5 minutes. The radioactivity was determined by an end-window Geiger tube counter, the window of which was covered with a 1.5 mm.-thick aluminum disc in which was cut a slit 0.5 cm. wide and 3.0 cm. long. The dry paper strip was taped to an aluminum slide which fitted snugly against the disc and exposed 0.5 cm. of the entire width of the paper to the tube window. The paper strip was moved by 0.5-cm. increments under the Geiger tube, each position being counted for 100 seconds. In this manner, the zones for I and II were found at R_f values 0.07 and 0.75, respectively.[7] The relative amounts of isomers could then be determined quantitatively by summing the counts of all 0.5-cm. increments at the respective zones.

Determination of the rate of isomerization of I to II was carried out as follows: A small amount of P^{32}-labeled I was placed in a small standard-tapered test-tube and placed in a bath of appropriate temperature. The effect of solvent on the isomerization was studied in a similar manner, the solutions being made up to about 0.1 *M* in I. Since the isomerization followed first-order kinetics, it was not necessary to know the absolute concentrations. At various time intervals, samples were removed by a capillary pipet and transferred to the silicone-treated paper strips. Care was taken to deliver an amount such that the maximum count through the 0.5-cm. slit at any spot after development was not more than 25 counts per second. The strips were developed with the ethanol–chloroform–water mixture, the solvent front being allowed to rise to about 13 or 14 cm. After drying for 5 minutes the chromatograms were analyzed for activity in the manner described above, by moving the strip of paper by 0.5-cm. increment under the end-window Geiger tube (0.5 cm. slit); each increment was counted for 100 seconds. The following data (Table II) are typical of those obtained.

TABLE II

THERMAL ISOMERIZATION OF THIONO I TO THIOL II ISOMER AT 78.2°

Time, sec. × 10^{-4}	Total counts I	Total counts II	Ratio I/I + II	k_1, sec.$^{-1}$ × 10^6
0	4795	330	0.935	..
5.4	15850	4650	.773	3.5
8.3	1888	882	.682	3.8
14.0	3093	2407	.563	3.6
17.2	2360	2549	.481	3.9
22.7	4149	6725	.381	3.9

The methyl ethyl ketone and ethyl acetate were Eastman Kodak Co. white label grade, used without further purification. 2,2,4-Trimethylpentane was ASTM grade, used without further purification. Dioxane, chloroform and benzene were purified according to the methods described by Fieser,[12] b.p. 100–101°, 60° and 79°, respectively. The ethyl alcohol was U. S. Industrial Chemicals Co. absolute grade, used without further purification.

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[12] L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1941, p. 358.

RIVERSIDE, CALIFORNIA

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF THE VETERANS HOSPITAL AND THE DEPARTMENT OF CHEMISTRY MUNICIPAL UNIVERSITY OF WICHITA]

The Synthesis of Dimethyl-(α-hydroxy-β-propiothetin) Hydrochloride and Related Compounds

BY N. F. BLAU, J. W. JOHNSON AND C. G. STUCKWISCH

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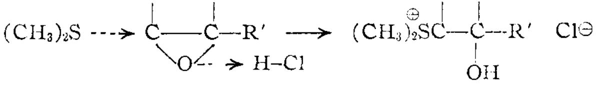
Dimethyl-(α-hydroxy-β-propiothetin) hydrochloride has been synthesized through several routes. The reaction of dimethyl sulfide with epoxides has been studied. The acid-catalyzed reaction of dimethyl sulfide with β-lactones has been extended to β-butyrolactone.

As part of a continuing study of sulfonium compounds as potential lipotropic agents, we have investigated the synthesis of dimethyl-(α-hydroxy-β-propiothetin) hydrochloride (IIb).

In view of the earlier synthesis of dimethyl-β-propiothetin hydrochloride[1] by the reaction of dimethyl sulfide and hydrogen chloride with β-propiolactone, the nucleophilic displacement reaction of dimethyl sulfide on glycidic acid seemed particularly inviting. Bartlett and Small[2] have pointed out the resemblance between nucleophilic displacement reactions upon epoxides on the one hand and β-propiolactone on the other. The present paper describes the reaction of dimethyl sulfide and hydrogen chloride on ethylene oxide (Ia), potassium glycidate (Ib), ethyl glycidate (Ic) and methyl β,β-dimethyl glycidate (Id). In all instances the corresponding sulfonium compounds were obtained, but the yields (10 to 20%) were much lower than with β-propiolactone. In the case of ethyl glycidate it was shown that epoxide ring cleavage by hydrogen chloride is a competing reaction. This is probably true for all the epoxides tried. The use of sulfuric acid or *p*-toluenesulfonic acid did not improve the yields.



