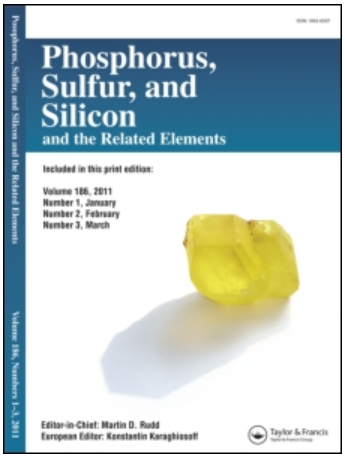

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Synthesis and Spectral Studies of 2,10-Dichloro-6-Bis(2-Chloroethyl)Amino-4,8-Dinitrodibenzo[d , g][1,3,6,2]-Dioxathiaphosphocin, 2,10-Dichloro-6-Bis(2-Chloroethyl)Amino-4,8-Dinitrodibenzo[d , g][1,3,6,2]Dioxathiaphosphocin 6-Oxide, 2-Bis(2-Chloroethyl)Amino-2,3-Dihydro-5-Thiophenoxy-1 H -1,3,2-Benzodiazaphosphole 2-Oxide, 2-Bis(2-Chloroethyl)Amino-1,2,3,4-Tetrahydro-1,3,2-Benzodiazaphosphorinane 2-Oxide, 5-Bromo-5-Nitro-2-Bis(2-Chloroethyl)Amino-1,3,2-Dioxaphosphorinane 2-Oxide, and 8-Bis(2-Chloroethyl)Amino-16 H -Dinaphtho[2,1- d :1',2'- g]1,3,2-Dioxaphosphocin 8-Oxide--Potential Anticancer Agents

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SYNTHESIS AND SPECTRAL STUDIES OF 2,10-DICHLORO-6-BIS(2-CHLOROETHYL)AMINO-4,8-DINITRODIBENZO[*d*,*g*][1,3,6,2]-DIOXATHIAPHOSPHOCIN, 2,10-DICHLORO-6-BIS(2-CHLOROETHYL)AMINO-4,8-DINITRODIBENZO[*d*,*g*][1,3,6,2]-DIOXATHIAPHOSPHOCIN 6-OXIDE, 2-BIS(2-CHLOROETHYL)AMINO-2,3-DIHYDRO-5-THIOPHENOXY-1*H*-1,3,2-BENZODIAZAPHOSPHOLE 2-OXIDE, 2-BIS(2-CHLOROETHYL)AMINO-1,2,3,4-TETRAHYDRO-1,3,2-BENZODIAZAPHOSPHORINANE 2-OXIDE, 5-BROMO-5-NITRO-2-BIS(2-CHLOROETHYL)AMINO-1,3,2-DIOXAPHOSPHORINANE 2-OXIDE, AND 8-BIS(2-CHLOROETHYL)AMINO-16*H*-DINAPHTHO-[2,1-*d*:1′,2′-*g*]1,3,2-DIOXAPHOSPHOCIN 8-OXIDE—POTENTIAL ANTICANCER AGENTS

L. Nagaprasada Rao,[a] *C. Devendranath Reddy,*[a] *V. Krishna Reddy,*[a] *Jacob D. Hagar,*[b] *Kevin Tran,*[b] *and K. Darrell Berlin*[b]
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*Several novel bis(2-chloroethyl)aminophosphoryl-containing compounds have been prepared as potential anticancer agents. 2,10-Dichloro-6-[bis(2-chloroethyl)]amino-4,8-dinitrodibenzo[d,g][1,3,6,2]-dioxathiaphosphocin 6-oxide (**5**), 2-bis(2-chloroethyl)amino-1,3,2-dioxaphosphorinane 2-oxide (**13**), and 8-bis(2-chloroethyl)amino-6*H*-dinaphtho[2,1-d:1′,2′]1,3,2-dioxaphosphocin 8-oxide (**15**) were synthesized from a reaction of equimolar quantities of the corresponding precursor diols **3**, **12**, and **14** with coreagent N,N-bis(2-chloroethyl)-phosphoramidic dichloride (**1**) at various temperatures in dry toluene/ether in the presence of triethylamine. In addition, 2-bis(2-chloroethyl)-amino-2,3-dihydro-5-thiophenoxy-1*H*-1,3,2-benzodiazaphosphole*

