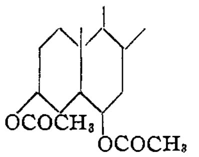
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. LXXXIV. Progesterone from Hyodesoxycholic Acid

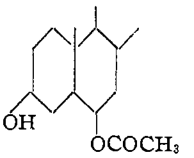
BY RUSSELL E. MARKER AND JOHN KRUEGER

Preferential reactions in the sterol series have been widely used. Thus, Marker and co-workers acetylated the 3-position in both desoxycholic acid[1] and *allo*-pregnanediol,[2] leaving intact the 12-hydroxy group and the 20-hydroxy group, respectively. Half-hydrolysis of the diacetate of pregnanediol-(α),(α) gave pregnanol-20(α)-one-3[3] and Ellis and Petrow[4] obtained 6-acetoxycholestane-3,5-diol from 3,6-diacetoxycholestane-5-ol. Ruzicka and Wettstein[5] and Butenandt and Hanisch[6] utilized the difference in hydrolytic rate between acetoxy groups substituted in the 3- and 17-positions in the preparation of testosterone.

We assumed that, in analogy to the hydrolytic reactions previously cited, the main product in the partial hydrolysis of a 3,6-diacetoxy derivative would be a 3-hydroxy-6-acetoxy compound. We investigated the series of reactions I to VI using cholestanediol-3,6. Cholestanediol-3,6 of m. p. 216° has been described by Windaus[7] as the product of the sodium–alcohol reduction of 6-keto-cholestanol. We found platinum oxide in alcohol solution a more convenient reagent for the hydrogenation of 6-keto-cholestanol. Under these conditions a practically quantitative yield of a cholestanediol-3,6 of m. p. 190° was obtained. This substance VIII is stereoisomeric with the compound of m. p. 216° described by Windaus.



I



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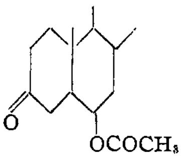

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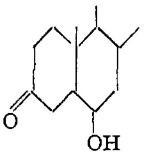

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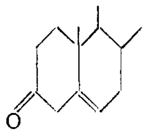

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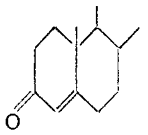
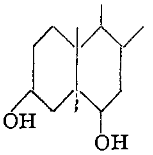
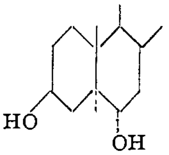


VI



VII



VIII

The diacetate (I) of cholestanediol-3,6 was preferentially hydrolyzed at position-3 either by potassium hydroxide in methanol at 20° or by refluxing with sodium bicarbonate in methanol a short time to yield the hydroxy acetate (II) which was not isolated but oxidized to 6-acetoxycholestanone (III). Hydrolysis of the 6-acetoxycholestanone and dehydration of the resulting 6-hydroxycholestanone by distillation over fused potassium bisulfate produced cholestenone (VI) in good yield.

We have now utilized the above reactions for the preparation of progesterone from hyodesoxycholic acid. The side chain of hyodesoxycholic acid was degraded by the Barbier–Wieland method to produce a keto group at C-20. The procedure used was similar to the directions of Hoehn and Mason[8] for the degradation of desoxycholic acid and the yields obtained were comparable to theirs. The 3,6-diacetoxy-*etio*-cholanyl methyl ketone was hydrolyzed preferentially at position 3. The resulting product was oxidized to a ketone which, after hydrolysis and sublimation from potassium bisulfate, yielded progesterone.

We wish to thank Parke, Davis and Company for their generous support and assistance in the various phases of this work.

Experimental Part

Cholestanediol-3,6.—6-Ketocholestanol,[9] m. p. 143°, (25 g.), 1.0 g. of platinum oxide catalyst and 300 cc. of methanol were shaken under 3 atm. of hydrogen. Reduction was complete within forty-five minutes. The catalyst and solid diol was filtered off, and the precipitate was then dissolved in warm alcohol and was filtered from the catalyst. The combined filtrates were concentrated by evaporation. The solution on cooling deposited 20 g. of white crystals which melted at 188°. The diol crystallized from methanol as large transparent prisms of m. p. 190°.

