Insect Chemosterilants. VI.[1] Oxidation of Hexamethylphosphoric Triamide and the Synthesis of N-Formylphosphoramides

PAUL H. TERRY AND ALEXEJ B. BOŘKOVEC

Entomology Research Division, U. S. Department of Agriculture, Beltsville, Maryland 20705

Received April 8, 1968

The chloroform-soluble products of oxidation of hexamethylphosphoric triamide with aqueous $KMnO_4$ were identified as pentamethylphosphoric triamide, N-[bis(dimethylamino)phosphinyl]-N-methylformamide, and N-[(dimethylamino)(methylamino)phosphinyl]-N-methylformamide. When the molar ratio of permanganate/amide was high, no pentamethyl compound was isolated but N-methylformamide appeared among the products. Oxidation of N,N,N',N'-tetramethyl-P-piperidinophosphonic diamide yielded N-[(dimethylamino)piperidinophosphinyl]-N-methylformamide but the other oxidation products were not identified. The three formylphosphoramides obtained by oxidation are examples of a new class of phosphoramides; they were also synthesized by a new formylation procedure. The pentamethylphosphoric triamide appears to be formed by the decomposition of the unstable methylol precursor rather than by the oxidative decarbonylation of the formyl compound.

Hexamethylphosphoric triamide (HEMPA) is an effective chemosterilant for house flies, *Musca domestica* L.[2,3] Concurrently with our study of the metabolism of HEMPA in male house flies,[4] which appeared to be an oxidative process, we have investigated the oxidation of HEMPA with aqueous $KMnO_4$. In the metabolic study, each fly was injected with 30 μg of HEMPA and only a few milligrams of metabolites was obtained from 1000 treated flies. Our knowledge of the structure and physical characteristics of the oxidation products *in vitro* was an invaluable guide in isolating and identifying the metabolites *in vivo*. To gain a better insight into the sequence of oxidation, the intermediates pentamethylphosphoric triamide and N-[bis(dimethylamino)phosphinyl]-N-methylformamide were oxidized separately and the products were isolated. HEMPA was also oxidized with aqueous hydrogen peroxide but the reaction was slow even at elevated temperatures. Permanganate oxidation was carried out on N,N,N',N'-tetramethyl-P-piperidinophosphonic diamide[5] which is only slightly effective as a chemosterilant for house flies but which is promising as a chemosterilant for the boll weevil, *Anthonomus grandis* Boheman.[6] N-Formyl compounds play an important role in the *in vitro* oxidation of methylphosphoramides but they were not detected among the metabolites of HEMPA *in vivo*. The identity of the formyl compounds isolated in the oxidation of phosphoramides was confirmed by independent synthesis.

Oxidation of HEMPA.—At temperatures below 50°, the oxidation of HEMPA can be easily controlled when the aqueous $KMnO_4$ is added gradually and with stirring to prevent local overheating. Two fractions are generally obtained: a chloroform-soluble organic fraction and a largely inorganic fraction, insoluble in chloroform, which contains phosphates, carbonates, manganese dioxide, and other products. Our investigation was restricted to the chloroform-soluble fraction. By increasing the ratio of permanganate to HEMPA the proportion of the two fractions could be changed in favor of the inorganic products. By keeping the molar ratio of permanganate to HEMPA below 3, the organic fraction predominated and a meaningful analysis of its constituents was possible. The effect of the ratio of reactants on the composition of products is shown in Table I. The isolation and identification of the individual components of the chloroform-soluble fraction indicated the sequence of reactions shown in Scheme I. There is little doubt that **1** is oxidized initially to the unstable hydroxymethyl derivative **2** though the latter compound was not isolated.

