cipitate washed with cold water. The yield was 5.27 g. (33.4% of the theoretical) of crude 5-chloromercuri-2-thiophenecarbinol. Repeated recrystallization from hot water produced a white powder melting at 183–185°, with decomposition.

Anal. Calcd. for $C_5H_5SOHgCl$: C, 17.18; H, 1.44; Hg, 57.4. Found: C, 16.80; H, 1.42; Hg, 56.31.

The free 2-thiophenecarbinol was isolated by treating a warm aqueous solution of the mercury derivative with hydrogen sulfide, removal of the mercuric sulfide and extraction of the carbinol with ether. The α-naphthylurethan derivative of this biologically synthesized thiophenecarbinol was prepared as described below. The melting point (148°) of this derivative and the corresponding derivative from synthetic thiophenecarbinol showed no depression when the two were mixed. The analysis of the α-naphthylurethan derivative further established the identity of the isolated thiophenecarbinol with the synthetic product.

Anal. Calcd. for $C_{16}H_{13}O_2SN$: C, 67.78; H, 4.62; N, 4.94; S, 11.31. Found: C, 67.78; H, 4.67; N, 4.98; S, 11.20.

Synthesis of 2-Thiophenecarbinol.—Into a three-necked flask, equipped with stirrer, dropping funnel and thermometer, were placed 3.5 g. of 2-thiophenealdehyde, 10 cc. of absolute methanol and 5 cc. of formalin. With stirring the mixture was heated on the water-bath to 65°, at which time a solution of 6 g. sodium hydroxide in 6 cc. of water was added. Heating was continued at 65° for thirty minutes, and then the solution was refluxed for a short time. The dark-colored reaction mixture was extracted with benzene. Distillation yielded 2.1 g. (59% of the theoretical) of the carbinol boiling at 102–105° (20 mm.).

Phenylurethan Derivative of 2-Thiophenecarbinol.—A mixture of a few drops of phenyl isocyanate with an equal volume of 2-thiophenecarbinol was heated on the water-bath for thirty minutes. Recrystallization of the product from petroleum ether produced colorless, monoclinic crystals melting at 72.3–74°.

Anal. Calcd. for $C_{12}H_{11}O_2SN$: C, 61.77; H, 4.75; N, 6.00; S, 13.74. Found: C, 61.69; H, 4.80; N, 6.13; S, 13.72.

α-Naphthylurethan Derivative of 2-Thiophenecarbinol.—A mixture of equal amounts of the carbinol and α-naphthyl isocyanate was heated for thirty minutes on the water-bath. After recrystallization from a mixture of chloroform and petroleum ether the colorless, monoclinic crystals melted at 148°.

Anal. Calcd. for $C_{16}H_{13}O_2SN$: C, 67.78; H, 4.62; N, 4.94; S, 11.31. Found: C, 67.81; H, 4.60; N, 4.97; S, 11.30.

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Summary

2-Thiophenecarbinol was synthesized from 2-thiophenealdehyde by fermenting yeast in a manner similar to the microbial synthesis of benzyl and furfuryl alcohols from the corresponding aldehydes. The carbinol obtained from the fermenting yeast was identical with 2-thiophenecarbinol synthesized from 2-thiophenealdehyde by a crossed Cannizzaro reaction with formaldehyde. Three derivatives of 2-thiophenecarbnol were prepared and described.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Δ^6-*i*-Cholestadiene

BY BYRON RIEGEL, GEORGE P. HAGER AND BERNARD L. ZENITZ

An investigation was made of the Barbier–Wieland degradation[1] of 3-hydroxy-5-cholenic acid where the 3-hydroxyl group and the 5–6 carbon–carbon double bond were protected by the *i*-ether structure. The 3-hydroxyl group and the double bond can be easily regenerated from the *i*-steroid structure. When the carbinol was dehydrated with activated alumina in boiling xylene, there was a simultaneous loss of methyl alcohol with the introduction of an ethylenic bond in ring B. An attempt to apply this reaction to the carbinol of the bis*nor*-cholenic acid[2] resulted in some tar formation but chiefly in recovery of the starting material.

To further clarify this reaction and the structure of the resulting hydrocarbon, *i*-cholesteryl methyl ether (I) was treated with alumina in boiling xylene. There was obtained a white, crystalline hydrocarbon that melted at 73°, with a specific rotation of −47°, for which formula (II) has been assigned as a result of the physical and chemical evidence.

There was also isolated a small quantity of cholesteryl methyl ether (V). In order to determine whether this was a reaction product or an inpurity in the starting material, the *i*-cholesteryl methyl ether was extensively purified by chromatographic technique. The normal ether, however, was isolated from the reaction using the purified *i*-ether and was considered to be a reaction product, probably formed by the addition of methanol to the *i*-diene.