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[1] Marker and Lawson, THIS JOURNAL, **60**, 1334 (1938).

[2] Marker, Kamm and Jones, *ibid.*, **59**, 1595 (1937).

[3] Marker, Kamm, Wittle, Oakwood, Lawson and Laucius, *ibid.*, **59**, 2291 (1937).

[4] Ellis and Petrow, *J. Chem. Soc.*, 1081 (1939).

[5] Ruzicka, THIS JOURNAL, **57**, 2011 (1935); Ruzicka and Wettstein, *Helv. Chim. Acta*, **18**, 1264 (1935).

[6] Butenandt and Hanisch, *Ber.*, **68**, 1859 (1935).

[7] Windaus, *ibid.*, **50**, 133 (1917).

[8] Hoehn and Mason, THIS JOURNAL, **60**, 1493 (1938).

[9] Cf. Heilbron, Jackson, Jones and Spring, *J. Chem. Soc.*, 104 (1938).

Anal. Calcd. for $C_{27}H_{48}O_2$: C, 80.1; H, 12.0. Found: C, 80.3; H, 12.0.

The diacetate was prepared by refluxing the diol for a short time in acetic anhydride. It crystallized from methanol as white flakes, m. p. 138°.

Anal. Calcd. for $C_{31}H_{50}O_4$: C, 76.5; H, 10.4. Found: C, 76.3; H, 10.5.

6 - Acetoxycholestanone.—Cholestanediol - 3,6 - diacetate, m. p. 138° (10 g.), was dissolved in 3 liters of methanol by warming, then cooled to 25° and a solution of 0.92 g. of potassium hydroxide in 177 cc. of methanol was added. The solution was allowed to stand at 20° for forty-eight hours. It was then exactly neutralized by addition of 16.9 cc. of 0.96 normal sulfuric acid. The solution was evaporated *in vacuo* and the residue was dissolved in 250 cc. of acetic acid. Chromic oxide (1.2 g.) dissolved in 50 cc. of 90% acetic acid was added to the reaction mixture. After standing at room temperature for three hours, water was added and the oily precipitate was extracted with ether. The ethereal solution was washed with water and then was evaporated. Remaining acetic acid was evaporated *in vacuo*. 6-Acetoxycholestanone crystallized from petroleum ether as thick white needles and from methanol as fine white needles of m. p. 101°.

Anal. Calcd. for $C_{29}H_{48}O_3$: C, 78.4; H, 10.9. Found: C, 78.3; H, 10.9.

6-Acetoxycholestanone also was prepared by refluxing 1.0 g. of the diacetate of cholestanediol-3,6 for one and one-half hours with 1.0 g. of sodium bicarbonate in a solution of 10 cc. of water and 250 cc. of methanol. The reaction mixture was poured into water and was extracted with ether. The residue left by evaporation of the ether was treated as described above, although in this case Girard's reagent was used to purify the product which melted at 100° and showed no depression with an analyzed sample of 6-acetoxycholestanone, m. p. 101°.

6-Hydroxycholestanone.—6-Acetoxycholestanone (3.7 g.) was refluxed for one and one-half hours with 150 cc. of 2% methanolic potassium hydroxide. Water was added and the precipitated product was allowed to stand overnight. The crystals collected by filtration weighed 3.0 g. and melted at 183–187°. Recrystallization from methanol gave white leaflets of m. p. 190°.

Anal. Calcd. for $C_{27}H_{46}O_2$: C, 80.5; H, 11.5. Found: C, 80.3; H, 11.6.

Cholestenone.—6-Hydroxycholestanone (100 mg.) and 0.5 g. of fused potassium bisulfate were pulverized together and heated for two hours at 125°, then at 185° for five hours under 4 mm. pressure. The distilled substance after crystallization from methanol melted at 80° and showed no depression in melting point when mixed with an authentic sample melting at the same temperature.

Methyl Ester of Hyodesoxycholic Acid.—The acid was refluxed for two hours with 1% methanolic hydrogen chloride. The solvent was evaporated *in vacuo*. Addition of benzene to the oily residue caused crystallization. It melted at 86°.

