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).

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

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

BY KENNETH L. MARSI, CALVIN A. VANDERWERF AND WILLIAM E. MCEWEN

RECEIVED FEBRUARY 3, 1956

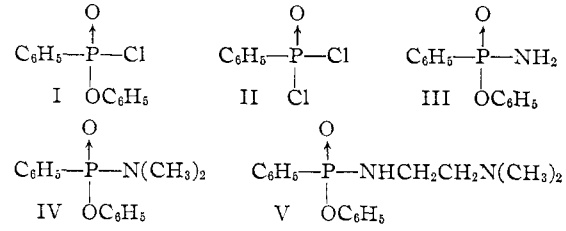
Treatment of phenyl phenylphosphonochloridate (I) with β-dimethylaminoethylamine (VII) gave O-phenyl-N-β-dimethylaminoethyl-P-phenylphosphonamidate (V), which was isolated as the methiodide VI. The latter compound was converted to a mixture of diastereoisomeric salts by reaction with the silver salt 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-l-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

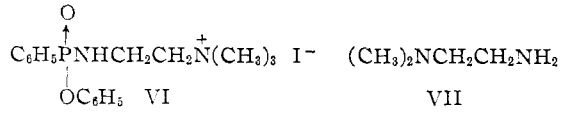
(1) D. M. Coyne, W. E. McEwen and C. A. VanderWerf, THIS JOURNAL, **78**, 3061 (1956).

organophosphorus compounds. From it were synthesized phenyl phenylphosphonamidate (III), O-phenyl-N,N-dimethyl-P-phenylphosphonamidate (IV) and O-phenyl-N-β-dimethylaminoethyl-P-phenylphosphonamidate (V).



Unsuccessful attempts were made to resolve compounds I, III and IV with the aid of a variety of optically active acids, such as *d*-camphorsulfonic acid, L(+)-dibenzoyltartaric acid, L(+)-tartaric acid, *d*-camphoric acid and L(−)-malic acid, in a variety of inert solvents. In no case was a crystalline salt obtained. Finally, it was decided that a successful resolution of a derivative of phenylphosphonic acid could best be effected if one of the groups bonded to the asymmetric phosphorus atom contained an ionic center. Therefore, attempts were made to synthesize the methiodide VI of O-phenyl-N-β-dimethylaminoethyl-P-phenylphosphonamidate (V).

The hydrochloride of V was prepared by reaction of equimolar amounts of β-dimethylaminoethylamine (VII) and phenyl phenylphosphonochloridate (I) in benzene solution. After neutralization of the hydrochloride and addition of methyl iodide to an ether solution of V, the methiodide VI was obtained in 58% yield.



The methiodide VI was first converted to the metho-L(+)-dibenzoylhydrogentartrate by reaction with silver dibenzoyl-L(+)-hydrogentartrate, but the salt proved to be too hygroscopic to permit convenient separation into diastereoisomers by fractional crystallization. Therefore, the methiodide VI was next converted to the metho-*d*-camphorsulfonate by treatment with silver *d*-camphorsulfonate. A crystalline salt was obtained which was subjected to fractional crystallization from acetone solution. After five successive recrystallizations a pure substance was obtained, m.p. 125.0–125.5°, $[\alpha]^{24}D$ + 20.51 ± 2.95°. However, after a metathesis reaction with sodium iodide in acetone solution, only the racemic methiodide was obtained. Exactly the same results were obtained in a second run. Evidently the compound of m.p. 125.0–125.5° is a diastereo compound, *d*-A *l*-B·*d*-A *d*-B. Davies and Mann[2] encountered the same difficulty in their attempt to separate the diastereoisomeric metho-*d*-camphorsulfonates of *p*-bromophenyl-*p*-dimethylaminophenylphenylphosphine sulfide.

A portion of the pure diastereo compound of m.p. 125.0–125.5° was digested with hot ethyl acetate, about half going into solution. The undissolved material was then recrystallized from anhydrous dioxane, giving material of m.p. 142.5–146.0°, $[\alpha]^{24}D$ + 16.00°. Further recrystallizations from dioxane gave material of m.p. 150.5–151.5°, $[\alpha]^{24}D$ +13.84 ± 2.52°.