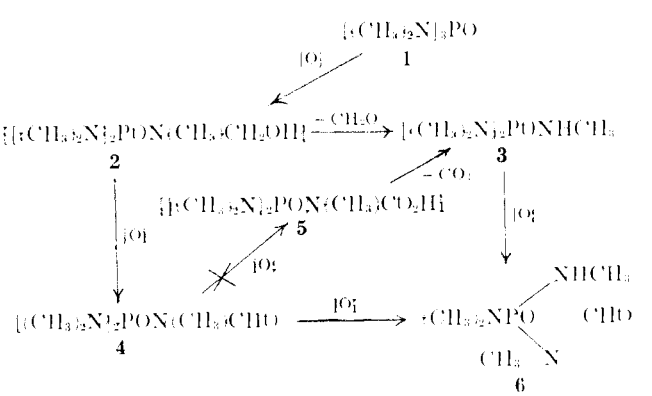
TABLE I

EFFECT OF MOLAR RATIO $KMnO_4$/HEMPA ON THE COMPOSITION OF PRODUCTS

$KMnO_4$/HEMPA	Fractions,[a] g		Products,[b] %				
	$CHCl_3$-soluble	$CHCl_3$-insoluble	**1**	**3**	**4**	**6**	CH_3N-HCHO
1	1.75	0.43	38.6	27.1	34.4	0	0
2	1.36	1.03	3.2	12.2	67.3	17.4	0
3	1.59	1.42	0	0	53.7	41.9	4.5
4	1.40	2.03	0	0	32.4	62.4	5.2
5	1.31	2.44	0	0	15.4	78.3	6.3

[a] Obtained from the oxidation of 1.79 g (10 mmoles) of HEMPA. [b] Some material was accidentally lost.

SCHEME I



In the insecticide octamethylpyrophosphoramide (schradan), **1** is a frequently found impurity and the metabolism and oxidation of both compounds have been

(1) Previous paper in the series: A. B. Bořkovec and A. B. DeMilo, *J. Med. Chem.*, **10**, 457 (1967).

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

(3) P. H. Terry and A. B. Bořkovec, U. S. Patent 3,205,130 (1965); *Chem. Abstr.*, **63**, 13974*a* (1965).

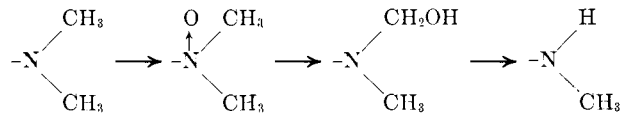
(4) S. C. Chang, P. H. Terry, C. W. Woods, and A. B. Bořkovec, *J. Econ. Entomol.*, **60**, 1623 (1967).

(5) P. H. Terry and A. B. Bořkovec, *J. Med. Chem.*, **10**, 118 (1967).

(6) W. Klassen, J. F. Norland, and A. B. Bořkovec, *J. Econ. Entomol.*, **61**, 401 (1968).

studied by many workers.[7] The demethylation of octamethylpyrophosphoramide to the heptamethyl stage has been well established and the reaction sequence shown in Scheme II was suggested by Hartley.[8] A

SCHEME II



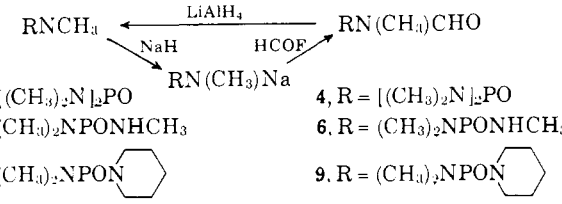
similar sequence has been proposed for **1**[7a,b,j,m] but the intermediate N-oxides and N-methylol compounds in the oxidation of octamethylpyrophosphoramide or **1** were not isolated or identified.

In the MnO_4^- oxidation of **1** we found no evidence that an N-oxide was formed but circumstantial evidence indicated that the methylol compound **2** was indeed an important intermediate. Formaldehyde was detected in the oxidation mixture, and the isolation of the formyl compound **4**[9] pointed to the methylol compound **2** as being its logical precursor. When only 1 equiv of MnO_4^- was used in the oxidation of **1** (Table I) the only products in the chloroform-soluble fraction were **3** and **4**. The possibility that **3** was formed by oxidation of **4** *via* the carbamic acid **5** can be eliminated. In a separate reaction, an authentic sample of **4** yielded upon oxidation with MnO_4^- **6** but not **3** (or **5**). During the oxidation, the dimethylamino groups in **3** and **4** were apparently attacked preferentially because both compounds were oxidized to **6** in separate experiments.

