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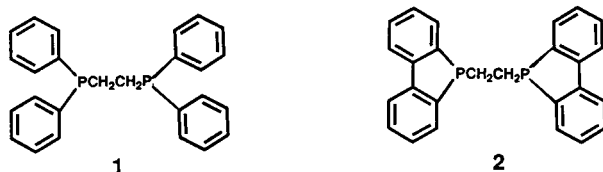
Synthesis of 1,2-bis(dibenzophospholyl-1)ethane (**2**) in 45% yield was accomplished in a single step *via* the coupling of 2,2'-dilithiobiphenyl with 1,2-bis(dichlorophosphino)ethane. The dilithio reagent was generated *in situ* by the metalation of 2,2'-dibromobiphenyl with *n*-butyl lithium. The $^{31}\text{P}\{^1\text{H}\}$ nmr chemical shift of **2** at δ 11.2 ppm (deuteriochloroform) is slightly upfield from the δ 12.8 ppm observed for 1,2-bis(diphenylphosphino)ethane, the nonconstrained analog **1**, relative to external trimethyl phosphate (δ ^{31}P 2.0 ppm). X-ray crystallography showed **2** crystallized in space group $\text{P}2_1/c$ with lattice constants $a = 5.752(1)$ Å, $b = 12.891(2)$ Å, $c = 13.675(3)$ Å and $\beta = 100.74(2)^\circ$ with $Z = 2$. Compound **2** formed a bis[chlorogold(I)] complex in a fashion similar to the known metal complexing ligand **1**. Evaluation of **2** in an ip P388 leukemia mouse model resulted in an increased life span (ILS) of 70% relative to controls, at a maximally tolerated dose (MTD) of 20.2 $\mu\text{mol}/\text{kg}$. By comparison **1** afforded an ILS of 100% at an MTD of 40 $\mu\text{mol}/\text{kg}$.

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1,2-Bis(diphenylphosphino)ethane (**1**) (dppe) is a versatile ligand, which forms complexes with a variety of metals in either a bridging or chelating manner [3]. This ligand, as well as its gold complexes, have been of recent interest to us because of their antitumor properties [4,5,6]. In pursuing structure-activity relationship studies of the ligand portion of these antitumor agents we envisioned restraining the phenyl rings of **1** into a planar configuration. This configuration is provided by 1,2-bis(dibenzophospholyl-1)ethane (**2**) in which the two phenyl rings attached to the phosphorous are joined together at the ortho positions by a carbon-carbon bond to give the fused dibenzophosphole moiety. The latter may be viewed as a conformationally constrained form of the diphenylphosphino portion of dppe (**1**).

Although **2** has been evaluated as a co-ligand in rhodium or cobalt-catalyzed hydroformylation reactions [7], the metal coordination chemistry of **2** remains undescribed and indeed its synthesis is limited to a single report by Braye, Caplier and Saussey [8]. These workers prepared **2** by addition of 1,2-dibromoethane to the phosphorus anion of dibenzophosphole generated *in situ* by the lithium metal dephenylation of P-phenyldibenzophosphole (**3**). While the melting point behavior of **2** was described, the yield and spectroscopic properties were not reported. Attempts by us to repeat this synthesis resulted in the formation of complex mixtures from which the isolation of **2** in pure form could be accomplished only with difficulty and in low yield (less than 10%). Subsequently, we sought an alternate synthetic route to **2** and, as an example of a metal coordination complex, to prepare and characterize its bis(chlorogold(I)) complex **8**.

Previously, we described the synthesis of some 1,2-bis-(diheterocyclophosphino)ethane congeners of **1** *via* the tetraarylation of 1,2-bis(dichlorophosphino)ethane (**4**) using lithium heterocycles obtained from thiophene, furan



and 2- and 4-bromopyridines [4,9]. Although complex reaction mixtures were observed, isolation of the desired ligand was accomplished readily. While this route represents something of a departure from the standard procedure for preparing bisphosphine ligands, which typically are prepared by alkylation of a diaryl phosphine anion [10], it has been employed to prepare 1,2-bis[bis(pentafluorophenyl)phosphino]ethane (**5**) [11].

