Of all the methods which we used in preparing dialkyl acetoxyalkylphosphonates, the acetylation of dialkyl hydroxyalkylphosphonates with ketene gave the highest yields (62% for diethyl 1-acetoxyethylphosphonate). We also prepared diethyl 1-acetoxybutylphosphonate in good yield (86.5%) from diethyl 1-hydroxybutylphosphonate and ketene.

Experimental

Diethyl 1-Hydroxyethylphosphonate.[6,7]—A mixture of acetaldehyde (44.0 g., 1.0 mole), diethyl hydrogen phosphite (138.1 g., 1.0 mole) and triethylamine (5 ml.) was heated with stirring at 90° for 2 hours. Fractionation of the reaction mixture under reduced pressure through a short Vigreux column gave 47.0 g. (26.0%) of a colorless liquid, b.p. 111–112° (2.2 mm.), $n^{20}\mathrm{D}$ 1.4340. This compound was soluble in water and the common organic solvents..

Anal. Calcd. for $C_6H_{15}O_4P$: C, 39.56; H, 8.30. Found: C, 39.49; H, 8.02.

Diethyl 1-Acetoxyethylphosphonate.—Diethyl 1-hydroxyethylphosphonate (7.0 g., 0.0385 mole) and 1 drop of boron trifluoride etherate were placed in a round-bottomed flask which was cooled in an ice-bath. The contents of the flask were stirred while ketene was bubbled in through a fritted glass disc. After 2.6 g. (0.062 mole) of ketene had condensed in the reaction mixture, the ketene source was removed and the mixture was stirred at 25° for 3 hours to allow the excess ketene to evaporate. The crude product was distilled under reduced pressure through a short Vigreux column. Diethyl 1-acetoxyethylphosphonate (5.3 g., 62%) was obtained as a colorless liquid, b.p. 88–91° (1.1 mm.), $n^{20}\mathrm{D}$ 1.4265. This compound is soluble in water and the common organic solvents.

Anal. Calcd. for $C_8H_{17}O_5P$: C, 42.85; H, 7.64. Found: C, 42.73; H, 7.57. The residue consisted of about 3 g. of an amber oil.

Reaction Product of Vinyl Acetate and Diethyl Hydrogen Phosphite Using a Sodium Alkoxide Catalyst (Diethyl 1-Acetoxyethylphosphonate).—Vinyl acetate (17.2 g., 0.2 mole) and diethyl hydrogen phosphite (40.0 g., 0.29 mole) were mixed, and 3.5 ml. of a concentrated solution of sodium ethoxide in ethyl alcohol was added dropwise with stirring. The reaction was mildly exothermic, and the temperature gradually rose to 40°. The reaction mixture was stirred for 2 hours and then dissolved in ethyl ether. The ether solution was washed twice with water and then dried over sodium sulfate. The ether was removed on a steam-bath, and the residual oil was distilled under reduced pressure through a short Vigreux column. After the excess diethyl hydrogen phosphite was removed, a colorless liquid (7.5 g., 16.7%) was obtained, b.p. 102–103° (1.3 mm.), $n^{20}\mathrm{D}$ 1.4268.

Anal. Calcd. for $C_8H_{17}O_5P$: C, 42.85; H, 7.64. Found: C, 42.21; H, 7.91.

Diethyl 1-Hydroxybutylphosphonate.[6,7]—A mixture of butyraldehyde (36.0 g., 0.5 mole), diethyl hydrogen phosphite (69.0 g., 0.5 mole) and triethylamine (5 ml.) was heated with stirring at 90° for 1.5 hours. Fractionation of the reaction mixture under reduced pressure through a short Vigreux column gave 53 g. (50%) of a colorless liquid, b.p. 125–129° (1.3–1.5 mm.), $n^{20}\mathrm{D}$ 1.4358. This compound is soluble in water and the common organic solvents.

Anal. Calcd. for $C_8H_{19}O_4P$: C, 45.71; H, 9.11. Found: C, 45.94; H, 9.15.