Anal. Calcd. for $C_{25}H_{42}O_4$: C, 73.8; H, 10.4. Found: C, 74.2; H, 10.0.

***nor*-Hyodesoxycholic Acid.**—The methyl ester from 200 g. of hyodesoxycholic acid was added in hot benzene solution to 16 moles of phenylmagnesium bromide in ether. The thick gray suspension was refluxed for two hours, then most of the solvent was distilled off. Dry benzene (or toluene) was added and the mixture was heated overnight on a steam-bath. The suspension was decomposed by pouring it on ice and hydrochloric acid. It was then extracted with ether. The ethereal extract was washed with dilute hydrochloric acid, dilute potassium hydroxide, and then finally with water. The solvents were completely evaporated and the crystalline diphenyl alcohol was refluxed for two hours with 600 cc. of acetic anhydride. This solvent was evaporated *in vacuo* and the oily residue was refluxed for six hours with acetic acid. Evaporation of the acetic acid left an oil which did not crystallize but which was oxidized by chromic oxide in acetic acid–chloroform–water mixture exactly as described by Hoehn and Mason.[8] After addition of water and reduction of the excess chromic anhydride with sulfur dioxide, the mixture was extracted with ether. The ethereal extract was well washed with water and was then extracted with 2 *N* potassium hydroxide solution. The basic solution was boiled one and one-half hours and was poured slowly on a stirred mixture of ice and hydrochloric acid. The flocculent white precipitate could be easily filtered and washed with water. It was crystallized from a large amount of ethyl acetate to give a product melting at 198°; yield 110 g. The mixed melting point with hyodesoxycholic acid was 175–180°.

Anal. Calcd. for $C_{23}H_{38}O_4$: C, 72.9; H, 10.1. Found: C, 72.6; H, 10.1.

The methyl ester was prepared by refluxing *nor*-hyodesoxycholic acid in 1% methanolic hydrogen chloride solution. The substance crystallized from benzene with benzene of crystallization. It melted at 95°. After drying in a vacuum at room temperature the analysis showed it to contain 1 mole of benzene.

Anal. Calcd. for $C_{24}H_{40}O_4 \cdot C_6H_6$: C, 76.5; H, 9.8. Found: C, 76.8; H, 9.6.

***bis-nor*-Hyodesoxycholic Acid.**—This acid was prepared in yields of 42 g. from 100 g. of *nor*-hyodesoxycholic acid by the method described for the preparation of *nor*-hyodesoxycholic acid. A crystalline diphenyl alcohol of m. p. 222° (from toluene) was obtained.

Anal. Calcd. for $C_{35}H_{45}O_3$: C, 81.3; H, 9.4. Found: C, 81.3; H, 9.4.

bis-nor-Hyodesoxycholic acid crystallized from a large volume of ethyl acetate as white crystals of m. p. 240°.

Anal. Calcd. for $C_{22}H_{36}O_4$: C, 72.5; H, 10.0. Found: C, 72.4; H, 10.0.

Methylation of this acid in methanolic hydrogen chloride yielded an unsharply melting substance. Methylation with excess diazomethane in ether alcohol solution furnished a quantitative yield of the methyl ester of *bis-nor*-hyodesoxycholic acid of m. p. 146°.

Anal. Calcd. for $C_{23}H_{38}O_4$: C, 72.9; H, 10.1. Found: C, 72.7; H, 10.1.

3,6-Diacetoxy-*etio*-cholanyl Methyl Ketone.—The methyl ester of *bis-nor*-hyodesoxycholic acid was added in benzene solution to 16 moles of phenylmagnesium bromide. The reaction was carried out as described for the preparation of *nor*-hyodesoxycholic acid. The alcohol was acetylated with acetic anhydride and pyridine at 100° for twenty hours. The solvents were evaporated *in vacuo* and the residue was taken up in ether. The ethereal solution was washed with dilute hydrochloric acid and sodium carbonate and was then evaporated to dryness. The residue was dehydrated for six hours by refluxing it with acetic acid. The solvent was evaporated *in vacuo*. The crude ethylenic compound was ozonized in chloroform solution at 0°. The ketones were separated by Girard's reagent and crystallized from ether–pentane. 3,6-Diacetoxy-*etio*-cholanyl methyl ketone melted at 100°.

