The solid which formed was collected on a filter and washed with 10 ml. of absolute ethanol followed by 10 ml. of absolute ether. Recrystallization from absolute ethanol yielded 2.38 g. (79%) of tetramethylammonium iodide, m.p. 241–270° dec.

Anal. Calcd. for $C_4H_{12}NI$: I, 63.1; N, 6.97. Found: I, 66.3; N, 7.04.

The ethanolic filtrate remaining after collecting tetramethylammonium iodide was concentrated to dryness, and the gummy residue was dissolved in ether. The ether solution was filtered, and the salt-free filtrate showed a greenish fluorescence. Concentration of the ether solution yielded a bright yellow gum which was not further investigated.

Attempts to suppress the disproportionation reaction by carrying out the methylation at low temperatures and in the presence of solid carbon dioxide were unsuccessful.

α-Cyano-3-piperidinomethylindole. Method A. The Strecker Reaction.—In a 50-ml. round-bottomed flask were placed, in the order named, 1.1 ml. of concentrated hydrochloric acid, 10 ml. of water, 3.1 g. (0.037 mole) of piperidine, 0.6 g. (0.012 mole) of sodium cyanide, 1.5 g. (0.010 mole) of indole-3-aldehyde and 10 ml. of 95% aqueous ethanol. The flask was closed with a lightly greased ground glass stopper, and the stopper was tightly secured with friction tape. The flask was immersed in a water-bath maintained at about 60° for 6 hours. At the end of the reaction period, the flask was cooled under the tap and its contents poured into 150 ml. of water. The product was collected on a filter, washed with water and air-dried. The yield of α-cyano-3-piperidinomethylindole was 2.4 g. (100%), m.p. 148–150°, with extensive decomposition, when introduced into the apparatus at 140°. Recrystallization from benzene caused no improvement in the melting point. The infrared spectrum of the compound in Nujol showed bands characteristic for the N–H bond of the indole nucleus (3.27 μ) and for the nitrile group (4.50 μ).

Anal. Calcd. for $C_{15}H_{17}N_3$: C, 75.28; H, 7.16; N, 17.56. Found: C, 75.46; H, 7.15; N, 17.32.

Method B. Amine Exchange with α-Cyanogramine.—A solution of 500 mg. of α-cyanogramine in 2 ml. of piperidine was heated under reflux in an atmosphere of nitrogen. After a period of about 2 hours the reaction mixture was concentrated to dryness. Addition of a few drops of low-boiling petroleum ether with stirring induced crystallization of the residue. The crystals were collected on a filter, then recrystallized from benzene. The resulting colorless crystals melted with extensive decomposition at 138–141° when introduced into the apparatus at 105°. A mixed melting point with authentic α-cyano-3-piperidino-methylindole, prepared by the Strecker reaction (method A), showed no depression. The infrared spectra of the compounds prepared by method A and by method B were identical.

3-Dimethylaminomethylene-3H-pseudoindole from α-Cyanogramine.—To a solution of 2.6 g. of α-cyanogramine in ether which had been freshly distilled from lithium aluminum hydride was added 100 ml. of a 0.1 *M* solution of triphenylmethylsodium in ether. The addition was complete in 6 hours, and after 30 hours, the suspension was filtered, and the clear filtrate was concentrated to dryness. The gummy residue was treated with absolute ether and the resulting solid material was filtered, yielding 1.3 g. (72%) of crude 3-dimethylaminomethylene-3H-pseudoindole, m.p. 149–160° (lit.[12] 152–154°). Recrystallization from benzene–cyclohexane yielded fine, pale orange needles. These needles appeared to be an intimate mixture of the pseudoindole and indole-3-aldehyde, the uniform crystal structure apparently being formed by cocrystallization. Under the microscope the two compounds of the mixture could be seen to melt independently. The pseudoindole melted at 155–160°, and at this temperature the crystal structure changed abruptly, revealing the characteristic crystal structure of indole-3-aldehyde mixed with the liquid pseudoindole. The crystals of aldehyde melted at 195–197°. Several recrystallizations from dry benzene failed to remove the aldehyde. The infrared spectrum of this sample was identical in all respects with that of 3-dimethylaminomethylene-3H-pseudoindole prepared according to Smith's procedure and also contaminated with approximately the same amount of indole-3-aldehyde. Both spectra are significantly different from the spectrum of pure indole-3-aldehyde.