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*2-oxide (**9**) and 2-bis(2-chloroethyl)amino-1,2,3,4-tetrahydro-1,3,2-benzodiazaphosphorinane 2-oxide (**11**) were derived from 4-thiophenoxy-1,2-diphenyldiamine (**8**) and 2-aminobenzylamine (**10**) respectively, under similar conditions. Interestingly, attempted oxidation of **5** to the corresponding sulfone **7** by H_2O_2 (30%) in acetic acid yielded only sulfoxide **6** {2,10-dichloro-6-bis(2-chloroethyl)amino-4,8-dinitrodibenzo[d,g][1,3,6,2]dioxathiaphosphocin 6-oxide}. In an alternative approach, oxidation of 5,5′-dichloro-3,3′-dinitro-2,2′-dihydroxydiphenyl sulfide (**3**) with H_2O_2 (30%) in acetic acid formed the corresponding sulfone **4**. However, attempted cyclization of **4** with **1**, in the presence of triethylamine, to give the sulfone expected from **5** was unsuccessful. NMR analysis of **6** suggests the presence of two conformers in solution.*

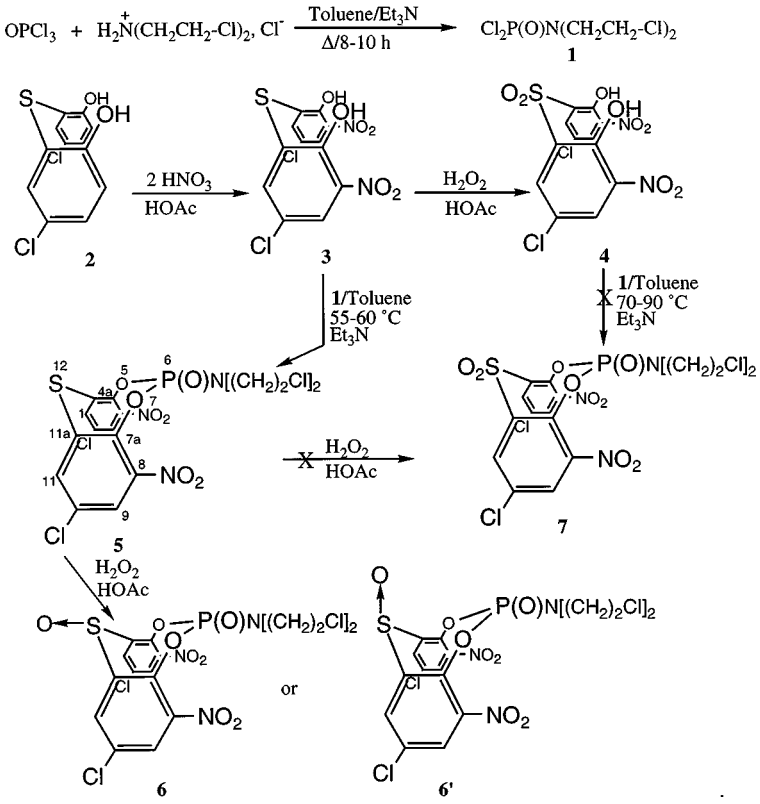
Keywords: Bis-(2-chloroethyl)aminodioxathiaphosphocins/dioxaphosphocin/benzodiazaphosphole/dioxaphosphorinane 1/5/6/8-oxides; Mass Spectral Data; NMR

INTRODUCTION

N-Phosphorylated nitrogen mustard compounds are proven agents in chemotherapy.[1] Cyclophosphamide is a well known antineoplastic drug having therapeutic activity against a relatively broad spectrum of human and animal tumors.[2] Ludeman and Zon[3] reported the synthesis of benzoannulated cyclophosphamide derivatives and evaluated the antitumor activity in mice against L_{1210} lymphoid leukemia. A nitrogen mustard derivative of a benzodiazaphosphole-containing system was prepared by Friedman and co-workers[4] and found to possess antitumor activity.[5] In view of the biological importance of such mustards, several novel five-, six-, and eight-membered *N*-phosphorylated nitrogen, mustard-containing heterocycles were prepared and characterized.

RESULTS AND DISCUSSION

The important intermediate *N*,*N*′-bis(2-chloroethyl)phosphoramidic chloride (**1**) was prepared in standard fashion Reaction of 4-chlorophenol with sulfur dichloride afforded a key starting material, namely 5,5′-dichloro-2,2′-dihydroxydiphenyl sulfide (**2**).[6] Nitration of **2** with HNO_3 in acetic acid gave 5,5′-dichloro-2,2′dihydroxy-3,3′-dinitrodiphenyl sulfide (**3**) (Scheme 1). Oxidation of **3** to the corresponding sulfone **4** was easily accomplished using H_2O_2. Cyclocondensation of **3** with **1** in the presence of triethylamine led to 2,10-dichloro-6-[bis(2-chloroethyl)amino]-4,8-dinitrodibenzo[*d*, *g*][1,3,6,2]dioxathiaphosphocin 6-oxide (**5**). The product was isolated by removal of



