5, 6-Epoxy-cholestane

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Ruzicka et al.[1] have first obtained 5, 6β-epoxy-5β-cholestane (II), m.p. 53°C, as a by-product of the reaction of cholest-5-ene (I) and peroxyacid. Recently Shoppee et al.[2] have reported that the melting point of 5, 6β-epoxy-5β-cholestane (II) obtained by the above method was 55°C. Henbest and Wrigly[3] have prepared II, m. p. 58°C, $[\alpha]_D-9°$, by the reduction of 5-bromo-5α-cholestan-6-one with lithium aluminum hydride, while Hallsworth and Henbest[4] have reported that the same epoxycholestane (II) prepared from 5, 6β-diacetoxy-5α-cholestane by the method which was adopted in the preparation of 5, 6β-epoxy-5β-cholestane 3β-ol from 3β, 5, 6β-triacetoxy-5α-cholestane[5] melted at 80°C and showed $[\alpha]_D+8°$.

Mori and the present author[6] have investigated the addition reaction of hypochlorous acid (isocyanuric chloride-acetic acid) to 3-substituted-Δ^5-steroids and found that the products were 5α-chloro-6β-hydroxy derivatives which have been converted by base to 5β, 6β-epoxides. In the same manner I was expected to be comverted to II. However the intermediate 5-chloro-6β-hydroxy-5α-cholestane (III) was not produced but 5, 6β-dichloro-5α-cholestane and oily substance were obtained.

Then, the author has turned to another route to obtain II. Thus, reduction of 5, 6β-epoxy-5β-cholestan-3β-yl halide (I_a, halogen = Cl; I_b, halogen = Br) with lithium in liquid ammonia or zinc-copper alloy in ethanol has lead to II, m.p. 79°C, $[\alpha]_D+80°$ in 70% yield. The structure of II assigned was confirmed in the following way. Reduction of II with hydroiodic acid (55%) in acetone gave I, and reduction with lithium aluminum hydride in ether gave cholestan-6β-ol. Treatment of II with 1 N sulfuric acid in acetone gave 5, 6β-dihydroxy-5α-cholestane.

It was interesting to notice that the oxide ring at $C_5\sim C_6$ was indifferent to the lithium-ammonia reducing system. By the similar reduction 5, 6α-epoxy-5α-cholestan-3β-yl halide (IV_a, halogen=Cl; IV_b, halogen=Br) yielded 5,6α-epoxy-5α-cholestan (V), m.p. 76°C, $[\alpha]_D-39.9°$, which showed no melting point depression upon admixture with an authentic specimen.

It has been reported[7,8] that the reaction of the halohydrins of the steroid series with zinc dust and acetic acid yielded the unsaturated steroids, but 6β-halo (chloro and bromo)-5α-cholestan-3β, 5-diol-3-monoester was exceptional. Thus, the latter was converted into the *trans*-triol 3, 6-diester and Δ^5-derivative was not produced at all. It seems to be noteworthy that in the case of 6β-chloro-5α-cholestan-5-ol (VI), 6β-acetoxy-5α-cholestan-5-ol was obtained being accompanied by a small amount of I[9]. III was converted into I with zinc dust and acetic acid or lithium in liquid ammonia. I was also obtained by the reduction of VI with lithium in liquid ammonia.

Experimental**

Attempted Hypochlorous Acid Addition on Cholest-5-ene (I).—To a mixture consisting of 0.5 g. of I, 0.2 g. of isocyanuric chloride and 15 ml. of acetone were added five drops of 30% aqueous acetic acid. The whole was refluxed for five minutes. After cooling to room temperature, the mixture was poured with stirring into 10% aqueous sodium carbonate, and then extracted with ether. The extract was washed with water and dried over magnesium sulfate. After removal of the solvent, the residue was recrystallized from methanol to yield 0.18 g. of needles, m.p. 120~121°C. The compound did not depress the melting point on admixture with the authentic sample of 5, 6β-dichloro-5α-cholestane. The filtrate was left to stand in a refrigerator for one month. However, only a gum was obtained.