Anal. Calcd. for a mixture of 58% 3-dimethylaminomethylene-3H-pseudoindole, $C_{11}H_{12}N_2$, and 42% indole-3-aldehyde, C_9H_7NO: C, 75.78; H, 6.11; N, 13.50. Found: C, 76.06; H, 5.83; N, 12.80.

Gramine from α-Cyanogramine.—An ether solution of 1.003 g. (5.04 millimoles) of α-cyanogramine was added over a period of 0.5 hour to a slurry of 0.134 g. (0.0134 equivalent) of lithium aluminum hydride in ether. The mixture was allowed to stand for 0.5 hour, then heated under reflux for 10 min. Ethyl acetate (2 ml.) was added to decompose the excess lithium aluminum hydride, and the ether solution was poured into a 5% aqueous solution of sodium hydroxide. The ether layer was separated and the aqueous layer was extracted several times with ether. The ether extracts were combined and dried over anhydrous magnesium sulfate, then filtered and concentrated to dryness. The solid residue was fractionally crystallized from benzene and petroleum ether, yielding about 0.1 g. of an unidentified solid and 0.75 g. (87%) of gramine, m.p. 129–131°, mixed m.p. with an authentic sample 130–132.5°. The aqueous solution remaining after extraction of the organic product with ether was titrated with a standard solution of silver nitrate, indicating the presence of 71% of the theoretical amount of cyanide ion.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN CO.]

The Conversion of Alkyl Halides to the Next Higher Homologous Phosphonates[1]

BY BARNEY J. MAGERLEIN AND FRED KAGAN

RECEIVED JUNE 12, 1959

Two methods for the conversion of alkyl halides to phosphonates having an additional methylene group [$RX \rightarrow RCH_2PO(OR')_2$] are described.

The wide distribution of phosphate in biological systems and the specificity of action shown by many naturally occurring organic phosphates makes them interesting targets for chemotherapeutic approaches to anticancer, antiviral and antibacterial agents. For this reason we have been interested in preparing phosphonic acid analogs of bio-active organic phosphates.

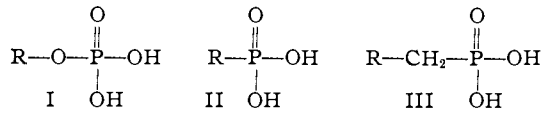
Burger and co-workers have prepared theophyllinyl alkylphosphonic acids,[2a] phosphonic acid esters of ribose and glucopyranosyl purine derivatives,[2b] and the phosphonic acid analog of glucose-6-phosphate.[3] Jensen and co-workers also have been active in the synthesis of "phosphonate analogs of biologically important phosphate com-

(1) For the previous paper in this series see F. Kagan and R. D. Birkenmeyer, THIS JOURNAL, **81**, 3026 (1959).

(2) (a) J. R. Parikh and A. Burger, *ibid.*, **77**, 2386 (1955); (b) J. R. Parikh, M. E. Wolff and A. Burger, *ibid.*, **79**, 2778 (1957).

(3) B. S. Griffin and A. Burger, *ibid.*, **78**, 2336 (1956).

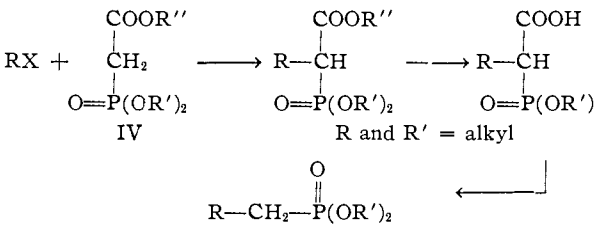
pounds" with the main emphasis on the phosphonate analogs of some of the phosphorylated catabolic products of glucose.[4-6] In these phosphonates the ester linkage, R–O–P, of the phosphate I was replaced by a direct R–P bond as in II.[2b,3,5] We desired, however, to prepare analogs in which the oxygen of the R–O–P ester I was replaced by a methylene group to form a phosphonate such as III. This