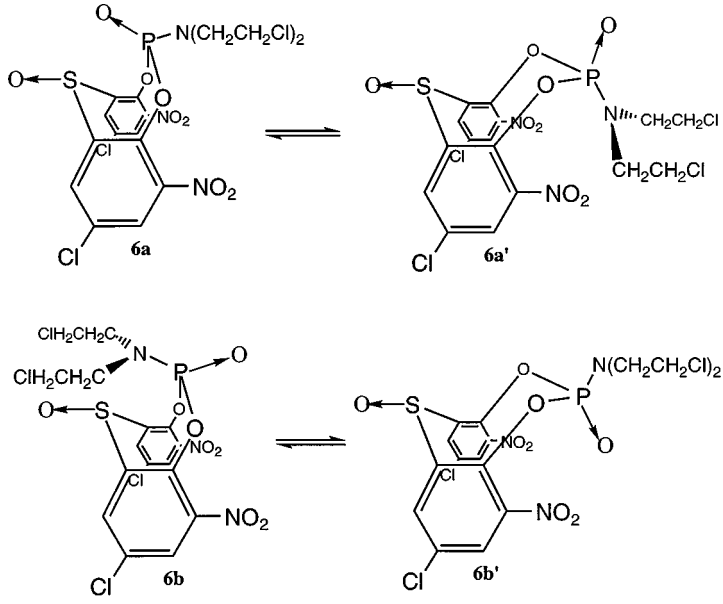
SCHEME 1

triethylamine hydrochloride, via filtration, followed by evaporation of the solvent. Further purification was accomplished by washing the solid with water and then recrystallizing (methanol:chloroform, 1:1). Oxidation of **5** with H_2O_2/HOAc led to sulfoxide **6** rather than the corresponding sulfone **7**. Possibly the steric bulk of the 4-chloro-2-nitrophenyl groups surrounding the sulfur atom prevented oxidation of **6** to **7**. Attempts to prepare **7** via reaction of **4** with **1** under the usual conditions and at temperatures up to 90°C also failed, suggesting the sulfone group may hinder the formation of **7**, possibly because of the bulk involving the close proximity of the nitro groups to the ortho-situated hydroxyl groups as well as an pseudo axial S→O bond.

From an examination of the potential orientations of the polar oxygen atom and the size of the bis(chloroethyl)amino group on the phosphorus atom, it is clear that two isomers like **6** or **6′** could be formed from the one isomer **5**. Groups are present in both molecules which can screen the upper portion of the sulfur atom, a situation that could prevent a

second oxidation of sulfur in **5** to yield the sulfone in **7** with an axial S→O bond. A major issue to be addressed pertains to the orientation of the $P(O)N[CH_2CH_2Cl]_2$ with respect to the S atom and to the flanking ortho nitro groups on the aryl rings. Molecular models imply that the proximity of the sulfur atom to the flattened aryl rings with ortho hydrogens, the P→O group and the bonded $N[CH_2CH_2Cl]_2$ substituent, and the flanking nitro groups, constitute a major steric congestion. Thus, one might estimate that only formation of a pseudo equatorial S→O bond, as in **6**, would be favored. Indeed, the bulky $P(O)N[CH_2CH_2Cl]_2$ group, assumed to be a dynamic function within the 8-memberd ring, could shield the sulfur atom in **6** from a second oxidation 'from the top,' or pseudo axial position. Similarly, **6′** possesses steric interactions as well by the same groups on P and the aryl ring. However, intuitively, one might also expect **6** to be favored over **6′** since the pseudo axial S→O bond in **6′** would expectedly raise the potential energy of the system because the O—P—O portion of the ring could be restricted in movement. Moreover, any group on P which was projected toward the axial S→O bond would experience severe interactions as suggested by models.

Isomer **6** crystallized as a single compound, but NMR analysis indicated two species. If one considers a possible equilibrium in solution between two conformers, such as in **6a** ⇄ **6a′** or **6b** ⇄ **6b′**, some



SCHEME 2

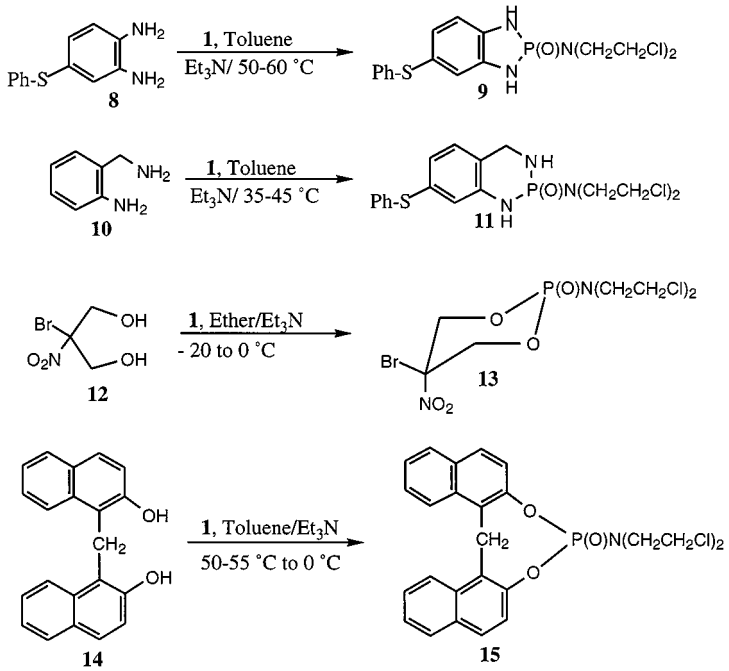
observations can be made in terms of an effect of steric interactions on conformer stability. It is noted that the P→O group is tilted away from the sulfur atom in **6a**′ and **6b**′, and thus internal repulsive energies could be reduced to some extent. On that basis, one would expect conformer **6b**′ to be dominant since the smaller P→O function could perhaps more easily reside between the nitro groups than could the bis(2-chloroethyl)amino moiety as illustrated in **6a**′. In contrast, conformers **6a** and **6b** would expectedly possess large interaction energies involving groups on phosphorus and the S atom or S→O group but probably less so in **6a**. Thus, the **6a** ⇄ **6a**′ is tentatively preferred with **6a** favored (Scheme 2).

