140. Steroids. XXVII¹⁾

**The Reaction of 6 β -Chlorocholestane-3 β ,5 α -diol Diacetate
with Silver Acetate. 1. Stereospecific Synthesis of
Cholestane-3 β ,5 α ,6 α -triol**

By Susumu MORI and Mutsuko YOSHIDA

Department of Chemistry, Faculty of Science, Tokyo Metropolitan University

(Comm. by Y. SHIBATA, M.J.A., Nov. 12, 1958)

There are four theoretically possible stereoisomers of cholestane-3 β ,5,6-triol (I)–(IV) with respect to the configurations at C₍₅₎, and C₍₆₎, and three of them (I)–(III) have already been described.

Among others, cholestane-3 β ,5 α ,6 β -triol (α -cholestanetriol) (I) may be obtained easily in several ways. The syntheses of the second triol cholestane-3 β ,5 α ,6 α -triol (β -cholestanetriol) (II), heretofore are known in four different ways. All these methods, however, are not convenient to obtain this substance, because the yields are very poor (5–10%)^{3)–5)} and moreover osmium tetroxide, an excellent reagent for the hydroxylation used by Ushakov,⁶⁾ is considerably expensive. Recently the third triol cholestane-3 β ,5 β ,6 β -triol (III) was obtained only in the form of the 3,6-diacetate by a peculiar stereospecific sequence of the reactions.⁷⁾ The fourth triol cholestane-3 β ,5 β ,6 α -triol (IV) has not yet been described.

In view of the stereochemical interests, for example to investigate the behaviors of the triols, when *N*-halogen compounds are used as the oxidising reagents^{8)–10)} in the specially controlled conditions, the present authors attempted to obtain the triols (II)–(IV) from cholesterol by the Prévost reaction^{11)–13)} or its modifications. We will now report a new stereospecific synthesis of β -cholestanetriol 3,6-diacetate (IX), which proceeds by six steps of the reactions starting from cholesterol. By this new procedure we could obtain the diacetate (IX) in an overall yield of 36.5% based on the starting material. The reactions may be shown as follows:

By esterification with formic acid and hydroxylation with hydrogen peroxide of cholesterol and subsequent alkaline saponification of the resulting product gave α -cholestanetriol (I).²⁾ The triol (I) was acety-

lated to the diacetate (V) by means of acetic anhydride and pyridine,¹⁴⁾ and the latter (V) was then converted into 6 β -chlorocholestane-3 β ,5 α -diol (VI) by refluxing with methanolic hydrogen chloride.¹⁵⁾ The yields of all steps above-mentioned were very good, namely about 90%. Acid catalysed acetylation^{16,17)} of the chlorohydrin (VI) with acetic anhydride and *p*-toluenesulfonic acid furnished 6 β -chlorocholestane-3 β ,5 α -diol diacetate (VIII), m. p. 170°, in 74% yield. This compound (VIII) was also obtained from the chlorohydrin (VI) by the separated 2-steps acetylation by way of the intermediary chlorohydrin 3-monoacetate (VII),¹⁵⁾ but the overall yield based on the chlorohydrin (VI) was less favored. Treatment of the chlorohydrin diacetate (VIII) with silver acetate in wet acetic acid gave β -cholestanetriol 3,6-diacetate in 67.5% yield, m.p. and mixed m.p. 187°, as the only product isolated, which was also identified by converting it into β -cholestanetriol (II), m.p. and mixed m.p. 236°. From the results above described and the analytical data, the structure (VIII) assigned for the chlorohydrin diacetate seems to be tenable.

It is noteworthy here that another possible reaction product β -cholestanetriol 3,5-diacetate (IX), which may be expected to arise from the cyclic intermediate such as (VIII A) or (VIII B), could not be isolated by us. This stereospecificity may be explained both by the steric acceleration and by the product development control that determine the direction of the intramolecular rearrangement.

The transacetylation of 5-cholestene-3 β ,4 β -diol 3-monoacetate,¹⁸⁾ the formation of epicholesterol from cholesterol by the action of chromic acid,¹⁹⁾ and the conversion of cholestane-3 β ,5 α -diol 3-tosylate 5-acetate into epicholesteryl acetate by treatment with boiling pyridine²⁰⁾ may be explained also by the similar stereochemical considerations.

Acknowledgment. The authors wish to thank Dr. M. Shiota of Ochanomizu University for his kindness to sending us the authentic samples and to Dr. R. Hayatsu of Takamine Research Laboratory, Sankyo Co., Ltd., for microanalysis. We are also indebted for supplies of cholesterol to Dr. S. Niinobe of Teikoku Hormone Mfg. Co., Ltd.

Experimental (All melting points are corrected). *6 β -Chlorocholestane-3 β ,5 α -diol* (VI). A mixture of 7g of cholestane-3 β ,5 α ,6 β -triol 3,6-diacetate and 240 ml of methanolic hydrogenchloride (37%) was refluxed at 60–80°C for 1 hour. As soon as the diacetate dissolved, voluminous white crystals appeared. After being kept in a refrigerator, the crystals were filtered off and kept in a desiccator containing sulfuric acid and sodium hydroxide. The yield was 5.5 g (90%). This substance when recrystallized from methanol was positive to the Beilstein test, melted with decomposition at 170°C and has shown no melting point depression when admixed with the authentic sample of 6 β -chlorocholestane-3 β ,5 α -diol.