Extension of this procedure to the synthesis of **2** required 2,2'-dibromobiphenyl (**6**) as starting material. This compound was prepared in 52% yield by treating 1,2-dibromobenzene with *n*-butyllithium as described [12,13] and was isolated and purified prior to the next step. Although **6** can be generated and used *in situ*, improved yields of **2** are obtained if **6** is purified first. Metalation of **6** in tetrahydrofuran at -50° with *n*-butyllithium yields 2,2'-dilithiobiphenyl (**7**) quantitatively [14]. Addition of a stoichiometric amount of 1,2-bis(dichlorophosphino)ethane (**4**) in tetrahydrofuran to **7** was carried out at -50° . The reaction mixture was allowed to warm to room tem-

perature, quenched with aqueous ammonium chloride and extracted with methylene chloride. Recrystallization of the residue from methylene chloride/hexanes gave **2**. Further workup of the residues (see Experimental) gave additional amounts of **2** in 45% yield overall as an air-stable, white crystalline solid. The analytically pure sample of **2** showed a sharp melting point at 186.5-187.5° which differed from the literature report of 250° with a transition point of 180° [8].

Direct current ionization mass spectroscopy using ammonia as a reagent gas gave the MH⁺ ion at m/e 395 as the parent peak with only minor further fragmentation consisting primarily of a peak at m/e 185 assigned to dibenzophosphole-H⁺ and a small peak at m/e 200. The proton decoupled ³¹P nmr spectrum of **2** in deuteriochloroform showed only a single peak at δ 11.2 ppm upfield from the external standard trimethylphosphate (δ ³¹P 2.0) and only slightly different from that of **1** observed at δ 12.8 ppm. The 250 MHz ¹H nmr spectrum of **2** (deuteriochloroform) was consistent with expectations, displaying three resonances (in a ratio of 1:1:3) as a triplet, J = 5.0 Hz at 1.49 ppm assigned to -CH₂-; an aromatic multiplet at 7.40 ppm and an aromatic doublet, J = 7.75 Hz, at 7.90 ppm.

X-Ray Crystal Structure.

A single crystal X-ray structure determination of **2** confirmed its identity. The ligand sits on an inversion center in the crystal, (between the central C-C bond) therefore only one-half of the molecule is unique crystallographically. The structure is displayed in Figure 1. The phosphorus atoms are 180° apart in the adopted conformation. Carbon phosphorus bond lengths to the two aryl carbons are equivalent and approximately 0.03 Å shorter than the bond between P and C7, as expected. Bond angles around

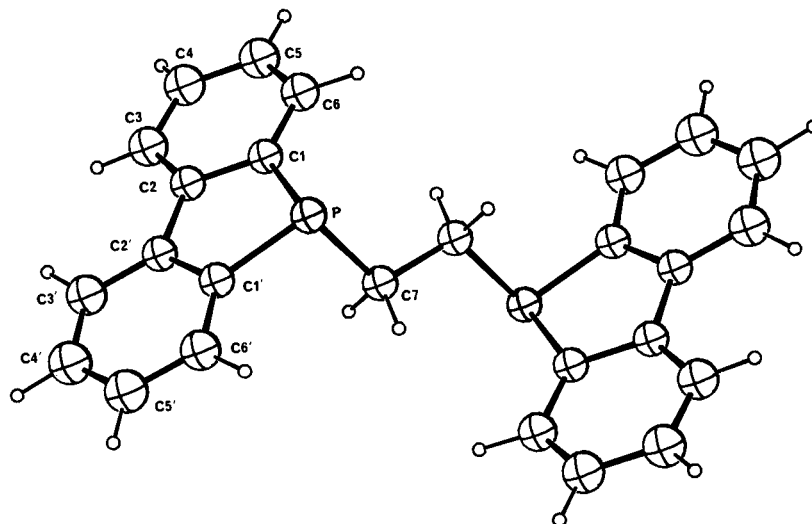


Figure 1. ORTEP drawing of **2**. Thermal ellipsoids are shown at the 50% probability level, H atoms as small spheres of arbitrary size. Atom labels are included for the crystallographically unique half of the

Table 1

Positional Parameters for **2** and Their Estimated Standard Deviations.

