Insect Chemosterilants. V. Derivatives of Melamine[1]

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The structure of 64 derivatives of melamine was correlated with the activity as chemosterilants for the house fly, *Musca domestica* L. The size and spatial requirements of substituents on the exocyclic nitrogens of melamine exerted a profound influence on the sterilizing activity; the electronic characteristics of the substituents appeared to be much less significant.

Sexual sterilization of harmful insects or of other pests affecting man and animals is a new and promising approach to the control and eradication of such organisms. The activity of biological alkylating agents in sterilizing male insects is now well established.[2] Occasionally, certain antimetabolites and other miscellaneous chemosterilants have exhibited a weak to moderate activity in male insects, but the majority of nonalkylating chemosterilants have been active exclusively in the females. In 1964, two male chemosterilants, HEMPA (hexamethylphosphoric triamide) and HEMEL (hexamethylmelamine), were discovered.[3] Neither of these dimethylamino derivatives is an alkylating agent in the generally accepted meaning of the term,[4] but their structural similarity to the well-known chemosterilants TEPA [tris(1-aziridinyl)phosphine oxide] and tretamine [2,4,6-tris(1-aziridinyl)-*s*-triazine] is striking. Our studies on the structure–activity relationship of melamine derivatives indicate that the steric requirements of the compounds are an important factor influencing their sterilizing activity. The activity is not, however, restricted to close structural analogs of tretamine or HEMEL. In this paper, only the derivatives of melamine will be described; other derivatives of *s*-triazine will be considered in a future publication.

Activities of 64 derivatives of melamine substituted on the exocyclic nitrogen are listed in Table I; 59 representative compounds were prepared in our laboratory, 5 others (**9**, **19**, **29**, **34**, **35**) were selected from 130 compounds obtained from various sources and screened as sterilants for the house fly (*Musca domestica* L.). The compounds in Table I are divided into six groups according to the degree of substitution, but the biological activity varies widely within each group. Because of the often striking differences between solubilities of the basic melamines, hydrochlorides were usually prepared; in most instances, their activity was somewhat higher and more uniform compared with that of the free bases.

Monosubstituted Melamines.—Substitution of one hydrogen in melamine (**1**) with an alkyl group containing less than three carbons in a chain (**2**, **3**, **5**) yielded highly active sterilants. Longer chain substituents (**4**, **6**), cycloalkyl (**8**), aryl (**9**), or other bulky groups (**10**, **11**, **13**) gave only marginally active or inactive compounds. Activities of **7**, **12**, and **15** were anomalous; steric properties of the *t*-butyl group in **7** may account for its unexpectedly low activity, but no explanation can be offered for the rather high activity of **12** compared with that of **10**. Two electron-withdrawing substituents, acetyl group in **14** and cyano group in **15**, gave rise to melamines with widely different activity.

Polysubstituted Melamines.—The activities of disubstituted melamines were similar to those of the corresponding monosubstituted compounds. Methyl and ethyl substituents attached to the same exocyclic nitrogen gave somewhat more active sterilants than when attached to different nitrogens (compare **16** with **25** and **17** with **26**). Cyclic substitution resulted in highly active compounds (**20**–**22**), but the piperazinyl derivatives **23** and **24** were inactive. All methylmelamines (**2**, **16**, **25**, **30**, **38**, **40**, **44**, **49**, **54**) were moderately or highly effective sterilants, but most of the larger groups required the presence of two free amino groups for maintenance of high activity. Introduction of a single methyl group into highly active **20** reduced its activity substantially (**39**); two methyl groups yielded still less active **45**. Similarly, highly methylated **57**, **58**, and **60** were only slightly active. In general, the spatial requirements of the substituents appeared to be of greater importance for sterilizing activity than their electronic characteristics. For example, the inductive effects of ethyl and acetyl groups are opposite, but the activities of ethyl compounds **3**, **26**, **31**, and **50** are analogous to the corresponding acetyl derivatives **14**, **29**, **37**, and **52**. Attempts to combine the structural features of effective sterilants HEMPA and HEMEL in **53** resulted in an almost inactive material.

