ORGANIC AND BIOLOGICAL CHEMISTRY

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF KANSAS]

The Synthesis and Resolution of Compounds of Tetracovalent Phosphorus. I. Resolution of the Methiodide of Methyl Methyl-*p*-dimethylaminophenylphosphinate

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The methiodide III of methyl methyl-*p*-dimethylaminophenylphosphinate (II) was converted to a mixture of diastereoisomeric salts by reaction with silver D(−)-dibenzoylhydrogentartrate. Fractional recrystallization from methanol gave pure levorotatory methyl methyl-*p*-dimethylaminophenylphosphinate metho-D(−)-dibenzoylhydrogentartrate, which was converted to the levorotatory methiodide by metathesis with potassium iodide in ethanol solution. The dextrorotatory methyl methyl-*p*-dimethylaminophenylphosphinate metho-L(+)-dibenzoylhydrogentartrate and the dextrorotatory methiodide were prepared by an analogous sequence of reactions starting with II and silver L(+)-dibenzoylhydrogentartrate. This represents the first resolution of a racemic pair of phosphinic acid derivatives with the phosphorus atom as the sole asymmetric center.

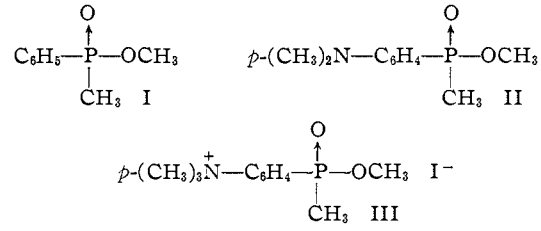
As part of a broad study of the synthesis and resolution of organophosphorus compounds containing an asymmetric phosphorus atom bonded to four fundamentally different groups, the first resolution of a derivative of phosphinic acid is herein reported. Although attempts at the resolution of asymmetric organophosphorus compounds have commanded the attention of a considerable number of chemists over the years, the successful or partially successful resolutions of only five organic compounds which owe their asymmetry to the phosphorus atom have heretofore been reported. These five represent three fundamentally different types of phosphorus compounds, namely, derivatives of phosphine oxide, of phosphine sulfide and of the phosphonium ion.

Meisenheimer and Lichtenstadt[1] obtained the enantiomorphs of methylethylphenylphosphine oxide as liquids *via* the *d*- and the *l*-bromocamphorsulfonates, and Meisenheimer and co-workers[2] achieved the resolution of methylphenylbenzylphosphine oxide *via* the *d*- and the *l*-camphorsulfonates. Salt formation with the resolving acid was, in each case, dependent upon the basicity of the coördinated oxygen atom, and in all cases seed crystals of the diastereoisomers were obtained only after months or years of standing.

Davies and Mann[3] succeeded in resolving phenyl-*p*-(carboxymethoxy)-phenyl-*n*-butylphosphine sulfide *via* the L(−)-α-phenylethylammonium salt, but were unable to obtain either enantiomorph in crystalline form. Holliman and Mann,[4] proceeding through the *d*-camphorsulfonate, were on one occasion able to isolate pure, crystalline dextrorotatory 2-phenyl-2-*p*-hydroxyphenyl-1,2,3,4-tetrahydroisophosphinolinium bromide, but they were later unable to repeat their initial success. Very recently Hart and Mann[5] accomplished the resolution of P-spiro-bis-1,2,3,4-tetrahydrophosphinolinium iodide into its dextro- and levorotatory isomers *via* the *d,l*-phosphonium *l*-menthoxyacetate. Kamai and Khismatullina[6] were able to effect some concentration of one of the diastereoisomers of allylbenzylbutylphenylphosphonium *d*-bromocamphorsulfonate.

Most of the numerous failures in the resolution of organic compounds containing an asymmetric phosphorus atom reported in the literature, are attributed either to failure of the compounds to form crystalline salts with the resolving agents or to the formation of diastereo compounds, less soluble than either of the diastereoisomers.

