TABLE II

dl-PANTOYLHYDRAZONES

Deriv of pantoylhydrazine and	Mp, °C[a]	Solvent[b] of reaction, crystn	Yield, %	C, % Calcd	C, % Found[c]	H, % Calcd	H, % Found[c]	N, % Calcd	N, % Found[c]
Benzaldehyde	155–155.5	A, A–E	72.8	62.46	62.23	7.24	7.19		
p-Methoxybenzaldehyde	145–146	B, F–D	70.8					10.00	10.01
p-Dimethylaminobenzaldehyde	188–189	A, G	57.3	61.19	61.34	8.22	7.92		
3-Pyridinecarboxaldehyde	150–151	C, F–D	93.5					16.77	16.58
Pyridoxal	175–176 dec	C, F–D	93.7					13.51	13.29
Sodium levulinate	260–261	C, F–D	63.7					9.74	9.70

[a] Melting points are uncorrected. [b] A, chloroform; B, ethanol; C, 2-propanol; D, diethyl ether; E, petroleum ether; F, methanol; G, ethyl acetate. [c] Analyses by Micro Tech Laboratories, Skokie, Ill.

Pantoylhydrazine.—*dl*-Pantolactone (2.6 g) was dissolved in 5 g of anhydrous hydrazine and the resulting mixture was refluxed for 1 hr. The reaction mixture was stored at ambient temperature for 24 hr and then evaporated at 60–70° under reduced pressure to a thick, clear syrup. Upon treatment with diethyl ether this syrup gave a white powder which was recrystallized from dioxane–diethyl ether to give hygroscopic white, cubic crystals. The pantoylhydrazones were prepared by refluxing the carbonyl compound with pantoylhydrazine in a suitable solvent followed by precipitation with diethyl ether or petroleum ether. Data describing the products are given in Table II. A typical preparation is given in the following paragraph.

Benzaldehyde *dl*-Pantoylhydrazone.—Redistilled benzaldehyde (0.94 g) in 5 ml of chloroform was added to a stirring solution of 1.0 g of *dl*-pantoylhydrazine in 10 ml of chloroform. The mixture was refluxed for 4 hr, cooled to ambient temperature, and poured into 15 ml of diethyl ether. The white solid which separated was collected and recrystallized from chloroform–petroleum ether.

Screening data[6] for these compounds have shown no activity in Sarcoma 180 tests. All compounds except the levulinate and cyclohexylamide were screened.

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(6) The authors are indebted to Drs. C. C. Stock, R. K. Barclay, Christine Reilly, Elvira Falco, and Sophronia Myron, Sloan Kettering Institute for Cancer Research, for conducting these tests. The rating scales and procedures for the Sarcoma 180 test are given in *Cancer Res. Suppl.*, **1**, 91 (1953); **2**, 179 (1955); and *Cancer Res.*, **18**, 49 (1958).

Insect Chemosterilants. IV. Phosphoramides[1]

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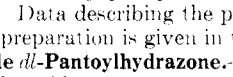
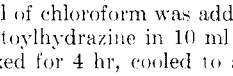
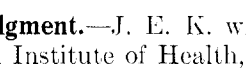
The discovery that hexamethylphosphoric triamide[2] (HEMPA) was capable of sterilizing insects led us to investigate other phosphoramides as possible insect chemosterilants. Variously substituted phosphoramides, thiophosphoramides, and related compounds were synthesized or obtained from commercial sources. Compounds related to HEMPA which were synthesized during this investigation and their activity as sterilants for the house fly, *Musca domestica* L., are shown in Table I; compounds previously reported in the literature which were found to be inactive are not listed.

