Since degradative evidence for the position of the second sulfur atom and the position of the oxygen atom would be difficult to obtain from the small amount of material available to us, we decided to investigate synthetically the series of parent disulfides, the thioctic acids.[2] The results of these studies are reported in detail in the following article.[9]

Experimental

S-Benzylthiuronium Salt.—A 32-mg. sample of Protogen-B was treated by the usual procedures[10] to give 47 mg. of benzylthiuronium salt, m.p. 129–132°. Recrystallized from aqueous alcohol or absolute alcohol and acetone it had m.p. 132–134°. *Anal.* Calcd. for $C_{16}H_{24}N_2S_3O_3$: C, 49.45; H, 6.23; N, 7.21; S, 24.76. Found: C, 48.68; H, 6.33; N, 7.57; S, 23.84.

Treatment with Raney Nickel.[11]—Twelve ml. of water, 0.2 ml. of 2 *M* sodium carbonate, 19.8 mg. of Protogen-B and 2 g. of Raney nickel catalyst (prepared without the use of ethanol) were shaken together 1.75 hr. at 78°. The catalyst was removed by centrifugation and washed with warm water. The combined washings and supernatant were distilled until 10 ml. of H_2O had been collected. By oxidation with acidic dichromate[12] at 100° it was found that only 12 μ equiv. of oxidizable material had distilled.

The alkaline boiler residue was acidified with sulfuric acid, and the oil which separated was extracted with ether. The extract was dried with sodium sulfate and the ether removed by evaporation with nitrogen at ice-bath temperature. The yield of crystalline residue, m.p. 13°, was 10.5 mg. The infrared spectrum of this material could not be distinguished from that of caprylic acid. The benzylthiuronium salt of this acid, m.p. 144.0–144.4° (elongated prisms from absolute ethanol), gave no depression in melting point with an authentic sample of the salt of caprylic acid, and the X-ray diffraction powder photographs of the unknown salt and the caprylate salt were indistinguishable although easily distinguished from those of the pelargonate and heptylate salts.

Titrations.—One to 3-mg. samples were obtained by evaporating aliquots of solutions of Protogen-B (purity greater than 80%) in chloroform. A syringe microburet[13] was used for delivering the titrating agents. Slow neutralization of an alcoholic solution with 0.2 *N* aqueous sodium hydroxide and with vigorous stirring (nitrogen stream) gave an equivalent weight of 224 (theory 222). Poor stirring or more concentrated alkali (1 *N*) gave low results indicative of the easily saponifiable group present. A potentiometric titration in 50% aqueous alcohol gave an apparent pK_a of 5.0.

Saponification was carried out under nitrogen in excess 0.2 *N* aqueous sodium hydroxide either for 16 hr. at room temperature or 1 hr. at 100–105°. Equivalent weights varied with the purity of the starting material, one of the better samples giving 119 (theory 111).

A 3.12-mg. sample of Protogen-B, found by neutralization and saponification to contain 12.8 μequiv. of carboxyl and 11.9 μequiv. of saponifiable group, was saponified under nitrogen with 200 μl of 0.2 *N* sodium hydroxide 1 hr. at 100°. One hundred μl. of 0.4 *N* acetic acid was added and standard 0.1 *N* iodine in potassium iodide solution added until an excess remained. After 5 minutes the excess was titrated with 0.1 *N* thiosulfate, showing that 11.7 μ eq. of iodine was reduced. Unsaponified Protogen-B did not take up any iodine under these conditions.

A second sample from the same batch, 3.07 mg. (12.6 μequiv. COOH), was saponified as above and then treated with 4 mg. of sodium borohydride at room temperature for 1.5 hr. One-hundred μl. of 2 *N* acetic acid was then added and after evolution of gas (H_2) ceased the sample was titrated with iodine and thiosulfate as above. A corresponding blank was run to take account of residual reducing action of the borohydride. The iodine required was 25.3 μequiv.

From a different batch of Protogen-B a 2.39-mg. sample required 10.3 μequiv. of sodium hydroxide for neutralization to phenolphthalein. The resulting solution was treated with 4.5 mg. of sodium borohydride for 2.5 hr. at room temperature. Acetic acid was then added and the iodine consumption found to be 20.3 μequiv. after correction for a corresponding blank.

Acknowledgments.—We would like to express our appreciation to Dr. R. C. Gore[14] for the infrared studies, to Dr. L. A. Siegel[14] for the X-ray studies, and to Mr. L. Brancone and staff for microanalytical determinations.

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(13) Micro-Metric Instrument Co., Cleveland, Ohio.

(14) Stamford Laboratories Division, American Cyanamid Co.