At higher ratios of MnO_4^- to HEMPA the formyl compounds **4** and **6** were the major products but the appearance of N-methylformamide in the chloroform extract pointed to an increasing degree of cleavage of the P–N bond. The resulting phosphoramidates and phosphorodiamidates would not be expected to partition into chloroform. Only a small amount of oxidation products was obtained when a mixture of **1** and 30% hydrogen peroxide was kept at 50° for 3 days. The products were analyzed by glpc and identified as **1**, **4**, and **6**.

Synthesis of N-Formylphosphoramides.—The formyl compounds **4**, **6**, and **9** were synthesized by a new formylation procedure shown in Scheme III. The monomethylamino compounds **3**, **7**, and **8** were converted

SCHEME III



to their sodium derivatives and treated with formyl fluoride.[10] The formyl group in **4** was easily reduced with $LiAlH_4$ to **3** but, as mentioned earlier, the oxidation of the formyl group appears to be more difficult. Although neither **4** nor **6** were found among the metabolites of **1** in male house flies[4] and **4**, **6**, and **9** were ineffective as house fly sterilants, **4** was metabolized by male flies to **3**.[11]

The oxidation of N,N,N′,N′-tetramethyl-P-piperidinophosphonic diamide (**10**) yielded **9** but because the other products in the chloroform-soluble fraction were not identified the relative susceptibility of the methylene and methyl groups in **10** to MnO_4^- oxidation could not be assessed.

Experimental Section

Boiling points are uncorrected. Where analyses[12] are indicated only by symbols of the elements, the analytical results obtained for those elements were within ±0.4% of the theoretical values. The identity of all new compounds was confirmed by ir, pmr, and mass spectra. Ir spectra were recorded with a Perkin-Elmer 521 spectrophotometer, pmr spectra with either a Varian A-60 or a Varian HA-100 spectrometer using TMS as an internal standard, and mass spectra with a CEC 21-110D spectrometer. Analytical glpc determinations were performed with an F & M Model 720 dual-column chromatograph. Company and trade names are given for identification purposes only and do not constitute endorsement by the U. S. Department of Agriculture.

Oxidation of Hexamethylphosphoric Triamide (1). A. With $KMnO_4$.—In each of the experiments outlined in Table I, 1.79 g (0.01 mole) of **1** and a 0.3 *M* $KMnO_4$ solution were allowed to react until all the $KMnO_4$ was decolorized (4–8 hr). The MnO_2 was filtered off; the clear filtrates were freed of the H_2O under vacuum. The resulting mixtures of liquid and solid materials were each extracted with two 50-ml portions of $CHCl_3$, the extracts were dried ($MgSO_4$), and the $CHCl_3$ was removed under vacuum. The $CHCl_3$-soluble material was analyzed semiquantitatively by glpc.[13] In these small-scale oxidations **1** was oxidized completely when 0.02 mole of $KMnO_4$ was used but when the reaction was repeated on a larger scale, larger ratios of $KMnO_4$ were required for complete oxidation. The $CHCl_3$-insoluble solids were dried to constant weight over P_2O_5. These solids evolved NH_3 (and perhaps other amines) on heating, gave off CO_2 on acidification, and after acidification contained 2.10% C and 1.26% H.

B. With H_2O_2.—A mixture of 0.286 g (1.6 mmoles) of 1, 25 ml of H_2O, and 0.36 g (3.2 mmoles) of 30% H_2O_2 was kept at room temperature for 1 day, and then heated in a hot-air bath for 3 days at 50°. Removal of the H_2O gave mostly unreacted **1** (glpc analysis), but a small amount of **4** and traces of **6** and N-methylformamide were detected. Compound **4** has also been