TABLE I

CHEMOSTERILANT ACTIVITY OF COMPOUNDS

Compd	Structure	Chemosterilant activity[a]
1	$[(CH_3)_2N]_2NH_2PO$	0
2[b]	$[(CH_3)_2N]_2NHCH_3PO$	+
3	$[(CH_3)_2N]_2NHC_2H_5PO$	+
4[c]	$[(CH_3)_2N]_2NH$-*i*-C_3H_7PO	+
5		+
6		+
7	$[(CH_3)_2N]_2N{=}C[N(CH_3)_2]_2PO$	0
8[d]	$[(CH_3)_2N]_3PO$	++
9	$(CH_3NC_2H_5)_3PO$	+
10	$([(CH_3)_2N]_2C{=}N)_3PO$	0
11[e]	$(NH_2)_3PS$	+
12[b]	$(CH_3NH)_3PS$	+
13[f]	$[(CH_3)_2N]_3PS$	++
14[g]		+
15[h]	$[(CH_3)_2N]_3P$	+
16	$[(CH_3)_2N]_3P^{\oplus}C_2H_5I^{\ominus}$	+

[a] Activity scale: ++ = as high as HEMPA,[2] + = lower than HEMPA, 0 = not detectable. [b] R. L. Arceneaux, J. G. Frick, Jr., E. K. Leonard, and J. D. Reid, *J. Org. Chem.*, **24**, 1419 (1959). [c] This compound is mentioned in connection with plant metabolism studies by D. F. Heath, D. W. J. Lane, and P. O. Clark, *Phil. Trans. Roy. Soc. London*, **239B**, 191 (1955). [d] M. Prianka and B. D. Owen, *J. Appl. Chem.* (London), **5**, 525 (1955). [e] R. Klement, *Inorg. Syn.*, **6**, 111 (1960); H. Tolkmith, *J. Am. Chem. Soc.*, **85**, 3246 (1963). [f] H. Tolkmith, *ibid.*, **84**, 2097 (1962). [g] L. F. Audrieth and A. D. F. Toy, *ibid.*, **64**, 1553 (1942). [h] This compound is mentioned in several references but no analytical data could be found for it: *cf.* J. R. Van Wazer, C. F. Collis, J. N. Shoolery, and R. C. Jones, *ibid.*, **78**, 5715 (1956); A. B. Burg and P. J. Slota, Jr., *ibid.*, **80**, 1107 (1958); H. Nöth and H.-J. Vetter, *Ber.*, **94**, 1505 (1961).

Physical characteristics and other data concerning compounds in Table I which have not been previously reported in the literature are shown in Table II or discussed in the Experimental Section.

Of over 50 compounds tested[3] only hexamethylthiophosphoric triamide (**13**) sterilized house flies as effectively as HEMPA (**8**). Replacement of one or more methyl groups in **8** or **13** with higher alkyls or with hydrogen led invariably to a decrease in activity. Compounds which differ only slightly from **8** or **13**,

(1) Previous paper: A. B. Bořkovec, C. W. Woods, and R. T. Brown, *J. Med. Chem.*, **9**, 522 (1966).

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

(3) Screening tests on house flies were performed by entomologists of the Entomology Research Division, Agricultural Research Service, U. S. Department of Agriculture, Gainesville, Fla. For details on screening procedure, *cf.* R. L. Fye, G. C. LaBreeque, and H. K. Gouck, *J. Econ. Entomol.* **59**, 485 (1966).

TABLE II
PHOSPHORAMIDES

No.	Yield,[a] %	Mp, °C	Bp, °C (mm)	$n^{20}D$	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	63	114.5–117.5[b]	...	...	$C_4H_{14}N_3OP$	31.78	9.34	27.80	31.68	9.36	27.70
3	40	35.5–38.5[c]	92–100 (0.03) dec	...	$C_6H_{18}NOP$	40.21	10.12	23.45	40.03	10.41	23.04
5	52	...	59.5–60 (0.1)	1.4815	$C_9H_{22}N_3OP$[d]	49.30	10.11	19.16	49.13	10.21	18.98
6	83	...	81 (0.005)	1.4826	$C_8H_{20}N_3O_2P$	43.43	9.11	18.99	43.13	9.07	19.15
7	75	...	95 (0.005)	1.4998	$C_9H_{24}N_5OP$	43.36	9.70	28.09	43.19	9.86	28.24

[a] Yields of pure products were determined from one run only. [b] Crystallized from benzene. [c] Crystallized from petroleum ether (bp 20–40°). [d] *Anal.* Calcd: P, 14.13. Found: P, 14.06.

i.e., **2–5** and **9**, were still moderately active sterilants, but when the structure of the candidate compound was substantially different from HEMPA, activity became very slight or not detectable. HEMPA and a few related compounds are active on insects other than house flies,[4] and the structural limitations indicated in Table I may not be generally valid.