PEARL RIVER, NEW YORK

[CONTRIBUTION FROM THE LEDERLE LABORATORIES DIVISION OF THE AMERICAN CYANAMID COMPANY]

Syntheses in the Thioctic Acid Series

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Treatment of γ-(2-tetrahydrofuryl)-butyric acid with hydrogen bromide, acetyl bromide or a solution of potassium iodide in phosphoric acid produces primarily the 8-halogen substituted-δ-lactone of octanoic acid along with the expected rearrangement products. These lactones are converted to the corresponding dithioloctanoic acids by treatment with thiourea and hydrobromic or hydriodic acid. The dithiol acids are oxidized to the cyclic disulfides with iodine. The expected 5-thioctic acid (5,8-dithioöctanoic acid) was obtained in 22% over-all yield from γ-(2-tetrahydrofuryl)-butyric acid. Small amounts of the isomeric 4-thioctic acid (4,8-dithioöctanoic acid) and 6-thioctic acid (6,8-dithioöctanoic acid) were also isolated from the reaction mixture. The biologically important 6-thioctic acid has been prepared by another synthesis. Ethyl adipyl chloride was added to ethylene in the presence of aluminum chloride to yield on distillation ethyl 6-keto-Δ^7-octenoate. Addition of thioacetic acid to the vinyl ketone followed by a sodium borohydride reduction gave ethyl 8-acetylthio-6-hydroxyoctanoate. Saponification of this ester and treatment of the resulting 8-thiol-6-hydroxyoctanoic acid with hydriodic acid and thiourea gave, after hydrolysis of the intermediate thiuronium salt, dihydro-6-thioctic acid (6,8-dithioloctanoic acid). The dithiol acid was readily oxidized to the cyclic disulfide (6-thioctic acid) with gaseous oxygen using ferric iron as catalyst.

Preliminary communications[1,2] from this laboratory have described the preparation, physical constants and biological activity of 6-thioctic acid, 5-thioctic acid and 4-thioctic acid. The isolation of 6-thioctic acid (*dl*-α-lipoic acid) from a synthesis designed to yield 5-thioctic acid has been described.[1-4]

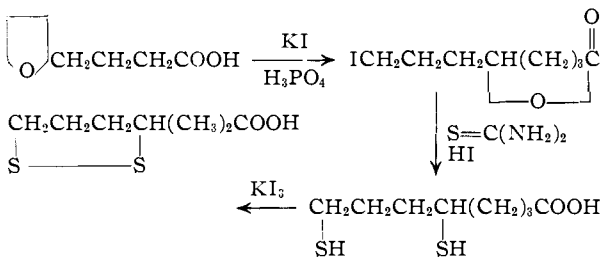
(1) M. W. Bullock, J. A. Brockman, Jr., E. L. Patterson, J. V. Pierce and E. L. R. Stokstad, THIS JOURNAL, **74**, 1868 (1952).

(2) M. W. Bullock, J. A. Brockman, Jr., E. L. Patterson, J. V. Pierce and E. L. R. Stokstad, *ibid.*, **74**, 3455 (1952).

(3) C. S. Hornberger, Jr., R. F. Heitmiller, I. C. Gunsalus, G. H. F. Schnakenberg and L. J. Reed, *ibid.*, **74**, 2382 (1952).

(4) C. S. Hornberger, Jr., R. F. Heitmiller, I. C. Gunsalus, G. H. F. Schnakenberg and L. J. Reed, *ibid.*, **75** 1273 (1953).

The synthesis of 5-thioctic acid from γ-(2-tetrahydrofuryl)-butyric acid has been accomplished by the following sequence of reactions



