pound 6. Crystallization from methanol yielded 3.10 g of **34** (94%) as a white solid: mp 38–39 °C; NMR (CCl_4) δ 1.27 (s, 24 H, CH_2), 2.23 (t, J = 6 Hz, 2 H, $CH_2C{=}O$), 2.57 (t, J = 6 Hz, 2 H, $PhCH_2$), 3.6 (s, 3 H, OCH_3), 7.15 (s, 5 H, aromatic); MS, m/z 332 (M^+, 18), 300 ($M^+ - CH_3OH$, 55), 91 [$M^+ - (CH_2)_{13}CO_2CH_3$, 100].

Methyl 15-(p-Iodophenyl)pentadecanoate (35). The ester **34** (664 mg, 2 mmol) and thallium(III) trifluoroacetate (1.62 g, 3 mmol) in 3 mL of trifluoroacetic acid were reacted and then treated with KI as described for compound **27**. The C_6H_6 fractions (20 mL) 5–7 were concentrated in vacuo to yield 816 mg (89%) of a solid. Crystallization from methanol yielded **35** as a pale yellow solid: mp 55–56 °C; NMR ($CDCl_3$) δ 1.27 (s, 24 H, CH_2), 2.23 (t, J = 6 Hz, 2 H, $CH_2C{=}O$), 2.57 (t, J = 6 Hz, 2 H, $PhCH_2$), 3.6 (s, 3 H, OCH_3), 7.27 (AA′BB′, J = 8 Hz, 4 H, aromatic); MS, m/z 458 (M^+, 3), 427 ($M^+ - CH_3O$, 2), 332 (M^+ + 1 –I, 70), 331 (M^+ – I, 35), 91 [M^+ – I, $CH(CH_2)_{12}CO_2CH_3$, 100].

14-(p-Iodophenyl)tetradecanoic Acid (36). The ethyl ester **33** (366 mg, 0.8 mmol) was dissolved in EtOH (10 mL) and treated with 1 N NaOH (2 mL) as described for compound **29**. Crystallization from MeOH yielded 310 mg of **36** (90%) as a white solid: mp 86–87 °C; analysis by TLC in two solvent systems indicated the presence of a single component: R_f (S-1) 0.50; R_f (S-2) 0.70; NMR ($CDCl_3$) δ 1.27 (s, 24 H, CH_2), 2.3 (t, J = 6 Hz, 2 H, $CH_2C{=}O$), 2.57 (t, J = 6 Hz, 2 H, $PhCH_2$), 7.27 (AA′BB′, J = 8 Hz, 4 H, aromatic); MS, m/z 430 (M^+, 5), 285 (M^+ – I, H_2O, 54) 217 [M^+ – I, $CH(CH_2)_2CO_2H$, 50], 91 [M^+ – I, $CH(CH_2)_{11}CO_2H$, 100].

15-(p-Iodophenyl)pentadecanoic Acid (37). The methyl ester **34** (458 mg, 1 mmol) was dissolved in EtOH (10 mL) and treated with 1 N NaOH (2 mL) as described for compound **29**. Crystallization from MeOH yielded 400 mg of **37** (90%) as a white solid: mp 92–93 °C (lit.[24] mp 94 °C); analysis by TLC in two solvent systems indicated the presence of a single component: R_f (S-1) 0.50; R_f (S-2) 0.70; NMR ($CDCl_3$) δ 1.27 (s, 26 H, CH_2), 2.3 (t, J = 6 Hz, 2 H, $CH_2C{=}O$), 2.57 (t, J = 6 Hz, 2 H, $PhCH_2$), 7.27 (AA′BB′, J = 8 Hz, 4 H, aromatic); MS, m/z 444 M^+, 5), 299 (M^+ – I, H_2O, 52), 217 [M^+ – I, $CH(CH_2)_2$ CO_2H, 43], 91 [M^+ – I, $CH(CH_2)_{12}CO_2H$, 100].

