The solution was filtered and treated dropwise with piperidine (17.0 g., 0.2 mole), while maintaining the solution at room temperature. The mixture was dried at the waterpump, the residue taken up in water and the aqueous mixture suction filtered. The precipitate was recrystallized twice from isoöctane. The white crystalline product which resulted (10 g., 40% yield, m.p. 157–158°) proved by comparison of infrared spectra to be the expected monocyclic phosphoramide XXI.

Ethyl Bicyclic Phosphate (XXII).—A nearly saturated solution of ethyl bicyclic phosphite in isopropyl alcohol was prepared. The alcoholic solution was chilled and a 35% solution of alcoholic hydrogen peroxide (made from 90% H_2O_2 in isopropyl alcohol) was added dropwise with stirring until heat evolution ceased. The oxidation was extremely exothermic, requiring constant cooling during the addition of the peroxide. On cooling and standing a nearly quantitative yield of ethyl bicyclic phosphate precipitated, m.p. 202°.

Anal. Calcd. for $C_6H_{11}O_4P$: C, 40.52; H, 6.19; P, 17.48. Found: C, 40.51; H, 6.31; P, 17.42.

Methacryloxymethyl Bicyclic Phosphate.—Methacryloxymethyl bicyclic phosphite (11.6 g., 0.05 mole) was added to 25 ml. of isopropyl alcohol at room temperature. The phosphite did not dissolve completely in the alcohol. Hydrogen peroxide, 34%, was added dropwise to the alcoholic solution with stirring and cooling. An excess of peroxide was avoided by testing the alcoholic solution during the addition with KI in acetic acid. The solution was cooled in a Dry Ice–acetone-bath, filtered, and the product recrystallized from ethyl acetate. The product (10.5 g., 84% yield) polymerized on heating. Rapid melting showed the product to melt below 200°.

Anal. Calcd. for $C_9H_{13}O_6P$: C, 43.51; H, 5.24; P, 12.58. Found: C, 43.66; H, 5.49; P, 12.64.

Ethyl Bicyclic Phosphate (XXII) from Phosphorus Oxychloride.—To trimethylolpropane (134.2 g., 1.0 mole) was added dropwise phosphorus oxychloride (153.4 g., 1.0 mole), keeping the temperature below 30°. Stirring was initiated as soon as the reaction mixture became fluid. The mixture was stirred at room temperature and nitrogen gas passed over the solution in order to sweep out hydrogen chloride as it was formed. At the end of 16 hours, the temperature was gradually raised to 70° with the stirring and passage of nitrogen continuing.

The tan semi-crystalline mixture which resulted was taken up in hot water and the solution heated over a steam-bath for 1 hour. The solution was cooled and filtered, giving a 51% yield of light tan crystalline precipitate. The product was recrystallized from hot water, m.p. 202°. A mixed melting point with an authentic sample was undepressed.

Reaction of Ethyl Bicyclic Phosphite with Benzoyl Peroxide.—Ethyl bicyclic phosphite (16.2 g., 0.1 mole) and benzoyl peroxide (24.2 g., 0.1 mole) were dissolved in 100 ml. of anhydrous ether. After the solution had refluxed gently for 4 days, it was cooled and filtered giving 12.0 g. of white crystalline product. The precipitate was recrystallized twice from ethanol, m.p. 203–205° (67% yield). The infrared spectrum of this material was identical with the spectrum of ethyl bicyclic phosphate.

The filtrate was freed of solvent and the liquid residue distilled under reduced pressure giving 11.0 g. of benzoic anhydride, b.p. 144–145° (0.2 mm.), 50% yield, infrared spectrum identical with that of an authentic sample.

Reaction of Ethyl Bicyclic Phosphite with *n*-Octyl Mercaptan.—Ethyl bicyclic phosphite (32.4 g., 0.2 mole), was added to 29.2 g. (0.2 mole) of *n*-octyl mercaptan, azoisobutyronitrile (0.65 g., 2 mole %), was added and the solution heated gently with stirring to 100° where it was maintained for 1 hour. On cooling to room temperature the solution deposited white crystals of ethyl bicyclic thiophosphate, m.p. 176–178° (from alcohol), 20% yield.

Anal. Calcd. for $C_6H_{11}O_3SP$: C, 37.18; H, 5.67; S, 16.51; P, 15.98. Found: C, 37.20; H, 5.64; S, 16.32; P, 16.24.

The filtrate was distilled giving 11.0 g. (48% yield) of *n*-octane, b.p. 123–125°, $n^{25}D$ 1.3972.

[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION, U. S. ARMY CHEMICAL RESEARCH AND DEVELOPMENT LABORATORIES, ARMY CHEMICAL CENTER, MD.]

