Dalmer for cholestanone-6 prepared from cholesteryl chloride and for the same ketone prepared from nitrocholestene by Windaus.[7] When mixed with an authentic specimen of this ketone no depression of the melting point was observed.

We wish to express our thanks to the Rockefeller Foundation and to the Chemical Foundation for the grants-in-aid which made this work possible.

## Summary

Evidence is submitted which leads to the conclusion that the hydroxyl group in *i*-cholesterol is in position six of the sterol molecule and that during its formation from cholesteryl *p*-toluenesulfonate a molecular rearrangement occurs. The results obtained and described in this paper substantiate the validity of the structural formula proposed by investigators in this Laboratory for *i*-cholesterol[3,5] and for the isomeric ethers of cholesterol.

PRINCETON, N. J. RECEIVED DECEMBER 18, 1937

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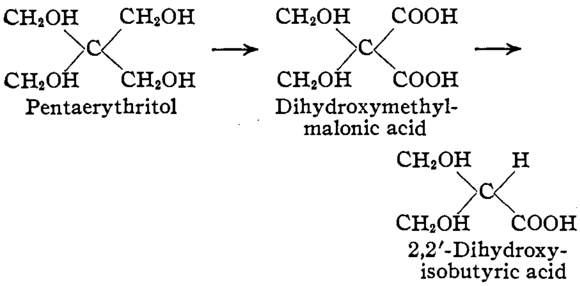
[CONTRIBUTION FROM THE KENT AND GEORGE HERBERT JONES CHEMICAL LABORATORIES, UNIVERSITY OF CHICAGO]

# The $C_4$-Saccharinic Acids. VIII. Some Reactions of Pentaerythritol. Preparation of 2,2′-Diiodoisobutyric Acid and its Hydrolysis to 2,2′-Dihydroxyisobutyric Acid[1]

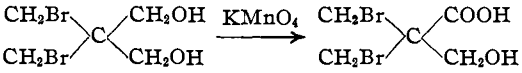
BY J. W. E. GLATTFELD AND JOHN M. SCHNEIDER

Previous attempts to prepare 2,2′-dihydroxyisobutyric acid in these Laboratories[2,3] indicated pentaerythritol to be the most promising starting material for the synthesis of this acid (hereafter referred to as the 2,2′-acid) so far untried. Oxidation of two hydroxymethyl groups to carboxyl groups and subsequent elimination of carbon dioxide according to the following scheme would give the desired 2,2′-acid



Pentaerythritol itself is broken down very readily by oxidizing agents. However, Just[4] obtained isobutyric acid from 2,2-dimethylpropandiol-(1,3) by oxidation and subsequent elimination of carbon dioxide. It appeared likely that a similar series of reactions might be carried out with pentaerythritol if two hydroxyl groups were protected during the process.

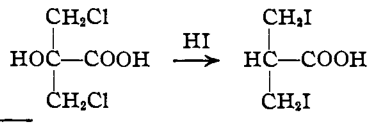
The dibromohydrin of pentaerythritol was therefore prepared by the procedure of Zelinsky and Krawetz.[5] This compound, when oxidized, yielded a monocarboxylic acid, 1,1-di-(bromomethyl)-2-hydroxypropionic acid, as indicated below



Further oxidation of the acid thus obtained caused complete destruction of the molecular structure. This acid melts at 146°. It has not been described in the literature.

An attempt was next made to prepare the diethyl ether of pentaerythritol by the ether-preparation method described by White and co-workers.[6] Pentaerythritol, when treated with two moles of sodium and two moles of ethyl bromide in liquid ammonia, gave a mixture of the di-, tri-, and tetraethyl ethers, with the tetraethyl ether as the main product. However, a satisfactory yield of the diethyl ether was obtained by treatment of the dibromohydrin with sodium ethylate in liquid ammonia. The diethyl ether was found to be far more easily attacked by oxidizing agents than pentaerythritol itself and was therefore of no service in this work.

2,2′-Diiodoisobutyric acid was prepared by the reduction of 1-hydroxy-2,2′-dichloroisobutyric acid with fuming hydriodic acid



$$\mathrm{HO}\overset{\displaystyle CH_2Cl}{\underset{\displaystyle CH_2Cl}{C}}\mathrm{—COOH}\xrightarrow{\mathrm{HI}}\mathrm{H}\overset{\displaystyle CH_2I}{\underset{\displaystyle CH_2I}{C}}\mathrm{—COOH}$$

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[1] This article is condensed from a dissertation presented by John M. Schneider in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Chicago.