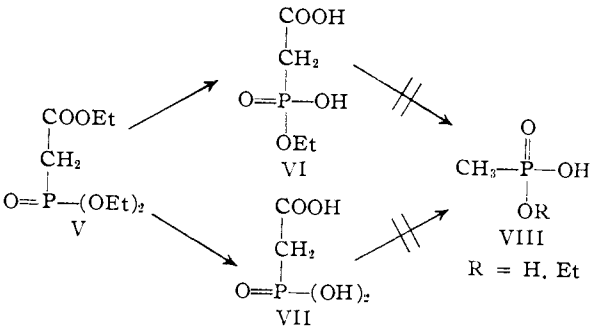
latter analog is isosteric with I (the methylene replaces the oxygen), and as such may be a more interesting phosphate analog than II. Two general methods for the introduction of the methylene phosphonate moiety into simple molecules are described in this paper, the first of which may be of value for the conversion of naturally occurring metabolites to the next higher homologous phosphonate.

The reactions involved in the first method which effects the conversion of RX to $RCH_2P(O)(OAlk)_2$ are shown in Chart I.

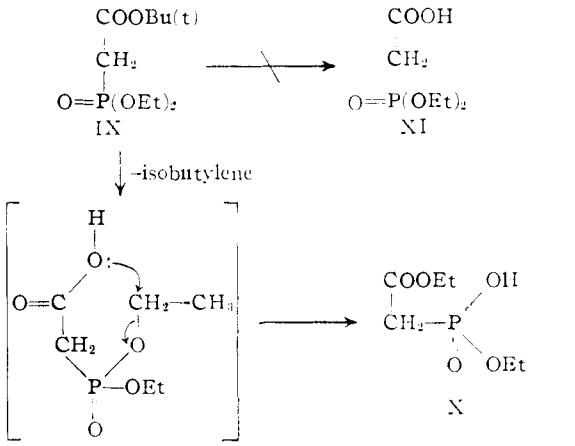
CHART I



The alkylation of a dialkylphosphonoacetic ester IV with alkyl halides is well documented,[7-12] so that the major obstacle in this sequence was the removal of the carboalkoxy group. Nylen has shown that treatment of triethyl phosphonoacetate V with alkali rapidly saponified one of the phosphonate esters and then more slowly the carboxylate ester[8] to form VI. Our attempts at mild acid hydrolysis failed to hydrolyze the carboxylate ester, while vigorous acidic hydrolysis yielded phosphonoacetic acid (VII).[8] Thus, diethyl carboxymethylphosphonate could not be prepared by alkaline or acidic hydrolysis of the triester V. Pyrolysis of the di- or tribasic acids VI and VII, with or without traces of acid or alkali, failed to yield the decarboxylated product, methylphosphonic acid (VIII). When heated to about 300° phosphonoacetic acid (VII) decomposed with gas evolution, but no entity could be isolated.



Since pyrolytic decarboxylation failed, degradation of the carboxyl group to a halide by the Hunsdiecker reaction[13] was investigated. For this purpose a dialkylphosphonoacetic acid (*e.g.*, XI) was desired so that the carboxyl group could be converted to the silver salt while leaving the phosphonic acid protected as the ester. Since attempts to prepare this compound by alkaline or acidic hydrolysis failed, the unmasking of the carboxyl group by pyrolysis of its *t*-butyl ester was attempted.



Diethyl carbo-*t*-butoxymethylphosphonate (IX) was prepared from *t*-butyl chloroacetate[14] and sodium diethyl phosphite. Pyrolysis of the *t*-butyl ester IX eliminated one mole of isobutylene to yield an oil. Infrared and potentiometric titration data indicated that this oil was chiefly the ester X and not the expected carboxylic acid XI. Similarly, hydrogenolysis of diethyl carbobenzyloxymethylphosphonate yielded an oil whose infrared spectrum and potentiometric titration curve showed strong evidence of similar transesterification. This reaction is reminiscent of the recently reported internal esterification of the carboxyl group observed in the reaction of triethyl phosphite (XII) with α,β-unsaturated acids (XIII).[15] Since this reaction (IX → X) appeared to take place *via* an internal nucleophilic attack on the alkyl group of the phosphonate, it seemed likely that the rate would be sensitive to branching in the alkyl group. This proved to be the case. Diisopropyl carbobenzyloxymethylphos-

(4) T. C. Myers, R. C. Harvey and E. V. Jensen, THIS JOURNAL, **77**, 3101 (1955).

