634. *The Preparation of Optically Active Phosphorus Compounds.*

By M. Green and R. F. Hudson.

The syntheses of methyl methyl-1-naphthylphosphinate, methyl 1-naphthyl methylphosphonate, and *S*-benzyl methyl-3-phenanthrylphosphinothiolate are described. The last two esters have been partially resolved by means of their complexes with (−)-α-(2 : 4 : 5 : 7-tetranitro-9-fluorenylideneamino-oxy)propionic acid.

Few optically active phosphorus compounds had been prepared until recently, owing to difficulty in crystallising the mixed diastereoisomers. Thus, in the resolution of phosphine oxides Meisenheimer *et al.*[1] found that crystallisation required several months. More progress has been made recently by incorporating well-defined acidic or basic groups into the asymmetric phosphorus compound. On this basis, Mann and his collaborators [2] resolved phosphonium salts; Aaron and Miller [3] resolved thiolic acids by conventional methods. Coyne, McEwen, and VanderWerf [4] resolved a phosphinic ester (I) containing quaternary ammonium groups, using (+)- and (−)-tartaric acid as resolving agents. On concentrating solutions of the (−)-di-*O*-benzoyltartrate of the ester in methanol, we obtained a thick syrup, and only 0·9 g. of pure (−)-methiodide was isolated from 120 g. of the racemate. Attempts to resolve compound (I) by reaction with silver α-bromo-π-camphorsulphonate or 10-camphorsulphonate also gave syrups; though crystals of the α-bromo-π-camphorsulphonate were obtained after 3 months by allowing the syrup to stand over phosphoric oxide in a vacuum-desiccator, no separation of the diastereoisomer was achieved. Attempted asymmetric solvation [5] of compound (I) by ethyl (+)-tartrate induced no optical activity in the ester.

$Me_3\overset{+}{N}\cdot C_6H_4\cdot PMeO\cdot OMe$

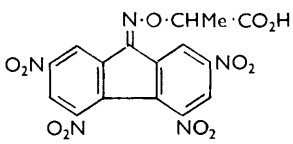
(I)

$1\text{-}C_{10}H_7\cdot PMeO\cdot OMe$

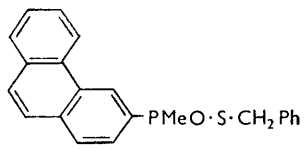
(III)

$1\text{-}C_{10}H_7\cdot O\cdot PMeO\cdot OMe$

(IV)



(II)



(V)

Newman and Lutz [6] introduced a method whereby a molecular complex is formed between an asymmetric compound containing a condensed aromatic nucleus and optically active α-(2 : 4 : 5 : 7-tetranitro-9-fluorenylideneamino-oxy)propionic acid (II), the acidic component being later removed by treatment with aqueous sodium hydrogen carbonate. We tried this method first with methyl methyl-1-naphthylphosphinate (III). Attempts to link the naphthyl group directly to the phosphorus atom by the Grignard reaction between 1-naphthylmagnesium bromide and *NN*-diethylmethylphosphonochloridamidate were abandoned as the product was contaminated with a large amount of naphthalene. An alternative route starting with phosphorus trichloride and the aryl cadmium,[7] prepared by the action of cadmium chloride on the Grignard reagent, was used to prepare methyl-1-naphthylphosphinic acid in 25% yield.

The methyl ester (III) did not form an addition compound with the acid (II), probably on account of steric hindrance between the oxygen atoms of the ester and the nitro-groups. Since Newman and Lutz [6] successfully resolved *sec.*-butyl 1-naphthyl ether by this method,

[1] Meisenheimer and Lichtenstadt, *Ber.*, 1911, **44**, 356; Meisenheimer, *Annalen*, 1926. **449**, 2136.
[2] Holliman and Mann, *J.*, 1947, 1634; Hart and Mann, *J.*, 1955, 4107.
[3] Aaron and Miller, *J. Amer. Chem. Soc.*, 1956, **78**, 3538.
[4] Coyne, McEwen, and VanderWerf, *ibid.*, p. 3061.
[5] Buchanan, *J.*, 1950, 500; Turner and Harris, *J.*, 1950, 1753.
[6] Newman and Lutz, *J. Amer. Chem. Soc.*, 1956, **78**, 2469.
[7] Fox, *ibid.*, 1950, **72**, 4147.

methyl 1-naphthyl methylphosphonate (IV), which similarly has an oxygen atom between the aromatic system and the asymmetric centre, was prepared from methylphosphonic dichloride through the intermediate methyl methylphosphonochloridate. Attempts to prepare the ester (IV) by way of 1-naphthyl methylphosphonochloridate were unsuccessful, indicating that the naphthyloxy-group is replaced in preference to the chlorine atom by one equivalent of alkoxide ions and suggesting that the substitution is controlled by steric interaction between the naphthyl group and the alkoxide ion. The ester (IV) readily formed a complex with tetranitrofluorenone and with the acid (II), from which a partially resolved, dextrorotatory ester was obtained. An attempt to isolate the lævorotatory ester was unsuccessful.