(7) (a) G. S. Hartley and D. F. Heath, *Nature*, **167**, 816 (1951); (b) D. F. Heath, D. W. J. Lane, and M. Llewellyn, *J. Sci. Food Agr.*, **3**, 69 (1952); (c) J. E. Casida, T. C. Allen, and M. A. Stahmann, *J. Am. Chem. Soc.*, **74**, 5548 (1952); (d) R. D. O'Brien and E. Y. Spencer, *J. Agr. Food Chem.*, **1**, 946 (1953); (e) J. E. Casida, T. C. Allen, and M. A. Stahmann, *Nature*, **170**, 243 (1953); (f) J. E. Casida, T. C. Allen, and M. A. Stahmann, *J. Biol. Chem.*, **210**, 607 (1954); (g) H. Tsuyuki, M. A. Stahmann, and J. E. Casida, *J. Agr. Food Chem.*, **3**, 922 (1955); (h) E. Y. Spencer, *Chem. Can.*, **10**, 33 (1955); (i) D. F. Heath, D. W. J. Lane, and P. O. Park, *Trans. Roy. Soc.* (London), **239B**, 191 (1955); (j) R. D. O'Brien and E. Y. Spencer, *J. Agr. Food Chem.*, **3**, 56 (1955); (k) H. Tsuyuki, M. A. Stahmann, and J. E. Casida, *Biochem. J.*, **59**, 1V (1955); (l) E. Y. Spencer, R. D. O'Brien, and R. W. White, *J. Agr. Food Chem.*, **5**, 123 (1957); (m) B. W. Arthur and J. E. Casida, *J. Econ. Entomol.*, **51**, 49 (1958).

(8) Reference 7i refers to a paper presented by G. S. Hartley at the 12th International Chemical Congress, New York, N. Y., 1951.

(9) Although the oxidation of phosphoramides to their N-formyl derivatives is unique, carboxylic amides and aromatic amines are known to give this type of oxidation product; see, *e.g.*, (a) M. V. Loch and B. F. Sagar, *J. Chem. Soc.*, 690 (1966); (b) A. M. Abdel-Wahab, R. J. Kuhr, and J. E. Casida, *J. Agr. Food Chem.*, **14**, 290 (1966); (c) A. M. Adbel-Wahab and J. E. Casida, *ibid.*, **15**, 479 (1967); (d) H. B. Henbest and A. Thomas, *Chem. Ind.* (London), 1097 (1956); (e) H. B. Henbest and A. Thomas, *J. Chem. Soc.*, 3032 (1957).

(10) Various amides, including **3**, have been *acylated* in this manner; see, *e.g.*, K. Sasse, Ed., "Organische Phosphorverbindungen," Vol. 2, Part 2, Georg Thieme Verlag, Stuttgart, 1964, pp 968–971.

(11) S. C. Chang, unpublished results.

(12) Microanalyses were by Galbraith Laboratories, Knoxville, Tenn.

(13) The column used in all glpc analyses was a 61 × 0.635 cm od stainless steel column containing 5% Carbowax 20M on 60–80 mesh base-washed Chromosorb W. The conditions used routinely were column, injection-port, and detector-block temperatures 190°, 225°, and 235°, respectively, He flow rate 60 ml/min, chart speed 2.54 cm/min, and attenuation 1. Under these conditions, compounds **1**, **3**, **4**, and **6** eluted at *ca.* 0.5, 1, 2, and 5.5 min, respectively. In addition, compounds **8**, **9**, and **10** eluted at *ca.* 3.25, 6.5, and 1.75 min, respectively.

detected, in very small quantities, in aged $CHCl_3$ solutions of HEMPA.

Formaldehyde in the Oxidation of 1.—A mixture of 0.60 g (3.33 mmoles) of **1**, 11.1 ml (3.33 mmoles) of 0.3 *M* $KMnO_4$, and 25 ml of H_2O was stirred until it decolorized (20 min) and then it was filtered directly into 83 ml of 2,4-dinitrophenylhydrazine solution.[14] After 2 hr, 0.049 g of crude formaldehyde 2,4-dinitrophenylhydrazone, mp 160–162°, precipitated. Recrystallization (EtOH–H_2O) gave a pure sample, mp 164–165° (lit.[15] mp 166°); ir spectrum was identical with that of the authentic compound.

