the combined filtrates were dried ($MgSO_4$). Removal of the drying agent and solvent left 28.24 g of a yellow liquid. Short-path distillation gave 24.56 g (77.5%) of **11** (*ca.* 99% pure by glpc). A single redistillation gave the analytical sample, $n^{20}D$ 1.4932, bp 77° (0.005 mm). *Anal.* ($C_7H_{16}ClN_2OP$) C, H, N, P.

**Isolation of N-Methylformamide from Oxidation Mixtures.**—In various oxidations of **1** (Table I) and in the oxidation of **3** to **6**, a low-boiling product was noted in the initial distillations of the crude products. The volatile material was identified as N-methylformamide by comparing its ir spectrum with that of the authentic compound.

**Acknowledgments.**—We thank Mr. E. L. Gooden and Dr. John L. Ruth of this Division for the pmr and mass spectra, respectively.

# Insect Chemosterilants. VII.[1] Oxidative Degradation of Hexamethylmelamine

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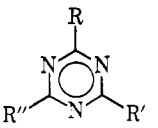
The chloroform- and ether-soluble products of the oxidation of hexamethylmelamine with potassium permanganate were identified as methylmelamines and mono- and diformylated methylmelamines. The formyl compounds were also synthesized by formylation of methylmelamines with formamide or with formyl fluoride.

In conjuction with our study of the metabolism of hexamethylmelamine (HEMEL)[2] in male house flies, *Musca domestica* L., we have investigated the oxidation of this chemosterilant with aqueous potassium permanganate. Our previous experiments with the chemosterilant HEMPA (hexamethylphosphoric triamide) showed that this dimethylamino compound was demethylated *in vivo*[3] and *in vitro*[1] to the corresponding pentamethyl derivative. The pentamethylphosphoric triamide is a much less effective sterilant than HEMPA and its further oxidation or demethylation does not yield active chemosterilants. On the other hand, a gradual demethylation of HEMEL leads to compounds of considerable activity that sometimes surpasses that of the initial compound.[2,4] In the present study, we have isolated and identified the chloroform-soluble and ether-soluble products of the oxidation of HEMEL: all were derivatives of *s*-triazine. The possibility that other *s*-triazines which were not extracted with chloroform or ether still remained in the mixture cannot be entirely eliminated but the solubility characteristics of most triazines which could be formed by oxidizing HEMEL do not support it.

The mildly exothermic oxidation of HEMEL with aqueous $KMnO_4$ was carried out at room temperature. Although the insoluble base was first dissolved in acid, the mixture became basic and heterogeneous as the reaction progressed. The solubility of methylmelamines in water increases with the decreasing number of methyl groups and the lower methylmelamines had to be extracted with ether from the aqueous phase. Higher methylmelamines and formylmelamines were extracted with chloroform from the solid phase. The products obtained from a typical reaction are shown in Table I. All possible methylmelamines, with the exception of $N^2,N^2$-dimethylmelamine were detected among the products. About 11% of the initial quantity of **1** was recovered and about 39% of it was converted to

TABLE I

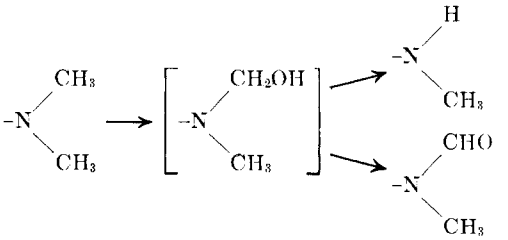
*s*-TRIAZINES OBTAINED BY OXIDATION OF HEMEL



| No. | R | R' | R'' | Yield[a] Wt % | Yield[a] Mole % |
|---|---|---|---|---|---|
| 1 | $N(CH_3)_2$ | $N(CH_3)_2$ | $N(CH_3)_2$ | 10.7[b] | 10.7 |
| 2 | $NHCH_3$ | $N(CH_3)_2$ | $N(CH_3)_2$ | 7.5[b] | 7.9 |
| 3 | $NH_2$ | $N(CH_3)_2$ | $N(CH_3)_2$ | 0.3[b] | 0.3 |
| 4 | $NHCH_3$ | $NHCH_3$ | $N(CH_3)_2$ | 9.5[b] | 11.0 |
| 5 | $NH_2$ | $NHCH_3$ | $N(CH_3)_2$ | 0.5[b] | 0.7 |
| 6 | $NHCH_3$ | $NHCH_3$ | $NHCH_3$ | 3.1[b] | 3.8 |
| | | | | 1.7[c] | 2.1 |
| 7 | $NH_2$ | $NHCH_3$ | $NHCH_3$ | 5.1[c] | 7.0 |
| 8 | $NH_2$ | $NH_2$ | $NHCH_3$ | 4.1[c] | 6.1 |
| 9 | $N(CH_3)CHO$ | $N(CH_3)_2$ | $N(CH_3)_2$ | 4.8[b] | 4.5 |
| 10 | $N(CH_3)CHO$ | $NHCH_3$ | $N(CH_3)_2$ | 3.2[b] | 3.2 |
| 11 | $N(CH_3)CHO$ | $N(CH_3)CHO$ | $N(CH_3)_2$ | 3.9[b] | 3.4 |
| 12 | $N(CH_3)CHO$ | $N(CH_3)CHO$ | $NHCH_3$ | Trace[b] | |