[2] Glattfeld, Leavell, Spieth and Hutton, THIS JOURNAL, **53**, 3164 (1931).

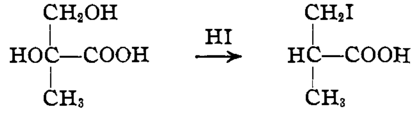
[3] Glattfeld and Klaas, *ibid.*, **55**, 1114 (1933).

[4] Just, *Monatsh.*, **17**, 76 (1896).

[5] Zelinsky and Krawetz, *Ber.*, **46**, 163 (1913).

[6] White, Morrison and Anderson, THIS JOURNAL, **46**, 961 (1924).

The product was found to be identical with the diiodoisobutyric acid of unknown structure reported by Fischer and Tafel,[7] who isolated it from a reaction mixture obtained in the reduction of trihydroxyisobutyric acid to isobutyric acid. That the two iodine atoms occupied the 2,2′-positions is indicated by the fact that a molecule of any other arrangement reasonable under the circumstances would yield, on hydrolysis, one of the ten known $C_4$-saccharinic acids. This was not found to be the case. Further evidence for this conclusion as to structure was obtained by treatment of 1,2-dihydroxyisobutyric acid[8] with hydriodic acid

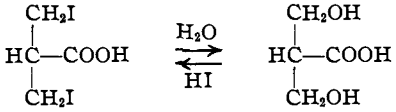


$$\mathrm{HO\overset{CH_2OH}{\underset{CH_3}{C}}{-}COOH} \xrightarrow{\mathrm{HI}} \mathrm{H\overset{CH_2I}{\underset{CH_3}{C}}{-}COOH}$$

1,2-Dihydroxyisobutyric acid 2-Iodoisobutyric acid

The product in this case was 2-iodoisobutyric acid. This reaction indicates that a tertiary alcohol group in the 1-position is reduced easily while primary hydroxyl groups are replaced by iodine to form iodo compounds stable to further reduction under the conditions used in these experiments.

2,2′-Diiodoisobutyric acid is easily and quantitatively hydrolyzed by hot water, presumably according to the forward reaction in the following scheme



$$\mathrm{H\overset{CH_2I}{\underset{CH_2I}{C}}{-}COOH} \underset{\mathrm{HI}}{\overset{\mathrm{H_2O}}{\rightleftarrows}} \mathrm{H\overset{CH_2OH}{\underset{CH_2OH}{C}}{-}COOH}$$

2,2′-Diiodoisobutyric acid 2,2′-Dihydroxyisobutyric acid

Removal of the hydrogen iodide with the calculated quantity of silver oxide and concentration of the filtrate gives a sirup which is miscible with most of the ordinary solvents. This sirup regenerates the diiodo acid when treated with hydriodic acid (reverse reaction in the above scheme). This indicates that no change in the carbon skeleton has occurred during hydrolysis and that the sirup contains the 2,2′-acid.

However, the sirup is complex in nature. When an aqueous solution of it is concentrated under reduced pressure, the neutralization equivalent of the residual sirup drops steadily until it reaches a value of about 105. During the concentration of the sirup, an amorphous white solid begins to separate and continues to separate as the concentration proceeds. If the concentration is continued long enough, practically all of the sirup can be transformed into the solid material. This solid is insoluble in all solvents tried with the single exception of alkalies. It is acidic and possesses a neutralization equivalent of about 95. It does not melt below 350° but chars upon ignition and behaves much like starch under similar conditions. Apparently it is a condensation product of the 2,2′-acid.

This behavior is without parallel in the chemistry of the $C_4$-saccharinic acids. The 2,2′-acid differs from all other members of this series in that it has a tertiary hydrogen atom in the 1-position to the carboxyl group. It is therefore possible that, because of the reactivity of this hydrogen atom, the 2,2′-acid loses a molecule of water to form a hydroxymethylacrylic acid which then undergoes some type of polymerization. It is quite evident that the carboxyl group is not involved in this condensation. The barium salt of the acid material was prepared under various conditions and at various stages, but this salt invariably had a higher barium content than the theoretical value for the barium salt of a $C_4$-saccharinic acid and showed considerable variation in barium content.