In order to prepare an ester with one replaceable group only and with the condensed aromatic system attached directly to the phosphorus atom, the phosphinothiolate (V) was prepared from 3-iodophenanthrene, itself synthesised by Bachmann's method.[8] This ester was chosen as it is the least sterically hindered phenanthryl derivative, and also because it was expected to be a solid. The ester (V) was synthesised by using the aryl-

$$LiPh + MePOCl\cdot NEt_2 \longrightarrow MePhPO\cdot NEt_2 \xrightarrow{HCl} MePhPO_2H \xrightarrow{SOCl_2} MePhPOCl \longrightarrow MePhPO\cdot OMe$$

lithium compound [9] in the first stage. According to Willans,[10] lithium aryls are much more reactive towards phosphonate esters than are Grignard compounds, and they have been used successfully for replacing chlorine in dialkyl phosphorochloridates [11] [attention has already been drawn to the difficulty experienced in the preparation of compound (III) from the Grignard reagent]. As a preliminary, methyl methylphenylphosphinate was prepared in 25% yield from phenyl-lithium by the annexed route. The same procedure was used to prepare *S*-benzyl methyl-3-phenanthrylphosphinothiolate (V), the phosphinyl chloride being treated with toluene-ω-thiol and pyridine in ether in the final stage. This ester readily formed a complex with the acid (II), and its regeneration therefrom gave a dextrorotatory fraction, $[\alpha]_D^{20}$ +17·0° (*c* 3·0 in C_6H_6). A lævorotatory fraction, $[\alpha]_D^{20}$ −13·1° (*c* 2·0 in C_6H_6), was obtained from the filtrate, giving a total recovery of 90% in these optically active forms. No attempt was made to obtain optically pure isomers by this method.

Experimental

p-Dimethylaminophenyldichlorophosphine, prepared (15% yield) by Michaelis and Schenk's method,[12] had b. p. 158—160°/0·6 mm. The following esters were prepared as described by Coyne, McEwen, and VanderWerf: [4] *p*-dimethyl dimethylaminophenylphosphonite, b. p. 125—126°/0·4 mm. (40%) (Found: C, 56·5; H, 7·7; N, 6·5. Calc. for $C_{10}H_{16}O_2NP$: C, 56·3; H, 7·6; N, 6·6%); methyl *p*-dimethylaminophenylmethylphosphinate, b. p. 170—172°/0·4 mm., m. p. 81° (Found: C, 56·0; H, 7·6; N, 6·5. Calc. for $C_{10}H_{16}O_2NP$: C, 56·3; H, 7·6; N, 6·6%); methyl *p*-dimethylaminophenylmethylphosphinate methiodide (as I), m. p. 159—160° (Found: I, 34·20. Calc. for $C_{11}H_{19}O_2NPI$: 34·3%).

Resolution of the Iodide (I).—(*a*) Silver camphor-10-sulphonate (3·38 g.) and the iodide (3·73 g.) in absolute methanol (10 ml.) were boiled for 10 min., and the silver iodide was then filtered off. No crystals were obtained on cooling, and slow evaporation gave a thick syrup. (*b*) α-Bromo-π-camphorsulphonic acid was prepared [13] from α-bromocamphor, itself prepared by Kipping and Pope's method.[14] The ammonium salt was obtained as needles, m. p. 269°. The resolution was attempted in the same way as above, and only a syrup was obtained after 3 months' storage over P_2O_5.

[8] Bachmann, *J. Amer. Chem. Soc.*, 1936, **58**, 2097, 2195.
[9] Freedman and Doak, *Chem. Rev.*, 1957, 479.
[10] Willans, *Chem. and Ind.*, 1957, 243.
[11] Burger and Dawson, *J. Org. Chem.*, 1951, **16**, 1250.
[12] Michaelis and Schenk, *Ber.*, 1888, **21**, 1497; *Annalen*, 1890, **260**, 1.
[13] Pope and Read, *J.*, 1914, **105**, 801.
[14] Kipping and Pope, *J.*, 1893, **63**, 576.

