tate was treated with ozone at −80° at the rate of 0.5 mmole per minute. After five minutes, unreacted ozone was present in the effluent gases whereupon ozonization was halted and the mixture concentrated to 20 ml. under reduced pressure. This residue was diluted to 250 ml. with water, and after standing for several days aliquot samples were removed and analyzed for formaldehyde. Colorimetric determination with chromotropic acid indicated a 14.6% yield of formaldehyde whereas gravimetric determination as the methone derivative gave a 12.2% recovery.

Diethyl Isopropyl Phosphate (IX) from VIII.—A solution of VIII (1.54 g., 7.9 mmoles) in 20 ml. of ethyl acetate was hydrogenated in the presence of 210 mg. of 10% palladium-on-charcoal. At the end of 42 minutes, 8.4 mmoles of hydrogen had been absorbed and further uptake ceased. After removal of the catalyst and the solvent, the residue was distilled to yield diethyl isopropyl phosphate (IX), 1.1 g., 70%, b.p. 84–86° (20 mm.), $n^{25}\text{D}$ 1.4038. This material is quite hygroscopic; a hydroxyl peak was observed in the infrared absorption spectrum unless determined in carbon tetrachloride solution immediately after drying over magnesium sulfate, in which case the infrared spectrum (characteristic peaks at 1167 and 1262 cm.$^{-1}$) was identical with that of a similarly dried solution of authentic diethyl isopropyl phosphate. Analytical results on a sample of the pure liquid IX dried with magnesium sulfate were not quite correct, but they were similar to those found with the authentic material (see below). Phosphorus analyses were low and varied widely on duplicate samples of this substance.

Anal. Calcd. for $C_7H_{17}O_4P$: C, 42.86; H, 8.67; neut. equiv., 196. Found: C, 41.50; H, 8.78; neut. equiv., 200.[19]

Diethyl Isopropyl Phosphate (IX) from Diethyl Phosphonate.[12]—A solution of diethyl phosphonate (13.8 g., 0.10 mole), dry isopropyl alcohol (20 ml.), bromotrichloromethane (20 ml.) and 2,6-lutidine (20 ml.) in 100 ml. of dry ether was allowed to stand overnight at room temperature whereupon a copious precipitate of amine hydrobromide was formed. This was removed by filtration, and the filtrate was washed with 15 ml. of water, dried and evaporated under reduced pressure. Distillation of the residue yielded diethyl isopropyl phosphate, 3.9 g., 24%, b.p. 101–103° (20 mm.), $n^{25}\text{D}$ 1.4042. The infrared spectrum of this compound (in CCl_4) showed characteristic peaks at 1167 and 1262 cm.$^{-1}$. As mentioned previously, because of the hygroscopic nature of this substance, it was necessary to dry the solution before determination of the spectrum, and the results obtained on microanalysis were not quite correct even after drying the sample with magnesium sulfate.

Anal. Calcd. for $C_7H_{17}O_4P$: C, 42.86; H, 8.67; P, 15.76; neut. equiv., 196. Found: C, 41.65; H, 8.92; P, 13.26; neut. equiv., 207.[19]

Diethyl Hydrogen Phosphate (X) from VIII.—Preliminary investigations of the hydrogenation of diethyl isopropenyl phosphate (VIII) using reduced platinum oxide in ethyl acetate indicated that two moles of hydrogen were absorbed to form a strongly acidic product. In one experiment VIII (186 mg., 0.96 mmole) in 15 ml. of ethyl acetate was hydrogenated using 45 mg. of platinum oxide, whereupon 1.69 mmoles of hydrogen were absorbed in 15 minutes. After filtration, the entire reduction mixture was titrated electrometrically with standard alkali to *p*H 7.9. In this way an equivalent weight of 202 was obtained for VIII as compared to the calculated value of 194.

To isolate the reduction product, a solution of VIII (3.5 g., 0.018 mole) in 35 ml. of absolute ethanol was hydrogenated in a Parr apparatus with 400 mg. of platinum oxide for 90 minutes. After filtration and evaporation of the solvent, the residue was distilled in a molecular still to yield diethyl hydrogen phosphate (X), 1.66 g., 60%, $n^{25}\text{D}$ 1.4170, reported[21] $n^{25}\text{D}$ 1.4152.