The Stereochemistry of Asymmetric Phosphorus Compounds. IV. The Synthesis and Stereochemistry of Displacement Reactions of Optically Active Isopropyl Methylphosphonochloridate

BY HERBERT S. AARON, ROY T. UYEDA, HAROLD F. FRACK AND JACOB I. MILLER

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The reaction of phosgene with (±)- or (−)-O-ethyl ethylphosphonothioic acid gives (±)-ethyl ethylphosphonochloridate. When the sodium salt of the (−)-acid is used, the (+)-chloridate is obtained. The (+)- and (−)-isopropyl methylphosphonochloridates have been similarly prepared. The stereochemical course of this reaction, which could not be varied whether run in hexane–phosgene, acetone–phosgene or dioxane–phosgene media, has been shown to proceed with inversion of configuration. Optically active dialkyl dialkylthionopyrophosphonates are formed as by-products. Displacement reactions of the (+)- and (−)-isopropyl methylphosphonochloridates which were carried out using hydrogen sulfide, *n*-propyl mercaptide and ethoxide ions in ethanolic solutions have been shown to occur with inversion of configuration.

The literature contains a number of reports[1] on the resolution of various types of compounds containing an asymmetric phosphorus atom, and, recently, reports[2] of investigations of the stereochemistry of the reactions of these materials have begun to appear.

Of the resolved compounds recently reported, the O-alkyl alkylphosphonothionic acids have been of interest to us for use as convenient starting materials for stereospecific synthetic routes to other resolved organophosphorus compounds.[3] Ac-

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(1) (a) D. M. Coyne, W. E. McEwen and C. A. VanderWerf, *J. Am. Chem. Soc.*, **78**, 3061 (1956) (the earlier literature is cited in this reference); (b) K. L. Marsi, C. A. VanderWerf and W. E. McEwen, *ibid.*, **78**, 3063 (1956); (c) K. F. Kumli, W. E. McEwen and C. A. VanderWerf, *ibid.*, **81**, 248 (1959); (d) G. Hilgetog and G. Lehmann, *J. prakt. Chem.*, **8**, 224 (1959); (e) G. Hilgetog and G. Lehmann, *ibid.*, **9**, 3 (1959); (f) M. Green and R. F. Hudson, *J. Chem. Soc.*, 3129 (1958); (g) M. Green and R. F. Hudson, *Proc. Chem. Soc.*, 145 (1961); (h) H. S. Aaron, T. M. Shryne and J. I. Miller, *J. Am. Chem. Soc.*, **80**, 107 (1958); (i) H. S. Aaron, J. Braun, T. M. Shryne, H. F. Frack, G. E. Smith, R. T. Uyeda and J. I. Miller, *ibid.*, **82**, 596 (1960); (j) I. G. M. Campbell and J. K. Way, *J. Chem. Soc.*, 5034 (1960); (k) I. G. M. Campbell and J. K. Way, *ibid.*, 2133 (1961); (l) L. Horner, H. Winkler, A. Rapp, A. Mentrup, H. Hoffmann and P. Beck, *Tetrahedron Letters*, **5**, 161 (1961).

(2) (a) K. F. Kumli, W. E. McEwen and C. A. VanderWerf, *J. Am. Chem. Soc.*, **81**, 3805 (1959); (b) A. Bladé-Font, C. A. VanderWerf and W. E. McEwen, *ibid.*, **82**, 2396 (1960); (c) A. Bladé-Font, W. E. McEwen and C. A. VanderWerf, *ibid.*, **82**, 2646 (1960); (d) C. B. Parisek, W. E. McEwen and C. A. VanderWerf, *ibid.*, **82**, 5503 (1960); (e) M. Green and R. F. Hudson, *Proc. Chem. Soc.*, 227 (1959); (g) J. Michalski and R. Ratajczak, *Chemistry & Industry*, 1241 (1960).

(3) H. S. Aaron, H. O. Michel, B. Witten and J. I. Miller, *J. Am. Chem. Soc.*, **80**, 456 (1958).

cordingly, the fact that phosgene is known[4] to be an excellent reagent for the facile conversion of phosphate and phosphonate esters into their corresponding chloridates led us to investigate the reaction of phosgene with some of the phosphonothioic acids and esters which were available in our laboratory. Apparently phosgene has not been reported[4a] as a chlorinating agent for thioörganic phosphorus compounds, although the reactions of chlorine,[2e,5] oxalyl chloride,[6] thionyl chloride[6] and sulfuryl chloride [2,5a,7] with such compounds have been described. Indeed, the reactions of sulfuryl chloride with resolved O-ethyl ethylphosphonothioic acid[7b] and with its S-alkyl esters[2g] have been reported in preliminary communications. The fact that optically active ethyl ethylphosphonochloridate was obtained from the latter reaction prompts us to report an alternate method by which both this and optically active isopropyl methylphosphonochloridate were prepared over four years ago in these laboratories. The isopropyl methylphosphonochloridate obtained was used to study the stereochemistry of anionic displacement reactions at the asymmetric phosphorus atom.

