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PHENOTHIAPHOSPHINES

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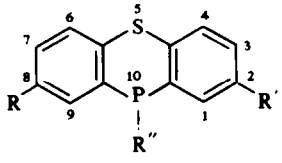
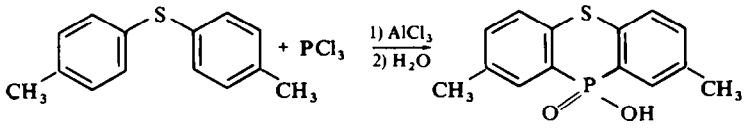
Abstract—The condensation of p,p'-disubstituted diphenyl sulphides with phosphorus trichloride, methylphosphonous dichloride and arylphosphonous dichlorides has been studied. Thus, various derivatives of phenothiaphosphine (I) have been prepared, and their physical and chemical properties have been studied.

IN SEARCH for new systems on which potential psychotropic agents could be based,[1] the phenothiaphosphine system I has been studied.

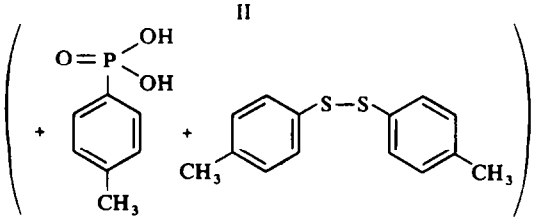


I

A derivative of this system has been described in the literature[2] and has been synthesized as follows in 25% yield:



II



The last two compounds were obtained only in traces. In our experiments, we confirmed the fission of the sulphide by aluminium chloride,[3] since we were able to isolate as by-products *p*-thiocresol (5–7%) and 2,8-dimethyl-10-(*p*-tolyl)-phenothiaphosphine (I, R = R' = CH_3, R'' = *p*-$CH_3 \cdot C_6H_4$) (2–3%). The formation of the latter compound can be rationalised by assuming that the tolyl moiety, split off from the

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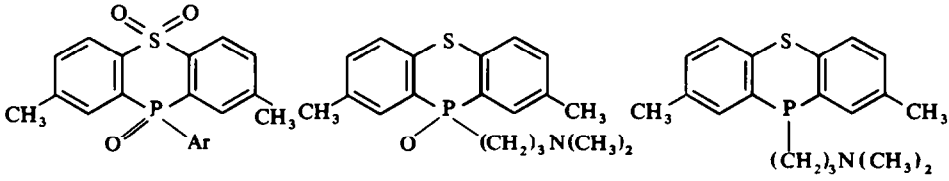
sulphide, combines with phosphorus trichloride to give *p*-tolylphosphonous dichloride which then reacts with unchanged di-*p*-tolyl sulphide in the presence of aluminium chloride.

Indeed, *p*-tolyl-phosphonous dichloride prepared separately does give this reaction, and generally 10-arylphenothiaphosphines (as I) can be prepared from arylphosphonous dichlorides and di-(*p*-tolyl) sulphide in the presence of aluminium chloride. However, when di-*p*-tolyl ether was employed instead of the sulphide, the phosphine *oxide* was formed, even in an inert atmosphere.[1]

The 10-arylphenothiaphosphines give well-defined methiodides and with hydrogen peroxide the corresponding phosphine oxide sulphones of type III. Di-*p*-chloro-



III IV V

phenyl sulphide, 4-chloro-4'-methyl-diphenyl-sulphide and 4-chloro-4'-fluorodiphenyl sulphide did not react with arylphosphonous dichlorides or methylphosphonous dichloride, whilst with phosphorus trichloride in the presence of aluminium chloride the phenothiaphosphine derivatives corresponding to II were obtained. From all three substituted diphenyl sulphides, only *p*-chlorothiophenol was formed by sulphide fission. In the third case, an additional product of formula $C_{18}H_{12}ClFS_2$ was formed; its structure has not yet been elucidated.

With di-(*p*-tolyl) sulphide, methylphosphonous dichloride reacts normally, yielding I (R = CH_3) which was isolated as its trioxide (as III).