Isolation of Pentamethylphosphoric Triamide[5] (3).—The filtered mixture from the $KMnO_4$ oxidation of **1** was extracted with $CHCl_3$ which removed all unreacted **1**, some **3**, and almost all **4**. A subsequent continuous extraction with $CHCl_3$ gave almost pure **3**, which on short-path distillation gave a material with ir spectrum identical with that of the authentic sample. *Anal.* ($C_5H_{16}N_3OP$) C, H, N, P.

Pure **3** was also obtained by glpc of the $CHCl_3$ extract, and collection of the corresponding fraction.

N-[Bis(dimethylamino)phosphinyl]-N-methylformamide (4). A. By Oxidation of 1.—The $CHCl_3$-soluble fraction from the oxidation of **1** was distilled in a spinning-band column. The last fraction, bp 102–107° (0.04 mm), contained **4**. Short-path distillation gave the analytical sample: bp 87° (0.01 mm); pmr spectrum (CCl_4), δ 8.56 (singlet,[16] 1 H, H_3CNCHO), 2.78 (doublet, 3 H, H_3CNCHO, J = 9 cps), 2.68 (doublet, 12 H, H_3CNCH_3, J = 10 cps); ν_{max}^{neat} 1682 cm^{-1} (CO); *m/e* 193. *Anal.* ($C_6H_{16}N_3O_2P$) C, H, N, P.

B. By Formylation of 3.—Only dry reagents were used in this experiment. A solution of 4.13 g (0.025 mole) of **3** in 150 ml of Et_2O was added, dropwise, to a slurry of 1.0 g (0.0416 mole) of pulverized NaH and 50 ml of Et_2O in N_2 atmosphere. The evolution of H_2 proceeded for several hours. The mixture was allowed to stand overnight, then it was cooled in a Dry Ice–acetone bath and a cold (Dry Ice–acetone) solution of 1.31 g (0.041 mole) of HCOF[17] in Et_2O was added within 2 min. The mixture was stirred for a few hours and filtered, and the Et_2O filtrate was evaporated under vacuum. The pale yellow, liquid residue (3.74 g) contained, by glpc analysis, 49% of **4**; the remainder of the material was mainly **3**. The ir spectrum of **4** (collected by glpc) was identical with that obtained under method A.

N,N,N′,N′-Tetramethylphosphoric Triamide (7).—Only dry reagents were used in this experiment. A flask containing 800 ml of $CHCl_3$ was cooled (Dry Ice–acetone) and 74.54 g (2.40 moles) of liquid methylamine was added. To the cold (−78°) amine solution was added, during 15 min, a solution of 48.60 g (0.30 mole) of dimethylphosphoramidic dichloride[18] in 200 ml of $CHCl_3$. The contents were then allowed to warm to room temperature and stand overnight. Removal of the salt and the solvent left 33.73 g (83%) of crude **7**. This material was thermally unstable and attempted purification by distillation or glpc was unsuccessful. The indicated small amounts of two impurities. Thus, crude **7** was used in the preparation of **6**.

N-[(Dimethylamino)(methylamino)phosphinyl]-N-methylformamide (6). A. By Oxidation of 3.—Although **6** can be obtained by the oxidation of **1** (see Table I) it was prepared more easily, and in higher yield, by the oxidation of **3**. A solution of 16.52 g (0.10 mole) of **3** in 100 ml of H_2O was stirred and 667 ml (0.20 mole) of 0.3 *M* $KMnO_4$ was added dropwise within 1 hr. The temperature was maintained at 30°. After 4 hr, the MnO_2 was filtered off, the H_2O was removed under vacuum, the residue was extracted three times with 100-ml portions of $CHCl_3$, and the extracts were dried ($MgSO_4$). Removal of the $CHCl_3$ under vacuum left 12.30 g (68.64%) of crude product that contained *ca.* 95% of **6** (glpc analysis). Two short-path distillations gave a colorless oil: bp 126.5° (0.005 mm); n^{20}D 1.4798; pmr spectrum (CCl_4), δ 8.74 (singlet, 1 H, H_3CNCHO), 4.28 (broad singlet, 1 H, H_3CNH), 2.87 (doublet, 3 H, H_3CNCHO, J = 8 cps), 2.73 (doublet, 6 H, H_3CNCH_3, J = 10 cps), 2.54 (doublet, 3 H, H_3CNH, J = 6 cps); ν_{max}^{neat} 1680 cm^{-1} (CO); *m/e* 179. *Anal.* ($C_5H_{14}N_3O_2P$) C, H, N, P.