A larger amount of the diastereo compound of m.p. 125.0–125.5° was dissolved in hot dioxane and the solution seeded with the pure diastereoisomer of m.p. 150.5–151.5°. After several additional recrystallizations of the first crop from dioxane, the pure diastereoisomer of m.p. 150.5–151.5° was obtained in fair quantity. As a result of a metathesis reaction with sodium iodide in acetone solution, the levorotatory enantiomorph of the methiodide VI of O-phenyl-N-β-dimethylaminoethyl-P-phenylphosphonamidate (V) was obtained, m.p. 160.0–160.8°, $[\alpha]^{24}D$ −6.42 ± 0.41°.

The resolution was successfully repeated in two additional runs. In these runs, the crude product resulting from the reaction of the racemic methiodide VI with silver *d*-camphorsulfonate was recrystallized directly from anhydrous dioxane.

Attempts to obtain the more soluble diastereoisomeric metho-*d*-camphorsulfonate of O-phenyl-N-β-dimethylaminoethyl-P-phenylphosphonamidate (V) from the various mother liquors were unsuccessful. Therefore, in order to obtain eventually the dextrorotatory form of VI, it was necessary to retrace the entire procedure, starting with the racemic methiodide VI and silver *l*-camphorsulfonate. Rewald's procedure,[3] with modifications, was used to obtain l-camphorsulfonic acid from racemic camphorsulfonic acid. Silver l-camphorsulfonate was prepared by treatment of the acid with silver oxide, and then the silver salt was caused to react with the racemic methiodide VI of O-phenyl-N-β-dimethylaminoethyl-P-phenylphosphonamidate (V) in acetone. The crystals obtained from the acetone solution gave evidence of partial separation of diastereoisomers, and, after several recrystallizations from dioxane, a moderately pure diastereoisomer was obtained, m.p. 150.5–151.0°, $[\alpha]^{24}D$ −13.33 ± 1.11° This was treated with sodium iodide in acetone in the usual manner, and the methiodide, after one recrystallization, had a m.p. of 160.0–160.5°, $[\alpha]^{24}D$ +4.44 ± 0.75°.

The racemic methiodide VI and the two enantiomorphs are being tested for pharmacological activity by Dr. Duane G. Wenzel, School of Pharmacy, University of Kansas. The results of these tests will be described elsewhere.

Acknowledgment.—This investigation was supported by a research grant, G-4215, from the National Institutes of Health, Public Health Service.

Experimental[4]

Phenylphosphonic Dichloride (II).—This compound, b.p. 108° (4 mm.), $n^{28}D$ 1.5570, was prepared by the method of Toy; reported b.p. 104° (4 mm.), $n^{25}D$ 1.5581.[5]

Phenyl Phenylphosphonochloridate (I).—A mixture of 293 g. (1.5 moles) of phenylphosphonic dichloride (II) and

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

(3) B. Rewald, *Ber.*, **42**, 3136 (1909).

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

(5) A. D. F. Toy, THIS JOURNAL, **70**, 186 (1948).

141 g. (1.5 moles) of freshly distilled phenol was heated at 150° for 24 hr., then distilled. After a forerun consisting of 66.1 g. (22.4%) of unreacted phenylphosphonic dichloride (II), b.p. 92–98° (0.3 mm.), phenyl phenylphosphonochloridate (I) distilled at 152–155° (0.3 mm.), $n^{31}D$ 1.5718, yield 223 g. (58.9%). This fraction was redistilled, and a central cut submitted for analysis.

Anal. Calcd. for $C_{12}H_{10}ClO_2P$: C, 57.1; H, 3.99; Cl, 14.0; P, 12.3. Found: C, 57.2; H, 3.99; Cl, 13.9; P, 12.5.

A residue was recovered from the still-pot and identified as diphenyl phenylphosphonate, yield 91.6 g. (19.7%). After recrystallization from 50% ethanol, this material melted at 74–75°, reported[6] m.p. 73–74°.

O-Phenyl-N,N-dimethyl-P-phenylphosphonamidate (IV).—A solution of 25.3 g. (0.1 mole) of phenyl phenylphosphonochloridate (I) in 200 ml. of anhydrous ether was placed in a three-necked flask fitted with a sealed stirrer, a thermometer, sodium carbonate drying tube and a delivery tube for introducing dimethylamine. The delivery tube dipped below the surface of the solution and was of sufficiently large diameter to prevent clogging by precipitated material. Dimethylamine was admitted slowly while the temperature of the solution was maintained at 15°. The reaction was stopped when dimethylamine began to be evolved in significant quantity from the sodium carbonate tube. The precipitated material was collected by filtration and washed with distilled water to rid it of dimethylamine hydrochloride. The dried precipitate amounted to 12.3 g. and was combined with 11.5 g. of solid obtained upon evaporation of the ether from the original filtrate. The crude O-phenyl-N,N-dimethyl-P-phenylphosphonamidate (23.8 g., 91.2%), m.p. 73.6–76.6°, was recrystallized several times from ethanol–ligroin, giving pure material of m.p. 74.2–75.8°.

