by the conversion of hippuric acid methyl ester into the hydrazide.[5]

The new pyrazoles (Ia,b,c) were prepared by using the conditions for the preparation of N^1-carbamoyl-3,5-diphenylpyrazoles earlier[2] and are listed in Tables I, II, and III.

Biological Results.—During a screening study in CF-1-S mice (Carworth Farms, 25–30 g) at 1.5 mmol/kg, compounds were administered as CMe-cellulose suspension. Controls received an equal volume of the vehicle. Blood samples (0.05 ml), obtained from retrobulbar plexuses at 0.3 and 5 hr after dosing, were assayed for blood glucose using the method of Hoffman[6] adopted for the technicon autoanalyzer. Compounds of the series 3,5-dimethyl-N^1-carbamoyl-pyrazoles, namely, 4-phenylazo-, 4-(2-nitrophenylazo)-, 4-(3-chlorophenylazo)-, 4-(2,5-dimethylphenylazo), 4-(2-methoxyphenylozo)- and 4-(2,5-dichlorophenylazo)-, and of the series 3-methyl-5-phenyl-N^1- carbamoylpyrazole, *viz.*, 4-(2-nitrophenylazo)-, 4-(4-sulfanilamidophenylazo)-, 4-(4-methoxyphenylazo)- were essentially inactive.[7]

Experimental Section

Melting points were determined on a Kofler hot-stage type apparatus. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.3% of the theoretical values.

3-Arylhydrazono-2,3,4-pentanetriones were obtained by the method of Garg and Singh.[3]

2-Arylhydrazono-1-phenyl-1,2,3-butanetriones were synthesized by the procedure of Garg and Singh.[4]

N^1-Carbamoyl(hippuryl-3-methyl-5-methyl)phenyl-4-arylazopyrazoles.—These were prepared by adopting the route of Garg and Singh[2] used for the preparation of 3,5-diphenyl congeners. Characteristics of 3,5-dimethyl-4-arylazo-N^1-carbamoylpyrazoles (Ia), 3-methyl-4-arylazo-5-phenyl-N^1-carbamoylpyrazoles (Ib), and 3,5-dimethyl-4-arylazo-N^1-hippurylpyrazoles (Ic) are given in Tables I, II, and III, respectively.

Acknowledgment.—Two of the authors (P.P.S. and Miss Veena Arora) are thankful to the Council of Scientific and Industrial Research, New Delhi for granting them Junior Fellowships.

(5) S. Grudzinski, *Roczniki Chem.*, **33**, 655 (1959), *Chem. Abstr.*, **50**, 8069 (1960).

(6) W. S. Woffman, *J. Biol. Chem.*, **120**, 51 (1937).

(7) The authors express their appreciation to Dr. D. A. Blickens of the Department of Metabolic Chemotherapy, Lederle Laboratories, Pearl River, N. Y. for testing results.

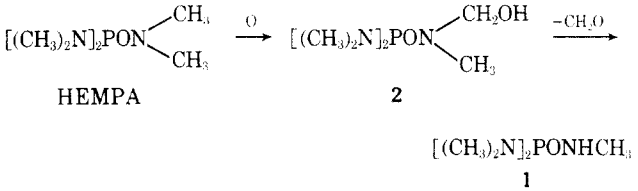
Insect Chemosterilants. IX.[1] *N*-(Hydroxymethyl)-*N*,*N*′,*N*′,*N*″,*N*″-pentamethylphosphoric Triamide