Radioiodinated Phenyl Fatty Acids. General Procedure. The ester (0.1 mmol) and thallium(III) trifluoroacetate (0.15 mmol) in 3 mL of trifluoroacetic acid were stirred under red lights for 5 days. Sodium [^{125}I]iodide (no carrier added) in 1 mL of H_2O was added, and the resulting mixture was stirred for 5 min. Potassium iodide (17 mg, 0.1 mmol) in 1 mL of H_2O was then added, the mixture was stirred for 5 min, followed by a second addition of potassium iodide (66 mg, 0.4 mmol) in 1 mL of H_2O, and the resultant mixture was stirred for 20 min. Sodium thiosulfate (1 g) was added, and the mixture was stirred for 5 min, poured into 50 mL of H_2O, and extracted several times with Et_2O. The Et_2O extracts were washed once with 50 mL of 10% sodium bisulfite and then thoroughly with H_2O and dried over anhydrous Na_2SO_4, and the solvent was removed via a stream of argon. The crude material was dissolved in 1 mL of C_6H_6 and applied to a silicic acid column (25 g, basic form) slurried in C_6H_6. Fractions 3–5 (20 mL in volume) were combined, and the solvent was removed by a stream of argon to afford the radioiodinated product. The radiochemical and chemical purity were confirmed by TLC (SiO_2-GF) in C_6H_6, R_f (0.50).

The radioiodinated ester was dissolved in EtOH (10 mL) and refluxed with 1 N NaOH (2 mL) for 90 min. The mixture was cooled, poured into H_2O, acidified to pH 2-3 with 1 N HCl, and extracted twice with Et_2O. Followed thorough washing with H_2O, the organic layer was dried over anhydrous Na_2SO_4 and the Et_2O evaporated by a stream of argon (See Table V). The free acids were analyzed in S-1 and S-2 solvent systems as described earlier.

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Phosphorus–Nitrogen Compounds. 24. Phosphoramide Mustard Carrier Derivatives[1,2]

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Diethylstilbestrol, psoralen, and propranolol were used as potential carrier molecules for selective concentrations of a nitrogen mustard moiety in breast, skin, and lung tissues, respectively. The propranolol derivative gave two racemic mixtures, which were tested to ascertain any differences in anticancer activity. The insertion of a P=O group between the carrier and oncolytic portions offsets the excess lipophilic contribution of the latter and possibly provides for latentiation of alkylating activity. Murine tumor testing of the phosphoramide mustard derivatives and two intermediates indicated that two compounds possessed marginal activity against mammary carcinoma and lymphocytic leukemia.

The concept of carrier molecules has been employed in the design of some of the earliest nitrogen mustard derivatives used in cancer chemotherapy. L-Phenylalanine mustard (melphalan), for example, was synthesized in an attempt to localize an oncolytic moiety in melanomas.[3] It was hoped that phenylalanine, being a precursor of melanin, would serve as a carrier molecule by selectively transporting and concentrating N,N-bis(2-chloroethyl)amine (nornitrogen mustard, nor-NH_2) in these tumors.

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Such selectivity was not realized in this and similar drugs; however, several aromatic derivatives became useful as chemotherapeutic agents because of latentiation of alkylating ability resulting from the electron-withdrawing effect of their ring moieties.

In 1976 other carriers for the nitrogen mustard group were proposed by Sieber and Adamson.[4] These included the melanizing drugs trioxsalen and methoxsalen, which localize in melanocytes of the skin, α-tocopherol for concentration in lymph channels, and (±)-propranolol, which accumulates in lung tissues. Thus, these agents were intended to provide greater specificity in the treatment of melanomas, lymphomas, and pulmonary carcinomas, respectively. The authors also indicated some possible nor-NH_2 analogues of these carrier molecules. These suggestions stimulated the synthesis and testing of the herein reported psoralen and propranolol derivatives to which was added the diethylstilbestrol (DES) analogue as a potential mammary or prostatic cancer therapeutic agent.

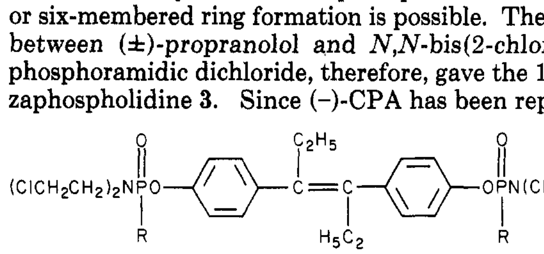
Two major problems were identified as being associated with the derivatives proposed by Sieber and Adamson. As with any type of carrier molecule, selectivity of bioactivity is related to its absorption and distribution, which, in turn, are governed by the partitioning properties of the entire molecule. This latter parameter is quantitated as a π (for a fragment of a molecule) or a log P (for the entire molecule) value, most frequently, as is the case in this report, with reference to the octanol/water system. As was demonstrated in a study involving diphenylhydantoin (DPH) as a carrier in the treatment of CNS tumors,[5] the attachment of a nor-NH_2 group adds a π value of 1.39 to a molecule. This increased lipophilicity necessitated the reduction of carbon content at the 5-position of DPH to achieve a log P value of ~2.0, which has been shown to approximate the optimum for organic drugs to penetrate the blood–brain barrier. A second possible difficulty with the proposed analogues was the absence of a mechanism to slow their rate of cyclization to reactive immonium ion forms and, thus, permit time for drug absorption and distribution before alkylation occurs at the target site.

