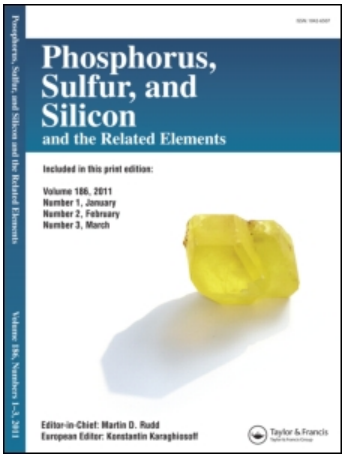

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SYNTHESIS, REACTIVITY AND CONFORMATION OF 10,11-DIHYDRODIBENZO-[*b,f*]PHOSPHEPIN AND DIBENZO[*b,f*]PHOSPHEPIN DERIVATIVES. PHOSPHORUS ANALOGUES OF IMINOBIBENZYL ANTIDEPRESSANTS

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SYNTHESIS, REACTIVITY AND CONFORMATION OF 10,11-DIHYDRODIBENZO-[*b*,*f*]PHOSPHEPIN AND DIBENZO[*b*,*f*]PHOSPHEPIN DERIVATIVES. PHOSPHORUS ANALOGUES OF IMINOBIBENZYL ANTIDEPRESSANTS

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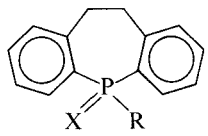
(*Received August 6, 1979; in final form September 28, 1979*)

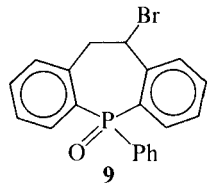
Derivatives of the novel dibenzo[*b*,*f*]phosphepin system are prepared from 10,11-dihydro-5-phenyl-5*H*-bibenzo[*b*,*f*]phosphepin 5-oxide (**2**). New members in the 10,11-dihydro-5*H*-dibenzo[*b*,*f*]phosphepin series, including phosphorus analogues (**7**, **10**) of the andidepressant drug imipramine (**30**), are also reported. Products of nucleophilic substitution at tetrahedral phosphorus in **2** appear to be determined by the relative apicophilicity of the nucleophile. Conformational analysis based on ^{1}H NMR data suggests folded ("butterfly") conformation for the tricyclic compounds. The twisted boat conformation of the central ring in the 10,11-dihydro compounds bears a pseudo-equatorial P=O oxygen or a P=S sulfur, in solution. Symmetric AA'BB' spin systems are found in **4**, **5** and **7**, and their solution conformations appear to be similar to those of analogous 10,11-dihydrodibenzo[*b*,*f*]azepine derivatives. The interaction of some compounds with NMR shift reagents and their mass spectral fragmentations are discussed.

In a systematic study[1,2] of the chemistry and conformation of six- and seven-membered dibenzoheterocycles, phosphorus analogues of nitrogenous drugs, we have turned our attention to the dibenzo[*b*,*f*]phosphepin ring system.[2d] Though interest in phosphorus heterocycles is increasing constantly,[3] dibenzo[*b*,*f*]phosphepin derivatives have received scant attention.[2b,4] This is probably a consequence of the lack of convenient synthetic routes to this ring system.[4] We have studied synthetic approaches, chemical reactivity and conformation of this ring system and related 10,11-dihydro derivatives, including a phosphorus analogue of the antidepressant drug imipramine.

The first derivative of 10,11-dihydrodibenzo [*b*,*f*]phosphepin, **1**, was prepared[4a] in 1953, and the original synthetic route remains the only one known to date.[4b] Only one report deals with the preparation and the isomerization of tribenzo [*b*,*d*,*f*]phosphepin.[4c]

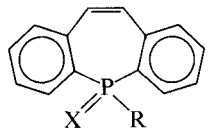


1, X = :, R = Ph
2, X = O, R = Ph
3, X = O, R = OH
4, X = O, R = Cl



9

5, X = O, R = MeO
6, X = O, R = H
7, X = O, R = $Me_2N(CH_2)_3$
10, X = :, R = $Me_2N(CH_2)_3$
8, X = S, R = Ph



11, X = O, R = Ph
12, X = O, R = OH

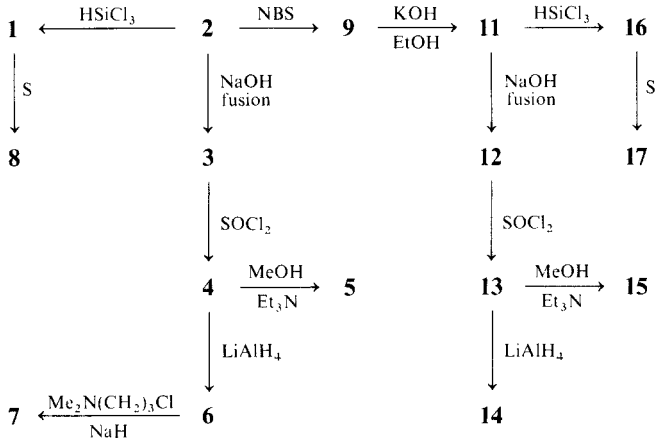
13, X = O, R = Cl
14, X = O, R = H
15, X = O, R = Me
16, X = :, R = Ph
17, X = S, R = Ph

RESULTS AND DISCUSSION

Synthesis

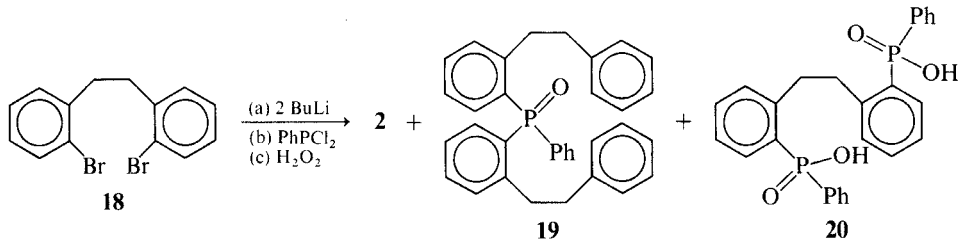
Based on the pioneering work of Mann[4a] and Freedman[4b] we have prepared a variety of derivatives as shown in Scheme I.

Our detailed study of the preparation of the key intermediate **2** from 2,2'-dibromobibenzyl (**18**) (Eq. 1) has shown that the yield of **2** is greatly dependent on the reaction conditions. Dilithiation of **18** in petroleum ether (bp 40–60°C) is obtained in 80% yield, determined by carbonation. However, in diethyl ether, **18** and *n*-butyllithium give mainly butylation of the aromatic rings, as shown



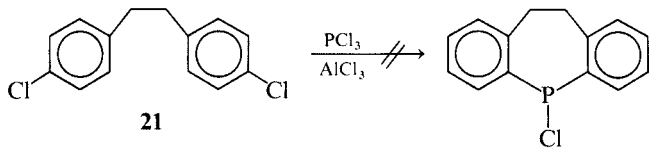
Scheme I

by ^{1}H NMR. Though the reaction (Eq. 1) was performed in high dilution, two by-products **19** and **20** were formed by intermolecular side-reactions. Diacid **20** was isolated by base extraction, while **19** could not be purified but it was identified by mass spectrometry.