(*c*) D(−)-Di-*O*-benzoyltartaric acid (m. p. 88—89°, $[\alpha]_D^{20}$ −113·5°; lit.,[15] m. p. 87—89°, $[\alpha]_D^{20}$ −114·8°) was prepared from the anhydride (m. p. 188—189°, $[\alpha]_D^{20}$ −156°; lit.,[15] m. p. 173°, $[\alpha]_D^{20}$ −142°) by Butler and Cretcher's method.[15] The acid (72·5 g.), suspended in distilled water (2·2 l.) containing ammonia (176 ml. of 1·14N), was heated at 90°, and silver nitrate (34 g.) was added. After cooling, the white crystalline precipitate was filtered off and washed with water (50 ml.). The silver D(−)-di-*O*-benzoyltartrate (50 g.) was dried in a vacuum-desiccator. This salt (88 g.) and the iodide (I) (120 g.) were refluxed in methanol (240 ml.) for 10 min., and the quantitative amount of silver iodide filtered off. The solution was cooled, yielding 70 g. of crystals, m. p. 120—121° (lit., m. p. 116—119°), $[\alpha]_D^{25}$ −80° (in MeOH). The partially resolved material was recrystallised seven times from methanol, to give 7·1 g. of solid, m. p. 139°, $[\alpha]_D^{25}$ −90° (in MeOH). No further crystals could be obtained on evaporation of the filtrates.

The pure diastereoisomer (7·1 g.) in 95% ethanol (40 ml.) was added to a solution of potassium iodide (2 g.) in 95% ethanol (40 ml.). The solution was boiled for 5 min., and the potassium D(−)-di-*O*-benzoyltartrate was then filtered off. After 24 hr., 4 g. of the methiodide, m. p. 146—149°, had crystallised. This was recrystallised five times from ethanol, giving 0·9 g. of the (−)-methiodide, m. p. 156°, $[\alpha]_D^{25}$ −28·7° (Found: C, 37·6; H, 5·2; N, 4·0; P, 9·0; I, 35·7. Calc. for $C_{11}H_{19}O_2NIP$: C, 37·2; H, 5·4; N, 3·95; P, 8·70; I, 35·7%).

NN-*Diethylmethylphosphonochloridamidate*.—Diethylamine (7·3 g.) and triethylamine (10·1 g.) in ether (50 ml.) were added with stirring and cooling to a solution of methanephosphonyl dichloride (13·3 g.) in ether (100 ml.). The mixture was stirred for 1 hr. and the amine hydrochloride filtered off. The ether was removed and the residue fractionally distilled, to yield NN-*diethylmethylphosphonochloridamidate* (17 g.), b. p. 80°/2 mm., n_D^{17} 1·4678 (Found: C, 35·4; H, 7·5; N, 8·3; P, 18·1; Cl, 20·9. $C_5H_{13}ONClP$ requires C, 35·4; H, 7·7; N, 8·3; P, 18·3; Cl, 20·7%).

α-*Naphthyldichlorophosphine*.—α-Bromonaphthalene (414 g.) in dry ether (500 ml.) was added slowly to magnesium (48·5 g.) in ether (500 ml.). When the reaction had ceased, anhydrous cadmium chloride (183·4 g.) suspended in ether (400 ml.) was added. The mixture was stirred for 2 hr., then added slowly with stirring to phosphorus trichloride (274·5 g.) in ether (1 l.) at −30°. The mixture was allowed to reach room temperature, and after 12 hr. the solid was filtered off and washed with ether. The solvent was removed on the water-bath and the residue distilled, to give α-*naphthyldichlorophosphine* (25%), b. p. 118—120°/0·5 mm., m. p. 54° (Found: C, 52·6; H, 3·0; P, 13·7; Cl, 30·0. $C_{10}H_7PCl_2$ requires C, 52·5; H, 3·1; P, 13·6; Cl, 30·7%).

Dimethyl α-*Naphthylphosphonite*.—α-Naphthyldichlorophosphine (37 g.) in dry ether (100 ml.) was added with stirring to methanol (30 g.) and diethylaniline (48·2 g.) in ether (200 ml.) at 0°. The mixture was stirred for 2 hr. and the amine hydrochloride then filtered off. The ether was removed on the water-bath and the residue fractionally distilled, to give *dimethyl* α-*naphthylphosphonite*, b. p. 101°/0·15 mm., n_D^{20} 1·6127 (Found: C, 64·9; H, 5·7; P, 14·1. $C_{12}H_{13}O_2P$ requires C, 65·2; H, 5·9; P, 14·1%).