5, 6β-Epoxy-5β-cholestane (II).—*i) From 5, 6β-epoxy-5β-cholestan-3β-yl chloride (I_a)*.—To a well stirred mixture of 50 mg. of lithium and 30 ml. of liquid ammonia, 0.3 g. of I_a in 40 ml. of dry ether was added. After thirty minutes, the excess of

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[1] L. Ruzicka, M. Furter and G. Thomann, *Helv. Chim. Acta.*, **16**, 327 (1933).

[2] C. W. Shoppee, R. H. Jenkins and G. H. R. Summer, *J. Chem. Soc.*, **1958**, 1657.

[3] H. B. Henbest and T. I. Wrigly, ibid., **1957**, 4596.

[4] A. S. Hallsworth and H. B. Henbest, ibid., **1957**, 4606.

[5] M. Davis and V. Petrow, ibid., **1949**, 2536.

[6] S. Mori, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **64**, 981 (1943); F. Mukawa, ibid., **78**, 452 (1957).

[7] S. Mori, ibid., **70**, 257, 303 (1949); L. Fieser and R. Ettorre, *J. Am. Chem. Soc.*, **75**, 1700 (1953) etc.

[8] S. Mori and F. Mukawa, *Proc. Japan Acad.*, **31**, 532 (1955).

[9] Cf. The reaction of epoxy-cholestane derivatives with boronfluoride etherate takes a different course when the substituent is persent at C_3. H. B. Henbest et al. *J. Chem. Soc.*, **1957**, 4765.

* All melting points are uncorrected.

lithium was destroyed by acetone. After two hours at room temperature, addition of water, extraction of ether and crystallization of the crude product from ethanol afforded II, m.p. 70~73°C, raised by crystallization from ethanol-*n*-hexane to 79°C, $[\alpha]_D$ +8°. It exhibited no absorption of hydroxyl band in the infrared spectrum.

Found: C, 83.85; H, 11.20. Calcd. for $C_{27}H_{46}O$: C, 83.87; H, 11.99%

A mixture of 0.3 g. of I_a, 0.2 g. of zinc-copper alloy and 20 ml. of alcohol was heated under reflux for 3 hr. But in this case only starting material was recovered.

ii) From 5, 6β-epoxy-5β-cholestan-3β-yl bromide[10] *(I_b)*.—To a well stirred mixture of 50 mg. of lithium and 30 ml. of liquid ammonia, 0.3 g. of I_b in 40 ml. of dry ether was added. There were obtained needles which melted at 79°C and did not depress the mixed melting point with the authentic 5, 6β-epoxy-5β-cholestane (II). The infrared spectra of the two compounds were identical.

In another rum with 0.5 g. of I_b, 0.2 g. of zinc-copper alloy and 30 ml. of ethanol were heated under reflux for 3 hr. There were obtained 0.3 g. of needles with a melting point 78~79°C. There did not depress the mixed melting points with an authentic sample.

Structure of 5, 6β-Epoxy-5β-cholestane (II).—The product obtained as described above was shown to be 5, 6-β-epoxy-5β-cholestane (II) by the following series of reactions.

i) A solution of II (0.2 g.) in acetone (5 ml.) was treated with two drops of hydroiodic acid (55%). After being kept to stand at room temperature (21°C) for 24 hr., the solution was poured into water and was extracted with ether. The extract was washed with sodium thiosulfate solution (5%) and water, dried and evaporated. Crystallization of the residue from alcohol gave 0.1 g. of I, m.p. 90~91°C and mixed m.p. with the authentic specimen showed no depression.

ii) II (0.5 g.) dissolved in anhydrous ether (80 ml.) was added dropwise to lithium aluminum hydride (0.1 g.) in ether for 20 min. at room temperature (20°C) and then refluxed for 5 hr. Chromatography of the product over florisil and elution with ether-methanol gave 5α-cholestan-6β-ol, m.p. 81°C (plates from alcohol), undepressed in m.p. on admixture with the authentic specimen.

iii) A mixture of II (0.3 g.), two drops of sulfuric acid (10%) and 50 ml. of methanol was heated under reflux. After two hours, addition of water, extraction with ether and crystallization of the crude product from alcohol afforded 5α-cholestan-5, 6β-diol, m.p. 60~73°C, raised by recrystallization from alcohol to 125°C, undepressed on admixture with the authentic sample.