It is not possible to rule out the presence of isomer **6**′ which possesses an axial S→O group and the P atom with substituents extended to make a chair type conformation, perhaps similar to that illustrated in **6a**′ and **6b**′. Because of an assumed equilibrium involving a tub ⇄ chair interconversion in **5** and because of the ortho-positioned C—O bonds and C—S bonds, oxidation of sulfur to give a pseudo equatorial S→O bond may be more defensible.

Assuming an equilibrium exists at room temperature between stable conformers of **6**, it is reasonable to predict that two ^{31}P NMR signals might be observed. Such signals appeared for ^{31}P at 18.83 ppm and 19.72 ppm in the ratio of ∼1:5. The presence of four doublets (δ 8.19–8.53 with J ∼ 2.5 Hz; this is fitting for a $^{4}J_{HH}$ coupling-meta coupling) for Ar—H was displayed in the ^{1}H NMR spectrum of a solution of **6** and supported two conformers in solution. Moreover, the ratio of areas to each other of the two sets of aryl protons in the ^{1}H NMR spectrum was nearly the same (∼1:4.2) as that of the ^{31}P signals. Interestingly, the aromatic protons in **6** at H-1, H-3,9, and H-11, were deshielded compared to the corresponding aromatic protons (δ 7.36–8.10) in **5**. In the ^{1}H NMR spectrum of sulfone **4**, two singlets appeared for H-4/H-4′ and H-6/H-6′ at δ 8.15 and 7.94 g respectively. The sulfone group apparently deshields signals for H-4/H-4′ and H-6/H-6′ in **4** compared to the counterparts (δ 7.48 and δ 8.01) in **3**. Unfortunately, the ^{13}C NMR analysis of a DMSO-d_6 solution of **6** was not especially instructive on a 300 MHz spectrometer since the solubility of all samples was relatively low, and very long acquisition times were required to obtain even a reasonable spectrum including a relatively high noise level. The ^{13}C NMR shifts were read as accurately as possible but must be accepted as best estimates. A rough assessment of the P—C coupling was $^{3}J_{PC}$ ∼ 4.6 Hz for the signal at 130.9 involving C(11a) attached to S. Attempts to grow a suitable single crystal for an X-ray diffraction analysis of **6** have not been successful to date.

Oxidation of **3** (Scheme 1) with hydrogen peroxide (30%) in acetic acid yielded sulfone **4** as stated earlier, and attempted cyclization of **4** with **1** at 70–90 °C in the presence of triethylamine did not produce **7**. Possibly some steric interactions between the oxygen atoms on the sulfur in **4** and the large groups attached directly to phosphorus, as discussed above, may be negating ring formation. An implication from these observations is that the presence of a pseudo axial S→O group may prevent formation of a dynamic, eight-membered ring system which also includes in close proximity a phosphoryl group possessing a very large external substituent.

A small series of structurally-related systems was also examined. The condensation of equimolar quantities of 4-thiophenoxy-1,2-phenylenediamine (**8**),[7] 2-aminobenzylamine (**10**),[8] 2-bromo-2-nitro-1,3-propanediol (**12**), and bis(2-hydroxy-1-naphthyl)methane (**14**)[9] with *N*,*N*-bis(2-chloroethyl)phosphoramidic dichloride (**1**) and two equivalents of triethylamine created **9**, **11**, **13**, and **15**, respectively (Scheme 3).



SCHEME 3

The use of two equivalents of triethylamine, dry toluene/ether, and a temperature of 35–60°C was found to be suitable to produce **9**, **11**, and **15**. However, cyclization of **12** with **1** required milder temperatures of

O °C to −20 °C. Purification of these products involved filtration of the triethylamine hydrochloride, evaporation of the solvent, washing the residue with water, and recrystallization of the solids from suitable solvents.

