[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Barbier-Wieland Degradation of 3-Hydroxy-12-ketocholanic Acid

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It is well known that Grignard reagents do not add readily to hindered ketones, and since the 12-keto group in steroids is highly hindered it was thought that it might be possible to carry out the Barbier-Wieland degradation on this class of compounds without destroying the keto group. For 3-hydroxy-12-ketocholanic acid this was found to be possible.

From the interaction of methyl 3-hydroxy-12-ketocholanate (I) and phenylmagnesium bromide 3-hydroxy-12-keto-*nor*-cholanyldiphenylcarbinol (II) was obtained in 32% yields. This carbinol (II) was dehydrated and acetylated by refluxing its acetic acid and acetic anhydride solution. The resulting 3-acetoxy-12-keto-*bisnor*-cholanyldiphenylethylene (III) was converted to the known 3-hydroxy-12-keto-*nor*-cholanic acid[1] (IV) by chromic acid oxidation followed by hydrolysis. This *nor*-acid (IV) was characterized both as the free acid and its methyl ester. The structures of the intermediate carbinol (II) and ethylene (III) were confirmed by synthesis from 3,12-dihydroxy-*nor*-cholanyldiphenylcarbinol[2] (V) and 3,12-dihydroxy-*bisnor*-cholanyldiphenylethylene (VI), respectively. This was accomplished for both by preparing the 3-acid succinate, carefully oxidizing the 12-hydroxyl group with chromic acid and then hydrolyzing.

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Experimental[3]

Methyl 3-Hydroxy-12-ketocholanate (I).—The excellent method of Freudenberg and Jakob[4] has been used for the esterification. To a solution of 5.95 g. of 3-hydroxy-12-ketocholanic acid[1] in 50 ml. of methanol was added 2 ml. of acetyl chloride. The solution was refluxed for fifteen minutes and then allowed to stand at room temperature for three hours. The ester was obtained in crystalline form by carefully diluting the solution to about 175 ml. with water. The yield was 5.10 g. (99%) of white crystalline material melting at 110–112°. A sample recrystallized from acetone melted at 111.5–113.5°.[5]

Isopropyl 3-Hydroxy-12-ketocholanate.—To a solution of 1.5 g. of 3-hydroxy-12-ketocholanic acid in 20 ml. of dry isopropyl alcohol was added 1 ml. of acetyl chloride, and the mixture was allowed to stand overnight. The solution was poured onto ice, and the precipitate was dissolved in ether, washed with 5% sodium carbonate, then with water, and dried over sodium sulfate. By concentrating the solution the crystalline ester was obtained. After recrystallization from a mixture of petroleum ether (b. p. 60–70°) and a little benzene, 1.02 g. (61.5%) of nicely crystalline ester melting at 149.5–151° was obtained.

Anal. Calcd. for $C_{27}H_{44}O_4$: C, 74.96; H, 10.25. Found: C, 75.15; H, 10.35.

3-Hydroxy-12-keto-*nor*-cholanyldiphenylcarbinol (II).—A solution of phenylmagnesium bromide was prepared from 7.78 g. (0.32 mole) of magnesium, 37.5 ml. of bromobenzene and 150 ml. of dry ether. To this was added slowly with stirring a solution of 8.05 g. (0.02 mole) of methyl 3-hydroxy-12-ketocholanate in 150 ml. of dry benzene. The resulting solution was refluxed for three and one-half hours, then decomposed by pouring it into a mixture of 500 ml. of ice and 50 ml. of concd. hydrochloric acid. The layers were separated and the aqueous layer was extracted with ether. The combined ether extracts were washed with dilute hydrochloric acid, water, 5% sodium carbonate solution and finally with water. The residue left after removing the solvent was steam distilled for two hours, collected and dried. The yield was 13.27 g. A 3-g. sample of this crude carbinol was shaken with a mixture of ether and 5% sodium hydroxide solution containing a little methanol. Most of the material dissolved, but 0.173 g. remained as a white precipitate. It melted at 209–215°.

In another run the ester from 4.14 g. (0.0086 mole) of 3-hydroxy-12-ketocholanic acid was allowed to react with phenylmagnesium bromide made from 1.07 g. (0.044 mole) of magnesium and 5 ml. of bromobenzene. The crude carbinol was refluxed for one hour with 75 ml. of 7.5% methanolic potassium hydroxide. Most of the solvent was removed and the product was taken up in water and ether A white powdery precipitate of the carbinol remained insoluble in both layers. It was separated by filtration and dried; yield 0.662 g.; m. p. 210–214°. Crystallization from 35 ml. of 95% ethanol gave 0.326 g. of material melting at 215–216.5°. When mixed with 3-hydroxy-12-keto-*nor*-cholanyldiphenylcarbinol, prepared as described below, it gave no m. p. depression.