After the beginning of this project, the suggestions of Sieber and Adamson were evaluated by Niculescu-Duvāz and Baracu,[6] who also indicated the desirability of having a poorly reactive alkylating moiety with a π value close to zero. In this report these investigators made reference to previous studies whereby a carbonyl group was inserted between nor-NH_2 and phenolic oxygen atoms in DES and estradiol and its 17-phosphate ester to yield derivatives with activity in prostatic carcinoma.[7,8] These carbamates apparently are catabolized to carbamic acids, which then decompose to liberate nor-NH_2. Feyns and co-workers, pursuing the suggestions of Sieber and Adamson, prepared and tested a propranolol derivative with a side-chain nor-NH_2 moiety.[9] This agent and a chloro analogue were screened against Lewis lung carcinoma, B16 melanoma, and P388 lymphocytic leukemia, with activity being found only against the latter system. These investigators also acknowledged the probably adverse effect as concerns log P resulting from the introduction of a nor-NH_2 group into the molecules.

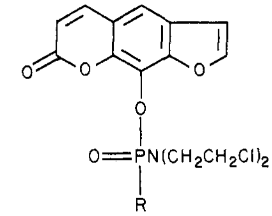
Results and Discussion

It was postulated that both difficulties ascribed to the originally proposed carrier molecules could be overcome to a degree by the insertion of a P=O group between the nor-NH_2 moiety and the carrier molecule portion. Such a system for latentiation of alkylating effect has been previously employed in a number of useful anticancer drugs, such as triethylenephosphoramide (TEPA) and cyclophosphamide (CPA), whereby the P=O moiety serves as the electron-withdrawing group in slowing chemical reactivity. The design of the new derivatives involves the attachment of the P=O group to the carrier portion through an oxygen atom, with the third substituent consisting of an amido moiety. Thus, the potential oncolytic portion is *N*,*N*-bis(2-chloroethyl)phosphorodiamidic acid (phosphoramide mustard), a potent cytotoxic metabolite of CPA. The hydrophilicity conferred by the P=O group as a means to offset the increased lipophilicity produced by the nitrogen mustard portion is more difficult to assess, since insufficient partitioning studies have been conducted using phosphorus compounds. It is, however, reasonable to expect that the P=O group has a value in the order of −1 to −2, which can be estimated for carbonyl and sulfoxide moieties, and that its insertion should negate the increase in lipophilicity conferred by the nor-NH_2 group.

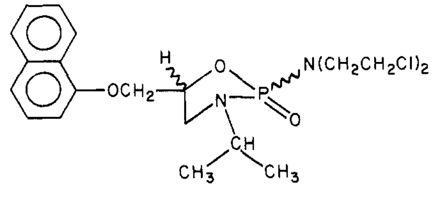
The synthesis of the phosphoramide mustard carrier molecules proceeded, as expected, with the greatest difficulties, as is the case with many organophosphorus compounds, involving isolation and purification. When amino alcohols are reacted with phosphorus dichlorides, cyclization invariably occurs as the principal reaction when five- or six-membered ring formation is possible. The reaction between (±)-propranolol and *N*,*N*-bis(2-chloroethyl)phosphoramidic dichloride, therefore, gave the 1,3,2-oxazaphospholidine **3**. Since (−)-CPA has been reported as



1a, R = Cl
b, R = NH_2



2a, R = Cl
b, R = NH_2



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possessing twice the oncolytic activity of the (+) isomer, at least against the PC6 murine system, it was deemed advisable to separate this related heterocycle into two