Interestingly, two different doublets were observed for the two endocyclic PNH protons at δ 8.55 ($J_{PH} \sim 17.2$ Hz) and δ 8.42 Hz ($J_{PH} \sim 17.6$ Hz) in **9**, suggesting nonequivalence.[13] The most likely explanation is that the two signals arise from the protons on the two nitrogen atoms being in slightly different environments created by the ring substitution. The small difference in ^{31}P chemical shifts (40.64 vs 40.80 ppm) support this position. A remote possibility might be that these two protons on nitrogen are frozen in a cis-trans forms, but there is no intuitively obvious reason for this situation.

Compounds **11**, **13**, and **15** gave simple proton NMR spectra. Somewhat surprising was the observation that the methylene protons of the *N*,*N*-bis(2-chloroethyl)amino moieties displayed two complex multiplets in the regions of δ 3.17–3.73 and δ 3.56–3.90, respectively,[14,15] in **5**, **6**, **9**, and **11**. In contrast, all methylene protons appeared as a broad multiplet[14] at δ 3.58–3.83 in **13** and **15**.

The ^{13}C NMR chemical shifts were recorded as best estimates for some examples of the title compounds, namely for **3**, **5**, **6**, and **9**, since the shifts were very close. Mass spectral analyses were conducted on representative compounds, and the data obtained were confirmatory for the molecular ions of **3**, **5**, and **11**.

In summary, we have developed syntheses for six heterocyclic systems containing a phosphoryl group bonded to a bis(chloroethyl)amino function. NMR analyses suggested that, in the case of **6**, more than one conformer was present in solution. Large substitutents bonded to phosphorus appear to screen the sulfur atom and permit only monooxidation to a sulfoxide and prevent further oxidation to a sulfone. The compounds await evaluation as potential anticancer agents.

EXPERIMENTAL

All melting points were determined on a Mel-Temp apparatus and were uncorrected. Elemental analyses were performed by Central Drug Research Institute (Lucknow, India). The IR spectra were taken (KBr pellets) on a Perkin-Elmer 683 unit. The ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a Varian Gemini 300 MHz NMR spectrometer operating at 299.9 MHz (^{1}H), 75.5 MHz (^{13}C), and 121.7 MHz (^{31}P). Compounds were dissolved in $DCCl_3$ or DMSO-d_6, and chemical shifts

were referenced to TMS (^{1}H and ^{13}C) or to 85% H_3PO_4 (^{31}P). The EI mass spectra data were collected on a JEOL JMSD-300 instrument at 70 eV with a direct inlet system. The gas atom bombardment mass spectral data were collected on a JEOL SX 102/DA-6000 system using argon/xenon (6 kV, 10 mA) as the FAB gas at RSIC, CDRI, Lucknow, India. Both **1**[13] and **2**[6] were prepared by known routes. No difficulty was experienced in manipulations of the products, but care should be exercised in handling any nitrogen mustard-type compound.

Preparation of 5,5′-Dichloro-3,3′-dinitro-2,2′-dihydroxydiphenyl Sulfide (3)

Nitric acid (7 mL, 0.1 mol) was added over 13–20 min to a stirred solution of 5,5′-dichloro-2,2′-dihydroxyldiphenyl sulfide (**2**, 14.25 g, 0.05 mol) in acetic acid (125 mL) at 13–15 °C. When the reaction was complete (2–3 h), crude 5,5′-dichloro-3,3′-dinitro-2,2′-dihydroxyldiphenyl sulfide was filtered off, washed (H_2O), dried, and recrystallized (ethyl acetate) to yield **3** (14.5 g, 75%), m.p. 188–189 °C. IR: 3210 (O—H), 1520, 1315, (Ar—NO_2) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 7.48 (d, 2 H, J ~ 2.6 Hz, Ar—H), 8.01 (d, 2 H, J ~ 2.7 Hz, Ar—H). ^{13}C NMR (DMSO-d_6): ppm 123.1 [C-1/1′], 124.5 [C-4/4′], 126.6 [C-5/5′], 136.6 [C-6/6′], 137.6 [C-3/3′], 150.2 [C-2/2′]. MS (EI) *m/z* (%): 380 [30, ($M^{+\cdot}$ + 4)], 378 [85, ($M^{+\cdot}$ + 2)], 376 [100, $M^{+\cdot}$], 358 [20], 328 [14], 314 [22], 293 [13], 284 [17], 282 [19], 279 [17], 254 [21], 226 [20], 192 [23], 173 [26], 157 [37], 141 [17]. Anal. Calcd for $C_{12}H_6Cl_2N_2O_6S$: C, 38.21: H, 1.60; N, 7.43. Found: C, 37.89; H, 1.94; N, 7.15.