Since the completion of this work, an article has appeared by Gault and Roesch[9] which describes the preparation of di-hydroxymethyl-malonic acid from malonic ester and formaldehyde. This is the acid which we had hoped to prepare from pentaerythritol. This acid, when heated, loses carbon dioxide and formaldehyde and gives a white solid similar in many respects to the material obtained by us from the 2,2′-acid. It is quite likely that the 2,2′-acid was an intermediate product in this reaction. Gault and Roesch were unable to prepare mono-hydroxymethyl-malonic ester from malonic ester and one mole of formaldehyde. Instead, they invariably obtained the dimer of methylenemalonic ester. This is added evidence of the ease with which water is lost from 2-hydroxy acids which have a tertiary hydrogen atom in the 1-position to the carboxyl group.

## Experimental Part

**Oxidation of Pentaerythritol Dibromohydrin.**—Ten grams of the dibromohydrin was dissolved in 500 cc. of water which contained 15 cc. of concentrated sulfuric acid. The exact amount of potassium permanganate required

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[7] Fischer and Tafel, *Ber.*, **22**, 106 (1889).

[8] Glattfeld and Sherman, This Journal, **47**, 1742 (1925).

[9] Gault and Roesch, *Bull. soc. chim.*, [5] **4**, 1434 (1937).

for the oxidation of two hydroxymethyl groups to carboxyl groups (16.1 g.) was dissolved in 400 cc. of water and added to the reaction mixture over a period of five hours. Manganese dioxide precipitated and the solution acquired a dark red color. Carbon dioxide and free bromine were present as reaction products. The manganese dioxide was removed by filtration, the filtrate was decolorized by means of sodium thiosulfate, and the clear solution was extracted twice with ether. The ether extract yielded 2.6 g. of white crystals which melted at 130–140°. Recrystallizations from chloroform and ligroin gave 1 g. of crystals which melted at 146°. Analysis showed that this product was a monocarboxylic acid formed by the oxidation of one hydroxymethyl group.

*Anal.* Calcd. for $C_5H_8O_3Br_2$: Br, 57.93; neut. equiv., 275.9. Found: Br, 57.99, 58.13; neut. equiv., 274, 275.

**Ethyl Ethers of Pentaerythritol.**—Sixty grams of pentaerythritol was dissolved in 1500 cc. of liquid ammonia contained in a large Dewar flask and 0.5-g. pieces of sodium were added one by one. A white precipitate formed which increased in bulk as the reaction proceeded. When 17 g. of sodium had been added, the mixture had become so thick that no more sodium could be brought into solution. The mixture was then treated with 75 cc. of ethyl bromide and set aside until the ammonia had evaporated. The addition of water to the residue produced an oil which formed a layer on the surface of the mixture. The entire mixture was extracted twice with ether and the oil obtained by the concentration of the ether extract was fractionated at 5 mm. pressure. Constant boiling fractions were found at 83, 94 and 116° (all at 5 mm.). Unchanged pentaerythritol was found in the water solution. The experiment was repeated by dissolving 24 g. of sodium in 1500 cc. of liquid ammonia and then adding 60 g. of pentaerythritol in small lots followed by 75 cc. of ethyl bromide. The same procedure was then followed as described above. The oily product obtained was fractionated at 5 mm. with the following results: 30–83°, 4 g.; 83°, 10 g.; 83–94°, 2 g.; 94°, 4 g.; 94–116°, 1.5 g.; 116°, 1.5 g. The products from several experiments were combined and fractionated. The three constant boiling fractions were then redistilled and analyzed. They were identified as the tetraethyl ether (b. p. 83° at 5 mm.), triethyl ether (b. p. 94° at 5 mm.) and diethyl ether (b. p. 116° at 5 mm.). In all experiments the tetraethyl ether was the main product.

*Anal.* Calcd. for tetraethyl ether: C, 62.85; H, 11.37. Found (83° fraction): C, 62.38, 62.44; H, 11.22, 11.26. Calcd. for triethyl ether: C, 59.93; H, 10.98. Found (94° fraction): C, 60.15; H, 10.92. Calcd. for diethyl ether: C, 56.22; H, 10.49. Found (116° fraction): C, 56.63, 56.52; H, 10.57, 10.38.