Anal. Calcd. for $C_4H_{11}O_4P$: C, 31.20; H, 7.14; P, 20.15. Found: C, 31.30; H, 7.37; P, 20.20.

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[21] A. D. F. Toy, THIS JOURNAL, **70**, 3882 (1948).

CHICAGO 37, ILLINOIS

[CONTRIBUTION FROM THE BEN MAY LABORATORY FOR CANCER RESEARCH AND THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF CHICAGO]

Phosphonic Acids. V.[1] An Improved Method for the Preparation of Sodium Diethyl Phosphonate and a Study of its Comparative Reactivity with Alkyl Halides and *p*-Toluenesulfonates[2]

BY RONALD G. HARVEY, TERRELL C. MYERS, HERBERT I. JACOBSON AND ELWOOD V. JENSEN

RECEIVED JUNE 18, 1956

Sodium diethyl phosphonate is prepared rapidly and conveniently by treatment of a solution of diethyl phosphonate with an excess of sodium hydride. In tetrahydrofuran solution, the relative reaction rates of primary alkyl halides and *p*-toluenesulfonates with sodium diethyl phosphonate are RBr > ROTs > RCl. The reaction of sodium diethyl phosphonate with trimethylene chlorobromide gives diethyl γ-chloropropylphosphonate, which on hydrolysis yields γ-chloropropylphosphonic acid.

Sodium diethyl phosphonate, or sodium diethyl phosphite, a reagent commonly used for the preparation of phosphonic acid esters, generally has been prepared[3] by treatment of a solution of diethyl phosphonate with either an equivalent amount of sodium ethoxide (or methoxide) or else with metallic sodium which dissolves with the evolution of hydrogen. Since alcohol and diethyl phosphonate probably do not differ greatly in their acid strengths the former method has the disadvantage that some sodium ethoxide may remain in the mixture either to compete with sodium diethyl phosphonate in its nucleophilic reactions or to react with the products formed. The latter procedure has the disadvantage that metallic sodium dissolves rather slowly in solutions of diethyl phosphonate so that many hours or even days may be required for completion of the reaction. Moreover, the dissolving metal acts as a reducing agent, and solutions of sodium diethyl phosphonate prepared in this way invariably are contaminated with phosphine compounds as indicated by the characteristic odor.[4]

It was found that the undesirable features of either procedure could be avoided by the use of sodium hydride as the basic reagent according to the equation

$$\text{HPO(OEt)}_2 + \text{NaH} \longrightarrow \text{NaPO(OEt)}_2 + {}^1/_2\text{H}_2$$

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[1] Paper IV, H. I. Jacobson, M. J. Griffin, S. Preis and E. V. Jensen, THIS JOURNAL, **79**, 2608 (1957).

[2] This investigation was supported in part by a grant from the National Institutes of Health, Public Health Service (RG-3053).

[3] G. M. Kosolapoff, "The Organic Chemistry of Phosphorus," John Wiley and Sons, Inc., New York, N. Y., 1950, Ch. 7.

[4] P. Nylen, Dissertation, Uppsala, 1930, p. 32.

A suspension of this substance reacts rapidly with a tetrahydrofuran solution of diethyl phosphonate with the evolution of hydrogen to produce a solution of sodium diethyl phosphonate free from phosphine odors.

Recently it was observed that primary and secondary alkyl esters of *p*-toluenesulfonic and methanesulfonic acids react with sodium diethyl phosphonate in a manner similar to that of alkyl halides to produce the corresponding diethyl alkyl-

$$\mathrm{ROTs + NaPO(OEt)_2 \longrightarrow RPO(OEt)_2 + NaOTs}$$

phosphonate esters.[5] In order to evaluate the potential usefulness of this reaction, a comparison was made of the relative reactivity of alkyl chlorides, bromides and tosylates toward sodium diethyl phosphonate. In this study, freshly prepared sodium diethyl phosphonate[6] was allowed to react at 20° in tetrahydrofuran solution with a threefold excess of *n*-butyl bromide, *n*-butyl chloride and *n*-butyl tosylate, respectively. The progress of these reactions was followed by measurement of the bromide, chloride or tosylate ions produced at various time intervals. As indicated by the data of Fig. 1, the relative reactivities are in the order Br > OTs > Cl with the initial rates in the approximate order of 280:70:1.

