*The Formation of Coprostane, 6β-Coprostanol, and 3α,6β-Coprostanediol by the Catalytic Reduction of Epicholesterol β-Oxide**

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M. Shiota and one of the authors (K. M.)[1] have previously reported on the reduction of epicholesterol β-oxide with lithium aluminum hydride and with sodium and amyl alcohol. In continuation, the present authors have examined the catalytic reduction of epicholesterol β-oxide (I) with Adams platinum oxide, and obtained coprostane (II), 6β-coprostanol (IIIa), and 3α,6β-coprostanediol (VIa). The 3,6-coprostanediol hitherto known being only the 3β,6β-isomer[2], the authors synthesized the 3α,6β-isomer by another method, and confirmed its structure.

Plattner et al.[3] reduced epicholesterol β-oxide with platinum oxide as the catalyst and obtained 3α-cholestanol besides an oily substance supposed to be a hydrocarbon. The present authors, however, obtained coprostane derivatives only, but no cholestane derivatives.

The products from the catalytic reduction of epicholesterol β-oxide (I) with platinum oxide were acetylated, and a chromatographical separation gave coprostane (II), 6β-coprostanol acetate (IIIb), and 3α,6β-coprostanediol diacetate (VIb). The structure of 6β-coprostanol acetate (IIIb) was determined by hydrolyzing the acetate to the free alcohol, 6β-coprostanol (IIIa), oxidizing the alcohol to the corresponding ketone, 6-coprostanone (IV), and isomerizing the latter to 6-cholestanone (V) by treatment with concentrated hydrochloric acid in acetic acid. The β-configuration of the 6-hydroxyl group comes from the β-configuration of the oxide ring of the starting material, epicholesterol β-oxide. The 6β-coprostanol acetate (IIIb) was also identical with the specimen obtained from 4-cholestene-6β-ol acetate by the method of Shoppee et al.[4].

Hydrolysis of 3α,6β-coprostanediol diacetate (VIb) and oxidation of the free diol (VIa) gave 3,6-coprostanedione (VII). The 3α,6β-coprostanediol diacetate synthesized by another method as described below was identical with the 3α,6β-coprostanediol diacetate (VIb) obtained from the catalytic reduction of epicholesterol β-oxide, and probably with the 3α,6β-coprostanediol diacetate prepared by Shoppee

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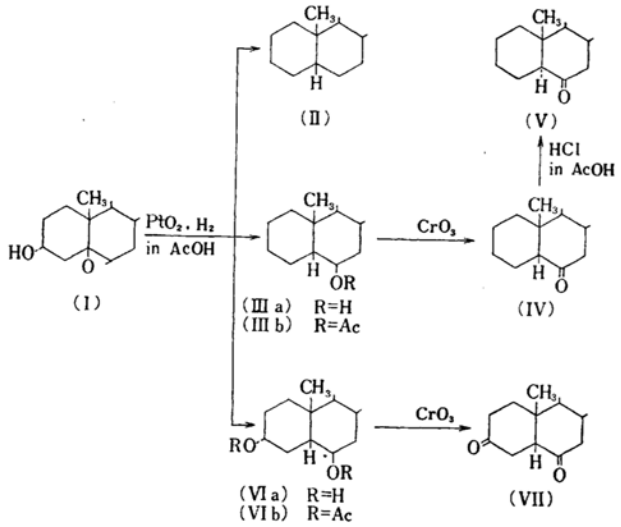
1) M. Shiota and K. Mori, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zassi*), **76**, 1192 (1955).

2) V. Prelog and E. Tagmann, *Helv. Chim. Acta*, **27**, 1880 (1944).

3) Pl. A. Plattner, A. Fürst, F. Koller and H. H. Kuhn, ibid., **37**, 258 (1954).

4) D. N. Jones, J. R. Lewis, C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, **1955**, 2876.



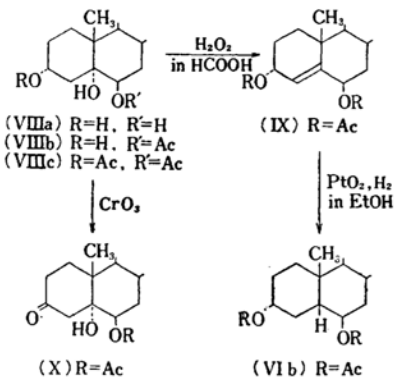
et al.[5] by the reduction of 6β-acetoxy-3-coprostanone followed by acetylation.