B. By Formylation of 7.—Crude **7** was formylated in a manner similar to the formylation of **3**, except THF was used as the solvent (**7** is insoluble in Et_2O). From 5.78 g (0.025 mole) of crude **7**, 2.80 g of product was obtained. The main component, by glpc analysis, was **6**.

C. The oxidation products of **4** with an equimolar quantity of $KMnO_4$ products were analyzed by glpc. Only **6**, N-methylformamide, and the starting material were detected.

Reduction of 4 to 3.—A solution of 1.93 g (0.01 mole) of **4** in 20 ml of dry Et_2O was added dropwise (10 min) to a stirred suspension of 1.14 g (0.03 mole) of $LiAlH_4$ in 50 ml of dry Et_2O. The mixture was heated under reflux for 2 hr, cooled, and treated with 10 ml of isopropyl alcohol followed by 8 ml of a saturated NaCl solution. After standing overnight the mixture was filtered, the solid was washed with isopropyl alcohol–Et_2O (2:3), and the combined filtrates were dried ($MgSO_4$). The solvent was removed under vacuum and a short-path distillation of the yellow liquid gave 1.00 g (60.5%) of **3**,[19] bp 75–78° (0.01 mm); glpc pure; ir spectrum identical with that of the authentic material.

N,N,N′-Trimethyl-P-piperidinophosphonic Diamide (8). A solution of *ca.* 27 g of dry $MeNH_2$ in 300 ml of anhydrous Et_2O cooled to −50° was treated dropwise with 31.60 g (0.15 mole) of N,N-dimethyl-P-piperidinophosphonamidic chloride (11) in 100 ml of dry Et_2O. Excess $MeNH_2$ was allowed to reflux 3–4 hr, and then to escape overnight. $MeNH_2$·HCl was filtered off and the solvent was removed under vacuum, leaving 27.46 g of yellow liquid. During short-path distillation some decomposition occurred, but 19.44 g (65.5%) of **8** (99% pure by glpc) was obtained. Redistillation (no decomposition) gave the analytical sample, n^{20}D 1.4867, bp 124–126° (0.015 mm). *Anal.* ($C_8H_{21}N_3OP$) C, H, N, P.

N-[(Dimethylamino)piperidinophosphinyl]-N-methylformamide (9). A. By Oxidation of 10.[5]—A solution of 109.63 g (0.50 mole) of **10** in 500 ml of H_2O was stirred, cooled, and oxidized at *ca.* 30° by dropwise addition (4 hr) of an aqueous solution of 158.05 g (1.00 mole) of $KMnO_4$. The mixture stood overnight, the MnO_2 was filtered off, and the H_2O was removed under vacuum. The residue, a mixture of liquids and solids, was filtered through a sintered-glass funnel and the solid was washed thoroughly with $CHCl_3$; the dry solid weighed 17.65 g. The filtrate formed two layers which were separated. The upper layer solidified to a yellow gum (14.82 g). The $CHCl_3$ layer was dried ($MgSO_4$) and freed of the solvent and 81.20 g of an orange liquid remained. Short-path distillation gave a fraction, bp 123–131° (*ca.* 0.025 mm), which contained *ca.* 80% of **9** (by glpc). Repeated distillation gave 4.60 g of **9**: bp 120–121° (0.005 mm); n^{20}D 1.4949 (pure by glpc analysis); pmr spectrum (CCl_4), δ 8.53 (singlet, 1 H, H_3CNCHO), 3.03 (broad multiplet, 4 H, piperidinyl $(CH_2)_2N$), 2.77 (doublet, 3 H, H_3CNCHO, J = 8 cps), 2.65 (doublet, 6 H, H_3CNCH_3, J = 10 cps), 1.59 (singlet, 6 H, the remaining six H of the piperidinyl system); ν_{max}^{neat} 1678 cm^{-1} (CO); *m/e* 233. *Anal.* ($C_9H_{20}N_3O_2P$) C, H, N, P.