Results

The reaction of phosgene with O-ethyl S-methyl ethylphosphonothioate [Et(EtO)P(O)SMe] or ethyl methyl ethylphosphonothionate [Et(EtO)P(S)-OMe] only led to a recovery of the unreacted starting materials. Racemic O-ethyl ethylphosphonothioic acid [Et(EtO)P(S)OH], however, readily was converted into ethyl ethylphosphonochloridate [Et(EtO)P(O)Cl]; apparently none of the corresponding chloridothioate [Et(EtO)P(S)Cl] was formed. When the reaction was carried out using the resolved acid, the racemic chloridate was obtained. If optically active product had been produced, it had been racemized, apparently by the hydrogen chloride formed. Conditions under which the chloride would precipitate from the system as an insoluble by-product were then investigated. Using the sodium salts of racemic O-ethyl ethylphosphonothioic and O-isopropyl methylphosphonothioic acids, it was found that the chloridates could best be prepared by the gradual addition of small portions of the solid salt with vigorous stirring to a solution of phosgene in hexane, acetone or dioxane at −40 to −60°. A high-boiling by-product, apparently the dialkyl dialkylthionopyrophosphonate, *e.g.*, Et(EtO)P(S)O(O)P(OEt)Et, was also formed, undoubtedly from the reaction of the sodium salt with the chloridate product.

When the sodium salt of (−)-O-ethylethylphosphonothioic acid was treated with phosgene in hexane, (+)-ethyl ethylphosphonochloridate, α_D + 18.3° (1 dm.), was obtained. The rotation of this freshly distilled material was observed to decrease to +13.9° during 132 min. standing in a stoppered polarimeter tube. Although this reaction had been run under anhydrous conditions, the product had been transferred to the polarimeter tube without any special precautions. Therefore, to minimize the possible effect of hydrolysis and subsequent racemization due to formation of chloride ion upon exposure to atmospheric water vapor, any sampling or handling of chloridates obtained from subsequent syntheses was carried out in the dry-box. The rotations of products thus obtained were measured in chloroform, acetone or more often benzene solutions rather than on the neat materials. The half-life of the racemization of ethyl ethylphosphonochloridate was about 6 hr. in dry acetone and 4 days in dry benzene solution at room temperature. In the presence of chloride ion, an extremely rapid racemization was observed. Here, an acetone solution, 0.17 *M* in chloridate and 0.30 *M* in ammonium chloride, showed zero rotation when first examined within 5 min. of mixing. A measured rate of this racemization in the presence of trace amounts of chloride ion was not determined. Because of their configurational instability, the optically active chloridates were studied in subsequent reactions as soon after their synthesis as was practicably possible. On occasions when it became necessary to save a chloridate for later use, it was stored in the Dry Ice chest. Under these conditions, one sample was kept overnight without any loss in its optical activity; another sample, however, lost most of its activity when similarly stored over the weekend.

The sodium salt of resolved O-ethyl ethylphosphonothioic acid has been converted into ethyl ethylphosphonochloridate a total of eight times, that of resolved O-isopropyl methylphosphonothioic acid into isopropyl methylphosphonochloridate a total of eleven times in these laboratories. In every instance, an inversion in the sign of the rotation of the isolated product was observed, whether the reaction was run in a hexane–phosgene, acetone–phosgene or dioxane–phosgene medium. The specific rotations of these products, however, varied considerably. The specific rotations of the optically pure chloridates, therefore, remain in doubt. The fact that the conditions were varied somewhat in these runs may have resulted in a variation either in the degree of the stereospecificity of the reaction or in the stability of the optically active product once formed. The fact that there did not appear to be any obvious correlation between the reaction conditions used and the optical purity of the product obtained, however, suggests that these results might well be due to varying traces of water vapor which may have been introduced, in spite of the precautions taken to prevent this possibility.

Using the optically active isopropyl methylphosphonochloridate thus obtained, a series of displacement reactions were carried out and the results have been used to establish the stereochemistry of the conversion of the O-alkyl alkylphosphonothioic acids into their corresponding chloridates. The interrelationships and the probable relative configu-

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(4) (a) A. H. Ford-Moore, L. J. Lermit and C. Stratford, *J. Chem. Soc.*, 1777 (1953); (b) D. G. Coe, B. J. Perry and R. K. Brown, *ibid.*, 3604 (1957).

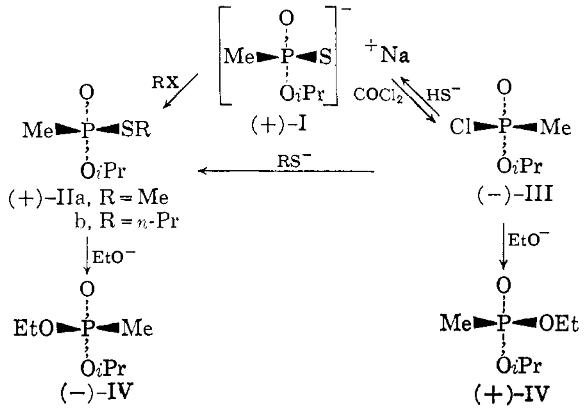
(4a) NOTE ADDED IN PROOF.—For a recent paper, however, see J. I. G. Cadogan, *J. Chem. Soc.*, 3067 (1961).

(5) (a) J. Michalski and A. Skowrvuska, *Chemistry & Industry*, 1199 (1958); (b) Ping-Fang H., Show-Chang L. and Wan-Yi C., *Hua Hsüeh Hsüeh Pao*, **22**, 49 (1956); *C. A.*, **52**, 6156 (1958); (c) C. J. M. Stirling, *J. Chem. Soc.*, 3597 (1957).

(6) Z. Pelchowicz, *ibid.*, 239 (1961).

