TABLE III

EFFECT OF VAPORS OF 5-SUBSTITUTED 2,4,6-TRICHLOROPYRIMIDINES ON FUNGAL SPORES INCORPORATED IN SABOURAUD DEXTROSE AGAR AT 28° AFTER 5 DAYS

Compd II	Spores from— *A. niger*	*T. viride*	*A. oryzae*
a	50[a]	10	+
b	+	10	+
c	+	+	+
d	+	+	+
e	+	+	+
f	+	+	+
g	+	+	+
h	+	+	+
i	+	+	+
j	S	S	S
k	+	+	+

[a] Symbols: a number = approximate per cent of area showing no growth, + = no inhibition, S = sporistatic.

Experimental Section[16]

5-Nonylbarbituric Acid (Ii).—To a solution prepared by dissolving 23 g (1 g-atom) of sodium in 1000 ml of anhydrous ethanol were added 34.5 g (0.57 mole) of dry urea in 300 ml of anhydrous ethanol and 165 g (0.57 mole) of diethyl nonylmalonate.[16] The mixture was heated under reflux with agitation for 2.5 hr. Excess alcohol was removed by flash evaporation, and the residue was dissolved in water and acidified to pH 1–2 with concentrated HCl. The compound was collected by filtration, washed free of salts with water, and dried at 70° overnight. The yield of product was 103 g (71%), mp 195–201°. An analytical sample was crystallized from methanol; mp 208–209°.

Anal. Calcd for $C_{13}H_{22}N_2O_3$: C, 61.39; H, 8.72; N, 11.02. Found: C, 61.25; H, 8.72; N, 11.28.

5-Octylbarbituric acid (Ih) was prepared in the same manner as Ii in 55% yield, mp 211–213° (from methanol).

Anal. Calcd for $C_{12}H_{20}N_2O_3$: C, 59.98; H, 8.39; N, 11.66. Found: C, 60.00; H, 8.31; N, 11.63.

5-Heptylbarbituric acid (Ig) was prepared in 51% yield in the same manner as Ii; mp 207–209° (from methanol).

Anal. Calcd for $C_{11}H_{18}N_2O_3$: C, 58.39; H, 8.02; N, 12.38. Found: C, 58.52; H, 7.87; N, 12.62.

5-Nonyl-2,4,6-trichloropyrimidine (IIi).—A mixture of 50 g (0.18 mole) of Ii, 500 ml of $POCl_3$, and 50 ml of dimethylaniline was heated under reflux with agitation for 2 hr. Most of the $POCl_3$ was removed by flash evaporation, and the residue was decomposed by pouring it onto 1.5 l. of ice flakes. The chloropyrimidine was extracted with ether. The extract was washed with water and dried over Na_2SO_4, and the ether was flash evaporated. The residue was distilled to yield 15 g of product (27%), bp 147–152° (0.45 mm). The analytical sample boiled at 141° (0.25 mm).

(16) Melting points were taken in a Mel-Temp melting point apparatus and are uncorrected. Ultraviolet data were obtained with a Perkin-Elmer Spectracord 4000A. The synthetic procedures are general, and the malonic esters were commercially available except where the alkyl groups were hexyl, heptyl, octyl, and nonyl. These were prepared by the method of B. Rothstein, *Bull. Soc. Chim. France*, **2**, 80 (1935).

Selenophosphorus Compounds as Powerful Cholinesterase Inhibitors

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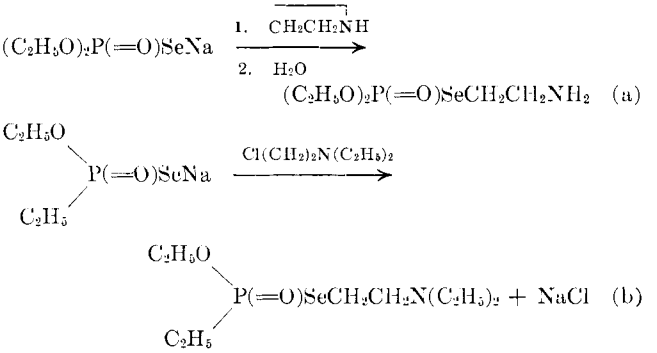
Certain organophosphorus compounds containing sulfur have been known for a long time to be powerful inhibitors of cholinesterase.[1] Very little is known, however, about the chemical properties and toxicity of the corresponding selenium compounds.