In the present study, repeated attempts to obtain crystalline salts of methyl methylphenylphosphinate (I) with the common resolving acids such as D(−)-tartaric, L(−)-malic, *d*-camphoric and *d*-camphorsulfonic acids in a wide variety of inert solvents were unsuccessful. This suggested that the successful resolution of a derivative of phosphinic acid might best be accomplished on a compound in which one of the groups attached to the asymmetric phosphorus atom incorporates an ionic center. Accordingly, the synthesis of the methiodide (III) of methyl methyl-*p*-dimethylaminophenylphosphinate (II) was undertaken



Reaction of *p*-dimethylaminophenyldichlorophosphine (IV) with sodium methoxide afforded a mixture of the isomers dimethyl *p*-dimethylaminophenylphosphonite (V) and II. Use of a catalytic amount of methyl iodide brought about typical Michaelis–Arbuzov rearrangement of V to II, which was converted to the crystalline methiodide III by the addition of excess methyl iodide. For purposes of resolution, III was converted by treatment with silver D(−)-dibenzoylhydrogentartrate into the crystalline metho-D(−)-dibenzoylhydro-

(1) J. Meisenheimer and L. Lichtenstadt, *Ber.*, **44**, 356 (1911).

(2) J. Meisenheimer, J. Casper, M. Horning and W. Lanter, *Ann.*, **449**, 2136 (1926).

(3) W. C. Davies and F. G. Mann, *J. Chem. Soc.*, 276 (1944).

(4) F. G. Holliman and F. G. Mann, *ibid.*, 1634 (1947).

(5) F. A. Hart and F. G. Mann, *ibid.*, 4107 (1955).

(6) G. Kamai and L. Khismatullina, *Doklady Akad. Nauk S.S.S.R.*, **92**, 69 (1951).

gentartrate of II, m.p. 116–119° dec., $[\alpha]^{25}D$ −78°.

p-$(CH_3)_2N—C_6H_4PCl_2$ (IV) p-$(CH_3)_2N—C_6H_4—P(OCH_3)_2$ (V)

Seven successive recrystallizations from methanol afforded a pure diastereoisomer of m.p. 139.2° dec., $[\alpha]^{25}D$ −89°. Metathetic reaction with potassium iodide in ethanol gave the levorotatory enantiomorph of the methiodide III of methyl methyl-p-dimethylaminophenylphosphinate (II), m.p. 155.8–156.4°, $[\alpha]^{25}D$ −29.0°. Treatment of the pure metho-D(−)-dibenzoylhydrogentartrate of II with a molar quantity of picric acid in boiling methanol yielded the levorotatory methopicrate of II, m.p. 170.5–171.5°, $[\alpha]^{25}D$ −22°.

Attempts to isolate the more soluble diastereoisomeric metho-D(−)-dibenzoylhydrogentartrate of II from the various mother liquors were unsuccessful. The dextrorotatory enantiomorph of the methiodide III was, however, obtained by a repetition of the resolution procedure with silver L(+)-dibenzoylhydrogentartrate as the resolving agent. A mixture of diastereoisomeric L(+)-dibenzoylhydrogentartrate salts, m.p. 101–105° dec., $[\alpha]^{25}D$ +81°, was obtained by reaction of III with the silver salt of the acid. Seven recrystallizations from methanol yielded a pure diastereoisomer, m.p. 139.2° dec., $[\alpha]^{25}D$ +88°. This underwent metathesis with potassium iodide in ethanol to give the pure dextrorotatory methiodide III of II, m.p. 155.6–156.4° dec., $[\alpha]^{25}D$ +28°. Treatment of the pure diastereoisomer with picric acid in boiling methanol afforded the dextrorotatory methopicrate of II, m.p. 170.5–171.5°, $[\alpha]^{25}D$ +22°.