Mode of Action.—All attempts to correlate the pK_b of the melamine bases, their hydrolytical stability, their solubility in polar or nonpolar solvents, or their spectral absorption characteristics with activity as chemosterilants were unsuccessful. Approximate correlation can be based on the size and distribution of substituents on the amino groups in melamine. It does not seem probable that compounds as different as **22** and **54**, both highly active, would be converted to a single (active) intermediate. Oxidative demethylation or dealkylation of some of the active compounds may be one of the metabolic pathways in insects, but it is probably not directly connected with sterilizing activity. The hydroxymethyl derivatives **36**, **59**, and **63**, which may be intermediates in the oxidative demethylation of **30** and **54**, are not more effective chemosterilants than the parent methyl compound. All the hydroxymethylmelamines easily liberate formalde-

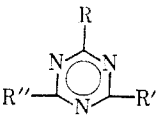
(1) Presented before the Symposium on Chemosterilants of the Division of Agricultural and Food Chemistry, 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 12–17, 1965. Previous paper: P. H. Terry and A. B. Bořkovec, *J. Med. Chem.*, **10**, 118 (1967).

(2) A. B. Bořkovec, *Advan. Pest Control Res.*, **7**, 1 (1966).

(3) S. C. Chang, P. H. Terry, and A. B. Bořkovec, *Science*, **144**, 57 (1964).

(4) W. C. J. Ross, "Biological Alkylating Agents," Butterworth and Co. (Publishers) Ltd., London, 1962, pp 3–18.

TABLE I
HOUSE FLY STERILIZING ACTIVITY OF SUBSTITUTED MELAMINES



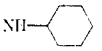
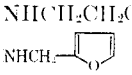
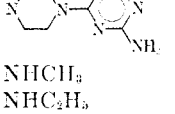
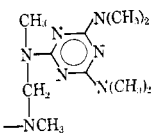
No.	R	R′	R″	Ref	Graded activity[a] Base	HCl salt
1	NH_2	NH_2	NH_2	*b*	+	−
			Monosubstituted			
2	NH_2	NH_2	$NHCH_3$	*c*	++	+++
3	NH_2	NH_2	NHC_2H_5	*d*	+++	+++
4	NH_2	NH_2	NH-*n*-C_3H_7	*e*	+	+
5	NH_2	NH_2	NH-*i*-C_3H_7	*e*	+++	+++
6	NH_2	NH_2	NH-*n*-C_4H_9	*f*	+	+
7	NH_2	NH_2	NH-*t*-C_4H_9	*g*	+	+
8	NH_2	NH_2		*c*	+	+
9	NH_2	NH_2	NHC_6H_5	*h*	+	
10	NH_2	NH_2	$NHCH_2CH_2OH$	*i*	+	
11	NH_2	NH_2	$NHCH_2CH_2NH_2$	*c*	+	+
12	NH_2	NH_2	$NHCH_2CH_2OC_2H_5$	*c*	++	++
13	NH_2	NH_2		*c*	0	
14	NH_2	NH_2	$NHCOCH_3$	*j*	+++	
15	NH_2	NH_2	NHCN	*k*	0	
			Disubstituted			
16	NH_2	NH_2	$N(CH_3)_2$	*l*	+	+++ (M)
17	NH_2	NH_2	$N(C_2H_5)_2$	*m*	+++	+++
18	NH_2	NH_2	$N(n\text{-}C_3H_7)_2$	*c*	0	0
19	NH_2	NH_2	$N(CH_2CH{=}CH_2)_2$	*n*	0	
20	NH_2	NH_2		*o*	+++	+++
21	NH_2	NH_2		*p*	++	++
22	NH_2	NH_2		*q*	+++	+++
23	NH_2	NH_2		*r*	0	0
24	NH_2	NH_2		*c*	0	
25	NH_2	$NHCH_3$	$NHCH_3$	*r, s*	++ (M)	++
26	NH_2	NHC_2H_5	NHC_2H_5	*l*	++	++
27	NH_2	NH-*n*-C_3H_7	NH-*n*-C_3H_7	*c*	0	+
28	NH_2	NH-*i*-C_3H_7	NH-*i*-C_3H_7	*c*	++	++
29	NH_2	$NHCOCH_3$	$NHCOCH_3$	*k*	++	
			Trisubstituted			
30	$NHCH_3$	$NHCH_3$	$NHCH_3$	*c*	++ (M)	++ (M)
31	NHC_2H_5	NHC_2H_5	NHC_2H_5	*a*	+	+
32	NH-*n*-C_3H_7	NH-*n*-C_3H_7	NH-*n*-C_3H_7	*c*	0	
33	NH-*i*-C_3H_7	NH-*i*-C_3H_7	NH-*i*-C_3H_7	*c*	++	++
34	NH-*n*-C_4H_9	NH-*n*-C_4H_9	NH-*n*-C_4H_9	*h*	0	
35	NH-*t*-C_4H_9	NH-*t*-C_4H_9	NH-*t*-C_4H_9	*h*	++	
36	$NHCH_2OH$	$NHCH_2OH$	$NHCH_2OH$	*t*	++ (M)	
37	$NHCOCH_3$	$NHCOCH_3$	$NHCOCH_3$	*u*	+	
38	NH_2	$NHCH_3$	$N(CH_3)_2$	*c*	++ (M)	+++ (M)
39	NH_2	$NHCH_3$		*c*	++	++
			Tetrasubstituted			
40	NH_2	$N(CH_3)_2$	$N(CH_3)_2$	*x*	+++ (M)	+++ (M)
41	NH_2			*c*	0	
42	NH			*c*	0	
43	NH_2			*y*	0	0