The phenothiaphosphinic acids (as II) all show a characteristic ultraviolet absorption maximum[2] at about 310 mμ) which is absent in compounds of type III, and have been characterized by several derivatives. The methyl ester of II, by reaction with γ-dimethylaminopropylmagnesium chloride gave 2,8-dimethyl-10-(γ-dimethylaminopropyl)-phenothiaphosphine-10-oxide (IV), which could be deoxygenated with trichlorosilane[1] to the corresponding phenothiaphosphine (V).

EXPERIMENTAL

The *diaryl sulphides* were prepared by Ziegler's method[4] as follows: The *p*-substituted aniline (1 mole) was diazotized in 500 ml 18% HCl with $NaNO_2$ in 200 ml water. The soln of the diazonium salt was added slowly and in an atmosphere of N_2 to a soln of the *p*-substituted thiophenol (1 mole) in 1 l. 4N NaOH, kept at 60°, and the mixture heated at 100° until no more N_2 was evolved (about 1 hr). Extraction with HEt_2O $CHCl_3$, treatment with 5N HCl and H_2O, and then evaporation of the dried soln yielded the desired sulphide, which was distilled *in vacuo*. The crude distillate was finally purified by trituration with boiling ethanol. Thus we obtained:

from *p*-toluidine and *p*-thiocresol *di-p-tolyl sulphide*, b.p. 122°/0·6 mm, m.p. 58°[5]—from *p*-chloroaniline and *p*-thiocresol *4-chloro-4'-methyldiphenyl sulphide*, b.p. 145°/1·5 mm, m.p. 73°[6]—from *p*-chloroaniline

and *p*-chlorothiophenol 4,4'-*dichlorodiphenyl sulphide*, b.p. 150°/0·1 mm, m.p. 94°[7]—from *p*-fluoroaniline and *p*-chlorothiophenol 4-*chloro*-4'-*fluorodiphenyl sulphide*, b.p. 116°/0·3 mm, m.p. 35°. (Found: C, 60·4; H, 3·2; Cl, 15·0; S, 13·2. Calc. for $C_{12}H_8ClFS$: C, 60·5; H, 3·4; Cl, 14·9; S, 13·4%).

Preparation of phenothiaphosphinic acids (*as* II)

General procedure. The diaryl sulphide (0·2 mole), $AlCl_3$ (0·26 mole; 34·7 g), and PCl_3 (0·8 mole, 109·6 g; 70 ml) were refluxed with stirring for 8–18 hr (until no more HCl was evolved). The mixture was poured into 800 g ice and the oily product taken up with 700 ml 5% NaOH aq. The *non-acidic* material was removed by filtration and the clear soln acidified. The *acid* was then freed from the thiophenol formed by treatment with Et_2O and EtOH (from which the thiophenol was recovered by evaporation).

Thus, e.g., 2,8-*dimethylphenothiaphosphinic acid* (II) was obtained[2] which was recrystallized from EtOH or dimethylformamide and melted at 315°. *Dicyclohexylammonium salt*, from the acid II and the amine in boiling alcohol, m.p. 254° (from EtOH), λ_{max}^{EtOH} 224 (4·69), 269 (4·91), 286[s] (4·73), 314[s] (3·92) [mμ (log ε)]; $\tilde{\nu}_{max}^{KBr}$ 1460, 1175 (P = O), 1120, 1070, 1025, 820, 810 cm^{-1}. (Found: C, 68·3; H, 8·0. Calc. for $C_{26}H_{36}NO_2PS$: C, 68·3; H, 7·9%).

