_3)$ 2.75 (6 H, s, 2 × CH_3), 3.58 (16 H, s, 8 × CH_2), 7.22 (1 H, d, CH), and 8.65 (1 H, br s, NH, disappears with D_2O).

1,4-*Bis*-[4,6-*bis*(*dimethylamino*)-1,3,5-*triazin*-2-*yl*]-1,4-*dihydro*-1,2,4,5-*tetrazine* (**2a**).—The triazine (**1h**) (1.0 g) was heated at 200 °C until evolution of gas (dimethylamine) ceased. The residue crystallised from chloroform–light petroleum to yield the *tetrazine* (**2a**) (0.6 g), m.p. 316—318 °C (Found: C, 46.5; H, 6.2; N, 47.1%; M^+, 414.2463. $C_{16}H_{26}N_{14}$ requires C, 46.4; H, 6.3; N, 47.3%; *M*, 414.2465); $\delta_H(CDCl_3)$ 3.15 (12 H, s, 4 × CH_3) and 8.10 (2 H, s, CH). The same (m.p. and i.r.) tetrazine (**2a**) slowly crystallised (10% yield) when the hydrazinotriazine (**1c**) was refluxed in triethyl orthoformate for 2 h.

Similarly prepared, by thermolysis of the morpholinotriazine (**1l**) at 240 °C for 0.5 h, was 1,4-(*bis*-4,6-*dimorpholino*-1,3,5-*triazin*-2-*yl*)-1,4-*dihydro*-1,2,4,5-*tetrazine* (**2b**) (50%), m.p. 340 °C (decomp.) (Found: M^+, 582.2887. $C_{24}H_{34}N_{14}O_4$ requires *M*, 582.2887).

5,7-*Bis*(*dimethylamino*)-1,2,4-*triazolo*[4,3-*a*][1,3,5]*triazine* (**3a**).—A mixture of 2,4-bis(dimethylamino)-6-(N^2-formylhydrazino)-1,3,5-triazine (**1d**) (1.5 g)[5] and phosphorus trichloride oxide (5 ml) was heated on a steam-bath for 3 h. The clear solution was cooled, quenched with ice–water, neutralised to pH 6.5 with sodium acetate trihydrate–aqueous ammonia, and extracted with chloroform (3 × 100 ml). The combined, dried (anhydrous sodium sulphate) extracts were evaporated to yield an oil which was dissolved in benzene and insoluble material separated out. The benzene-soluble product was precipitated with light petroleum and afforded the triazolotriazine (**3a**) (0.55 g), identical (i.r.) with an authentic specimen.[5]

2-*Benzylidenehydrazino*-4,6-*bis*(*dimethylamino*)-1,3,5-*triazine* (**4a**).—A mixture of hydrazinotriazine (**1c**) (3.0 g) and benzaldehyde (1.8 g) was refluxed in ethanol (10 ml) containing toluene-*p*-sulphonic acid (0.05 g) for 2 h. Work-up gave the *benzylidene-derivative* (**4a**) (89%), m.p. 100—102 °C (cream needles from ethanol) (Found: C, 58.8; H, 6.9; N, 34.5%; M^+, 285. $C_{14}H_{19}N_7$ requires C, 58.9; H, 6.7; N, 34.4%; *M*, 285).