Diethyl 1-Acetoxybutylphosphonate.—The reaction of diethyl 1-hydroxybutylphosphonate (10.5 g., 0.05 mole), ketene (3.0 g., 0.0715 mole) and boron trifluoride etherate (2 drops) was carried out according to the procedure described for diethyl 1-acetoxyethylphosphonate. Distillation of the reaction product under reduced pressure through a short Vigreux column gave 10.9 g. (86.5%) of diethyl 1-acetoxybutylphosphonate, b.p. 101–102° (1.0 mm.), $n^{20}\mathrm{D}$ 1.4308.

Anal. Calcd. for $C_{10}H_{21}O_5P$: C, 47.61; H, 8.39. Found: C, 47.56; H, 8.38.

Diethyl 2-Acetoxyethylphosphonate.—A mixture of 2-bromoethyl acetate (83.5 g., 0.5 mole) and triethyl phosphite (124.4 g., 0.75 mole) was refluxed with stirring for 13 hours when the evolution of ethyl bromide was complete. The reaction mixture was distilled under reduced pressure through a short Vigreux column to obtain 31.5 g. (28%) of a colorless liquid, b.p. 94–99° (1.2 mm.), $n^{20}\mathrm{D}$ 1.4359. This material was distilled over 1 g. of anhydrous sodium carbonate to obtain an analytical sample, b.p. 105–107° (1.0 mm.), $n^{20}\mathrm{D}$ 1.4350.

Anal. Calcd. for $C_8H_{17}O_5P$: P, 13.82. Found: P, 13.82.

Reaction Product of Vinyl Acetate and Diethyl Hydrogen Phosphite Using a Benzoyl Peroxide Catalyst (Diethyl 2-Acetoxyethylphosphonate).—A mixture of vinyl acetate (17.2 g., 0.2 mole), diethyl hydrogen phosphite (110 g., 0.8 mole) and benzoyl peroxide (0.1 g.) was heated with stirring on the steam-bath for 9 hours. During the initial stages of the reaction, the vinyl acetate refluxed gently. The reaction mixture was allowed to stand overnight at 25°, and then 0.2 g. of hydroquinone was added. The mixture was then fractionated under reduced pressure through a short Vigreux column. After the excess diethyl hydrogen phosphite was removed, a colorless oil (6.2 g., 14%) was obtained, b.p. 96–97° (0.7 mm.). This material was distilled over 0.3 g. of anhydrous sodium carbonate to obtain an analytical sample, b.p. 101–103° (1.0 mm.), $n^{20}\mathrm{D}$ 1.4322. This compound is soluble in water and the common organic solvents.

Anal. Calcd. for $C_8H_{17}O_5P$: C, 42.85; H, 7.64. Found: C, 42.73; H, 7.65.

The residue consisted of 20.2 g. of a dark, viscous oil containing 5.73% phosphorus.

Acknowledgment.—The authors wish to thank Dr. H. W. Patton and Mr. M. V. Otis for their help in interpreting the nuclear magnetic resonance spectra and the infrared spectra, respectively.

KINGSPORT, TENNESSEE

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(6) E. K. Fields (to Research Corporation), U. S. Patent 2,579,810 (1951). In this patent only the boiling points of the products are listed.

(7) V. S. Abramov, *J. Gen. Chem.* (*U.S.S.R.*), Consultants Bureau English Translation, **22**, 709 (1952).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, TENNESSEE EASTMAN COMPANY, DIVISION OF EASTMAN KODAK COMPANY]