Thus it was concluded that the catalytic reduction of epicholesterol β-oxide (I) gave coprostane (II), 6β-coprostanol (IIIa), and 3α,6β-coprostanediol (VIa):

The catalytic reduction of cholesteryl acetate β-oxide with platinum oxide gave cholestane, 3β-cholestanol acetate, and 3β, 6β-cholestanediol 3-acetate but no coprostane derivatives[6,7]. Hence, the formation of the coprostane derivatives in the catalytic reduction of epicholesterol β-oxid may be caused by the effect of the α-configuration of the 3-substituent. Because the 3α-substituent in epicholesterol β-oxide possesses the axial conformation, it may be possible for it to compel the β-face, rather than the normally more easily adsorbed α-face, of the steroid molecule to be adsorbed on the surface of the catalyst, and the subsequent transfer of hydrogen will lead to the formation of coprostane derivatives. Shoppee et al.[8] observed a similar effect of the 3α-substituents on the catalytic reduction of Δ^5-steroids; however, they obtained, besides 3α-coprostanol, about 40% yield of 3α-cholestanol in the case of epicholesterol, and an exclusive yield of coprostane derivatives when the 3α-substituents were greater than the hydroxyl group. The catalytic reduction of epichlesterol β-oxide by the present authors yielded no cholestane derivatives. Shiota et al.[9] observed recently a similar effect of the 3α-substituent on the catalytic reduction of epicholesteryl chloride.

3α,6β-Coprostanediol diacetate (VIb) was synthesized by another route as follows: Treatment of epicholesterol with formic acid and hydrogen peroxide, followed by hydrolysis, acetylation and chromatographic separation, gave 3α,5,6β-cholestanetriol 3,6-diacetate (VIIIc), 3α,5,6β-cholestanetriol 6-acetate (VIIIb), and 3α, 5,6β-cholestanetriol (VIIIa). The structure of 3α,5,6β-cholestanetriol 6-acetate (VIIIb) was determined by oxidizing the 6-acetate to 5,6β-cholestanediol-3-one 6-acetate (X)[10]. 3α,5,6β-Cholestanetriol 3,6-diacetate (VIIIc) and 3α,5,6β-cholestanetriol 6-acetate (VIIIb) are probably identical with the substances obtained by the hydration of epicholesterol α-oxide and β-oxide by Plattner et al.[3]. The authors presume that 3α,5,6β-cholestanetriol 6-acetate (VIIIb) and 3α,5,6β-cholestanetriol (VIIIa) were produced by the hydrolysis of the primary product, 3α, 5,6β-cholestanetriol 3,6-diacetate (VIIIc), on aluminum oxide in chromatographic separation. The 3α,5,6β-cholestanetriol 3,6-diacetate (VIIIc) was dehydrated to 4-cholestene-3α,6β-diol diacetate (IX), and catalytic reduction of the latter gave 3α, 6β-coprostanediol diacetate (VIb), which was identical with the specimen from the catalytic reduction of epicholesterol β-oxide.

5) C. W. Shoppee, R. J. Bridgwater, D. N. Jones and G. H. R. Summers, ibid., **1956**, 2492.
6) M. Chuman, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zassi*), **64**, 1486 (1943); Y. Urushibara and M. Chuman, This Bulletin, **22**, 69 (1949).
7) Pl. A. Plattner, Th. Petrzilk and W. Lang, *Helv. Chim. Acta*, **27**, 513 (1944).
8) J. R. Lewis and C. W. Shoppee, *J. Chem. Soc.*, **1955**, 1365.
9) M. Shiota, Y. Kita and T. Sano, Presented at the 11th Annual Meeting of the Chemical Society of Japan held in Tokyo, April, 1958.
10) B. Ellis and V. Petrow, *J. Chem. Soc.*, **1939**, 1078.