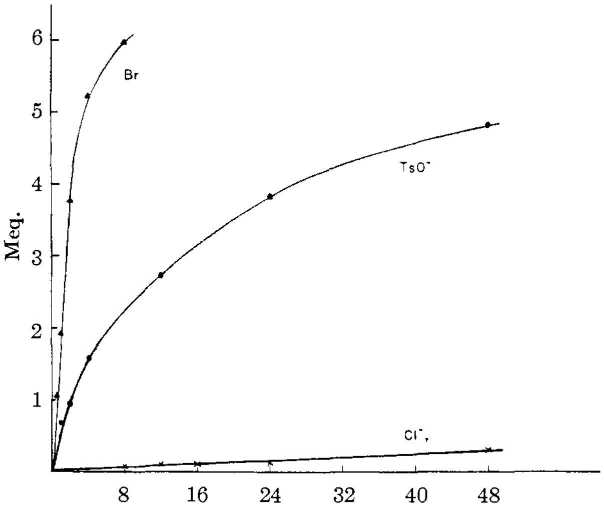

Fig. 1.—Liberation of ions from the reaction of sodium diethyl phosphonate (10 meq. from Na) with either *n*-butyl bromide, *n*-butyl tosylate or *n*-butyl chloride (30 meq.) at 20°.

When sodium diethyl phosphonate is allowed to react with a mixture of excess *n*-butyl bromide and *n*-butyl tosylate at 30°, bromide ion is liberated at about 4 times the rate of tosylate (Fig. 2). The concentration of bromide ion reaches a maximum in about 2 hr., whereupon it begins to disappear rapidly with an accompanying increase in the rate of appearance of tosylate ion. Similarly, when sodium diethyl phosphonate is allowed to react with a mixture of butyl chloride and butyl tosylate, chloride ion reaches a maximum concentration and then disappears (Fig. 3).

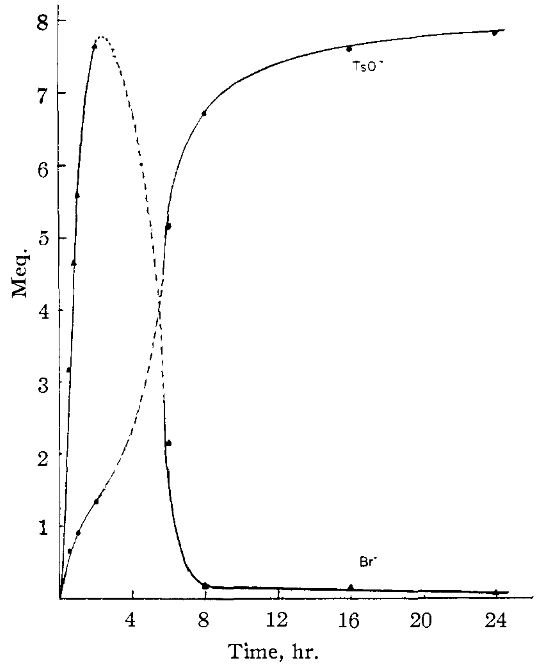

Fig. 2.—Liberation of ions from the reaction of sodium diethyl phosphonate (10 meq. from NaH) with a mixture of *n*-butyl bromide (30 meq.) and *n*-butyl tosylate (30 meq.) at 30°.