Atom	x	y	z	B(A ²)
P	0.22144(7)	0.11322(3)	0.92700(3)	2.590(8)
C1	0.4210(3)	0.1924(1)	0.8696(1)	2.52(3)
C1'	0.0587(3)	0.0790(1)	0.8040(1)	2.59(3)
C2	0.3564(3)	0.1939(1)	0.7652(1)	2.58(3)
C2'	0.1481(3)	0.1292(1)	0.7278(1)	2.61(3)
C3	0.4899(3)	0.2503(1)	0.7095(1)	3.35(3)
C3'	0.0418(3)	0.1130(1)	0.6287(1)	3.46(4)
C4	0.6884(3)	0.3038(1)	0.7568(1)	3.67(4)
C4'	-0.1507(3)	0.0467(2)	0.6072(1)	3.91(4)
C5'	-0.2362(3)	-0.0038(2)	0.6822(2)	3.89(4)
C5	0.7516(3)	0.3027(1)	0.8597(2)	3.52(4)
C6'	-0.1332(3)	0.0119(1)	0.7806(1)	3.32(3)
C6	0.6178(3)	0.2485(1)	0.9164(1)	3.10(3)
C7	0.3977(3)	-0.0071(1)	0.9562(1)	2.61(3)

Anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as: $(4/3) * [a^2 * B(1,1) + b^2 * B(2,2) + c^2 * B(3,3) + ab(\cos \gamma) * B(1,2) + ac(\cos \beta) * B(1,3) + bc(\cos \alpha) * B(2,3)]$.

phosphorus are asymmetric due in part to the ring constraints; the largest is the C1-P-C7 angle at 101.5(1)° and the smallest is the angle internal to the five-membered ring C1-P-C1' (89.7(1)°). The C1'-P-C7 angle of 99.4(1)° differs by 10° from its counterpart and shows that the dibenzophospholyl ring is not evenly bisected by the phosphorus-ethano linkage. The two unique aryl rings are rigorously planar and are virtually coplanar. The dihedral angle between planes is 3.8(6)°. Atomic coordinates are listed in Table 1 and bond distances and bond angles are given in Table 2.

50% probability level, H atoms as small spheres of arbitrary size. Atom labels are included for the crystallographically unique half of the

Table 2
Principal Bond Distances(Å) and Angles(°) for **2**

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance
P	C1	1.8197(9)	C1'	C6'	1.391(1)	C4	C5	1.387(2)
P	C1'	1.8207(9)	C2	C2'	1.471(1)	C4'	C5'	1.380(2)
P	C7	1.8558(9)	C2	C3	1.385(1)	C5'	C6'	1.381(1)
C1	C2	1.406(1)	C2'	C3'	1.395(1)	C5	C6	1.379(1)
C1	C6	1.394(1)	C3	C4	1.386(1)			
C1'	C2'	1.403(1)	C3'	C4'	1.386(1)			

Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle
C1	P	C1'	89.69(4)	C1'	C2'	C2	113.02(7)
C1	P	C7	101.46(4)	C1'	C2'	C3'	119.79(8)
C1'	P	C7	99.36(4)	C2	C2'	C3'	127.17(8)
P	C1	C2	112.14(6)	C2	C3	C4	119.81(9)
P	C1	C6	128.08(7)	C2'	C3'	C4'	119.13(9)
C2	C1	C6	119.78(8)	C3	C4	C5	120.4(1)
P	C1'	C2'	112.16(6)	C3'	C4'	C5'	120.95(9)
P	C1'	C6'	127.73(7)	C4'	C5'	C6'	120.50(9)
C2'	C1'	C6'	120.11(8)	C4	C5	C6	120.48(9)
C1	C2	C2'	112.90(8)	C1'	C6'	C5'	119.51(9)
C1	C2	C3	119.83(8)	C1	C6	C5	119.70(9)
C2'	C2	C3	127.25(8)				

Gold Complex.