Similarly prepared were the following hydrazones: 2,4-*bis*(*dimethylamino*)-6-(2-*nitrobenzylidenehydrazino*)-1,3,5-*triazine* (**4b**), in 70% yield, m.p. 167—169 °C (yellow needles from ethanol) (Found: C, 50.7; H, 5.6; N, 33.8. $C_{14}H_{18}N_8O_2$ requires C, 50.9; H, 5.5; N, 33.9%); 2,4-*bis*(*dimethylamino*)-6-(3-*nitrobenzylidenehydrazino*)-1,3,5-*triazine* (**4c**), in 98% yield, m.p. 175—177 °C (cream needles from ethanol) (Found: C, 50.8; H, 5.4; N, 33.6%); 2,4-*bis*(*dimethylamino*)-6-(4-*nitrobenzylidenehydrazino*)-1,3,5-*triazine* (**4d**), in 95% yield, m.p. 226—228 °C (yellow needles from acetic acid–ethanol) (Found: C, 50.7; H, 5.5; N, 33.7%); 2-(2-*chlorobenzylidenehydrazino*)-4,6-*bis*(*dimethylamino*)-1,3,5-*triazine* (**4e**), as white needles, m.p. 138—140 °C (from ethanol) (Found: C, 52.2; H, 5.7; N, 30.4. $C_{14}H_{18}ClN_7$ requires C, 52.6; H, 5.6; N, 30.7%); 2-(3-*chlorobenzylidenehydrazino*)-4,6-*bis*(*dimethylamino*)-1,3,5-*triazine* (**4f**), as white crystals, m.p. 158—160 °C (from ethanol) (Found: C, 52.8; H, 5.7; N, 30.9%); 2-(4-*chlorobenzylidenehydrazino*)-4,6-*bis*(*dimethylamino*)-1,3,5-*triazine* (**4g**), as white crystals, m.p. 207—209 °C (Found: C, 52.5; H, 5.8; N, 30.7%); 2,4-*bis*(*dimethylamino*)-6-(2,4-*dinitrobenzylidenehydrazino*)-1,3,5-*triazine* (**4h**), in 90% yield, m.p. 262—263 °C (decomp.) (golden needles from dimethylformamide) (Found: C, 44.5; H, 4.3; N, 33.3. $C_{14}H_{17}N_9O_4$ requires C, 44.8; H, 4.5; N, 33.6%); 2,4-*dimorpholino*-6-(2-*nitrobenzylidenehydrazino*)-1,3,5-*triazine* (**4m**), in 83% yield, m.p. 226—228 °C (from light petroleum–chloroform) (Found: C, 52.3; H, 5.5; N, 27.2 $C_{18}H_{22}N_8O_4$ requires C, 52.2; H, 5.3; N, 27.0%); 2,4-*dimorpholino*-6-(4-*nitrobenzylidenehydrazino*)-1,3,5-*triazine* (**4n**), in 92% yield, m.p. 298—300 °C (as yellow crystals from ethanol–chloroform) (Found: C, 52.4; H, 5.5; N, 27.2%).

5,7-*Bis*(*dimethylamino*)-3-*phenyl*-1,2,4-*triazolo*[4,3-a]-[1,3,5]*triazine* (**6a**).—The hydrazone (**4a**) (2.85 g) was dissolved in dichloromethane (100 ml) and the solution was treated at 25 °C during 5 min with a solution of lead(IV) acetate (6.0 g; Aldrich Chemical Co. Ltd.) in dichloromethane (10 ml). The solution warmed up to 38 °C and developed a red-brown colour. After being stirred for 1.5 h the mixture was shaken with water (100 ml) for 2 h. The dichloromethane layer was separated and the aqueous layer was re-extracted with more dichloromethane (3 × 50 ml). The pooled organic layers were shaken with aqueous sodium hydrogen carbonate to remove acetic acid, then dried (anhydrous sodium sulphate) and evaporated to yield a cream gum which crystallised when stirred with light petroleum. The triazolotriazine (80%) crystallised from toluene–light petroleum with m.p. 173—174 °C (lit.,[5] 172—173 °C).

When the triazolotriazine (**6a**) was shaken in dichloromethane containing 5% acetic acid the *acetic acid solvate* was formed. The solvate crystallised as thick needles from toluene–light petroleum or ethanol with m.p. 126—128 °C (Found: C, 55.6; H, 5.9; N, 28.2 $C_{14}H_{17}N_7 \cdot CH_3CO_2H$ requires C, 56.0; H, 6.1; N, 28.6%); $\nu_{max.}$(KBr) 2 700—2 300 (bonded OH) and 1 725 cm^{-1} (C=O). The solvated triazolotriazine (**6a**) (95%) was also formed when the hydrazone (**4a**) was oxidised (as above) with lead(IV) acetate but the step involving the sodium hydrogencarbonate wash was omitted.

When the acetic acid solvate was shaken with dichloromethane and aqueous sodium hydrogencarbonate, only the unsolvated triazolotriazine was recovered.