The disappearance of bromide (and chloride) ion probably results from a reaction with butyl tosylate in the following manner

$$\mathrm{ROTs + Br^- \longrightarrow RBr + TsO^-}$$

However, a suspension of finely pulverized sodium bromide in tetrahydrofuran shows little tendency to react with butyl tosylate. It would appear that the sodium bromide produced from the reaction of sodium diethyl phosphonate with alkyl bromides may be in an extremely finely divided or otherwise reactive form. That this reactivity is gradually lost is indicated by an experiment in which sodium diethyl phosphonate was allowed to react with butyl bromide for 15 hr. at 30° and then butyl tosylate added. As is shown in Fig. 4, again there is a disappearance of bromide ion accompanied by an appearance of tosylate ion, but in this case it is much less rapid or complete than when the butyl tosylate is present during the liberation of the sodium bromide.

In all the reactions studied, using sodium diethyl phosphonate prepared both from sodium and from sodium hydride, the amount of halide or tosylate ions liberated was never greater than 70 to 80% of that calculated on the basis of the diethyl phosphonate employed, even after very long reaction

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[5] T. C. Myers, S. Preis and E. V. Jensen, THIS JOURNAL, **76**, 4172 (1954).

[6] A number of these experiments were carried out previous to the development of the sodium hydride method for the preparation of sodium diethyl phosphonate, and in these studies metallic sodium was employed for the preparation of this reagent. However, the rates of liberation of sodium bromide from *n*-butyl bromide at 30° with sodium diethyl phosphonate prepared by either method were found to be similar. The results obtained with a mixture of butyl bromide and butyl tosylate illustrated in Fig. 2 for sodium diethyl phosphonate prepared with sodium hydride are entirely analogous to those obtained with the reagent prepared from metallic sodium.

periods. These results indicate either that excess sodium or sodium hydride does not convert diethyl phosphonate completely to the sodium derivative or, more probably, that sodium diethyl phosphonate does not react completely with excess alkyl halide or tosylate. Evidence suggesting the latter possibility has been obtained by other investigators.[7]

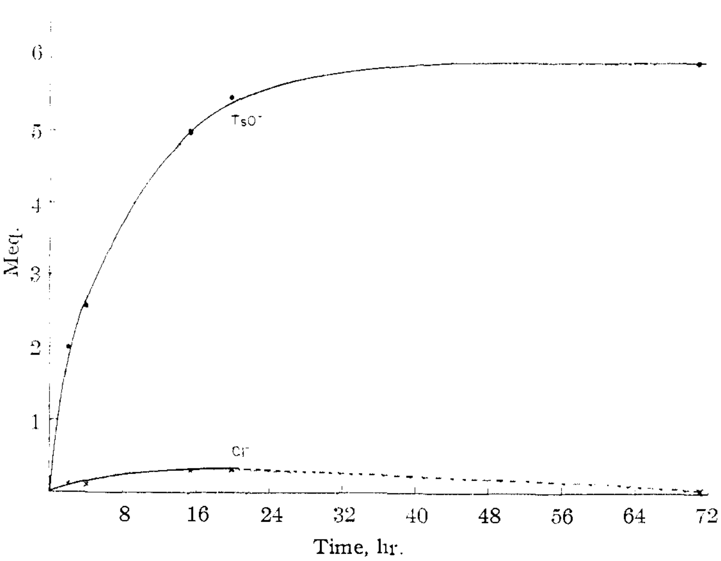
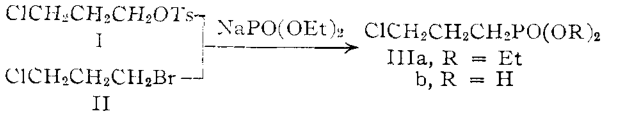


Fig. 3.—Liberation of ions from the reaction of sodium diethyl phosphonate (10 meq. from Na) with a mixture of *n*-butyl chloride (30 meq.) and *n*-butyl tosylate (30 meq.) at 30°.



$$\left.\begin{array}{c}\underset{\text{I}}{ClCH_2CH_2CH_2OTs}\\ \underset{\text{II}}{ClCH_2CH_2CH_2Br}\end{array}\right] \xrightarrow{NaPO(OEt)_2} \begin{array}{c}ClCH_2CH_2CH_2PO(OR)_2\\ \text{IIIa, R = Et}\\ \text{b, R = H}\end{array}$$

When sodium diethyl phosphonate was allowed to react in tetrahydrofuran with an equimolar amount of trimethylene chlorohydrin tosylate (I), diethyl γ-chloropropylphosphonate (IIIa) was isolated in 22% yield; with two molar proportions of trimethylene chlorobromide (II) the yield of IIIa was 54% based on sodium diethyl phosphonate. Hydrolysis of IIIa with concentrated hydrochloric acid gave crystalline γ-chloropropylphosphonic acid (IIIb).