Experimental**

Catalytic Reduction of Epicholesterol β-oxide (I). — A suspension of epicholesterol β-oxide (I) (180 mg.) in acetic acid (18 cc.) was shaken with hydrogen in the presence of Adams platinum oxide (36 mg.) at the ordinary temperature and pressure. The reaction was completed in one hour, one mole and a half of hydrogen being absorbed. Evaporation of acetic acid under a reduced pressure from the solution filtered from the catalyst gave an oily substance (178 mg.). Acetylation of the oil with acetic anhydride and pyridine gave an oily substance (183 mg.). It was chromatographed on a column of aluminum oxide (9 g.) prepared in petroleum ether. Elution with petroleum ether (40 cc.) gave an oily material (13.5 mg.), which was brought to crystallization by dissolving it in methanol and placing the solution in a refrigerator. Recrystallization from acetone gave coprostane (II) in needles, m. p. and mixed m. p. 67~70°C.

Elution with petroleum ether-benzene (9 : 1, 60 cc.) gave another material (27 mg.) which on recrystallization from methanol gave a crystalline product (24 mg.), m. p. 108~109°C. It was identified with 6β-coprostanol acetate (IIIb) as follows. It was dissolved in anhydrous ether (1 cc.), the solution was dropped into a solution of lithium aluminum hydride (10 mg.) in anhydrous ether (1 cc.), and the mixture was boiled under a reflux condenser for one hour. The ethereal solution, after being washed and dried, was evaporated to give an oily substance (19.5 mg.). The substance (6β-coprostanol, IIIa) did not crystallize even when placed in a refrigerator in methanol solution, as it did not in the case of Shoppee et al.[4]. The substance was dissolved in acetic acid (0.2cc.) and the solution was mixed with a solution of chromic anhydride (12.5 mg.) in 90% acetic acid (0.5 cc.). After the mixture was left to stand overnight, a small amount of water was added, when crystals (15 mg.), m. p. 125~131°C, were obtained, which were recrystallized from methanol to yield 6-coprostanone (IV) (12 mg.), m. p. 128~129.5°C. The substance (8 mg.) was dissolved in acetic acid (1 cc.) and the solution was refluxed for 30 minutes after adding one drop of concentrated hydrochloric acid. The product (7 mg.) thus obtained was recrystallized from methanol to give 6-cholestanone (V) (5 mg.), m. p. and mixed m. p. 85°C.

The 6β-coprostanol acetate (IIIb) showed no depression of the m. p. in admixture with 6β-coprostanol acetate prepared by the catalytic reduction of 4-cholestene-6β-ol acetate[4].

Fractions (21.5 mg. in total) eluted with benzene-ether (19 : 1, 60 cc.; 9 : 1, 40 cc.) were combined and brought to crystallization by keeping them in a refrigerator in methanol solution. Repeated recrystallization from methanol gave 3α, 6β-coprostanediol diacetate (VIb) (6.5 mg.) in needles, m. p. 103~106.5°C. The substance showed no depression of the m. p. in admixture with the 3α, 6β-coprostanediol diacetate prepared by the catalytic reduction of 4-cholestene-3α, 6β-diol diacetate as described below, but a depression of the m. p. with 3α, 6β-cholestanediol diacetate. Deacetylation of the 3α, 6β-coprostanediol diacetate (VIb) with lithium aluminum hydride gave free 3α, 6β-coprostanediol (VIa) in a glassy mass, m. p. 134~136°C. Oxidation of the latter with chromic anhydride in acetic acid gave 3, 6-coprostanedione (VII) in needles, m. p. 174~175.5°C, which showed no depression of the m. p. on admixture with an authentic specimen of 3, 6-coprostanedione prepared by the oxidation of 3β, 6β-coprostanediol[2], but a depression with 3, 6-cholestanedione.

3α, 5, 6β-Cholestanetriol 3, 6-diacetate (VIIIc).—A suspension of epicholesterol (1 g.) in 90% formic acid (10 cc.) was heated to 70~80°C with stirring for 5 minutes to form the 3-formate which separated in an oily layer, and the mixture was cooled to 25°C. The solidified 3-formate was shaken occasionally with 30% hydrogen peroxide (1 cc.), the temperature being kept at 40°C. In about 30 minutes the solid dissolved and the solution was allowed to stand overnight at room temperature. The mixture was treated with boiling water (15 cc.), and allowed to cool. The white granular solid material was collected, and dissolved in methanol (30 cc.), and the solution was treated with 25% aqueous sodium hydroxide (1 cc.), warmed on the water-bath for 10 minutes, acidified with hydrochloric acid, diluted with water, and extracted with ether. Isolation in the usual way gave 3α, 5, 6β-cholestanetriol (VIIIa) in a glassy mass. Acetylation of the 3α, 5, 6β-cholestanetriol (VIIIa) with acetic anhydride (7 cc.) and pyridine (10 cc.) gave an oily substance (1.2 g.).