TABLE I (*Continued*)

No.	R	R′	R″	Ref	Graded activity[a] Base	Graded activity[a] HCl salt
44	$NHCH_3$	$NHCH_3$	$N(CH_3)_2$	*c*, *s*	++ (M)	++ (M)
45	$NHCH_3$	$NHCH_3$		*c*	0	+
46	$NHCH_3$	$NHCH_3$		*c*	0	0
47	$N(CH_3)_2$	NHC_2H_5	NHC_2H_5	*c*	+	+
48	NHC_2H_5	NHC_2H_5		*c*	0	0
			Pentasubstituted			
49	$N(CH_3)_2$	$N(CH_3)_2$	$NHCH_3$	*c*	++ (M)	++ (M)
50	$N(CH_3)_2$	$N(CH_3)_2$	NHC_2H_5	*c*	++	++ (M)
51	$N(CH_3)_2$	$N(CH_3)_2$	NH-*i*-C_3H_7	*c*	+	++ (M)
52	$N(CH_3)_2$	$N(CH_3)_2$	$NHCOCH_3$	*c*, *s*	+	+++ (M)
53	$N(CH_3)_2$	$N(CH_3)_2$	$NHPO[N(CH_3)_2]_2$	*c*, *s*	+	
			Hexasubstituted			
54	$N(CH_3)_2$	$N(CH_3)_2$	$N(CH_3)_2$	*s*	+++ (M)	+++ (M)
55	$N(CH_3)_2$	$N(CH_3)_2$	$CH_3NC_2H_5$	*c*	++ (M)	++ (M)
56	$N(CH_3)_2$	$N(CH_3)_2$	$N(C_2H_5)_2$	*c*	++ (M)	++ (M)
57	$N(CH_3)_2$	$N(CH_3)_2$		*c*	+	+
58	$N(CH_3)_2$	$N(CH_3)_2$		*c*	+	+
59	$N(CH_3)_2$	$N(CH_3)_2$	CH_3NCH_2OH	*c*, *s*	++ (M)	
60	$N(CH_3)_2$	$N(CH_3)_2$		*c*	+	+
61	$N(CH_3)_2$	$N(CH_3)_2$		*c*, *s*	0	
62	$N(C_2H_5)_2$	$N(C_2H_5)_2$	$N(C_2H_5)_2$	*z*	++	
63	$N(CH_2OH)_2$	$N(CH_2OH)_2$	$N(CH_2OH)_2$	*aa*	0	
64				*bb*	0	
65				*cc*	0	