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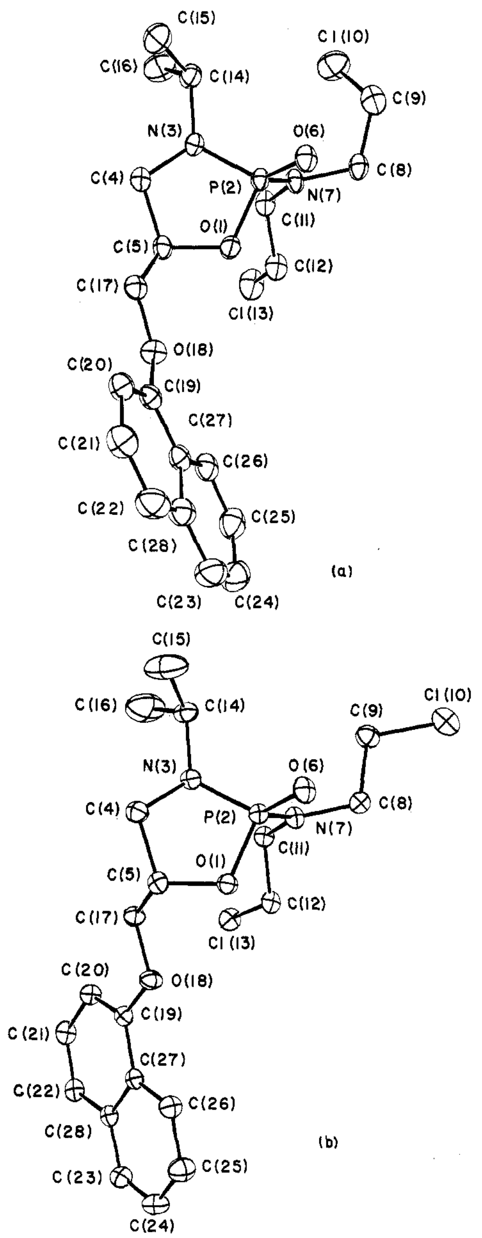

Figure 1. A perspective view of (a) **3a** and (b) **3b**.[24] The views shown have the configurations 2*R*,5*R* and 2*R*,5*S*, respectively.

racemic mixtures, **3a** (rac-2*R*,5*R*) and **3b** (rac-2*R*,5*S*) (Figure 1), for antitumor testing of each. In addition, (+)-propranolol is inactive as an α-adrenergic blocker, and its derivatives have been suggested as ones causing fewer untoward reactions.[4] (+)-Propranolol[11] was therefore employed as the amino alcohol in subsequent reactions. While chromatographic separation of products from these reactions was successful, only semisolid products, not suitable for X-ray diffraction study, were obtained.

A comparison of the conformational angles in **3a,b** (Table I) indicates two major differences between these compounds. Configurational differences cause the five-membered ring in **3a** to assume a nearly ideal half-twist conformation ($\Delta C_2^{O(1)} = 0.38°$), while the ring in **3b** has an envelope conformation ($\Delta C_s^{C(4)} = 1.86°$).[12] The chloroethyl group that includes Cl(10) in **3a** has an N(7)–C(8)–C(9)–Cl(10) angle of −57.92 (19)°. All other N–C–C–Cl angles are within ±10° of ±180°. Such conformational differences in exocyclic mustard groups have been seen in comparisons of CPA and its congeners.[13] Bond lengths and angles are in good agreement with the corresponding values in cyclophosphamide,[14,15] trofosfamide,[13] and (2*S*,4*S*,5*R*)- and (2*R*,4*S*,5*R*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine 2-sulfide.[16,17]

Table I. Selected Conformational Angles[a]

	3a	3b
O(1)-P(2)-N(3)-C(4)	16.27 (12)	23.87 (16)
P(2)-N(3)-C(4)-C(5)	−25.50 (15)	−30.40 (21)
N(3)-C(4)-C(5)-O(1)	23.79 (16)	23.43 (23)
C(4)-C(5)-O(1)-P(2)	−14.35 (15)	−8.50 (21)
C(5)-O(1)-P(2)-N(3)	−0.30 (13)	−8.27 (15)
C(5)-O(1)-P(2)-O(6)	126.74 (10)	119.79 (14)
C(5)-O(1)-P(2)-N(7)	−112.08 (10)	−118.21 (14)
C(4)-N(3)-P(2)-O(6)	−105.91 (12)	−98.08 (17)
C(4)-N(3)-P(2)-N(7)	128.02 (11)	135.40 (16)
O(1)-P(2)-N(7)-C(8)	−121.77 (12)	−121.67 (17)
O(1)-P(2)-N(7)-C(11)	49.77 (14)	56.10 (19)
N(3)-P(2)-N(7)-C(8)	135.54 (13)	136.72 (17)
N(3)-P(2)-N(7)-C(11)	−52.92 (14)	−45.51 (20)
P(2)-N(7)-C(8)-C(9)	−80.83 (17)	−93.29 (22)
P(2)-N(7)-C(11)-C(12)	−91.65 (15)	−93.08 (21)
N(7)-C(8)-C(9)-Cl(10)	−57.92 (19)	−173.66 (16)
N(7)-C(11)-C(12)-Cl(13)	−170.32 (11)	174.19 (15)
C(9)-C(8)-N(7)-C(11)	107.27 (17)	88.82 (24)
C(8)-N(7)-C(11)-C(12)	80.28 (18)	84.78 (24)
O(6)-P(2)-N(7)-C(8)	2.76 (14)	3.03 (20)
O(6)-P(2)-N(7)-C(11)	174.30 (12)	−179.20 (17)
O(1)-P(2)-N(3)-C(14)	176.00 (12)	178.99 (17)
C(5)-C(4)-N(3)-C(14)	174.41 (13)	173.55 (19)
P(2)-N(3)-C(14)-C(15)	−111.43 (16)	−98.56 (27)
P(2)-N(3)-C(14)-C(16)	122.93 (16)	134.33 (25)
C(4)-N(3)-C(14)-C(15)	46.71 (21)	54.61 (32)
C(4)-N(3)-C(14)-C(16)	−78.94 (20)	−72.50 (31)
O(6)-P(2)-N(3)-C(14)	53.82 (15)	57.04 (21)
N(7)-P(2)-N(3)-C(14)	−72.25 (14)	−69.48 (19)
P(2)-O(1)-C(5)-C(17)	−134.49 (11)	112.31 (17)
N(3)-C(4)-C(5)-C(17)	141.95 (13)	−96.83 (21)
O(1)-C(5)-C(17)-O(18)	−68.04 (15)	64.76 (23)
C(4)-C(5)-C(17)-O(18)	174.61 (13)	−176.43 (18)
C(5)-C(17)-O(18)-C(19)	160.65 (13)	168.47 (18)