Anal. Calcd. for $C_{14}H_{16}NO_2P$: C, 64.4; H, 6.17; N, 5.36; P, 11.9. Found: C, 64.4; H, 6.32; N, 5.10; P, 11.4.

After having stood in contact with air for about nine months, this compound was converted into one of m.p. 121.0–122.8°. The latter was found to be soluble in water, and its analysis also indicated it to be the dimethylammonium salt of phenylphenylphosphonic acid.

Anal. Calcd. for $C_{14}H_{18}NO_3P$: C, 60.4; H, 6.48; N, 5.07; P, 11.1. Found: C, 60.4; H, 6.32; N, 5.10; P, 11.4.

Phenyl Phenylphosphonamidate (III).—This compound was prepared in the same way as O-phenyl-N,N-dimethyl-P-phenylphosphonamidate (IV), with the exception that ammonia was used in place of dimethylamine. The compound, obtained in 44% yield, was recrystallized several times from benzene, m.p. 136.5–137.5°.

Anal. Calcd. for $C_{12}H_{12}O_2NP$: C, 61.8; H, 5.19; N, 6.00; P, 13.3. Found: C, 62.0; H, 5.01; N, 5.89; P, 13.4.

Attempted Resolution of Phenyl Phenylphosphonochloridate (I).—To 76 ml. of an ethyl acetate solution containing 3.631 g. (0.0156 mole) of *d*-camphorsulfonic acid was added 3.948 g. (0.0156 mole) of phenyl phenylphosphonochloridate. No formation of crystals occurred during a period of one year.

Attempted Resolution of O-Phenyl-N,N-dimethyl-P-phenylphosphonamidate (IV).—A mixture of 1.125 g. (0.0043 mole) of IV and 1.000 g. (0.0043 mole) of *d*-camphorsulfonic acid was dissolved in 50 ml. of ethyl acetate. After 3 days crystals appeared, and a week later the precipitate was collected (0.171 g.). After several recrystallizations from chloroform and ligroin, the material was found to melt at 162.5–163.0°, $[\alpha]^{28}D$ +29.74° (*c* 1.0 in chloroform). A mixture of this compound and authentic dimethylammonium *d*-camphorsulfonate (see below) melted undepressed. No diastereoisomeric salts of IV were obtained.

Attempted Resolution of Phenyl Phenylphosphonamidate (III).—To 0.50-g. (0.0021 mole) portions of III dissolved in 25 ml. of the solvent specified was added each of the following optically active acids in both equimolar and equivalent amounts: L(+)-dibenzoyltartaric acid, ethyl acetate; L(+)-tartaric acid, methanol; *d*-camphoric acid, ethyl acetate; L(−)-malic acid, ethyl acetate. In every case, the racemic amide III crystallized from solution after several days.

To a mixture of 0.50 g. (0.0021 mole) of III and 0.47 g. (0.0021 mole) of *d*-camphorsulfonic acid was added 250 ml. of ethyl acetate. After several days, 0.136 g. of crystals was collected. After four crystallizations from ligroin, the compound melted at 243–244° dec. Since it contained no phosphorus, it was thought to be ammonium *d*-camphorsulfonate.

Anal. Calcd. for $C_{10}H_{22}NO_3S$: S, 12.7. Found: S, 12.9.

The Methiodide VI of O-Phenyl-N-β-dimethylaminoethyl-P-phenylphosphonamidate (V).—To a solution of 25.3 g. (0.10 mole) of phenyl phenylphosphonochloridate (I) in 115 ml. of anhydrous benzene was added dropwise, with stirring, in the course of an hour, a solution of 8.82 g. (0.10 mole) of β-dimethylaminoethylamine (VII) in 50 ml. of anhydrous benzene. During the course of the reaction a yellow-orange liquid precipitated from the solution. After the amine had been added, the mixture was refluxed for 2 hr. with continued stirring and then allowed to cool. The supernatant benzene was decanted and the oily residue washed with two 50-ml. portions of anhydrous benzene. The oil was then treated with 100 ml. of 10% sodium bicarbonate solution at 0°. The milky suspension was stirred vigorously for several minutes and then extracted with ether in a continuous extractor for 60 hours. To the ether solution, previously dried over anhydrous sodium sulfate, was added 14.1 g. (0.10 mole) of methyl iodide. The ether solution was decanted from an oily material which had separated, and the oil was dissolved in 20 ml. of anhydrous acetone. The acetone solution deposited 13.48 g. (58%) of crude VI, m.p. 131.3–136.5°. The crystalline product was recrystallized once from ethanol–ethyl acetate and twice from *t*-butyl alcohol, m.p. 136–137°.