Experimental Section[5]

N,N,N′,N′-Tetramethyl-N″-isopropylphosphoric Triamide (4).—Bis(dimethylamino)phosphoryl chloride[6] (34.28 g, 0.2 mole) was added dropwise over a period of 1 hr to isopropylamine (59.11 g, 1 mole) which had been cooled to 2°. The stirred mixture was then warmed slowly and kept under reflux for 1 hr. After distilling the excess amine, the residue was dissolved in CH_2Cl_2, the solution was washed with water to remove the salt, and the organic layer was dried ($MgSO_4$). Filtration and removal of the solvent left a waxy solid which was crystallized from the minimum quantity of petroleum ether (bp 30–40°); yield 19.3 g (50%), mp 112–118°; five recrystallizations from hexane gave colorless, waxy plates, mp 118–122° (prior sintering).

Anal. Calcd for $C_7H_{20}N_2OP$: C, 43.51; H, 10.43; N, 21.75; P, 16.03. Found: C, 43.45; H, 10.51; N, 21.77; P, 16.04.

N,N,N′,N′-Tetramethylphosphoric triamide (**1**), N,N,N′,N′-tetramethyl-N″-ethylphosphoric triamide (**3**), N,N,N′,N′-tetramethyl-P-piperidinophosphonic diamide (**5**), N,N,N′,N′-tetramethyl-P-morpholinophosphonic diamide (**6**), and N,N,N′,N′-tetramethyl-P-tetramethylguanidinophosphonic diamide (**7**) were prepared in an analogous manner. A solvent and a low reaction temperature were necessary for the amines with the lower boiling points. When morpholine and piperidine were used, the mixture was heated at 50° for several hours after the addition of the acid chloride was completed. Compounds **1**, **3**, and **4** are somewhat hygroscopic, and **3** showed evidence of decomposition when stored in a desiccator for 1 year though it could be purified again by recrystallization.

N,N′,N″-Trimethyl-N,N′,N″-triethylphosphoric Triamide (9).—N,N′,N″-Trimethyl-N,N′,N″-triethylphosphorous triamide[7] (4.1 g, 0.02 mole) in 25 ml of acetone and 10 g (0.03 mole) of 10% H_2O_2 was kept at 4° for 1 hr[8] and then heated under reflux for several hours. Then the acetone was removed, and the residue was treated with 20 ml of aqueous KI (8.3 g, 0.05 mole). After 12 hr, the mixture was extracted three times with 25 ml of $CHCl_3$; the combined extracts were dried ($MgSO_4$) and evaporated to 2.43 g (55%) of an orange liquid. Distillation in a short-path apparatus gave 1.55 g (35%) of colorless liquid, bp 52–53° (0.1 mm), $n^{20}D$ 1.4553; glpc gave a single peak.

Anal. Calcd for $C_9H_{24}N_3OP$: C, 48.85; H, 10.93, N, 18.99; P, 14.00. Found: C, 49.07; H, 10.98; N, 18.86; P, 13.87.