The following triazolo[4,3-*a*][1,3,5]triazines were prepared by oxidising the corresponding hydrazones with lead(IV) acetate in dichloromethane and washing the dichloromethane fractions with aqueous sodium hydrogencarbonate: 5,7-*bis*(*dimethylamino*)-3-(2-*nitrophenyl*)-1,2,4-*triazolo*[4,3-a][1,3,5]*triazine* (**6b**) (78%) as golden prisms, m.p. 253—255 °C (efferv.) (from ethanol) (Found: C, 51.3; H, 5.0; N, 34.3. $C_{14}H_{16}N_8O_2$ requires C, 51.2; H, 4.9; N, 34.1%); 5,7-*bis*(*dimethylamino*)-3-(3-*nitrophenyl*)-1,2,4-*triazolo*[4,3-a][1,3,5]*triazine* (**6c**) (80%) as yellow rosettes, m.p. 195—197 °C (from toluene–light petroleum) (Found: C, 51.5; H, 5.1; N, 34.0%); 5,7-*bis*(*dimethylamino*)-3-(4-*nitrophenyl*)-1,2,4-*triazolo*[4,3-a][1,3,5]*triazine* (**6d**) (65%) as yellow crystals, m.p. 260—262 °C (decomp.) from ethanol (Found: C, 51.3; H, 5.1; N, 34.15%); 3-(2-*chlorophenyl*)-5,7-*bis*(*dimethylamino*)-1,2,4-*triazolo*[4,3-a][1,3,5]*triazine* (**6e**) (80%) as white crystals, m.p. 222—224 °C (from chloroform–methanol) (Found: C, 52.6; H, 5.0; N, 30.7. $C_{14}H_{16}ClN_7$ requires C, 52.9; H, 5.0; N, 30.9%); 3-(3-*chlorophenyl*)-5,7-*bis*(*dimethylamino*)-1,2,4-*triazolo*[4,3-a][1,3,5]*triazine* (**6f**) (60%) as white crystals, m.p. 191—193 °C (from chloroform–methanol) (Found: C, 52.6; H, 5.0; N, 30.3%); 3-(4-*chlorophenyl*)-5,7-*bis*(*dimethylamino*)-1,2,4-*triazolo*[4,3-a][1,3,5]*triazine* (**6g**) (55%) as white crystals, m.p. 197—199 °C (from chloroform–methanol) (Found: C, 52.7; H, 5.7; N, 31.1%); 5,8-dihydro-5-hydroxy-5,7-dimorpholino-3-(2-nitrophenyl)-1,2,4-triazolo-[4,3-a][1,3,5]*triazine* (**8b**) (35%), m.p. 275—278 °C (efferv.) (from toluene–ethanol) (Found: M^+, 430. $C_{18}H_{22}N_8O_5$ requires *M*, 430); 5,8-dihydro-5-hydroxy-5,7-dimorpholino-3-(4-

nitrophenyl)-1,2,4-triazolo[4,3-*a*][1,3,5]triazine (**8c**) (35%), m.p. 261—263 °C (chloroform–light petroleum) (Found: M^+, 430. $C_{18}H_{22}N_8O_5$ requires *M*, 430).

5,7-*Bis*(*dimethylamino*)-2-*phenyl*[1,2,4]*triazolo*[1,5-a]-[1,3,5]*triazine* (**7a**).—The triazolo[4,3-*a*][1.3,5]triazine (**6a**) (1.8 g) was boiled (1 h) in methanol (20 ml) containing sodium hydroxide (0.4 g). The mixture was diluted with water (30 ml) and the white solid was collected. The phenyltriazolotriazine (**7a**) (96%) crystallised from methanol as white needles, m.p. 235—236 °C (lit.,[5] 230—231 °C). The same phenyltriazolotriazone (85%) was isolated when the acetic acid solvate of (**6a**) was employed as starting material.

Similarly prepared by rearrangement of the corresponding triazolo[4,3-*a*][1,3,5]triazines (**6**) were the following: 5,7-*bis*-(*dimethylamino*)-2-(2-*nitrophenyl*)[1,2,4]*triazolo*[1,5-a][1,3,5]-*triazine* (**7b**) (94%) as cream needles, m.p. 239—241 °C (from methanol) (Found: C, 51.3; H, 5.1; N, 34.1. $C_{14}H_{16}N_8O_2$ requires C, 51.2; H, 4.9; N, 34.1%); 5,7-*bis*(*dimethylamino*)-2-(3-*nitrophenyl*)[1,2,4]*triazolo*[1,5-a][1,3,5]*triazine* (**7c**) (70%) as fine cream needles, m.p. 251—253 °C (from ethanol) (Found: C, 50.9; H, 5.0; N, 34.0%); 5,7-*bis*(*dimethylamino*)-2-(4-*nitrophenyl*)-[1,2,4]*triazolo*[1,5-a][1,3,5]*triazine* (**7d**) (70%) as cream needles, m.p. 277—279 °C (from chloroform–light petroleum) (Found: C, 51.0; H, 4.8; N, 34.0%); 2-(2-*chlorophenyl*)-5,7-*bis*(*dimethylamino*)[1,2,4]*triazolo*[1,5-a][1,3,5]*triazine* (**7e**) (87%) as white crystals, m.p. 206—208 °C (from chloroform–methanol) (Found: C, 52.8; H, 5.1; N, 30.8. $C_{14}H_{16}ClN_7$ requires C, 52.9; H, 5.0; N, 30.9%); 2-(3-*chlorophenyl*)-5,7-*bis*(*dimethylamino*)[1,2,4]*triazolo*[1,5-a][1,3,5]*triazine* (**7f**) (90%) as white crystals, m.p. 211—213 °C (from chloroform–methanol) (Found: C, 52.7; H, 5.0; N, 30.8%); 2-(4-*chlorophenyl*)-5,7-*bis*(*dimethylamino*)[1,2,4]*triazolo*[1,5-a][1,3,5]*triazine* (**7g**) (85%) as white crystals, m.p. 170—172 °C (from chloroform–methanol) (Found: C, 53.0; H, 5.0; N, 30.6%); 5,7-*dimorpholino*-2-(2-*nitrophenyl*)[1,2,4]*triazolo*[1,5-a][1,3,5]*triazine* (**7m**), prepared from compound (**8b**) and methanolic sodium hydroxide in 85% yield, m.p. 208 °C (from chloroform–light petroleum) (Found: C, 52.2; H, 4.9; N, 27.6. $C_{18}H_{20}N_8O_4$ requires C, 52.4; H, 4.9; N, 27.2%).