[a] In degrees.

The phosphoramide mustard derivatives and two intermediates were screened for oncolytic activity in tests involving four different murine antitumor systems (Table II). Only **2a** and **1b** displayed marginal degrees of effect against P388 lymphocytic leukemia and CD8F$_1$ mammary tumor, respectively. The confirmed activity of the chloride intermediate **2a** led to the resynthesis of **1a**, the corresponding precursor to the phosphoramide mustard derivative **1b**; however, greater effect was not noted in this case. The external testing organization elected to screen **2a,b** against P388 lymphocytic leukemia rather than B16 melanoma; therefore, any degree of selectivity toward the latter tumor system has yet to be ascertained. During a subsequent study of propranolol derivatives possessing aromatic phosphoramide mustard substituents, new dihydroxynaphthalene esters (**4a,b**) were synthesized and incidentally screened for activity against L1210 lymphoid leukemia (Table II). The anticipated higher selectivity of anticancer activity in the phosphoramide mustard carrier

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Table II. Antitumor Activity[a]

compd	tumor system	dose,[f] mg/kg	T/C[g]
1a	LE[b]	500	100
1b	CD[c]	300	39
	LE	300	113
	PS[d]	200	100
	PS	200	104
2a	PS	100	128
	PS	200	123
2b	PS	200	114
3a	LL[e]	400	90
	LL	50	95
3b	LE	500	130
	LE	500	110
	LE	500	90
4b	LE	500	95

[a] Performed by contractors of the National Cancer Institute using protocols described in ref 23. [b] L1210 lymphoid leukemia. [c] CD8F$_1$ mammary tumor. [d] P388 lymphocytic leukemia. [e] Lewis lung carcinoma. [f] Highest dose permitting all mice to survive using treatment schedules of one (LE and CD), nine consecutive (LL), and five consecutive (PS) injections, beginning 1 day (20 days for CD) after injection of tumor cells. [g] T/C = (treated animals/control animals) × 100%.

compounds was not, to date, realized. The potential for antitumor activity in these agents apparently resides in their ability to undergo enzymatic and/or other in vivo chemical transformations. The slight oncolytic effects displayed by the two derivatives might be explained on the basis of limited liberation of alkylating phosphoramide mustard or nornitrogen mustard or by a role in phosphoryl-group transfer via a metaphosphorodiimide intermediate.[18]

Experimental Section

Melting points were determined by the capillary method (oil bath) and are corrected to reference standards. All compounds had IR and NMR spectra consistent with their assigned structures. IR spectra were obtained on a Perkin-Elmer 282 spectrophotometer using KBr pellets. ^{1}H NMR were recorded on a Varian T-60 or FT-80A spectrometer using Me_4Si as the internal standard. Mass spectra were recorded on a Hewlett-Packard 58930 GC/MS with a 5933A data system, and molecular ion mass and relative intensities (RI) are given. Elemental analyses were performed on all new products by Atlantic Microlab, Atlanta, GA, and the results are within ±0.2% of theoretical values. Silica gel 60 (70–230 mesh) was used for column chromatography, and silica gel GHLF (Analtech) was used for TLC. *N,N*-Bis(2-chloroethyl)phosphoramidic dichloride was synthesized according to the method of Cates and Li.[1]

