modified for the Technicon Autoanalyzer, were not depressed below those of untreated controls after 3 hr in rats and 2 hr in chicks. For comparison, tolbutamide (**1**) effects an approximately 35% drop in blood sugar levels in rats and chicks when administered at a dose of 50 mg/kg under the same test conditions.

Experimental Section[6]

Benzyl Phenylphosphonamidate (5a).—The general method of Hersman and Audrieth[7] was followed. To a stirred solution of 83 g (0.43 mole) of phenylphosphonyl dichloride in 200 ml of ether was added a solution of 48 g (0.45 mole) of benzyl alcohol, 34 g (0.43 mole) of pyridine, and 200 ml of ether. The mixture was stirred for 45 min at room temperature, heated under reflux for 15 min, and filtered. The filtrate was added dropwise to a solution of 200 ml of liquid NH_3 and 200 ml of ether. The mixture was concentrated to dryness, and the residue was taken up in $CHCl_3$. Evaporation of the solvent left a solid residue, which was recrystallized from CCl_4–ethanol to provide 67 g (63%) of crystals, mp 112–114°. Three additional recrystallizations gave the analytical sample, mp 121–123°.

Anal. Calcd for $C_{13}H_{14}NO_2P$: C, 63.15; H, 5.70; N, 5.67; P, 12.53. Found: C, 63.33; H, 5.79; N, 5.81; P, 12.66.

Benzyl *p*-Tolylphosphonamidate (5b).—To a stirred solution of 68.3 g (0.33 mole) of *p*-tolylphosphonyl dichloride[8] in 200 ml of ether was added a solution of 37.0 g (0.34 mole) of benzyl alcohol, 25.5 g (0.32 mole) of pyridine, and 200 ml of ether. The mixture was heated under reflux for 15 min and filtered. The filtrate was slowly added to a solution of 200 ml of liquid NH_3 and 200 ml of ether. The mixture was concentrated to dryness, and the solid residue was taken up in $CHCl_3$. Evaporation of the $CHCl_3$ left a solid which was recrystallized from CCl_4–ethanol to provide 45 g (52%) of crystals, mp 115–125°. Recrystallization from CCl_4 gave colorless fine needles, mp 120–124°.

Anal. Calcd for $C_{14}H_{16}NO_2P$: C, 64.36; H, 6.17; N, 5.36. Found: C, 64.33; H, 6.21; N, 5.24.

Benzyl N-(Butylcarbamoyl)phenylphosphonamidate (6a).—To a cold mixture of 19.6 g (0.08 mole) of **5a** and 8.0 g (0.08 mole) of *n*-butyl isocyanate in 250 ml of glyme was slowly added with stirring 3.6 g (0.08 mole) of 55% sodium hydride dispersion. After 16 hr, the mixture was acidified with ethanolic HCl and filtered. The filtrate was concentrated under reduced pressure to a glass which was dissolved in methanol. Addition of water to the solution effected precipitation of a solid which, after recrystallization from acetonitrile, amounted to 5.4 g (19%) of colorless crystals, mp 120–124°. Three recrystallizations from ethyl acetate afforded the analytical sample, mp 125–126°.

Anal. Calcd for $C_{18}H_{23}N_2O_3P$: C, 62.43; H, 6.65; N, 8.09; P, 8.96. Found: C, 62.72; H, 6.67; N, 8.08; P, 8.76.

Benzyl N-(Butylcarbamoyl)-*p*-tolylphosphonamidate (6b).—To a cold mixture of 5.4 g (0.02 mole) of **5b**, 2.0 g (0.2 mole) of *n*-butyl isocyanate, and 60 ml of glyme was slowly added with stirring 0.9 g (0.02 mole) of 55% sodium hydride dispersion. After 16 hr, the mixture was acidified with ethanolic HCl and filtered. The filtrate was concentrated under reduced pressure to 9.0 g of colorless solid. Three recrystallizations from isopropyl alcohol gave 0.6 g (8%) of colorless microcrystals, mp 132–135°.

Anal. Calcd for $C_{19}H_{25}N_2O_3P$: C, 63.33; H, 6.94; N, 7.78; P, 8.61. Found: C, 63.72; H, 7.35; N, 7.63; P, 8.63.

Sodium N-(Butylcarbamoyl)phenylphosphonamidate (7a).—A mixture of 1.0 g (2.75 mmoles) of **6a**, 1.10 g of 10% palladium on charcoal, and 50 ml of glyme was hydrogenated at 30 psi and room temperature for 1.5 hr. The mixture was diluted with 100 ml of water and filtered, and the filtrate was titrated to a phenolphthalein end point with 26 ml of 0.1 *N* NaOH. The solution was concentrated under reduced pressure at 35° to 0.6 g (78%) of a colorless solid which did not melt below 310°. Recrystallization from methanol gave the analytical sample.