Nitration of 5,7-*Bis*(*dimethylamino*)-2-*phenyl*[1,2,4]*triazolo*[1,5-a][1,3,5]*triazine* (**7a**).—The triazolo[1,5-*a*]triazine (**7a**) (1.0 g) was added portionwise during 0.5 h to a mixture of concentrated sulphuric acid (15 ml) and concentrated nitric acid (*d* 1.42; 15 ml) maintained at 25—30 °C. The mixture was maintained at 25 °C overnight and then basified with a concentrated aqueous ammonia–ice mixture. The cream solid (1.12 g) was collected, washed with water, dissolved in chloroform, and chromatographically fractionated on silica gel plates (0.25 mm) employing acetone–toluene (3:7) as developing solvent and the triazolotriazines (**7a**—**d**) and (**7h**) as reference compounds. The main product (R_F 0.78) and minor product (R_F 0.44) did not co-chromatograph with any of the reference compounds, and the main product is possibly the dinitrophenyltriazolotriazine (**7i**).

2-(2-*Aminophenyl*)-5,7-*bis*(*dimethylamino*)[1,2,4]*triazolo*-[1,5-a][1,3,5]*triazine* (**7j**).—(i) A solution of 5,7-bis(dimethylamino)-2-(2-nitrophenyl)[1,2,4]triazolo[1,5-a][1,3,5]triazine (**7b**) (2.0 g) in ethanol (200 ml) was hydrogenated for 3 d over a 5% palladium–charcoal catalyst (0.3 g) at atmospheric pressure. The strongly blue fluorescent mixture was filtered through Kieselguhr to remove the catalyst and the solvent was evaporated off. The *aminophenyltriazolotriazine* (**7j**) (95%) crystallised from chloroform–methanol as cream prisms, m.p. 219—221 °C (Found: C, 56.2; H, 6.0; N, 37.3. $C_{14}H_{18}N_8$ requires C, 56.4; H, 6.0; N, 37.3%); $\nu_{max.}$(KBr) 3 420 and 3 310 cm^{-1} (NH).

(ii) The same (m.p. and i.r.) aminophenyltriazolotriazine (85%) was formed when the nitrophenyltriazolotriazine (**7b**) was reduced with Raney-nickel and hydrazine[15] in ethanol at 60—65 °C.

When the aminophenyltriazolotriazine (**7j**) (1.0 g) was refluxed in acetic acid (10 ml) and acetic anhydride (5 ml) for 2 h, 2-(2-*acetamidophenyl*)-5,7-*bis*(*dimethylamino*)[1,2,4]*triazolo*[1,5-a][1,3,5]*triazine* (**7k**) (65%), m.p. 263—265 °C (from aqueous acetic acid), was formed (Found: C, 56.6; H, 5.9; N, 33.0. $C_{16}H_{20}N_8O$ requires C, 56.5; H, 5.9; N, 32.9%); $\nu_{max.}$(KBr) 3 270 (NH) and 1 969 cm^{-1} (C=O).

2-(2-*Azidophenyl*)-5,7-*bis*(*dimethylamino*)[1,2,4]*triazolo*-[1,5-a][1,3,5]*triazine* (**7l**).—A solution of the amine (**7j**) (2.0 g) in 2M-hydrochloric acid (20 ml) was cooled to 0 °C and diazotised by an aqueous solution of sodium nitrite (0.7 g in 5 ml). Addition of sodium azide (1.0 g) to the stirred mixture (1 h), followed by basification with aqueous ammonia, gave a mixture which was extracted with chloroform (4 × 25 ml). The combined extracts were dried (anhydrous sodium sulphate) and evaporated to yield the *azidophenyltriazolotriazine* (**7l**) which crystallised from chloroform–methanol as brown prisms, m.p. 178—180 ° (decomp.), which darkened on exposure to light (Found: C, 51.6; H, 5.0; N, 43.0. $C_{14}H_{16}N_{10}$ requires C, 51.9; H, 4.9; N, 43.2%); $\nu_{max.}$(KBr) 2 120 and 2 090 (N_3) cm^{-1}.

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