(5) S. Preis, T. C. Myers and E. V. Jensen, *ibid.*, **77**, 6225 (1955).

(6) H. I. Jacobson, M. J. Griffin, S. Preis and E. V. Jensen, *ibid.*, **79**, 2608 (1957).

(7) A. E. Arbuzov and A. A. Dunin, *J. Russ. Phys. Chem., Gesell* **46**, 295 (1914); *Chem. Ber.*, **60**, 291 (1927).

(8) P. Nylen, *ibid.*, **57**, 1023 (1924); **59**, 1119 (1926).

(9) A. E. Arbuzov and A. I. Razumov, *J. Russ. Phys. Chem. Soc.*, **61**, 623 (1929).

(10) A. E. Arbuzov and A. I. Razumov, *J. Gen. Chem.*, **4**, 834 (1934).

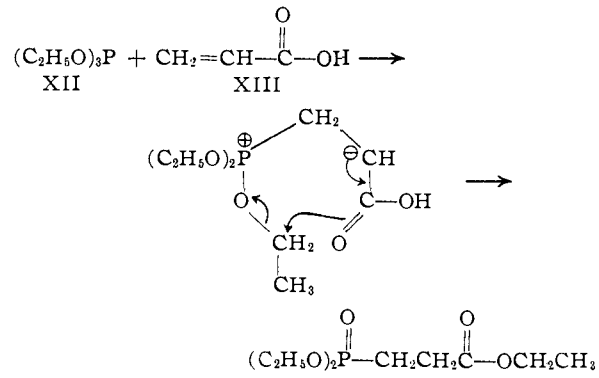
(11) G. M. Kosolapoff and J. S. Powell, THIS JOURNAL, **72**, 4198 (1950).

(12) N. Kreutzkamp, *Chem. Ber.*, **88**, 195 (1955).

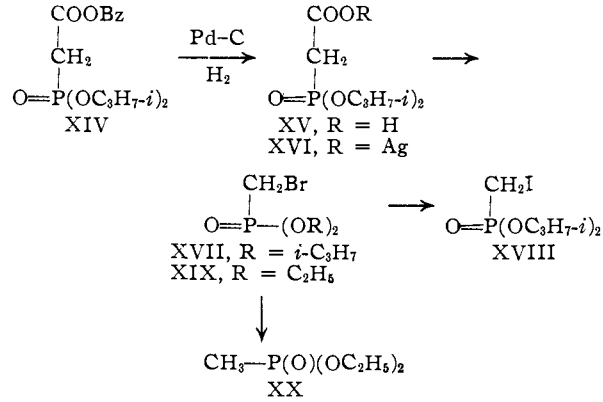
(13) C. V. Wilson, "Organic Reactions," Vol. IX, John Wiley and Sons, Inc., New York, N. Y., 1957, p. 332.

(14) W. S. Johnson, J. S. Belew, L. J. Chinn and R. H. Hunt, THIS JOURNAL, **75**, 4995 (1953).

(15) Kamai and Kukhtin, *Proc. Sci., U.S.S.R.* (Eng. Trans.), **112**, 129 (1957).



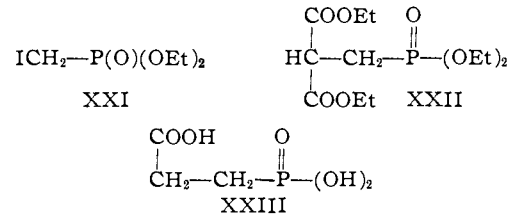
phonate (XIV) was prepared from benzyl chloroacetate and triisopropyl phosphite by the Arbuzov reaction.[16]



Hydrogenolysis formed the oily acid XV which was converted to its amorphous silver salt XVI with moist silver oxide. When treated with bromine in carbon tetrachloride, carbon dioxide was evolved leading to the isolation of diisopropyl bromomethylphosphonate (XVII) in 10–20% yield. Replacement of the bromine in XVII by iodine, using sodium iodide in methyl ethyl ketone, afforded diisopropyl iodomethylphosphonate (XVIII) identical with a sample prepared from diiodomethane and triisopropyl phosphite. The debromination of XVII was not attempted; however, hydrogenation of the diethyl ester XIX over palladium gave the known diethyl methylphosphonate XX in good yield

This series of reactions, *i.e.*, alkylation, decarboxylation and hydrogenolysis, complete the formal conversion of R–X to R–CH_2–P(O)$(OR')_2$ as outlined in Chart I.