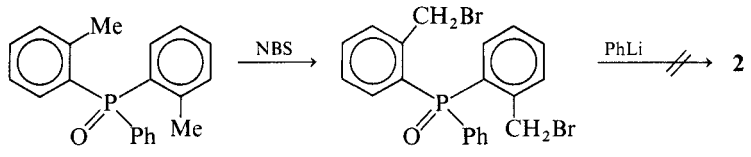


(1)

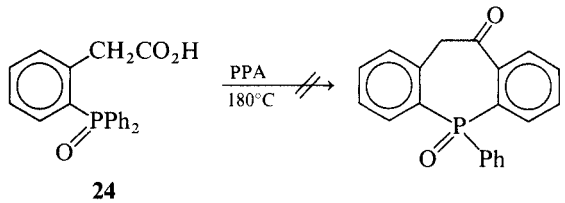
The attempted syntheses described by Eqs. (2)–(4) gave polymeric products and not the desired heterocycles. These efforts were induced by successful Friedel–Crafts type syntheses of six-membered ring C—P heterocycles,[1,2] and analogous syntheses of 10,11-dihydrodibenzo[*b*, *f*]azepines.[5,6]



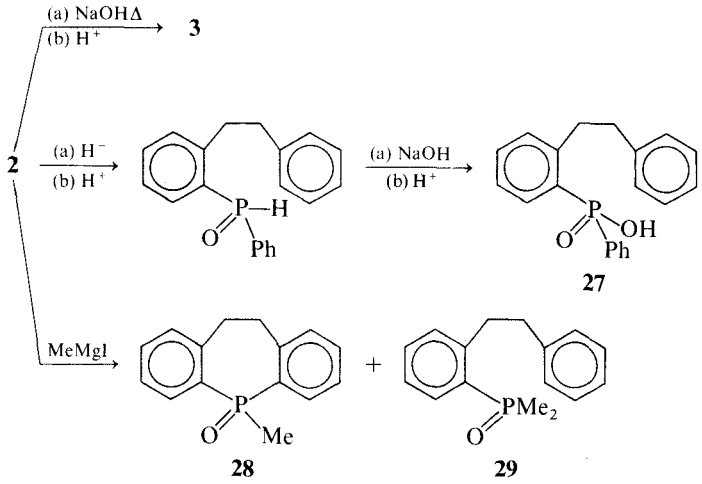
(2)



(3)

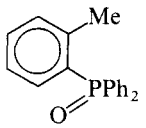


(4)



Scheme II

Fusion of **2** with sodium hydroxide followed by acidification gives exclusively acid **3**.[4b] Endocyclic P—C bond cleavage (ring opening) is not observed. It has been suggested[4b] that this selectivity results from considerably better stabilization of the phenyl anion, obtained in this reaction, over that of the alternative substituted tolyl anion. This interpretation can be overruled as follows. Diphenyl-2-tolylphosphine oxide (**25**) fusion with sodium hydroxide followed by protonation yields a 2:1 mixture of acids **26** and diphenylphosphinic acid. Clearly, the statistical distribution of these acids suggests that there is no preference of phenyl *vs.* 2-tolyl cleavage from the tertiary phosphine oxide by sodium hydroxide fusion.



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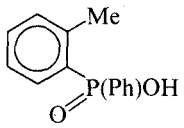


26

In a preliminary communication, we have reported[2d] that the degree of exocyclic *vs.* endocylic C—P bond rupture in the reactions of **2** with some nucleophiles can be correlated with the relative apicophilicity of the nucleophile. Assuming a trigonal bipyramidal intermediate, or transition state, in these reactions, relatively highly apicophilic nucleophiles (such as H^-) would give ring cleavage. Poorly apicophilic nucleophiles (such as HO^-)[7] would lead to exocyclic C—P bond rupture and ring retention. This is shown in Scheme II.

Acid chloride **4**, prepared from **3** and $SOCl_2$, is a convenient intermediate in the preparation of the phosphorus analogue of imipramine (**10**). It is reduced by $LiAlH_4$ to give the secondary phosphine oxide **6**, after hydrolysis. Deprotonation of **6** followed by alkylation gives the desired phosphine oxide **7**. It is noteworthy that both **4** and **5** failed to react with 3-dimethylaminopropylmagnesium chloride. This result is contrasted by the successful analogous reaction of phenoxaphosphinyl chloride.[1a] Phosphine **10** (phosphaimipramine) is obtained from phosphine oxide **7** by $HSiCl_3$ reduction.

Phosphine oxide **2** allows easy access to dibenzo[*b*,*f*]phosphepin derivatives. Bromination of **2** by *N*-bromosuccinimide (NBS) followed by dehydrobromination gives phosphine oxide **11**. The chemical reactivity of **11** is similar to that of **2**, as shown in Scheme I. Olefin phosphine oxide **11** is regioselectively reduced by $HSiCl_3$ giving olefin phosphine **16**, or by $LiAlH_4$ yielding phosphine oxide **2**. We have reported analogous regioselective reductions of dibenzo[*b*,*e*]-phosphorin derivatives.[2a,b] Other olefins or phosphine oxides are reduced by $HSiCl_3$,[8] or $LiAlH_4$,[9] respectively. These observations can partly be rationalized as follows. The P=O oxygen in these tricyclic compounds, in solution, appears to be pseudoequatorially oriented and sterically encumbered by protons ortho to phosphorus.[2b,c] This is a consequence of the pseudoboat conformation adopted by the central ring of these tricyclic compounds. The $LiAlH_4$ aggregates in ether or THF are large enough to prevent P=O reduction while the less bulky $HSiCl_3$ molecule in benzene is not. Hydride addition to aromatic olefins, such as in the

reduction of **11** to **2** with $LiAlH_4$, has been discovered in this study. The scope and limitations of this reaction have been reported recently.[10,11]

^1H NMR Spectra and Conformational Analysis

In addition to the H-Ar multiplet, some of the compounds described above show a low-field multiplet, assigned to two (peri) protons ortho to phosphorus, and a characteristic pattern associated with H–10,11, which are helpful in conformational analysis. All the heterocyclic phosphine oxides and sulfides described above exhibit the typical low-field multiplet, well separated from the H–Ar multiplet. Double irradiation experiments reveal $^3J_{HP}$ = 12–16 Hz for these protons (see Experimental Section), characteristic of aromatic protons ortho to phosphorus. This typical multiplet is not observed in the ^1H NMR spectra of either cyclic phosphines or related acyclic phosphine oxides, such as **22**.[12] The close proximity of the appropriate ortho protons to the P=O oxygen or P=S sulfur is probably causing the "through space" shielding of these protons. This is further supported by using shift reagents (*vide infra*). This proximity can be achieved in a preferred conformation with a pseudoequatorial phosphinoyl oxygen and a pseudoaxial P-substituent in solution. Such a conformation has also been found to be the more stable one in tribenzo[*b,d,f*]phosphepin[4c] and dibenzo[*b,e*]phosphorin derivatives in solution, but not in the crystal.[13] ^1H NMR spectra of representative derivatives of 10,11-dihydro-dibenzo[*b,f*]phosphepin and dibenzo [*b,f*]phosphepin are shown in Figures 1 and 2, respectively.

