



			Yield,		Chemical shifts, ppm	
Compd	Х	Mp, °C	%	Analyses	Ha	\mathbf{H}_{D}
VIa	ОΠ	a	82		4.67	4.06
b	OH	$97 - 98^{b,c}$	98		4.10^{d}	4.10
(·	ОH	65-67 ^{e,f}	85	С, Н	5.02	4.02
VHa	OTs	$112.5 - 113.5^{g}$	86	С, Н	4.72	4.40
b	OT_8	$119 - 120^{e}$	83	С, Н	(4.16-	$(4.38)^{(-)}$
С	OTs	$112 - 114^{c}$	88	С, Н	5.06	4.43
VIIIa	Ι	h	55	С, Н	4.83	3.60
e	1	$126 - 128^{e}$	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-H₂O. ^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 Me₂CO-H₂O. ^d Bp 172-174° (0.7 mm). ^e Recrystallized from Me₂CO-cyclohexane. ^h Bp 164-166° (0.15 mm). ^e 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 (H₂O) and recrystallized from Me₂CO–H₂O to afford pure VIIIc (1.2 g), mp 126–128° (see Table I).

1-(o-Chlorophenyl)-1-(p-chlorophenyl)-2-iodoethane-¹²⁵I.— A solution of VIIIa (0.20 g) and Na¹²⁵I (2 mCi)¹⁸ in Me₂CO (10 ml) was stirred at the reflux temperature for 12 hr. The Me₂CO was evaporated and the residue was dissolved in ether. The ether solution was washed (H₂O, two 20-ml portions) and dried (Na₂SO₄), 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 radioidinated VIIIa (58.4 mg) as a colorless oil with a specific activity of 0.4 μ Ci/mg. Chemical and radio-chemical purity was established by the 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 Na¹²⁵I (1 mCi)¹⁸ in Me₂CO (7 mI) was stirred and gently refluxed for 5 hr. The solution was allowed to cool and poured into H₂O (25 mI), and the resulting precipitate was collected by filtration. The product was washed well (H₂O) and dried to give 91 mg, specific activity 0.89 μ Ci/mg. The as above gave a single spot (R_t 0.38) coincident with the single radioactive area shown on a radiochromatogram scan.

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(48) 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	
$\mathbf{L}\mathbf{c}$	COMOTOR ACTIVITY	Effects
AND	ANTICONVULSANT 1	ROPERTIES

	Dose, mg/kg	C_{6} decrease in motor activity"		Auti- electroshock, ^k	
Compound		30 min	60 min	% block	
30	406	83	-31		
	800	18	7		
3d	800	.).)	48		
Зе	100			1.05	
	200	67	67	-4() ^d	
Зf	-400	94	74	20^d	
	800	34	36	3 0°	
Bg	800	24	12		
4a	200	40	-1-1		
	400	36	34		
4b	200	50	4.6		

^{*a*} Expressed as the percentage decrease in activity from the controls. ^{*b*} All control mice convulsed, 2/10 deaths. ^{*a*} 0/10 deaths.

Estimations of toxicities⁴ 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 $25 \cdot 50\%$ LD₅₀. 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. Sol., 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 IV



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 alkyl⁷ and aryl⁸ isocyanates condense with hydroxylamine, several attempts at synthesis of phosphorylated hydroxurea derivatives by treating hydroxylamine with phosphinylidyne tris(isocyanate) and various other phosphoro(thio) isocvanates failed to yield stable products. The resulting materials were deliquescent, and underwent spontaneous and vigorous decomposition, but gave positive FeCl₃ tests. Only water-soluble 1b of the three phosphorohydroxamic acids gave this test; 2a also gave a negative FeCl₃ test.⁵ Positive Tollens tests were shown with 4a, b, and **3d**, the latter due to oxidation of the hydrazo link.

- (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, 9886h (1963).

Experimental Section

All compounds shown in Schemes I-IV were analyzed for C. H, and $N^{\hat{9}}$ (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). —Hydroxylamine¹⁰ or methoxyamine¹¹ and a polyhalogen were treated with diphenyl phosphite (CCl₄, ether) or disopropyl phosphite (CBrCl₂, 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-H₂O (1a, C₁₂H₁₂NO₄P, mp 151-152°) and Et₂Opetroleum ether (bp 30-60°) (1b, C₆H₁₆NO₄P, mp 118-119°, and 1c, C₁₃H₁₄NO₄P, mp 57-58°).

N-Hydroxydiphenylphosphinamide (2a).-Diphenylchlorophosphine (60 mmoles) added to hydroxylamine (145 mmoles, Et₂O) at 5° gave a precipitate which was filtered off, washed (H_2O) , and crystallized from hot EtOH in an air stream; $C_{12}H_{12}$ -NO₂P, 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 (Et₂O-petroleum ether) and crystallized from Et₂O; C_sH₁₃N₂O₃P, 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, C7H12N3O6P, mp 102° dec. Similarly, EtOH (50 mmoles) and the isocyanate (50 mmoles) reaction followed by ethyl carbazate (50 mmoles) addition, gave 3b, C₈H₁₄N₅O₇P, mp 164° dec. Equimolar 3a (CH_3CN) or **3b** (dioxane) treated as above with methoxyamine for several days gave 3c (C₈H₁₇N₄O₇P, mp 140° dec) and 3d (C₉H₁₉N₆O₈P, 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 (Pv) or phosphino trisisocyanate (P^{III}, freshly distilled from phosphorus cyanate¹³ under N_2) were treated in a manner previously de-scribed. Equimolar ET-P^v-DP-MA, ET-P^v-MA (1:1:2), School = Lagrandian LT = MA (2:1:1) gave 3e (C₉H₁₇Cl₂-N₄O₇P, mp 103° dec), 3f (C₇H₁₆N₆O₇P, mp 122° dec), 4a (C₆H₁₅-N₆O₆P, mp 115° dec), and 4b (C₈H₁₇N₄O₆P, 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 Dews¹⁴ 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 $\pm 0.4\%$ of the theoretical values.

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 - (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. Seav, 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.

⁽⁵⁾ N. Kreutzkamp and H. Schindler, Arch. Pharm., 293, 296 (1960).