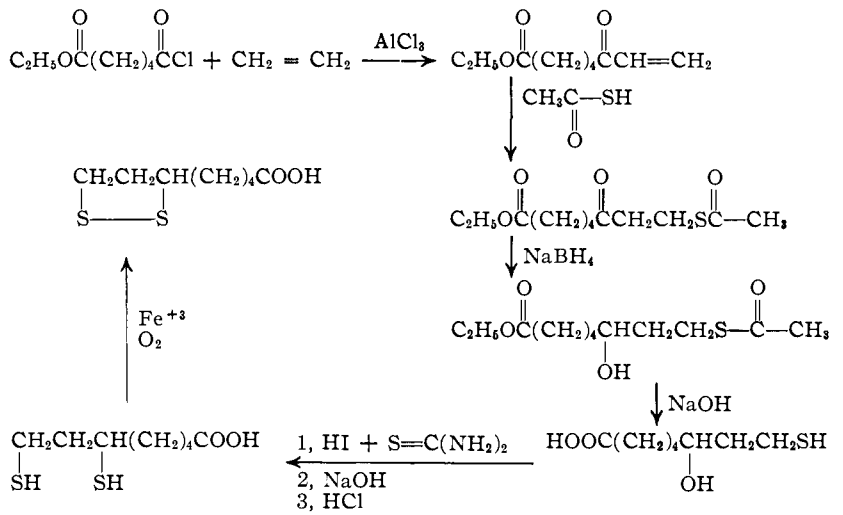
The cleavage of the tetrahydrofuran ring is accompanied by an appreciable amount of rearrangement and as a result the synthesis yields small amounts of other isomers which are not readily separated from the principal product. The reaction product obtained from the cleavage of the furan derivative with potassium iodide–phosphoric acid mixture appears to be a mixture of the diiodoöctanoic acid and the monohydroxy derivative both of which yield the lactone on distillation. The tetrahydrofuran can be treated with anhydrous hydrogen bromide to yield a mixture of the γ- and δ-lactones of 8-bromo-4- and -5-hydroxyoctanoic acids. Reaction of the γ-(2-tetrahydrofuryl)-butyric acid with acetyl bromide gave the same lactones as did the hydrogen bromide cleavage and in better yield. However, the product prepared by this method is difficult to purify, presumably due to a small amount of the 8-acetoxylactones being formed along with the bromolactones.

The halogen-substituted lactones can react with thiourea to yield, after hydrolysis of the intermediate thiuronium salts, the mercapto-hydroxy acids or lactones, or be converted directly to the dithiol compounds by treatment with excess thiourea in hydriodic or hydrobromic acid.[5] The resulting dithiol derivatives are difficult to purify due to both the presence of small amounts of isomeric compounds and to the fact that the dithiol acids are not generally completely lactonized on distillation. The products are most conveniently purified after oxidation to the cyclic disulfides which are solids and can be purified by crystallization from suitable solvents.

The 5-thioctic acid can be prepared in 22% yield from γ-(2-tetrahydrofuryl)-butyric acid without purifying the intermediates. A small amount of 4-thioctic acid can be isolated from the crude product or crystallization residues since this isomer is more difficultly soluble in nitromethane. The isomeric 6-thioctic acid could be separated from the reaction mixture only after oxidation to the thiosulfinate form and extensive purification involving countercurrent distribution and chromatography. The infrared absorption spectrum of the methyl ester of the thiosulfinate moiety was identical with that of the methyl ester of the product isolated from liver by Patterson and co-workers.[6]

The identity of the isomeric products has been confirmed by synthesis. 4-Thioctic acid was the only product that could be isolated when a sample of 4-hydroxy-8-bromoöctanoic acid lactone[7] was treated with excess thiourea in hydrobromic acid.

The biologically important 6-thioctic acid was prepared by the following sequence of reactions



The aluminum chloride-catalyzed addition of simple acid chlorides to ethylene has been discussed by J. R. Gatch and G. Baddeley and their co-workers.[8,9] We have modified the experimental conditions employed by these workers and have improved our yields. The reaction has been found to proceed most satisfactorily in nitrobenzene. The aluminum chloride complex is insoluble in carbon disulfide and the use of ethyl bromide, which is a good solvent for the complex, results in the formation of a small amount of unidentified hydrocarbon which co-distils with the product. Some hydrogen chloride is eliminated during the addition reaction and the remainder is eliminated during the distillation of the solvent and product so that the product obtained is the vinyl ketone. The conjugated ketone polymerizes slowly on storage unless stabilized with small amounts of hydroquinone. Thioacetic acid adds rapidly to ethyl 6-keto-Δ^7-octenoate to give good yields of ethyl 8-acetylthio-

(5) Hydrobromic acid is known to cause rearrangements during the conversion of secondary alcohols to bromides. See H. Pines, A. Reedin and V. N. Ipatieff, THIS JOURNAL, **74**, 4063 (1952). It has been observed in these laboratories that the product obtained when hydriodic acid is used is relatively free of rearrangement products.

(6) E. L. Patterson, J. V. Pierce, E. L. R. Stokstad, C. E. Hoffmann, J. A. Brockman, Jr., F. P. Day, M. E. Macchi and T. H. Jukes, *ibid.*, **76**, 1823 (1954).

(7) The lactone was isolated from the γ-(2-tetrahydrofuryl)-butyric acid–hydrogen bromide reaction mixture by chromatography (eluted from silicic acid with benzene) and identified as the γ-lactone by infrared analysis. The γ-lactones have a carbonyl absorption peak at 5.65 μ. See R. Rasmussen and R. R. Brattain, *ibid.*, **71**, 1073 (1949).

(8) J. R. Gatch, D. H. Hey, E. H. R. Jones and W. Wilson, *J. Chem. Soc.*, 278 (1948).