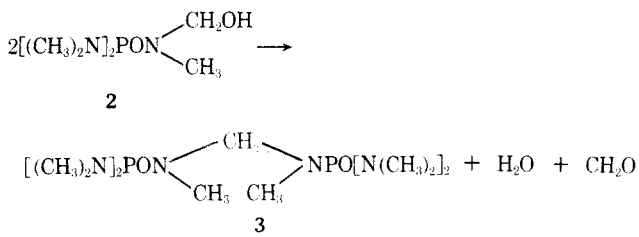
PAUL H. TERRY AND ALEXEJ B. BOŘKOVEC

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

Received February 9, 1970

Hexamethylphosphoric triamide (HEMPA) is a chemosterilant of various vertebrate[2] and invertebrate[3] animals but its physiological effects and metabolism have been studied most extensively in the house fly, *Musca domestica* L.[4] Though HEMPA lacks any apparent alkylating properties, its cytological effects in the reproductive organs of flies are similar to those of aziridinyl alkylating agents.[4a,b] The principal metabolic pathway of HEMPA in house flies is its demethylation to pentamethylphosphoric triamide (**1**) which is rapidly excreted.[4c] The demethylation is accomplished by microsomal enzymes[4d] but any further demethylation of the pentamethyl compound is so slow that lower methylphosphoric triamides are never isolated in substantial quantities. Since the pentamethyl compound is almost without any sterilizing activity in house flies, HEMPA itself or its intermediates during the first demethylation appear to be the sterilizing agents. In the previously proposed degradation scheme for HEMPA[5] the formation of formaldehyde was supported by experimental evidence but the intermediate hydroxymethyl compound (**2**) was never isolated or synthesized. We have now prepared **2** by an exceedingly simple procedure, *i.e.*, by treating **1** with aq CH_2O at room temperature. The properties of **2** account for the difficulties connected with its previously attempted isolation and synthesis. Although **2** is stable at 25°, a rapid conversion of **2** into **3** occurs at elevated temperatures. However, aqueous solutions of **2** decompose slowly to **1** even at room temperature. The condensation product **3** is thermally more stable than **2** but on glpc it decomposes to **1**. Consequently, glpc analyses of solutions containing **1**, **2**, **3**, or their mixtures yield only peaks corresponding to **1**.





Because hexamethylphosphorothioic triamide,[6] the sulfur analog of HEMPA, closely resembles the latter in its sterilizing effect we attempted to prepare the corresponding hydroxymethyl compound by a reaction of pentamethylphosphorothioic triamide (**4**) with formaldehyde. However, the only product that could be isolated from this reaction was the bridged compound **5**.

(1) Previous paper in the series: J. A. Settepani, J. B. Stokes, and A. B. Bořkovec, *J. Med. Chem.*, **13**, 128 (1970).

(2) H. Jackson and A. W. Craig, *Nature*, **212**, 86 (1966).

(3) A. B. Bořkovec, "Insect Chemosterilants," Interscience Publishers, New York, N. Y., 1966, p 99.

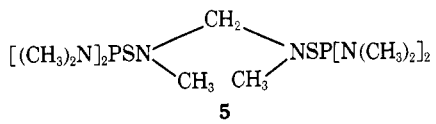
(4) (a) P. B. Morgan, *Ann. Entomol. Soc. Amer.*, **60**, 812 (1967); (b) B. Řežábová, *Acta Entomol. Bohemoslov.*, **65**, 331 (1968); (c) S. C. Chang, P. H. Terry, C. W. Woods, and A. B. Bořkovec, *J. Econ. Entomol.*, **60**, 1623 (1967); (d) S. Akov, J. E. Oliver, and A. B. Bořkovec, *Life Sci.*, **7** (II), 1207 (1968).

(5) P. H. Terry and A. B. Bořkovec, *J. Med. Chem.*, **11**, 958 (1968).

(6) P. H. Terry and A. B. Bořkovec, *ibid.*, **10**, 118 (1967).

$[(CH_3)_2N]_2PSNHCH_3$ ⟶

4



5

Biological Activity.—The injection dose of HEMPA that reduced the fertility of male house flies by 50% (SD_{50}) was 5.67 μg/fly.[7] Formaldehyde, **1**, or **3** had no sterilizing effect at 5–10 μg/fly; however, when **2** was injected into male flies its SD_{50} was equal to that of HEMPA. The reactive hydroxymethyl group in **2** may give rise to certain alkylating characteristics. Although no color was obtained in the colorimetric test with 4-(*p*-nitrobenzyl)pyridine, a modified procedure with 4-(*p*-nitrobenzyl)pyridine perchlorate[8] gave a cranberry red color with **2**, **3**, and **5**. Nevertheless, since **1** and **4** (but neither HEMPA nor hexamethylphosphorothioic triamide) gave the same color reaction, the hydroxymethyl compound cannot be unequivocally designated as an alkylating agent.

Experimental Section

Where analyses[9] 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 the compounds was confirmed by ir, pmr, and mass spectra. Ir spectra were recorded with a Perkin-Elmer Model 137 Infracord, pmr spectra with a Varian HA-100 spectrometer, and mass spectra with a CEC 21-110D spectrometer. Company and trade names are given for identification purposes only and do not constitute endorsement by the U. S. Department of Agriculture.