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.7; H, 9.2. Found: C, 72.0; H, 9.0.

Progesterone.—To 0.9 g. of 3,6-diacetoxy-*etio*-cholanyl methyl ketone in 200 cc. of methanol at 20° was added 42 cc. of methanolic potassium hydroxide containing 0.8 mole of base. The solution was allowed to stand at 20° for forty-eight hours. It was then exactly neutralized by addition of 1.7 cc. of 0.96 *N* sulfuric acid. The solvent was completely evaporated *in vacuo*, and the oily residue was oxidized in one hour at room temperature in 25 cc. of acetic acid with a solution of 5 cc. of 90% acetic acid containing 0.5 g. of chromic oxide. Water was added and the precipitated material was extracted with ether. The ethereal solution was washed with water, and then concentrated. This product was refluxed with 40 cc. of 2% methanolic potassium hydroxide for seventy-five minutes. Water was added and the organic material was extracted with ether. The ethereal solution was washed with water and was then evaporated to dryness. The solid remaining was covered with 5.0 g. of fused potassium bisulfate and was heated at 4 mm. at 130° for an hour and a half. The temperature was then raised to 180° for four hours. The ethereal solution of the distillate on evaporation left a pale, mobile oil, which, when crystallized from acetone–water, yielded greasy crystals. Recrystallization from ether–pentane produced small white crystals of m. p. 120°, which gave no depression in melting point with an authentic sample of progesterone.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.2; H, 9.6. Found: C, 80.4; H, 9.6.

Summary

The Barbier–Wieland degradation applied to hyodesoxycholic acid produced 3,6-diacetoxy-*etio*-cholanyl methyl ketone. This compound was converted into progesterone by a method described for the conversion of 3,6-cholestanediol diacetate into cholestenone.

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY, THE UNIVERSITY OF CHICAGO]

The Peroxide Effect in the Addition of Reagents to Unsaturated Compounds. XXIV. The Addition of Hydrogen Iodide to Propene, 1-Bromopropene, Allyl Chloride, and Allyl Bromide

BY M. S. KHARASCH, JAMES A. NORTON,[1] AND FRANK R. MAYO

The work here reported was undertaken in extension of the previous studies of Kharasch and Hannum,[2] and for the purpose of discovering, if possible, the reasons for the discordance between the results of those studies and that of Ingold and Ramsden.[3]

The consensus among the earlier workers has been that isopropyl iodide is the sole product of the addition of hydrogen iodide to propene.[4] The cited work of Kharasch and Hannum confirms that opinion. Ingold and Ramsden, however, report addition products comprising as much as 25% of normal propyl iodide. The highest yields of the normal iodide were obtained in the absence of solvent and in the presence of the typically non-polar solvent propane. Relatively polar solvents, such as nitrobenzene, acetic acid, and water, were said to give rise to relatively smaller yields of the normal iodide. According to Ingold and Ramsden, the "solvent effect" varies with the "mean molecular fraction of hydrogen iodide in its mixture with the solvent (if any) during the course of the reaction." Unfortunately the "mean molecular fraction" is not precisely defined, nor are complete details of the experiments given. Their method consisted in breaking a sealed tube of propene within a sealed tube of hydrogen iodide (and solvent, if any) at a temperature of 18 ± 2°, which was maintained throughout the reaction.

Discussion

The Addition of Hydrogen Iodide to Propene.—A series of experiments performed in accordance with our usual technique (i. e., with exclusion of air, moisture, and light), and with hydrogen iodide–propene ratios varying from 0.36/

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[1] University Fellow, 1938–1939. This paper is an abstract of a thesis submitted by James A. Norton in partial fulfilment of the requirements for the Ph.D. degree, the University of Chicago, 1939.

[2] Kharasch and Hannum, THIS JOURNAL, **56**, 712, 1782 (1934).

[3] Ingold and Ramsden, *J. Chem. Soc.*, 2746 (1931).

[4] For references see ref. 2; *cf.* also Emschwiller, *Ann. chim.*, (10) **17**, 500 (1932).