Anal. Calcd. for $C_{17}H_{24}IN_2O_2P$: C, 45.8; H, 5.42; I, 28.5; N, 6.28; P, 6.94. Found: C, 46.0; H, 5.48; I, 28.4; N, 5.90; P, 6.86.

Attempted Resolution of O-Phenyl-N-β-dimethylaminoethyl-P-phenylphosphonamidate (V) with *d*-Camphorsulfonic Acid.—The amine V was prepared in the same manner as described above. The ether extract, after having been dried over anhydrous sodium sulfate, was distilled to remove the solvent. To 7.38 g. (0.024 mole) of the residue, crude O-phenyl-N-β-dimethylaminoethyl-P-phenylphosphonamidate (V), a pale yellow oil, was added 5.65 g. (0.024 mole) of *d*-camphorsulfonic acid and 110 ml. of anhydrous ethyl acetate. No crystals appeared after several days of refrigeration, so 70 ml. of ethyl acetate was removed by distillation and 10 ml. of anhydrous ether was added to the residual solution. Eventually, 0.51 g. of crude dimethylammonium *d*-camphorsulfonate precipitated. This substance was twice recrystallized from ethanol, m.p. 162.5–163.0°, $[\alpha]^{21}D$ +17.88°.

Anal. Calcd. for $C_{12}H_{23}NO_4S$: C, 52.0; H, 8.36; N, 5.05; S, 11.6. Found: C, 52.7; H, 8.09; N, 4.98; S, 11.8.

No diastereoisomeric salts of V were obtained.

L(+)-Dibenzoyltartaric Acid.—This compound was prepared by the method of Butler and Cretcher.[7]

Silver L(+)-Dibenzoylhydrogentartrate.—This compound was prepared by the method of Coyne, McEwen and VanderWerf.[1]

Attempted Resolution of O-Phenyl-N-β-dimethylaminoethyl-P-phenylphosphonamidate (V) *via* its Metho-L(+)-dibenzoylhydrogentartrate Salt.—To 170 ml. of C.P. acetone was added a finely pulverized mixture of 4.77 g. (0.01 mole) of silver L(+)-dibenzoylhydrogentartrate and 4.46 g. (0.01 mole) of the methiodide, VI, of O-phenyl-N-β-dimethylaminoethyl-P-phenylphosphonamidate (V). The suspension was heated on the steam-bath for several minutes, filtered to remove silver iodide, the precipitate washed with 40 ml. of acetone and the wash solution added to the filtrate. A solid material separated from the solution when it was cooled in a Dry Ice–acetone-bath. The mother liquor was decanted, the precipitate dissolved in fresh acetone and then precipitated once again by being cooled in a Dry Ice–acetone-bath. This process was repeated three times. The resulting solid was extremely deliquescent and had to be

(6) Mueller, Dissertation, Stuttgart, 1944; G. M. Kosolapoff, "Organophosphorus Compounds," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 163.

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

dried in a vacuum desiccator immediately after separation from the acetone mother liquor. The dried product was a glass, yield 0.98 g., m.p. 65–71°, $[\alpha]^{25}D$ −42.44° (*c* 1.93 in absolute ethanol). Since the product had such undesirable physical properties, no attempt was made to separate diastereoisomers by fractional crystallization.

Silver *d*-Camphorsulfonate.—To a solution of 22.2 g. (0.129 mole) of silver nitrate in 40 ml. of distilled water was added a solution of 6.0 g. (0.15 mole) of sodium hydroxide in 60 ml. of water. The precipitate which formed was collected by filtration and washed several times with distilled water. The precipitate was then added to a solution of 28.0 g. (0.12 mole) of *d*-camphorsulfonic acid in 200 ml. of distilled water. The mixture was stirred for several minutes and unreacted silver oxide removed by filtration. The filtrate was concentrated to dryness, giving 32.0 g. (79%) of crude silver *d*-camphorsulfonate.

