*The Synthesis of 3α-Chloro-5, 6α-epoxy-5α-cholestane**

By Michio SHIOTA and Taeko TOYOTA**

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One of the present authors (M. S.) and his co-workers have previously reported on a study of the formation and the reactions of 3α-chloro-5, 6β-epoxy-5β-cholestane.1) This paper will describe a study of the synthesis of an isomeric epoxide, 3α-chloro-5, 6α-epoxy-5α-cholestane.

6β-Chloro-5α-cholestane-3β, 5-diol2) (I) was chlorinated with phosphorus oxychloride and pyridine.3) The elementary analysis and infrared spectrum of the product II showed that one of the hydroxyl groups in I was replaced by chlorine. The chlorohydrine II was not acetylated with acetic anhydride and pyridine at room temperature, and it differed from 3β, 6β-dichloro-5α-cholestan-5-ol derived from 3β-chloro-5, 6α-epoxy-5α-cholestane.4) From these observations it was concluded that the chlorohydrin II is 3α, 6β-dichloro-5α-cholestan-5-ol. The configuration at C_3 was further confirmed by a study of the reactions of the epoxide derived from II.

The chlorohydrin was treated with alkali to afford 3α-chloro-5, 6α-epoxy-5α-cholestane (III). The epoxide was converted into II with hydrochloric acid, and the reaction of III with boron trifluoride-ether complex5) gave 6-ketone. Whereas 3α-chloro-5, 6β-epoxy-5β-cholestane failed to be reduced with lithium aluminum hydride at the boiling point of ether,1) the epoxide III was reduced with the reagent to give 3α-chloro-5α-cholestan-5-ol.3) Hydrolytic cleavage was also effected to give 3α-chloro-5α-cholestane-5, 6β-diol. These reactions confirmed that the epoxide is 3α-chloro-5, 6α-epoxy-5α-cholestane.

Experimental***

3α, 6β-Dichloro-5α-cholestan-5-ol (II). — To a stirred solution of 1 g. of 6β-chloro-5α-cholestane-3β, 5-diol in 25 ml. of pyridine, 10 ml. of freshly distilled phosphorus oxychloride was added over a period of 30 min. at room temperature. Stirring was continued for another hour at room temperature, and then the product was isolated according to the procedure of Shoppee.3) A pale yellow, oily residue was dissolved in 50 ml. of *n*-hexane, and the solution was stirred with 2 g. of silica gel for 30 min. at room temperature. The removal of the solvent from the filtered solution afforded a colorless crystalline residue. Recrystallization from acetone gave 180 mg. of 3α, 6β-dichloro-5α-cholestan-5-ol (m. p. 118∼119.5°C) $[\alpha]_D$ 0° (*c* 2.23, $CHCl_3$).

Found: C, 70.86; H, 10.04. Calcd. for $C_{27}H_{46}Cl_2O$: C, 70.87; H, 10.13%.

The acetylation of the chlorohydrin with acetic anhydride and pyridine at room temperature was attempted, but the starting material was recovered unchanged. 3β, 6β-Dichloro-5α-cholestan-5-ol (m. p. 149∼150°C) derived from 3β-chloro-5, 6α-epoxy-5α-cholestane was different from II.

3α-Chloro-5, 6α-epoxy-5α-cholestane (III). — A mixture of 130 mg. of II, 9 ml. of ethanol and 0.4 ml. of 15% aqueous sodium hydroxide was heated under reflux for 30 min. The solvent was then removed under reduced pressure, and the product was isolated with ether in the usual way. Two recrystallizations from methanol gave 72 mg. of the colorless crystalline product, which sintered at 158°C and melted at 160∼162°C. Filtration through alumina, followed by recrystallization from methanol, did not raise the melting point. $[\alpha]_D$ −37.7° (*c* 3.18, $CHCl_3$). It gave no yellow color with tetranitromethane and showed no hydroxyl infrared absorption. Infrared absorptions at 1261, 1036 and 875 cm^{-1} (KBr disk) seemed to indicate the 5,6-epoxy group.