The racemic methiodide III, the two enantiomorphic methiodides and the corresponding methopicrates are being tested for pharmacological activity by Dr. Duane G. Wenzel of the School of Pharmacy, University of Kansas.

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Experimental[7]

Phenyldichlorophosphine.—Prepared in 23% yield by Friedel–Crafts reaction of benzene and phosphorus trichloride according to the method of Michaelis[8] as modified by Dye,[9] the product distilled at 109° (23 mm.), reported[6] 220–222° (1 atm.).

Dimethyl Phenylphosphonite.—Reaction of phenyldichlorophosphine with a 2 molar quantity of methanol in ether in the presence of dimethylaniline by the method of Arbuzov and Razumov[10] afforded a mixture, dimethyl phenylphosphonite, b.p. 105–108° (22 mm.),[11a] in 28% yield and methyl methylphenylphosphinate (I), b.p. 147–148° (22 mm.),[11b] in 44% yield.

Methyl Methylphenylphosphinate (I).—Methyl iodide-catalyzed isomerization of dimethylphenylphosphonite to I, b.p. 147° (22 mm.), by the method of Arbuzov and Razumov[10] proceeded in 67% yield.

Attempted Resolution of I.—Solutions of I with equivalent quantities of D(−)-tartaric acid, L(−)-malic acid, d-camphoric acid and of d-camphorsulfonic acid in such solvents as methanol, acetone, benzene, ethyl acetate and dioxane were stored in an ice-chest for periods of several months. In the cases of the dibasic acids, both one and two equivalents of I were used. No crystalline diastereoisomers were formed. The fact that d-camphorsulfonic acid, which is itself only slightly soluble in benzene, dissolved readily upon the addition of an equivalent amount of I, suggested that the salt of d-camphorsulfonic acid with I may well exist in benzene solution. All attempts to obtain the salt in crystalline form were, however, unsuccessful.

p-Dimethylaminophenyldichlorophosphine (IV).—Prepared in 20% yield by Friedel–Crafts reaction of dimethylaniline with phosphorus trichloride according to Michaelis and Schenk,[12] IV melted at 64.0–65.1°, reported[12] 66°.

Dimethyl p-Dimethylaminophenylphosphonite (V).—A solution of 98.3 g. (0.444 mole) of IV in 200 ml. of dry benzene was added dropwise with stirring under a nitrogen atmosphere to an ice-cold solution of sodium methoxide prepared by addition of 20.4 g. (0.888 mole) of sodium to 400 ml. of methanol. The resulting mixture was stirred for 1 hr. and the suspended sodium chloride was then removed by filtration and the solvents by distillation. Fractional distillation of the oily residue afforded 43.7 g. (46% of the theoretical) of V, b.p. 112–114° (0.35 mm.), and 23.5 g. (25% of the theoretical) of II, b.p. 159–163° (0.35 mm.), m.p. 64–72°. Fractional distillation of the first fraction through a packed column gave pure V, b.p. 119–120° (0.8 mm.).

Anal. Calcd. for $C_{10}H_{16}NO_2P$: C, 56.3; H, 7.6; N, 6.6; P, 14.5. Found: C, 56.1; H, 7.5; N, 6.6; P, 14.8.

Recrystallization of the second fraction from anhydrous ether gave pure II, m.p. 81.0–82.2°.

Anal. Calcd. for $C_{10}H_{16}NO_2P$: C, 56.3; H, 7.6; N, 6.6; P, 14.5. Found: C, 56.5; H, 7.5; N, 6.9; P, 14.5.

Methyl Methyl-p-dimethylaminophenylphosphinate (II).—A solution containing 35.6 g. (0.167 mole) of V and 1 ml. of methyl iodide in 100 ml. of dry benzene was heated to reflux on a steam-bath with caution. Refluxing was continued for 1 hr., and the solution was then cooled and filtered. Distillation of the residue after removal of the benzene gave 29.4 g. (82.6% of the theoretical) of II, m.p. 81.0–82.2°.