*Methyl Methyl-*α-*naphthylphosphinate*.—Dimethyl α-naphthylphosphonite (23 g.) and methyl iodide (2 ml.) in benzene (50 ml.) were heated on a water-bath for 24 hr. After removal of the solvent, distillation gave *methyl methyl-*α-*naphthylphosphinate* (18%), b. p. 128—130°/0·1 mm. (Found: C, 65·6; H, 5·8; P, 14·0. $C_{12}H_{13}O_2P$ requires C, 65·2; H, 5·9; P, 14·1%).

The ester (0·55 g.) and 2 : 4 : 5 : 7-tetranitrofluorenone (0·87 g.) were separately dissolved in the minimum quantity of hot glacial acetic acid. No colour was produced on mixing the solutions and, on cooling, tetranitrofluorenone, m. p. 254° (from acetic acid), was obtained.

α-*Naphthyl Methylphosphonochloridate*.—α-Naphthol (48 g.), diethylaniline (49·7 g.), and methylphosphonyl dichloride (44·3 g.) were heated for 4 hr. in sodium-dried benzene (200 ml.). After removal of the benzene, ether was added, and the precipitated diethylaniline hydrochloride filtered off. Fractional distillation of the filtrate gave the *chloridate* (61·5 g.), b. p. 142—144°/0·1 mm., m. p. 46—47° (Found: C, 55·0; H, 4·2; P, 12·3; Cl, 14·9. $C_{11}H_{10}O_2ClP$ requires C, 54·7; H, 4·3; P, 12·9; Cl, 14·4%).

A solution of sodium (3·9 g.) in methanol (100 ml.), added at 0° to this ester (40·7 g.) in ether (200 ml.), gave dimethyl methylphosphonate, b. p. 50°/0·1 mm., n_D^{20} 1·4136, and α-naphthol, m. p. 94° (picrate, m. p. 187°).

Methyl α-*Naphthyl Methylphosphonate*.—Methyl methylphosphonochloridate (39·9 g.) was

[15] Butler and Cretcher, *J. Amer. Chem. Soc.*, 1933, **55**, 2605.

added with stirring to a suspension of sodium methoxide (5·1 g. of sodium in 100 ml. of alcohol) and α-naphthol (31·9 g.) in benzene (500 ml.) at 0°. After removal of the benzene and alcohol, ether was added and the sodium chloride filtered off. The *ester* (15·5 g.) obtained by fractional distillation had b. p. 128—130°/0·1 mm., n_D^{20} 1·5807 (Found: C, 60·8; H, 5·5; P, 13·0. $C_{12}H_{13}O_3P$ requires C, 60·5; H, 5·4; P, 13·0%).

Resolution. A brick-red complex (m. p. 124°) was obtained on mixing solutions of the ester and 2 : 4 : 5 : 7 tetranitrofluorenone in 1 : 1 propionic acid–light petroleum. A similar *complex* (Found: C, 50·1; H, 3·1; N, 10·1; P, 4·6. $C_{28}H_{22}O_{14}N_5P$ requires C, 49·3; H, 3·1; N, 10·3; P, 4·5%) was obtained with the (−)-form (m. p. 112°) of the resolving agent. Methyl α-naphthyl methylphosphonate (4·7 g.) and (−)-α-(2 : 4 : 5 : 7-tetranitro-9-fluorenylideneamino-oxy)-propionic acid (9·0 g.) were dissolved in hot 1 : 1 propionic acid–light petroleum (b. p. 60—80°). Three portions of light petroleum (10 ml.) were added to the cold solution, giving three fractions of complex. The solid was filtered off and dried in a vacuum-desiccator for 24 hr.

The molecular complex (10 g.), suspended in ether (200 ml.), was treated with saturated sodium hydrogen carbonate solution (100 ml.) and then with dilute sodium hydrogen carbonate solution (2 × 100 ml.). The combined extracts were treated with ether (5 × 100 ml.), and the combined ether solutions were dried ($MgSO_4$). Removal of the ether and distillation gave the active *ester* (2·0 g.), b. p. 116—118°/10^{-3} mm., n_D^{20} 1·5813, $[\alpha]_D^{20}$ +44° (*c* 1·5 in dioxan) (Found: C, 60·5; H, 5·5; P, 13·0. $C_{12}H_{13}O_3P$ requires C, 60·5; H, 5·4; P, 13·0%). The filtrates obtained from the initial precipitation were treated with sodium hydrogen carbonate solution as described above, and the aqueous solution was extracted with ether. The yield of (−)-ester was too small to be distilled satisfactorily.