A further yield of 0.84 g. of less pure material, m. p. 205–208°, was obtained by concentrating the ether extract. The total yield of once crystallized carbinol was 1.5 g. (32%).

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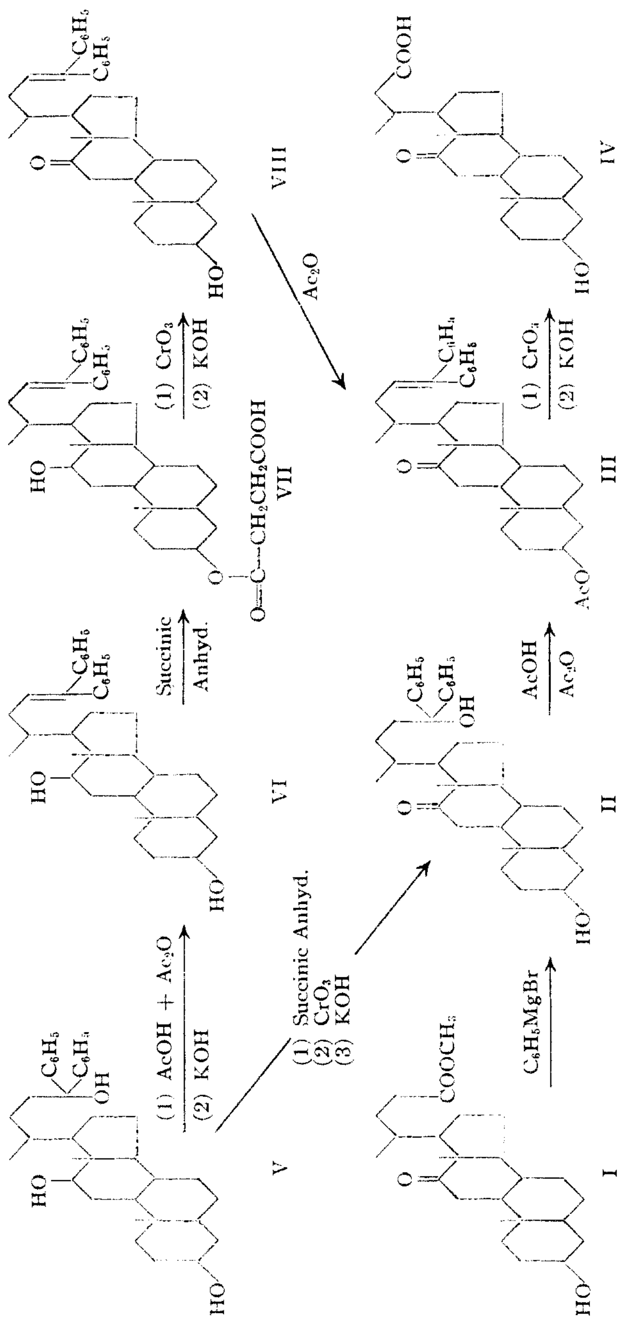
[1] E. Schwenk, B. Riegel, R. B. Moffett and E. Stahl, THIS JOURNAL, **65**, 549 (1943).

[2] J. Sawlewicz, *Roczniki Chem.*, **18**, 250, 755 (1938).

[3] All melting points are corrected. Analyses by Dr. T. S. Ma, University of Chicago.

[4] K. Freudenberg and W. Jakob, *Ber.*, **74**, 1001 (1941).

[5] T. Reichstein and M. Sockin, *Helv. Chim. Acta*, **25**, 797 (1942), prepared this ester by the partial hydrolysis of methyl 3-acetoxy-12-ketocholanate and reported a m. p. of 110–111.5°.



Anal. Calcd. for $C_{36}H_{48}O_3$: C, 81.79; H, 9.15. Found: C, 82.08; H, 9.06.

3-Acetoxy-12-keto-*bisnor*-cholanyldiphenylethylene (III).—A sample of 7.2 g. of the crude carbinol (II) was dissolved in 50 ml. of acetic acid and 25 ml. of acetic anhydride and refluxed for two and one-half hours. The solvent was removed by vacuum distillation and the gummy residue was dissolved in hot acetone. On standing in the cold room crystals separated. The yield was 1.454 g. (24% based on methyl 3-hydroxy-12-ketocholanate); m. p. 175-178°. Recrystallization from acetone gave material melting at 180.5-182° and a mixed m. p. with a sample of 3-acetoxy-12-keto-*bisnor*-cholanyldiphenylethylene, prepared as described below, gave no depression.