Reaction of Triethyl Phosphite with 2-Haloacrylates

BY H. W. COOVER, JR., MARVIN A. MCCALL AND J. B. DICKEY

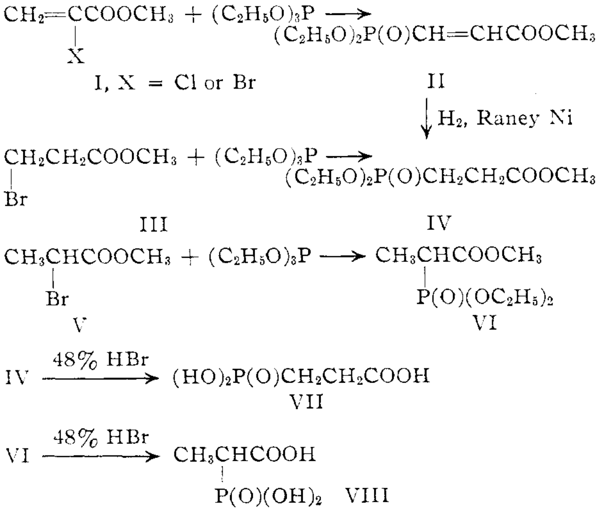
RECEIVED JUNE 29, 1956

The reaction of triethyl phosphite with methyl 2-haloacrylates was investigated. The product of the reaction was catalytically reduced, and the resulting compound was compared with authentic samples of methyl 2- and 3-diethylphosphonopropionates. On the basis of infrared absorption spectra and physical properties it was shown that the reduced product was methyl 3-diethylphosphonopropionate. It is therefore concluded that the product formed by the reaction of triethyl phosphite with methyl 2-haloacrylates is methyl 3-diethylphosphonoacrylate. A possible mechanism to explain the formation of the 3- rather than the 2-diethylphosphonoacrylate is discussed.

Several abnormal products have been reported[1-4] for the reaction of trialkyl phosphites or alkali dialkyl phosphites with secondary alkyl halides. This paper concerns the reaction of triethyl phosphite with methyl 2-haloacrylates and the proof of structure of the product. The reaction product was found to be the 3- rather than the 2-diethylphosphonoacrylate.[5] The methyl 2-haloacrylates were used because the methyl esters of 3-diethylphosphonoacrylic and 2- and 3-diethylphosphonopropionic acids had not previously been characterized. The ethyl esters of 2-haloacrylic acids react in an analogous manner to give ethyl 3-diethylphosphonoacrylate. Presumably the higher alkyl esters would react in a similar manner.

Discussion

Methyl 2-bromoacrylate (I) reacted with triethyl phosphite to give methyl 3-diethylphosphonoacrylate (II) in 68% yield. Methyl 2-chloroacrylate (I) gave the same product but in lower yield. The structure of this compound was proved by hydrogenation in the presence of Raney nickel at 33 to 44° to methyl 3-diethylphosphonopropionate (IV) in an almost theoretical yield. Analysis and the boiling point, refractive index and infrared spectrum showed that the reduced product was identical with methyl 3-diethylphosphonopropionate (IV) synthesized from methyl 3-bromopropionate (III). Methyl 2-diethylphosphonopropionate (VI) was prepared from methyl 2-bromopropionate (V) and triethyl phosphite in 70% yield. Analyses and physical properties showed that VI and IV were isomers. Compounds IV and VI were hydrolyzed with 48% hydrobromic acid to the corresponding tribasic acids, VII and VIII, respectively. These acids were shown to be different by means of melting points and mixed melting points.



$$\underset{\text{I, X = Cl or Br}}{CH_2{=}\underset{\displaystyle X}{\underset{|}{C}}COOCH_3} + (C_2H_5O)_3P \longrightarrow \underset{\text{II}}{(C_2H_5O)_2P(O)CH{=}CHCOOCH_3}$$

$$\text{II} \xrightarrow{H_2,\ \text{Raney Ni}} \text{IV}$$

$$\underset{\text{III}}{\underset{\displaystyle Br}{\underset{|}{CH_2}}CH_2COOCH_3} + (C_2H_5O)_3P \longrightarrow \underset{\text{IV}}{(C_2H_5O)_2P(O)CH_2CH_2COOCH_3}$$

$$\underset{\text{V}}{CH_3\underset{\displaystyle Br}{\underset{|}{C}}HCOOCH_3} + (C_2H_5O)_3P \longrightarrow \underset{\text{VI}}{CH_3\underset{\displaystyle P(O)(OC_2H_5)_2}{\underset{|}{C}}HCOOCH_3}$$