Tris(tetramethylguanidino)phosphine Oxide (10).—A solution of $POCl_3$ (15.34 g, 0.1 mole) in 100 ml of dry ethyl ether was added dropwise (2 hr) to a stirred solution of 1,1,3,3-tetramethylguanidine (69.11 g, 0.6 mole) in 600 ml of dry ethyl ether at −30 to −50°. The mixture was allowed to warm to room temperature and to stand overnight. The ethereal solution was filtered, dried ($MgSO_4$), and evaporated to a yellow liquid. Distillation in a Hickman still at 0.05 mm gave 23.40 g (60%) of a very viscous liquid which solidified to a waxy solid when touched. Recrystallization from cyclohexane gave 17.55 g (45%) of solid, mp 96–121°. Four more recrystallizations from cyclohexane gave the analytical sample, 11.70 g (30%), of tiny, white hexagons, mp 118–123°. The nmr spectrum ($DCCl_3$), taken at 35°, consisted of a single peak at δ = 2.83 ppm. Width at half peak height ($W_{1/2}$) was 1 cps [tetramethylsilane (TMS), $W_{1/2}$ = 1 cps]. On cooling to −68.5° the singlet peak had shifted slightly to δ = 2.86 ppm and the peak had broadened, $W_{1/2}$ = 5 cps (TMS, $W_{1/2}$ = 1.5 cps).[9]

Anal. Calcd for $C_{15}H_{36}N_9OP$: C, 46.26; H, 9.32; N, 32.36. Found: C, 46.38; H, 9.41; N, 32.03.

Hexamethylphosphorous triamide (15) has been prepared previously (see Table I for references), but no analytical data were reported. In our preparation, the yield of crude material was 75%; two distillations gave the analytical sample, bp 66° (27 mm), $n^{20}D$ 1.4642.

Anal. Calcd for $C_6H_{18}N_3P$: C, 44.16; H, 11.12; N, 25.75; P, 18.98. Found: C, 43.96; H, 11.00; N, 25.74; P, 18.98.

Tris(dimethylamino)ethylphosphonium Iodide (16).—A solution of ethyl iodide (3.12 g, 0.02 mole) in 25 ml of dry ethyl ether was added to a solution of hexamethylphosphorous triamide (**15**) (3.26 g, 0.02 mole) in 25 ml of dry ethyl ether. Unlike the reaction with methyl iodide[10] which we observed to be very rapid and almost quantitative, compound **16** precipitated slowly. The reaction flask was stoppered tightly, and after 2 days the colorless solid was filtered, washed with dry ethyl ether, and dried in a vacuum desiccator; yield 2.5 g (39%). Two recrystallizations from chloroform–ethyl ether gave the analytical sample, mp 280–317° dec.

Anal. Calcd for $C_8H_{23}N_3PI$: C, 30.10; H, 7.26; N, 13.16. Found: C, 29.83; H, 7.30; N, 13.08.

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

(5) Melting points were determined in sealed capillaries using a coil-heated, stirred, silicone oil bath with a calibrated thermometer (Drechsel melting point apparatus). Boiling points are uncorrected. Glpc data were obtained on an F & M Scientific Corp. Model 720 gas chromatograph. Nmr spectra were obtained on a Varian A-60 instrument with tetramethylsilane as an internal reference. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Mention of a proprietary product or company does not necessarily imply endorsement of the product or company by the U. S. Department of Agriculture.

(6) P. Lester, U. S. Patent 2,678,325 (1954); *Chem. Abstr.*, **49**, 6300*g* (1955). The acid chloride prepared according to this method was distilled until a fraction was obtained which showed only one peak by glpc.

(7) Prepared in a manner similar to **15**. The elemental analysis of this compound was not satisfactory because of contamination with the amine salt.

(8) C. Stuebe and H. P. Lankelma [*J. Am. Chem. Soc.*, **78**, 976 (1956)] have prepared other phosphoric triamides by this method.

(9) A. J. Papa [*J. Org. Chem.*, **31**, 1426 (1966)] has found that the proton nmr spectrum of 2-chlorotetramethylguanidine shows two singlets of equal intensity of δ = 2.68 and 2.81 ppm. On the other hand, dimethyl N-chloroiminocarbonate, even at a temperature of −60°, gave only a single peak at δ = 3.89 ppm.

(10) See the last two references under *h* in Table I.