The physical evidence for the cyclopropane ring conjugate to the ethylenic bond was the ultraviolet absorption spectrum of the hydrocarbon.[3] The *i*-diene showed a maximum absorption near 2100 Å., which is between the absorption peaks of a conjugated diene and an ethylenic double bond. This was analogous to the shift of the absorption maxima of *i*-cholestenone and carone compared to those of 4-cholestene-3-one and 5-cholestene-3-one.

The hydrocarbon was found to display unusual addition reactions. When refluxed with glacial acetic acid, cholesteryl acetate (IV) was obtained.

(1) B. Riegel, M. F. W. Dunker and M. J. Thomas, THIS JOURNAL, **64**, 2115 (1942).

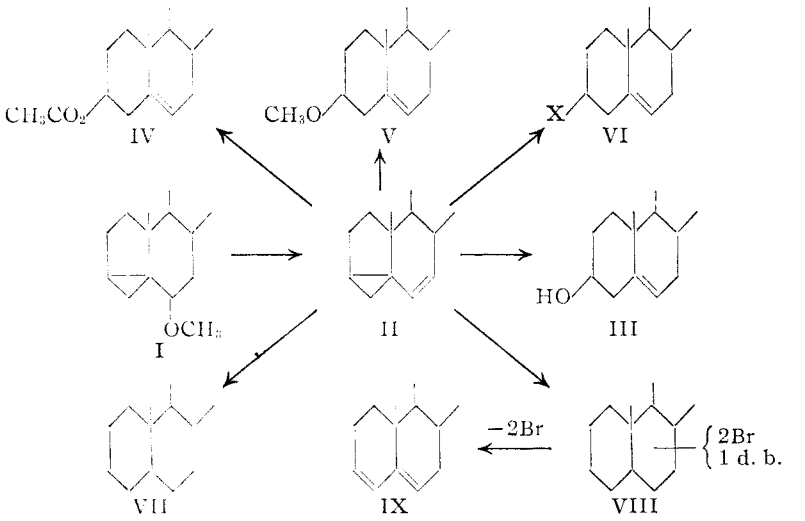
(2) B. Riegel and E. W. Meyer, *ibid.*, **68**, 1097 (1946).

(3) I. M. Klotz, *ibid.*, **66**, 88 (1944).

Sulfuric acid catalyzed the addition of water from an aqueous acetone solution and the addition of methanol from a methanol solution to the *i*-diene, when refluxed, to give cholesterol (III) and cholesteryl methyl ether (V), respectively. The hydrohalides in acetone solution added in a similar manner to give the cholesteryl halides (VI).

Hydrogenation at room temperature using palladium-on-charcoal added two moles of hydrogen and gave cholestane (VII). Bromination of the *i*-diene gave an unknown cholesteryl dibromide (VIII), which after debromination with sodium iodide gave cholesterilene (IX). Treatment of *i*-diene with sodium iodide and iodine under similar conditions gave only starting material. Therefore, the cholesterilene produced was not due to debromination to reform the *i*-diene and subsequent rearrangement under the influence of iodine.

Rapid titrations with bromine resulted in the addition of 0.96 and 1.07 moles of bromine. However, upon standing overnight with an excess of bromine, 1.90 moles were consumed by the *i*-diene. Titrations with hypobromous acid showed 1.64 and 1.74 moles consumed. Perbenzoic acid titrations added 1.28, 1.24 and 1.25 moles of the acid. Attempts at ozonolysis gave only indefinite results.



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Experimental[4]

***i*-Cholesteryl Methyl Ether.**—The isomeric ether was prepared from cholesteryl *p*-toluenesulfonate by the method of Stoll.[5] The product was extensively purified by dissolving in Skellysolve F (petroleum ether, b. p. 30–60°) and passing the solution through a column of activated alumina (chromatographic, 80–200 mesh, Aluminum Ore Co. of America). The *i*-ether was eluted with the same solvent in the first fractions of percolate and after recrystallization from acetone, melted at 79.5–80°.