(7) (a) C. Borecki, J. Michalski and S. Musierowicz, *ibid.*, 4081 (1958); (b) J. Michalski and A. Ratajczak, *Chemistry & Industry*, 539 (1959).

rations which have been established are summarized in the scheme



As indicated in this scheme, the sodium salt of (+)-O-isopropyl methylphosphonothioic acid (I) has been converted into (−)-isopropyl methylphosphonochloridate (III) by reaction with phosgene in various media, and into (+)-O-isopropyl S-methyl methylphosphonothioate (IIa) by reaction with methyl iodide in alcoholic solution. (−)-Isopropyl methylphosphonochloridate (III), in turn, has been converted back into (+)-O-isopropyl methylphosphonothioic acid (the acid corresponding to I) on treatment with sodium hydrogen sulfide, and into (+)-O-isopropyl S-propyl methylphosphonothioate (IIb) on treatment with sodium propyl mercaptide, both in ethanolic solution. The indicated relationship between (−)-isopropyl methylphosphonochloridate (III) and (+)-ethyl isopropyl methylphosphonate (IV) was established by conversion of the enantiomorphic (+)-III into (−)-IV with sodium ethoxide in ethanol. Finally, (+)-O-isopropyl S-methyl methylphosphonothioate (IIa) was converted into (−)-ethyl isopropyl methylphosphonate (IV) on treatment with sodium ethoxide in ethanol.

In addition to the reactions outlined above, the (+)- and (−)-isopropyl methylphosphonochloridates have been characterized by their reaction with aniline to give solid (−)- and (+)-phosphonamidate derivatives, respectively.

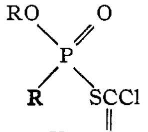
Discussion

Although the products obtained from the reactions of the optically active chloridate were considerably racemized, such racemization would not conceivably affect the validity of the conclusions made regarding the relative configurations of the optically active forms. That the mechanism of hydrolysis of phosphonochloridates appears to be bimolecular[8] suggests that the racemization obtained in these products is due to the racemic content of the optically active chloridate, rather than to racemization which accompanies S_N1 type displacement reactions. Whether the observed racemization of the optically active chloridate can occur as a spontaneous phenomenon, perhaps resulting from internal return[9] of thermally generated $R(RO)P(O)^+Cl^-$ ion pairs, or whether a trace amount of hydrolysis resulting in free chloride ion must occur to initiate the racemization is uncertain and was not investigated.

The relative configurations of the compounds depicted in the preceding scheme have been deduced as follows: The fact that (+)-O-isopropyl S-methyl methylphosphonothioate (IIa) and (−)-isopropyl methylphosphonochloridate (III) may be converted by ethoxide into the opposite configurations of ethyl isopropyl methylphosphonate (IV) proves that (+)-IIa and (−)-III are themselves of opposite configuration. This proof is independent of the steric course (*i.e.*, inversion or retention) by which the leaving groups (mercaptide and chloride ion, respectively) are displaced by the ethoxide ion, but it does depend upon the reasonable assumption that the same steric course is followed in both cases. That IIa and IIb of the same sign are also of the same configuration was established by the synthesis of the two (−)-esters from the sodium salt of (−)-O-isopropylmethylphosphonothioic acid (I) under conditions which give exclusively the S-alkylated product.[10]

Being of opposite configuration, therefore, the conversion of (−)-III into (+)-IIb must take place with inversion of configuration. Furthermore, based upon the reasonable assumption that the displacements of chloride from (−)-III by ethoxide and by mercaptide follow the same steric course, the conversion of (−)-III into (+)-IV hence also that of (+)-IIa into (−)-IV must take place with inversion of configuration. Moreover, since the sodium salt of (+)-O-isopropyl methylphosphonothioic acid (I) and its corresponding (+)-S-propyl ester (IIb) are of the same configuration (no bonds around the phosphorus atom being broken in the preparation of (+)-IIb from (+)-I), and since (+)-IIb and (−)-III have been shown to be of opposite configuration, therefore (+)-I and (−)-III must also be of opposite configuration. From the preceding analogies, the reaction of III with hydrogen sulfide in ethanol would be expected to occur with inversion of configuration. Indeed, as indicated above, (+)-I was reobtained when (−)-III was treated in this manner.

Stereochemistry of the Phosgene Reaction.—The reaction of phosgene with the sodium salt of an O-alkyl alkylphosphonothioic acid could give rise to two possible *a priori* intermediates



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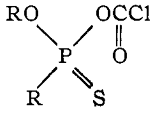

VI

The fact that phosphonochloridate III is formed to the apparent exclusion of any phosphonochloridothioate suggests that V is the intermediate formed. However, the fact that acetylation of phosphonothioic acids with acetyl chloride gives exclusively the O-acetylated product,[10] and phosphorylation of phosphorothioic acids gives exclusively the O-phosphorylated product,[11] leads one to

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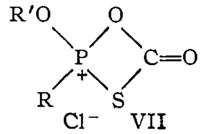
(8) R. F. Hudson and L. Keay, *J. Chem. Soc.*, 1865 (1960).

(9) S. Winstein and K. C. Schreiber, *J. Am. Chem. Soc.*, **74**, 2165 (1952).

