Summary

Attempts to prepare hexa-β-styrylethane and di-β-styryltetraphenylethane have yielded isomeric stable hydrocarbons. In the second of these cases the hydrocarbon has been definitely identified as 1,1,3,4,6,6-hexaphenylhexadiene-1,5, showing that a 1,3-rearrangement had preceded the coupling reaction involved in the synthesis.

URBANA, ILLINOIS RECEIVED DECEMBER 24, 1937

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

Molecular Rearrangements in the Sterols. III. The Constitution of *i*-Cholesterol and of the Isomeric Ethers of Cholesterol

BY E. GILMORE FORD,[1] PURNENDUNATH CHAKRAVORTY[2] AND EVERETT S. WALLIS

In a paper recently published[3] from this Laboratory certain experimental results were reported on the action of anhydrous potassium acetate on cholesteryl *p*-toluenesulfonate in acetic anhydride solution. The preparation of a new isomer of cholesterol, designated as *i*-cholesterol, was described. Some important chemical properties of this new compound and of its acetate were also recorded. From the chemical behavior of these two new compounds the authors were led to the conclusion that in this reaction a molecular rearrangement occurred. Accordingly, they suggested a tentative formula, I, for *i*-cholesterol. They also pointed out that a close relationship exists between this new alcohol and the isomeric ethers of cholesterol discovered by Stoll.[4] In Part II[5] of this series this relationship was clarified, and evidence was submitted which shows conclusively that the abnormal ethers of cholesterol recently referred to in the literature as "*cis*-cholesteryl ethers" are in reality ethers of *i*-cholesterol.

We are now able to substantiate the validity of the formula suggested for *i*-cholesterol, I, by the series of reactions shown in the chart.

As shown in Part I[3] of this series *i*-cholesterol on oxidation in glacial acetic acid solution with chromic acid (CrO_3) gives a ketone which was isolated in the form of its oxime (m.p. 143–144°). From this oxime we have been able to prepare *i*-cholestanone, II, whose crystals melt at 110–111°, and have the specific rotation $[\alpha]^{25}D$ +64.9°. Treatment of this compound with dry hydrogen chloride dissolved in glacial acetic acid yields a crystalline chloro ketone, III, which is easily purified as such and which forms a characteristic oxime. This chloro ketone was found by determinations of the melting point and mixed melting point to be identical with the α-3-chlorocholestanone-6 prepared by Windaus and Dalmer[6] from cholesteryl chloride. Removal of hydrogen chloride by means of alkali produces the same "heterocholestenone," IV (m. p. 95–96°). Hydrogenation of samples of this unsaturated ketone obtained from both sources with palladium black gives the same cholestanone (m. p. 98–99°) identical with the compound prepared from cholestene by the method of Windaus.[6,7]

From these facts it can be seen that in *i*-cholesterol the hydroxyl group is in position 6 of the sterol molecule and that during its formation from cholesteryl *p*-toluenesulfonate a molecular rearrangement occurs. We think, therefore, that the structural formulas for *i*-cholesterol and the isomeric ethers of cholesterol first discovered by Stoll[4] are now established and that the recent arguments and contentions of Heilbron, *et al.*,[8] are untenable.

In conclusion we also would like to point out that in this new isomer of cholesterol there are interesting possibilities. The method of breaking the cyclopropane ring gives a new route to the preparation of many highly interesting compounds and further investigations in this direction are in progress.

Experimental Part

Preparation of α-3-chlorocholestanone-6 (III) from *i*-Cholestanone Oxime.—*i*-Cholestanone oxime (m. p. 143–144°) prepared by the method of Wallis, Fernholz and

(1) Research Assistant on special funds from the Chemical Foundation.

(2) Research Fellow on special funds from the Rockefeller Foundation.

(3) Wallis, Fernholz and Gephart, THIS JOURNAL, **59**, 137 (1937).