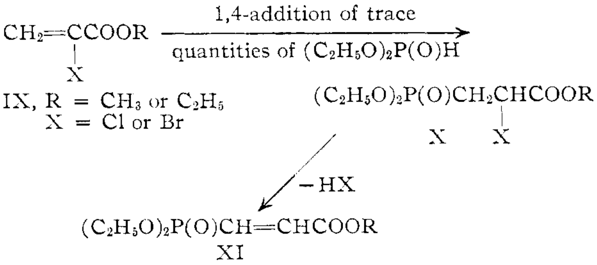
$$\text{IV} \xrightarrow{48\%\ HBr} \underset{\text{VII}}{(HO)_2P(O)CH_2CH_2COOH}$$

$$\text{VI} \xrightarrow{48\%\ HBr} CH_3\underset{\displaystyle P(O)(OH)_2}{\underset{|}{C}}HCOOH \quad \text{VIII}$$

The infrared absorption spectrum[6] of II indicates a mixture of compounds believed to be the *cis* and *trans* isomers. The absorption band at 14.6 μ suggests the *cis* configuration. A doublet at 7.95 and 8.05 μ for the ester C–O linkage also suggests two configurations. A P=O stretching frequency at 7.65 μ, the P–O–C linkage absorption at 9.75 μ, a conjugated –CH=CH– band at 6.2 μ and a C=O band at 5.75 μ confirm the structure of II.

The infrared absorption spectrum of IV prepared by reducing II is identical with that of the product obtained by reaction of triethyl phosphite with methyl 3-bromopropionate (III). This spectrum is different from that of the reaction product VI of triethyl phosphite and methyl 2-bromopropionate (V). These two spectra differ in the position of the P=O absorption band (7.80 μ for IV and 7.60 μ for VI). Another difference is the position of the ester C–O– stretching absorption band (8.05 μ for IV and 8.00 μ for VI). Differences are also found in the region of 7.5, 8.4, 11.6 and 12.1 μ. These observations support the assigned configurations given for these compounds based on the structure–spectra correlations of phosphorus compounds reported by Daasch and Smith.[7]

In order to explain the formation of the 3- rather than the 2-diethylphosphonoacrylate by the reaction of triethyl phosphite with 2-haloacrylates, two possible mechanisms were tested. One involved the 1,4-addition of diethyl hydrogen phosphite to methyl 2-haloacrylate (IX) to obtain X which was dehydrohalogenated to obtain XI. The initial diethyl hydrogen phosphite could have originated as an impurity in the triethyl phosphite or could have resulted from the reaction of triethyl phosphite with traces of hydrogen halide in the reaction mixture.



$$\underset{\substack{\text{IX, R = CH}_3\text{ or C}_2\text{H}_5\\ \text{X = Cl or Br}}}{CH_2{=}\underset{\displaystyle X}{\underset{|}{C}}COOR} \xrightarrow[\text{quantities of } (C_2H_5O)_2P(O)H]{\text{1,4-addition of trace}} (C_2H_5O)_2P(O)CH_2\underset{\displaystyle X}{\underset{|}{C}}HCOOR \quad X$$

$$\xrightarrow{-HX} \underset{\text{XI}}{(C_2H_5O)_2P(O)CH{=}CHCOOR}$$

The process could be repeated since the hydrogen halide from the dehydrohalogenation reaction would in turn react with triethyl phosphite to form more diethyl hydrogen phosphite and liberate ethyl halide.

$$(C_2H_5O)_3P + HX \longrightarrow (C_2H_5O)_2P(O)H + C_2H_5X$$

This mechanism, however plausible, was found to be untenable since diethyl hydrogen phosphite did not add to methyl 2-bromoacrylate even in the presence of sodium diethyl phosphite, a strong basic catalyst. Addition of small amounts of triethyl phosphite as a basic catalyst also failed to bring about the addition of diethyl hydrogen phos-

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(1) A. H. Ford-Moore and J. H. Williams, *J. Chem. Soc.*, 1465 (1947).

(2) de M. M. Vincent Chavanne and P. Rumpf, *Compt. rend.*, **225**, 1322 (1947).