5, 6α-Epoxy-5α-cholestan-3β-yl Bromide (IV_b).—Cholesteryl bromide (0.5 g.) was added to a cold solution of perbenzoic acid (1.3 equiv.) in 20 ml. of chloroform, the reaction mixture briefly stirred and then allowed to stand at room temperature (18°C) for 48 hr. before pouring into a solution of sodium carbonate. The organic phase was separated, washed with water to neutrality, dried and evaporated. The product crystallized from alcohol to afford IV_b, m.p. 87~89°C, $[\alpha]_D = -21.2°$.

Found: C, 68.90; H, 9.70. Calcd. for $C_{27}H_{45}OBr$: C, 69.74; H, 9.75.

5, 6α-Epoxy-5α-cholestane (V).—The procedure of II was followed. The product was recrystallized from methanol, yielded V, m.p. 76°C, $[\alpha]_D -39.9°$. It was identified by mixed melting points with the authentic sample.

5-Chloro-5α-cholestan-6β-ol (III).—A solution of the epoxy-cholestan II (0.2 g.) in alcohol-free chloroform (2 ml.) was treated with a saturated solution of anhydrous hydrogen chloride in alcohol-free chloroform (10 ml.). After standing at 0°C for 4.5 hr., the solution was evaporated to dryness. The residue was recrystallized from aetone-water to give III, yield, 0.12 g., m.p. 121~123°C, $[\alpha]_D = -12°$.[11]

Found: C, 76.51; H, 11.45. Calcd. for $C_{27}H_{47}OCl$; C, 76.10; H, 11.29%.

i) With zinc dust.—A mixture of 0.1 g. of III, 0.2 g. of zinc dust, and 5 ml. of acetic acid was heated under reflux for 3 hr. The solids were filtered off and water was added to produce faint turbidity. The crystals were then crystallized from chloroform-methanol and melted at 91°C. The compound did not depress the melting point with the authentic sample of cholest-5-ene (I).

ii) With lithium in liquid ammonia.—The chlorohydrin (III) (0.3 g.) in dry ether was added with vigorous stirring to a solution of lithium (50 mg.) in liquid ammonia (50 ml.). After 30 min., excess lithium was destroyed by acetone. The reaction mixture was then diluted with ether and the ether solution was washed with cold hydrochloric acid solution (1%). Finally the solution was washed with water, dried sodium sulfate and the solvent removed. Crystallization of the product from methanol afforded I, yield, 0.2 g., m.p. 90~91°C, undepressed on admixture with the authentic sample.

Reduction of 6β-Chloro-5α-cholestan-5-ol (VI).—*i) With zinc dust.*—A mixture of 1 g. of VI, 0.5 g. of zinc dust and 50 ml. of acetic acid was heated under reflux for 1.5 hr. The solids were filtered off and diluted with water. The product was extracted with ether. The ether solution washed with sodium bicarbonate solution (5%) and then with water, dried, and evaporated. The residue was chromatographed on 20 g. of neutral alumina, the petroleum ether elute yielding, after crystallization from chloroform-methanol, 0.1 g. of I, undepressed on admixture with the authentic sample. Chromatography gave in the ether-methanol (1 : 1) fractions, 0.4 g. of 6β-acetoxy-5α-cholestan-5-ol, m.p. 80~82°C, $[\alpha]_D = -20°$, the melting point being raised by recrystallization from methanol to 108°C.

Found: C, 77.90; H, 11.00. Calcd. for $C_{29}H_{50}O_3$: C, 77.97; H, 11.28%.

ii) With lithium in liquid ammonia.—Reduction of 0.3 g. of VI with lithium in liquid ammonia under conditions described for the 5-chloro-isomer afforded 0.1 g. of I. It was identified by mixed melting point with the authentic sample.

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[10] S. Mori, *J. Chem. Soc. Japan, Pure Chem. Sec. (Nippon Kagaku Zasshi)*, 74, 89 (1953).

[11] C. W. Shoppee et al., *J. Chem. Soc.*, 1958, 1657, reported 108~109°C, $[\alpha]_D$ −22°.

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