10,11-Dihydrodibenzo[b,f]phosphepin

Another useful probe for conformational analysis **1–8** is the ^1H NMR line shape associated with C–10,11 protons. The conformers of 5-alkyl-10,11-dihydrodibenzo[*b,f*]azepine, including imipramine (**30**), interconvert at room temperature fast enough to exhibit an A_4 singlet for the ethylene bridge protons.[14] Conversely, C–10,11 protons of **4**, **5** and **7** are magnetically nonequivalent at

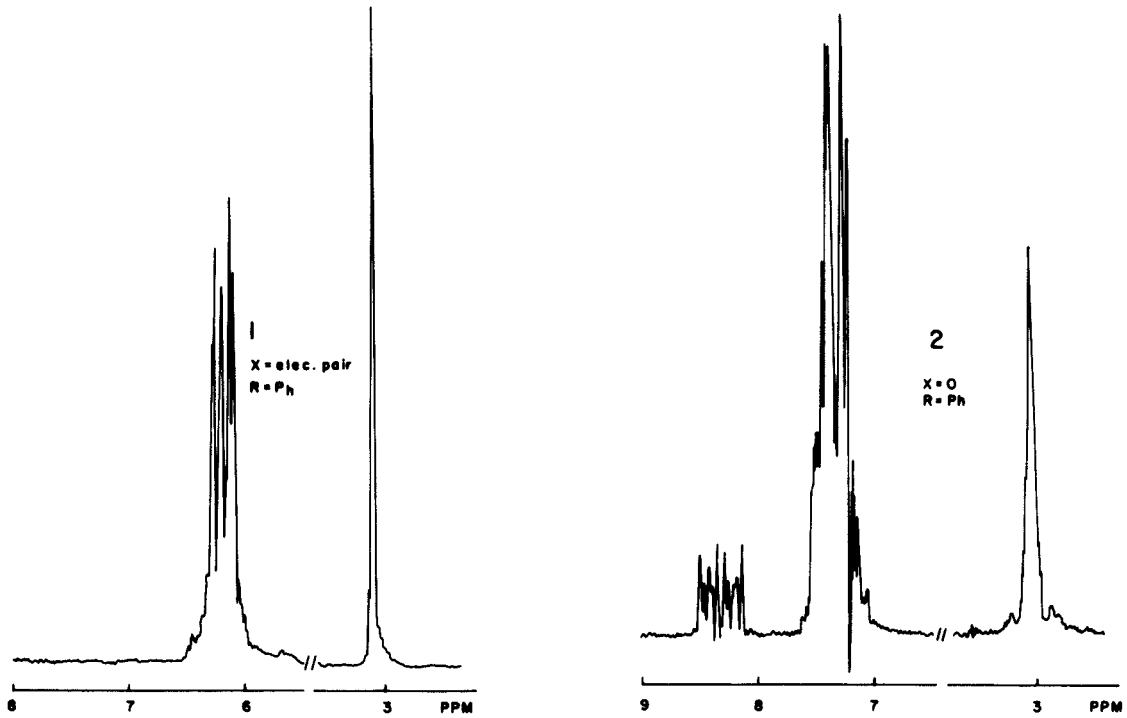


FIGURE 1 Representative ^1H NMR spectra of 10,11-dihydrodibenzo[*b,f*]phosphepin derivatives.

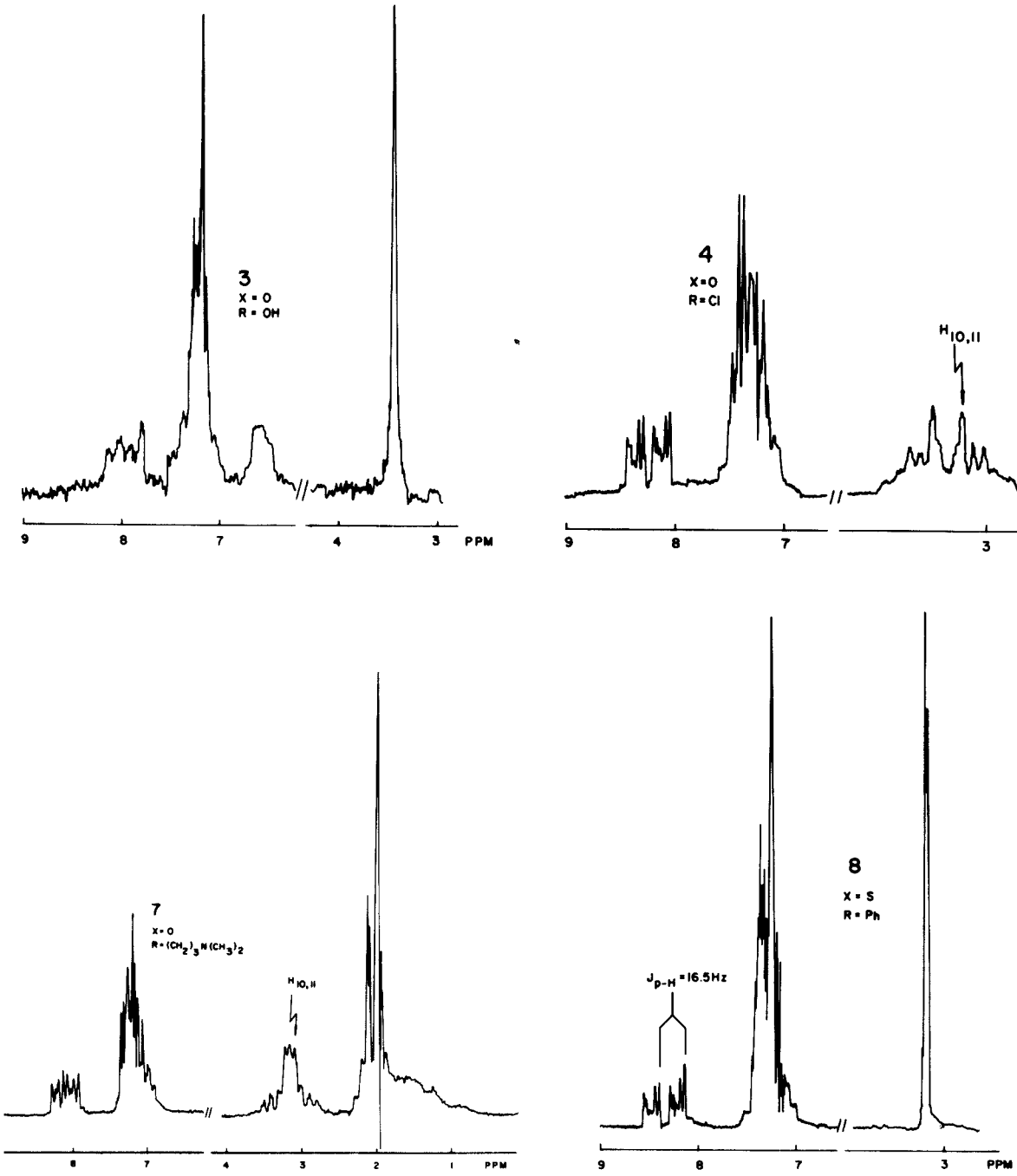


FIGURE 1 Representative ^1H NMR spectra of 10,11-dihydrobenzo[*b*,*f*]phosphepin derivatives.