Anal. Calcd. for $C_{33}H_{48}O_3$: C, 82.56; H, 8.75. Found: C, 82.78; H, 8.44.

3-Hydroxy-12-keto-*nor*-cholanic Acid (IV).—To a suspension of 1 g. of 3-acetoxy-12-keto-*bisnor*-cholanyldiphenylethylene in 1 ml. of chloroform and 5 ml. of acetic acid was added slowly with stirring a solution of 0.63 g. of chromic acid in 0.5 ml. of water and 3 ml. of acetic acid. The temperature was kept at about 35° by slight cooling during the addition which required about thirty minutes. After stirring for about five minutes more the excess chromic acid was reduced by adding 2 ml. of methanol while cooling. The reaction mixture was concentrated *in vacuo* at room temperature until quite viscous. Water and ether were added and the aqueous layer was repeatedly extracted with ether. The combined ether extracts were washed several times with dilute hydrochloric acid and then with water. The clear colorless ether solution was extracted several times with 1% sodium hydroxide solution (total about 70 ml.). The basic solution was concentrated to 30-35 ml. and 2 g. of solid sodium hydroxide was added. After refluxing for one and one-half hours it was diluted with water and filtered into 20 ml. of 6 *N* hydrochloric acid. The 3-hydroxy-12-keto-*nor*-cholanic acid which precipitated was separated and dried. It weighed 0.470 g. and melted at 230-245°. Crystallization from ethanol gave material melting at 248-250° which did not depress the m. p. of an authentic sample.[1] The methyl ester likewise gave the same m. p. and mixed m. p. as methyl 3-hydroxy12-keto-*nor*-cholanate, described below.

Methyl 3-Hydroxy-12-keto-*nor*-cholanate.—To a solution of 0.58 g. of 3-hydroxy-12-keto-*nor*-cholanic acid[1] in 10 ml. of methanol was added 0.5 ml. of acetyl chloride. The solution was refluxed for fifteen minutes, cooled and 0.2 ml. more of acetyl chloride was added. After standing at room temperature for two days the solution was diluted with cold water until turbid. By scratching crystallization was induced and then the mixture was diluted to about 30 ml. The solid ester was separated by filtration, washed with water and dried. It weighed 0.581 g. and melted at 147-149°. After crystallization from aqueous ethanol and then from ether it melted at 149.5-151°.

The Preparation of Carbinol (II) from 3,12-Dihydroxy-*nor*-cholanyldiphenylcarbinol (V).—A solution of 5 g. of 3,12-dihydroxy-*nor*-cholanyldiphenylcarbinol[2] (m. p. 114-119°) and 10 g. of succinic anhydride in 50 ml. of dry pyridine was allowed to stand overnight at room temperature, and then filtered from a little succinic anhydride which had separated. The product was precipitated from the solution by slowly dropping it into ice and hydrochloric acid. After filtration, washing with water, and drying the precipitate weighed 5.34 g. and melted at 97-115°.

A sample of 4.0 g. of this crude acid succinate was dissolved in 25 ml. of acetic acid and a solution of 0.633 g. of chromium trioxide in 3 ml. of water and 5 ml. of acetic acid was added with cooling. After standing at room temperature for five hours the solution was poured into ice water containing a little sodium bisulfite. The precipitate was separated by filtration and hydrolyzed by refluxing for two hours, its methanolic potassium hydroxide solution. After diluting with water the mixture was extracted with ether and the ether solution was dried over sodium sulfate. By concentrating and cooling a precipitate of 0.481 g. of 3-hydroxy-12-keto-*nor*-cholanyldiphenylcarbinol melting at 202–210° was obtained. Crystallization from ethyl alcohol gave material melting at 210–213°, and further fractional crystallization from benzene gave a sample melting at 214–215°.