Methiodide III of Methyl Methyl-p-dimethylaminophenylphosphinate (II).—Refluxing for 48 hr. of a solution of 25.6 g. (0.120 mole) of II and 25.0 g. (0.176 mole) of methyl iodide in 100 ml. of benzene afforded 40.3 g. (94.2%) of the crystalline methiodide III of II, m.p. 161.0° dec.

Anal. Calcd. for $C_{11}H_{19}INO_2P$: C, 37.2; H, 5.4; I, 35.7; N, 3.9; P, 8.7. Found: C, 37.1; H, 5.4; I, 35.4; N, 4.0; P, 8.7.

Methopicrate of Methyl Methyl-p-dimethylaminophenylphosphinate (II).—A solution of 1.0 g. (0.00282 mole) of III and 0.71 g. (0.00282 mole) of sodium picrate in 10 ml. of methanol was refluxed for 10 minutes. Cooling brought about crystallization of 0.700 g. (53.2% of the theoretical) of the methopicrate of II as yellow crystals, m.p. after one recrystallization from methanol 176.0–176.6°.

Anal. Calcd. for $C_{17}H_{21}N_4OP$: C, 44.7; H, 4.6; N, 12.3; P, 6.8. Found: C, 44.7; H, 4.9; N, 12.0; P, 7.0.

Silver D(−)-Hydrogentartrate.—A solution of 17.0 g. (0.100 mole) of silver nitrate in 100 ml. of water was added with vigorous stirring to a solution of 15.0 g. (0.100 mole) of tartaric acid in 44 ml. of 2.27 N (0.100 mole) ammonium hydroxide solution. The silver D(−)-hydrogentartrate, 16.0 g., which formed as a flocculent precipitate was filtered, washed with water and dried.

Attempted Isolation of the Metho-D(−)-hydrogentartrate of II.—A mixture of 5.00 g. (0.0141 mole) of methiodide of II, 3.60 g. (0.0141 mole) of silver D(−)-hydrogentartrate and 35 ml. of methanol was refluxed for 30 minutes. The precipitated silver iodide was removed by filtration and the mother liquor was concentrated to 15 ml. All attempts to induce crystallization by means of cooling, freezing and use of solvent pairs were unsuccessful.

D(−)-Dibenzoyltartaric Acid Monohydrate and L(+)-Dibenzoyltartaric Acid Monohydrate.—Both enantiomorphs were prepared from the corresponding tartaric acids by the

(7) All m.p.'s are corrected, all b.p.'s uncorrected. Analyses by Clark Microanalytical Laboratory, Urbana, Illinois.

(8) A. Michaelis, *Ann.*, **181**, 282 (1876).

(9) W. T. Dye, THIS JOURNAL, **70**, 2595 (1948).

(10) A. E. Arbuzov and A. I. Razumov, *Bull. acad. sci. U.R.S.S., Classe sci. chim.*, **1945**, 167.

(11) (a) Reported[11] 94.5° (13 mm.); (b) reported[10] 137.2–138.2° (13 mm.).

(12) A. Michaelis and A. Schenk, *Ber.*, **21**, 1497 (1888); *Ann.*, **260**, 1 (1890).

method of Butler and Cretcher.[13] The D-isomer, m.p. 88.0–89.8°, reported[13] 88–89°, $[\alpha]^{25}D$ −114.8°, reported[13] −116°, was obtained in 65% yield, and the L-isomer, m.p. 84.0–86.0°, reported[13] 85°, $[\alpha]^{25}D$ +109°, reported[13] +103°, in 92% yield.