**Pentaerythritol Diethyl Ether and its Oxidation.**—A satisfactory yield of the diethyl ether was obtained from the dibromohydrin. Twelve grams of sodium was dissolved in 1000 cc. of liquid ammonia and 100 cc. of ethyl alcohol was added. To this solution was added 52.4 g. of pentaerythritol dibromohydrin. The same procedure as that previously described was followed except that no ethyl bromide was used. This reaction produced 8 g. of the diethyl ether, a yield of about 25%.

A solution was prepared which contained 10 g. of the diethyl ether and 5 cc. of concentrated sulfuric acid in 300 cc. of water. To this was added a solution of 22 g. of potassium permanganate in 400 cc. of water. The permanganate was decolorized as rapidly as it was added. A brisk evolution of gas accompanied the reaction. It was quite evident that the diethyl ether was far less stable toward oxidation than pentaerythritol itself.

**Preparation of 2,2′-Diiodoisobutyric Acid.**—Glycerol dichlorohydrin[10] was prepared and oxidized to symmetrical dichloroacetone.[11] Liquid hydrogen cyanide was added to the dichloroacetone and the nitrile thus obtained was hydrolyzed with hydrochloric acid. The procedure described by Grimaux and Adam[12] was used with only minor modifications and the yield of 1-hydroxy-2,2′-dichloroisobutyric acid was almost quantitative. These investigators established the structure of the product by converting it into citric acid.

The hydroxydichloro acid was reduced to 2,2′-diiodoisobutyric acid with aqueous hydriodic acid saturated at 0° (sp. gr. 2.0). Eight sealed tubes, each of which contained 10 g. of the hydroxydichloro acid and 40 cc. of the fuming hydriodic acid were heated in a bath of boiling water for about thirty hours. The citrate of magnesia type of pressure bottles may be used instead of sealed tubes, but in this case the rubber washers must be renewed after about fifteen hours. At the end of the heating period, the tubes were cooled and the contents were poured into about 1000 cc. of cold water. A voluminous precipitate was formed. The precipitate was separated by suction filtration and washed with cold water. Thirty-five grams of slightly-yellow crystals was thus obtained. Recrystallization from chloroform and ligroin gave 30 g. (20% yield) of pure white crystals which melted with slight decomposition at 128–130°. For this recrystallization, the material was dissolved in hot chloroform and ligroin was then added to the hot solution to the point of incipient crystallization, after which the mixture was cooled. A very pure product can be obtained if the material is dissolved in hot water and the solution is cooled quickly. This product does not darken as rapidly on standing as does the product recrystallized from chloroform. However, the recrystallization from water must be carried out quickly to avoid undue loss by hydrolysis.

*Anal.* Calcd. for $C_4H_6O_2I_2$: I, 74.63; neut. equiv., 340. Found: I, 74.52; neut. equiv., 339.

**Hydrolysis of 2,2′-Diiodoisobutyric Acid.**—A solution of 18.97 g. of the diiodo acid in 1000 cc. of water was heated under a reflux condenser at 90–100° for approximately eight hours. The solution was then made up to exactly 1000 cc. and a 50-cc. portion was titrated. This required 74.0 cc. of 0.1127 *N* alkali which corresponds to a normality for the solution of 0.1668 (calcd. for complete hydrolysis: 0.1674 *N*). The remainder of the solution was treated with the silver oxide freshly precipitated from 18.02 g. of silver nitrate. The silver iodide formed was collected and weighed. Found: 24.68 g. Calcd.: 24.82 g. The diiodo acid evidently was hydrolyzed quantitatively.

The filtrate from the silver iodide was concentrated at 30° under 15 mm. pressure to a thick sirup. Neutraliza-

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(10) "Organic Syntheses," John Wiley and Sons, Inc., New York, 1922, Vol. II, p. 13.

(11) *Ibid.*, p. 29.