The *l*-Methiodide of O-Phenyl-N-β-dimethylaminoethyl-P-phenylphosphonamidate. Run 1.—To 20 ml. of C.P. acetone was added a finely pulverized mixture of 1.520 g. (0.0045 mole) of silver *d*-camphorsulfonate and 2.000 g. (0.0045 mole) of the *d,l*-methiodide of O-phenyl-N-β-dimethylaminoethyl-P-phenylphosphonamidate (V). The suspension was heated under reflux for 10 minutes, then filtered. The precipitate of silver iodide, after having been washed with acetone and dried, weighed 1.044 g. (95%). Crystals of the metho-*d*-camphorsulfonate of V appeared in the filtrate after several days; yield 1.920 g. (78%), m.p. 124–126°. After five recrystallizations from acetone there was obtained material of m.p. 125.0–125.5°, $[\alpha]^{24}D$ +20.51 ± 2.950 (*c* 1.36 in ethanol).

Anal. Calcd. for $C_{27}H_{39}N_2O_6PS$: C, 58.9; H, 7.14; N, 5.09; P, 5.63; S, 5.82. Found: C, 58.8; H, 6.92; N, 4.85; P, 5.66; S, 5.92.

Run 2.—A second run with 21.3 g. (0.0627 mole) of silver *d*-camphorsulfonate and 28.01 g. (0.0627 mole) of the *d,l*-methiodide of O-phenyl-N-β-dimethylaminoethyl-P-phenylphosphonamidate (V) gave a 72% yield of the product of m.p. 125.0–125.5°, $[\alpha]^{24}D$ +18.50 ± 1.55°.

Upon addition of 0.551 g. (0.001 mole) of this material to 10 ml. of a 0.1 *M* solution of sodium iodide in acetone, followed by heating, a precipitate of 0.25 g. (100%) of sodium *d*-camphorsulfonate formed and was collected by filtration. The filtrate, upon refrigeration, gave crystals of the *d,l*-methiodide VI of O-phenyl-N-β-dimethylaminoethyl-P-phenylphosphonamidate (V), m.p. 136–137°.

To 0.206 g. (0.00091 mole) of picric acid dissolved in 5 ml. of absolute ethanol was added 0.500 g. (0.00091 mole) of the *d*-camphorsulfonate of m.p. 125.0–125.5°. After several days there was obtained a precipitate of 0.045 g. of yellow crystals of trimethylammonium picrate, m.p. 215° dec., reported[8] m.p. 216° dec.

A suspension of 1.35 g. of the *d*-camphorsulfonate of m.p. 125.0–125.5° in 58 ml. of anhydrous ethyl acetate was refluxed for 5.5 hr. The insoluble material, 0.70 g., was collected by filtration and recrystallized from 10 ml. of anhydrous dioxane. There was obtained 0.23 g. of colorless crystals, m.p. 142.5–146.0°, $[\alpha]^{24}D$ +16.00°. After two more recrystallizations from anhydrous dioxane, pure material of m.p. 150.5–151.5°, $[\alpha]^{24}D$ +13.84 ± 2.52° (*c* 0.795 in ethanol) was obtained.

Anal. Calcd. for $C_{27}H_{39}N_2O_6PS$: C, 58.9; H, 7.14; N, 5.09; P, 5.63; S, 5.82. Found: C, 59.1; H, 7.30; N, 4.76; P, 5.60; S, 5.61.

To a solution of 5.21 g. of the *d*-camphorsulfonate of m.p. 125.0–125.5° in anhydrous dioxane was added a seed crystal of the pure diastereoisomer of m.p. 150.5–151.5°. The crop of crystals which came down was recrystallized six more times from dioxane, eventually giving 0.68 g. of the pure diastereoisomer of m.p. 150.5–151.5°, $[\alpha]^{24}D$ +13.84 ± 2.52°. A 0.455-g. portion of this material was added to 8.3 ml. of a 0.1 *M* solution of sodium iodide in acetone, and the mixture was refluxed for 10 minutes. A precipitate of 0.21 g. (92%) of sodium *d*-camphorsulfonate was collected by filtration. Upon refrigeration of the filtrate there was obtained 0.17 g. of the *l*-methiodide of O-phenyl-N-β-dimethylaminoethyl-P-phenylphosphonamidate, m.p. 158.5–159.2°, $[\alpha]D^{24}$ −7.40°. After three recrystallizations from acetone colorless crystalline material of m.p. 160.0–160.8°, $[\alpha]^{24}D$ −6.42 ± 0.41° (*c* 5.40 in ethanol), was obtained.