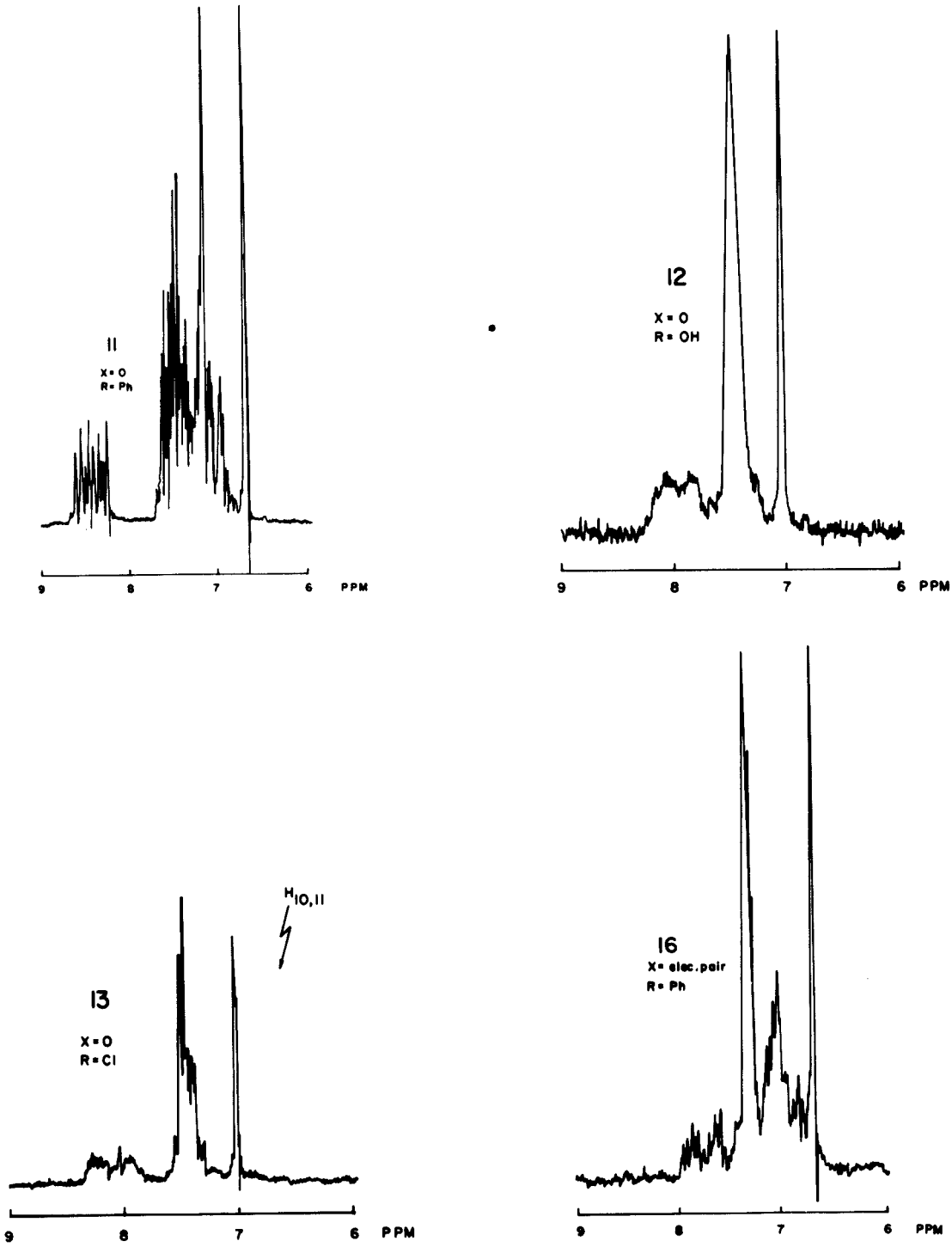


FIGURE 2 Representative ^{1}H NMR spectra of dibenzo[*b*,*f*]phosphepin derivatives.

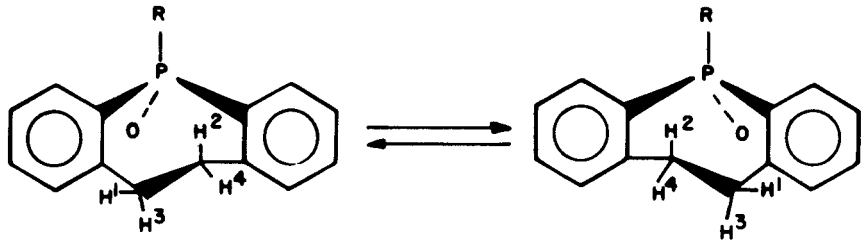
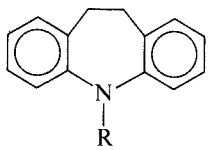


FIGURE 3 Interconverting enantiomers of a 10,11-dihydrobenzo[*b*,*f*]phosphepin.

ambient temperature, indicating restricted central ring inversion.



30, R = $Me_2N(CH_2)_3$
31, R = MeCO

AA'BB' pattern is found for the bridge protons of **4** and **5**, while **7** in CCl_4 shows a pattern intermediate between that of AA'BB' and AA'A"A'". AA'BB' symmetry is found for **7** in C_6D_6. A twisted boat conformation of the seven-membered ring fits these observations. The appropriate protons of **1** and **8** or **2** and **3** show sharp or broad singlets corresponding to equivalent or near-equivalent protons, due to fast flipping at ambient temperature.

The two AA'BB' multiplets of **4**, **5** and **7** are mirror-symmetrical, separated by 30, 36 and 24 Hz, respectively. A molecular fragment which oscillates between two mirror-image conformations would produce such symmetric AA'BB' spin system. An interconversion of two enantiomers illustrated in Figure 3 accounts for these observations. Newman projection of the ethylene fragment is shown in Figure 4.

The ^{1}H NMR spectrum of **4** reveals three coupling constants for the four ethylene protons (Figures 1, 4): $^3J_{1,2} = 6.0$ Hz, $^3J_{1,4} = 7.9$ Hz and $^2J_{1,3} = -15.8$ Hz,[15] assigned in analogy to those in the dibenzo[*b*,*f*]azepine series.[14] The dihedral angle ϕ (Figure 4) can be calculated using the equation: $J = 12.95 \cos^2 \phi$,[15] derived from correlation of the low temperature coupling constants of vicinal protons and dihedral angles in tetradeuteriocyclohexane.[15] The conformation of seven-membered N-acetyl-10,11-dihydrodibenzo[*b*,*f*]azepine (**31**) ring has also been deduced by using this equation.[14] The approximate twisting angle between the aromatic rings of **4** is found to be $\phi = 47°$. A value of $\phi = 51°$ has been found for **31**.[14] These findings suggest a similar conformation for these two compounds in spite of the bulk and bond length differences associated with N and P. On the other hand, it should be noted that by replacement of nitrogen with phosphorus, i.e., on going from **30** to **7** or **10**, a more rigid system is obtained. This is manifested in the A_4 pattern observed in the ^{1}H NMR spectra of **30** even down to $-100°$C.[14] Conversely, **7** reveals the AA'BB' spin system already at room temperature.

Dibenzo[b,f]phosphepin

Concerted rotation-inversion observed for 10,11-dihydrodibenzo[*b*,*f*]phosphepin derivatives is not available to substituted dibenzo[*b*, *f*]phosphepin. The ^{1}H NMR spectra of **11**–**17** suggest that they are intermediates between two pseudoboat conformations shown in Figure 5.

Central ring flipping in these compounds is analogous to those discussed earlier.[2b,c,4c,13,16] The olefinic bridge protons show $^4J_{HP} = 1$–1.5 Hz,

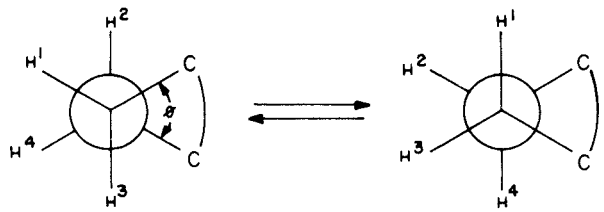


FIGURE 4 Newman projection of the ethane bridge in a 10,11-dihydrodibenzo[b,f]phosphepin.