(12) Grimaux and Adam, *Bull. soc. chim.*, **36**, 20 (1881).

tion equivalents obtained for this sirup varied from 105 to 130, depending on the degree of concentration. The sirup was soluble in water, alcohol, acetone, ether, ethyl acetate and dioxane. An ether solution of the sirup was filtered to remove traces of insoluble impurities and concentrated at 5 mm. without heating. When the sirup was concentrated from either an aqueous or an ether solution to a neutralization equivalent of less than 120 (the theoretical for a $C_4$-saccharinic acid), an amorphous, white solid began to separate. In some cases this solid separated from sirups of lower concentration which had been left standing. The remainder of the sirup was separated from the solid by solution in ether. This ether extract gave a second crop of the white solid when concentrated at 5 mm. pressure. This procedure could be repeated until practically all of the sirup had been converted into the solid. This solid was insoluble in all solvents tried except alkalies. It is acidic and gives neutralization equivalents which show some variation, but which generally lie near 95. It did not melt but, upon ignition, it charred and burned and left no residue. Acidification of a solution of this solid in alkali produced a gelatinous precipitate which formed a resinous mass when collected and dried.

Various attempts were made to obtain a crystalline product or a pure product of definite composition from the sirup, but without success. Barium salts were prepared from the sirup at various stages and also from the dilute hydrolysis solution before it had been concentrated to the sirup, by boiling aqueous solutions with an excess of barium carbonate. The filtrates from the barium carbonate were concentrated under reduced pressure to sirups and these were triturated with absolute alcohol to give crystalline products. These barium salts showed considerable variation in barium content although excellent checks were generally obtained for duplicate determinations on a given sample. Values were obtained which ranged from 36.71 to 38.79% (calcd. for $Ba[C_4H_7O_4]_2$: 36.58). Most of the values were near 37.7%.

**2,2′-Dihydroxyisobutyric Acid.**—Evidence for the existence of the 2,2′-acid as a constituent of the sirup obtained from the hydrolysis of 2,2′-diiodoisobutyric acid was obtained by regenerating the diiodo acid from the sirup. Approximately 2 cc. of the sirup was dissolved in 50 cc. of constant-boiling hydriodic acid and the solution was heated on the steam-bath for forty-eight hours. The reaction mixture was diluted with an equal volume of water and extracted with ether. The ether extract was shaken with 10% sodium thiosulfate solution to remove free iodine and the clear ether solution was concentrated to a thick sirup. The addition of water to this sirup caused the separation of a voluminous, white precipitate which, when dry, weighed 0.8 g. (15% yield). This precipitate was found to be identical with the original diiodoisobutyric acid. It had a neutralization equivalent of 338 and its melting point was not depressed by the addition of the pure diiodo acid.

**Reduction of 1,2-Dihydroxyisobutyric Acid.**—A solution of 20 g. of 1,2-dihydroxyisobutyric acid in 500 cc. of constant-boiling hydriodic acid to which had been added 2 g. of red phosphorus, was refluxed for twenty hours. The reaction mixture was extracted with ether and the ether extract was decolorized with sodium thiosulfate solution. Concentration of the ether extract gave 20 g. of a crystalline product (50% yield) which, after recrystallization from water, melted at 39°. Analysis and the melting point showed that this material was 2-iodoisobutyric acid.

*Anal.* Calcd. for $C_4H_7O_2I$: I, 59.31; neut. equiv., 213.9. Found: I, 59.00; neut. equiv., 212.3.

## Summary

1. Pentaerythritol dibromohydrin was oxidized to 1,1-di-(bromomethyl)-2-hydroxypropionic acid which was broken down on further oxidation.

2. The reaction of pentaerythritol with sodium and ethyl bromide in liquid ammonia gave a mixture of the di-, tri-, and tetraethyl ethers of pentaerythritol. The tetraethyl ether was the main product.

3. Pentaerythritol diethyl ether was prepared by the reaction of the dibromohydrin with sodium ethylate in liquid ammonia. The diethyl ether is broken down upon oxidation more easily than is pentaerythritol itself.

4. 2,2′-Diiodoisobutyric acid was prepared and evidence for its structure is advanced.

5. Hydrolysis of 2,2′-diiodoisobutyric acid gave a sirup of complex nature. Evidence is given for the presence of 2,2′-dihydroxyisobutyric acid in this sirup.

6. Attempts to obtain 2,2′-dihydroxyisobutyric acid in pure condition resulted in the isolation of an amorphous solid which was apparently a condensation product of the acid.

CHICAGO, ILLINOIS RECEIVED DECEMBER 17, 1937