Δ^6-*i*-Cholestadiene.—Seventy grams of alumina and 700 ml. of xylene were refluxed, using a moisture determination tube between the condenser and reaction flask to remove the water present. When water ceased to collect in the tube, 20 g. of *i*-cholesteryl methyl ether was added. After refluxing for twenty hours, an additional 5 g. of alumina was added and refluxing continued for ten more hours. The alumina was removed by filtration and washed with three portions of hot xylene. The filtrate and washings were combined and the xylene removed under reduced pressure. There remained a pale yellow oil which crystallized on standing. The residue was dissolved in 50 ml. of Skellysolve F and passed through a 75-g. column of alumina. The first four 25-ml. fractions, eluted with the same solvent, gave 14.1 g. (77%) of colorless crystals, which after recrystallization from 110 ml. of acetone gave 13.2 g. of thick needles, m. p. 73°, $[\alpha]^{25}_D$ −47.2 ± 0.7° (28.2 mg. made up to 2 ml. with chloroform, α_D −1.33°, *l*, 2 dm.).

Anal. Calcd. for $C_{27}H_{44}$: C, 87.96; H, 12.03. Found: C, 87.78, 87.96; H, 12.07, 11.80.

Later fractions eluted with benzene–ethanol mixtures gave 0.2 g. of cholesteryl methyl ether, m. p. 82–83°.

Cholesteryl Acetate.—A mixture of 1 g. of the *i*-diene and 25 ml. of glacial acetic acid containing several drops of concentrated sulfuric acid was refluxed for one hour. The acetic acid was removed under reduced pressure and the residue crystallized from methanol. There was obtained 1.05 g. of pale yellow crystals, m. p. 104–106°, which, after recrystallization from an acetone–methanol mixture, gave 0.85 g. of colorless crystals, m. p. 112–113°. A mixed melting point with an authentic sample of cholesteryl acetate gave no depression.

Cholesteryl Chloride.—A solution of 0.5 g. of *i*-diene in 15 ml. of acetone and 0.5 ml. of concentrated hydrochloric acid was refluxed for four hours. After standing in the cold, 0.43 g. of colorless crystals was obtained, m. p. 93.4–93.5°. From the mother liquor there was obtained an additional 0.07 g., m. p. 89–90°. No depression was observed in a mixed melting point with cholesteryl chloride.

Cholesteryl Bromide.—A solution of 0.4 g. of *i*-diene in 15 ml. of acetone and 0.4 ml. of hydrobromic acid (42%) was refluxed for three hours. After cooling, there was obtained 0.52 g. of white crystals, m. p. 99°. There was no depression in a mixed melting point with an authentic sample of cholesteryl bromide.

Cholesteryl Iodide.—To a solution of 0.5 g. of the *i*-diene in 35 ml. of dry acetone was added 1 ml. of hydroiodic acid (Merck, 55–58%). After one minute a crystalline precipitate separated. The solution was warmed until the precipitate dissolved and the solution cooled for several hours. The crystalline product, 0.58 g. of fine colorless needles, was removed by filtration. The product melted at 106–106.5°, $[\alpha]^{25}_D$ −12.6° (lit.[6] m. p. 106.5–107°, $[\alpha]^{20}_D$ −11.94°).

Cholesterol.—A solution of 0.5 g. of the *i*-diene in 20 ml. of acetone and 2.5 ml. of 65% sulfuric acid was refluxed for three hours. After cooling, there was obtained 0.37 g. of cholesterol, m. p. 144.5–145°. A mixed melting point with cholesterol gave no depression.

Cholesteryl Methyl Ether.—A solution of 0.5 g. of the *i*-diene in 70 ml. of anhydrous methanol containing 5

(4) All melting points are corrected. Analyses by Dr. T. S. Ma, University of Chicago.

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

(6) J. H. Beynon, I. M. Heilbron and F. S. Spring, *J. Chem. Soc.*, 907 (1936).

drops of concentrated sulfuric acid was refluxed twenty-four hours. After standing at room temperature, pearly crystals, m. p. 82–83°, separated from the solution. A second crop, m. p. 82–82.5°, was obtained by concentrating the mother liquor and cooling, giving a total yield of 0.4 g. A mixed melting point with a sample of cholesteryl methyl ether gave no depression.

Bromination of the *i*-Diene.—A solution of 5.0 g. of *i*-diene in 20 ml. of chloroform was brominated in the cold by the slow addition of 2.17 g. of bromine in 25 ml. of chloroform. The solvent was removed under reduced pressure without heat, leaving a yellow, partly crystalline residue. Acetone was added to the residue and the insoluble crystalline material was removed by filtration and washed with acetone until colorless. The product, 3.45 g., melted at 138–140°. After concentrating the mother liquor and recrystallization of the product, there was obtained a total of 5.41 g. of material, m. p. 140–141°. Further crystallizations raised its m. p. to 143–144°.

Anal. Calcd. for $C_{27}H_{44}Br_2$: C, 61.36; H, 8.39; Br, 30.25. Found: C, 61.60; H, 8.41; Br, 26.15.