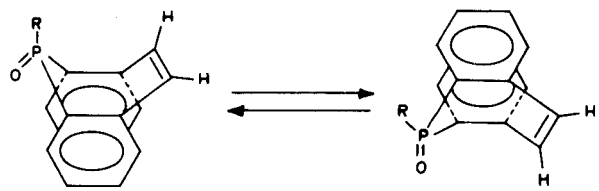


FIGURE 5 Pseudoboat conformers of a dibenzo[b,f]phosphepin.

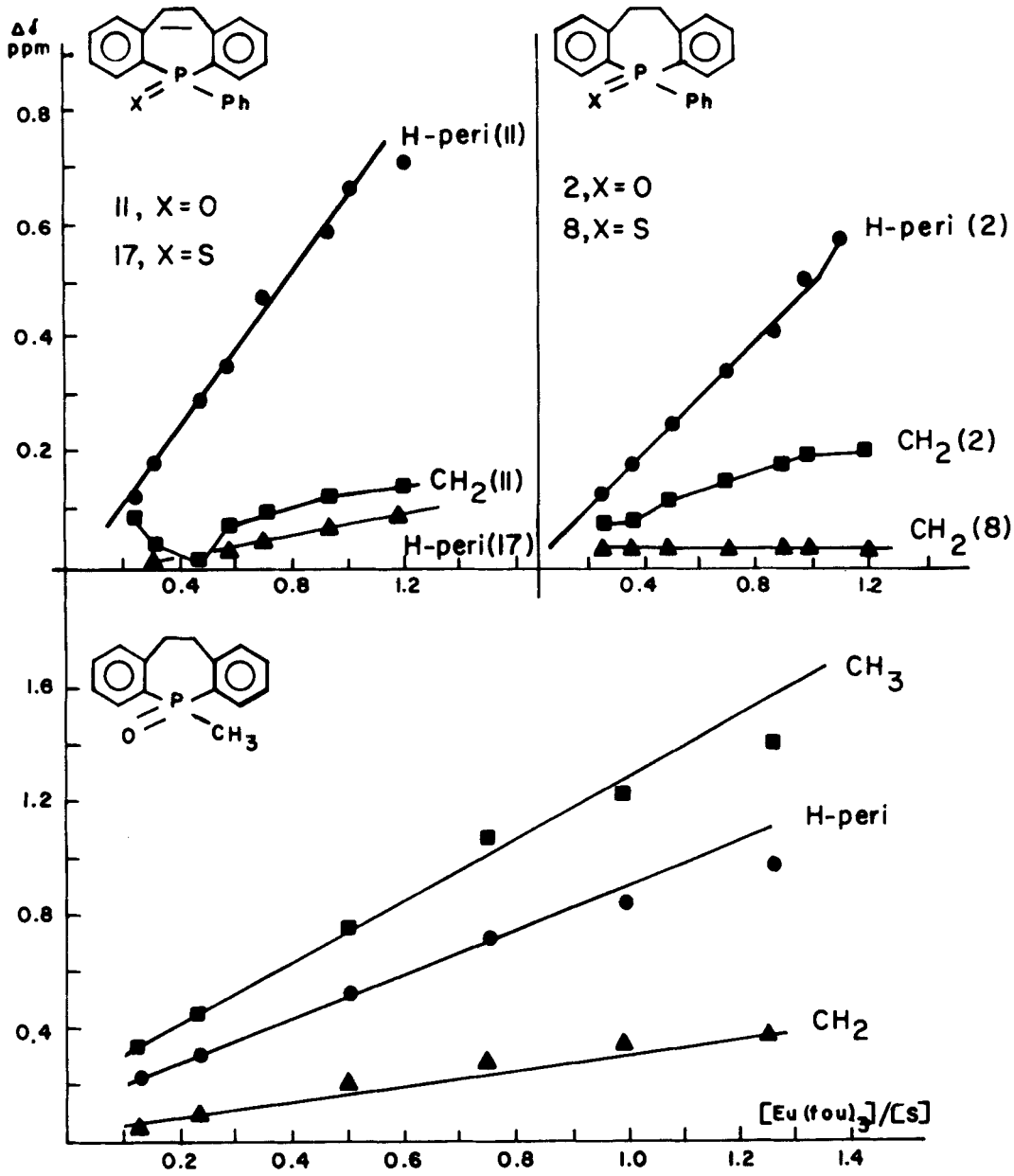


FIGURE 6 Induced shift of selected protons in **2**, **8**, **11**, **16**, **17** and **28** as a function of lanthanide [Eu(fod)$_3$] and substrate concentration.

confirmed by double irradiation. The latter experiment allows also determination of $^3J_{HP}$ = 13 Hz for the peri protons ortho to phosphorus, e.g. in **15**.

Shift Reagents

Application of shift reagents[17] to conformational analysis is well established. Phosphine oxides are known to be strongly complexed with these reagents.[18] The induced shift $\Delta\delta$ is generally larger for α- than for β- or γ-protons, but it also depends on the through-space distance of a given proton from the complexation center. The induced shift ($\Delta\delta$) of some protons in **2**, **8**, **11**, **16**, **17** and **28** as a function of Lanthanide [Eu(fod)$_3$] to substrate concentration ratio are shown in Figure 6.

Generally the complexation of the shift reagent with the P=S group is weak.[19] The peri protons ortho to phosphorus are shifted downfield more than any other protons in these compounds, excluding the Me protons of **28**. This is further support for the earlier mentioned preferred pseudo-equatorial orientation of the P=O oxygen in these compounds in solution. It is also consistent with the assumption that only a slight, if any, conformational change occurs in these compounds upon complexation with the shift reagent. Pseudoaxial P=O oxygen would lead to larger $\Delta\delta$ values for the ethylene C-10,11 protons, as compared with the protons ortho to phosphorus.

While induced $\Delta\delta$ is nearly linear for the peri protons, it is not so for the C-10,11 protons, expecially in the case of **11**. The decrease in $\Delta\delta$ of **11** upon addition of Eu(fod)$_3$ in the [Eu(fod)]/[S] range of 0.25–0.45 is extraordinary and calls for further detailed studies.

Mass Spectrometry

Mass spectral fragmentations of organophosphorus compounds have been reviewed.[20] A typical electron impact induced decomposition of several 10,11-dihydrodibenzo[*b*,*f*]metallepins produces the $C_{14}H_{12}^+$ ion from the molecular ion.[21] Abundant molecular and $C_{14}H_{10}$ ions characterize the mass spectra of derivatives of both dibenzo[*b*,*f*] phosphepin and the 10,11-dihydro analogues. Generally, the mass spectral fragmentations of the compounds in this report are reminiscent of those of Ph_3PO.[22] Typically, the ionized **2** (*m/e* 304, 88%) decomposes stepwise to M—H (303, 55), M—H—C_6H_6 (225, 16), and M—H—C_6H_6—PO (178, 40). A prominent straightforward loss of the P-substituent from the molecular ion is obsrved when the substituent is alkyl, alkoxy or proton (**6**). The molecular ions of dibenzo[*b*,*f*]phosphepin derivatives appear to directly lose the RPO· fragment and yield the stable $C_{14}H_{10}^+$ ion.