The second method for the introduction of a methylenephosphonate group into a simple molecule utilized the alkylation of an active methylene group with diethyl iodomethylphosphonate (XXI). The use of this compound in C-alkylation has not been reported previously.[17] Alkylation of sodium diethylmalonate with XXI yielded the expected ester XXII which on acid hydrolysis gave the crystalline acid XXIII whose physical constants agreed with those previously described.[7]



Acknowledgment.—The authors are indebted to Dr. E. Olson for the potentiometric titrations, to W. A. Struck and associates for elemental analyses, to M. Grostic for infrared data, and to V. R. Shellman for technical assistance.

Experimental

Diisopropyl Carbobenzyloxymethylphosphonate (XIV).—A solution of 48 g. of benzyl chloroacetate and 64 ml. of distilled triisopropyl phosphite was heated to about 160°. An exothermic reaction occurred which carried the temperature to 200°. During the reaction the distillate was removed. When the initial reaction subsided the mixture was heated at 200° for 15 minutes. The reaction mixture was distilled at 0.7 mm. to yield 11.5 g. of XIV, b.p. 135–143°, $n^{25}D$ 1.4810, and 32 g., b.p. 143–145°, $n^{25}D$ 1.4815.

Anal. Calcd. for $C_{15}H_{23}PO_5$: C, 57.32; H, 7.37; P, 9.86. Found: C, 57.48; H, 7.26; P, 10.00.

Diethyl Carbo-*t*-butoxymethylphosphonate (IX).—Diethyl phosphite (97 g.) was added to a previously prepared suspension of 18.5 g. of sodium hydride in 400 ml. of *t*-butyl alcohol at such a rate as to keep the temperature just below the boiling point. When the addition was completed and all of the hydride reacted, the mixture was cooled to 10° and 114.4 g. of *t*-butyl chloroacetate[4] was slowly added. After stirring for one hour, the precipitate was removed by filtration and the solvent distilled under vacuum. The residue was distilled in small portions over copper carbonate to give IX, b.p. 77–86° (0.1 mm.), $n^{25}D$ 1.4298. A portion was redistilled at 0.05 mm., b.p. 82–82.5°, $n^{25}D$ 1.4291.

Anal. Calcd. for $C_{10}H_{21}O_5P$: C, 47.61; H, 8.39; P, 12.28. Found: C, 47.06; H, 8.21; P, 12.22.

Pyrolysis of Diethyl Carbo-*t*-butoxymethylphosphonate (IX).—Pyrolysis of 10.0 g. of ester IX at 140–150° evolved 900 ml. of isobutylene (theoretical volume was 980 ml.). Potentiometric titration of the residual oil showed a trace of a material with $pK_{a'}$ of 7.0, but the major portion was $pK_{a'}$ of less than 5.0. The infrared spectrum showed strong absorption at 1733 cm.$^{-1}$ indicative of a carboalkoxy group, with no evidence of carboxyl absorption. In addition to the usual bands assignable to phosphorus, P–OH bands at 2620 and 2280 cm.$^{-1}$ were present.

Diisopropyl Carboxymethylphosphonate (XV).—In a Parr hydrogenator, 25.8 g. of benzyl ester XIV was hydrogenolyzed in 100 ml. of ethanol over 1.0 g. of 10% palladium–charcoal. The theoretical amount of hydrogen was absorbed within 10 minutes. The reaction mixture was cooled to room temperature and filtered. The solvent was distilled from a portion of the solution to yield a colorless oil. Infrared absorption bands at 1720 cm.$^{-1}$ were assigned to C=O and 3420, 3220, 2780, 2620 and 2500 cm.$^{-1}$ to bonded OH (carboxylic acid).