B. By Formylation of 8.—This preparation was analgous to the synthesis of **4**; thus, when 1.00 g (0.0416 mole) of NaH, 5.15 g (0.025 mole) of **8**, and 1.31 g (0.041 mole) of HCOF were allowed to react in Et_2O, 5.60 g of a pale, yellow liquid was obtained. Short-path distillation gave 3.80 g of a clear liquid containing 61% of **9** and 37% of **8** (by glpc). The ir spectrum of **9** collected by glpc from this mixture and the spectrum of **9** prepared by oxidation were identical.

N,N-Dimethyl-P-piperidinophosphonamidic Chloride (11). A solution of 24.30 g (0.15 mole) of dimethylphosphoramidic dichloride[18] in 500 ml of dry hexane was cooled in an ice bath and stirred while a solution of 25.55 g (0.30 mole) of piperidine in 50 ml of hexane was added dropwise (1 hr). After 1 day, the mixture was filtered, the solid was washed with hexane, and

(14) Prepared by the method of S. Rawalay and H. Shechter, *J. Org. Chem.*, **32**, 3129 (1967).

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

(16) We cannot explain why the N-formyl proton appears as a singlet, rather than a doublet. The sample was run at room temperature neat, in CCl_4, in $CDCl_3$, and in D_2O; at 120°, 130°, 150°, and 180° neat; in $Cl_2C{=}CCl_2$ at 60°, 80°, 90°, and 115°; and in $CDCl_3$ at −60°. In all cases the peak remained a singlet.

(17) (a) A. N. Nesmejanow and E. J. Kahn, *Ber.*, **67**, 370 (1934); (b) G. Olah, S. Kuhn, and S. Beke, *ibid.*, **89**, 862 (1956); (c) G. Olah, Ed., "Friedel-Crafts and Related Reactions," Vol. 3, Part 2, Interscience Publishers, Inc., New York, N. Y., 1964, p 1179.

(18) (a) A. Michaelis, *Ann.*, **326**, 170 (1903); (b) J. B. Dickey, T. E. Stamp, and H. W. Coover, Jr., U. S. Patent 2,487,859 (1949); *Chem. Abstr.*, **44**, 2546*g* (1950).

(19) The reduction of **4** to **3** is an example of reductive decomposition (for other examples see N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956). On the other hand, reduction of dibutyl N-formylphosphoramidate to dibutyl N-methylphosphoramidate has been reported by K. D. Berlin and M. V. R. Khaya, *Tetrahedron*, **22**, 987 (1966).

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

ALBERT B. DEMILO AND ALEXEJ B. BOŘKOVEC

Entomology Research Division, U. S. Department of Agriculture, Beltsville, Maryland 20705

Received April 8, 1968

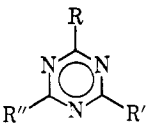
The chloroform- and ether-soluble products of the oxidation of hexamethylmelamine with potassium permanganate were identified as methylmelamines and mono- and diformylated methylmelamines. The formyl compounds were also synthesized by formylation of methylmelamines with formamide or with formyl fluoride.

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

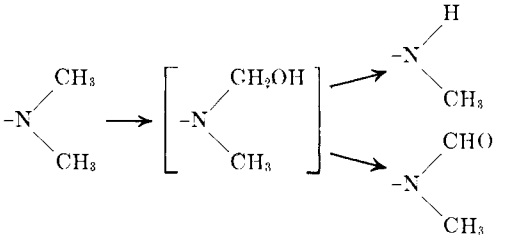
s-TRIAZINES OBTAINED BY OXIDATION OF HEMEL



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).