[a] +++, high activity (flies of both sexes treated with 0.1% or less of the compound produced no pupae); ++, moderate activity (0.1–1% of compound produced no pupae); +, low but significant activity at 1% treatment level; 0, activity insignificant at 1% treatment level; M, significant activity in males treated with 1% or less of the compound. [b] Distillation Products Industries, Eastman Kodak Co. [c] See Table II. [d] Mp 168–170°, lit.[10] 171–172°. [e] Mp 216–222°; D. Kaiser [U. S. Patent 2,567,847 (1951)] reports mp 216–218°. [f] Mp 164–168°, lit.[10] 167–169°. [g] Mp 161–162°; M. Bortnick [U. S. Patent 2,628,234 (1953)] reports mp 156–158°. [h] Monsanto Co. [i] Mp 224–227°; J. Thurston [U. S. Patent 2,482,076 (1949)] reports mp 223–225°. [j] Mp 273–274°; M. Tanaka, H. Hosokawa, and H. Kitajima [*Yuki Goei Kagaku Kyokai Shi*, **19**, 704 (1961)] report mp 273–274°. [k] D. Kaiser and B. Redmon, U. S. Patent 2,510,981 (1950)]. [l] Mp 304–306°; E. P. Taylor [*J. Pharm. Pharmacol.*, 11, 374 (1959)] reports mp 306–307°. [m] Mp 169–172°, lit.[10] 168–170°. [n] American Cyanamid Co. [o] Mp 289–292°; W. Detweiler and E. Amstutz [*J. Am. Chem. Soc.*, **74**, 1483 (1952)] report mp 295.2–297.2°. [p] Mp 217–220° dec; D. Walker, Y. L'Italien, W. Pearlman, and C. Banks [*J. Am. Pharm. Assoc.*, **39**, 383 (1950)] report mp 216–217°. [q] Mp 246.5–250°, lit.[o] 250–250.2°. [r] Mp 204–208°; W. O. Foye and L. Chafetz [*J. Am. Pharm. Assoc.*, **46**, 366 (1957)] report mp 210–211°. [s] See Experimental Section. [t] Mp 156.5–160°, lit.[10] 156–158°. [u] Mp 70–74.5°, lit.[10] 72–75°. [v] J. K. Dixon, N. T. Woodberry, and G. W. Costa, *J. Am. Chem. Soc.*, **69**, 599 (1947). [w] Mp 306–308° dec; J. Cason [*ibid.*, **69**, 495 (1947)] reports dec 310°. [x] Mp 227.5–228.5°; W. Zerweck and K. Keller [U. S. Patent 2,228,161 (1941)] report mp 222°. [y] Mp 166–171°, lit.[10] 170°. [z] Bp 132–134° (0.27 mm), lit.[10] 151–154° (2–3 mm). [aa] A. Gams, G. Widmer, and W. Fisch, *Helv. Chim. Acta*, **24E**, 302 (1941). [bb] Mp 185–188°, lit.[o] 186.6–189.8°. [cc] Mp 279–288°, lit.[o] 284–289° dec.

hyde, a mild alkylating and mutagenic agent. Although formaldehyde was ineffective as a chemosterilant when it was added to insects' diet, its liberation *in situ* may account for the activity of HEMEL (**54**) or other methylmelamines. However, the rather low activity of **36** and **59** and the inactivity of **63** make this hypothesis improbable.

Certain *s*-triazines function as antimetabolites of pyrimidines.[5] Because several other pyrimidine antimetabolites, *e.g.*, 5-fluorouracil, are effective chemosterilants of female house flies,[2] the possibility that substituted melamines act as antimetabolites must be considered. Unfortunately, no melamine derivatives similar to the compounds in Table I are known to function as antimetabolites in any organism; those *s*-triazines which were shown to be competitive antagonists of uracil or had some antitumor properties[5] were inactive in house flies.