6 β -Chlorocholestane-3 β ,3 α -diol 3-monoacetate (VII). A mixture of 1.5 g of 6 β -chlorocholestane-3 β ,5 α -diol (VI) and 15 ml of acetic anhydride was heated under reflux for 1 hour. Crystals were obtained on cooling melted at 180–182°C. Recrystallization from alcohol gave needles melting at 186.5°C. Yield 1.3 g (79%).

6 β -Chlorocholestane-3 β ,5 α -diol 3,5-diacetate (VIII). a) Acetylation of 6 β -chlorocholestane-3 β ,5 α -diol (VI): A mixture of 305 mg of the diol, 20 ml of acetic anhydride, and 200 mg of *p*-toluenesulfonic acid was heated on a steam bath for 30 minutes. Water was added to the resulting yellowish solution and the mixture was extracted with ether. The extract was washed with dil. aqueous sodium bicarbonate. After the ether and the excess of acetic anhydride were removed, methanol was added and careful dilution with water gave crystalline material. After being kept in a refrigerator, the crystals which melted at 164°C were collected. The yield was 269 mg (74%). Repeated re-

crystallization from methanol gave colorless needles melting at 170°C, $[\alpha]_D^{25} - 39$ (C, 1.09, CHCl₃).

Anal. Calcd. for C₃₁H₅₁O₄Cl: C, 71.16%; H, 9.82%; Cl, 6.79%

Found: C, 71.39%; H, 9.48%; Cl, 6.85%

b) Acetylation of 6β-chlorocholestane 3β,5α-diol 3-monoacetate (VII): A mixture of 480 mg of the monoacetate (VII), 8 ml of acetic anhydride, and 200 mg of *p*-toluenesulfonic acid was heated on a water bath for 30 minutes. Then methanol was added and the reflux was continued for a while to decompose the excess of acetic anhydride. On addition of water, a crystalline substance of m.p. 163° was obtained. After recrystallization from alcohol it showed m.p. 169°, which was identified with the sample above described by a mixed m.p. determination. Yield 410 mg (78.4%).

Cholestane-3β, 5α, 6α-triol 3, 6-diacetate (IX). A suspension of 100 mg of silver acetate in 4 ml of glacial acetic acid was heated under reflux for a while. Then four drops of water and 200 mg of 6β-chlorocholestane-3β,5α-diol 3,5-diacetate (VIII) were added and refluxed on a wire gauze for 15 hours. Silver chloride precipitated was filtered off and washed well with warm acetic acid and then the filtrate was concentrated to a small volume. A few drops of water were added to the warmed solution to produce faint turbidity and 130 mg (67.5%) of brown crystals of m.p. 181.5°C was obtained after standing at room temperature, which were negative to the Beilstein test. Recrystallization from methanol gave white crystals, m.p. 186°, which showed no depression of the melting point when admixed with the authentic sample of cholestane-3β,5α,6α-triol 3,6-diacetate. Alkaline saponification of the diacetate gave cholestane-3β,5α,6α-triol (II), which was identified by a mixed m.p. determination.

References

- 1) T. Nakao, M. Matsuba, K. Hiraga, M. Inaba, M. Hirai, S. Kanemoto, T. Yanagita, S. Sato, S. Takeyama, Y. Hishikawa, M. Iwasaki, M. Kitazume, and S. Mori: Steroids. XXVI, Endocrinol. Japan, **5**, no. 3, 149 (1958).
- 2) L. F. Fieser and S. Rajagopalan: J. Am. Chem. Soc., **71**, 3938 (1949).
- 3) A. Windaus: Ber., **40**, 257 (1907).
- 4) M. Shiota: J. Chem. Soc. Japan, **77**, 1245 (1956).
- 5) C. W. Shoppee, D. N. Jones, and G. H. R. Summers: J. Chem. Soc., 3100 (1957).
- 6) M. I. Ushakov and A. I. Lutenberg: Nature, **140**, 466 (1937).
- 7) H. B. Henbest and R. A. L. Wilson: J. Chem. Soc., 1958 (1957).
- 8) F. Mukawa: J. Chem. Soc. Japan, Pure Chem. Sec. (Nippon Kagaku Zasshi), **78**, 450 (1957).
- 9) K. Morita: Bull. Chem. Sec. Japan, **31**, 347 (1958).
- 10) T. Sakan: Jikken-kagaku-koza, **17**, 2311 (1957).
- 11) C. Prevost: Compt. Rend., **196**, 1129 (1933).
- 12) S. Winstein and R. E. Buckles: J. Am. Chem. Soc., **64**, 2780 (1942).
- 13) K. B. Wiberg and K. A. Saegebanth: J. Am. Chem. Soc., **79**, 6256 (1957).
- 14) H. Aebli, G. A. Grob, and E. Shumacher: Helv. Chim. Acta, **41**, 774 (1958).
- 15) S. Mori: J. Chem. Soc. Japan, **70**, 257 (1949).
- 16) Huang-Minlon, E. Wilson, N. L. Wendler, and M. Tishler: J. Am. Chem. Soc., **74**, 5394 (1952).
- 17) R. B. Turner: J. Am. Chem. Soc., **75**, 3489 (1953).
- 18) V. A. Petrow, O. Rosenheim, and W. W. Starling: J. Chem. Soc., 135 (1943).
- 19) L. F. Fieser: J. Am. Chem. Soc., **75**, 4377 (1953).
- 20) P. A. Plattner, A. Fürst, K. Koller, and W. Lang: Helv. Chim. Acta, **31**, 1455 (1948).