(9) G. Baddeley, H. T. Taylor and W. Pickles, *ibid.*, 124 (1953).

6-ketoöctanoate, which is reduced to the corresponding hydroxyester in 62% yield with sodium borohydride. Hydrolysis yields 8-thiol-6-hydroxyoctanoic acid which on distillation yields a mixture of the acid and its lactone along with an undistillable residue. This residue appears to be a linear polymeric ester since it can be used in the next reaction to yield the dithioloctanoic acid in about the same yield as the distilled product. It is not necessary to distil the hydroxy acid since the crude product is entirely satisfactory for use in the next synthesis.[10] Reaction of the saponified product with excess thiourea in hydrobromic acid or better hydriodic acid yields the dithiol acid after hydrolysis of the intermediate thiuronium salt.[11] The 6,8-dithioloctanoic acid was purified by distillation, dissolved in a molar amount of potassium carbonate and oxidized with gaseous oxygen using ferric chloride as catalyst and indicator. This procedure has been found to be superior to oxidation with potassium triiodide.

Experimental[12]

Cleavage of γ-(2-Tetrahydrofuryl)-butyric Acid with Potassium Iodide and Phosphoric Acid.—γ-(2-Tetrahydrofuryl)-butyric acid was prepared from 3-(2-tetrahydrofuryl)-propanol-1[13] by the method of Gilman and Hewlett.[14] A solution of 95% phosphoric acid was made by dissolving 11 g. of phosphorus pentoxide in 100 g. of 85% phosphoric acid. The solution was cooled and 50 g. (0.316 mole) of γ-(2-tetrahydrofuryl)-butyric acid and 200 g. of potassium iodide were added. The resulting mixture was stirred rapidly and heated at 125–140° for three hours. The solution was diluted with enough water to dissolve the solid phase and the product extracted with two 100-ml. portions of ether. The combined ether extracts were washed with dilute sodium thiosulfate solution and dried over sodium sulfate. Distillation of the ether left 85.5 g. of yellow oil. An infrared analysis of the crude product showed that the oil was primarily a mixture of 8-iodo-5-hydroxycaprylic acid and its lactone together with the expected rearrangement products. Distillation of an aliquot of this material gave a lactone,[15] b.p. 148–150° at 0.1 mm., $n^{24}D$ 1.5496.

Anal. Calcd. for $C_8H_{13}O_2I$: sapon. equiv., 134.1; C, 35.84; H, 4.89; I, 47.34. Found: sapon. equiv., 132.5; C, 32.97; H, 4.88; I, 50.84.

Cleavage of γ-(2-Tetrahydrofuryl)-butyric Acid with Hydrogen Bromide.—Dry hydrogen bromide was passed into 100 g. (0.631 mole) of γ-(2-tetrahydrofuryl)-butyric acid at 100° until the solution was saturated with the gas. The excess hydrogen bromide was removed by heating on the steam-bath under the reduced pressure of a water aspirator, the product purified by distilling twice under reduced pressure. The purified product distilled at 139° at 0.1 mm. and had $n^{20}D$ 1.5001. The yield was 78.5 g. (56%) of a mixture of 8-bromo-5-hydroxy- and 8-bromo-4-hydroxycaprylic acid lactones as shown by infrared analysis.

Anal. Calcd. for $C_8H_{13}O_2Br$: sapon. equiv., 110.5; C, 43.45; H, 5.92; Br, 36.14. Found: sapon. equiv., 110.6; C, 43.26; H, 6.21; Br, 36.30.

Cleavage of γ-(2-Tetrahydrofuryl)-butyric Acid with Acetyl Bromide.—One hundred grams (0.63 mole) of γ-(2-tetrahydrofuryl)-butyric acid was placed in a 250-ml. round bottom flask equipped with a condenser and 117 g. (0.955 mole) of acetyl bromide was poured slowly down the condenser. The solution became dark and refluxed from the heat of reaction. After the spontaneous reflux subsided the reaction mixture was refluxed two hours. The reaction mixture was cooled and poured over 400 g. of crushed ice and the product recovered by extraction of the solution with two 200-ml. portions of chloroform. The combined chloroform extracts were dried over sodium sulfate and the solvent distilled. The residue was purified by vacuum distillation, b.p. 141–156° at 0.1–0.5 mm. The yield was 105 g. (0.48 mole), 75%. A thrice distilled sample had $n^{20}D$ 1.4985. The material from this reaction did not give a satisfactory analysis; however, the data indicate that the cleavage yields the expected primary bromide.

Anal. Calcd. for $C_8H_{13}O_2Br$: sapon. equiv., 110.5; C, 43.45; H, 5.92; Br, 36.14. Found: sapon. equiv., 116.6; C, 42.71; H, 6.19; Br, 40.19.