Inhibition of dihydrofolic reductase by 2,4-diamino-*s*-triazines has been reported recently.[6] The same

(5) G. M. Timmis, *Advan. Cancer Res.*, **6**, 369 (1962).

(6) B. R. Baker and B. T. Ho, *J. Heterocyclic Chem.*, **2**, 340 (1965).

TABLE II
CHEMICAL DATA FOR SUBSTITUTED MELAMINES

No.	Bp (mm) or mp, °C	Yield, %	Procedure[a]	Crystn solvent	Formula	Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
2	265–269	70	C	Water	$C_4H_8N_6$	34.30	5.75	59.99	34.43	5.80	59.92
4	195–201	86	C	Ethyl acetate	$C_6H_{12}N_6$	42.85	7.68	49.96	43.01	7.43	49.78
8	146.5–148[b]	62	C	Ethanol–water	$C_9H_{16}N_6$	51.89	7.73		51.92	7.79	
11[c]	Dec	30	C	Ethanol–water	$C_3H_{11}N_7 \cdot HCl \cdot H_2O$	26.84	6.31	43.83	27.40	6.31	43.73
12	118–123	46	C	Water	$C_7H_{14}N_6O$	42.42	7.13	42.40	42.64	7.30	42.28
13	150–152	80	C	Chloroform–ethanol	$C_8H_{16}N_6O$	46.60	4.89		46.30	4.88	
18	197.5–200	47	C	Methanol	$C_9H_{18}N_6$	51.40	8.64	39.96	51.51	8.72	40.03
24	Dec[d]	99	C	Water	$C_{10}H_{16}N_{22}$	39.46	5.30		39.08	5.50	
25	206.5–209[e]	65	B	Ethanol	$C_5H_{10}N_6$	38.94	6.54	54.50	39.04	6.56	54.61
27	160 (0.15)	42	B		$C_9H_{18}N_6$	51.40	8.64	39.96	51.26	8.65	39.89
28	120–122.5	36	B	Isooctane	$C_9H_{18}N_6$	51.40	8.64	39.96	51.20	8.62	39.68
30	129–131[f]	70	C	Chloroform–cyclohexane	$C_6H_{12}N_6$	42.85	7.68	49.96	43.08	7.34	50.22
32	168 (0.1)	36	C		$C_{12}H_{24}N_6$	57.09	9.58	33.30	57.10	9.62	33.14
33	143.5–145	42	C	Benzene	$C_{12}H_{24}N_6$	57.09	9.58	33.30	57.01	9.49	33.30
38	191–192	67	C[g]	Ethanol	$C_6H_{12}N_6$	42.85	7.68	49.96	42.78	7.42	49.46
39	214–216.5	70	C[g]	Ethanol	$C_8H_{14}N_6$	49.47	7.27	43.27	49.37	7.18	43.44
41	228.5–229.5	58	B	Ethanol	$C_{11}H_{18}N_6$	56.39	7.74		56.60	7.90	
42	195–198	27	B	Ethanol	$C_{13}H_{22}N_6$	59.55	8.45	32.03	59.66	8.56	31.87
44	91–91.2	78	C	Cyclohexane	$C_7H_{14}N_6$	46.14	7.74	46.12	46.39	7.89	45.92
45	110–110.5	73	C	Cyclohexane	$C_8H_{16}N_6$	51.90	7.74	40.34	51.85	7.90	40.25
46	144–146	63	C	Water	$C_9H_{16}N_6O$	48.19	7.19	37.47	47.97	7.28	37.50
47	108–109	52	C	Ethanol–water	$C_9H_{18}N_6$	51.40	8.64	39.96	51.16	8.60	39.76
48	92–94	24	C	Acetone–water	$C_{12}H_{22}N_6$	57.57	8.86	33.56	57.34	8.74	33.60
49	98–103	92	C	Ethanol–water	$C_8H_{16}N_6$	48.95	8.21	42.81	49.02	8.40	42.60
50	54.5–59[e]	66	C		$C_9H_{18}N_6$	51.40	8.64	39.96	51.13	8.70	39.96
51	98.5–100.5	48	C	Hexane	$C_{10}H_{20}N_6$	53.54	8.99	37.47	53.92	8.72	37.49
52	154–156	80		Benzene	$C_9H_{14}N_6O$	48.20	7.19	37.43	48.31	7.24	37.70
53	159–160	56		Ether	$C_{11}H_{25}N_8OP[i]$	41.77	7.97	35.42	41.90	7.95	35.18
55	111–113	58	C	Ethanol–water	$C_{10}H_{20}N_6$	53.54	8.99	37.47	53.65	8.98	37.68
56	110 (0.3)	24	C		$C_{11}H_{22}N_6$	55.43	9.31	35.26	55.21	9.17	34.98
57	129–131	73	C	Ethanol–water	$C_{11}H_{20}N_6$	55.90	8.53	35.57	55.82	8.66	35.50
58	85.5–87.5	92	C	Ethanol	$C_{12}H_{22}N_6$	57.57	8.86	33.56	57.59	8.80	33.69
59	119.5–123	31		Hexane	$C_9H_{18}N_6O$	47.76	8.01	37.13	47.90	7.97	37.30
60	121–124.5	87	C	Ethanol	$C_{11}H_{20}N_6O$	52.36	7.99	33.31	52.51	8.05	33.40
61[j]	195–196	20		Cyclohexane	$C_{17}H_{32}N_{12}$	50.48	7.97	41.55	50.30	7.81	41.82

