TABLE I

TOXICITY AND CHOLINESTERASE-INHIBITING EFFECT OF SOME OF THE PREPARED COMPOUNDS

Compound	LD_{50}, mg/kg in mice	pI_{50} erythrocyte enzyme
$(C_2H_5O)_2P(O)SeNa$	>15	...
$(C_2H_5O)_2P(O)SeCH_2CH_2NH_2 \cdot (COOH)_2$	...	6.8
$\begin{matrix} C_2H_5O \\ \\ C_2H_5 \end{matrix}\!\!>\!P(O)SeCH_2CH_2N(C_2H_5)_2$	0.021	9.0–9.7
$(C_2H_5O)_2P(O)SeCH_2CH_2N(C_2H_5)_2$	0.06	8.2

chloride[9] was vigorously stirred under an argon atmosphere. Selenium (39.5 g, 0.5 g-atom) was added in small portions during about 15 min whereafter the mixture was stirred for another 3 hr. The temperature was never allowed to exceed 45°. Distillation gave 73 g (70%) of product, bp 70° (10 mm). The compound is very easily oxidized in the presence of air.

O-Ethylethylphosphonoselenoic Acid.[10]—To a chilled solution of 24 g (0.6 mole) of NaOH in 300 ml of ethanol was slowly added 42.0 g (0.2 mole) of ethylphosphonoselenoic dichloride, the temperature being maintained at 0–4°. The reaction was carried out in an atmosphere of argon. After the addition of the dichloride the mixture was refluxed for 5 hr whereafter the solution was filtered. Remaining ethanol was driven off *in vacuo*. The solid residue was dissolved in 30 ml of water and the solution was washed twice with 20 ml of ether. A small amount of selenium was formed and precipitated out during this operation. The water phase was separated, filtered, chilled to about 4°, and acidified with 20 ml of concentrated HCl. The product, which precipitated out during this operation, was extracted into two 25-ml portions of ether. The ether was removed *in vacuo* and the remaining substance was distilled, bp 85° (0.2 mm), yield 10 g (50%), $n^{25}D$ 1.516.

Anal. Calcd for $C_4H_{11}O_2PSe$: C, 23.9; H, 5.51. Found: C, 23.9; H, 5.57.

Sodium O-ethyl ethylphosphonoselenoate was prepared by allowing equimolar amounts of NaOH and O-ethylethylphosphonoselenoic acid to react in ethanol at 0° under argon. After evaporation, the sodium salt was obtained in quantitative yield. It was readily soluble in ether and benzene (*cf.* ref 7).

O,O-Diethyl Se-(2-Aminoethyl)phosphoroselenoate.—Sodium O,O-diethyl phosphoroselenoate (2.4 g, 0.010 mole) was dissolved in 2.0 ml (0.039 mole) of aziridine, and the solution was evaporated to dryness under a rotating evaporator at 20°. The crystalline residue was dissolved in 25 ml of methanol and a solution of 2.5 g (0.020 mole) of oxalic acid dihydrate in 15 ml of methanol was added. The precipitated sodium oxalate was filtered off. The residue was evaporated to about 20 ml and 150 ml of ether was added. A total of 2.1 g (0.006 mole, 60%) of the crystalline oxalate of the product was thus obtained, mp 94–95°.

Anal. Calcd for $C_8H_{18}NO_7PSe$: C, 27.4; H, 5.2; P, 8.85; N, 4.00. Found: C, 27.6; H, 5.3; P, 8.8; N, 3.95.

O,O-Diethyl Se-(2-Diethylaminoethyl)phosphoroselenoate.—A mixture of 12.2 g (0.051 mole) of sodium O,O-diethyl phosphoroselenoate and 6.4 g (0.047 mole) of 2-diethylaminoethyl chloride was stirred for 24 hr at 20° under argon, after which time 15 ml of water was added. The solution was extracted with three 20-ml portions of benzene. The benzene phases were separated, dried (K_2CO_3), and evaporated to dryness at 30° under high vacuum, yield 12.0 g (81%), $n^{25}D$ 1.4830, d^{22}_4 1.230.

Anal. Calcd for $C_{10}H_{23}NO_3PSe$: C, 38.0; H, 7.65; P, 9.8. Found: C, 37.5; H, 7.64; P, 9.7.

