*The Formation and the Reactions of 3α-Chloro-5, 6β-epoxy-5β-cholestane**

By Michio SHIOTA, Taeko OGIHARA** and Yumi WATANABE***

(Received July 26, 1960)

The present paper describes a study on the configuration of the epoxide derived from 3α-chlorocholest-5-ene[1] by oxidation with monoperphthalic acid and also on the reaction of the epoxide with boron trifluoride-ether complex.

Oxidation of 3α-chlorocholest-5-ene with monoperphthalic acid gave an epoxide. The epoxide could not be reduced with lithium aluminum hydride in the usual way, but it was catalytically reduced with platinum oxide to afford, besides other products, 5β-cholestane (II) and 5β-cholestan-6β-ol (IIIa). The formation of the 5β-cholestane derivatives is of interest, and this reduction is analogous to the catalytic reduction of 5, 6β-epoxy-5β-cholestan-3α-ol[2]. The reductive cleavage of the

---

* Presented at the 11th Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1958 and at the 13th Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1960.

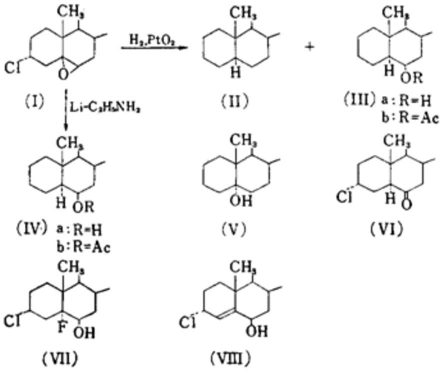
** Present address, The Textile Research Institute of the Japanese Government, Kanagawa-ku, Yokohama.

*** Present address, Tokyo Yushi Kogyo Co., Nagashima-chō, Edogawa-ku, Tokyo.

[1] C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, **1952**, 1790.

[2] Y. Urushibara and K. Mori, This Bulletin, **31**, 1068 (1958).

3α-chlorocholest-5-ene oxide with lithium-ethylamine[3] was also effected to give 5α-cholestan-6-β-ol (IVa) as the major product, along with an unsaturated material. In both of the above reductions, no 5α-cholestan-5-ol (V) was found in the products. On the basis of these observations, it was concluded that the epoxide is 3α-chloro-5,6β-epoxy-5β-cholestane (I). An isomeric α-oxide was not obtained by the peracid oxidation of 3α-chlorocholest-5-ene.



The reaction of the epoxide with boron trifluoride-ether complex was investigated to complement the study by Henbest[4,5]. This lacks the reaction of a 3α-substituted 5,6β-epoxide with the reagent.

On treatment with boron trifluoride-ether complex, the epoxide was easily isomerized to 3α-chloro-5α-cholestan-6-one (VI) in a 35% yield. A "non-polar" oil[6] (13%) and an unsaturated substance (36%) were also produced. The yield of the 6-ketone was considerably lower than in the case of 3α-acetoxy-5,6α-epoxy-5α-cholestane[5]. It is probably because the resulting 6-ketone is a 5α-cholestane derivative (cis migration of C$_6$-hydrogen[4]) with 3α-chlorine and the 3-axial substituent decreases the yield of the 6-ketone. Since 5β-cholestane-3,6-dione was not transformed into 5α-cholestane-3,6-dione under the same condition, 3α-chloro-5α-cholestan-6-one was formed directly from 3α-chloro-5,6β-epoxy-5β-cholestane and, therefore, the above assignment of a β-configuration to the epoxide is further confirmed.

The formation of a diaxial fluorohydrin (5α-fluoro, 6β-hydroxy) (VII) was probably discouraged because 1,3-diaxial interaction between 3α-chlorine and 5α-fluorine was involved.

Experimental****

3α-Chloro-5,6β-epoxy-5β-cholestane (I).—A mixture of 200 mg. of 3α-chlorocholest-5-ene and 2 equivalents of monoperphthalic acid in 10 ml. of dry ether was allowed to stand at room temperature overnight. The solution was washed with 5% aqueous sodium hydroxide and then with water to neutral reaction. Removal of the solvent from the dried (sodium sulfate) solution afforded a colorless crystalline residue. Recrystallization from methanol gave 120 mg. of 3α-chloro-5,6β-epoxy-5β-cholestane in needles, m. p. 98~99°C. Filtration through alumina, followed by recrystallization from methanol, raised the m. p. to 101.5~103°C. $[\alpha]_D^{16}$ $-7°$ (c 2.65, chloroform).

Found: C, 77.06; H, 10.92. Calcd. for $C_{27}H_{45}\cdot ClO$: C, 77.01; H, 10.77%.