[a] See Experimental Section. [b] S. Okumura and S. Bando [Japanese Patent 9597 (1962)] report mp 136–138°. [c] Characterized as hydrochloride monohydrate. *Anal.* Calcd: Cl, 15.85. Found: Cl, 16.10. [d] Lit. (ref *o*, Table I) mp 398–400°. [e] Zerweck and Keller (ref *x*, Table I) prepared **25** from melamine and methylamine hydrochloride (mp 260–262° dec); A. Hoffman [*Ber.*, **18**, 2755 (1855)] used procedure C (no melting point given). [f] P. Klason [*J. Prakt. Chem.*, [2] **33**, 290 (1886)] reports mp 115°. [g] Prepared from 2-amino-4-chloro-6-(methylamino)-*s*-triazine. [h] Bp 100.5° (0.05 mm). [i] *Anal.* Calcd: P, 9.79. Found: P, 9.94. [j] Prepared in anhydrous media.

enzyme is inhibited by aminopterin and by other antagonists which are excellent house fly sterilants.[2] Such inhibition, however, has not been reported for melamine and its derivatives. Furthermore, the sterilizing activity of compounds **20** and **54** was not significantly changed when they were administered with as much as a 100-fold excess of folic acid. Also aminopterin does not sterilize male insects[2] though certain melamines are quite effective male sterilants. Apparently then, the mode of action of melamines is different from that of the pyrimidine and folid acid antagonists.

Male-Sterilizing Activity.—The grades of activity for the substituted melamines given in Table I relate to the sterilizing effects in both sexes. However, the effects of chemosterilants on male insects only are of great practical importance.[2] As a group, only the methylated melamines (**16**, **25**, **30**, **38**, **40**, **44**, **49**, **54**) sterilized male flies. Other male sterilants (**50–52**, **55**, **56**, **59**), also highly methylated, contained one or two larger substituents. None of the melamines with cyclic substituents (see Table I) sterilized males.

Experimental Section

Biological Testing.—All compounds listed in Table I were tested at various concentrations as additives to the diet of house flies[5] by LaBrecque and his associates of the Entomology Research Division, Agricultural Research Service, U. S. Department of Agriculture, Gainesville, Fla. Certain nonalkylating derivatives of melamine sterilized other insect species,[6] but the structure–activity relationships discussed here apply only to house flies. Species specificity is one of the outstanding characteristics of *s*-triazine chemosterilants.