4,4′-Bis[*N,N*-bis(2-chloroethyl)phosphoramidochloridic acid ester] of α,α′-Diethyl-4,4′-stilbenediol (1a). To a solution of diethylstilbestrol (5.36 g, 20 mmol) and *N,N*-bis(2-chloroethyl)phosphoramidic dichloride (10.35 g, 40 mmol) in dry Et_2O (250 mL) was added triethylamine (4.5 g, 44 mmol), the mixture was refluxed for 16 h and filtered, and the filtrate was evaporated in vacuo. The residue was placed on a chromatographic column and eluted with 5% MeOH in $CHCl_3$ to give 8.7 g (61%). The purified material was recrystallized from Et_2O to yield the white product: mp 125–127 °C; IR 1610 (C=C), 1200 (P=O) cm^{-1}; NMR ($CDCl_3$) δ 0.75 (t, 6 H, 2 CH_3), 2.06 (q, 4 H, 2 CH_2), 3.74 (m, 16 H, 4 CH_2CH_2Cl), 7.25 (s, 8 H, arom). Anal. ($C_{26}H_{34}Cl_6N_2O_4P_2$) C, H, N.

4,4′-Bis[*N,N*-bis(2-chloroethyl)phosphorodiamidic acid ester] of α,α′-Diethyl-4,4′-stilbenediol (1b). Compound **1a** was prepared in situ by conditions identical with those described in the preceding section. Ammonia was bubbled into the Et_2O solution for 30 min. The suspension was filtered, and the filtrate was evaporated in vacuo. The crude material was subjected to column chromatography with 5% MeOH in $CHCl_3$ as the eluent to yield 6.2 g (46%) and the purified material was recrystallized from benzene and then from CH_2Cl_2 to yield the wite product: mp 135–138 °C; IR 3120, 3220, and 3310 [P(O)NH_2], 1600 (C=C), 1200 (P=O), 970 (P=N) cm^{-1}; NMR (Me_2SO-d_6) δ 0.73 (t, 6 H, 2 CH_3), 2.08 (q, 4 H, 2 CH_2), 3.10–3.75 (m, 16 H, 8 CH_2), 4.83 (d, 4 H, 2 NH_2), 7.20 (s, 8 H, arom). Anal. ($C_{26}H_{38}Cl_4N_4O_4P_2$) C, H, N.

***N,N*-Bis(2-chloroethyl)phosphoramidochloridic Acid Ester of 9-Hydroxypsoralen (2a).** Xanthotoxin was demethylated to yield 9-hydroxypsoralen.[19,20] 9-Hydroxypsoralen (2.0 g, 9.8 mmol) was suspended in CH_2Cl_2 (250 mL). *N,N*-Bis(2-chloroethyl)phosphoramidic dichloride (2.56 g, 9.8 mmol) and then triethylamine (1.1 g, 10.8 mmol) were added to yield a clear solution, which was heated to 50 °C while stirring under N_1 for 18 h. The reaction mixture was evaporated in vacuo, and the residue was subjected to column chromatography with 10% EtOAc in $CHCl_3$ as the eluent to yield 2.1 g (50%) of the product: mp 149–150 °C; IR 1710 (C=O), 1580 (C=C), 1280 (P=O) cm^{-1}; NMR ($CDCl_3$) δ 3.65–4.05 (m, 8 H, 2 CH_2CH_2), 6.35 (d, 1 H, H_6), 6.85 (d, 1 H, H_3), 7.55 (s, 1 H, H_4), 7.70 (d, 1 H, H_2), 7.78 (d, 1 H, H_5). The NMR assignments and psoralen numbering system is taken from Ivie:[19] MS, *m/z* (relative intensity) 423 (M^+, 0.6), 425 (M^{2+}, 0.4). Anal. ($C_{15}H_{13}Cl_3NO_5P$) C, H, N.

