NOTES

New Routes for the Preparation of 5, 6-Epoxy-6-methylcholestan-3β-ols

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(Received September 30, 1963)

The reaction of 3β-acetoxy-6-methylcholest-5-ene with monoperphthalic acid has been shown to afford 5α, 6α-epoxide and 5β, 6β-epoxide.[1,2] The present paper will describe new routes to these epoxides.

The acetylation of 3β-acetoxy-6-methyl-5α-cholestan-5, 6β-diol[1] with acetic anhydride and *p*-toluenesulfonic acid at room temperature gave a diacetate (I), which in turn afforded 5, 6α-epoxy-6-methyl-5α-cholestan-3β-ol when refluxed with alcoholic potassium hydroxide. This reaction is analogous to the formation of 5β, 6β-epoxides from 3β, 5, 6β-triacetoxy-5α-steroids,[3] and it has been inferred that the diacetate I is 3β, 6β-diacetoxy-6-methyl-5α-cholestan-5-ol, because the configuration at C_5 is retained in the course of the epoxide formation.

3β-Acetoxy-5-fluoro-5α-cholestan-6-one[4] reacted with methylmagnesium iodide to give 5, 6β-epoxy-6-methyl-5β-cholestan-3β-ol. 3β-Acetoxy-5-chloro-5α-cholestan-6-one[5] also gave 6-methyl-5β, 6β-epoxide, but the reaction of 3β-acetoxy-5-bromo-5α-cholestan-6-one[6] with methylmagnesium iodide afforded 3β-hydroxy-5α-cholestan-6-one[7].

Experimental***

3β, 6β-Diacetoxy-6-methyl-5α-cholestan-5-ol (I).—A solution of 43.1 mg. of *p*-toluenesulfonic acid monohydrate in 6.5 ml. of acetic anhydride was warmed on a water-bath at 90°C for 10 min. and then cooled to room temperature. 3β-Acetoxy-6-methyl-5α-cholestane-5,6β-diol (113.0 mg.) was added to the solution, and the resultant suspension was stirred at room temperature to give a clear reaction mixture in 1 hr. Stirring was continued for another hour, and then the solution was allowed to stand at room temperature overnight. The reaction mixture was treated with water, and the crystalline material which precipitated was collected by filtration. Recrystallization from methanol gave 63.7 mg. of the product (m. p. 137.5~138°C). Additional recrystallization from methanol raised the melting point to 138.5~139°C. $[\alpha]_D$ −26° (*c* 1.03, chloroform). The product gave no yellow color with tetranitromethane and showed hydroxyl absorption in its infrared spectrum. Analysis produced results which agreed with the formula of a diacetate.

Found: C, 73.93; H, 10.60. Calcd. for $C_{32}H_{54}O_5$: C, 74.09; H, 10.49%.

3β-Acetoxy-5, 6α-epoxy-6-methyl-5α-cholestane.—A solution of 41.6 mg. of I and 60 mg. of potassium hydroxide in 2 ml. of absolute ethanol was heated under reflux for 2 hr. The solvent was removed under reduced pressure, and the product was extracted with ether. When the ethereal solution was washed with water a neutral reaction occurred. The removal of the solvent from the dried solution (sodium sulfate) afforded a jelly residue, which was acetylated with acetic anhydride and pyridine at room temperature to give 32.7 mg. of a crystalline, acetylated product (m. p. ca. 142~143°C). Recrystallization from methanol gave 20.7 mg. of 3β-acetoxy-5, 6α-epoxy-6-methyl-5α-cholestane as needles (m. p. 139.5~140°C and 150.5~151°C (double melting points)). The epoxide was identified by the mixed melting point test with an authentic sample. (Found: C, 78.77; H, 11.02%).

3β-Acetoxy-5, 6β-epoxy-6-methyl-5β-cholestane (II).—To a solution of methylmagnesium iodide prepared from 700 mg. of methyl iodide, 116 mg. of magnesium and 11 ml. of absolute ether, 360 mg. of 3β-acetoxy-5-fluoro-5α-cholestan-6-one was added in 9 ml. of absolute ether at 0°C. The reaction mixture was heated under reflux for 2 hr. The solution was treated with an ammonium chloride solution, and the ethereal solution was worked up in the usual way. An oily residue (277 mg.) was

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[2] M. Davis and G. H. R. Summers, *J. Chem. Soc.*, **1960**, 4707.

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*** All melting points are uncorrected.

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[7] Cf. M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York (1954), p. 189.

acetylated with acetic anhydride and pyridine at room temperature to afford 280 mg. of a crystalline, acetylated product (m. p. 75~82°C). Filtration through alumina, followed by recrystallization from methanol, gave 196 mg. of 3β-acetoxy-5, 6β-epoxy-6-methyl-5β-cholestane (m. p. 93.5~94.5°C), $[\alpha]_D$ 0° (*c* 1.60, chloroform). (lit.,[2] m. p. 95~95.5°C, $[\alpha]_D$ $-2°$ (*c* 0.94, chloroform)).

Found: C, 78.26; H, 10.72. Calcd. for $C_{30}H_{50}O_3$: C, 78.55; H, 10.99%.

In the attempted reaction carried out at -70°C[8] to obtain 5α-fluoro-6-methyl-6-ol, the starting material was recovered almost quantitatively.

The hydrolysis of II with alkali afforded a free alcohol (m. p. 131~131.5°C) (lit.,[2] m. p. 133~135°C).

Reactions of the Epoxide II.—The reduction of 50 mg. of II with 50 mg. of lithium aluminum hydride in 15 ml. of absolute ether at the boiling point of the reaction mixture afforded 13.4 mg. of 6-methyl-5α-cholestan-3β, 6β-diol[9] (m. p. 191°C).

The hydrolytic cleavage of 49 mg. of II with a 5% solution of phosphomolybdic acid in acetone[10] gave 48 mg. of crude 3β-acetoxy-6-methyl-5α-cholestan-5, 6β-diol (m. p. ca. 185°C). Recrystallization from methanol raised the melting point to 191.5~192.5°C.

These reactions confirm that the epoxide II is 6-methyl-5β, 6β-epoxide.

3β-Acetoxy-5α-cholestan-6-one from 3β- Acetoxy-5-bromo-5α-cholestan-6-one. — 3β-Acetoxy-5-bromo-5α-cholestan-6-one (144 mg.) in 9 ml. of absolute ether was allowed to react with a Grignard reagent prepared from 240 mg. of methyl iodide, 44 mg. of magnesium and 5 ml. of absolute ether for one hour at the boiling point of the reaction mixture. The solution was then worked up in the usual way to give 113 mg. of a semicrystalline residue. The residue was acetylated with acetic anhydride and pyridine at room temperature, and the resultant oily product was crystallized from methanol. The crystalline product (54.8 mg., m. p. ca. 108°C) was recrystallized from methanol to give 25.6 mg. of 3β-acetoxy-5α-cholestan-6-one[11] (m. p. 127.5~128°C). The product was identified by the mixed melting point test and its infrared spectrum.

The authors wish to express their thanks to the Ministry of Education for its grant-in-aid for Fundamental Scientific Research.

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