Anal. Calcd for $C_{11}H_{16}N_2NaO_3P$: C, 47.48; H, 5.86; N, 10.07; Na, 8.27; P, 11.15. Found: C, 47.70; H, 5.94; N, 9.60; Na, 8.78; P, 10.75.

Sodium N-(Butylcarbamoyl)-*p*-tolylphosphonamidate (7b).—A mixture of 5.3 g (0.015 mole) of **6b**, 7.0 g of 10% palladium on charcoal, and 500 ml of glyme was hydrogenated at 30 psi at room temperature for 12 hr. The mixture was diluted with 500 ml of water and filtered, and the filtrate was titrated to a phenolphthalein end point with 14 ml of 1 *N* NaOH. The solution was concentrated to dryness under reduced pressure at 50°, and the colorless solid residue was recrystallized from isopropyl alcohol–water to provide 1.1 g (25%) of colorless crystals which did not melt below 310°.

Anal. Calcd for $C_{12}H_{18}N_2NaO_3P$: C, 49.31; H, 6.21; N, 9.59; Na, 7.87; P, 10.60. Found: C, 48.89; H, 6.33; N, 9.45; Na, 7.27; P, 10.80.

(6) Melting points were determined in a Hershberg apparatus and are uncorrected. Microanalyses were performed by Mr. L. M. Brancone and staff. We thank Mr. R. Schirner for the synthesis of **5a** and Mr. L. Binovi for the synthesis of **5b**.

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(8) A. D. F. Toy, *J. Am. Chem. Soc.*, **70**, 186 (1948).

Pantothenic Acid Derivatives

RICHARD H. WILEY[1] AND JOHN E. KENNEDY, JR.

Department of Chemistry, College of Arts and Sciences, University of Louisville, Louisville, Kentucky

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Interest in the suppression of the physiological activity of 6-substituted purines[2,3] by coenzyme A has suggested the desirability of examining the effect of structural variation in the pantothenic acid moiety of the CoA molecule.

A continuing interest in the physiological activity of hydrazones, and the possibility that hydrazones prepared from pantoylhydrazine might, like purines,[4] be incorporated into the CoA molecule, prompted the preparation of several pantoylhydrazones.

Experimental Section

Pantoylhydrazine has been obtained previously[5] but in low (30%) yield. The technique used in this preparation was modified to give a higher yield and a cleaner product and was then used in the preparation of pantoyl derivatives of substituted hydrazines and alicyclic amines. Data describing the products are given in Table I. The preparation of the hydrazine is typical and is described in the following paragraph.

TABLE I

PANTOYLAMINES AND -HYDRAZINES

Pantoyl deriv of	Mp, °C[a]	Yield, %	Crystn solvent[b]	N, %[c] Calcd	N, %[c] Found
Cyclohexylamine	109–110	99.4	A	6.16	5.91
Cyclopentylamine	64–65	67.0	B	6.52	6.37
Hydrazine	99–100	57.0	C	17.30	17.60
Methylhydrazine	102–103	63.8	D	15.99	16.24
N,N-Dimethylhydrazine	120–121	60.0	B	14.72	14.68

[a] Melting points are uncorrected. [b] A, ethyl acetate–petroleum ether (bp 60–110°); B, petroleum ether; C, dioxane–diethyl ether; D, chloroform. [c] Analyses by Micro Tech Laboratories, Skokie, Ill.

(1) To whom correspondence should be addressed at Hunter College, The City University of New York, New York, N. Y. 10021.

(2) D. A. Clark, F. S. Phillips, S. S. Sternberg, and C. C. Stock, *Ann. N. Y. Acad. Sci.*, **60**, 235 (1955).

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TABLE II

dl-PANTOYLHYDRAZONES

Deriv of pantoylhydrazine and	Mp, °C[a]	Solvent[b] of reaction, cryst	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	61.31	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]

PAUL H. TERRY AND ALENEJ B. BOŘKOVEC

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

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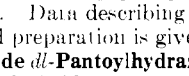
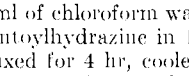
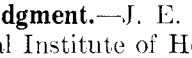
The discovery that hexamethylphosphoric triamide[2] (HEMPA) was capable of sterilizing insects led us to investigate other phosphoramides as possible insect chemosterilants. Variously substituted phosphoramides, thiophosphoramides, and related compounds were synthesized or obtained from commercial sources. 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[f]	$(CH_3NH)_3PS$	+
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] B. 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. Callis, 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. Borkovec, C. W. Woods, and R. T. Brown, *J. Med. Chem.*, **9**, 522 (1966).

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(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. LaBrecque, and H. K. Gouck, *J. Econ. Entomol.* **59**, 485 (1966).