Diisopropyl Carboxymethylphosphonate, C-Silver Salt (XVI).—Moist silver oxide was prepared from 51 g. of silver nitrate and 25 g. of potassium hydroxide in 350 ml. of water. The oxide was filtered and washed with water until free of alkali. The acid prepared above in the alcoholic solution was shaken with the silver oxide for 10 minutes. The excess silver oxide was removed by filtration and the filtrate evaporated. The crystalline salt was triturated with 300 ml. of acetone. The silver salt was recovered by filtration and dried under vacuum at 55° for 17 hours (21 g., 76.6%).

Anal. Calcd. for $C_8H_{16}AgO_6P$: Ag, 32.6. Found: Ag, 32.9.

(16) G. M. Kosolapoff, "Organophosphorus Compounds," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 121.

(17) M. H. Maguire and G. Shaw, *J. Chem. Soc.*, 1756 (1955), reported O-alkylation of phenols with diethyl iodomethylphosphonate (XIX). The reaction of XIX with ammonia [Kabachnik and Medved, *Izvest. Akad. Nauk, U.S.S.R., Otdel Khim. Nauk*, 635 (1950); *C. A.*, **45**, 8444 (1951)] and with alkali [Kabachnik and Shepeleva, *ibid.*, 185 (1951); *C. A.*, **45**, 10, 191 (1951)] are also described.

Diisopropyl Bromomethylphosphonate (XVII).—Fifty-three grams (0.16 mole) of silver salt XVI was suspended in 300 ml. of carbon tetrachloride dried over phosphorus pentoxide. A solution of 25.7 g. (0.16 mole) of bromine, dried over sulfuric acid, in 50 ml. of carbon tetrachloride was slowly added. A vigorous reaction ensued accompanied by the evolution of carbon dioxide. When the addition of the bromine was completed and the evolution of the carbon dioxide had ceased, the yellow silver bromide was removed by filtration. The carbon tetrachloride was distilled *in vacuo* to yield 41 g. of an oil which was dissolved in ether and washed with saturated sodium bicarbonate solution. A yield of 8 g. of crude product was obtained on evaporation of the ether. Distillation at 0.5 mm. yielded 3.4 g., b.p. 80–92°, $n^{25}D$ 1.4652, and 2.8 g., b.p. 92–104°, $n^{25}D$ 1.4733. The infrared spectrum of the lower boiling fraction was very similar to that of XVIII.

Diisopropyl Iodomethylphosphonate (XVIII). Method A.—A solution of 6.2 g. of bromide XVII and 4.28 g. of sodium iodide in 35 ml. of acetone was heated under reflux for two hours. After this time, only 200 mg. of sodium bromide had precipitated. The acetone was distilled under vacuum and the residue dissolved in 40 ml. of 2-butanone. The mixture was heated under reflux for 17 hours. A quantitative yield of precipitated sodium bromide (2.48 g.) was obtained. The solvent was distilled *in vacuo*. The residue was dissolved in 50 ml. of ether and 3 ml. of water. The ether solution was washed with 3 ml. of dilute sodium thiosulfate solution, dried over sodium sulfate and evaporated. The residue was distilled at 0.5 mm. yielding 0.6 g., b.p. 84–90°, $n^{25}D$ 1.4718, and 1.4 g., b.p. 90–92°, $n^{25}D$ 1.4798. The infrared spectrum of the major fraction was identical with that of the known compound prepared in method B.

Method B.—A solution of 53.6 g. (0.2 mole) of methylene diiodide and 41.6 g. of triisopropyl phosphite was heated to 145° at which point an exothermic reaction occurred. When the vigorous reaction subsided the residue was distilled at 0.4 mm. The fraction, b.p. 76–100°, was collected and fractionated at 0.5 mm. to yield 28.7 g. (46.9%), b.p. 80–83°, $n^{25}D$ 1.4802.

Anal. Calcd. for $C_7H_{16}IO_3P$: C, 27.47; H, 5.27; I, 41.46; P, 10.12. Found: C, 27.36; H, 5.52; I, 40.86; P, 10.30.