(3) G. M. Kosolapoff, THIS JOURNAL, **68**, 1103 (1946).

(4) B. A. Arbuzov and B. P. Lugovkin, *J. Gen. Chem. U.S.S.R.*, **21**, 109 (1951).

(5) J. B. Dickey and H. W. Coover (to Eastman Kodak Co.), U. S. Patent 2,559,854 (1951).

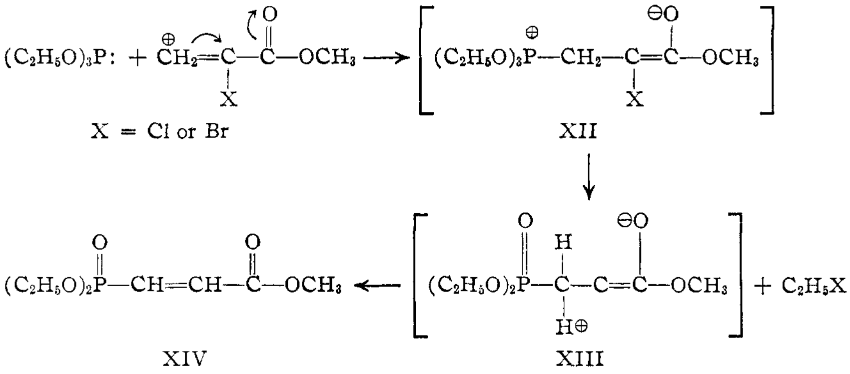
(6) The infrared spectra were obtained on a recording spectrophotometer made by Baird Associates, Inc. The spectra have been submitted to the National Research Council Committee on spectral absorption data.

(7) L. W. Daasch and D. C. Smith, *Anal. Chem.*, **23**, 853 (1951)

phite to the 1,4-unsaturation of methyl 2-bromoacrylate.

Another possible mechanism is the dehydrohalogenation of IX to give methyl propiolate followed by the addition of dialkyl hydrogen phosphite (from reaction of HX with trialkyl phosphite) to the acetylenic ester; however, the dehydrohalogenation of IX would hardly be expected under the reaction conditions.

The course of the reaction of methyl 2-haloacrylates with triethyl phosphite is probably best explained as a nucleophilic attack of the triethyl phosphite on the most electropositive carbon atom of the acrylate molecule, namely, the one in the 3-position. The resulting intermediate is then stabilized by loss of ethyl halide to form methyl 3-diethylphosphonoacrylate. The transformations involved may be illustrated stepwise as the formation of an intermediate XII followed by an elimination of the halogen atom with its electrons as ethyl halide. The resulting structure, XIII, is immediately or simultaneously stabilized by a 1,2-shift of the hydride ion allowing ketonization and formation of the conjugated structure XIV. The expulsion of the halogen atom with its electrons from the intermediate XII followed by shift of the hydride ion is essentially a Whitmore 1,2-shift.[8]



Experimental

Methyl 2-Chloro- and 2-Bromoacrylates (I).—These compounds were prepared in 65 to 71% yield by the method described by Marvel and Cowan.[9]

Methyl 3-Diethylphosphonacrylate (II).—Triethyl phosphite (24.9 g., 0.15 mole) was added dropwise to methyl 2-bromoacrylate (24.7 g., 0.15 mole) with stirring and external cooling. A small quantity of white precipitate formed and then slowly dissolved. After the initial exothermic reaction had subsided, ethyl bromide (11.5 g., 70%) was distilled from the reaction mixture. The reaction mixture was then distilled under reduced pressure to yield 22.6 g. (68%) of methyl 3-diethylphosphonoacrylate, b.p. 109–110° (1.0 mm.), $n^{20}\text{D}$ 1.4483.

Anal. Calcd. for $C_8H_{15}O_5P$: C, 43.24; H, 6.81; P, 13.94. Found: C, 43.09; H, 6.89; P, 13.82.

About 3.5 g. of a higher boiling product was also obtained, b.p. 174° (1.5 mm.), $n^{20}\text{D}$ 1.4686. This compound has not yet been identified. The analysis was as follows: C, 38.63; H, 6.19; P, 10.63; Br, 13.48.