Reductive Cleavage of the Epoxide I.—*Catalytic Reduction.*—A mixture of 150 mg. of I and 20 mg. of Adams platinum oxide in 10 ml. of acetic acid was agitated with hydrogen at room temperature. In 1.5 hr. the hydrogen uptake was complete (2 mol.). The catalyst was removed by filteration and the solvent was evaporated under reduced pressure. The colorless oily residue was acetylated in the usual way and the product was chromatographed on 4.5 g. of alumina. Fractions eluted with petroleum ether gave oily residues (108 mg. in total), some of which were crystallized from methanol to give 3 mg. of 5β-cholestane (II), m. p. 63~65°C (recrystallized from methanol) and 20 mg. of 5β-cholestan-6β-ol acetate[7] (IIIb), m. p. 108~108.5°C (recrystallized three times from methanol; the yield of the crude product was 46 mg.). These compounds were identified by the mixed melting point test with authentic samples. Further elution of the column with benzene-petroleum ether (1 : 9) afforded a small amount of a halogen-containing substance in needles, m. p. 117~124°C, which was not further investigated. The oily residues from other fractions failed to crystallize, and 5α-cholestan-5-ol was not isolated from them.

Reduction with Lithium-Ethylamine.—A solution of 150 mg. of I in 4.3 g. of ethylamine was treated with 100 mg. of lithium at room temperature. A deep blue color appeared after 20 min., and persisted during 40 min. The reaction product was isolated according to the procedure of Benkeser[8] to give 137 mg. of a pale yellow oily product, which gave a yellow color with tetranitromethane and showed a negative Beilstein test. The oil (81 mg.) was acetylated in the usual way and the resulting yellow oil (80.5 mg.) was treated with monoperphthalic acid, and the resulting epoxide was subjected to hydrolytic cleavage with phosphomolybdic acid[9]. An oily product (75.4 mg.), which did not give a yellow color with tetranitromethane, was chromatographed on 2.1 g. of alumina, and from the fractions

---

[3] A. S. Hallsworth, H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, **1957**, 1969, 4604.

[4] H. B. Henbest and T. I. Wrigley, ibid., **1957**, 4596.

[5] H. B. Henbest and T. I. Wrigley, ibid., **1957**, 4765.

[6] An oily substance which was not adsorbed on alumina.

**** All melting points were not corrected.

[7] D. N. Jones, J. R. Lewis, C. W. Shoppee and G. H. Summers, ibid., **1955**, 2876.

[8] R. A. Benkeser, R. E. Robinson, D. M. Sauve and O. H. Thomas, *J. Am. Chem. Soc.*, **77**, 3230 (1955).

[9] By this procedure, the unsaturated material was converted into a 1,2-*trans*-glycol (M. Sawai, presented at the 10th Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1957).

eluted with petroleum ether, 43.9 mg. of an oily residue was obtained. This was crystallized from methanol to give 34 mg. of 5α-cholestan-6β-ol acetate[10] (IVb) in needles, m. p. and mixed m. p. 74~75°C. The amount of the unsaturated material in the above reduction products was estimated by catalytic reduction. From the amount of hydrogen uptake, it was inferred that the unsaturated material amounted to about 30% of the total.

Attempted Reduction with Lithium Aluminum Hydride. — I was treated with lithium aluminum hydride at the boiling point of ether in the usual way, but the reduction was not effected. An attempt to effect the reduction at the boiling point of benzene was also unsuccessful.

Reaction of I with Boron Trifluoride-Ether Complex. — Freshly distilled boron trifluoride-ether complex (4 drops) was added to a solution of 200 mg. of I in 20 ml. of dry benzene. After 4 min. at room temperature, the solution was treated with aqueous sodium bicarbonate, and washed with water. Removal of the solvent from the dried (sodium sulfate) solution afforded a semi-solid residue, which was crystallized from acetone to give 3α-chloro-5α-cholestan-6-one (VI), m. p. 178~180°C. Under the same condition, 5β-cholestane-3, 6-dione was not converted into 5α-cholestane-3, 6-dione.

The chromatography of the above semi-solid residue (200 mg.) afforded 26.9 mg. of a "non-polar" oil, 69 mg. of 3α-chlorocholestan-6-one, and 73.2 mg. of an oily material. The oily substance gave an intense yellow color with tetranitromethane and showed a positive Beilstein test and hydroxyl infrared absorption. Since it was readily acetylated in the usual way, and the 3α-chlorine in 3α-chloro-cholest-5-ene and in 3α-chloro-5α-cholestan-6-one was not eliminated with boron trifluoride-ether complex to give unsaturated compounds, it is probable that the oily material consisted mainly of 3α-chlorocholest-4-en-6β-ol (VIII).

The authors express their thanks to Professor Y. Urushibara of the University of Tokyo for his valuable advice, and to Mrs. Y. Fujita for her assistance in the preliminary course of this study. The authors are also indebted to the Ministry of Education for the Grant in Aid for the Fundamental Scientific Research.

Chemical Laboratory
Ochanomizu University
Bunkyo-ku, Tokyo

---

[10] C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, **1952**, 3361.