[a] The individual yields refer to the initial amount of HEMEL used in the reaction. They were calculated from glpc peak areas ($CHCl_3$ fraction) or estimated by tlc ($Et_2O$ fraction). [b] In $CHCl_3$ extract. [c] In $Et_2O$ extract.

lower methylmelamines. In analogy to HEMPA, the oxidation of **1** follows two routes which appear to have a



common intermediate. None of the possible methylol intermediates was found in the oxidation mixture but some of them have been synthesized previously and were sufficiently stable to be used in confirmatory reactions. Thus, when {[4,6-bis(dimethylamino)-*s*-triazin-2-yl]-methylamino}methanol[4b] was oxidized with aqueous permanganate, both expected products **2** and **9** were isolated.

(1) Previous paper in the series: P. H. Terry and A. B. Bořkovec, *J. Med. Chem.*, **11**, 958 (1968).

(2) S. C. Chang, A. B. DeMilo, C. W. Woods, and A. B. Bořkovec, *J. Econ. Entomol.*, in press.

(3) S. C. Chang, P. H. Terry, C. W. Woods, and A. B. Bořkovec, *ibid.*, **60**, 1623 (1967).

(4) (a) A. B. Bořkovec and P. H. Terry, U. S. Patent 3,189,521 (1965); (b) A. B. Bořkovec and A. B. DeMilo, *J. Med. Chem.*, **10**, 457 (1967).

The formylmelamines are not decarbonylated during the oxidation. For example, **9** did not decompose in a solution buffered to pH 10,[5] and its oxidation with permanganate gave **11** but not **2**. Apparently, the only pathway for the gradual removal of methyl groups in the oxidation of **1** is the elimination of formaldehyde from methylol intermediates. Indeed, formaldehyde was detected in the oxidation mixture at equimolar concentration of **1** and permanganate.

The four formyl compounds **9**–**12** were synthesized independently by formylation of the appropriate methylmelamines with formamide or formyl fluoride. Formamide is a convenient reagent for the monoformylation of melamines[5] but diformyl compounds **11** and **12** were produced in very low yields by this method. The method of Terry and Bořkovec[1] in which sodium salts of amides are treated with formyl fluoride appears to be more suited for the preparation of diformylmelamines. N-[4,6-Bis(dimethylamino)-*s*-triazin-2-yl]-formamide was also synthesized by the formamide procedure but neither this compound nor any other triazinylformamide were detected in the oxidation of **1**. Apparently, the $-NHCH_2OH$ group eliminates formaldehyde much faster than the $-N(CH_3)CH_2OH$ group.

Most of the lower methylmelamines obtained in the permanganate oxidation were also found among the metabolites of HEMEL *in vivo*;[2] however, formyl compounds were detected and identified only in the *in vitro* oxidation. The formylmelamines prepared in our study were either ineffective or only moderately effective as chemosterilants of house flies.[6]

## Experimental Section

Melting points were taken in a capillary tube and are corrected. Glpc data were obtained with an F & M 720 gas chromatograph. The column used was a 61 × 0.6 cm (o.d.) stainless steel column packed with 10% diethylene glycol succinate on 60–80 mesh acid-washed Chromosorb W. All tlc plates were prepared by mixing 1% of copper–zinc sulfide phosphor (Kensington Scientific Corp., Oakland, Calif.) with the adsorbent. The adsorbent layer was 200 $\mu$ thick and the plates were usually dried at 110° for 0.5 hr prior to use. By employing a short-wave uv lamp the triazines appeared as dark blue spots on a light background.