3,12-Dihydroxy-*bisnor*-cholanyldiphenylethylene (VI).—A mixture of 10 g. of 3,12-diacetoxy-*bisnor*-cholanyldiphenylethylene[6] (recrystallized from acetone, m. p. 156–157°) and 100 ml. of 10% methanolic potassium hydroxide solution was refluxed for three hours, diluted with water, and extracted with ether. The ether solution was washed with water, dried over sodium sulfate, and distilled to dryness on a steam-bath. The residue was dissolved in methanol, and on standing it crystallized in white, silky needles melting at 108–110°. A second crystallization of the compound did not raise its melting point. The yield was 7.5 g. (87%). The silky needles analyzed for one-half molecule of solvent even after drying at 78° and 1 mm. pressure for two hours.

Anal. Calcd. for $C_{36}H_{48}O_2 \cdot {}^1/_2CH_3OH$: C, 82.90; H, 9.53. Found: C, 82.51, 82.98; H, 9.56, 9.64.

3-Acid Succinate of 3,12-Dihydroxy-*bisnor*-cholanyldiphenylethylene (VII).—A solution of 5 g. of 3,12-dihydroxy-*bisnor*-cholanyldiphenylethylene and 10 g. of succinic anhydride in 50 ml. of dry pyridine was warmed on a steam-bath for five minutes, and then allowed to stand at room temperature for twenty-four hours. The solution was decanted from a few crystals of succinic anhydride and slowly dropped into a stirred mixture of 500 ml. of ice and 35 ml. of concd. sulfuric acid. The crude acid succinate separated as a white solid, and was collected and dried in a vacuum desiccator. The yield was about quantitative.

A sample crystallized from a mixture of ether and petroleum ether, and then from ether melted at 198–201°.

Anal. Calcd. for $C_{40}H_{52}O_5$: C, 78.39; H, 8.55. Found: C, 78.60; H, 8.37.

3-Hydroxy-12-keto-*bisnor*-cholanyldiphenylethylene (VIII).—A solution of 4.5 g. of the crude acid succinate of 3,12-dihydroxy-*bisnor*-cholanyldiphenylethylene (VII) in 200 ml. of acetic acid and 25 ml. of water was cooled to 0–5°. A solution of 0.6 g. of chromium trioxide in 10 ml. of acetic acid and 10 ml. of water was added slowly with stirring over a period of one and one-fourth hours. The temperature was kept at 0–5° during the addition, and then the mixture was allowed to stand in the cold room overnight. About 5 ml. of methanol was added and the solution was concentrated by distillation under reduced pressure. After diluting to about 300 ml. with water the precipitate was collected and dried. The yield of the crude 3-acid succinate of 3-hydroxy-12-keto-*bisnor*-cholanyldiphenylethylene was 3.93 g. (87.7%).

A solution of 2.84 g. of this crude acid succinate in a mixture of 5 ml. of 40% aqueous potassium hydroxide and 35 ml. of ethyl alcohol was refluxed for one and one-half hours. Part of the solvent was evaporated and the mixture was diluted with water and extracted with ether. The ether solution was dried and the solvent was removed. About 50 ml. of hot methanol was added, and on cooling the product separated in powdery form. The yield was 1.177 g. (77%).

A sample crystallized again from methanol and then twice from ethanol separated in plates which melted at 158–159°. These crystals also retained one-half molecule of solvent after vacuum drying (78° at 1 mm.) for two hours.

Anal. Calcd. for $C_{36}H_{46}O_2 \cdot {}^1/_2C_2H_5OH$: C, 83.25; H, 9.25. Found: C, 83.27; H, 9.46.

Ethylene III from 3-Hydroxy-12-keto-*bisnor*-cholanyldiphenylethylene (VIII).—A solution of 0.84 g. of crude 3-hydroxy-12-keto-*bisnor*-cholanyldiphenylethylene in 5 ml. of dry pyridine and 1 ml. of acetic anhydride was warmed on a steam-bath for one hour. The cooled solution was poured into a mixture of ice and 10 ml. of concd. hydrochloric acid. The mixture was extracted with ether and the ether solution was dried and concentrated. The product separated as white crystals. After cooling, the crystals were collected and dried, giving 0.670 g. (73.6%) of material melting at 180.5–182°. Crystallization of the product from acetone raised its m. p. to 181.5–182.5°.

Summary

1. 3-Hydroxy-12-ketocholanic acid has been degraded to the *nor*-acid by the Barbier–Wieland method.

2. The intermediate 3-hydroxy-12-keto-*nor*-cholanyldiphenylcarbinol and 3-hydroxy-12-keto-*bisnor*-cholanyldiphenylethylene have been isolated.

3. The structure of these compounds has been proved by synthesis.

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[6] W. M. Hoehn and H. L. Mason, THIS JOURNAL, **60**, 1493 (1938).