cyclohexenyl ester II in 95% ethanol was reduced over 10% palladium on charcoal in a Parr hydrogenation apparatus. Fractional distillation of the product gave a 62% yield of the saturated ester, b.p. 97° (23 mm.), $n^{25}D$ 1.4387 (lit.,[11] b.p. 195–200, $n^{25}D$ 1.4396).

Alkaline Hydrolyses.—Except in the case of ethyl acetate, approximately 0.1 *M* solutions of the esters were prepared by dissolving the required amount of ester in 70 ml. of anhydrous acetone and diluting with 30 ml. of water. In the case of ethyl acetate an approximately 0.4 *M* aqueous solution was prepared and 30 ml. of this solution diluted with 70 ml. of acetone. The concentration of each ester solution was checked before use by complete hydrolysis with excess base and back titration with acid.

For the alkaline hydrolyzing agent, 30 ml. of *ca.* 0.33 *M* carbonate free sodium hydroxide was diluted with 70 ml. of acetone.[12] The concentration of this solution was determined by titration immediately before use.

After the ester and base solutions had both equilibrated at 25.0°, 50 ml. of each solution was transferred into a 100-ml. volumetric flask which was stoppered, well shaken and quickly returned to the thermostat. The reaction was followed by withdrawing 5-ml. aliquots at suitable time intervals, running them into 10 ml. of 0.05 *N* hydrochloric acid, and finally titrating the excess acid with 0.05 *N* sodium hydroxide solution against phenolphthalein.

The second-order rate constants were computed by the Widequist technique.[13]

Acid Hydrolyses.—The ester and hydrochloric acid solutions were prepared in the same manner as described under the base hydrolyses. Because of the slow rate of reaction and the volatility of the solvent, 5-ml. aliquots were sealed in glass ampoules and these equilibrated at 25.0°. At suitable time intervals the contents of a tube were titrated with sodium hydroxide solution.

The rate constants were calculated in the standard fashion.[5]

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[11] S. Ono and T. Yamauchi, *Bull. Chem. Soc. Japan*, **25**, 404 (1952).

[12] In an attempt to prepare 0.2 *N* solutions of sodium hydroxide in 70% acetone–water, a difficulty visible phase separation occurred. The volumes and composition of the two phases appears to be critically dependent on the concentration of base. With the 0.1 *N* base employed here no phase separation was noted.

[13] A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, 1953, p. 18.

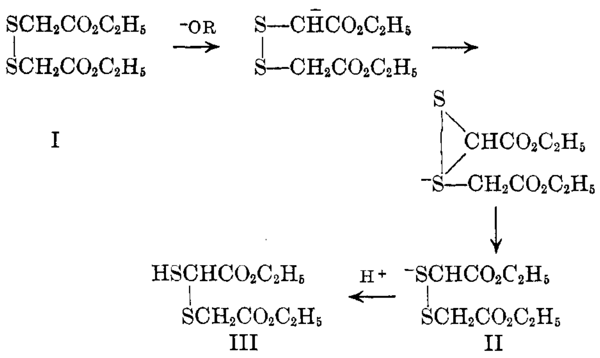
Base-Catalyzed Rearrangement of Diethyl Dithiodiglycolate

E. G. Howard

Contribution No. 695 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Co., Wilmington, Del.

Received June 8, 1961

The diethyl ester of dithiodiglycolic acid (I) has been found to undergo a rapid rearrangement, even at −50°, when treated with sodium alkoxide, and the product has proved to be the sodium salt of diethyl 2-mercapto-3-thiaglutarate (II). The ionization of a methylene group is pictured as being the first step in the rearrangement. The carbanion possibly forms a three-membered ring that rearranges to the product II.

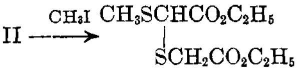


The assignment of structure is based on the following physical and chemical properties of compound III. (1) The infrared absorption spectrum possesses a band at 3.95 μ, which is indicative of the mercaptan group. (2) Slow distillation of III gives ethyl mercaptoacetate and a liquid believed to be a trimer of ethyl thioglyoxylate. (3) Compound III gives a positive sodium nitroprusside test. (4) Titration of III with iodine solution requires more titer when smaller samples or more dilute solutions are used or when the titrations are carried out over an extended period of time. These are conditions which would permit the hydrolysis of an unstable hemimercaptal group to a mercaptan

$$\mathrm{III} \xrightarrow[\text{vacuum}]{\text{heat}} \mathrm{HSCH_2CO_2C_2H_5} + (\mathrm{SCHCO_2C_2H_5})_n$$

$$\xrightarrow{\mathrm{H_2O}} \mathrm{H_2S} + \mathrm{HSCH_2CO_2C_2H_5} + \mathrm{OCHCO_2C_2H_5}$$