O-Ethyl Se-(2-diethylaminoethyl)ethylphosphonoselenoate.—Sodium O-ethyl ethylphosphonoselenoate (2.5 g, 0.011 mole) and 1.35 g (0.01 mole) of 2-diethylaminoethyl chloride were stirred at 20° for 24 hr under argon. Water (4 ml) was added and the solution was extracted with three 5-ml portions of benzene. The benzene phases were treated as above, yield 2.1 g (70%), $n^{25}D$ 1.4950, d^{22}_4 1.185.

Anal. Calcd for $C_{10}H_{24}NO_2PSe$: C, 40.0; H, 9.0; P, 10.3. Found: C, 39.7; H, 8.0; P, 10.5.

(9) P. O. Granboin, to be published.

(10) The corresponding sulfur analog was prepared by F. W. Hoffman, R. Kagan, and J. H. Canfield, *J. Am. Chem. Soc.*, **81**, 148 (1959).

Phosphorus Analogs of Sulfonylureas. Sodium N-Carbamoylphosphonamidates

WILLIAM J. FANSHAWE, VICTOR J. BAUER, AND S. R. SAFIR

Organic Chemical Research Section, Lederle Laboratories, A Division of American Cyanamid Company, Pearl River, New York

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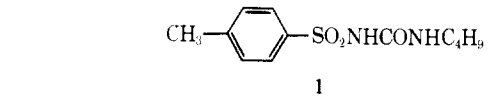
Sulfonylureas, particularly tolbutamide (**1**),[1] have won wide acceptance in the treatment of maturity-onset diabetes. Other than a representative sulfinylurea (**2**)[2] and a sulfenylurea (**3**),[3] both of which are reported to be hypoglycemic agents, analogs which differ from **1** by more extensive modification of the sulfonyl group appear to be unknown. We have now prepared the phosphorus analogs **7a** and **7b** of the sulfonylureas for evaluation as potential hypoglycemic agents.

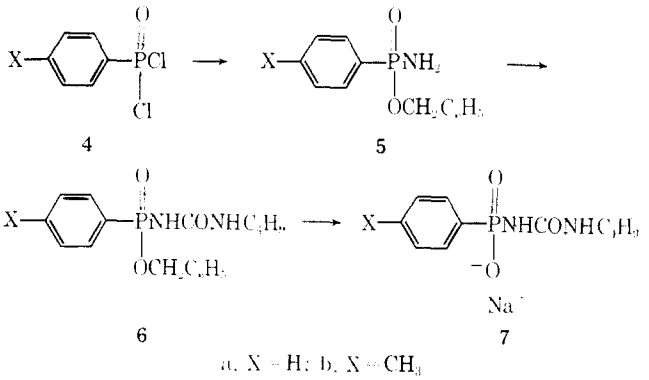


1

2 **3**

Reaction of the known phosphonyl dichlorides **4a** and **4b** with benzyl alcohol, followed by ammonia, provided the benzyl phosphonamides **5a** and **5b** which were converted to the benzyl N-carbamoylphosphonamidates **6a** and **6b** by addition to *n*-butyl isocyanate under basic conditions (Scheme I). Hydrogenolysis

SCHEME I



a, X = H; b, X = CH_3

of the benzyl esters **6a** and **6b** was accomplished in the presence of large amounts of palladium on charcoal, and the products were isolated as the sodium salts **7a** and **7b**. The structures **7** were confirmed by infrared spectra which exhibit bands at 6.0 (C=O), 8.3, and 8.8 (P=O) μ.[4]

The phosphonylureas **7a** and **7b** were administered intraperitoneally at a dose of 200 mg/kg to normal, fasted rats and orally at a dose of 250 mg/kg to normal, fasted chicks. Blood glucose levels, estimated as "reducing-sugar" content by the method of Hoffman[5] as

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(3) Y. Nitta, *et al.*, *J. Pharm. Soc. Japan*, **82**, 191 (1962).

(4) N. B. Colthup, L. H. Daly, and S. E. Wiberly, "Introduction to Infrared and Raman Spectroscopy," Academic Press Inc., New York, N. Y., 1964, p 299.

(5) W. S. Hoffman, *J. Biol. Chem.*, **120**, 51 (1937). We thank Drs. N. Bauman, C. Boshart, S. Riggi, and E. Tocus for furnishing the results of animal testing.

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.

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(3) J. J. Biesele, *ibid.*, **60**, 228 (1955).

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