Experimental

Reagents.—Commercial diethyl phosphonate, *n*-butyl chloride, *n*-butyl bromide and *n*-butyl tosylate[8] were redistilled before use. Tetrahydrofuran was dried by distillation from calcium hydride and stored over sodium. The sodium hydride used was a bluish material obtained from the du Pont Co.: the gray product obtained from Metal Hydrides, Inc., was found unsatisfactory in that it produced brown solutions and formed gelatinous material which prevented filtration of the final solution. It was found convenient to weigh out several 4-g. portions of du Pont sodium hydride in a dry-box and store these in stoppered bottles in a desiccator. The entire contents of one bottle then was used for an individual preparation of sodium diethyl phosphonate as described below without further need for the dry-box.

In the competition experiments which were carried out previous to the development of the sodium hydride method for the preparation of sodium diethyl phosphonate, this reagent was prepared in the conventional manner[3] by dissolving metallic sodium in a tetrahydrofuran solution of diethyl phosphonate. The method of preparation of sodium diethyl phosphonate is specified for each experiment.

Preparation of Sodium Diethyl Phosphonate with Sodium Hydride.—The reaction of diethyl phosphonate with sodium hydride was carried out conveniently in a dry 300-ml. 2- or 3-necked flask equipped with a dropping funnel with pressure equalizer and an outlet protected by a drying tube. In the bottom of the flask was sealed a medium porosity fritted glass disk[9] through which the final solution could be filtered through an all-glass connection into a 250-ml. volumetric flask. A continuous stream of dry helium or nitrogen at about 5 cm. pressure was introduced through this disk both to flush out the system and to stir the contents of the flask during the reaction.

Approximately 100 ml. of dry tetrahydrofuran was placed in the flask and a bottle of sodium hydride containing a 10% molar excess over the diethyl phosphonate to be used was opened and quickly emptied into the tetrahydrofuran. This mixture was cooled to −12° by immersion in a Dry Ice–chloroform–carbon tetrachloride mixture, and then diethyl phosphonate was added from the dropping funnel at such a rate that the evolution of hydrogen did not become too vigorous. After addition was complete the mixture was allowed to stand at room temperature until the evolution of hydrogen from the sodium hydride particles had practically ceased. The helium stream, now at about 20 cm. pressure, was transferred to the original outlet tube forcing the reaction mixture through the fritted disk into the volumetric flask. The residual sodium hydride was washed with two portions of dry tetrahydrofuran which were then filtered into the volumetric flask. The latter was now removed and its contents made up to volume with dry tetrahydrofuran. Such stock solutions of sodium diethyl phosphonate are colorless, free of phosphine odors and appear to be stable for several days when stored in the refrigerator.

Rate Studies.—The reaction of *n*-butyl chloride, bromide and tosylate with sodium diethyl phosphonate were carried

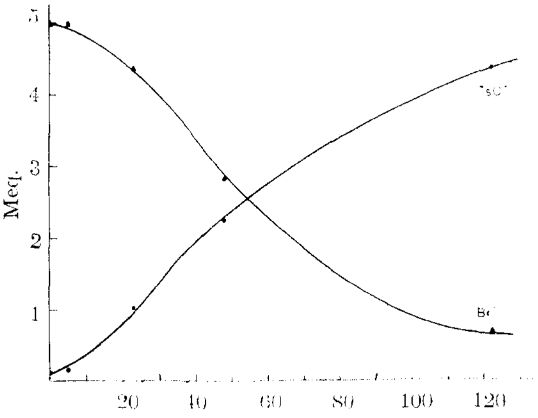


Fig. 4.—Ionic composition of a mixture of sodium diethyl phosphonate (10 meq. from NaH) and *n*-butyl bromide allowed to react for 15 hr. at 30° and then treated (at 0 time) with *n*-butyl tosylate (30 meq.) at 30°.