Silver D(−)-Dibenzoylhydrogentartrate and Silver L(+)-Dibenzoylhydrogentartrate.—For the preparation of the D-isomer, 28.8 ml. (0.266 mole) of *N* ammonium hydroxide was added to a slurry of 10.0 g. (0.0266 mole) of D(−)-dibenzoyltartaric acid monohydrate in 300 ml. of distilled water. The mixture was heated at 85–90° until all the solid material had dissolved and was then cooled to 45°. A solution of 4.52 g. (0.0266 mole) of silver nitrate in 75 ml. of distilled water was added dropwise. Filtration and drying of the flocculent precipitate afforded 6.5 g. (51.3% of the theoretical) of silver D(−)-dibenzoylhydrogentartrate.

Silver L(+)-dibenzoylhydrogentartrate was similarly prepared in 55.6% yield from L(+)-dibenzoyltartaric acid.

The Levorotatory Methiodide of Methyl Methyl-*p*-dimethylaminophenylphosphinate (II).—Fifteen grams (0.0310 mole) of silver D(−)-dibenzoylhydrogentartrate was treated with 11.0 g. (0.0310 mole) of III in 30 ml. of boiling methanol. The theoretical quantity of silver iodide was filtered from the reaction mixture. After 14 hr. of cooling, 9.3 g. (0.0159 mole) of a mixture of the diastereoisomeric metho-D(−)-dibenzoylhydrogentartrates of methyl methyl-*p*-dimethylaminophenylphosphinate (II), m.p. 116–119° dec., $[\alpha]^{25}D$ −78° (*c* 1.08 in methanol), was obtained. Seven successive recrystallizations from methanol gave 0.95 g. of an optically pure diastereoisomer, m.p. 139.2° dec., $[\alpha]^{25}D$ −89° (*c* 0.490 in methanol), of the metho-D(−)-dibenzoylhydrogentartrate of II.

Anal. Calcd. for $C_{29}H_{32}NO_{10}P$: C, 59.48; H, 5.51; N, 2.39; P, 5.29. Found: C, 59.21; H, 5.48; N, 2.35; P, 5.24.

A solution of 0.880 g. (0.00150 mole) of the pure diastereoisomer in 5 ml. of boiling 95% ethanol was treated with 0.250 g. (0.00151 mole) of potassium iodide in 5 ml. of ethanol. A precipitate of 0.550 g. (0.00139 mole) of potassium D(−)-dibenzoylhydrogentartrate was removed by filtration and the hot mother liquor was diluted with 10 ml. of ether and the resulting solution stored in the ice-chest. Filtration gave 0.490 g. (0.0014 mole) of the impure methiodide, m.p. 144–148°. Four recrystallizations from absolute ethanol gave 0.170 g. of the pure levorotatory methiodide, m.p. 155.8–156.4°, $[\alpha]^{25}D$ −29° (*c* 1.70 in methanol), of methyl methyl-*p*-dimethylaminophenylphosphinate (II).

Anal. Calcd. for $C_{11}H_{19}O_2INP$: C, 37.19; H, 5.39; N, 3.94; P, 8.73; I, 35.73. Found: C, 37.43; H, 5.26; N, 3.87; P, 8.80; I, 36.03.

Levorotatory Methiopicrate of Methyl Methyl-*p*-dimethylaminophenylphosphinate (II).—Treatment of 0.30 g. of the pure diastereoisomer of the metho-D(−)-dibenzoylhydrogentartrate of II with 0.12 g. (0.0053 mole) of picric acid gave 0.16 g. (69% of the theoretical) of the levorotatory methiopicrate, m.p. 170.5–171.5°, $[\alpha]^{25}D$ −22° (*c* 0.873 in methanol) of II.

Anal. Calcd. for $C_{17}H_{21}N_4O_9P$: C, 44.7; H, 4.6; N, 12.3; P, 6.8. Found: C, 45.0; H, 4.6; N, 12.2; P, 6.9.