8-Thiol-5-hydroxyoctanoic Acid Lactone.—A solution of 25 g. (0.113 mole) of 8-bromo-5-hydroxycaprylic acid, 8.6 g. (0.113 mole) of thiourea and 50 ml. of methanol was refluxed three hours. The thiuronium salt did not crystallize from the cooled solution and distillation of the solvent left an oily residue which was hydrolyzed by refluxing one hour with 15 g. of potassium hydroxide in 150 ml. of water. The cooled alkaline solution was extracted with 50 ml. of chloroform to remove a small amount of insoluble oil. The aqueous layer was acidified with hydrochloric acid and the precipitated oil extracted with two 40-ml. portions of chloroform. The combined chloroform extracts were dried over sodium sulfate and distilled. The product was vacuum distilled and the fraction distilling 116–122° at 0.15 mm. collected as product. The yield was 6.6 g. (0.38 mole), 33%. The purified lactone,[16] b.p. 121–122° at 0.15 mm., had $n^{20}D$ 1.5100 and d^{20} 1.116.

Anal. Calcd. for $C_8H_{14}O_2S$: C, 55.13; H, 8.09; S, 18.39; sapon. equiv., 174; MR_D, 46.2. Found: C, 54.86; H, 8.1; S, 18.22; sapon. equiv., 172; MR_D, 46.6.

5-Thioctic Acid (5,8-Dithioöctanoic Acid).—A solution of 111 g. of 95% phosphoric acid, 50 g. (0.316 mole) of γ-(2-tetrahydrofuryl)-butyric acid and 200 g. of potassium iodide was stirred rapidly and heated at 125–140° for three hours. The solution was cooled and diluted with enough water to dissolve the salts. The product was extracted with chloroform. Distillation of the solvent left 102 g. of oil. This oil was mixed with 200 ml. of 50% hydriodic acid and 120 g. of thiourea and refluxed eight hours. The reaction mixture was made alkaline with 20% potassium hydroxide and refluxed an additional 1/2 hr. The aqueous solution was acidified and the dithiol acid extracted with chloroform. The chloroform solution (500 ml.) was stirred rapidly while aqueous KI_3 solution was added slowly from a dropping funnel until the iodine color persisted. The excess iodine was destroyed by washing the chloroform solution with dilute sodium thiosulfate. The chloroform solution was dried over sodium sulfate and distilled leaving 74 g. of a yellow oil. The product was purified by vacuum distillation. The fraction distilling 160–160° at 0.1 mm. was collected as product. This fraction solidified to a waxy solid, m.p. 42–46°, weighing 26.3 g. The crude product was recrystallized from cyclohexane to yield 14.3 g. (0.0695 mole), 22%, of white crystals, m.p. 58°.

Anal. Calcd. for $C_8H_{14}S_2O_2$: C, 46.56; H, 6.83; S, 31.08; mol. wt., 206. Found: C, 46.22; H, 7.04; S, 31.50; mol. wt. (Rast camphor), 225.

Two isomeric compounds were isolated from this reaction mixture in low yields. One of the isomers 4-thioctic acid (4,8-dithioöctanoic acid), m.p. 81–86°, was obtained by several recrystallizations of the crude distillate from nitromethane.

Anal. Calcd. for $C_8H_{14}S_2O_2$: C, 46.56; H, 6.83; S, 31.08; mol. wt., 206. Found: C, 46.69; H, 7.04; S, 31.63; mol. wt. (Rast camphor), 200.

The second isomer, 6-thioctic acid (6,8-dithioöctanoic acid), was separated from the reaction mixture by countercurrent distribution and chromatography on silicic acid by a process outlined for the naturally occurring product.[6] The yellow oil, which had neutralization equivalent of 208,

(10) It has been found necessary to saponify the ethyl 8-acetylthio-6-hydroxyoctanoate before attempting the next synthesis. An attempt to convert this product directly to the dithiol acid did not yield the expected product. The products from this reaction are being investigated.

(11) This general procedure was developed by J. M. Sprague and T. B. Johnson, THIS JOURNAL, **59**, 1837 (1937); and R. L. Frank and P. V. Smith, *ibid.*, **68**, 2103 (1946).

(12) Melting points are uncorrected.

(13) A. Hintz, G. Meyer and G. Schucking, *Ber.*, **76**, 676 (1943).

(14) H. Gilman and A. P. Hewlett, *Rec. trav. chim.*, **51**, 93 (1932).

(15) Infrared analysis showed that the product contained some of the γ-lactone and hydroxy acid along with the expected δ-lactone.