This substance was chromatographed on a column of aluminum oxide (30 g.) prepared in petroleum ether. Fractions (450 mg. in total) eluted with petroleum ether-benzene (9 : 1, 2100 cc.; 4 : 1, 2300 cc.) were combined and recrystallized from methanol to give 3α, 5, 6β-cholestanetriol 3, 6-diacetate (VIIIc) (270 mg.), m. p. 86~87°C.

Fractions (190 mg. in total) eluted with petroleum ether-benzene (1 : 1, 300 cc.), benzene (400 cc.) and benzene-ether (99 : 1, 100 cc.; 98 : 2, 100 cc.; 95 : 5, 100 cc.) showed no sharp melting point. The substance is presumed to be a mixture of

** Melting points are uncorrected.

3α, 5, 6β-cholestanetriol 3, 6-diacetate (VIIIc) and 3α, 5, 6β-cholestanetriol 6-acetate (VIIIb), because it gave 3α, 5, 6β-cholestanetriol 3, 6-diacetate (VIIIc) on acetylation.

Fractions (165 mg. in total) eluted with benzene-ether (9 : 1, 200 cc.; 4 : 1, 200 cc.; 1 : 1, 100 cc.) and ether (600 cc.) were recrystallized from methanol to give 3α, 5, 6β-cholestanetriol 6-acetate (VIIIb) (125 mg.), m. p. 177~178°C. The structure of this compound was determined by oxidizing it to a product, m. p. 159~160°C, which showed no depression of the m. p. on admixture with the 5, 6β-cholestanediol-3-one 6-acetate (X), m. p. 163~164°C, prepared by oxidation of 3β, 5, 6β-choletanetriol 6-acetate.

Fractions (170 mg. in total) eluted with ether-acetone (600 cc.) were a gel. The substance is presumed to be a mixture of 3α, 5, 6β-cholestanetriol 6-acetate (VIIIb) and 3α, 5, 6β-cholestriol (VIIIa), for on acetylation it gave 3α, 5, 6β-cholestanetriol 3, 6-diacetate (VIIIc).

4-Cholestene-3α, 6β-diol diacetate (IX).— 3α, 5, 6β-Cholestanetriol 3, 6-diacetate (VIIIc) (165 mg.) was treated with thionyl chloride (2 drops) in pyridine (1 cc.) at 0°C. After 5 minutes the mixture was poured into ice water. Working up in the usual way, it gave a substance and recrystallization from methanol gave 4-cholestene-3α, 6β-diol diacetate (IX) (130 mg.) in needles, m. p. 102.5~103.5°C; $[\alpha]_D^{30}$ +117° (c, 2.20 in chloroform).

Anal. Found: C, 76.30; H, 10.59. Calcd. for $C_{31}H_{50}O_4$: C, 76.50; H, 10.36%.

3α, 6β-Coprostanediol diacetate (VIb).— Platinum oxide (10 mg.) in ethanol (50 cc.) was saturated with hydrogen, and 4-cholestene-3α, 6β-diol diacetate (IX) (47 mg.) was added, and the mixture was shaken with hydrogen at the ordinary temperature and pressure. The reaction was completed in 20 minutes, about one mole of hydrogen being absorbed. Evaporation of ethanol from the filtered solution gave an oil (46 mg.). It was chromatographed on a column of aluminum oxide (1.5 g.) prepared in petroleum ether. Fractions (23 mg. in total) eluted with petroleum ether-benzene (4 : 1, 30 cc.; 7 : 3, 20 cc.; 1 : 1, 20 cc.) were recrystallized from methanol to give 3α, 6β-coprostanediol diacetate (VIb) (18 mg.), m. p. 103~104°C; $[\alpha]_D^{18}$ +56° (c, 1.85 in chloroform).

Anal. Found: C, 76.07; H, 10.79. Calcd. for $C_{31}H_{52}O_4$: C, 76.18; H, 10.72%.

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