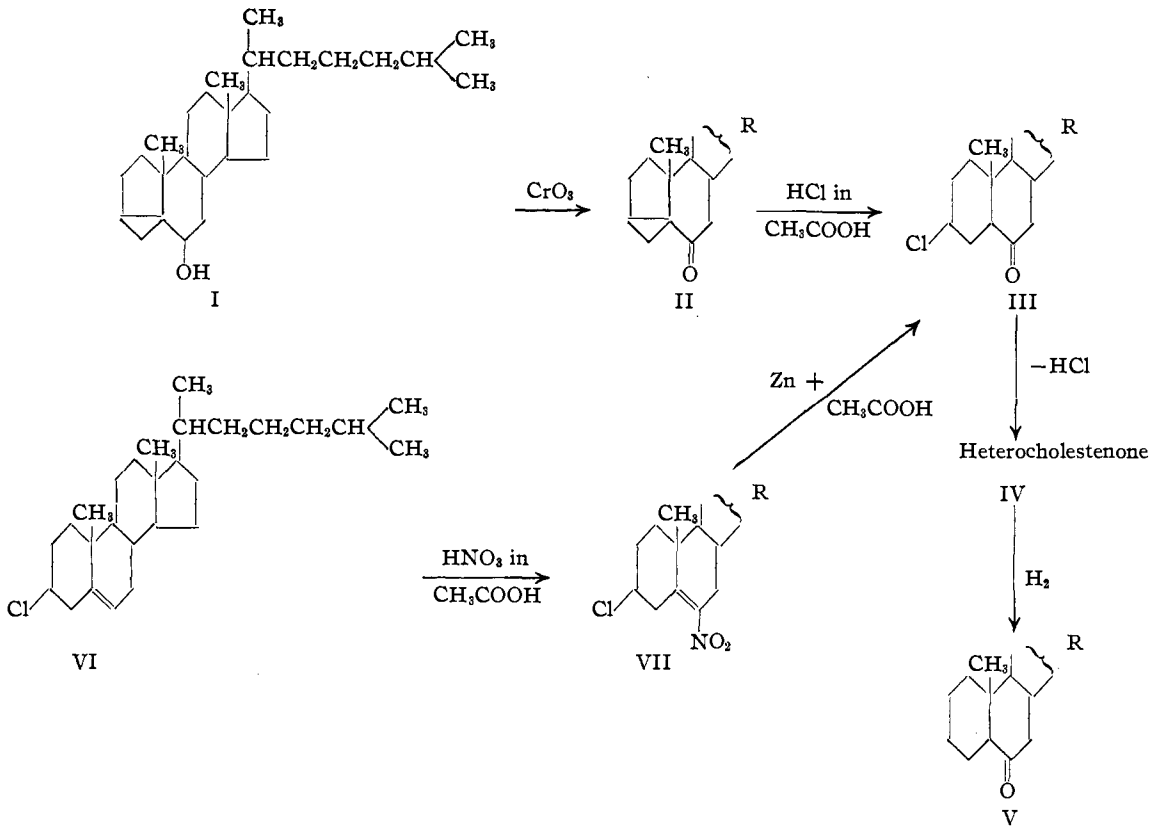
(4) Stoll, *Z. physiol. Chem.*, **207**, 147 (1932).

(5) Ford and Wallis, THIS JOURNAL, **59**, 1415 (1937).

(6) Windaus and Dalmer, *Ber.*, **52**, 168 (1919); see also Mauthner and Suida, *Monatsh.*, **24**, 656 (1903).

(7) Windaus, *Ber.*, **53**, 492 (1920).

(8) Heilbron, *et al.*, *J. Chem. Soc.*, 406, 1459 (1937).



Gephart[3] was hydrolyzed with dilute sulfuric acid in alcohol solution. The solution was boiled for one-half hour, diluted with water, and extracted several times with ether. The ether solution was then freed from acid and dried over anhydrous sodium sulfate. Evaporation of the ether gave a gummy material. Recrystallization from dilute alcohol, dilute acetone and dilute methyl alcohol gave a crystalline ketone which melted at 110–111°; $[\alpha]^{25}D$ +64.9° (11.1 mg. in 2 cc. of chloroform solution gave $\alpha^{25}D$ +0.36°).