In this reaction, a 5–7% yield of *p*-thiocresol was obtained, which showed the m.p. and mixed m.p. 43° with an authentic specimen; the IR spectra of the two preparations were superimposable. As the *non-acidic* by-product 2,8-*dimethyl*-10-(p-*tolyl*)-*phenothiaphosphine* (I, R = R' = CH_3, R'' = p-$CH_3 \cdot C_6H_4$) was isolated in 2–3% yield; from EtOH, m.p. 167°; λ_{max}^{EtOH} 227 (4·51), 269 (4·10), 304 (3·74) [mμ (log ε)]; $\tilde{\nu}_{max}^{KBr}$ 1450, 1380, 1260, 1120, 1110, 1035, 820, 812 cm^{-1}. (Found: C, 76·2; H, 5·6; S, 9·4; P, 9·4; mol. wt. (mass spectrum), 334.•Calc. for $C_{21}H_{19}PS$: C, 75·4; H, 5·7; S, 9·6; P, 9·3%; mol. wt., 334). The product was identified as *methiodide*, prepared in toluene soln and recrystallized from acetone–ether, m.p. 348°; λ_{max}^{EtOH} 220 (4·65), 267 (4·07), 304[s] (3·77), 318 (3·81) [mμ (log ε)]; $\tilde{\nu}_{max}^{KBr}$ 1600, 1380, 1315, 1150, 1130, 1115, 1040, 910, 835, 802, 782 cm^{-1}. (Found: C, 55·6; H, 4·7; S, 7·2. Calc. for $C_{22}H_{22}IPS$: C, 55·5; H, 4·6; S, 6·7%).

This methiodide was also prepared by an unambiguous way as follows: A mixture of 10·7 g di-*p*-tolyl sulphide, 19·0 g *p*-tolylphosphonous dichloride[8] and 8·5 g $AlCl_3$ was refluxed for 12 hr in an atmosphere of N_2. The reaction mixture was poured into 100 ml ice water and the product washed with water and dissolved in warm toluene. This soln was washed with 10% NaOH aq and water and evaporated, leaving an oil which could not be crystallized and was therefore heated with MeI in ethanolic soln. Thus, 1·5 g (6%) of the above *methiodide*, m.p. 348°, was obtained which showed the same UV and IR spectrum. (Found: C, 56·3; H, 4·7; I, 27·0; P, 6·0. Calc. for $C_{22}H_{22}IPS$: C, 55·5; H, 4·7; I, 26·6; P, 6·5%).

The oil, remaining from the mother liquor of the methiodide, was dissolved in glacial AcOH and refluxed with 5 ml 30% H_2O_2 for 30 min. Thus, an oily product was obtained, which solidified on trituration with 10% NaOH aq and was recrystallized from toluene; yield 2·0 g (10%); m.p. 205–210°. The product, 2,8-*dimethyl*-10-(p-*tolyl*)-phenothiaphosphine-5,5,10-*trioxide* (III, Ar = p-$CH_3 \cdot C_6H_4$), could not be obtained in analytically pure form; λ_{max}^{EtOH} 225 (4·63), 269[s] (3·67), 279 (3·67), 288 (3·63) [mμ (log ε)]; $\tilde{\nu}_{max}^{KBr}$ 1320 (SO_2), 1220, 1200, 1160 (SO_2), 1130 (P = O), 1120, 1030, 830, 805, 707 cm^{-1}. (Found: C, 67·0; H, 5·2; S, 8·2; mol. wt. (mass spectrum), 382. Calc. for $C_{21}H_{19}O_3PS$: C, 66·0; H, 5·0; S, 8·4%; mol. wt., 382).

Analogously, the following *phenothiaphosphinic acids* were obtained: 2-*Chloro*-8-*methylphenothiaphosphinic acid*, yield 38%, characterized as *dicyclohexylammonium salt*, m.p. 258°, λ_{max}^{EtOH} 219 (4·40), 258[s] (3·86), 272 (4·14), 288[s] (3·86), 312 (3·44) [(mμ (log ε)]; $\tilde{\nu}_{max}^{KBr}$ 1460, 1120, 1080, 1070, 1030, 820, 815 cm^{-1}. (Found: C, 62·9; H, 6·8; Cl, 6·9; P, 6·5. Calc. for $C_{25}H_{33}ClNO_2PS$: C, 62·9; H, 7·3; Cl, 7·4; P, 6·5%).