Anal. Calcd. for $C_{17}H_{24}IN_2O_2P$: C, 45.8; H, 5.42; I, 28.5; N, 6.28; P, 6.94. Found: C, 46.0; H, 5.34; I, 28.4; N, 6.09; P, 6.90.

Run 3.—In this run, a seed crystal of the pure diastereoisomer of m.p. 150.5–151.5° was added to the original acetone filtrate. The crop of crystals which resulted was recrystallized several times from anhydrous dioxane to give eventually a 23% yield of the pure diastereoisomer, m.p. 150.5–151.5°, $[\alpha]^{24}D$ +14.31 ± 1.11°.

Run 4.—This was carried out in the same manner as the above run, and the pure diastereoisomer was obtained in 24% yield.

***l*-Camphorsulfonic Acid.**—To a warm solution of 50.0 g. (0.215 mole) of *d,l*-camphorsulfonic acid in 500 ml. of distilled water was added 83.6 g. (0.215 mole) of *l*-brucine in small portions. After 24 hr. at room temperature the mixture was filtered, and 56.80 g. of precipitate was collected, $[\alpha]^{24}D$ −16.11° (*c* 5.40 in water). By a process of fractional crystallization, 12.51 g. of reasonably pure *l*-brucine *l*-camphorsulfonate was obtained as the more soluble fraction. The purification process could not be followed by m.p. determinations, since the salts had somewhat indefinite decomposition points. Therefore the determination of specific rotations served this purpose. The 12.51 g. of fairly pure *l*-brucine *l*-camphorsulfonate was found to have the specific rotation, $[\alpha]^{24}D$ −29.26°. The entire 12.51 g. of this material, dissolved in 195 ml. of warm distilled water, was treated with 3.25 g. (0.01 mole) of barium hydroxide octahydrate. A precipitate formed immediately, and the suspension was heated on a steam-bath for 2 hr. Filtration yielded 7.09 g. (90%) of *l*-brucine. The filtrate was treated with 20 ml. of 0.50 *M* sulfuric acid, the mixture filtered to remove barium sulfate and the filtrate evaporated to dryness on a steam-bath. The yellow-brown residue was extracted with four 24-ml. portions of hot, anhydrous benzene. The combined extract on refrigeration gave 3.35 g. of colorless crystals of *l*-camphorsulfonic acid, m.p. 197.4–198.0° dec., $[\alpha]^{24}D$ −18.52° (*c* 5.40 in water); reported m.p. 193–195°, $[\alpha]^{20}D$ −20.75° (*c* 3.716 in water).[8] An additional 0.37 g. of the same product was obtained on concentration of the benzene mother liquor.

Silver *l*-Camphorsulfonate.—This compound was prepared in 93% yield in the same manner reported above for silver *d*-camphorsulfonate.

The *d*-Methiodide of O-Phenyl-N-β-dimethylaminoethyl-P-phenylphosphonamidate.—The *l*-methocamphorsulfonate was prepared from silver *l*-camphorsulfonate and the *d,l*-methiodide of O-phenyl-N-β-dimethylaminoethyl-P-phenylphosphonamidate as described above for the *d*-methocamphorsulfonate. Colorless crystals were obtained from anhydrous dioxane, m.p. 150.5–151.0°, $[\alpha]^{24}D$ −13.33 ± 1.11° (*c* 5.40 in ethanol).

Anal. Calcd. for $C_{27}H_{39}N_2O_6PS$: C, 58.9; H, 7.14; N, 5.09; P, 5.63; S, 5.82. Found: C, 59.1; H, 7.01; N, 4.90; P, 5.80; S, 5.64.

The *l*-methocamphorsulfonate was subjected to a metathesis reaction with sodium iodide in acetone solution, and shiny leaflets of the *d*-methiodide were obtained from acetone, m.p. 160.0–160.5°, $[\alpha]^{24}D$ +4.44 ± 0.75° (*c* 5.40 in ethanol).

Anal. Calcd. for $C_{17}H_{24}IN_2O_2P$: C, 45.8; H, 5.42; I, 28.5; N, 6.28; P, 6.94. Found: C, 45.8; H, 5.66; I, 28.3; N, 6.30; P, 6.96.

LAWRENCE, KANSAS

(8) M. Delépine, *Compt. rend.*, **122**, 1272 (1896).