To a solution of 6 cc. of glacial acetic acid containing 3% hydrogen chloride there was added 120 mg. of the above described ketone (*i*-cholestanone). The solution so obtained was allowed to stand overnight at room temperature. It was then diluted with 3 volumes of water and extracted several times with ether. The ether solution was freed from acid and worked up in the usual manner. Crystals were readily obtained from alcohol which melted at 129–130°. Subsequent recrystallizations gave a product which melted at 129.5–130.5; yield 120 mg. Twenty milligrams of this material dissolved in 2 cc. of chloroform solution showed no appreciable rotation. When mixed with an authentic specimen of the chloro ketone prepared from cholesteryl chloride by the method of Windaus and Dalmer[6] no depression of the melting point was observed. As a further check on the identity of the two compounds samples of each were converted in the usual manner into their oximes. In both cases crystals were obtained from alcohol which melted at 175°, identical with the melting point recorded by Windaus and Dalmer for the oxime of α-3-chlorocholestanone-6 prepared from cholesteryl chloride. When samples of the oxime from each source were mixed no depression of the melting point was observed.

It also should be noted that in subsequent experiments it was found that α-3-chlorocholestanone-6 could be obtained easily in a pure form from an impure specimen of *i*-cholestanone. It is a compound which crystallizes with great readiness and is very easy to purify.

Preparation of Cholestanone-6 (V).—A sample of α-3-chlorocholestanone-6 (0.25 g.) prepared from *i*-cholesterol by the method described above was dissolved in a 5% alcoholic potassium hydroxide solution and boiled for one-half hour. The solution was then diluted and worked up in the usual manner. Recrystallization from methyl alcohol gave a product which melted at 95–96°, the melting point recorded for "heterocholestenone" prepared from cholesteryl chloride by Windaus and Dalmer. When mixed with an authentic specimen of "heterocholestenone" prepared by Windaus and Dalmer's method no depression of the melting point was observed.

One-tenth of a gram of this unsaturated ketone was dissolved in 20 cc. of glacial acetic acid, and was hydrogenated in the presence of palladium black. On working up the solution in the usual manner crystals were obtained from alcohol which melted at 88–90°. An oxime was prepared in the usual manner from a portion of this material. Recrystallization from alcohol gave a crystalline product which melted at 195°, the melting point recorded for the oxime of cholestanone-6 prepared by the method of Windaus and Dalmer from cholesteryl chloride. Further purification of the ketone itself gave crystals which melted at 98–99°, the melting point recorded by Windaus and

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.

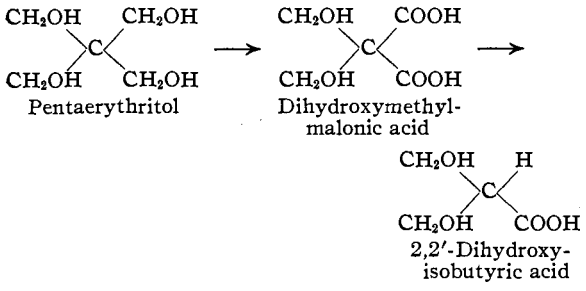
PRINCETON, N. J. RECEIVED DECEMBER 18, 1937

[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]

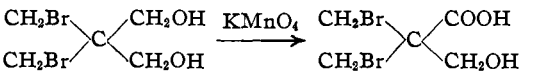
BY J. W. E. GLATTFELD AND JOHN M. SCHNEIDER

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.

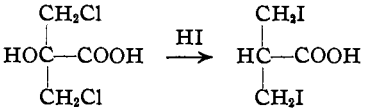
The dibromohydrin of pentaerythritol was therefore prepared by the procedure of Zelinsky and Krawetz.[5] This compound, when oxidized, yielded a monocarboxylic acid, 1,1-di-(bromomethyl)-2-hydroxypropionic acid, as indicated below



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



(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).