(10) M. I. Kabachnik, *et al.*, *Zhur. Obshch. Khim.*, **26**, 2228 (1956); *C. A.*, **51**, 1823*f* (1957).

(11) R. A. McIvor, G. D. McCarthy and G. A. Grant, *Can. J. Chem.*, **34**, 1819 (1956).

expect that phosgene, by analogy, should give rise to VI as a first intermediate in the above reaction. If indeed VI is formed, then it would have to rearrange into a second intermediate in order to give the observed product. Since the acetylated and phosphorylated products did not rearrange into their corresponding thiolo isomers, it is not likely that VI, if formed, would give rise to chloridate III by first rearranging into V in this system. The rearrangement of VI into the four-membered cyclic intermediate VII is suggested, therefore, if one should be forced to reconcile the observed product with an O-acylation course for the phosgene reaction. A not too dissimilar four-membered ring has



VII

been postulated[12] in the Schönberg rearrangement of diaryl thioncarbonates under much more drastic conditions, but with a much less labile system.

The relative configurations established by means of the displacement reactions discussed above prove that the reaction of phosgene with the O-alkyl alkylphosphonothioic acid sodium salts occurs with over-all inversion of configuration. In contrast to the results obtained from the decomposition of chlorocarbonate[13] and chlorosulfite[14] intermediates, this inversion could not be altered whether the reaction was run in hexane–phosgene, acetone–phosgene or dioxane–phosgene media. These results are compatible either with the collapse of a cyclic intermediate VII to form III, or with a backsided attack of (presumably) a phosgene molecule on V. Although these results do not permit us to choose between paths which lead through V or VI → VII, they do rule out any S_Ni reaction of the possible intermediate V, since such a reaction would lead to retention of configuration.

Experimental

Sodium Salts of the O-Alkylphosphonothioic Acids (*e.g.*, I).—These salts were obtained as deliquescent solids in 85–90% yields by mixing a freshly prepared solution of sodium in methanol with an equivalent quantity of the acid in a little methanol, then removing the solvent under reduced pressure at room temperature. The salt cake residue was broken up under ether, filtered and dried in a vacuum desiccator over phosphorus pentoxide. The sodium salt thus obtained from (±)-O-ethylethylphosphonothioic acid[15] had m.p. 188–190° (reported[10] 185–186°); that from the (−)-isomer[1h] had m.p. 145–147°, $[\alpha]^{30}\text{D}$ − 9.5 ± 0.1° (0.1 *N* aqueous sodium hydroxide, *c* 2.5). The sodium salt of (±)-O-isopropyl methylphosphonothioic acid[15] had m.p. 275–278°; that of the (−)-isomer,[11] m.p. 195–197°; that of the (+)-isomer[1i] I, m.p. 194–197°, $[\alpha]^{26.5}\text{D}$ + 11.5 ± 0.4° (0.1 *N* aqueous sodium hydroxide, *c* 3.7). The (+)- and (−)-O-isopropyl methylphosphonothioic acid sodium salts were readily soluble in acetone or dioxane, while the (±)-acid sodium salt was not soluble in these media.

(±)-Ethyl Ethylphosphonochloridate from (±)-O-Ethyl Ethylphosphonothioic Acid.—Phosgene was bubbled through (±)-O-ethyl ethylphosphonothioic acid (5.0 g., 0.032 mole) for 5 hr. under anhydrous conditions at 10 to 20°. The mixture was allowed to stand overnight at room temperature, then degassed at 200 mm. at room temperature. The residue was distilled to give 3.8 g. (0.024 mole, 75%) of (±)-ethyl ethylphosphonochloridate, b.p. 49–50° (3 mm.), $n^{26}\text{D}$ 1.4347 (reported[16] $n^{25}\text{D}$ 1.4345; reported[17] for Et(EtO)P(S)Cl, $n^{25}\text{D}$ 1.4911).

Anal. Calcd. for $C_4H_{10}ClO_2P$: C, 30.69; H, 6.44. Found: C, 30.5; H, 6.45.

(+)-Ethyl Ethylphosphonochloridate.—This material was prepared in about 50% yield from the sodium salt of (−)-O-ethyl ethylphosphonothioic acid at −55 to −60° according to the procedure described below for (−)-III from a hexane medium. One of the highest specific rotations recorded for this product was $[\alpha]\text{D}$ + 37.0° (acetone, *c* 1.4). Another sample had $[\alpha]^{27}\text{D}$ + 39.0° (chloroform, *c* 3.9) and + 31.5° (benzene, *c* 3.3), but was not measured in acetone solution.

(+)-Diethyl diethylthionopyrophosphonate was obtained as probably impure (based on the analysis) high boiling residue after the distillation of the (+)-ethyl ethylphosphonochloridate; recovery: 0.6 g. (15% yield), b.p. 94° (0.13 mm.), αD + 38.7° (1 dm.), decreasing to +37.7° after standing 3 days in the polarimeter tube.

Anal. Calcd. for $C_8H_{20}O_4P_2S$: C, 35.0; H, 7.35; P, 22.6; S, 11.7; hydrolytic equiv. wt., 137. Found: C, 34.4; H, 7.8; P, 21.1; S, 13.0; equiv. wt., 143.