Debromination of Diethyl Bromomethylphosphonate (XIX).—Eight grams of diethyl bromomethylphosphonate (XIX) in 100 ml. of ethanol containing 10 g. of 10% Pd–C and 1.0 g. of magnesium oxide was shaken in a Parr apparatus under 45-pound pressure of hydrogen. The theoretical quantity of hydrogen was absorbed within one hour. The reaction mixture was filtered and the solvent distilled. The infrared spectrum of the residual oil was identical with that of a known sample of XX.

Diethyl β,β-Dicarboethoxyethylphosphonate (XXII).—To a solution of 3.44 g. of sodium in 100 ml. of ethanol there was added 24 g. of diethyl malonate. After 5 minutes, 41.7 g. of diethyl iodomethylphosphonate (XXI) was added and the reaction mixture heated under reflux for 2 hours. Most of the solvent was distilled *in vacuo*. The residue was dissolved in ether–dilute hydrochloric acid and worked up in the usual manner. Distillation of the product at 0.15 mm. gave 13.4 g. (30.4%), of crude XXII, b.p. 142–146°, $n^{25}D$ 1.4378. This material was not further purified but analyzed and used in the next step.

Anal. Calcd. for $C_{12}H_{23}O_7P$: P, 9.98. Found: P, 8.26.

β-Carboxyethylphosphonic Acid (XXIII).—One gram of the oily ester XXII was refluxed with 8 ml. of 48% hydrobromic acid for 6 hours. The acid was distilled under vacuum to yield a crystalline residue. This solid on recrystallization from acetone gave 50 mg. of XXIII, m.p. 149–156°. Recrystallization raised the m.p. to 166–167° (Arbuzov and Dunin[7] report a m.p. of 167–168°).

KALAMAZOO, MICH.

[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION, U. S. ARMY CHEMICAL WARFARE LABORATORIES]

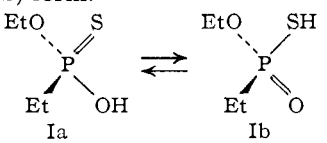
The Stereochemistry of Asymmetric Phosphorus Compounds. III. The Resolution of a Series of O-Alkyl Alkylphosphonothioic Acids[1]

BY HERBERT S. AARON, JANET BRAUN, THOMAS M. SHRYNE, HAROLD F. FRACK, GARY E. SMITH, ROY T. UYEDA AND JACOB I. MILLER

RECEIVED APRIL 15, 1959

A series of five O-alkyl alkylphosphonothioic acids [(RO)R'P(S)OH] were resolved, and the enantiomorphs thus obtained were characterized as their dicyclohexylamine salts. All of the *l*-enantiomorphs of these acids apparently possess the same configuration.

The resolution of O-ethyl ethylphosphonothioic acid (I) has been described.[2] This acid exists as a thionate (Ia) form in tautomeric equilibrium with a thiolate (Ib) form.



Ia Ib

In this sense, therefore, the acid possesses two reactive functional groups attached directly to the phosphorus atom. Since a host of asymmetric organophosphorus compounds can be synthesized through the reactions of these two functional groups, resolved acids of this general class become extremely useful for the synthesis of other resolved organophosphorus compounds. The compounds thus obtained can be used, in turn, to study the stereochemistry of displacement reactions at the asymmetric phosphorus atom.

We now wish to report the resolution of the following O-alkyl alkylphosphonothioic acids: O-ethyl methylphosphonothioic acid (II), O-isopropyl methylphosphonothioic acid (III), O-ethyl isopropylphosphonothioic acid (IV), O-methyl ethylphosphonothioic acid (V) and O-methyl methylphosphonothioic acid (VI).

The acids were resolved as their quinine or brucine salts and characterized as their dicyclohexylamine salts. The physical constants and analytical data on both the alkaloid and dicyclohexylamine salts of the resolved acids are summarized in Table I. Similar data on the *d*, *dl*-dicyclohexylamine salts of IV and V are given in the Experimental section; those of II, III and VI have been reported previously.[3]

(1) Presented in part before the 133rd Meeting of the American Chemical Society, San Francisco, Calif., April, 1958.

(2) H. S. Aaron, T. M. Shryne and J. I. Miller, THIS JOURNAL, **80**, 107 (1958).

(3) F. W. Hoffmann, B. Kagan and J. H. Canfield *ibid.*, **81**, 148 (1959).