All melamines used in this study as standards or as starting materials were prepared by methods previously described.[4b] The identity of all new compounds was confirmed by pmr spectra. Where analyses are indicated only by symbols of the elements analytical results obtained for those elements were within ±0.4% of the theoretical values. Mention of a proprietary product or company does not necessarily imply endorsement of the product or company by the U. S. Department of Agriculture.

**Oxidation of HEMEL Hydrochloride.**—To a suspension of 14.70 g (0.070 mole) of **1** in 35 ml of $H_2O$ was added 70 ml of 1 *N* HCl. When dissolution was complete, 60.9 g (0.39 mole) of $KMnO_4$ in 980 ml of $H_2O$ was added (5 min). The suspension was stirred (1 hr) and filtered (1 hr), the filter cake was washed with $H_2O$, and the aqueous filtrates were combined. The solids were further extracted with $CHCl_3$ to provide 6.4 g of products which were analyzed by glpc. The individual products along with their respective glpc peak areas (%) are listed in order as they eluted from the column:[7] **1** (glpc, nmp), 24.5; **2** (glpc, ir, nmp), 17.0; **3** (glpc, ir, mp), 0.7; **4** (glpc, ir, mmp), 21.9; **9** (glpc, ir, mmp, tlc), 11.1; **5** (ir, tlc), 1.3; **6** (glpc, ir), 7.0; **10** (glpc, ir), 7.3; **11** (glpc, ir, mmp, pmr), 8.9; **12** (ir, mp), trace.

After the $KMnO_4$ had completely reacted, the combined aqueous filtrates were again filtered and concentrated to 300 ml under vacuum. The solution was neutralized with HCl and extracted for 5 days with $Et_2O$. The extract was filtered and the filtrate was evaporated. The filter cake (4.2 g) was analyzed by tlc on silica gel G and developed with MeOH–$CHCl_3$ (1:1). The products were identified as **7** (ir, mmp, tlc) with $R_f$ 0.55, and **8** (ir, tlc) with $R_f$ 0.43. The two compounds were also separated by crystallization from MeOH. Evaporation of the ethereal filtrate gave 0.4 g of a mixture of **6** and **7**.

**Detection of Formaldehyde in the Oxidation of HEMEL Hydrochloride.**—To a solution of 0.79 g (5.0 mmoles) of $KMnO_4$ in 75 ml of $H_2O$ was added 1.23 g (5.0 mmoles) of 1·HCl. After stirring (40 min), the mixture (pH 4.85, no excess $KMnO_4$ remaining) was filtered and the filtrate was added to 150 ml of an acidified solution of 2,4-dinitrophenylhydrazine. After 2 hr, 20.5 mg (0.14%) of the 2,4-dinitrophenylhydrazone of formaldehyde precipitated. Recrystallization from 95% EtOH gave the pure hydrazone, mp 165.5–168° (lit.[8] mp 166°), which did not depress the melting point of an authentic sample. A solution of **1** in HCl did not give a positive test for formaldehyde.

**Oxidation of {[4,6-Bis(dimethylamino)-*s*-triazin-2-yl](methylamino)methanol.**—To a solution of 0.40 g (2.53 mmoles) of $KMnO_4$ in 15 ml of $H_2O$ was added 0.28 g (1.25 mmoles) of the powdered title compound. After stirring the slurry (1 hr), the solids were collected by filtration, washed with $H_2O$, and dried. The products were extracted with $CHCl_3$ and the extract was examined by glpc and tlc. Separation by preparative glpc afforded pure samples which were identified by ir, glpc, and tlc as **2**, **9**, **10**, and **11**, with glpc peak areas of 17.3, 45.5, 10.6, and 25.9%, respectively.

**N-[4,6-Bis(dimethylamino)-*s*-triazin-2-yl]-N-methylformamide (9). A.**—Sodium pentamethylmelamine was prepared by stirring 1.44 g (0.06 mole) of NaH in 150 ml of dry $Et_2O$ containing 9.5 g (0.05 mole) of **2** for 19 hr at room temperature and finally by keeping the slurry under reflux for 2 hr. To this mixture was added (10 min) 55 ml of an ethereal solution containing 5.6 g (0.12 mole) of formyl fluoride;[9] the temperature was maintained at −15°. Additional 100 ml of $Et_2O$ was added and the mixture was stirred at −15° for 1 hr before allowing it to come to room temperature. After stirring overnight, the solids were removed by filtration and the filtrate was evaporated to dryness under vacuum. Two recrystallizations of the residue from cyclohexane gave 1.86 g (16.6%) of **9**, mp 129.5–132°. *Anal.* ($C_8H_{16}N_6O$) C, H, N.