***N,N*-Bis(2-chloroethyl)phosphorodiamidic Acid Ester of 9-Hydroxypsoralen (2b).** Ammonia was bubbled through a solution of **2a** (1.6 g, 3.8 mmol) in dry benzene (250 mL) for 0.5 h. The precipitate was washed with acetone, and the washings were evaporated in vacuo to yield 1.38 g (90%) of the product: mp 175–176 °C; IR 3330 and 3240 (NH_2), 1710 (C=O), 1590 (C=C), 1230 (P=O) cm^{-1}; NMR (Me_2SO-d_6) δ 3.15–3.85 (m, 8 H, 4 CH_2), 4.95 (d, 2 H, NH_2), 6.40 (d, 1 H, H_6), 7.02 (d, 1 H, H_3), 7.75 (s, 1 H, H_4), 8.05 (d, 1 H, H_2), 8.10 (d, 1 H,H_5). Anal. ($C_{15}H_{15}Cl_2N_2O_5P$) C, H, N.

2-[Bis(2-chloroethyl)amino]-3-isopropyl-5-(1-naphthoxymethyl)-1,3,2-oxazaphospholidine 2-Oxide (3a,b). Propranolol was prepared from its HCl salt by treating the latter with NaOH solution, collecting the resultant precipitate on a filter, and repeatedly washing it with water. The residue was dried in a vacuum oven and recrystallized from acetone to yield the free base: mp 92–93 °C. To a solution of propranolol (10.0 g, 3.9 mmol) in dry benzene (400 mL) was added triethylamine (8.0 g, 7.9 mmol) and then *N,N*-bis(2-chloroethyl)phosphoramidic dichloride (10.0 g, 3.9 mmol). The mixture was heated at 80 °C for 18 h, cooled, and filtered. The filtrate was evaporated under reduced pressure, and the residue was subjected to column chromatographic separation to isolate the products corresponding to spots with R_f values of 0.4 and 0.5, which were obtained by TLC (5% MeOH in $CHCl_3$). The elution was accomplished with the following series of consecutive eluents: $CHCl_3$ (100 mL), 1% MeOH in $CHCl_3$ (200 mL), 2% MeOH in $CHCl_3$ (200 mL), 3% MeOH in $CHCl_3$ (200 mL), and 4% MeOH in $CHCl_3$ (400 mL). Fractions containing only **3a** were combined and evaporated to dryness in vacuo, and the residue (7.4 g, 43%) was recrystallized from Et_2O to yield the white product: mp 91–93 °C. Fractions containing 8.5 g (49%) of **3b** only were treated the same to give the white product, mp 102–103 °C. IR, NMR, and MS of **3a,b** are all identical: IR 1580, 1595 (C=C), 1240, 1270 (P=O) cm^{-1}; NMR ($CDCl_3$) δ 1.2 (d, 6 H, 2 CH_3), 3.1–3.8 (m, 11 H, 2 CH_2CH_2Cl and CH_2NCH), 4.3 (m, 2 H, OCH_2), 4.8 (m, 1 H, OCH), 6.7–8.3 (m, 7 H, aromatic); MS, *m/z* (relative intensity) 444 (M^+, 10). Anal. ($C_{20}H_{27}Cl_2N_2O_3P$) C, H, N.

1,5-Bis[*N,N*-bis(2-chloroethyl)phosphoramidochloridic acid ester] of 1,5-Dihydroxynaphthalene (4a). To 1,5-dihydroxynaphthalene (4.0 g, 25 mmol) in dry Et_2O (300 mL) was added *N,N*-bis(2-chloroethyl)phosphoramidic dichloride (6.5 g, 25 mmol), followed by triethylamine (2.78 g, 27.5 mmol), and the mixture was refluxed for 16 h. The suspension was filtered, the filtrate was evaporated in vacuo, and the residue was subjected to column chromatography using 5% MeOH in $CHCl_3$ as the eluent. Fractions containing the desired product were combined and evaporated in vacuo, and the residue was recrystallized from benzene to yield 2.4 g (32%) of the product: mp 147–148 °C; IR

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1600 (C=C), 1220 (P=O) cm^{-1}; NMR ($CDCl_3/Me_2SO$-d_6) δ 3.35–3.90 (m, 16 H, 8 CH_2), 7.42–8.10 (m, 6 H, arom); MS, *m/z* (relative intensity) 602 (M^+, 49). Anal. ($C_{18}H_{22}Cl_6N_2O_4P_2$) C, H, N.

1,5-Bis[*N*,*N*-bis(2-chloroethyl)phosphorodiamidic acid ester] of 1,5-Dihydroxynaphthalene (4b). Ammonia was bubbled into a benzene solution (100 mL) of **4a** (1.8 g, 3 mmol) for 30 min, the suspension was stirred for 30 min and filtered, and the filtrate was evaporated in vacuo. The residue was extracted with hot acetone and filtered. Upon cooling, the filtrate formed the product (0.5 g, 34%) as a white, crystalline material: mp 174–175 °C; IR 3120, 3220 and 3310 [$P(O)NH_2$], 1600 (C=C), 1200 (P=O), 970 (P=N); NMR (Me_2SO-d_6) δ 3.10–3.82 (m, 16 H, 8 CH_2), 4.90 (d, 4 H, 2 NH_2), 7.31–8.01 (m, 6 H, arom). Anal. ($C_{18}H_{26}Cl_4N_4O_4P_2$) C, H, N.