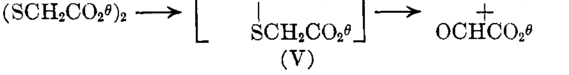
(5) Methylation of the anion II with methyl iodide gave IV which is stable and easily purified by distillation



$$\mathrm{II} \xrightarrow{\mathrm{CH_3I}} \begin{array}{l}\mathrm{CH_3SCHCO_2C_2H_5}\\ \quad\ |\\ \quad\mathrm{SCH_2CO_2C_2H_5}\end{array}$$

IV

It is suggested that compounds of type III are involved in the cleavage of dithiodiglycolic acids by aqueous base where the product is in turn hydrolyzed to salts of hydrogen sulfide, mercaptoacetic acid, and glyoxylic acid.[1] Supporting evidence is found in the fact that I gave the typical yellow color of II even when treated with 30% aqueous sodium hydroxide at 0°. A yellow color similar to that of II has also been observed in the rearrangement of dithiodiglycolic acid.[2]



$$(\mathrm{SCH_2CO_2}^{\ominus})_2 \xrightarrow{\mathrm{OH^-}} \left[\begin{array}{l}{}^{\ominus}\mathrm{S{-}CHCO_2}^{\ominus}\\ \quad\ |\\ \quad\mathrm{SCH_2CO_2}^{\ominus}\end{array}\right] \longrightarrow \begin{array}{c}{}^{\ominus}\mathrm{SCH_2CO_2}^{\ominus} + \mathrm{S^=}\\ +\\ \mathrm{OCHCO_2}^{\ominus}\end{array}$$

(V)

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[1] A. Schobel, *Ber.*, **70**, 1186 (1937), *et seq.*

[2] N. A. Rosenthal and G. Oster, Organic Section, 126th Meeting of the American Chemical Society, September, 1954, New York, N. Y., report that a chromophore is produced in the reaction. We found the color to be yellow.

Experimental

Rearrangement of Diethyl Dithiodiglycolate (I).—To sodium methoxide prepared by the addition of 2.3 g. (0.1 g.-atom) of sodium to methanol was added 250 ml. of absolute ether. To the stirred mixture was added at −20° a solution of 23.8 g. (0.1 mole) of diethyl dithioglycolate. The mixture immediately turned deep yellow in color and a small amount of solid precipitated. To obtain the free mercaptan, a mixture of ice, 20 ml. of concd. hydrochloric acid, and water was added to the cold reaction mixture. The organic layer was separated and dried over anhydrous magnesium sulfate. Removal of the solvent by vacuum distillation gave a pale yellow oil possessing a mercaptan odor. When the material was distilled rapidly through a short head still, a fraction was obtained, b.p. 103–104° (0.10 mm.), $n^{25}D$ 1.5042, which possessed a penetrating mercaptan odor.

Anal. Calcd. for $C_8H_{14}O_4S_2$: C, 40.31; H, 5.92; S, 26.91; mol. wt., 238. Found: C, 39.68; H, 5.53; S, 29.95; mol. wt., 208.

The infrared absorption spectrum possessed a band at 3.95 μ, which is characteristic of the mercaptan group.

The product (109 g., 92%) from a similar reaction using five times the above quantities was subjected to a slow precision distillation through an 18-in. column. The distillate, b.p. 28–30° (0.4 mm.) (pot temperature, 110°), weighed 42 g. The residue (51 g.) did not distill up to 170° (0.4 mm.) and was a liquid polymer of ethyl thioglyoxylate The distillate was redistilled, b.p. 60–61° (21 mm.), and was ethyl mercaptoacetate.

Anal. Calcd. for $C_4H_8O_2S$: C, 39.98; H, 6.71; S, 26.68. Found: C, 40.08; H, 6.79; S, 26.60.

Addition of diethyl dithiodiglycolate to either 20% aqueous sodium hydroxide at 25° or 30% aqueous sodium hydroxide at 0° gave the characteristic intense yellow color of the anion II.