Chromatographic Separation of Methyl α-Naphthyl Methylphosphonate.—The complex (0·12 g.) in benzene (100 ml.) was placed on an alumina column, and eluted with benzene. The complexing acid was strongly absorbed. Separation of the α-naphthyl ester was followed by its fluorescence in ultraviolet light. The benzene was removed by continuous azeotropic distillation with spectroscopically pure ethanol. The ethanol solution (25 ml.) had α 0·13° in a 1 dm. tube. The ester was characterised spectroscopically ($\lambda_{max.}$ 254·5 mμ, $\lambda_{min.}$ 245 mμ).

Methyl Methylphenylphosphinate.—The concentration of active phenyl-lithium in ether, prepared by Gilman's method,[16] was estimated by titration of an aliquot part in water with hydrochloric acid, and by adding a second part to benzyl chloride (2 ml.) in ether (10 ml.) and titration in water after 4 min.

NN-Diethylmethylphosphonochloridamidate (4 g.) in ether (100 ml.) was added with stirring to phenyl-lithium (2·0 g.) in ether (101 ml.) at 0°. The mixture was stirred for 1 hr., the ether removed, and concentrated hydrochloric acid (500 ml.) added. After 3 hours' boiling, methylphenylphosphonic acid was extracted with ether, dried, recovered, and allowed to solidify. The acid in hot benzene (50 ml.), was heated for 6 hr. with an excess of thionyl chloride. After the removal of thionyl chloride and benzene, the residue was boiled for 1 hr. with an excess of methanol and pyridine. The mixture was poured into water (200 ml.), and an ether extract of it dried ($MgSO_4$). *Methyl methylphenylphosphinate* obtained by fractional distillation (25%) had b. p. 83—85°/0·1 mm. (Found: C, 62·1; H, 7·4; P, 20·0. $C_8H_7O_2P$ requires C, 62·4; H, 7·4; P, 20·0%).

S-*Benzyl Methyl-3-phenanthrylphosphinothiolate.*—*n*-Butyl-lithium in ether (48 ml.; 0·925M) was added at 6—20° to 3-iodophenanthrene [8] (12·2 g.) in ether (200 ml.). The temperature was then allowed to rise, and *NN*-diethylmethylphosphonochloridamidate (6·8 g.) in ether (50 ml.) added dropwise. The mixture was stirred for 2 hr., boiled for 10 min., and evaporated. The residue was boiled with concentrated hydrochloric acid (200 ml.) for 1½ hr., cooled, and continuously extracted with ether for 4 hr. The ether solution was dried ($MgSO_4$) the solvent removed, and the residue dissolved in benzene (100 ml.). The solution was heated for 6 hr. with an excess of thionyl chloride. After removal of the benzene and thionyl chloride under reduced pressure, a slight excess of toluene-ω-thiol and of pyridine was added. Ether (100 ml.) was next added and the mixture boiled for 2 hr., then poured into water (250 ml.). The ether layer was dried ($MgSO_4$) and fractionally distilled. The fraction of b. p. 136—142°/0·2 mm. solidified and recrystallised from ethanol, to give the *ester*, m. p. 69° (4·2 g.) (Found: C, 72·1; H, 5·41; S, 8·9; P, 8·01. $C_{22}H_{19}OSP$ requires C, 72·8; H, 5·23; S, 9·09; P, 8·54%). It formed a molecular complex, m. p. 195°, with 2 : 4 : 5 : 7-tetranitrofluorenone.

[16] Gilman, " Organic Reactions," Wiley, Vol. VIII, p. 286.

Resolution. The ester (4·2 g.) was added to the propionic acid resolving agent (5·2 g.) in glacial acetic acid (50 ml.). The dark yellow complex was filtered off and dried in a vacuum-desiccator, the filtrate being retained. The same procedure was then followed as described above for methyl α-naphthyl methylphosphonate. Recrystallisation from ethanol gave the active ester (2·0 g.), m. p. 67°, $[\alpha]_D^{20}$ +17° (*c* 1·7 in C_6H_6). Treatment of the acetic acid filtrate with aqueous sodium hydrogen carbonate solution yielded, after recrystallisation from ethanol, the lævorotatory ester (1·73 g.), m. p. 69·5°, $[\alpha]_D^{20}$ −13·1° (*c* 2·0 in C_6H_6).

Optical activity measurements were made on a Hilger microptic polarimeter, and the analyses carried out by The Chemistry Department of Imperial College, London.

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