The relative number of pupae produced by treated flies compared with untreated flies is a more general manifestation of sterility than fecundity or egg hatch. Effects of the melamines on female fecundity usually are minor. Some melamines do not appreciably affect the hatch of eggs laid by treated females, but the emerged larvae die before pupation. Also, considerable and as yet unexplained differences exist between the chemosterilant effect of compounds administered in different diets.[7] The graded activities in Table I are based on the most effective dietary mixtures administered to both sexes of house flies. For determination of male sterility, treated males were mated to untreated females.

(7) For detailed experimental procedures, *cf.* R. L. Fye, G. C. LaBrecque and H. K. Gouck, *J. Econ. Entomol.*, **59**, 485 (1966).

(8) A. B. Borkovec and P. H. Terry, U. S. Patent 3,189,521 (1965).

Synthesis of Melamines.—The melamines listed in Table I were prepared by the methods previously described.[9] Table II gives additional data for the new compounds only; previously reported compounds are listed only if the analytical data were incomplete or markedly different from ours. General synthetic methods are exemplified by model preparations (procedures A, B, C). Melamine monohydrochlorides were prepared by dissolving the base in 1 equiv of dilute HCl. The salts were sufficiently pure for biological testing. Melting points were taken in a capillary tube and are corrected.

Procedure A.—To 120 g (0.653 mole) of cyanuric chloride dissolved in 800 ml of $CHCl_3$ was added, with stirring, a solution containing 200 g (4.32 moles) of anhydrous dimethylamine in 300 ml of $CHCl_3$; the temperature was kept at 25–30°. The solution was heated under reflux for 1 hr, cooled, and extracted four times with 500-ml portions of water. The organic layer was dried ($MgSO_4$), the solvent was removed, and 127 g (93%) of crude product was obtained. Recrystallization from methanol yielded 95 g (72%) of hexamethylmelamine (**54**), mp 170.5–173° (lit.[10] mp 172–174°).

Procedure B.—Into a 2-l. stainless steel autoclave equipped with a stirring device was placed 300 ml of toluene and 19 g (0.115 mole) of 2-amino-4,6-dichloro-*s*-triazine.[11] The suspension was cooled to −5°, and a cold solution of 17.8 g (0.578 mole) of anhydrous methylamine in 50 ml of toluene was slowly added. The mixture was kept at 115° for 2 hr. The solids were collected by filtration and added to 100 ml of a saturated K_2CO_3 solution, and the slurry was stirred at 50° for 15 min. The insoluble product was collected by filtration, washed with 50 ml of ice-cold water, and dried in a vacuum oven at 75° for 3 hr; 11.5 g of N^2,N^4-dimethylmelamine (**25**) was obtained.

Procedure C.—To a solution of 45 g (1 mole) of dimethylamine in 150 ml of water was added 17.4 g (0.1 mole) of 2-chloro-4,6-bis(methylamino)-*s*-triazine.[12] The slurry was heated to reflux, and as the reaction proceeded, the solution became increasingly homogeneous. During the reaction, a solution of 4 g of NaOH in 5 ml of water was slowly added; after the solid had completely dissolved, the mixture was held under reflux for 20 min. The solution was filtered hot, and the water was removed to leave an oily residue which solidified on cooling. The solids were triturated with 50 ml of ice-cold water, filtered, and dried; 14.3 g of crude product was recrystallized from cyclohexane to give 9.9 g of N^2,N^2,N^4,N^6-tetramethylmelamine (**44**).

N-[4,6-Bis(dimethylamino)-*s*-triazin-2-yl]acetamide (52).—To 4.55 g (0.025 mole) of 2-amino-4,6-bis(dimethylamino)-*s*-triazine (**40**) in 50 ml of xylene was added 3 g (0.03 mole) of acetic anhydride. The mixture was held under reflux for 2.5 hr. When it cooled, 4.5 g of crude product (mp 149–155°) crystallized from the solution. Recrystallization from benzene gave pure **52**.

