Steroid Studies. III. A New Route for the Preparation of Cholestane-3β, 5α, 6α-triol 3, 6-Diacetate from Cholesterol*

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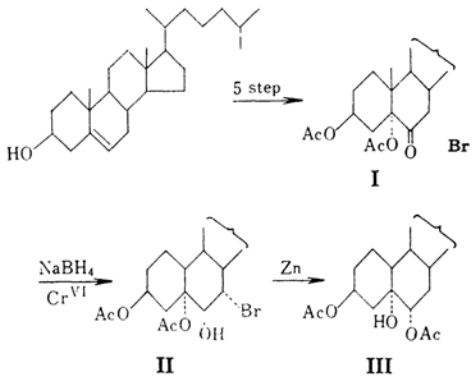
(Received May 30, 1962)

Several methods have been reported for the preparation of cholestane-3β, 5α, 6α-triol from cholesterol, but none of them are practicable for large-scale preparation because of their low yields[1,2] or because of the necessity for an expensive reagent[3]. Recently, Mori and Yoshida[4] reported a stereospecific synthesis of this triol in a 36.5% yield from cholesterol, the method involving a treatment of 6β-chlorocholestane-3β, 5α-diol diacetate with silver acetate.

Fieser and Rajagopalan have converted cholesterol in a good yield (52%) to 7α-bromocholestane-3β, 5α-diol-6-one diacetate (I)[5]. This procedure consists of no less than five steps, but each step is conducted without difficulty and is not time-consuming. We found that this bromodiolone diacetate I is convertible to cholestane-3β, 5α, 6α-triol 3, 6-diacetate (III) simply by borohydride reduction and by debromination with zinc. The over-all yield of triol diacetate III from cholesterol is about 32%.

Thus, the bromodiolone diacetate (I) obtained from cholesterol is reduced with sodium borohydride in methanol-dioxane to give exclusively a *cis*-bromohydrin[6], 7α-bromocholestane-3β, 5α, 6α-triol 3, 5-diacetate (II), the configuration of which will be discussed below. The solvents used in this reduction must be purified carefully to exclude a trace of heavy-metal impurities, especially those of lead, since its catalytic action alters the reaction course and produces cholestane-3β, 5α-diol-6-one diacetate[8].



The *cis*-bromohydrin II thus obtained was debrominated on refluxing with zinc dust in ethanol. During the reaction, the acetyl group at the C_5 position migrates to the C_6 position to produce cholestane-3β, 5α, 6α-triol 3, 6-diactate (III). Bromohydrins, both cis and trans, when refluxed with zinc dust in ethanol or in acetic acid, usually give monoenes[9]. However, not even in boiling acetic acid was bromohydrin II reduced to Δ^6-cholestene-3β, 5α-diol diacetate; on the contrary, it afforded, though in a lower yield, the same triol diacetate III.

The formation of the known 5, 6-cis compound III indicates that the hydroxyl group at the C_6 position in bromohydrin II must have α-configuration. Although an attempted acetylation with acetic anhydride and pyridine at room temperature was unsuccessful, bromohydrin II gave, by dichromate oxidation, bromodiolone diacetate I. This means that the acetyl

* Part II; T. Goto and Y. Kishi, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **83**, 1135 (1962).

1) A. Windaus, *Ber.*, **40**, 257 (1907).

2) M. Shiota, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zassi*), **77**, 1245 (1956).

3) M. I. Ushakov and A. I. Lyutenberg, *J. Gen. Chem.*, **9**, 69 (1939),

4) S. Mori and M. Yoshida, *Proc. Japan Acad.*, **34**, 612 (1958).

5) L. F. Fieser and S. Rajagopalan, *J. Am. Chem. Soc.*, **71**, 3938 (1949).

6) On borohydride reduction, 3β-acetoxycholestan-6-one gives exclusively the corresponding 6β-ol, whereas 5α-bromo- and 7α-bromo-3β-acetoxycholestan-6-one afford mixtures of *cis*- and *trans*-bromohydrins[7]. The greater the shielding of the α-side of 6-ketone, the more the corresponding 6α-ol is produced. Although, therefore, it is quite reasonable that the bromodiolone diacetate (I) gives the corresponding 6α-ol, it is curious that cholestane-3β, 5α-diol-6-one diacetate is not reduced under the same reaction conditions. The difference in those reactivities may be due to the inductive effect of the bromine atom.