(16) Infrared studies show that both the starting material and the product contained small amounts of isomeric γ-lactone.

was oxidized with *t*-butyl hydroperoxide in chloroform to the monoxide and characterized as the S-benzylthiuronium salt, m.p. 143–144°. This salt was shown by X-ray diffraction studies to be identical with the S-benzylthiuronium salt of an authentic sample of 6-thioctic acid.

Anal. Calcd. for $C_{16}H_{24}N_2O_2S_3$: C, 49.45; H, 6.23; N, 7.21; S, 24.76. Found: C, 49.81; H, 6.30; N, 7.31; S, 25.39; C-methyl, negative.

Methyl 6-Thioctate Monoxide (Methyl 6,8-Dithioöctanoate Monoxide).—A 1.31-g. sample of crude 6-thioctic acid isolated from the tetrahydrofurylbutyric acid synthesis was left standing 48 hours in a solution of 2.5 ml. of *t*-butyl hydroperoxide and 50 ml. of chloroform. The product was separated from unreacted starting material by a 65 tube countercurrent distribution between chloroform and 3% acetic acid, and chromatographic adsorption on silicic acid and eluting with 10% acetone in benzene. The yield was 105 mg. of an oil. Twenty mg. of this oil was esterified by dissolving in 1 ml. of benzene and adding a 1:1 ligroin–benzene solution of diazomethane to the cold solution until the yellow color persisted. Evaporation of the solvents left 23.6 mg. of colorless oil which had an infrared absorption spectrum identical with the methyl ester of the natural product.

4-Thioctic Acid (4,8-Dithioöctanoic Acid).—A solution of 1.30 g. (0.0059 mole) of chromatographically pure 8-bromo-4-hydroxyoctanoic acid lactone,[7] 1.82 g. (0.024 mole) of thiourea and 10 ml. of 50% hydriodic acid was refluxed eight hours. The solution was cooled and the *p*H adjusted to 12 with sodium hydroxide. After warming on the steam-cone for one-half hour, the solution was acidified with hydrochloric acid and extracted twice with an equal volume of chloroform. The combined chloroform extracts were washed with water and evaporated leaving a yellow oil. This oil was taken up in sodium bicarbonate solution and oxidized by titrating the stirred solution with potassium triiodide solution until an excess was present. The solution was acidified and extracted with chloroform. Distillation of the dried (sodium sulfate) chloroform extract left an oil which was purified by chromatographic adsorption on silicic acid and elution with a chloroform–methanol mixture. After crystallization from toluene and recrystallization from a toluene–petroleum ether, b.p. 65–68°, mixture, the crystals had m.p. 79–81°. The yield was 87 mg., 7%. The infrared spectrum of this compound was identical with the product, m.p. 81–86°, isolated from the 5-thioctic acid synthesis.

Ethyl 6-Keto-Δ^7-octenoate.—In a 3-liter, 3-neck flask equipped with stirrer, dropping funnel and gas outlet was placed 700 ml. of nitrobenzene. The reaction flask was cooled in an ice-bath and 500 g. (3.78 moles) of powdered anhydrous aluminum chloride was added in portions over a period of 5 minutes. Now 360 g. (1.87 mole) of ethyl adipyl chloride[17] was added from the dropping funnel over a period of 15 minutes. The dropping funnel was replaced by a gas inlet tube of the sintered glass type and ethylene gas was bubbled through the rapidly stirred solution for 4.5 hours. The temperature of the reaction mixture was maintained at 45 ± 3° during the first 3 hours and then allowed to cool. The reaction mixture was stirred into a mixture of ice and chloroform containing a small amount of hydroquinone as a stabilizer. The organic layer was separated, washed with water, with dilute sodium hydroxide and again with water. The organic layer was dried over sodium sulfate and the chloroform removed by distillation on the steam-cone. The nitrobenzene was distilled off at 10 mm. Copious quantities of hydrogen chloride were evolved during the distillation of this solvent. The product was vacuum distilled through a 24″ heated Vigreux column using an oil-bath to supply the heat. After a small forerun the product distilled 110–115° at 2–3 mm. The yield was 165.5 g. (0.905 mole), 48%. The pure material had $n^{25}D$ 1.4481, $n^{20}D$ 1.4500.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75; sapon. equiv., 184. Found: C, 64.50; H, 9.12; sapon. equiv., 183.

An attempt to run this reaction with one mole of aluminum chloride under the same conditions as the above experiment resulted in complete failure. One half of the starting material was recovered as monoethyl adipate and no identifiable reaction products could be obtained.