N″-[4,6-Bis(dimethylamino)-*s*-triazin-2-yl]-N,N,N′,N′-tetramethylphosphoric Triamide (53).—To 2.99 g (0.01 mole) of [4,6-bis(dimethylamino)-*s*-triazin-2-yl]phosphoramidic dichloride[13] in 300 ml of anhydrous ether was added an ether solution containing 4.5 g (0.1 mole) of anhydrous dimethylamine. The reaction mixture was held under reflux for 1 hr, cooled, and filtered, and the filtrate was concentrated; 1.78 g of **53** crystallized from the concentrate.

{[4,6-Bis(dimethylamino)-*s*-triazin-2-yl]methylamino}methanol[14] (59).—To 110 g of aqueous formaldehyde (37.5%) adjusted to pH 8.9 with 0.1 *N* NaOH, was added 26.7 g (0.136 mole) of pentamethylmelamine (**49**) and 65 ml of ethanol. The slurry was heated and kept under reflux for 3 min (total heating time 17 min). The mixture was cooled rapidly in an ice–water bath until crystallization of the product was complete. After the solid was filtered out and washed with water, the damp filter cake was thoroughly dried by dissolving it in ether and allowing the solution to stand over $MgSO_4$. The solvent was removed *in vacuo;* when the residue was recrystallized from hexane, it yielded 9.4 g of **59**. Prolonged heating during any step in the procedure caused decomposition of the product. Infrared spectrum (KBr) showed absorptions of 3.00 (OH) and 9.75 μ (CO); nmr ($CDCl_3$), singlet at δ 5.07 (2 H), singlet at 4.31 (1 H), and singlets at 3.20 and 3.12 (19 H combined area, peak ratio 1:4). Acid hydrolysis of the hydroxymethyl group in **59** yielded 13.69% of formaldehyde (calcd 13.27%).

Our attempted synthesis of **59** in an anhydrous medium[15] yielded the methylene bridged compound **61**.

$N^2,N^{2\prime}$-Methylenebis(N^2,N^4,N^4,N^6,N^6-pentamethylmelamine) (61).—A sealed glass tube containing an intimate mixture of 4.91 g (0.025 mole) of pentamethylmelamine (**49**) and 0.78 g (0.026 mole) of paraformaldehyde was heated at 125° for 4 hr and then at 145° for 75 min. After cooling, the contents were recrystallized from cyclohexane to give 1 g of **61**; nmr ($CDCl_3$), singlets at δ 5.71 (2 H), 3.11 and 3.05 (30 H combined area, peak ratio 4:1). Acid hydrolysis of **61** gave rise to formaldehyde and pentamethylmelamine. A higher yield of **61** was obtained in aqueous medium. To 24 g of aqueous formaldehyde (37.5%), adjusted to pH 9.3 with 0.1 *N* NaOH, was added 5.9 g (0.03 mole) of pentamethylmelamine and 15 ml of ethanol. The mixture was held under reflux for 30 min. After cooling, 2 g (33%) of crude product was collected by filtration and recrystallized from ethanol.

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(10) D. W. Kaiser, J. T. Thurston, J. R. Dudley, F. C. Schaefer, I. Hechenbleikner, and D. Holm-Hansen, *J. Am. Chem. Soc.*, **73**, 2984 (1951), reported only a 37% yield from their more laborious procedure.

(11) J. T. Thurston, J. R. Dudley, D. W. Kaiser, I. Hechenbleikner, F. C. Schaefer, and D. Hol-Hansen, *ibid.*, **73**, 2981 (1951).

(12) W. Pearlman and C. Banks, *ibid.*, **70**, 3726 (1948).

(13) A. B. Bofkovec, C. W. Woods, and R. T. Brown, *J. Med. Chem.*, **9**, 522 (1966).

(14) R. Zeidler, W. Ruettiger, W. Ruemans, and N. Getz, *Textil-Rundschau*, **16**, 734 (1961), and *Melliand Textilber.*, **43**, 608 (1962). Synthetic procedure not mentioned in these references.

(15) H. Bohme, O. Dick, and G. Driesen, *Ber.*, **94**, 1879 (1961).