Dextrorotatory Methiodide of Methyl Methyl-*p*-dimethylaminophenylphosphinate (II).—A pure diastereoisomer, m.p. 139.2° dec., $[\alpha]^{25}D$ +88° (*c* 0.650 in methanol), of the metho-L(+)-dibenzoylhydrogentartrate of II was prepared and isolated by the exact procedure described for its enantiomorph, with L(+)-dibenzoyltartaric acid as the resolving acid. Seven recrystallizations from methanol starting with the mixture of diastereoisomers, m.p. 101–105° dec., $[\alpha]^{25}D$ +81° (*c* 1.05 in methanol), which crystallized from the reaction mixture, were required for isolation of the pure isomer.

Anal. Calcd. for $C_{29}H_{32}NO_{10}P$: C, 59.5; H, 5.5; N, 2.4; P, 5.3. Found: C, 59.2; H, 5.6; N, 2.4; P, 5.1.

Treatment of the pure diastereoisomer with potassium iodide by the exact procedure described for its enantiomorph afforded the dextrorotatory methiodide, m.p. 155.6–156.4°, $[\alpha]^{25}D$ +28° (*c* 1.92 in methanol), of methyl methyl-*p*-dimethylaminophenylphosphinate (II).

Anal. Calcd. for $C_{11}H_{19}INO_2P$: C, 37.2; H, 5.4; I, 35.7; N, 3.9; P, 8.7. Found: C, 37.4; H, 5.6; I, 35.8; N, 4.2; P, 8.6.

Dextrorotatory Methopicrate of Methyl Methyl-*p*-dimethylaminophenylphosphinate (II).—Treatment of the pure diastereoisomer of the metho-L(+)-dibenzoylhydrogentartrate of II according to the exact procedure described for its enantiomorph yielded the pure dextrorotatory methopicrate of II, m.p. 170.5–171.5°, $[\alpha]^{25}D$ +22° (*c* 0.843 in methanol) in 60% yield.

Anal. Calcd. for $C_{17}H_{21}N_4O_9P$: C, 44.7; H, 4.6; N, 12.3; P, 6.8. Found: C, 45.0; H, 4.3; N, 12.0; P, 6.8.

LAWRENCE, KANSAS

(13) C. L. Butler and L. H. Cretcher, THIS JOURNAL, **55**, 2605 (1933).

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The Synthesis and Resolution of Compounds of Tetracovalent Phosphorus. II. Resolution of the Methiodide of O-Phenyl-N-β-dimethylaminoethyl-P-phenylphosphonamidate

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Treatment of phenyl phenylphosphonochloridate (I) with β-dimethylaminoethylamine (VII) gave O-phenyl-N-β-dimethylaminoethyl-P-phenylphosphonamidate (V), which was isolated as the methiodide VI. The latter compound was converted to a mixture of diastereoisomeric salts by reaction with the silver salt of *d*-camphorsulfonic acid. Fractional crystallization from dioxane gave pure dextrorotatory O-phenyl-N-β-dimethylaminoethyl-P-phenylphosphonamidate metho-*d*-camphorsulfonate, which was converted to the levorotatory methiodide by a metathesis reaction with sodium iodide in acetone solution. The levorotatory O-phenyl-N-β-dimethylaminoethyl-P-phenylphosphonamidate metho-1-camphorsulfonate and dextrorotatory methiodide were prepared by an analogous sequence of reactions.

As a continuation of a study of the synthesis and resolution of organophosphorus compounds containing an asymmetric phosphorus atom bonded to four fundamentally different groups, the first resolution of a derivative of phosphonic acid is herein reported. The previous article[1] contained a description of the first resolution of a derivative of phosphinic acid, as well as a summary of earlier successful or partially successful resolutions of derivatives of phosphine oxide, phosphine sulfide and the phosphonium cation.

Phenyl phenylphosphonochloridate (I), prepared in 57–64% yield by reaction of phenylphosphonic dichloride (II) with phenol at an elevated temperature, proved to be a useful intermediate in the preparation of a variety of asymmetric

(1) D. M. Coyne, W. E. McEwen and C. A. VanderWerf, THIS JOURNAL, **78**, 3061 (1956).