This preparation was also carried out with methyl 2-chloroacrylate. The product obtained was the same, but the yield was only 28%.

Methyl 2-bromoacrylate was also treated with sodium diethyl phosphite instead of triethyl phosphite. The product was methyl 3-diethylphosphonoacrylate, but the yield was only 20%.

Methyl 3-Diethylphosphonopropionate (IV). A. By Reduction of Methyl 3-Diethylphosphonoacrylate (II).—Methyl 3-diethylphosphonoacrylate (12.0 g., 0.053 mole) was placed in a magnetically stirred hydrogenator containing 50 ml. of absolute ethyl alcohol and about two grams of Raney nickel–ethyl alcohol suspension. Hydrogen was then admitted until the pressure at 33° was 45 p.s.i. After stirring for 20 minutes, 0.052 mole of hydrogen was absorbed. The catalyst was then removed by filtration. The reaction mixture was distilled under reduced pressure to yield 10.9 g. (90%) of product, b.p. 108° (0.7 mm.), $n^{20}\text{D}$ 1.4339.

Anal. Calcd. for $C_8H_{17}O_5P$: C, 42.85; H, 7.64; P, 13.82. Found: C, 42.71; H, 7.66; P, 13.80.

All attempts to reduce methyl 3-diethylphosphonoacrylate with PtO_2 failed.

B. By Reaction of Triethyl Phosphite with Methyl 3-Bromopropionate.—A mixture of methyl 3-bromopropionate (16.7 g., 0.1 mole) and triethyl phosphite (16.6 g., 0.1 mole) was heated in a distilling flask until all the ethyl bromide formed was removed. The reaction mixture was then distilled under reduced pressure to obtain 15.0 g. (67%) of product, b.p. 110° (1.0 mm.), $n^{20}\text{D}$ 1.4339.

Anal. Calcd. for $C_8H_{17}O_5P$: C, 42.85; H, 7.64; P, 13.82. Found: C, 43.15; H, 8.10; P, 13.80.

This product was hydrolyzed with 48% hydrobromic acid to yield the known tribasic acid, 3-phosphonopropionic acid (VII), m.p. 165.5–167°. The m.p. recorded in the literature was 167–168°[10] and 178–180°.[11]

Anal. Calcd. for $C_3H_7O_5P$: C, 23.39; H, 4.58; P, 20.11. Found: C, 23.79; H, 4.73; P, 19.65.

The m.p. of a mixture of VII and VIII was depressed 10 to 15° below the m.p. of the lower melting isomer, VIII.

Methyl 2-Diethylphosphonopropionate (VI).—A mixture of methyl 2-bromopropionate (37.0 g., 0.22 mole) and triethyl phosphite (37.0 g., 0.22 mole) was heated in a distilling flask until all the ethyl bromide formed was removed. The reaction mixture was then distilled under reduced pressure to yield 34.0 g. (70%) of product, b.p. 95° (1.0 mm.), $n^{20}\text{D}$ 1.4330.

Anal. Calcd. for $C_8H_{17}O_5P$: C, 42.85; H, 7.64; P, 13.82. Found: C, 42.81; H, 7.71; P, 13.90.

This product was hydrolyzed with 48% hydrobromic acid to yield a hygroscopic, sirupy mass. The product was purified by heating an aqueous solution of the sirup with activated charcoal (Darco), filtering and evaporating the filtrate to dryness. This purification process was repeated. The hygroscopic, sirupy mass crystallized after standing for several weeks in a vacuum desiccator over concentrated sulfuric acid. The yield of crystals, m.p. 105–109°, was 92%. The melting points given in the literature for this tribasic acid are quite varied: Arbuzov and Razumov[12] reported 119–132°; Nylen,[13] 75–95°; and Kosolapoff and Powell,[14] above 70° (indefinite).

Anal. Calcd. for $C_3H_7O_5P$: C, 23.39; H, 4.58; P, 20.11. Found: C, 22.99; H, 4.74; P, 19.45.