Ia, R = R′ = H
b, R = H, R′ = CO_2H
c, R = H, R′ = $CO_2C_2H_5$
d, R = CH_3, R′ = CO_2CH_3

IIa, R = R′ = H
b, R = H, R′ = CO_2H
c, R = H, R′ = $CO_2C_2H_5$
d, R = CH_3, R′ = CO_2CH_3

The yield of potassium glycidate was improved by substituting methyl alcohol for ethyl alcohol[3] as the solvent.

β-Chlorolactic acid and ethyl β-chlorolactate gave unsatisfactory yields of the corresponding β-methylmercapto compounds when refluxed with an ethanol solution of sodium methylmercaptide.[4] β-Iodolactic acid and dimethyl sulfide failed to yield the dimethyl-(α-hydroxy-β-propiothetin) hydroiodide under a variety of conditions.

Acknowledgment.—The authors thank Dr. J. W. Dubnoff, Kerckhoff Laboratories of Biology, California Institute of Technology, for ascertaining the biochemical activity of a sample of crude racemic

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[1] N. F. Blau and C. G. Stuckwisch, THIS JOURNAL, **73**, 2355 (1951).

[2] P. D. Bartlett and G. Small, Jr., *ibid.*, **72**, 4867 (1950).

[3] W. Freudenberg, *Ber.*, **47**, 2027 (1914).

[4] Koelsch encountered similar difficulties in the reaction of ethyl β-chlorolactate with potassium xanthate and sodium hydrosulfide, THIS JOURNAL, **52**, 1105 (1930).

dimethyl-(α-hydroxy-β-propiothetin) hydrochloride which they had submitted for his examination during the early stages of the work.

Experimental

Potassium Glycidate.—β-Chlorolactic acid was prepared from epichlorohydrin *via* glycerol-α-monochlorohydrin[5] by the procedure of Koelsch[4]; 62.2 g. (0.52 mole) of the compound, melting at 77°, was dissolved in 110 ml. of absolute methanol. A solution of 70 g. of potassium hydroxide in absolute methanol was shaken for 5 to 10 minutes with 5 to 10 g. of silica gel and then filtered. The acid–base ratio of the two solutions was determined by titration. The β-chlorolactic acid solution was added dropwise to the required volume of alkali with vigorous mechanical stirring. The rate of addition to the ice-cooled alkali was so regulated that the internal temperature did not rise above 20°. The ice-bath was then removed and stirring continued for an additional hour. Subsequent to cooling overnight in the refrigerator, the potassium chloride was removed by filtration and was washed with cold methanol. The combined filtrate and washings were treated with ether to the maximum yield of a colorless, granular precipitate. Solution in methanol and reprecipitation with ether yielded a chloride-free product. The yield was 53 g. or 85%. Purity as established by oxirane oxygen determination was 99.5%.[6]

Anal.[7] Calcd. for $C_3H_3O_3K$: K, 31.5. Found: K, 31.3.

Dimethyl-(α-hydroxy-β-propiothetin) Hydrochloride (IIb). From Potassium Glycidate and Hydrogen Chloride.—Potassium glycidate, 12.6 g. (0.1 mole), was added to a solution of 9.4 g. (0.15 mole) of dimethyl sulfide in 80 ml. of nitromethane. The mixture was cooled to 10° and treated with dry hydrogen chloride. The nitromethane was decanted from the gummy precipitate and the precipitate was suspended in 80 ml. of acetone. The acetone was filtered off and the white residue was extracted with 40 ml. of boiling ethanol. Fifty milliliters of acetone was then added to the hot ethanol extract. Dimethyl-(α)-hydroxy-β-propiothetin) hydrochloride separated in colorless crystals (10.7% yield) were obtained, m.p. 143°.

Anal. Calcd. for $C_5H_{11}O_3ClS$: Cl, 19.6; neut. equiv., 186.2. Found: Cl, 19.4; neut. equiv., 186.2.

The compound was similarly prepared with the sulfate and *p*-toluenesulfonate serving as intermediates. Treatment of β-chlorolactic acid or of ethyl β-chlorolactate with sodium methyl mercaptide in absolute ethanol, followed by the addition of methyl iodide and of silver chloride in the usual manner, likewise yielded a crystalline product of the same melting point and chemical composition as the preparation from potassium glycidate. Mixed melting points of the crystals from the four methods of synthesis showed no depression.