X-ray Diffraction. Crystals of (±)-**3a** formed as colorless blocks from ether. The cell constants [a = 26.366 (13), b = 8.826 (7), c = 19.224 (10) Å; β = 96.67 (8)°; vol = 4443.3 Å^3] were determined at 138 (2) K. The space group was found to be $C_{2/c}$ with Z = 8. From the 4556 unique data, 3969 were judged observed [$F > 4\sigma(F)$]. The structure was solved by MULTAN[21] and refined by SHELX.[22] The final conventional R and weighted R were 0.035 and 0.047 for the observed data. A final difference electron density map showed no peaks greater than 0.31 e$^-$/Å^3.

Crystals of (±)-**3b** grew as colorless rods from ether with $P2_{1/a}$ (Z = 4) symmetry. The cell constants [a = 6.939 (3), b = 26.747 (13), c = 11.828 (6) Å; β = 102.91 (4)°; vol = 2139.8 Å^3] were determined at 138 (2) K. A total of 3514 data were judged observed [$F > 4\sigma(F)$] from the 4392 unique data. The structure was solved by the SHELX direct methods package and refined using SHELX.[22] The final conventional R and weighted R were 0.040 and 0.047 for the observed data. A final difference electron density map had no peaks larger than 0.39 e$^-$/Å^3.

Data for both compounds were collected at 138 (2) K on an Enraf-Nonius CAD-4 diffractometer using Mo $K\alpha$ radiation (λ = 0.71069Å). For both compounds, intensity data were collected using the θ-2θ scan method with $2\theta \leq 53°$. Lattice constants were determined from a least-squares fit of the $\pm 2\theta$ values of 48 intensity maxima taken from all regions of reciprocal space. The function minimized in the structure refinements was $\sum \omega (|F_o|-|F_c|)^2$ with $\omega = 1/\sigma^2(F)$. Tables of fractional coordinates, thermal parameters, bond distances and bond angles for **3a** and **3b** are given in the supplementary material.

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Registry No. **1a**, 88181-16-2; **1b**, 88181-17-3; **2a**, 88181-18-4; **2b**, 88181-19-5; (±)-**3a**, 88181-20-8; (±)-**3b**, 88181-21-9; **4a**, 88181-22-0; **4b**, 88181-23-1; DES, 56-53-1; 9-hydroxypsoralen, 2009-24-7; propanolol, 525-66-6; (±)-propanolol hydrochloride, 3506-09-0; 1,5-dihydroxynaphthalene, 83-56-7; phosphoramide mustard, 10159-53-2.

Supplementary Material Available: Tables of fractional coordinates, thermal parameters, bond distances and bond angles for **3a** and **3b** (8 pages). Ordering information is given on any current masthead page.

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Notes

(±)-4-Aryl-4,5-dihydro-3*H*-1,3-benzodiazepines. 3. 2-Phenyl and 2-Amino Analogues as Potential Antihypertensive Agents[1]

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A series of 2-phenyl- and 2-amino-4-aryl-4,5-dihydro-3*H*-1,3-benzodiazepines was prepared and submitted for broad biological screening, including evaluation for potential antihypertensive activity. Compound **4a** [(±)-4,5-dihydro-2,4-diphenyl-3-methyl-3*H*-1,3-benzodiazepine hydrochloride] was the most active member of the series in the spontaneously hypertensive rat (SHR) model, producing a 56 mmHg decrease in systolic blood pressure at an oral screening dose of 50 mg/kg. The synthesis of **4a** analogues containing nuclear substituents in the 4-phenyl moiety resulted in a marked decrease of antihypertensive activity. It was not possible to improve on the antihypertensive properties of **4a** through further synthetic modifications.

We previously reported the synthesis and biological evaluation of many 2-alkyl and several 2-aryl analogues of 4-aryl-4,5-dihydro-3*H*-1,3-benzodiazepines as potential psychotropic agents.[2,3] While optimum antidepressant-like properties were associated with a small 2-alkyl substituent, the 2-aryl series was virtually inactive in assays reflecting antidepressant-like activity. However, in broad

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