Bisdibenzophosphole **2** formed a bischlorogold(I) complex **8**, in a manner similar to the formation of the gold complex of dppe (**1**) [15], upon addition of **2** to an aqueous solution of the thiodiglycol gold(I) chloride complex formed *in situ* by thiodiglycol (excess) reduction of chloroauric acid. Product **8** formed as a precipitate and was readily isolated. The use of **8** as a chemical intermediate and its antitumor activity are reported elsewhere [16].

Antitumor Activity.

Compound **2** was tested for antitumor activity in mice bearing i.p. P388 leukemia following a published procedure [4,17]. The endpoint was median survival time (MST) and increase in life span (ILS), which is the percentage of increase in MST relative to untreated controls. Data obtained from **2** was compared to dppe (**1**) which was included as a standard together with cisplatin. The compounds were evaluated in two independent dose-response studies to obtain an accurate estimate of the maximally tolerated dose (MTD) and the extent and reproducibility of the antitumor effect.

Ligand **2** showed a 70% ILS, relative to controls, at a maximally tolerated dose of 20.2 $\mu\text{mol/kg}$. Dppe (**1**), by comparison, showed a 100% ILS at an MTD of 40 $\mu\text{mol/kg}$. These data suggest that **2** was somewhat less effective against P388 leukemia than **1**. In contrast, the clinically useful antineoplastic agent, cisplatin (cis-PtCl₂(NH₃)₂, **9**), produced an average ILS of 125 \pm 38% in numerous experiments at 6.6 $\mu\text{mol/kg}$ (2 mg/kg) [4]. In light

of the potency of **9**, our interest in the ligands **1** and **2** as potential antitumor agents has subsided.

EXPERIMENTAL

1,2-Bis(dichlorophosphino)ethane was purchased from Strem Chemicals, Inc., P. O. Box 108, Newburyport, MA 01950 and was used without further purification. Thioglycol, *n*-butyllithium (2.5 *M* in hexanes) and dry tetrahydrofuran were obtained from Aldrich Chemical Co., Inc., Milwaukee, WI 53233 and 2,2'-dibromobiphenyl [18] was prepared as described [12,13]. Melting points, obtained on a Thomas-Hoover melting point apparatus, are uncorrected.

NMR Spectra and Mass Spectra.

The ¹H nmr spectra were obtained in deuteriochloroform using a Bruker AM 250 spectrometer operating at 250 MHz and recorded at 297°K. The ¹H chemical shifts were measured relative to tetramethylsilane. The ³¹P[¹H] nmr spectra were recorded at 297°K using a Bruker WM 360 spectrometer at 145.8 MHz. The ³¹P nmr samples were run in deuteriochloroform with trimethylphosphate ((CH₃O)₃PO) in deuteriochloroform as the external standard (δ ³¹P-2.00 upfield from 85% phosphoric acid). Mass spectra were measured on a 4610 Finnigan Mass Spectrometer at 115 eV at 7.5 x 10⁻⁶ torr using ammonia as a reagent gas.

X-ray Analysis of **2**.

A crystal of approximate dimensions 0.70 x 0.70 x 0.50 mm, grown by slow evaporation from ethyl acetate, was mounted using epoxy on a glass fiber for data collection. Crystal orientation and data collection were performed on an Enraf-Nonius CAD4 diffractometer equipped with graphite monochromated MoK α radiation ($\lambda\text{MoK}\alpha = 0.71073$ Å). A total of 2625 reflections ($2\theta \leq 56^\circ$; $0 \leq h \leq 7$, $0 \leq k \leq 17$, $-18 \leq l \leq 18$) were collected