Debromination of the Dibromide.—A solution of 2.67 g. of the dibromide and 6 g. of sodium iodide in 300 ml. of dry acetone was refluxed for three hours. Free iodine was removed by means of a 10% sodium thiosulfate solution. The solution was concentrated to 20 ml., water added and the solution extracted with ether. The ether solution was washed and dried and the ether removed under reduced pressure. There remained 1.96 g. of a pale yellow crystalline residue. This residue was dissolved in 25 ml. of Skellysolve F and chromatographed on 28 g. of alumina. The column was eluted with the same solvent collecting first a 20 ml. fraction and a second 40 ml. fraction. From the first fraction was obtained 1.05 g. of residue, which after four crystallizations from acetone melted at 80–80.5°, $[\alpha]^{25}D$ −81.5° (0.1212 g. made up to 5 ml. with chloroform, *l*, 1 dm.). A mixed melting point with cholesterilene, m. p. 78.5–79.5°, $[\alpha]^{25}D$ −91.5° (0.1267 g. made up to 5 ml. with chloroform, *l*, 1 dm.), prepared by the method of Müller and Page[7] from monocholesteryl phosphoric acid, gave no depression.

Attempted Rearrangement of *i*-Diene.—A solution of 2.0 g. of *i*-diene, 4 g. of sodium iodide and 1 g. of iodine in 100 ml. of dry acetone was refluxed for twenty-four hours. Twenty ml. of 10% thiosulfate solution was added to remove the free iodine and the solution concentrated under reduced pressure to 10 ml. The solution was diluted with water and extracted with ether. The ether solution was washed with water and dried over anhydrous sodium sulfate. The dark, oily residue obtained by the removal of ether was dissolved in 30 ml. of Skellysolve F and filtered through 28 g. of alumina. The column was then eluted with 100 ml. of the same solvent. Removal of the Skellysolve left a solid, 1.78 g., which after recrystallization from acetone proved to be the starting material.

Hydrogenation of the *i*-Diene.—Twenty ml. of dioxane was shaken with 0.3 g. of palladium-on-charcoal at room temperature until saturated with hydrogen. Then 0.4 g. of the *i*-diene was added and hydrogenation continued. After fifty minutes, 25.2 ml. of hydrogen was absorbed. The theoretical for two double bonds was 25.0 ml. The catalyst was removed by filtration and the solvent removed under reduced pressure, leaving a colorless oil. After repeated crystallizations from methanol, a small amount of crystalline material was obtained, m. p. 78–79°. A mixed melting point with cholestane showed no depression.

Perbenzoic Acid Titrations of *i*-Diene.—Two ml. of perbenzoic acid solution was added to 100 mg. of the *i*-diene in 10 ml. of chloroform at 0° and allowed to stand for twenty hours at 0 to −5°. Then a solution of 50 ml. of water, 2 g. of potassium iodide, and 5 ml. of 5 *N* sulfuric acid was added and the liberated iodine titrated with 0.0946 *N* thiosulfate solution. A blank was run for each determination.

Anal. Calcd. for 1 double bond. Found: 1.28, 1.24, 1.25 double bonds.

Titration with Bromine.—To a chloroform solution of the *i*-diene was added an excess of bromine in chloroform. An aqueous solution of potassium iodide was then added and the liberated iodine titrated with thiosulfate solution. A blank was run for each determination.

Anal. Calcd.: 1 double bond. Found: 0.96, 1.07.

A solution of the *i*-diene was allowed to stand with excess bromine solution (more than 2 molar equivalents) at −5° for forty-eight hours in the dark. The consumed bromine was analyzed in the same manner.

Anal. Calcd.: 2 double bonds. Found: 1.9.

Hypobromous Acid Titration of *i*-Diene.—A chloroform solution of the *i*-diene was placed in an ice-bath and shaken with a standardized hypobromous acid solution. Then aqueous potassium iodide and dilute sulfuric acid was added and the liberated iodine titrated with standard thiosulfate solution.

Anal. Calcd.: 2 double bonds. Found: 1.64, 1.74.

Summary

1. The preparation of a new steroid hydrocarbon, Δ^6-*i*-cholestadiene and its physical properties are described.

2. The addition of hydrohalic acids, methanol, acetic acid and water to the *i*-diene formed the cholesteryl halides, cholesteryl methyl ether, cholesteryl acetate and cholesterol, respectively.

3. Hydrogenation of this material gave cholestane. The addition of bromine forms an unidentified dibromide which on debromination produces cholesterilene.

4. Various analytical data are presented in support of the structure.

(7) E. Müller and I. H. Page, *J. Biol. Chem.*, **101**, 127 (1933).

EVANSTON, ILLINOIS RECEIVED AUGUST 19, 1946