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[7] D. H. Chadwick and S. Kaufman, private communication, A. F. Isbell, Abstracts of the 129th Meeting of the American Chemical Society, Dallas, Texas, April, 1956, p. 2 Q.

[8] Addition of a small amount of solid sodium carbonate prevents darkening of butyl tosylate during distillation.

[9] This flask was similar to that obtainable from the Scientific Glass Apparatus Co. (#J-1779) or the H. S. Martin Co. (#M-21180) except that the connection to the fritted disk was of capillary tubing without a stopcock, terminating with a vapor outlet and standard taper connection to the volumetric flask.

out in 250-ml. volumetric flasks agitated on an Eberbach shaking machine. Reactions at 20 ± 1° were carried out in air conditioned room; reactions at 30 ± 0.2° were immersed in a constant temperature water-bath. In each flask there was placed 30 millimoles of the butyl halide or tosylate dissolved in 10 ml. of dry tetrahydrofuran. At zero time there was added 10 ml. of a tetrahydrofuran solution containing sodium diethyl phosphonate (prepared from 10 millimoles of diethyl phosphonate). After shaking for the appropriate time period, the reaction was stopped by the addition of 150 ml. of water and 60 ml. of pentane. After thorough mixing, the pentane layer was removed; the aqueous layer was diluted to volume and aliquot portions were analyzed for halide ion by the Volhard titration and for tosylate ion by comparison of the ultraviolet absorption at 261 mμ with that of a standard solution of sodium tosylate.

Diethyl γ-Chloropropylphosphonate (IIIa) from Trimethylene Chlorohydrin Tosylate (I).—A solution of I (14.9 g., 0.06 mole) and sodium diethyl phosphonate, prepared by the action of excess sodium on diethyl phosphonate (8.57 g., 0.06 mole), in tetrahydrofuran (50 ml.) was stirred at room temperature for 72 hr. Then dry pentane (70 ml.) was added and the mixture filtered. The solid residue (9.41 g.) contained chlorine (6.0%), sulfur (13.1%) and phosphorus (2.6%). The filtrate was concentrated under reduced pressure and the residue (14.2 g.) distilled. The fraction (4.3 g.) boiling at 59–78° (0.04 mm.) was redistilled to yield diethyl γ-chloropropylphosphonate (IIIa), 2.1 g., 16%, b.p. 68–70° (0.05 mm.), $n^{25}\text{D}$ 1.4423.

Anal. Calcd. for $C_7H_{16}O_3PCl$: C, 39.16; H, 7.51; P, 14.44. Found: C, 38.53; H, 7.80; P, 14.10.

The higher boiling fraction (6.7 g.) appeared to be a mixture from which no pure substances could be isolated.

Repetition of the above reaction on a 0.4 molar scale yielded similar results with diethyl γ-chloropropylphosphonate isolated in 22% yield.

From Trimethylene Chlorobromide (II).—To a stirred solution of sodium diethyl phosphonate, prepared by the action of excess sodium on diethyl phosphonate (27.6 g., 0.20 mole) in tetrahydrofuran (400 ml.), trimethylene chlorobromide (63.0 g., 0.40 mole) was added. After 15 minutes a white solid began to separate. After stirring at room temperature for 4 hr. the reaction mixture was filtered, the filtrate concentrated under reduced pressure and the residue distilled. After recovery of the excess chlorobromide, a fraction boiling at 85–100° (0.32 mm.) was collected and redistilled to yield diethyl γ-chloropropylphosphonate (IIIa), 23.2 g., 54%, b.p. 97–99° (0.25 mm.), $n^{25}\text{D}$ 1.4429.