The (±)-diethyl diethylthionopyrophosphonate was obtained as the only product after phosgene was passed through a hexane (25 ml.) suspension of the sodium salt obtained from 5 g. (0.03 mole) of (±)-O-ethyl ethylphosphonothioic acid at 10–15° for 6 hr.; recovery: 3.8 g. (0.014 mole, 93%), b.p. 97–99.5° (0.15 mm.), $n^{25}\text{D}$ 1.4601 (reported[4b] 1.4652).

Anal. Calcd. for $C_8H_{20}O_4P_2S$: C, 35.0, H, 7.35; P, 22.6; S, 11.7. Found: C, 35.7; H, 7.6; P, 21.1; S, 13.0.

(−)-Isopropyl Methylphosphonochloridate (III) from a Hexane Medium.—Phosgene was collected in hexane (25 ml.) at −40° in a flask equipped with a drying tube and a magnetic stirrer, until a total volume of 50 ml. was obtained. The sodium salt of (+)-O-isopropyl methylphosphonothioic acid (I), 4.8 g. (0.027 mole), was added in small portions with stirring by means of an enclosed solid addition funnel. The rate of the addition was controlled by raising and lowering a glass plunger which ran down to the base of the funnel, and was connected through a glass sleeve at its top by means of a piece of flexible rubber tubing. After the addition, which required about 2 hr., the mixture was allowed to stir an additional 2 hr. at −40 to −60°, then allowed to warm to room temperature. (Alternately, the mixture could be stored overnight in the Dry Ice chest before being worked up, with no apparent effect.) The mixture was degassed at 200 mm. at room temperature for about 30 min., and the hexane and chloridate product were removed from the sodium chloride (and thionopyrophosphonate by-product) by evaporating at 0.1 mm. and room temperature. (Alternately, the sodium chloride could be removed by filtration in the dry-box with good results.) The hexane was removed under reduced pressure at room temperature and the residue was distilled to give (−)-III, 1.8 g. (0.012 mole, 44%), b.p. 37° (1.2 mm.), $n^{25}\text{D}$ 1.4281 (reported[18] 1.4282); reported[17] for Me(iPrO)P(S)Cl, 1.4821), $[\alpha]\text{D}$ − 35.6° (benzene, *c* 2.7).

Anal. Calcd. for $C_4H_{10}ClO_2P$: C, 30.7; H, 6.4. Found: C, 30.3; H, 6.4.

Product of the highest recorded rotation, $[\alpha]^{27}\text{D}$ −52.3° (benzene, *c* 2.8), was obtained in 54% yield in another run according to this procedure.

(−)- and (+)-III from an Acetone Medium.—The (+)-sodium salt (I), 5.4 g. (0.031 mole), in 25 ml. of acetone (previously distilled from phosphorus pentoxide, then from a mixture of Drierite and anhydrous potassium carbonate) was added dropwise with stirring to 50 ml. of acetone–phosgene (4:1) at −40° during 3 hr., then worked up as described above for the first preparation of (−)-III to give 1.5 g. (31%), b.p. 35–37° (1.5 mm.), $[\alpha]^{25}\text{D}$ −49.2° (ben-

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[12] D. H. Powers and D. S. Tarbell, *J. Am. Chem. Soc.*, **78**, 70 (1956).

[13] K. B. Wilberg and T. M. Shryne, *ibid.*, **77**, 2774 (1955).

[14] C. E. Boozer and E. S. Lewis, *ibid.*, **75**, 3182 (1953).

[15] F. W. Hoffmann, B. Kagan and J. H. Canfield, *ibid.*, **81**, 148 1959).

[16] F. W. Hoffmann, T. C. Simmons and L. J. Gluntz III, *ibid.*, **79**, 3570 (1957).

[17] F. W. Hoffmann, D. H. Wadsworth and H. D. Weiss, *ibid.*, **80**, 3945 (1958).

[18] P. J. R. Bryant, A. H. Ford-Moore, B. J. Perry, A. W. H. Wardrop and T. F. Watkins, *J. Chem. Soc.*, 1553 (1960).

zene, *c* 4.4). Similarly, 2.6 g. of (−)-I in 10 ml. dry acetone added to 50 ml. of acetone–phosgene (9:1) during 6 hr., then stored in the Dry Ice chest overnight gave 0.63 g. of (+)-III, b.p. 48–49° (3.5 mm.), n^{25}D 1.4289, $[\alpha]^{31}$D + 31.4° (benzene, *c* 2.2).

(+)-III **from a Dioxane Medium.**—Compound (−)-I (3.5 g., 0.020 mole) in 50 ml. of dioxane (freshly distilled over sodium) was added dropwise to 60 ml. of dioxane–phosgene (35:25) at −40° during 2 hr., then stored overnight in the Dry Ice chest. The mixture was degassed at 125 mm., then filtered in the dry-box to remove the sodium chloride. The dioxane was distilled at 27–29° (16 mm.), and the product (containing some dioxane) then was evaporated from thionopyrophosphonate residue at 0.2 mm. and a bath temperature of 57°. The unweighed distillate, diluted to 50 ml. with fresh dioxane, had α^{25}D +8.6° (2 dm.). That III is thus obtained was shown in a preliminary experiment in which 5 g. of (±)-I was added to 70 ml. of phosgene–dioxane (1:1) at −30 to −25° during 6 hr., then worked up as described above to give (±)-III, 1.0 g. (23%), b.p. 40–41° (1.3 mm.), n^{25}D 1.4275. An estimated 1 g. of thionopyrophosphonate residue remained after the distillation.