7) D. R. James and C. W. Shoppee, *J. Chem. Soc.*, **1954**, 4224.

8) 4γ Lead acetate/200 mg. bromoketone (I) is still effective for debromination: T. Goto and Y. Kishi, *Tetrahedron Letters*, 513 (1961).

9) For example, 7α-bromo-3β-acetoxycholestane-6β-ol, 7α-bromo-6α-ol, and 6β-bromo-7α-ol all afford the same ethylenic compound, 3β-acetoxy-Δ^6-cholestene; D. R. James, R. W. Rees and C. W. Shoppee, *J. Chem. Soc.*, **1955**, 1370.

group migration occurred during the debromination reaction and not during the borohydride reduction.

Experimental

7α-Bromocholestane-3β, 5α-diol-6-one Diacetate (I) from Cholesterol. — Essentially according to Fieser and Rajagopalan's procedure[3]. Cholestane-3β, 5α, 6β-triol: m. p., 236~238°C (not recrystallized); 90% yield. Cholestane-3β, 5α-diol-6-one: m. p., 232~233°C (not recrystallized.); 95% yield. Cholestane-3β, 5α-diol-6-one 3-acetate: m. p., 233~234°C (not recrystallized); 95% yield. 7α-Bromocholestane-3β, 5α-diol-6-one 3-acetate: m. p., 160~165°C (recrystallized from methanol); 80% yield. 7α-Bromocholestane-3β, 5α-diol-6-one diacetate; m. p. 215~216°C (recrystallized from methanol); 80% yield. The overall yield from cholesterol is 52%. In the last step, the diolone monoacetate was brominated and then acetylated since in the alternate procedure the brominated product of the diolone 3, 5-diacetate was very difficult to purify.

7α-Bromocholestane-3β, 5α, 6α-triol 3, 5-Diacetate (II).—Two milliliters of EDTA solution (1 mol./l. in methanol) and 2.0 g. of sodium borohydride were added to a solution of 3.0 g. of the bromoketone I in 450 ml. of dioxane and 300 ml. of methanol. After having been allowed to stand at room temperature for 45 min., the mixture was acidified with acetic acid and diluted with 700 ml. of water. The precipitates obtained were crystallized from methanol to give plates melting at 148~149°C (2.4 g., 80%); IR 3380, 1740, 1720 cm^{-1} (in carbon disulfide).

Found: C, 63.72; H, 8.64. Calcd. for $C_{31}H_{51}O_5Br$: C, 63.79; H, 8.67%.

After having been treated with acetic anhydride and pyridine at room temperature overnight, the bromohydrin was recovered unchanged.

Dichromate Oxidation of Bromohydrin II.—To a solution of 110 mg. of bromohydrin II in 3 ml. of acetic acid was added a solution of 50 mg. of sodium dichromate in 1 ml. of acetic acid; the mixture was allowed to stand overnight at room temperature. The addition of water and extraction with ether in the usual way gave a crystalline solid which on several recrystallizations from methanol gave needles (m. p., 208~209°C), the mixed melting point of which with ketone I was 210~214°C and the infrared spectra of which are superimposable. From the mother liquor, a small quantity of starting material was recovered.

Cholestane-3β, 5α, 6α-triol 3, 6-Diacetate (III).—A solution of 3.0 g. of bromohydrin II in 70 ml. of ethanol was refluxed with 5.0 g. of zinc dust for 30 hr. and then filtered. The filtrate was diluted with water and extracted with ether in the usual way, and the ether solution was evaporated to dryness. The solid residue was crystallized from methanol to give prisms (2.0 g., 77%) (m. p., 186~187°C); no melting point depression was observed when this was admixed with an authentic sample.

Found: C, 73.74; H, 10.19. Calcd. for $C_{31}H_{52}O_5$: C, 73.76; H, 10.38%.

When treated with acetic anhydride and pyridine, diacetate III was recovered unchanged.

The authors are indebted to Professor Yoshimasa Hirata for his interest in this research. They are also grateful for a grant from the Ministry of Education.

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