**B.**—A mixture of 10.0 g (0.051 mole) of **2** and 25 ml of formamide was heated with stirring at 185° for 2 hr. The melt was poured into 50 ml of $H_2O$ and the insoluble product was collected by filtration. The crude product weighing 8.2 g (70.2%) was *ca.* 98% pure by glpc.

**N-[4-(Dimethylamino)-6-(methylamino)-*s*-triazin-2-yl]-N-methylformamide (10). A.**—The sodium salt of **4** was prepared by stirring 0.96 g (0.04 mole) of NaH in 55 ml of dry $Et_2O$ containing 5.47 g (0.03 mole) of **4** for 28 hr at room temperature. To this slurry, cooled to −60°, was rapidly added 40 ml of $Et_2O$ containing 4.0 g (0.125 mole) of formyl fluoride. After the slurry was stirred at −60° for 0.75 hr, at 0° for 1 hr, and at room temperature for 17 hr, the solids were filtered and the filter cake was washed with ether. Evaporation of the combined filtrates gave 2.51 g of material estimated by glpc to contain 1.98 g (31.5%) of **10** and 0.53 g (7.4%) of **11**. The solids were taken up in $CHCl_3$ and washed with $H_2O$ and the $CHCl_3$ layer was dried ($MgSO_4$). Removal of the solvent under vacuum and recrystallization of the residue from benzene gave 0.8 g of **10**, mp 131.5–134°. *Anal.* ($C_8H_{14}N_6O$) C, H, N.

**B.**—Compound **10** was also prepared in a 63% yield from **4** by the method in B above.

**N,N′-[6-(Dimethylamino)-*s*-triazin-2,4-diyl]bis(N-methylformamide) (11). A.**—The disodium salt of **4** was prepared by stirring 1.44 g (0.06 mole) of NaH in 60 ml of dry $Et_2O$ containing 4.56 g (0.025 mole) of **4** for 23 hr at room temperature. To this slurry, cooled to −70°, was added with stirring 4.6 g (0.09 mole) of formyl fluoride dissolved in 45 ml of $Et_2O$. After the mixture

(5) E. M. Smolin and L. Rapoport, "*s*-Triazines and Derivatives," Interscience Publishers, Inc., New York, N. Y., 1959, p 343, state that N-formylmelamine is easily hydrolyzed. In our experiments, oxidation mixtures with excess permanganate were always alkaline.

(6) G. C. LaBrecque, unpublished data.

(7) Notations in parentheses indicate the physical methods by which the identity of the compounds was confirmed in comparing them with the standards.

(8) R. L. Shriner, R. C. Fuson, and N. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, John Wiley and Sons, Inc., New York, N. Y., 1956, p 283.

(9) G. Olah, S. Kuhn, and S. Beke, *Chem. Ber.*, **89**, 862 (1956).

was kept at −70° for 1 hr, at 0° for 1 hr, and at room temperature overnight, the solids were collected by filtration and washed with $Et_2O$. The filtrate and washings were combined and treated in the same manner as described for the preparation of **10**. The filter cake was washed with $H_2O$ and the insoluble solids were combined with the residue from the $Et_2O$ filtrate to give 3.13 g of products. Glpc analysis showed that the mixture consisted of 1.67 g (27.9%) of **11** and 1.46 g (27.6%) of **10**. The mixture was stirred in 40 ml of 0.1 *N* HCl, and the acid-insoluble product was collected by filtration. A second treatment with acid and recrystallization of the insoluble product from cyclohexane gave 0.9 g of **11**, mp 182.5–184.5°. *Anal.* ($C_9H_{14}N_6O_2$) C, H, N.

**B.**—A mixture of 500 mg (2.75 mmoles) of **4** and 3 ml of formamide was heated at 180° for 3 hr under reduced pressure (315 mm). The melt was poured into 20 ml of $H_2O$ and 330 mg of insoluble solids was collected by filtration (21.3% of **11** by glpc). The solids were triturated with 10 ml of 1 *N* HCl, and the acid-insoluble product was collected by filtration, washed with $H_2O$, and dried. Recrystallization from cyclohexane gave 106 mg of **11**.

**C.**—Oxidation of 336 mg of **9** with aqueous $KMnO_4$ and extraction of the solids with $CHCl_3$ gave 1.1 mg of **10** and 9.9 mg of **11**; compound **2** could not be detected among the products.