Found: C, 76.95; H, 10.29. Calcd. for $C_{27}H_{45}ClO$: C, 77.01; H, 10.77%.

The Reduction of the Epoxide III with Lithium Aluminum Hydride.—The epoxide was reduced with lithium aluminum hydride at the boiling point of ether in the usual way to give 3α-chloro-5α-cholestan-5-ol in an almost quantitative yield (m. p. 118∼120°C (lit.,3) m. p. 118∼119°C)).

The Reaction with Boron Trifluoride - Ether Complex. — Freshly-distilled boron trifluoride-ether complex (4 drops) was added to a solution of 50 mg. of III in 5 ml. of dry benzene. After the mixture had been allowed to stand at room temperature for 20 min., it was treated with aqueous sodium bicarbonate and washed with water. The removal of the solvent from the dried solution gave a brown oily residue (52 mg.), which showed hydroxyl and ketonic infrared absorptions. The attempted crystallization of the oil from various

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[**] Present address: Yawata Chemical Engineering Co., Ltd., Ginza-higashi, Chuo-ku, Tokyo.

1) M. Shiota, T. Ogihara and Y. Watanabe, This Bulletin, **34**, 40 (1961).

2) D. H. R. Barton and E. Miller, *J. Am. Chem. Soc.*, **72**, 370 (1950).

3) Cf. A. J. Fudge, C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, **1954**, 958.

4) C. W. Shoppee, R. J. Bridgwater, D. N. Jones and G. H. R. Summers, ibid., **1956**, 2492.

5) H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, **1967**, 4596, 4765.

[***] All melting points are uncorrected

solvents was not successful. The oily material was heated with 3 drops of concentrated hydrochloric acid in 10 ml. of ethanol to give a semicrystalline product, from which 3α-chloro-5α-cholestan-6-one was isolated in about a 50% yield by recrystallization from acetone. From this result, it was inferred that the oily product contained 3α-chloro-5β-cholestan-6-one,[4] a rearrangement product of the epoxide III, which was isomerized to 5α-6-one by treating it with hydrochloric acid.

The Hydrolytic Cleavage of the Epoxide III. — A mixture of 60 mg. of III, 4 ml. of acetone and 0.1 ml. of a 5% phosphomolybdic acid solution (in acetone) was kept at 28~30°C for 2.5 hr.[6] The solution was then treated with ammonia solution to remove phosphomolybdic acid, and the product was isolated with ether. An oily residue (60 mg.) was crystallized from methanol to give a crystalline product (30 mg.). Recrystallization from methanol gave 3α-chloro-5α-cholestane-5, 6β-diol in needles (20 mg.) (m. p. 130~134°C). The acetylation of the diol afforded an acetate (m. p. 129~130°C). The acetate was identified by comparing it with the acetate derived from 6β-acetoxy-5α-cholestane-3β, 5-diol.

6β-Acetoxy-3α-chloro-5α-cholestan-5-ol from 6β-Acetoxy-5α-cholestane-3β, 5-diol. — 6β-Acetoxy-5α-cholestane-3β, 5-diol[7] (1 g.) was chlorinated with 10 ml. of freshly-distilled phosphorus oxychloride in 25 ml. of pyridine as described above. An oily product was crystallized from methanol to give 650 mg. of a crude crystalline product (m. p. ca. 118°C). Two recrystallizations from acetone-methanol gave 350 mg. of 6β-acetoxy-3α-chloro-5α-cholestan-5-ol (m. p. 129~131°C). $[\alpha]_D$ −34.9°C (*c* 1.65, $CHCl_3$).

Found: C, 72.41; H, 10.17. Calcd. for $C_{29}H_{49}\cdot ClO_3$: C, 72.39; H, 10.27%.

The acetate was identical with the acetate derived from the hydrolytic cleavage product of 3α-chloro-5, 6α-epoxy-5α-cholestane (mixed melting point test and infrared spectrum).

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Chemical Laboratory
Ochanomizu University
Bunkyo-ku, Tokyo

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[6] Procedure according to M. Sawai, presented at the 10th Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1957.

[7] B. Ellis and V. A. Petrow, *J. Chem. Soc.*, 1939, 1078.