Ethyl 8-Acetylthio-6-ketoöctanoate.—In a 250-ml. round bottom flask equipped with a condenser was placed 100 g. (0.544 mole) of ethyl 6-keto-Δ^7-octenoate. The flask was cooled in an ice-bath and 40 ml. (0.57 mole) of thioacetic acid was poured slowly down the condenser. The reaction mixture was shaken frequently during the addition. The resulting solution was warmed on the steam-bath 20 minutes, and the excess thioacetic acid distilled off under the reduced pressure of an aspirator. The product was distilled through a 6″ vacuum jacketed Vigreux column. The fraction distilling 148–150° at 0.03 mm. was collected as product. An additional 20.9 g. of product was obtained from the lower boiling forerun by adding more thioacetic acid and redistilling, bringing the total yield to 128.9 g. (0.496 mole), 91.2%. The product, m.p. 10°, had d^{20} 1.094 and $n^{20}D$ 1.4798.

Anal. Calcd. for $C_{12}H_{20}O_4S$: C, 55.35; H, 7.74; S, 12.31. Found: C, 55.22; H, 8.02; S, 12.41.

8-Acetylthio-6-hydroxyoctanoate.—In a 2-liter, 3-neck flask equipped with stirrer, condenser and dropping funnel were placed 95.2 g. (0.356 mole) of ethyl 8-acetylthio-6-ketoöctanoate and 200 ml. of distilled methanol. The flask was cooled in an ice-bath while 180 ml. of a methanol solution of sodium borohydride containing 1 mole of sodium borohydride per liter was added. A test for excess reducing agent (acidified aliquot) showed that no excess sodium borohydride was present. An additional 100 ml. of the sodium borohydride solution was added. An excess of sodium borohydride was now present. The solution was allowed to warm up to room temperature and the methanol distilled off. The sirupy residue was diluted with chloroform and then water. The chloroform which had a milky appearance was washed once with dilute sulfuric acid and dried over a mixture of sodium bicarbonate and sodium sulfate. Distillation of the chloroform solution left a thick oil containing some solid. Five ml. of water and 20 ml. of chloroform were added and the solvents distilled off under reduced pressure on the steam-bath. The oily product, wt. 77 g., was purified by vacuum distillation. The fraction distilling 130–132° at 0.05 mm. was collected as product. The yield was 57.7 g. (0.220 mole), 62%. The pure material has $n^{20}D$ 1.4670 and d^{20} 1.055.

Anal. Calcd. for $C_{12}H_{22}O_4S$: C, 54.93; H, 8.45; S, 12.22; MR_D, 68.51. Found: C, 54.69; H, 8.52; S, 12.6, 13.02; MR_D, 70.0.

8-Thiol-6-hydroxyoctanoic Acid.—A solution of 11.0 g. (0.166 mole) of potassium hydroxide in 40 ml. of water was added to 20 g. (0.0763 mole) of ethyl 8-acetylthio-6-hydroxyoctanoate. The reaction appeared to be exothermic and the second phase disappeared when the flask was shaken. The resulting solution was left standing 36 hours. The solution was diluted with 400 ml. of water and extracted with 100 ml. of ether. Distillation of the ether extract left 0.5 g. of oil which was discarded. The aqueous solution was acidified with hydrochloric acid and extracted thrice with 100-ml. portions of ether. The combined ether extracts were dried over sodium sulfate and distilled leaving 13.5 g. of oil. This product was subjected to vacuum distillation. The product distilled at 142–172° at 0.05 mm.

Yield of distillate was 10 g. (0.052 mole), 68% calculated as the acid. The product was shown by infrared analysis to be a mixture of 8-thiol-6-hydroxyoctanoic acid and its lactone.

6-Thioctic Acid (6,8-Dithioöctanoic Acid).—A solution of 15 g. (0.376 mole) of sodium hydroxide in 150 ml. of water was added to 27 g. (0.103 mole) of undistilled ethyl 8-acetylthio-6-hydroxyoctanoate. The solution became homogeneous when shaken. The solution was refluxed 35 minutes, cooled and acidified with concentrated hydrochloric acid. The product was extracted with two 100-ml. portions of ether. The combined ether extracts were dried over sodium sulfate and distilled leaving a residue weighing 26 g. and having the odor of acetic acid. To this crude product was added 75 g. of thiourea and 200 ml. of 50% hydriodic acid. The resulting solution was heated at reflux 10 hours and cooled. The solution was made alkaline by the addition of 50 g. of sodium hydroxide in 150 ml. of water and refluxed 30 minutes. The solution was cooled and acidified with hydrochloric acid. The product was extracted with three 80-ml. portions of chloroform. The combined chloroform extracts were dried over sodium sulfate and distilled leaving 21.5 g. of an oil. This oil was

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purified by vacuum distillation. The fraction distilling 150–168° at 0.15 mm. was collected as product.