**N,N'-[6-(Methylamino)-*s*-triazin-2,4-diyl]bis(N-methylformamide) (12).**—A mixture of 7 g (0.042 mole) of **6** and 18 ml of formamide was heated at 185° for 2 hr. The melt was poured into 40 ml of $H_2O$ and the mixture was chilled in an ice bath. The insoluble products were collected by filtration and triturated with 40 ml of 1 *N* HCl.[10] The acid-insoluble product was collected by filtration, washed with $H_2O$, and dried. Recrystallization from $CCl_4$ gave 0.26 g (3%) of **12**, mp 207.5–209°. *Anal.* ($C_8H_{12}N_6O_2$) C, H, N.

**N-[4,6-Bis(dimethylamino)-*s*-triazin-2-yl]formamide** was prepared in 28% yield from **3** by method B. The product was recrystallized from EtOH, mp 182.5–184.5°. *Anal.* ($C_8H_{14}N_6O$) C, H, N.

**Acknowledgments.**—We thank Mr. Robert Brouillette for valuable technical assistance and Mr. E. L. Gooden for the pmr spectra.

(10) The major product of the reaction which was soluble in HCl was identified as N-[4,6-bis(methylamino)-*s*-triazin-2-yl]-N-methylformamide, mp 168–171° (analytical sample). *Anal.* ($C_7H_{12}N_6O$) C, H, N.

# Potential Antitumor Agents. IX. Bisquaternary Salts

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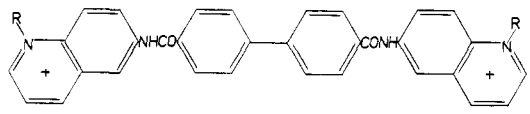
The postulate that a close approach to over-all planarity in bisquaternary ammonium heterocycles is essential for maximum activity when tested against the L1210 system has been further investigated. The preparation of L1210 active quaternary salts containing a diphenyl system suggests that complete planarity in this type of molecule is not an essential requirement.

In an earlier paper[2] we demonstrated that a close approach to over-all planarity of certain quaternary heterocycles was apparently essential for significant activity in the L1210 system in mice. Proceeding from this point we prepared[3,4] active agents whose length exceeded 30 Å. This paper details an investigation into these longer molecules in which deliberate attempts have been made to introduce a small degree of twist in the central area of the molecules.

Using the biphenyl moiety as a central fragment having the desired degree of twist about the pivot bond, activity was first found in series I. Here, convincing



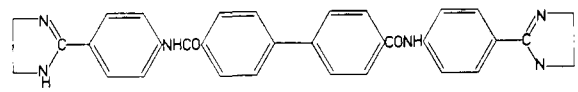

I

activity against the L1210 system could be demonstrated in the series from methyl through *n*-butyl quaternary salts (Table I).

Higher activity was shown by the bis(ethyl and bis-(*n*-propyl quaternary) salts as compared to the other homologs, but the precision of the test system does not allow a clear cut distinction between these two molecules.

It is interesting to observe that the relative $R_f$ values for the ethyl and *n*-propyl quaternary salts of I lie on either side of the figure noted for the optimum members in a series prepared earlier.[2-4] Thus it would appear that, even with the structural changes introduced into I, the $R_f$ values can still serve as a reliable guide to the relative hydrophilic–lipophilic balance.[2]

A marked contrast exists between the active series I and the completely inactive biphenyl analog II reported




II

by Bennett.[5] Our results so far are now able to resolve this apparent discrepancy. In our lead series, the quaternary salts from N,N'-bis(6-quinolyl)terephthalamide, optimum activity is associated with the bis-*n*-butyl salt, the higher *n*-hexyl homolog being inactive. In variant I, where biphenyl replaces phenylene, in our lead series, a lower quaternary salt (ethyl or *n*-propyl) exhibits maximum activity. The change from phenyl to biphenyl has thus increased the lipophilic character of the resultant series by a factor equivalent to several methylene groups. Thus, if in the active 4',4''-bis-(2-imidazolin-2-yl)terephthalanilide[5] the imidazoline as

(1) Author to whom correspondence should be addressed.
(2) G. J. Atwell and B. F. Cain, *J. Med. Chem.*, **10**, 706 (1967).
(3) G. J. Atwell and B. F. Cain, *ibid.*, **11**, 295 (1968).
(4) B. F. Cain, G. J. Atwell, and R. N. Seelye, *ibid.*, **11**, 300 (1968).
(5) L. L. Bennett, Jr., *Progr. Exp. Tumor Res.*, **7**, 259 (1965).