Sulfocholine Hydrochloride (IIa).—To 30 ml. of nitromethane in a 100-ml. graduated cylinder equipped with gas inlet and exit tubes and a thermometer, was added 9.3 g. (0.15 mole) of dimethyl sulfide. The solution was cooled to 5° in a mixture of ice and salt, and 5.0 g. (0.114 mole) of ethylene oxide was added. Dry hydrogen chloride was passed intermittently through the solution for 20 minutes. With the addition of small increments of hydrogen chloride the temperature would rise rapidly, but was kept below 14°. During the last three minutes the temperature remained at 8°. The gain in weight was measured at five-minute intervals until 4.3 g. (0.118 mole) of hydrogen chloride had been absorbed. The clear solution was stoppered and set in the refrigerator. After two days no turbidity had developed. A small portion of the solution was treated with chloroplatinic acid and acetone was added to incipient cloudiness. The product crystallized rapidly when cooled under running tap water. The sulfocholine chloroplatinate crystals were recrystallized from aqueous ethanol. The melting point after three recrystallizations was 189°. After removing the solvent from the original reaction mixture under reduced pressure, the residue solidified in the refrigerator. The weight of the residue was 2.52 g. (16% yield). An authentic specimen was obtained by treating β-hydroxyethyl methyl sulfide[8] with methyl iodide, followed by treating the sulfonium iodide with silver chloride. The chloroplatinate of the resulting sulfocholine hydrochloride melted at 189°. A mixed melting point of the two preparations showed no depression.

(2-Hydroxy-2-carbethoxy)-ethyldimethylsulfonium Chloride (IIc).—Ethyl glycidate[9] (5.8 g., 0.05 mole) and 6.2 g. (0.1 mole) of dimethyl sulfide were dissolved in 20 ml. of nitromethane. The mixture was treated as described in the ethylene oxide experiment. The solvent was removed at reduced pressure and the oily residue was extracted with ether. The ether extract yielded 4.6 g. of ethyl β-chlorolactate. Since the ether-insoluble fraction was extremely hygroscopic and difficult to crystallize, it was dissolved in 95% ethanol and treated with chloroplatinic acid. The chloroplatinate, 2.1 g. (13%), after crystallization from aqueous ethanol, melted at 149–150°.

Anal. Calcd. for $C_{14}H_{30}O_6S_2 \cdot PtCl_6$: S, 4.93; Cl, 32.8. Found: S, 5.12; Cl, 32.6.

(1,1-Dimethyl-2-hydroxy-2-carbomethoxy)-ethyldimethylsulfonium Chloride (IId).—Methyl β,β-dimethylglycidate,[10] 6.5 g. (0.05 mole), was treated with dimethyl sulfide and hydrogen chloride under the same conditions as ethyl glycidate in the preceding experiment. The sulfonium chloride, crystallized from an ethanol–ether mixture, melted at 109–110°. The yield was 2.3 g. or 20%.

Anal. Calcd. for $C_8H_{17}O_3ClS$: S, 14.0; Cl, 15.5. Found: S, 14.1; Cl, 15.7.

Reaction of Dimethyl Sulfide and Hydrogen Chloride with β-Butyrolactone.—Dimethyl sulfide, 6.0 g. (0.097 mole), was dissolved in 30 ml. of nitromethane contained in an absorbing cylinder and 4.5 g. (0.0523 mole) of β-butyrolactone[11,12] was added. A slow stream of hydrogen chloride was passed through the cooled solution for 30 minutes while the temperature was kept below 15° with external cooling. After 2.5 g. (0.0685 mole) of hydrogen chloride had been absorbed, the cylinder was stoppered and set in the refrigerator. Ethyl ether was added to incipient turbidity and after two days standing the mixture was filtered. After three recrystallizations from aqueous ethanol, a product was obtained which melted at 123°.

Anal. Calcd. for $C_6H_{13}N_2ClS$: neut. equiv., 184.7; Cl, 19.2; S, 17.3. Found: neut. equiv., 184.1; Cl, 19.5; S, 17.1.

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[5] E. Fisher and E. Pfahler, *Ber.*, **53**, 1606 (1920).

[6] S. Siggia, "Quantitative Organic Analysis *via* Functional Groups," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 108.

[7] C. B. Hurd and W. Fiedler, Jr., *Anal. Chem.*, **9**, 116 (1937).

[8] A. H. Blatt, Editor, "Organic Syntheses," Coll. Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 345.

[9] P. Melikoff and N. Zelinsky, *Ber.*, **21**, 2052 (1888).

[10] W. S. Johnson, *et al.*, This Journal, **75**, 4995 (1953).

[11] H. Johansson, *Ber.*, **48**, 1262 (1915).

[12] H. Johansson and S. M. Hagman, *ibid.*, **55**, 647 (1922).