Attempted Addition of Diethyl Hydrogen Phosphite to Methyl 2-Bromoacrylate. A. Without a Catalyst.—A mixture of diethyl hydrogen phosphite (41.4 g., 0.3 mole) and methyl 2-bromoacrylate (49.5 g., 0.3 mole) was stirred on the steam-bath for 5 hr. and then allowed to stand overnight. About 36.0 g. of methyl 2-bromoacrylate and 31.0 g. of diethyl hydrogen phosphite were recovered by distilla-

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[8] F. C. Whitmore, THIS JOURNAL, **54**, 3274 (1932).

[9] C. S. Marvel and J. C. Cowan, *ibid.*, **61**, 3156 (1939).

[10] A. E. Arbuzov and A. A. Dunin, *Ber.*, **60**, 291 (1927).

[11] P. Nylen, *ibid.*, **59**, 1119 (1926).

[12] Arbuzov and Razumov, *J. Russ. Phys. Chem. Soc.*, **61**, 623 (1929).

[13] P. Nylen, *ibid.*, **57**, 1023 (1924).

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

tion of the mixture. The solid residue (14.0 g.) was dissolved in acetone and then precipitated in methanol to obtain 5.0 g. of white, powdered polymethyl bromoacrylate. This material contained no phosphorus. The recovery of starting materials either unreacted or as polymethyl bromoacrylate amounted to 89%.

B. In the Presence of Triethyl Phosphite.—A mixture of diethyl hydrogen phosphite (41.4 g., 0.3 mole), methyl 2-bromoacrylate (49.5 g., 0.3 mole) and triethyl phosphite (1.0 g.) was heated on the steam-bath for 5 hr. After standing 3 days, the reaction mixture was distilled. The recovery of starting materials either unreacted or as polymethyl bromoacrylate amounted to 89%.

C. In the Presence of Sodium Diethyl Phosphite.—Diethyl hydrogen phosphite (41.4 g., 0.3 mole) was treated with sodium (0.05 g., 0.002 mole), then added to methyl 2-bromoacrylate (49.5 g., 0.3 mole). The mixture was heated at 75–80° for 4 hr., then distilled. Recovery of diethyl hydrogen phosphite and methyl 2-bromoacrylate amounted to over 95%.

Acknowledgments.—We wish to thank Mr. Marshall Otis and Mr. Cham Canon for their help in interpreting the infrared absorption spectra.

KINGSPORT, TENNESSEE

[CONTRIBUTION FROM THE CARLSBERG LABORATORY]

The Iron Catalysis of Thioglycolate Oxidation by Oxygen

BY HILDEGARD LAMFROM[1] AND SIGURD OLAF NIELSEN

RECEIVED NOVEMBER 9, 1956

The rate of anaerobic bleaching of red ferric thioglycolate in mixed thioglycolate (0.2 *M*)–acetate (0.1 *M*)–phosphate (*M*/15) buffers *p*H 4.6–5.8 at 37° (system I) has been measured spectrophotometrically and shown to follow second-order kinetics, whereas the anaerobic bleaching of the labile blue ferric thioglycolate in 0.07 *M* thioglycolic acid in 60% ethanol at −35° follows first-order kinetics. In the air saturated system I the rate of oxidation, catalyzed by 1.4×10^{-5} *M* iron salt, was measured, as well as the steady-state concentration of red ferric thioglycolate. The oxidation rate was maximal at *p*H 4.9. The iron catalysis of thioglycolate (RSH^-) oxidation by oxygen has sometimes been assumed to proceed as follows: (a) formation of ferrous complex, Fe(II)RS-complex, (b) oxidation: Fe(II)RS-complex + O_2 → Fe(III)RS-complex, and (c) autoöxidation–reduction: Fe(III)RS-complex → Fe(II)RS-complex + $RSSR^{--}$. It is shown that the oxidation rate calculated for this scheme can account for only 1–3% of the experimentally observed oxidation rate. A modification of this reaction scheme involving free radicals is discussed.