Oxidation of 5,5′-Dichloro-3,3′-dinitro-2,2′-dihydroxydiphenyl Sulfide (3) to Sulfone 4

To sulfide **3** (3.77 g, 0.01 mol) dissolved in acetic acid (50 mL) was added dropwise H_2O_2 (30%) over 10 min at 15 °C. When the addition was completed, the temperature was raised to RT, and the mixture was stirred for 2–3 h. Acetic acid was evaporated, the crude solid was washed with water, and the final product was recrystallized (ethyl acetate) to give **4** (3.64 g, 86%), m.p. 197–198 °C. IR: 1316 (Ar—NO_2), 1120 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 4.21 [bs, 2 H, OH], 7.94 [s, 2 H, H-6/6′, Ar—H], 8.15 [s, 2 H, H-4/4′, Ar—H]. Anal. Calcd for $C_{12}H_6Cl_2N_2O_8S$: C, 35.23; H, 1.48; N, 6.85. Found: C, 35.12; H, 1.64; N, 6.76. Using the conditions in which **3** → **5** was conducted, attempts to cyclize **4** failed even at temperatures of 70–90 °C.

Preparation of 2,10-Dichloro-6-bis(2-chloroethyl)amino-4,8-dinitrodibenzo[*d,g*][1,3,6,2]dioxathiaphosphocin (5)

N,*N*-bis (2-Chloroethyl)phosphoramidic dichloride (**1**, 1.30 g, 0.005 mol) in dry toluene (20 mL) was added dropwise over 15 min to a stirred solution of **3** (1.89 g, 0.005 mol) and triethylamine (1.01 g, 0.01 mol) in dry toluene (50 mL) at 0–5 °C. When the addition was complete, the temperature was slowly raised to 55–60 °C and stirring was continued for 6 h. The mixture was cooled, filtered to remove triethylamine hydrochloride, and evaporated to a residue. The residue was washed with water and recrystallized (methanol:$HCCl_3$; 1:10) to give **5** (1.54 g, 55%), m.p. 260–261 °C. IR: 1345 (Ar—NO_2), 1270 (P=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.48–3.61 [m, 4 H, NCH_2], 3.70–3.78 [m, 4 H, H_2CCl_2], 7.36–8.10 [m, 4 H, H-1/11, H-3/9, Ar—H]; ^{13}C NMR (DMSO-d_6): ppm 40.6 [H_2CCl_2], 47.5 [NCH_2], 124.8 [C-11a/12a], 126.2 [C-3/9], 129.1 [C-2/10], 136.5 [C-1/11], 151.5 [C-4a/7a]; ^{31}P NMR (DMSO-d_6): ppm 10.45; MS (FAB) *m/z* (%): 584 [13, ($M^{+\cdot}$ + Na)], 562 [82, ($M^{+\cdot}$ + H)], 548 [6], 528 [10], 514 [8], 460 [13], 379 [7], 351 [6], 329 [35], 307 [98], 289 [72], 273 [25], 258 [15], 242 [17], 176 [60], 154 [100], 137 [97], 120 [35], 107 [65], 89 [60]. Anal. Calcd for $C_{16}H_{12}Cl_4N_3O_7PS$: C, 34.13; H, 2.15; N, 7.46. Found: C, 34.02; H, 2.08; N, 7.53.

Oxidation of 5 to 2,10-Dichloro-6-bis(2-chloroethyl)-amino-4,8-dinitrodibenzo[*d,g*][1,3,6,2]-dioxathiaphosphocin 6-Oxide (6)

To oxide **5** (1.41 g, 0.0025 mol) dissolved in acetic acid (40 mL) was added dropwise H_2O_2 (30%) over 5 min at 15 °C. When the addition was complete, the temperature was allowed to rise slowly to RT, and the mixture was stirred for 3 h. Excess acetic acid was evaporated from the mixture, the crude solid was washed with water, and the final solid was recrystallized ($HCCl_3$ with hexane added to induce crystallization) to yield **6** (1.12 g, 78%), m.p. 276–278 °C. IR: 1347 (Ar—NO_2), 1291 (P=O), 1099 (S=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.64–4.74 [m, 4 H, NCH_2], 3.84–3.90 [m, 4 H, H_2C—Cl], 8.19–8.53 [m, 4 H, H-1, H-3/11, H-/9, Ar—H]; ^{13}C NMR (DMSO-d_6): ppm 41.4 [H_2C—$Cl)_2$], 48.5 [$N(CH_2)_2$], 128.4 [C-3/9], 130.7 [C-2/10], 130.9 [C-11a/12a], 141.8 [C-1/11], 142.8 [C-4/8]; ^{31}P (DMSO-d_6): ppm 18.83, 19.72. Anal. Calcd for $C_{16}H_{12}Cl_4N_3O_8PS$: C, 33.18; H, 2.09; N, 7.25. Found: C, 33.02; H, 1.98; N, 7.31.