The crude dihydro-6-thioctic acid, wt. 10.5 g. (0.0505 mole), was transferred to a 500-ml. erlenmeyer flask with a few ml. of 3A ethanol and 6.5 g. (0.0505 mole) of potassium carbonate was added. One hundred fifty ml. of water was added, and the *p*H of the resulting solution was adjusted to 7 with a few drops of hydrochloric acid. After the addition of 2 ml. of 1% ferric chloride, the resulting deeply colored solution was transferred to a 250-ml. graduate and a rapid stream of oxygen was bubbled through the solution from a sintered glass inlet tube until the color changed to pale yellow (20 minutes). The solution was acidified and the product extracted with two 150-ml. portions of chloroform. The combined chloroform extracts were dried over sodium sulfate and distilled. The residue, which crystallized, was vacuum distilled. The fraction distilling 150° at 0.1 mm. and crystallizing in the receiver was collected as product. This crude product weighed 6.5 g. and m.p. 58°. A small amount of additional product was obtained by stirring the forerun with cold cyclohexane. Recrystallization of the combined products from cyclohexane gave 5.4 g. of bright yellow crystals m.p. 61°. An additional 1.0 g. of crystals was obtained by concentrating the mother liquors, bringing the total yield to 6.4 g. (0.031 mole) or 30.1% from the ethyl 8-acetylthio-6-hydroxyoctanoate.

Anal. Calcd. for $C_8H_{14}O_2S_2$: neut. equiv., 206; C, 46.57; H, 6.84; S, 31.08. Found: neut. equiv., 202; C, 46.96; H, 6.92; S, 30.68; mol. wt. (Rast camphor), 215.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

A Synthesis of Quinolizinium and Dehydroquinolizinium Derivatives[1]

BY V. BOEKELHEIDE AND WALTER G. GALL[2]

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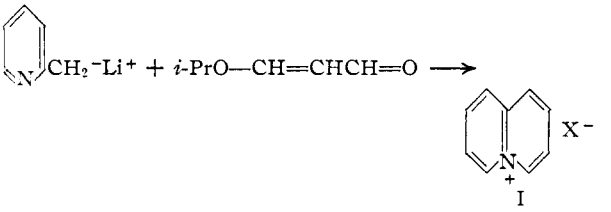
A practical preparation of the quinolizinium and dehydroquinolizinium ions is reported. The dehydroquinolizinium ion, which is the parent nucleus of many alkaloids, has been subjected to chemical and spectral studies which substantiate its assigned structure. An attempt to obtain quinolizine, as the free base, gave only 1-(α-pyridyl)-1,3-butadiene.

The dehydroquinolizinium ion (I) represents the nitrogen analog of naphthalene in which the nitrogen atom occurs at a bridgehead position. In contrast to quinoline and isoquinoline, the other two simple nitrogen analogs of naphthalene, the chemistry of the dehydroquinolizinium ion has been little studied and knowledge regarding this ion has been gained almost entirely from investigations of alkaloids containing this nucleus as part of a fairly complex structure. Among the alkaloids, the dehydroquinolizinium nucleus probably occurs most widely as its dihydro derivative, the quinolizinium ion. For example, the dibenzoquinolizinium ion is the parent structure for the various berberine alkaloids,[3-6] palmatine,[7] columbamine,[8] jatrorrhizine,[9] coptisine,[10] worenine,[11] dehydrocorydaline[12] and dehydrothalictrifoline.[13] Here again, although methods for the synthesis of dibenzoquinolizinium derivatives are well described,[7,14] the preparation of the simple quinolizinium ion has not previously been reported.

Actually, the occurrence among alkaloids of the fully unsaturated dehydroquinolizinium ion was first recognized when Woodward and Witkop proposed that sempervirine contained this nucleus.[15] This was immediately confirmed by Woodward and McLamore's synthesis of sempervirine methochloride.[16] Recently, Schwyzer has suggested on the basis of spectral evidence that flavocorynanthyrine also contains the dehydroquinolizinium nucleus.[17]



I

Of the syntheses previously investigated the most promising one for preparing the dehydroquinolizinium ion itself would appear to be that of Woodward and McLamore.[16] For example, by this method these authors were able to prepare 2,3-tetramethylenedehydroquinolizinium picrate in 51% yield. However, when 2-picolyllithium was treated with β-isopropoxyacrolein following this general method as shown below, Beaman found that salts of the dehydroquinolizinium ion could be isolated only with great difficulty and in very poor yield.[18] Since the preparation of the necessary starting material, β-isopropoxyacrolein, is tedious and proceeds in very poor yield, this approach to

(1) Supported in part by the Office of Ordnance Research, Army Ordnance Contract No. DA-30-115-O.R. D-421.

(2) National Science Foundation Predoctoral Fellow, 1952–1953.

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