The present paper describes some methods which have been found convenient for the preparation of certain types of compounds containing the PSeC group. The synthetic routes adopted consist of reactions of phosphoro- or phosphonoselenoates with (a) aziridine or its derivatives, or (b) aminoalkylhalogenides, as exemplified below. In principle, these reactions are analogous to the ones used for phosphorothioates.[2]



Reaction a proceeds almost immediately at room temperature. Reaction b is slower, but is best carried out at room temperature. The isolated compounds are less stable than the corresponding sulfur compounds. The intermediates especially are rapidly attacked by oxygen from the air and become discolored due to the formation of elemental selenium.

The purity of the compounds was checked by gas chromatography,[3] and their structure was confirmed by infrared and nmr spectra.[4] The shift in the nmr spectra of CH_2OP is about 6.0 ppm, whereas that of CH_2SeP is about 7.0 ppm in this type of compounds.[5] The infrared spectra of the prepared compounds are practically identical with the ones obtained from the corresponding sulfur analogs.

The selenium derivatives reported belong to the most toxic phosphorus compounds known having LD_{50} values ranging from 0.02 to 0.06 mg/kg when injected subcutaneously in mice, *i.e.*, they are more toxic than the corresponding sulfur analogs. The toxicity is due to the ability of these compounds to inhibit cholinesterase, as shown in tests with human erythrocyte enzyme. The pI_{50} values[6] were in the range 6.8–9.7 as shown in Table I.

Experimental Section

Sodium O,O-diethyl phosphoroselenoate was prepared according to Foss.[7]

Anal. Calcd for $C_4H_{10}NaO_3PSe$: C, 20.1; H, 4.23; P, 13.0. Found: C, 19.8; H, 4.20; P, 12.9.

Ethylphosphonoselenoic Dichloride.[8]—A mixture of 8 g of dry, powdered $AlCl_3$ and 65.5 g (0.5 mole) of ethylphosphonous di-

(1) For a recent summary see E. Heilbronn-Wilkström, *Svensk Kem. Tidskr.*, **77**, 598 (1965).

(2) (a) S. Åkerfeldt, *Acta Chem. Scand.*, **16**, 1897 (1962); (b) *ibid.*, **17**, 329 (1963); (c) *Svensk Kem. Tidskr.*, **75**, 231 (1963).

(3) Aerograph 1520, SE 30 column at 162–170° with nitrogen as carrier gas (60 ml/min). FID detector.

(4) Varian A-60 A spectrophotometer; TMS as external reference.

(5) B. Östman, personal communication.

(6) $pI_{50} = -\log$ (molar concentration for 50% inhibition).

(7) O. Foss, *Acta Chem. Scand.*, **1**, 8 (1947).

(8) This preparation procedure is similar to the one used for the sulfur analogs as described by F. W. Hoffman, D. H. Wadsworth, and H. D. Weiss, *J. Am. Chem. Soc.*, **80**, 3945 (1958).

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
$(C_2H_5O)_2P(O)SeCH_2CH_2N(C_2H_5)_2$	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

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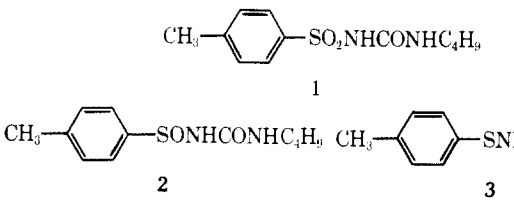
Sulfonylureas, particularly tolbutamide (**1**),[1] have won wide acceptance in the treatment of maturity-onset diabetes. Other than a representative sulfinylurea (**2**)[2] and a sulfenylurea (**3**),[3] both of which are reported to be hypoglycemic agents, analogs which differ from **1** by more extensive 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.

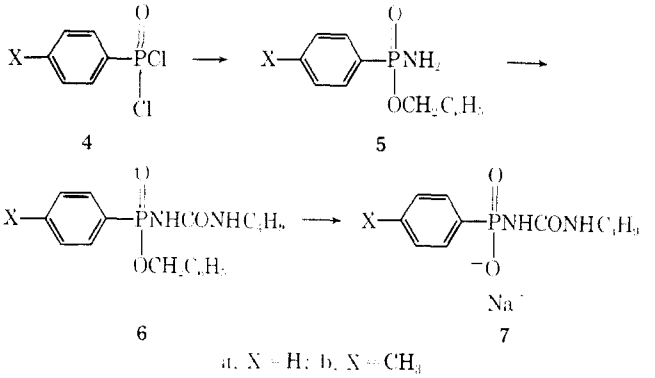


1

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



4 **5**

6 **7**

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

(1) W. C. Cutting, "Handbook of Pharmacology," Appleton-Century-Crofts, New York, N. Y., 1962, p 372.

(2) Y. Nitta, N. Ando, and Y. Ikeda, *Yakugaku Zasshi*, **82**, 967 (1962).

(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.