Pharmacology

States of depression in experimental animals are ill-defined.[23] Thus, evaluation of novel potential antidepressant compounds is difficult. However, preliminary comparative tests in mice of **7**, **10** and the reference compound **30** suggest the following general patterns. The new phosphorus heterocycles are less toxic than **30**, e.g. LD_{50} s.c. (mice) of **10** is greater than 1 g/Kg. Phosphine **10** behaves significantly different from its oxide **7** indicating fairly slow *in vivo* oxidation of **10** to **7**. Generally, both **7** and **10** exhibit antidepressant profiles similar to that of **30** in a variety of tests, excluding the antioxotremorine test.[24] Consequently, more detailed and extensive pharmacological tests seem desirable.

EXPERIMENTAL

^{1}H NMR chemical shifts are reported in parts per million downfield from Me_4Si. Unless otherwise stated. NMR spectra were obtained for $DCCl_3$ solutions. Mass spectra were obtained at 70 eV and 150–200°C source temperature using the direct insertion probe. Only peaks of intensity greater than 20% of the base peak are given. UV and IR spectra were recorded for 96% ethanol and $HCCl_3$, respectively. Solutions of products in organic solvents were dried ($MgSO_4$) and evaporated under reduced pressure. Elemental analyses are within 0.4% of calculated values, unless otherwise noted.

10,11-Dihydro-5-phenyl-5H-dibenzo[b,f]phosphepin 5-oxide (**2**). 2,2′-Dibromobibenzyl[25] (170g, 0.5 mol) was dissolved in a mixture of petrol ether b.p. 30–40°C (1L) and dry benzene (300mL) and *n*-butyllithium (525mL of 2M in hexane) was added and stirring under dry N_2. This mixture was refluxed for 12h, cooled, diluted with petrol ether (2L) and phenylphosphonous dichloride (89g, 0.5 mol), in petrol ether (750mL) was then added dropwise while keeping the internal temperature between 0–5°C by external cooling. This mixture was refluxed for 2h and then 3.5L of the solvents were distilled off and benzene (0.4L) was added. Dilute (5%) HCl (300mL) was carefully added, followed by enough water to dissolve the salts. The organic layer was collected, cooled, stirred and 30% NaOH (0.3L) was added, followed by dropwise addition of 30% H_2O_2 (150mL). The organic layer yielded a yellow oil which was recrystallized from ethanol. This impure product (63g) was thrice triturated with boiling petrol ether (100mL), leaving pure **2** (53g, 35%). Recrystallization gave needles (ethanol) m.p. 177°C or hexagonal plates (benzene) m.p. 185°C: UV 230nm (ε 21,100), 271

(1100); IR 1184, 1174 cm^{-1} (P=O); ^1H NMR δ 3.02 (4H, m, CH_2), 7.12–7.63 (6H, m, Ar-H), 8.18–8.52 (2H, m, $^3J_{PH}$ = 12 Hz, H-ortho to P); MS *m/e* 304 (M^+, 90%), 303 (M-H, 55), 213 (M-C_7H_7, 100), 178 ($C_{14}H_{10}^+$, 40), 165 ($C_{13}H_9^+$, 26), 78 ($C_6H_5^+$, 56).

10,11 - Dihydro - 5 - phenyl - 5H - dibenzo[b,f]phosphepin (**1**). Phosphine oxide **2** (2g, 6.7mmol), trichlorosilane (4mL) and dry benzene (50mL) were refluxed under dry N_2 for 2h, cooled and then decomposed with 30% aqueous sodium hydroxide (100mL). The desired phosphine was obtained from the organic layer (1.8g, 95%), mp 94°C (EtOH); ^1H NMR δ 3.15 (4H, s, CH_2), 7.00–7.45 (13H, m, Ar-H).

10,11 - Dihydro - 5 - hydroxy - 5 - H - dibenzo[b,f]phosphepin 5 - oxide (**3**). Phosphine oxide **2** (1g, 3.3 mmol) and finely divided dry sodium hydroxide (0.3g, 7.5 mmol) were heated in a round bottom flask, immersed in an oil bath which was maintained at 225–260°C for 1h. Benzene distilled off. The residue was then cooled, ground and heated again as above and then cooled again. Water (30mL) extraction, charcoal treatment, filtration and acidification of the residue gave the desired acid (0.76g, 95%), mp 255–260°C (EtOH); IR (nujol) 2597 cm^{-1} (POH), 1149 (P=O); UV 230 nm (ε 10,000), 270 (1600), 277 (1400); ^1H NMR (CF_3CO_2H) δ 3.39 (4H, br s, CH_2), 7.18–7.70 (6H, m, Ar-H), 7.18–8.25 (2H, m, $^3J_{HP}$ = 13.5 Hz, H-peri); MS *m/e* 244 (M^+, 100%), 243 (M-H, 58), 229 (M-Me, 22), 226 (M-H_2O, 79), 225 (M-H-H_2O, 83), 179 ($C_{14}H_{11}^+$, 34), 178 ($C_{14}H_{10}^+$, 81).

10,11 - Dihydro - 5 - chloro - 5H - dibenzo[b,f]phosphepin 5 - oxide (**4**). Acid **3** (0.5g), 2mmol) and thionyl chloride (10mL) were refluxed for 1.5h, then the excess of the reagent was distilled off under reduced pressure. Dry benzene (10mL) was added and then removed as above to insure complete absence of thionyl chloride from the residue. The remaining solid (0.5g), mp 75–80°C was used without further purification; ^1H NMR δ 3.45 (4H, m, CH_2), 7.05–7.59 (6H, m, Ar-H), 8.08–8.42 (2H, m, $^3J_{HP}$ = 15 Hz, H-peri).

10,11 - Dihydro - 5 - methoxy - 5H - dibenzo[b,f]phosphepin 5 - oxide (**5**). Dry methanol (0.6g, 19mmol) and triethylamine (2g, 20mmol) were dissolved in dry benzene 10mL) and added to a cooled solution of chloride **4** (5g, 19mmol) in dry benzene (50mL). This mixture was stirred for 2h at ambient temperature; then the organic layer was washed with water (20mL) and dried to give **5** (3.7g, 74%), mp 54°C (cyclohexane); ^1H NMR δ 2.63–3.86 (4H, m, CH_2), 3.53 (3H, d, $^3J_{HP}$ = 12 Hz, MeO), 6.97–7.50 (6H, m, ArH), 7.92–8.31 (2H, m, $^3J_{HP}$ = 13 Hz, H-peri); MS *m/e* 258 (M^+, 100%), 257 (M-H, 46), 243 (M-Me, 24), 228 (M-CH_2O, 43) 226 (M-H-MeO, 83), 225 (93), 179 (44), 178 (83), 165 (20).

10,11 - Dihydro - 5H - dibenzo[b,f]phosphepin 5 - oxide (**6**). Lithium aluminum hydride (0.5g, 13.5 mmol) was added in 5 portions to a solution of chloride **4** (2g, 7.6mmol) in a mixture of dry ether (40mL) and tetrahydrofuran (THF) (20mL), under N_2. This mixture was stirred for 2h at ambient temperature, then refluxed for 0.5h, cooled and decomposed with 20% hydrochloric acid (100mL). The organic layer and a benzene (50mL) extract yielded the air sensitive **6** (1.8g, 65%), mp 94°C (cyclohexane); IR 2727 cm^{-1} (P—H), 1163 (P=O); ^1H NMR δ 3.33 (4H, s, CH_2), 8.20 (1H, d, $^1J_{HP}$ = 473 Hz, H—P), 7.03–7.45 (6H, m, ArH). 7.72–8.11 (2H, m, H-peri).