As by-product, *p*-chlorothiophenol, m.p. and mixed m.p. 52°, was obtained in 5% yield.

2-*Chloro*-8-*fluorophenothiaphosphinic acid*, yield, 15%, m.p. 288°, from EtOH. In this case the mixture of the acid with *p*-chlorothiophenol was separated by treatment with dicyclohexylamine in DMF. The *salt* which precipitated was treated with base and the acid obtained as usual; λ_{max}^{EtOH} 219 (4·34), 256[s] (3·81), 269 (4·13), 288[s] (3·70), 316 (3·50) [(mμ (log ε)]; $\tilde{\nu}_{max}^{KBr}$ 2600, 2320, 1640 (POH), 1450, 1260, 1215, 1200 (P = O), 1160, 1140, 1050, 975, 825 cm^{-1}. (Found: C, 48·1; H, 2·3; S, 10·9; P, 10·5. Calc. for $C_{12}H_7ClFO_2PS$: C, 48·0; H, 2·3; S, 10·7; P, 10·3%).

From the DMF mother liquor of the salt of the above acid, the *dicyclohexyl-ammonium salt of* p-*chlorothiophenol* was obtained, m.p. 125° (from ligroin); it was identical with a specimen prepared from *p*-chlorothiophenol. (Found: C, 66·3; H, 8·5; Cl, 10·8; S, 10·2. Calc. for $C_{18}H_{28}ClNS$: C, 66·4; H, 8·9; Cl, 10·9; S, 9·9%).

Furthermore, a *neutral* compound was isolated from the reaction mixture, m.p. 158° (from DMF); $\tilde{\nu}_{max}^{KBr}$ 1480, 1470, 1390, 1225, 1095, 1020, 823, 812 cm^{-1}. (Found: C, 62·8; H, 3·6; Cl, 10·8; F, 4·2; S, 20·1. Calc. for $C_{18}H_{12}ClFS_2$: C, 62·4; H, 3·5; Cl, 10·1; F, 5·5; S, 18·5%).

2,8-*Dichlorophenothiaphosphinic acid*, yield 52%, was isolated in form of its well-crystallized *dibenzylammonium salt*, m.p. 281° from DMF in which the salt had also been prepared; λ_{max}^{EtOH} 216 (4·51), 274 (4·32), 289^{sh} (4·09), 312^{sh} (3·68) [mμ (log ε)]; $\tilde{\nu}_{max}^{KBr}$ 1620, 1430, 1185 (P = O), 1145, 1090, 1075, 1030, 820, 745 cm^{-1}. (Found: C, 61·3; H, 4·1; Cl, 13·7; P, 5·5. Calc. for $C_{26}H_{22}Cl_2NO_2PS$: C, 60·7; H, 4·3; Cl, 13·8; P, 6·0%). *p*-Chlorothiophenol was isolated as a by-product in 3% yield.

Whilst the method of preparation of *aminoalkyl esters* of the phenothiaphosphinic acids has been described before[1] for the corresponding phenoxaphosphine derivatives, the *methyl esters* were prepared as follows: The *crude* acid (0·02 mole) was refluxed for 2 hr with 50 ml $SOCl_2$, the reagent removed *in vacuo*, the residue treated with 20 ml toluene and the latter again evaporated *in vacuo*. The acid chloride was then suspended in 100 ml dry benzene and a soln of NaOMe (0·02 mole) or pyridine (0·02 mole) in 25 ml anhyd MeOH slowly added. The mixture was refluxed for 1 hr and evaporated and the residue dissolved in benzene. After treatment with 5% Na_2CO_3aq and water, the benzene left a solid residue which was recrystallized from ligroin. The esters are described in Table 1.

