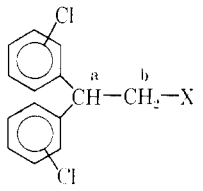
TABLE I



Compd	X	Mp, °C	Yield, %	Analyses	Chemical shifts, ppm Ha	Hb
VIa	OH	*a*	82		4.67	4.06
b	OH	97–98[b,c]	98		4.10[d]	4.10
c	OH	65–67[c,e]	85	C, H	5.02	4.02
VIIa	OTs	112.5–113.5[a]	86	C, H	4.72	4.40
b	OTs	119–120[b]	83	C, H	(4.16–4.38)[f]	
c	OTs	112–114[c]	88	C, H	5.06	4.43
VIIIa	I	*h*	55	C, H	4.83	3.60
c	I	126–128[e]	87	C, H	5.20	3.60

[a] Bp 157–158.5° (0.125 mm), lit.[8] 168–174° (0.4 mm). [b] O. Grummitt, A. A. Arters, and J. A. Stearns [*J. Am. Chem. Soc.*, **73**, 1856 (1951)] reported mp 98.5–99.5°. [c] Recrystallized from MeOH–H_2O. [d] The deshielding effect of *ortho*-substituted chlorine on benzylic protons has been noted previously: R. E. Counsell and R. E. Willette, *J. Pharm. Sci.*, **55**, 1012 (1966). [e] Recrystallized from Me_2CO–H_2O. [f] Bp 172–174° (0.7 mm). [g] Recrystallized from Me_2CO–cyclohexane. [h] Bp 164–166° (0.15 mm). [i] Multiplet.

crude product prior to distillation showed the ratio of VIIIa to IXa to be approximately 2:1.

1,1-Bis(*o*-chlorophenyl)-2-iodoethane (VIIIc).—A mixture of VIIc (1.6 g), KI (1.8 g), and MeCN (40 ml) was heated to reflux and sufficient H_2O was added to effect homogeneity. Gentle reflux was continued for 5 days, whereupon the solvent was removed by distillation *in vacuo*. The resulting solid was washed (H_2O) and recrystallized from Me_2CO–H_2O to afford pure VIIIc (1.2 g), mp 126–128° (see Table I).

1-(*o*-Chlorophenyl)-1-(*p*-chlorophenyl)-2-iodoethane-^{125}I.—A solution of VIIIa (0.20 g) and $Na^{125}I$ (2 mCi)[18] in Me_2CO (10 ml) was stirred at the reflux temperature for 12 hr. The Me_2CO was evaporated and the residue was dissolved in ether. The ether solution was washed (H_2O, two 20-ml portions) and dried (Na_2SO_4), and the solvent was removed *in vacuo*. The residue was dissolved in hexane and chromatographed on silica gel (20 g). The column was eluted with hexane–benzene (9:1) and the radioactive fractions were collected. Removal of the solvent afforded radioiodinated VIIIa (58.4 mg) as a colorless oil with a specific activity of 0.4 μCi/mg. Chemical and radiochemical purity was established by tlc using hexane as the eluent. Analysis under uv light revealed a single spot (R_f 0.62) coincident with the single radioactive area shown on a radiochromatogram scan.

1,1-Bis(*o*-chlorophenyl)-2-iodoethane-^{125}I.—A solution of VIIIc (0.1 g) and $Na^{125}I$ (1 mCi)[18] in Me_2CO (7 ml) was stirred and gently refluxed for 5 hr. The solution was allowed to cool and poured into H_2O (25 ml), and the resulting precipitate was collected by filtration. The product was washed well (H_2O) and dried to give 91 mg, specific activity 0.89 μCi/mg. Tlc as above gave a single spot (R_f 0.38) coincident with the single radioactive area shown on a radiochromatogram scan.

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(18) Obtained from New England Nuclear Corp., Boston, Mass. 02118.

Phosphorus–Nitrogen Compounds. IX.[1,2] Hydroxylamine Derivatives

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In the course of continuing study on oncolytic properties of compounds containing PNO and PNHCONO groups[2,3] it was thought that certain of these derivatives might lead to interesting CNS activities.

An examination of **3c–g** structures reveals the presence of both hypnotic–anticonvulsant pharmacophores and the weak central depressant, urethan. This suggests that the derivatives may be bioisosteric with, and possess mild depressant properties similar to, those of acyclic ureides. These compounds were consequently tested for reduction in locomotor activity and protective action against electroshock (Table I). The former screening included the phosphorous triamides (**4a**, **b**) and triethyl phosphinylidynetricarbamate (**3g**).

TABLE I

LOCOMOTOR ACTIVITY EFFECTS AND ANTICONVULSANT PROPERTIES

Compound	Dose, mg/kg	% decrease in motor activity[a] 30 min	60 min	Anti-electroshock,[b] % block
3e	400	83	31	...
	800	18	7	...
3d	800	55	48	...
3e	100	...	...	10[c]
	200	67	67	40[d]
3f	400	94	74	20[d]
	800	34	36	30[c]
3g	800	24	12	...
4a	200	40	44	...
	400	36	34	...
4b	200	50	46	...