10,11 - Dihydro - 5 - (3'dimethylaminopropyl) - 5H - dibenzo[b,f]-phosphepin 5 - oxide (**7**). Phosphine oxide **6** (7.3g, 32mmol) in dry THF (110mL) was added dropwise to a stirred suspension of sodium hydride (1.7g, 55% in oil, 36mmol) (prewashed with pentane) in dry THF (40mL), under dry N_2 atmosphere at ambient temperature. This mixture was refluxed for 6h and cooled, and then 3 - dimethylaminopropyl chloride (5.1g, 39 mmol) in dry THF (50mL) was added dropwise. The resulting mixture was refluxed for 14h, then concentrated to 100mL, cooled and washed with 20% NaOH (100mL). The organic layer and two benzene (2 × 50mL) extracts from the aqueous layer yielded the crude product which was recrystallized from pentane to give **7** (5.0g, 50%), mp 67–68°C (hygroscopic); UV 227 nm (sh, ε 12,600) 263 (sh 1390), 270 (1850), 277 (1680), 301 (350); ^1H NMR δ 1.75–2.30 (6H, m, H_2), 1.98 (6H, s, Me), 2.65-3.78 (4H, m, CH_2Ar), 6.92–7.36 (6H, m, ArH), 7.92–8.28 (2H, m, H-peri); MS *m/e* 313 (M^+, 5%), 242 (M-C_4H_9N, 100), 241 (M-$C_4H_{10}N$, 91).

Hydrochloride salt of **7** was obtained by passing dry HCl though an ethereal solution of **7**. The crystalline monohydrate hydrochloride of **7** has mp 156–157°C (benzene-ether); ^1H NMR (D_2O) δ 1.58–2.40 (6H, m, CH_2), 3.00 (6H, s, Me), 2.70–3.45 (4H, m, CH_2Ar), 7.05–7.67 (6H, m, ArH), 7.92–8.37 (2H, m, H-peri).

10,11 - Dihydro - 5 - (3' - dimethylaminopropyl) - 5H - dibenzo-[b,f]phosphepin (**10**). Phosphine oxide **7** (0.5g, 1.6mmol), trichlorosilan (2mL) and dry benzene (20mL) were refluxed for 2h. The product was isolated as described above for **1** (0.24g, 51%), oil; ^1H NMR (CCl_4) δ 1.25–2.45 (6H, m, CH_2), 2.08 (6H, s, Me), 2.80–3.55 (4H, m, CH_2Ar), 7.10–8.18 (8H, m, ArH).

10,11 - Dihydro - 5 - phenyl - 5H - dibenzo[b,f]phosphenin 5 - sulfide (**8**). Phosphine **1** (3.1g, 11mmol), sulfur (0.35g, 0.011g atom) and benzene (100mL) were refluxed for 1h. Evaporation of the solvent followed by recrystallization (EtOH) of the residue gave 3.4g (97%) of **8**, mp 157–158°C; UV 220 nm (ε 20,400), 258 (4900); ^1H NMR δ 3.20 (4H, s, CH_2), 7.00–7.53 (6H, m, ArH), 8.14–8.55 (2H, m, $^3J_{HP}$ = 16.5 Hz, H-peri); MS *m/e* 320 (M^+ 90%), 288 (M-S, 30) 287 (M-HS, 50), 273 (30), 229 (95), 211 (M-S-Ph, 70), 210 (M-HS-Ph, 100), 196 (60), 183 (40), 178 (55), 165 (35), 133 (25), 91 (30).

10 - Bromo - 10,11 - dihydro - 5 - phenyl - 5H - dibenzo[b,f] - phos - phepin 5 - oxide (**9**). Phosphine oxide **2** (6.0g, 19.7mmol), *N* - bromosuccinimide (3.74g, 21mmol), dibenzoyl peroxide (24.2mg, 0.1mmol) and dry carbon tetrachloride (200mL) were refluxed for 2.5h. The organic layer yielded the desired bromide **9** (7.0g, 93%), mp 172–173°C (EtOH); UV 231nm (ε 17,590), 262 (2410), 266.5 (2770), 269 (2630), 285 (1740); IR 1184 cm^{-1} (P=O); ^1H NMR δ 3.14–3.68 (2H, m, CH_2), 5.70 (1H, m, CH), 6.87–7.13 (6H, m, ArH), 8.15–8.57 (2H, m, H-peri); MS *m/e* 303 (M-Br, 39%), 302 (M-HBr, 100), 301 (41), 212 (20), 195 (44), 178 (85), 162 (22).

5 - Phenyl - 5H - dibenzo[b,f]phosphepin 5 - oxide (**11**). Phosphine oxide **9** (3.38g, 10mmol) was dissolved in hot ethanol (130mL) and KOH (1.3g, 23mmol) was then added at ambient temperature. This mixture was stirred for 6h, then the solvent was removed and the residue was washed with water (100mL) and recrystallized from EtOH, (2.7g, 90%), mp 231–232°C; UV 220nm (ε 43,700), 272 (6600), 302 (11,400); IR 1177 cm^{-1} (P=O); ^1H NMR δ 6.70 (2H, d, $^4J_{HP}$ = 1 Hz, CH), 6.80–7.70

(6H, m, ArH), 8.25–8.61 (2H, m, $^3J_{HP}$ = 12Hz, H-peri); MS *m/e* 302 (M^+, 67%), 301 (M-H, 21), 272 (28), 196 (85); 178 (100).

5 - Hydroxy - 5H - dibenzo[b,f]phosphepin 5 - oxide (**12**). Phosphine oxide **11** (1.42g, 4.7mmol) and powdered NaOH (0.38g, 9.4mmol) were heated as described above for the preparation of **3**, yielding eventually **12** (0.9g, 79%), mp 310–314°C (EtOH); UV 224 nm (ε 33,00), 272 (10,100), 294 (14,500); IR (nujol) 2597 (P—OH), 1147 cm^{-1} (P—O); ^1H NMR (CF_3CO_2H) δ 7.05 (2H, s, CH), 7.30–7.62 (6H, m, ArH), 7.80–8.17 (2H, m, $^3J_{HP}$ = 12Hz, H-peri); MS *m/e* 242 (M^+, 79%), 178 (M-PO_2H, 100).

5 - Chloro - 5H - dibenzo[b,f]phosphepin 5 - oxide (**13**). Acid **12** (2.4g, 10mmol) and thionyl chloride (10mL) were refluxed for 1h and the desired product was isolated as described above for **4**. This product was not further purified and was used as the crude compound; ^1H NMR ($SOCl_2$) δ 7.00 (2H,d, $^4J_{HP}$ = 1Hz, CH), 7.28–7.52 (6H, m, ArH), 7.90–8.32 (2H, m, $^3J_{HP}$ = 14.5 Hz, H-peri).