(+)-**Diisopropyl dimethylthionopyrophosphonate** was presumed to be the high boiling residue obtained from the synthesis of III and was not usually isolated. One such residue obtained from the preparation of (+)-III was distilled to give (probably impure) product, b.p. 82–85° (0.2 mm.), n^{25}D 1.4559 (reported[4b] 1.4616), $[\alpha]$D + 30.7° (benzene, *c* 5.4).

The addition of (±)-sodium salt (I) to phosgene–hexane at room temperature gave the pure (±)-thionopyrophosphonate product, b.p. 79–80° (0.25 mm.), n^{25}D 1.4602, hydrolytic equiv. wt. 139, 140 (theory, 137).

Anal. Calcd. for $C_8H_{20}O_4P_2S$: C, 35.0; H, 7.4; S, 11.7. Found: C, 35.2; H, 7.2; S, 12.1.

(+)-, (−)- **and** (±)-O-**Isopropyl N-Phenyl Methylphosphonoamidates.**—A solution of (+)-III, 0.2 g. in 5 ml. of benzene, $[\alpha]$D +52.8°, was added dropwise to an ice-cold mixture of 5 ml. of aniline and 2.5 ml. of benzene, then allowed to evaporate to dryness. The residue was extracted with two 25-ml. portions of boiling petroleum ether (30–60°), which were combined, filtered and concentrated to about 20 ml. On standing at room temperature, a crop of white needles (0.15 g.), m.p. 122–124°, $[\alpha]^{30}$D −116° (benzene, *c* 1.0), was obtained. Concentration of the filtrate gave a mixture of (−)- and (±)-product, m.p. 100–108°.

Similarly from (−)-III, 0.13 g. in 5 ml. of benzene, $[\alpha]$D −35.6°, and 1 ml. of aniline in 4 ml. of benzene there was obtained the (+)-phosphonamidate, 0.03 g., m.p. 120–122° (121–122° on recrystallization from petroleum ether), $[\alpha]^{26}$D + 115° (benzene, *c* 4.6).

The (±)-product, similarly prepared from (±)-III, had m.p. 95–98° on recrystallization from petroleum ether (reported[18] 90–91°). A mixed melting point between the (+)- and (−)-phosphonamidates gave 95–98°.

Anal. Calcd. for $C_{10}H_{16}NO_2P$: C, 56.4; H, 7.5. Found (−)-isomer: C, 56.8; H, 7.4; (±)-racemate: C, 56.0; H, 7.4.

(−)-O-**Isopropyl S-Methyl Methylphosphonothioate** (IIa) **from** (−)-I.—(−)-Sodium salt I (5.0 g., 0.029 mole) prepared from acid of αD −12.94° (1 dm.), was dissolved in 40 ml. of methanol. Methyl iodide (5 ml.) was added and the solution refluxed for 5 hr., then concentrated by distillation on the steam-bath. The residual solvent was removed under reduced pressure at room temperature. The residue was taken up in ether, filtered to remove sodium iodide, concentrated and distilled to give 3.2 g. (0.019 mole, 66%) of (−)-IIa, b.p. 76° (4.5 mm.), n^{25}D 1.4705, $[\alpha]^{29}$D −83.5° (benzene, *c* 3.1), − 86.6° (ethanol, *c* 11.4).

Anal. Calcd. for $C_5H_{13}O_2PS$: C, 35.7; H, 7.8. Found: C, 35.4; H, 7.8.

(+)-O-**Isopropyl S-Methyl Methylphosphonothioate** (IIa) **from** (+)-I.—(+)-O-Isopropyl methylphosphonothioic acid[11] (5.0 g., 0.033 mole), $[\alpha]^{25}$D + 13.91° (1 dm.), was neutralized with 50 ml. of freshly prepared 0.66 *N* methanolic sodium methoxide, and an excess of methyl iodide (14 g., 0.1 mole) was added. The solution was refluxed for 5 hr., then worked up as described for (−)-IIa, above, to give 4.0 g. (0.024 mole, 73%) of (+)-IIa, b.p. 73–75° (4 mm.), n^{25}D 1.4712, α^{25}D + 114.4° (1 dm.), $[\alpha]^{28}$D + 87.8° (benzene, *c* 3.3), $[\alpha]^{26}$D + 91.4° (ethanol, *c* 14.8).

In a preliminary experiment, (±)-IIa, n^{25}D 1.4714, was similarly prepared in ethanol solution.