[a] Expressed as the percentage decrease in activity from the controls. [b] All control mice convulsed, 2/10 deaths. [c] 0/10 deaths. [d] 1/10 deaths.

Estimations of toxicities[4] gave LD_{50} values of 550 (**3e**, **4b**), 800 (**4a**), and >1600 (**3c**, **d**, **f**) mg/kg. The anticipated greater toxicity of phosphorous over phosphoric triamides, and chlorinated carbamate over urethan derivatives, was realized.

The greatest motor activity reduction occurred with the most toxic derivatives (**4a**, **b**, **3e**) at about 25–50% LD_{50}. A comparison between equidoses of **3c**, **f**, and **g** indicates that two or three urethan moieties produce a greater reduction in activity than one such group. In addition, **3c** and **g** were the only derivatives showing appreciable induction latency. Preliminary screening using five animals showed anticonvulsant activity in all four phosphoric triamides containing urethan and methoxyurea moieties. The two most active, **3e** and

(1) This investigation was supported by Grant CA-08711 from the National Cancer Institute, U. S. Public Health Service.

(2) For the previous paper, see L. A. Cates and J. A. Nelson, *J. Pharm. Sci.*, in press.

(3) L. A. Cates, *J. Med. Chem.*, **10**, 924 (1967).

(4) C. S. Weil, *Biometrics*, **8**, 249 (1952).

f, gave mild, but definite, electroshock protection when further tested at two dose levels using ten mice.

The compounds shown in Schemes I–IV are new chemical entities with the exception of **3g**[2] and **2a**, the latter being synthesized by a different procedure.[5]

SCHEME I

$$(RO)_2P(O)H \xrightarrow[CX_4]{NH_2OR'} (RO)_2P(O)NHOR'$$

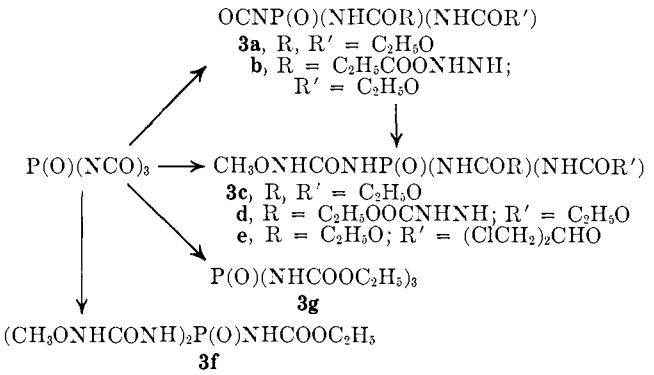
1a, R = C_6H_5; R′ = H
b, R = $(CH_3)_2CH$; R′ = H
c, R = C_6H_5; R′ = CH_3

SCHEME II

$$(C_6H_5)_2PCl \xrightarrow{NH_2OH} \xrightarrow{(O)} (C_6H_5)_2P(O)NHOH$$
2a

$$C_6H_5P(O)Cl_2 \xrightarrow{NH_2OCH_3} C_6H_5P(O)(NHOCH_3)_2$$
2b

SCHEME III



SCHEME IV

$$P(NCO)_3 \longrightarrow RCONHP(NHCOR')_2$$
4a, R, R′ = CH_3ONH
b, R = CH_3ONH;
R′ = C_2H_5O

The phosphorylation of N in lieu of O of hydroxylamine, as shown by Kreutzkamp and Schindler,[5] is in agreement with comparable hydroxamic acid formation.[6] Although alkyl[7] and aryl[8] isocyanates condense with hydroxylamine, several attempts at synthesis of phosphorylated hydroxurea derivatives by treating hydroxylamine with phosphinylidyne tris(isocyanate) and various other phosphoro(thio) isocyanates failed to yield stable products. The resulting materials were deliquescent, and underwent spontaneous and vigorous decomposition, but gave positive $FeCl_3$ tests. Only water-soluble **1b** of the three phosphorohydroxamic acids gave this test; **2a** also gave a negative $FeCl_3$ test.[5] Positive Tollens tests were shown with **4a**, **b**, and **3d**, the latter due to oxidation of the hydrazo link.

(5) N. Kreutzkamp and H. Schindler, *Arch. Pharm.*, **293**, 296 (1960).
(6) C. D. Hurd in "Organic Chemistry", H. Gilman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1938, p 630.
(7) Olin Mathieson Corp., British Patent 930,844 (1963).
(8) Allied Chemical Corp., French Patent 1,320,068 (1963); *Chem. Abstr.*, **59**, 9886*h* (1963).

Experimental Section

All compounds shown in Schemes I–IV were analyzed for C, H, and N[9] (Coleman C H and N analyzers). Melting points are uncorrected (Fisher-Johns apparatus). All starting materials, excepting hydroxylamine, and products were examined with a Beckman IR-8 and gave spectra in agreement with proposed structures. Locomotor activities were determined using an actophotometer (Metro Scientific) and electroshock was administered by a Grass S4 stimulator.