2,8-*Dimethyl*-10-*phenyl-phenothiaphosphine* (I, R = R′ = CH_3, R″ = C_6H_5). In an atmosphere of N_2 and with vigorous stirring, a mixture of 32·0 g di-*p*-tolyl sulphide, 25·5 g $AlCl_3$ and 81·0 g phenylphosphonous dichloride was heated at 110–130° for 5 hr, cooled, diluted with 200 ml $CHCl_3$ and hydrolyzed by addition of 200 g crushed ice. The reaction mixture which did not separate into two phases, was made strongly alkaline with NaOHaq, whereupon the layers separated. The $CHCl_3$ residue was recrystallized from glacial AcOH, m.p. 147°; yield 8·0 g (17%); λ_{max}^{EtOH} 226 (4·54), 269 (4·09), 304 (3·76) [mμ (log ε)]; $\tilde{\nu}_{max}^{KBr}$ 1445, 1265, 1230, 1200, 1130, 1120, 1040, 820, 740, 690 cm^{-1}. (Found: C, 75·3; H, 5·4; S, 10·7; P, 9·1. Calc. for $C_{20}H_{17}PS$: C, 75·0; H, 5·3; S, 10·0; P, 9·7%).

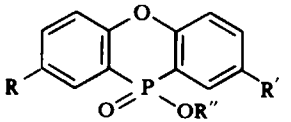
2,8-*Dimethyl*-10-*phenyl-phenothiaphosphine*-5,5,10-*trioxide* (III, Ar = C_6H_5). When the foregoing substance, dissolved in glacial AcOH was refluxed with 30% H_2O_2, the above trioxide was obtained in 30% yield, m.p. 263° (from aqueous AcOH); λ_{max}^{EtOH} 224 (4·71), 269 (3·61), 277 (3·64), 287 (3·63) [mμ (log ε)]; $\tilde{\nu}_{max}^{KBr}$ 1585, 1445, 1320 (SO_2), 1220, 1200, 1160 (SO_2), 1130 (P = O), 1110, 750, 707 cm^{-1}. (Found: C, 64·9; H, 4·6; S, 8·9; P, 8·1. Calc. for $C_{20}H_{17}O_3PS$: C, 65·2; H, 4·6; S, 8·7; P, 8·4%).

2,8-*Dimethyl*-10-(γ-*dimethylaminopropyl*)*phenothiaphosphine*-10-*oxide* (IV). A Grignard reagent was prepared in the normal way from 7·3 g γ-dimethylaminopropyl chloride and 1·46 g Mg, activated with ethylene dibromide, in 30 ml THF. Then, 5·8 g methyl 2,8-dimethylphenothiaphosphinate in 80 ml of the same solvent was added and the mixture refluxed for 3 hr. The product was decomposed with 30 g $AlCl_3$ in 110 ml water and extracted with $CHCl_3$ and benzene. The oily product was transformed with ethereal HCl into its hydrochloride which could be recrystallized from dioxan; yield 2·0 g (26%), m.p. 118; λ_{max}^{EtOH} 223 (4·28), 267 (4·03), 294 (3·68), 305^{s} (3·64) [mμ (log ε)]; $\tilde{\nu}_{max}^{KBr}$ 3580, 3450, 2960, 2700, 1650, 1460, 1225, 1185 (P = O), 1050, 830, 760 cm^{-1}. (Found: C, 59·4; H, 6·9; Cl, 9·5; S, 8·0; P, 7·3. Calc. for $C_{19}H_{25}ClNOPS$: C, 59·5; H, 6·3; Cl, 9·3; S, 8·4; P, 8·2%).

2,8-*Dimethyl*-10-(γ-*dimethylaminopropyl*)*phenothiaphosphine* (V). To a soln of 3·4 g of IV in 30 ml dry benzene, 4·0 ml trichlorosilane was added and the mixture refluxed for 3 hr, diluted with 100 ml benzene and decomposed with 100 ml 30% NaOHaq. The oily product which remained upon evaporation of the solvent, was dissolved in dry ether and treated with ethereal HCl. Thus, an oil was obtained which solidified upon trituration with acetone and was recrystallized from the same solvent to give the *dihydrochloride hydrate*; hygroscopic crystals, yield 2·1 g (50%); m.p. 95°; $\tilde{\nu}_{max}^{KBr}$ 3450, 2960, 2700, 1460, 1260, 1150, 1120, 1030, 815 cm^{-1}. (Found: C, 54·6; H, 7·0; Cl, 17·0; P, 6·7. Calc. for $C_{19}H_{26}Cl_2NPS \cdot H_2O$: C, 54·3; H, 6·7; Cl, 17·0; P, 7·4%).