(−)-O-**Isopropyl S-Propyl Methylphosphonothioate** (**IIb**) **from** (−)-I.—(−)-O-Isopropyl methylphosphonothioic acid (3.0 g., 0.019 mole), αD −13.92° (1 dm.), was neutralized with a solution of 0.45 g. (0.019 mole) of sodium in 30 ml. of methanol. An excess of *n*-propyl iodide (10 g.) was added and the solution was refluxed for 5 hr., then worked up as described for (−)-IIa, above, to give 2.3 g. (0.012 mole, 63%) of (−)-IIb, b.p. 80° (2 mm.), n^{25}D 1.4661, αD −34.40 (0.5 dm.), $[\alpha]^{27}$D −50.3 (benzene, *c* 2.5).

(+)-O-**Isopropyl S-Propyl Methylphosphonothioate** (IIb) **from** (−)-III.—A solution of (−)-III (2.2 g., 0.014 mole), $[\alpha]$D −20.0° (benzene, *c* 2.1) (38% of maximum observed rotation of III), in 20 ml. of dry benzene was added dropwise with stirring to an ice-cold solution of sodium (0.7 g., 0.03 mole) in 16 ml. of absolute ethanol containing an excess (3 ml.) of *n*-propyl mercaptan. The solution was allowed to warm to room temperature, filtered to remove sodium chloride, concentrated and distilled to give (+)-IIb, b.p. 62–63° (0.75 mm.), in two fractions: 0.66 g. (0.0034 mole), n^{25}D 1.4666, $[\alpha]^{28}$D + 11.2 ± 0.1° (benzene, *c* 1.8) (22% optically pure), and 0.49 g. (0.0025 mole), n^{25}D 1.4674. A forerun of 0.11 g., n^{25}D 1.4641, also was obtained.

Anal. Calcd. for $C_7H_{17}O_2PS$: C, 42.8; H, 8.7. Found: C, 43.3; H, 8.5.

(+)-O-**Isopropyl Methylphosphonothioic Acid from** (−)-III.—A solution of (−)-III (1 g., 0.006 mole), $[\alpha]^{27}$D − 52.3° (benzene, *c* 2.8), in 25 ml. of benzene was added dropwise with stirring under anhydrous conditions at −60° to 40 ml. of a 2 *N* solution of sodium ethoxide which had been freshly saturated with hydrogen sulfide. The mixture was allowed to warm to room temperature and the solvent was removed under reduced pressure. The salt residue was taken up in water, acidified and filtered, and the solution then saturated with potassium chloride and extracted with ether. The ether solution was dried (Drierite) and filtered. Dicyclohexylamine (1.2 g., 0.0066 mole) was added and the ether was distilled off. The crystalline solid thus obtained was recrystallized from acetone–ether to give a first crop of 0.57 g. of essentially (±)-dicyclohexylamine salt, m.p. 164–165° (reported[15] 168.5–170.5°). By concentrating the filtrate, there was obtained a second crop which was recrystallized from ether–petroleum ether to give 0.17 g. of the dicyclohexylamine salt of the (+)-acid, $[\alpha]^{27}$D + 7.30 ± 0.07° (methanol, *c* 2.2), m.p. 124–125°, mixed melting point with authentic[11] sample, 124–124.5°. An additional crop of (+)-acid dicyclohexylamine salt, 0.37 g., m.p. 123–124°, was obtained by addition of petroleum ether to the filtrate.

(−)-**Ethyl Isopropyl Methylphosphonate (IV) from** (+)-**IIa.**—Compound (+)-IIa (3.70 g., 0.022 mole) was mixed with a freshly prepared solution of sodium (1.8 g., 0.0 78 mole) in ethanol, then diluted to 100 ml. with absolute ethanol. The reaction was followed polarimetrically from the first recorded rotation of + 8.34° (3 min. after mixing) to − 0.20° (53 min. from the time of mixing). After a total of 90 min., the reaction mixture was brought to *p*H 7 with aqueous hydrochloric acid. The ethanol was distilled off, and the residual aqueous solution was saturated with sodium chloride, then extracted with ether. The ether solution was dried (Drierite), concentrated, and distilled to give 1.7 g. (0.010 mole, 46%) of (−)-IV, b.p. 60° (3.5 mm.), n^{25}D 1.4096, αD − 0.90 ± 0.02° (1 dm.).

In a preliminary run, (±)-IV, b.p. 72–73° (4 mm.), n^{25}D 1.4095, was obtained from (±)-IIa and sodium ethoxide after 16 hr. in ethanol at room temperature.

Anal. Calcd. for $C_6H_{15}O_3P$: C, 43.4; H, 9.1. Found: C, 42.9; H, 9.0.

(−)-**Ethyl Isopropyl Methylphosphonate** (IV) **from** (+)-III.—A mixture of (+)-III in hexane, 3.7 g. (α^{27}D + 0.75° (2 dm.) for 0.17 g. in 5 ml. benzene), was added dropwise with stirring to 13 ml. of 2 *N* sodium ethoxide in ethanol at −25° under anhydrous conditions. The reaction was allowed to warm to room temperature with stirring, then neutralized with aqueous hydrochloric acid and worked up as described for (−)-IV, above, to give (−)-IV, 0.6 g., b.p. 61–62° (4 mm.), n^{25}D 1.4096, α^{29}D − 0.331 ± 0.014° (1 dm.) (37% of maximum rotation observed above).