Synthesis. Hydroxy- and Methoxyphosphoramidates (1a–c).—Hydroxylamine[10] or methoxyamine[11] and a polyhalogen were treated with diphenyl phosphite (CCl_4, ether) or diisopropyl phosphite ($CBrCl_3$, ether) according to the method of Atherton and Todd.[12] Spin evaporation of the reaction mixtures yielded solid (**1a**) or oil (**1b**, **c**) residues. The products were crystallized from EtOH–H_2O (**1a**, $C_{12}H_{12}NO_4P$, mp 151–152°) and Et_2O–petroleum ether (bp 30–60°) (**1b**, $C_6H_{16}NO_4P$, mp 118–119°, and **1c**, $C_{13}H_{14}NO_4P$, mp 57–58°).

N-Hydroxydiphenylphosphinamide (2a).—Diphenylchlorophosphine (60 mmoles) added to hydroxylamine (145 mmoles, Et_2O) at 5° gave a precipitate which was filtered off, washed (H_2O), and crystallized from hot EtOH in an air stream; $C_{12}H_{12}NO_2P$, mp 123° dec (lit.[5] 131° dec).

N,N′-Dimethoxyphenylphosphonamide (2b).—Phenylphosphonic dichloride (85 mmoles), added to methoxyamine and Et_3N (180 mmoles, Et_2O), gave a precipitate which was separated by filtration. Spin evaporation of the filtrate gave an oil which was purified (Et_2O–petroleum ether) and crystallized from Et_2O; $C_8H_{13}N_2O_3P$, mp 70–72°.

Phosphinylidyne Isocyanates (3a, b) and Phosphoric triamides (3c, d).—EtOH (100 mmoles), added to phosphinylidyne trisisocyanate (50 mmoles, ether) with rapid stirring at 5–10°, gave a precipitate which was separated by filtration, washed with ether, and dried *in vacuo* to yield **3a**, $C_7H_{12}N_3O_6P$, mp 102° dec. Similarly, EtOH (50 mmoles) and the isocyanate (50 mmoles) reaction followed by ethyl carbazate (50 mmoles) addition, gave **3b**, $C_8H_{14}N_5O_7P$, mp 164° dec. Equimolar **3a** (CH_3CN) or **3b** (dioxane) treated as above with methoxyamine for several days gave **3c** ($C_8H_{17}N_4O_7P$, mp 140° dec) and **3d** ($C_9H_{19}N_6O_8P$, mp 153° dec).

Phosphoric Triamides (3e, f) and Phosphorous Triamides (4a, b).—Ethanol (ET) or 1,3-dichloro-2-propanol (DP) and/or methoxyamine (MA) and phosphinylidyne trisisocyanate (P^V) or phosphino trisisocyanate (P^{III}, freshly distilled from phosphorus cyanate[13] under N_2) were treated in a manner previously described. Equimolar ET–P^V–DP–MA, ET–P^V–MA (1:1:2), P^{III}–MA (1:3), and ET–P^{III}–MA (2:1:1) gave **3e** ($C_9H_{17}Cl_2N_4O_7P$, mp 103° dec), **3f** ($C_7H_{16}N_5O_7P$, mp 122° dec), **4a** ($C_6H_{15}N_6O_6P$, mp 115° dec), and **4b** ($C_8H_{17}N_4O_6P$, undistillable viscous mass), respectively.

Pharmacological Screening Methods.—Male Yale–Swiss mice (23–27 g) were used in the tests and compounds were administered intraperitoneally in 2% sodium carboxymethylcellulose.

Locomotor Activity Test.—Groups of five mice for each dose level were investigated using the method of Dews[14] as modified by Moffett, Seay, and Reid.[15]

Anticonvulsant Test.—Electroshock was administered to groups of ten mice/dose level *via* ear electrodes (60 ma, 0.3 sec) according to the procedure of Cashin and Jackson.[16]

Anticancer screening reports have been received only on **1a**, which gave T/C of 101, 95, and 100% at 50, 100, and 200 mg/kg, respectively (leukemia L1210), and 81% at 100 mg/kg (Walker carcinosarcoma 256, intramuscular).[17]

(9) Analytical results obtained for these elements were within ±0.4% of the theoretical values.
(10) C. D. Hurd, *Inorg. Syn.*, **1**, 87 (1939).
(11) T. C. Bissot, R. W. Parry, and D. H. Campbell, *J. Am. Chem. Soc.*, **79**, 796 (1957).
(12) F. R. Atherton and A. R. Todd, *J. Chem. Soc.*, 674 (1947).
(13) Termed phosphorus isocyanate by Alfa Inorganics, Inc.
(14) P. V. Dews, *Brit. J. Pharmacol.*, **8**, 46 (1953).
(15) R. B. Moffett, P. H. Seay, and W. B. Reid, *J. Med. Pharm. Chem.*, **2**, 179 (1960).
(16) C. H. Cashin and H. Jackson, *J. Pharm. Pharmacol.*, **14**, 44T (1962).
(17) Test results furnished by the Cancer Chemotherapy National Service Center, Bethesda, Md.