with variable speed ω - 2θ scans. Data were corrected for Lorentz and polarization effects and for absorption. The empirical absorption correction was based on Psi scans of eight reflections with $80^\circ \leq x \leq 90^\circ$. Correction factors were 0.9827 (min) and 1.000 (max). Intensity standards, monitored at the beginning, end and at 3 hour intervals during collection time, showed only random fluctuation (max change 0.7%). Symmetry equivalent data were averaged, $R_{int} = 0.024$. The structure was solved by direct methods and refined by full-matrix least squares minimizing the function $\sum w(|F_o| - |F_c|)^2$. Non-hydrogen atoms were treated with anisotropic thermal parameters. All hydrogen positions were located from a difference Fourier map and were allowed to refine. Temperature factors for the hydrogens were assigned as $1.3 \times B_{iso}$ of the attached atom. The refinement converged (max $\Delta/\sigma = 0.00$) to values of the standard crystallographic residuals of $R = 0.0396$ and $R_w = 0.0562$. The "goodness of fit" was 3.55 for a refinement with 2154 observations ($I \geq 3\sigma(I)$) and 158 variables. An extinction coefficient included in the latter stages refined to $8.62(1) \times 10^{-7}$. Maximum excursions in a final difference Fourier map were of heights $\pm 0.734e \text{ \AA}^{-3}$. Neutral atom scattering factors from International Tables for X-ray crystallography [19] were used; crystal data: monoclinic $P2_1/c$, $a = 5.752(1)$, $b = 12.891(2)$, $c = 13.675(3) \text{ \AA}$, $\beta = 100.74(2)^\circ$, $z = 2$, $D_c = 1.315 \text{ mgm}^{-3}$, $\mu = 2.207 \text{ cm}^{-1}$, $T = 296\text{K}$.

5,5'-(1,2-Ethanediy)bis(5*H*-dibenzophosphole) (**2**) [1].

A hexane solution of *n*-butyllithium (19.2 ml of 2.5 *M*, 0.05 mole) was added dropwise to a solution of 2,2'-dibromobiphenyl [12] (7.8 g, 0.025 mole) in dry tetrahydrofuran (50 ml) maintained at -50° under an argon atmosphere. The rate of addition was such that the temperature did not exceed -40° (30 minutes) and gave a heavy off-white suspension. A solution of 1,2-bis(dichlorophosphino)ethane (2.89 g, 0.0125 mole) in dry tetrahydrofuran (5 ml) was then added over 15 minutes at -50° . The mixture was allowed to warm to ambient temperature, quenched in a saturated solution of aqueous ammonium chloride (100 ml) and extracted with methylene chloride. The solvent was removed at reduced pressure and the residue stirred with cold ethanol. The resulting solid was collected and recrystallized from methylene chloride/hexanes to give 1.4 g of product **2**, mp 186 - 188° . The filtrate was subjected to flash chromatography (silica gel, methylene chloride) and the early fractions collected. The solvent was reduced in volume and the residue recrystallized as above to give an additional 0.8 g, mp 186° , total yield, 2.2 g (45%). Recrystallization of a portion gave an analytical sample, mp 186.5° to 187.5° ; m/z 395 (MH^+ , 100%), 200 (18%), 185 (60%); 1H nmr (deuteriochloroform): 7.90 (d, $J = 7.75 \text{ Hz}$, 4H, aromatic CH), 7.40 (m, 12H, aromatic H), 1.49 (t, $J = 5.0 \text{ Hz}$, 4H, CH_2).

Anal. Calcd. for $C_{26}H_{20}P_2$: C, 79.18; H, 5.11. Found: C, 79.23; H, 5.29.

μ [1,2-Bis(5-*H*-dibenzophospholo)ethane]bis[chlorogold(I)] (**8**).

Thiodiglycol (3.22 g, 26.4 mmoles) was added to a solution of chloroauric acid tetrahydrate (2.72 g, 6.6 mmoles) in water (4 ml) kept at 0° and the solution was stirred until colorless. Acetone (16 ml) was added and the solution warmed to ambient temperature. A solution of **2** (1.18 g, 3 mmoles) in warm acetone (100 ml) was then added and the mixture was stirred 1 hour. The resulting solid was collected, washed with 1:1 acetone/water and dried *in*

vacuo to give 2.05 g (79%) of **8**, mp $> 300^\circ$.

Anal. Calcd. for $C_{26}H_{20}Au_2Cl_2P_2$: C, 36.34; H, 2.35; Cl, 8.25; P, 7.21. Found: C, 36.52; H, 2.67; Cl, 8.36; P, 7.11.

Recrystallization of **8** to give needles was accomplished by dissolving in dimethylformamide (boiling required), treating with activated carbon, dilution with an equal volume of methanol and cooling, dec 325° .

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REFERENCES AND NOTES

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