Introduction

The oxidation of sulfhydryl compounds has attracted much interest following the discovery of cysteine and its metal-catalyzed oxidation by molecular oxygen.[2] It could be demonstrated that carefully purified samples of cysteine show but slow oxidation,[3] and that iron and copper ions are potent catalysts for the oxidation of a variety of sulfhydryl compounds by oxygen.[4] The nature of this catalysis was exemplified by the behavior of neutral solutions of ferric salt and thioglycolate. The initial red color formed on addition of ferric salt gradually fades, but can be regenerated by shaking the solution with air as long as there is unreacted thioglycolate present.[5] When iron is replaced by cobalt a stable brown cobalti-complex is formed upon aeration.[6] On the basis of these observations a mechanism A has been proposed for the iron-catalyzed oxidation of sulfhydryl compounds, exemplified by cysteine and thioglycolic acid. This scheme involves 3 principal steps[7]: (a) formation of a ferrous complex with the sulfhydryl compound, (b) oxidation of the ferrous complex to a ferric complex by oxygen, and (c) autoöxidation-reduction of the ferric complex forming the corresponding disulfide and ferrous complex.[8]

$$\mathrm{Fe(II)} + \mathrm{RSH^-} \longrightarrow \mathrm{Fe(II)RS\text{-}complex}$$
$$\mathrm{Fe(II)RS\text{-}complex} + \mathrm{O_2} \longrightarrow \mathrm{Fe(III)RS\text{-}complex}$$
$$\mathrm{Fe(III)RS\text{-}complex} \longrightarrow \mathrm{Fe(II)RS\text{-}complex} + \mathrm{RSSR^{--}}$$

A restatement of this principal scheme has recently appeared in the literature.[9] Accurate determinations of the composition[10] and rate of break-down[11] of the red ferric thioglycolate in the alkaline *p*H range have been made. A check of reaction scheme A now seems possible by comparing the observed over-all rate of oxidation by oxygen with the oxidation rate calculated on the basis of A from the rate of break-down of ferric thioglycolate and its steady state concentration in air-saturated solution. Such a comparison is undertaken in the present investigation.

Experimental

Thioglycolic acid (80% Merck puriss.) was purified by vacuum distillation and stored as a 7 *M* aqueous solution in a glass stoppered bottle at 3°. After 4 months of use the disulfide content was estimated spectrophotometrically to be less than 3%. All other chemicals were of analytical grade. Glass distilled water was used throughout. Spectrophotometric measurements were made in a Beckman DU spectrophotometer equipped with a 2 sec. Brown recorder[12] and thermostated cell compartment.

Bleaching of Red Complex.—For measuring the bleaching of the red ferric thioglycolate complex in an oxygen-free system

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(1) This work was done during the tenure of a Research Fellowship of the American Heart Association.

(2) E. Baumann, *Hoppe Seylers Z. physiol. Chem.*, **8**, 299 (1883–1884).

(3) O. Warburg and S. Sakuma, *Pflügers Arch. ges. Physiol.*, **200**, 203 (1923).

(4) F. Bernheim and M. L. C. Bernheim, *Cold Spring Harbor Symposia Quant. Biol.*, **7**, 174 (1939).

(5) R. Andreasch, *Ber.*, **12**, 1390 (1879).

(6) L. Michaelis and M. P. Schubert, THIS JOURNAL, **52**, 4418 (1930).

(7) M. P. Schubert, *ibid.*, **54**, 4077 (1932). Several similar proposals have appeared in the literature, see ref. 11.

(8) The following abbreviations are used: thioglycolic acid, HRSH and dithiodiglycolic acid HRSSRH.

(9) A. E. Martell and M. Calvin, "Chemistry of the Metal Chelate Compounds," Prentice–Hall, Inc., New York, N. Y., 1952, p. 384.

(10) D. L. Leussing and I. M. Kolthoff, THIS JOURNAL, **75**, 3904 (1953).

(11) D. L. Leussing and L. Newman, *ibid.*, **78**, 552 (1956).

(12) S. O. Nielsen, *Rev. Sci. Instr.*, **26**, 516 (1955).