2,8,10-*Trimethylphenothiaphosphine* 5,5,10-*trioxide* (as III). In an atmosphere of N_2, a mixture of 23·5 g di-*p*-tolyl sulphide, 17·0 g $AlCl_3$ and 46·8 g methylphosphonous dichloride was stirred, refluxed for 4 hr, cooled and hydrolyzed by dropwise addition of 50 ml water. The product was extracted with 200 ml benzene, the extract washed with 10% NaOHaq and water and concentrated to yield 13·5 g of a crude mixture of I (R = R′ = R″ = CH_3) and (R = R′ = CH_3; R″ = *p*-$CH_3 \cdot C_6H_4$). The latter was present to the extent of 4%, and its formation is undoubtedly due to the presence of small quantities of PCl_3 in the methylphosphonous dichloride used. The mixture was worked up as follows: The crude product was dissolved in hot glacial AcOH; upon cooling, the by-product (I, R = R′ = CH_3; R″ = *p*-$CH_3C_6H_4$) crystallized; it was identical with an authentic specimen (see above) (m.p. and mixed m.p. 160°; UV and IR spectra). The mother-liquor was boiled for 15 min with 30% H_2O_2. Concentration and trituration with 10% NaOHaq yielded the trioxide (38%), m.p. 256° (toluene); λ_{max}^{EtOH} 229 (4·31), 254^{s} (3·52), 268^{s} (3·36), 277 (3·46), 285 (3·55) [mμ (log)]; $\tilde{\nu}_{max}^{KBr}$ 1320 (SO_2), 1280, 1210, 1160 (SO_2), 1130 (P = O), 890, 746, 715, 700 cm^{-1}. (Found: C, 58·7; H, 4·8; S, 10·7; P, 9·8. Calc. for $C_{15}H_{15}O_3PS$: C, 58·8; H, 4·9; S, 10·5; P, 10·1%).

TABLE 1. ALKYL PHENOTHIAPHOSPHINATES



R	R′	R″	Formula	M.P. (°C)	Yield (%)	Calc.					Found				
						C	H	Cl	S	P	C	H	Cl	S	P
CH_3	CH_3	CH_3	$C_{15}H_{15}O_2PS$	176	50	62·1	5·2	—	11·0	10·7	61·7	5·3	—	11·6	10·0
CH_3	CH_3	 [a]	$C_{21}H_{24}NO_2PS$	157	60	65·5	6·3	—	8·3	8·1	65·2	6·1	—	8·8	7·7
CH_3	Cl	 . HCl	$C_{20}H_{22}Cl_2NO_2PS$ [b]	279	30	54·3	5·0	16·1	—	7·0	54·1	5·3	16·2	—	6·9
F	Cl	CH_3	$C_{13}H_9ClFO_2PS$	115	40	49·6	2·9	11·1	—	9·9	49·5	2·9	10·7	—	9·7

[a] Hydrochloride, m.p. 285° (from butanol). Anal. Calc. for $C_{21}H_{25}ClNO_2PS$: C, 59·8; H, 6·0; Cl, 8·3; P, 7·4. Found: C, 59·4; H, 6·2; Cl, 8·5; P, 7·1.
[b] Recrystallised from *n*-butanol.

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After this paper had been completed, the abstract of a paper by R. A. Wiley and J. H. Collins (156th ACS National Meeting, September 1968, Division of Medicinal Chemistry, No. 13) came to our attention. In this abstract, the biological properties of 2-substituted 10-(γ-dimethylaminopropyl)-phenothiaphosphines and of their 10-oxides have been described, but no details on their synthesis and properties have been given.