γ-Chloropropylphosphonic Acid (IIIb).—A mixture of IIIa (3.0 g.) and concentrated hydrochloric acid (30 ml.) was heated under reflux overnight. Then the hydrochloric acid was removed under reduced pressure, and benzene (10 ml.) was added and distilled away to remove the last traces of acid. The crystalline residue (2.0 g., m.p. 95–102°) was recrystallized from chloroform to give γ-chloropropylphosphonic acid, 1.7 g., 76%, m.p. 101–104°. Further recrystallization from chloroform furnished the analytical sample, m.p. 104–105°.

Anal. Calcd. for $C_3H_8O_3PCl$: C, 22.72; H, 5.08; P, 19.55; Cl, 22.37; neut. equiv., 158.6. Found: C, 23.12; H, 5.12; P, 19.60; Cl, 22.14; neut. equiv., 158.

CHICAGO 37, ILLINOIS

[CONTRIBUTION FROM THE CHEMOTHERAPY BRANCH, CHEMICAL WARFARE LABORATORIES AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF DELAWARE]

Synthesis of a Series of Vicinally Substituted Hydroxamic Acids[1]

BY MARVIN A. STOLBERG,[2] WILLIAM A. MOSHER AND THEODOR WAGNER-JAUREGG

RECEIVED JULY 17, 1956

A series of hydroxamic acids were prepared by standard procedures from the corresponding esters with the exception of *o*-methoxybenzohydroxamic acid which was obtained from the acid chloride. Compounds which have not been previously reported in the literature are: *o*-nitrobenzohydroxamic, *o*-methoxybenzohydroxamic, *o*-dimethylaminobenzohydroxamic, *cis*-hexahydrophthalohydroxamic and *exo-cis*-3,6-endoxohexahydrophthalohydroxamic acids. *cis*-N-Hydroxyhexahydrophthalamide and *endo-cis*-N-hydroxy-3,6-endomethylene-Δ^4-tetrahydrophthalimide were obtained from the reaction of the corresponding anhydrides with hydroxylamine. Their infrared spectra were compared to that of N-hydroxyphthalimide and N-hydroxyisophthalimide.

Hydroxamic acids may be prepared by treating esters, acid chlorides or acid anhydrides with hydroxylamine.[3] Other methods, although useful in certain specific cases, generally have limited application. The hydroxamic acids described in this paper were prepared from the corresponding esters with the exception of *o*-methoxybenzohydroxamic acid which was obtained from the acid chloride. Since difficulties were encountered in the isolation and purification of the hydroxamic acids and prime attention was paid to the purity of the products, the yields reported do not necessarily reflect efforts to reach a maximum. A good general method for the separation of certain hydroxamic acids from the corresponding carboxylic acids which are frequent impurities is by treatment of an alkaline aqueous solution with carbon dioxide, which results in precipitation of the hydroxamic acid. This method is applicable to water-insoluble hydroxamic acids that have a pK_a above 9.0.

Compounds prepared for this investigation which have not been previously reported in the literature are: *o*-nitrobenzohydroxamic,[4] *o*-methoxybenzohydroxamic,[4] *o*-dimethylaminobenzohydroxamic, *cis*-hexahydrophthalohydroxamic and *exo-cis*-3,6-endoxohexahydrophthalohydroxamic acids. The latter compound proved to be a powerful vesicant and contact with the skin should be avoided. This compound has a basic structure similar to cantharidine, which is a well known vesicant.

An attempt was made to prepare *o*-hydroxymethylbenzohydroxamic acid from phthalide and hydroxylamine. A small portion of the crude sodium salt of the product obtained produced a deep wine color when treated with ferric chloride in 0.1 *N* HCl which is typical of hydroxamic acids. However, treatment of an aqueous solution of the salt with carbon dioxide or hydrochloric acid

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[1] Abstracted from the dissertation submitted by M. A. Stolberg to the University of Delaware in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1956.

[2] To whom inquiries should be forwarded: Tracerlab, Inc., 1601 Trapelo Rd., Waltham, Mass.

[3] H. L. Yale, *Chem. Revs.*, **33**, 209 (1943); F. Mathis, *Bull. soc. chim., France*, **5**, D9 (1953).

[4] These compounds were reported as the barium salts by R. D. Bright and C. W. Hauser, THIS JOURNAL, **61**, 618 (1939).