Preparation of 2-Bis(2-chloroethyl)amino-2,3-dihydro-5-thiophenoxy-1*H*-1,3,2-benzodiazaphosphole 2-Oxide (9)

N,*N*-bis(2-Chloroethyl)phosphoramidic dichloride (**1**, 1.30 g, 0.005 mol) in dry toluene (20 mL) was added dropwise to a stirred solution of

4-thiophenoxy-1,2-diphenyldiamine[7] (**8**, 1.08 g, 0.005 mol) and triethylamine (1.01 g, 0.01 mol) in dry toluene (50 mL) at 0 °C. When the addition was completed, the mixture was brought to 50–60 °C and was maintained at that temperature for 5 h with stirring. The mixture was cooled to RT, the triethylamine hydrochloride was filtered off, and the filtrate was gummy solid which separated was triturated with fresh isopropyl alcohol to yield **9** (0.92 g, 46%), m.p. 210 °C (dec). IR: 3385 N—H), 1265 (P=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.17–3.26 [m, 4 H, N(CH_2)$_2$], 3.67–3.72 [m, 4 H, H_2C—Cl], 6.76 [d, J ~ 7.1 Hz, 1 H, H-7], 6.78 [s, 1 H, H-4], 6.86 [d, J ~ 7.7 Hz, 1 H, H-6] 7.08–7.30 [m, 5 H, PhS], 8.42 [d, J ~ 17.6 Hz, 1 H, PN—H], 8.55 [d, J ~ 17.2 Hz, 1 H, PN—H]; ^{13}C NMR (DMSO-d_6): ppm 41.2 [H_2C—Cl], 49.1 [NCH_2], 110.5 [C-4], 114.2 [C-7], 120.8 [C-5], 125.6 [C-4′/6], 126.2 [C-1′], 127.4 [C-2′/6′], 129.1 [C-3′/5′], 133.8 [C-8], 138.5 [C-9]; ^{31}P (DMSO-d_6): ppm 40.64, 40.80. Anal. Calcd for $C_{15}H_{18}Cl_2N_3OPS$: C, 47.77; H, 4.51; N, 10.45. Found: C, 47.98; H, 4.35; N, 10.32.

Preparation of 2-Bis(2-chloroethyl)amino-1,2,3,4-tetrahydro-1,3,2-benzodiazaphosphorinane 2-Oxide (11)

N,*N*-bis(2-Chloroethyl)phosphoramidic dichloride (**1**, 2.59 g, 0.01 mol) in dry toluene (25 mL) was added dropwise (20 min) to a cold (0 °C) solution of 2-aminobenzylamine[8] (**10**, 1.22 g, 0.01 mol) and triethylamine (2.02 g, 0.02 mol) in dry toluene (20 mL). After stirring for 1 h at 0 °C, the temperature of the mixture was raised slowly to 35–45 °C, and stirring was continued for 4 h. After cooling to RT, the workup was identical to that given for **9**. The white solid formed was recrystallized (isopropyl alcohol) to give **11** (1.99 g, 65%), m.p. 165–166 °C. IR: 3330 (PN—HPh), 3210 [PN—H(CH_2)], 1285 (P=O) cm^{-1}; ^1H NMR ($DCCl_3$ + DMSO-d_6): δ 3.24–3.37 [m, 4 H, N(CH_2)$_2$], 3.56–3.66 [m, 4 H, H_2C—Cl)], 3.91–4.21 [m, 2 H, H-4], 4.75 [d, 1 H, H-3 (NH)], 6.72–7.11 [m, 4 H, H-5/6/7/8], 7.50 [d, 1 H, H-1 (NH)]; MS (EI) *m*/*z* (%): 311 [2, ($M^{+\cdot}$ + 4)], 309 [9, ($M^{+\cdot}$ + 2)], 307 [17, $M^{+\cdot}$], 271 [7.6], 258 [74], 222 [25.7], 167 [76], 149 [19.5], 119 [7.4], 97 [9.2], 85 [16.5]. Anal. Calcd for $C_{16}H_{16}Cl_2N_3OP$: C, 42.87; H, 5.23; N, 13.64. Found: C, 43.05; H, 5.10; N, 13.72.

Preparation of 5-Bromo-5-nitro-2-bis(2-chloroethyl)-amino-1,3,2-dioxaphosphorinane 2-Oxide (13)

A solution of 2-bromo-2-nitro-1,3-propanediol (**12**, 1.00 g, 0.005 mol, Aldrich) and triethylamine (1.01 g, 0.01 mol) in dry ether (30 mL) was stirred and cooled to 20 °C. To this solution was added dropwise over 15 min a solution of *N*,*N*-bis(2-chloroethyl)phosphoramidic dichloride

(**1**, 1.30 g, 0.005 mol) in dry ether. The mixture was stirred at this temperature for 4 h, and then the mixture was allowed to warm slowly to RT. Stirring was continued for 15–20 min, after which time the mixture was filtered, and the filtrate was evaporated to a gummy solid. The solid was washed with water and cold isopropyl alcohol, and finally it was recrystallized ($HCCl_3$-hexane) to yield **13** (0.81 g, 42%), m.p. 246–248 °C. IR: 1305 (P=O) cm^{-1}; ^1H NMR ($DCCl_3$): δ 3.65–4.82 [m, 8 H, $N(CH_2CH_2Cl)_2$], 4.65–5.12 [m, 4 H, H-4/6, CH_2]. Anal. Calcd for $C_7H_{12}BrCl_2N_2O_5P$: C, 21.78; H, 3.13; N, 7.26. Found: C, 21.92; H, 3.06; N, 7.32.