5 - Methoxy - 5H - dibenzo[b,f]phosphepin 5 - oxide (**15**). Absolute methanol (0.4g 12.5mmol) and dry triethylamine (1.3g, 13mmol) in benzene (5mL) were added dropwise to **13** (1g, 3.8mmol) in dry benzene (30mL) and the mixture was refluxed for 15 min, cooled and water (100mL) were added. The organic layer and a $HCCl_3$ extract (30mL) yielded a residue which was dissolved in $HCCl_3$ (5 mL) and then ether (100mL) was added. This mixture was cooled to −18°C overnight and filtered. The resulting filtrate yielded the crude **15** which was recrystallized from pentane (0.5g, 51%), mp 67–68°C; UV 225nm (ε 32,000), 269 (7800), 300 (13,100); IR 1235 (P=O), 1183 cm^{-1} (P-OMe); ^1H NMR δ 3.27 (3H, d, $^3J_{HP}$ = 11Hz, Me), 6.93 (2H, d, $^4J_{HP}$ = 0.5Hz, CH), 7.15–7.50 (6H, m, ArH), 7.83–8.32 (2H, m, $^3J_{HP}$ = 13Hz, H-peri); MS *m/e* 256 (M^+, 37%), 179 (23), 178 (100).

5 - Phenyl - 5H - dibenzo[b,f]phosphepin (**16**). Phosphine oxide **11** (0.5g, 1.7mmol), trichlorosilane (1.6g, 12.3mmol), and dry benzene (20mL) were refluxed under dry N_2 atmosphere for 3h. The resulting mixture was cooled and 30% NaOH (40mL) was added dropwise with vigorous stirring and cooling (ice-water bath). The organic layer gave phosphine **16** (0.45g, 95%) mp 135–136°C (EtOH); UV 215nm ε (39,200), 232 (31,200), 250 (17,500), 302 (10,800); ^1H NMR δ 6.68 (2H, s, CH), 6.77–7.95 (13H, m, ArH); MS *m/e* 286 (M^+, 100%), 285 (M-H, 54) 208 (M-H-Ph, 66), 207 (M-H-C_6H_6, 33), 178 (10).

5 - Phenyl - 5 H - dibenzo [b,f] phosphepin 5 - sulfide (**17**). Phosphine **16** (0.58g, 2mmol), sulfur (64mg, 0.002g atom), and benzene (25mL) were refluxed for 1h, and gave **17** (0.6g, 93%), mp 218–219°C (EtOH); UV 219nm (ε 46,800), 259 (9100), 304 (10,600); ^1H NMR 6.63 (2H, d, $^4J_{HP}$ = 1Hz, CH), 6.90–7.60 (6, H, m, ArH), 8.47–8.90 (2H, m, H-peri); MS *m/e* 318 (M^+, 63%), 239 (M-H-C_6H_6, 22), 209 (M-PhS, 71), 207 (M-H-S-C_6H_6, 35), 196 (81), (62), 178 ($C_{14}H_{10}^+$, 100), 166 (26), 108 (23).

Bibenzyl - 2,2'bis(phenylphosphinic acid) (**20**). The aqueous layer and base extract in the preparation of **2**, described above, gave **20** upon acidification (0.9g, 0.6%), mp 284–288°C (EtOH); UV 227nm (ε 44,500), 265 (8240), 271 (9860) 278 (7890); ^1H NMR (CF_3CO_2H) δ 2.98 (4H, s, CH_2), 7.15–7.82 (8H, m, ArH); MS *m/e* 462 (M^+, 100%), 461 (M-H, 22), 445 (M-OH, 48), 322 (M-$PhPO_2$, 30), 321 (M-$PhPO_2H$, 72), 299 (24), 245 (32), 232 (56), 217 (48), 216 (70), 214 (44), 178 (30), 167 (26), 165 (62), 106 (36), 91 (54), 77 (46).

10,11 - Dihydro - 5 - methyl - 5H - dibenzo[b,f]phosphepin 5 - oxide (**28**) *and Dimethyl - 2 - bibenzylphosphine oxide* (**29**). Methylmagnesium iodide was prepared from methyl iodide (3g, 10 mmol) and magnesium shavings (0.5g) in THF-benzene 3:7, by volume, (100mL). Phosphine oxide **2** (3g, 10mmol) was added to this mixture which was then refluxed for 12h. The mixture was cooled and decomposed with 5% HCl (200 mL). The organic layer and a benzene (50 mL) extract gave the crude products as an oil (2.6 g) composed of **28** and **29** in a 2:1 ratio (by ^1H NMR). Column chromatography on silica eluting with 5% methanol in chloroform gave **28** (1.6g, 66%) as a colorless oil; ^1H NMR δ 1.85 (3H, d, $^2J_{HP}$ = 12Hz, Me), 2.80–3.35 (4H, m, CH_2), 6.90–7.45 (6H, m, ArH), 7.92–8.28 (2H, m, H-peri); MS *m/e* 242 (M^+, 98%), 241 (M-H, 100), 178 (29); UV 225 nm (ε 7540), 264 (sh, 1250), 271 (1610), 278 (1410), 302 (sh, 200).

Phosphine oxide **29**, coming second off the column, was obtained as a colorless oil; UV 225nm (ε 7200), 264 (sh, 1850), 270 (2070), 277 (1790), 296 (sh, 330); ^1H NMR δ 1.71 (6H, d, $^2J_{HP}$ = 12Hz, Me), 3.10 (4H, m, CH_2), 7.10–7.55 (9H, m, ArH); MS *m/e* 258 (M^+, 100%), 257 (M-H, 53), 181 (M-Ph, 24), 180 (M-C_6H_6, 21), 167 (33), 154 (27), 91 (33).

Phenyl - 2 - bibenzylphosphonic acid (**27**). (a) A mixture of sodium hydride (0.5g, 20mmol) and phosphine oxide **2** (3g, 10mmol) was held at 200°C for 15min, then at 230–240°C for 40min. The resulting mixture was cooled, and then stirred for 10 min. with water (30mL) and 30% H_2O_2 (5mL). Filtration recovered 0.25g of **2**. The filtrate was acidified (HCl) and the product, acid **27** was collected and recrystallized from ethanol (2.2g, 69%), mp 235–245°C. Similar results were obtained by refluxing **2** and NaH in xylene for 10h, followed by H_2O_2 oxidation; ^1H NMR (CF_3CO_2H) δ 3.35 (4H, s, CH_2), 7.00–8.15 (14H, m, ArH); MS *m/e* 322 (M^+, 13%), 321 (M-H, 55), 304 (M-H_2O, 70), 303 (M-H-H_2O, 55), 244 (27), 243 (37), 229 (100), 225 (38), 213 (89), 212 (34), 196 (21), 178 (70), 165 (90), 152 (23), 91 (31). (b) Phosphine oxide **2** (1.0g, 3.3mmol) and $LiAlH_4$ (0.5g, 13.5mmol) were refluxed in dry diglyme (50mL) for 20 min. The resulting solution was cooled and carefully decomposed with 5% HCl (10mL), followed by water (300mL). The precipitate was dissolved in 10% NaOH (50mL) and 30% H_2O_2 (3mL). The clear solution was acidified (HCl), giving 0.8g (75%) of **27**, identical with a sample prepared as under *a* above.

Diphenyl - 2 - tolylphosphine oxide fusion with sodium hydroxide. Diphenyl - 2 - tolylphosphine oxide[2b] (2.9g, 10mmol) and powdered sodium hydroxide (0.8g, 20mmol) were mixed well in a distillation apparatus and kept at 240–260°C until no more volatile liquids distilled off. Dissolution of the residue in water (50mL), filtration and acidification yielded a 2:1 mixture (by ^1H NMR) of **26** and diphenylphosphinic acid (2.2g). The crude distillate was also examined by ^1H NMR, and proved to contain a 2:1 mixture of benzene and toluene.

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