Methylation of the Sodium Salt of Diethyl 2-Mercapto-3-Thiaglutarate (II).—The rearranged product from 71.5 g. (0.3 mole) of diethyl dithiodiglycolate and 0.33 mole of sodium ethoxide was stirred vigorously at −30°. When 47 g. (0.33 mole) of methyl iodide was added, the temperature rose to −10°. After 1 hr. at 0° and 2 hr. at 30°, the mixture was poured into water. The organic layer was taken up in ether, washed with dilute aqueous sodium hydroxide and water, and dried over anhydrous magnesium sulfate. The fraction (42 g.) boiling between 40 and 150° was rectified by precision distillation through an 8-in. spinning-band column using a reflux ratio of 10:1. The product weighed 21 g. (28%), b.p. 116–118° (0.40 mm.), $n^{25}D$ 1.4990 to 1.5033, proved to be diethyl 2-methylmercapto-3-thiaglutarate (IV). A center cut of this fraction, 4.6 g., b.p. 117–118° (0.40 mm.), $n^{25}D$ 1.4990, was analyzed.

Anal. Calcd. for $C_9H_{16}S_2O_4$: C, 42.84; H, 6.39; mol. wt., 252. Found: C, 42.89; H, 6.45; mol. wt., 250.

Amperometric titration with silver nitrate indicated the presence of less than 0.7% mercaptan group. The infrared absorption spectrum resembled that of compound III except that there was no characteristic band for the mercaptan group. Also the 7.3-μ band for methyl was stronger.

The Synthesis of Tetrahydropalmatrubine[1]

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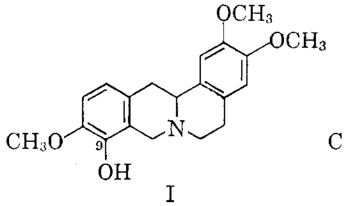
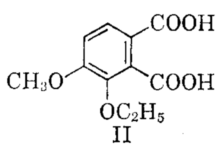
The chloride salt of the berberine alkaloid palmatine undergoes monodemethylation to yield a red compound, palmatrubine.[2] Späth and Burger[3] reduced palmatrubine to tetrahydropalmatrubine (I), and by ethylation, followed by oxidation to 3-ethoxy-4-methoxybenzene-1,2-dicarboxylic acid (II), established beyond doubt that the free hydroxyl group must have been at position 9.



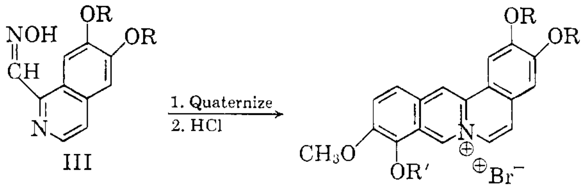
I



II

Since it has been shown that the aromatic cyclodehydration method makes possible the formation of the dehydroberberinium nucleus under very mild conditions,[4–6] it seemed probable that the first unequivocal synthesis of the tetrahydrapalmatrubine nucleus could be effected.

Crude 2-hydroxy-3-methoxybenzyl bromide formed with 6,7-dimethoxyisoquinoline-1-carboxaldoxime[6] (III. R = CH_3), a quaternary salt which cyclized in concentrated hydrochloric acid at 100° in only a few minutes to afford the new dehydropalmatrubinium bromide (IV. R = CH_3). Catalytic reduction of the bromide salt gave tetrahydropalmatrubine[1]:



III

IV. R′=H
V. R′=CH3

Dehydroberberubinium bromide (IV. R—R = —CH_2—) and its acetate were prepared also. A comparison of the ultraviolet absorption spectra of the new dehydro systems (IV) with those of the related dehydroberberinium salts (V)[5, 6] is shown in Table I.

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[1] This research was supported by a research grant (H-2170) from the National Heart Institute of the National Institutes of Health.

[2] K. Feist and G. L. Dschu, *Arch. Pharm.*, **263**, 294 (1925).

[3] E. Späth and G. Burger, *Ber.*, **59**, 1486 (1926).

[4] C. K. Bradsher and J. H. Jones, *J. Org. Chem.*, **23**, 430 (1958).

[5] C. K. Bradsher and N. L. Dutta, *J. Am. Chem. Soc.*, **82**, 1145 (1960).

[6] C. K. Bradsher and N. L. Dutta, *J. Org. Chem.*, **26**, 2231 (1961).

[7] All melting points are uncorrected. The ultraviolet absorption spectra were determined in 95% ethanol using the Warren Spectracord spectrophotometer with 1-cm. silica cells.

[8] N. Mauthner, *J. prakt. Chem.*, **158**, 321 (1941).