Preparation of 8-Bis(2-chloroethyl)amino-16*H*-dinaphtho[2,1-*d*:1′,2′-*g*]1,3,2-dioxaphosphocin 8-Oxide (15)

N,*N*-bis(2-Chloroethyl)phosphoramidic dichloride (**1**, 1.30 g, 0.005 mol) in dry toluene (20 mL) was added dropwise (15 min) to a stirred solution of bis(2-hydroxy-1-naphthyl)methane[9] (**14**, 1.50 g, 0.005 mol) and triethylamine (1.01 g, 0.01 mol) in dry toluene (50 mL) at 0 °C. When the addition was completed, the mixture was warmed slowly to 50–55 °C and then was maintained at that temperature with stirring for 6 h. The mixture was cooled to RT, filtered, and the filtrate was evaporated to a residue. The residue was washed with water and cold isopropyl alcohol and then recrystallized (ethanol) to yield **15** (1.65 g, 68%), m.p. 208–209 °C. IR: 1245 (P=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.58–3.77 [m, 8 H, N $(CH_2CH_2—Cl)_2$], 4.74 [d, J ~ 16.1 Hz, 1 H, H_b-bridged CH_2], 5.18 [d, J ~ 16.3 Hz, 1 H, H_a-bridged CH_2], 7.11–8.19 [m, 12 H, Ar—H]; ^{31}P NMR (DMSO-d_6): ppm 6.52. Anal. Calcd for $C_{25}H_{22}Cl_2NO_3P$: C, 61.74; H, 4.56; N, 2.88. Found: C, 61.82; H, 4.42; N, 2.92.

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REFERENCES

[1] H. Arnold and F. Bourseaux, *Nature*, **181,** 131 (1958).
[2] H. Arnold and F. Bourseaux, *Angew. Chem*., **70,** 539 (1958).
[3] S. M. Ludeman and G. Zon, *J. Med. Chem*., **18,** 1251 (1975).
[4] O. M. Friedman, Z. V. Papanasatadsiou, and R. S. Levi, *J. Med. Chem*., **6,** 82 (1963).

[5] P. Hsu, I. S. Kao, J. S. T. Sai, C. H. Chou, M. C. Liv, R. C. Pan, and S. W. Li, *Sci. Sinica (Penking)*, **13,** 789 (1964).
[6] F. Dunning, B. Dunning, and W. E. Drake, *J. Am. Chem. Soc*., **53,** 3466 (1931).
[7] E. A. Averkin, C. C. Beard, C. A. Dvorak, J. A. Edwards, J. H. Fried, J. G. Kilian, and R. A. Schilz, *J. Med. Chem*., **18,** 1164 (1975).
[8] R. F. Nystrom and W. G. Brown, *J. Am. Chem. Soc*., **70,** 2589 (1948).
[9] Y. Ogata and A. Kowasaki, *Tetrahedron*, **25,** 2589 (1969).
[10] J. D. Goddard, A. W. Payne, N. Cook, and H. R. Luss, *J. Heterocyclic Chem*., **25,** 575 (1998).
[11] S. D. Pastor and J. D. Spivak, *J. Heterocyclic Chem*., **28,** 1561 (1991).
[12] R. P. Arishinova, *Phosphorus, Sulfur, and Silicon*, **68,** 1555 (1992).
[13] L. N. Rao, C. Nagaraju, C. D. Reddy, T. S. Auschwitz, C. W. Brown, J. Klucik, M. R. Hickey, C. A. Wakefield, and K. D. Berlin, *Phosphorus, Sulfur, and Silicon*, **158,** 39 (2000).
[14] P. B. Farmer and P. J. Cox, *J. Med. Chem*., **18,** 1106 (1975).
[15] Z. M. Ludeman, G. Zon, and W. Egan, *J. Med. Chem*., **22,** 151 (1979).
[16] S. M. Ludeman, K. L. Shao, G. Zon, V. L. Himes, A. D. Mighell, S. Takagi, and K. Mizuta, *J. Med. Chem*., **26,** 1788 (1983).
[17] D. W. White, D. E. Gibbs, and J. G. Verkade, *J. Am. Chem. Soc*., **101,** 1937 (1979).