***N*-(Hydroxymethyl)-*N*,*N*′,*N*′,*N*″,*N*″-pentamethylphosphoric Triamide (2).**—To a flask containing 6.60 g (0.04 mol) of pentamethylphosphoric triamide (**1**) and 10 ml of H_2O was added 3.56 g (0.044 mol) of 37% aq CH_2O. The reactants were allowed to stand overnight at room temperature. H_2O and excess CH_2O were then removed under vacuum in a rotary evaporator followed by direct evacuation with a vacuum pump at room temperature.[10] The yield of **2** was 7.65 g (98%). When 97 mg (0.5 mmol) of **2** was treated with a 2,4-dinitrophenylhydrazine solution, formaldehyde 2,4-dinitrophenylhydrazone was formed in a 94% yield. The hydroxymethyl compound could not be distinguished by glpc from either **1** or **3**; neither could these compounds be distinguished by tlc. The pmr spectrum [(D_2O) δ4.50 (doublet, H_3CNCH_2OD, J = 13 cps)], mass spectrum (*m*/*e* 195, from probe with ion source at 100°), and the ir spectrum corresponded to the structure of **2**. *Anal.* ($C_6H_{18}N_3O_2P$) C, H, N, P.

***N*,*N*‴-Methylenebis[pentamethylphosphoric triamide] (3).**—Upon short path distillation of 4.0 g of **2**, 3.0 g (85%) of **3** was obtained, bp 150° (0.01 mm). The colorless liquid quickly solidified to a white, hygroscopic solid. Recrystallization from hexane gave a nonhygroscopic solid, mp 78–86° (unimproved by further recrystallization). Its pmr spectrum [(D_2O) δ4.12 (triplet, $CH_3NCH_2NCH_3$, J = 7 cps)], mass spectrum (*m*/*e* 342), and ir spectrum corresponded to the structure of **3**. *Anal.* ($C_{11}H_{32}N_6O_2P_2$) C, H, N, P.

When **3** was treated with a 2,4-dinitrophenylhydrazine solution, a quantitative yield of formaldehyde 2,4-dinitrophenylhydrazone was obtained. Alternately, **3** was obtained by allowing a thin layer of **2** to stand *in vacuo* over P_2O_5 for several days.

***N*,*N*‴-Methylenebis[pentamethylphosphorothioic triamide] (5).**—A solution of 7.24 g (0.04 mol) of **4**[11] in 30 ml of acetone (the compound is insoluble in H_2O) was mixed with 3.56 g (0.044 mol) of 37% aq CH_2O and allowed to stand for 1 day. Me_2CO was removed on a rotary evaporator and the H_2O and excess CH_2O were removed as in the preparation of **2**, leaving 7.80 g of a white waxy solid. Recrystallization from 200 ml of hexane gave 5.45 g (73%) of **5**, mp 122–130° dec. Further recrystallization did not improve the melting point. Its pmr spectrum [(CCl_4) δ4.75 (triplet, $H_3CNCH_2NCH_3$, J = 9.5 cps)] and ir spectrum corresponded to the structure of **5**. As with **2** and **3**, **5** could not be distinguished by glpc from its starting material **4**. *Anal.* ($C_{11}H_{32}N_6P_2S_2$) C, H, N, P.

Oxidation of 2.—When 0.39 g (0.002 mol) of **2** in 10 ml of H_2O was allowed to react with 0.23 g (0.002 mol) of 30% H_2O_2 for 3 days, conversion into a 1:1 mixture of **1** and *N*-[bis(dimethylamino)phosphinyl]-*N*-methylformamide[5] occurred.

Reduction of 2.—In agreement with the LAH reduction of *N*-[bis(dimethylamino)phosphinyl]-*N*-methylformamide,[5] the treatment of 0.01 mol of **2** with 0.06 mol of LAH in Et_2O or THF gave **1** as the only product.

Acknowledgments.—We thank the following members of this Division: Dr. S. C. Chang for performing the biological tests, Mr. E. L. Gooden for the pmr spectra determinations, and Dr. John L. Ruth and Mr. David Osheim for the mass spectra determinations.

(7) S. C. Chang and A. B. Bořkovec, *J. Econ. Entomol.*, **59**, 1359 (1966).

(8) R. Preussmann, H. Schneider, and F. Epple, *Arzneim. Forsch.*, **19**, 1059 (1969).

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

(10) P. E. Alimov and O. N. Fedorova [*Izv. Akad. Nauk SSSR Ser. Khim.*, 1461 (1966)] used a similar procedure for the preparation of *N*-methylolphosphoramidates.

(11) A. R. Jones and H. Jackson, *Biochem. Pharm.*, **17**, 2247 (1968) have reported this compound as an oil. Our synthesis, accomplished prior to their report, gave a white crystalline solid, mp 79–80° (hexane).