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A-Substituted 5β-Steroids. IX. Preparation of 5β-Cholest-1-ene and 2-ene from 2β-Bromo-5β-cholestan-3-one[1]

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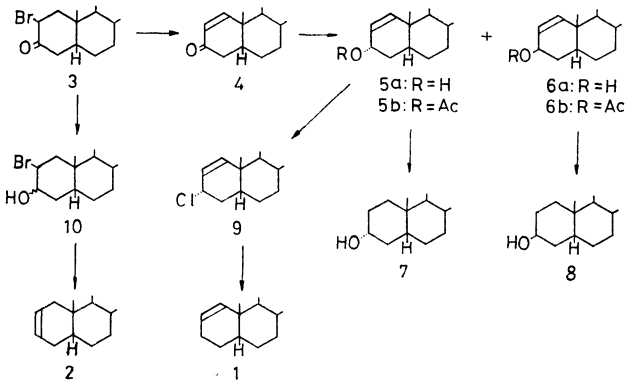
Synopsis. 5β-Cholest-1-ene has been prepared from 2β-bromo-5β-chloestan-3-one. An alternative route to 5β-cholest-2-ene has also been developed by use of bromoketone. These olefins are less stable, being oxidized gradually by air to 5β-cholest-1-en-3-one at room temperature.

In a previous paper[2] a report was given on the preparation of 5β-cholest-2-ene (**2**) by the treatment of 2β,3-bis(methylsulfonyloxy)-5β-cholestane, obtained from 2β-acetoxy-5β-chloestan-3-one *via* 5β-cholestane-2β,3-diols, with sodium iodide in boiling cyclohexanone. The process is tedious as compared with the one-step preparation from 3-substituted 5β-cholestanes[3] although undesirable contamination of 5β-cholest-3-ene can be reduced. 2β,4β-Dibromo-5β-cholestan-3-one, on treatment with chromium(II) acetate, is reduced to 2β-bromo-5β-cholestan-3-one (**3**), which is further converted into 5β-cholest-1-en-3-one (**4**) on reaction with calcium carbonate and *N*,*N*-dimethylformamide.[4] In this paper we describe the preparation of 5β-cholest-1-ene (**1**) and 2-ene (**2**) from **3**, and give some observations on the oxygenation of these olefins on exposure to air at room temperature.

The procedures for the preparation of **1** and **2** are summarized in the Scheme.



Scheme. Pathway to 5β-cholest-1-ene and 2-ene.

The reduction of **4** with lithium aluminium hydride readily gave a mixture of allyl alcohols. The major product, obtained by crystallization from acetone, was characterized as 5β-cholest-1-en-3α-ol (**5a**) on the basis of its transformation into 5β-cholestan-3α-ol (**7**) on hydrogenation in cyclohexane in the presence of palladium catalyst. Concentration of the mother liquor and crystallization several times from ether–methanol gave a small amount of the isomeric allyl alcohol, which was determined to be 5β-cholest-1-en-3β-ol (**6a**) by catalytic reduction to 5β-cholestan-3β-ol (**8**). Treatment of **5a** with thionyl chloride gave a chloro compound in 73% yield. The compound is regarded as 3α-chloro-5β-cholest-1-ene (**9**) by a comparison of its NMR spectrum with those of **5a** and **6a**: In the NMR spectrum of **9**, the signals at δ 4.50 showed double-doublet couplings, the constants (J=7.0, 10.0 Hz) of which were similar to those of the signals at δ 4.16 (J=5.0, 8.2 Hz) due to 3β-H in **5a**, but quite distinct from those of the multiplet signals at δ 3.98 ($W/2$=8.5 Hz) due to 3α-H in **6a**. 5β-Cholest-1-ene (**1**) was obtained by the reduction of **9** with lithium aluminium hydride.

5β-Cholest-2-ene (**2**) was obtained from **3** by the method used for the preparation of 5α-cholest-2-ene.[5]

The olefins were relatively less stable at room temperature. **1** and **2** remained unchanged for a long time at room temperature. However, these olefins were gradually oxidized by air (see Table). 5β-Cholest-1-en-3-one (**4**) was mainly obtained from the samples of **1** and **2** which had been preserved for about a year at room temperature.[6] On the other hand, oxygenation scarcely took place in the samples of **1** and **2** preserved in a refrigerator kept below 5 °C. The results indicate that the oxygenation of the olefins is promoted by light and temperature. However, the mechanism of oxygenation has not been clarified because of complex factors participating in the reaction.

TABLE. OXYGENATION PRODUCTS OF THE OLEFINS AGED FOR A YEAR

Olefin	Temperature	Yield(%) Recovered olefin	Yield(%) 5β-Cholest-1-en-3-one
5β-Cholest-1-ene	r. t.[a]	15	80
	<5 °C	100	—
5β-Cholest-2-ene	r. t.[a]	20	79
	<5 °C	100	—

a) Room temperature.

Experimental

All melting points are uncorrected. IR spectra were determined with a Hitachi Model 215 grating instrument. NMR spectra were measured with a Hitachi Perkin-Elmer Model R-20A spectrometer in carbon tetrachloride with reference to tetramethylsilane as an internal standard.

Lithium Aluminium Hydride Reduction of 5β-Cholest-1-en-3-one (4). Lithium aluminium hydride (0.5 g) was added to a solution of **3**[4] (2.5 g) in dry ether (100 ml) at temperature below 0 °C. The mixture was allowed to warm to room temperature. The excess hydride was then decomposed with acetone and dil sulfuric acid. The organic layer was washed with aq sodium hydrogencarbonate and water, dried and

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evaporated. Crystallization from acetone gave 5β-cholest-1-en-3α-ol (**5a**, 1.6 g) as needles, melting at 122—124 °C. IR (KBr): 3300, 3020, 1650, 1065, 1047, 760, and 738 cm^{-1}; NMR δ: 0.65 (3H, s, 18-CH_3), 1.00 (3H, s, 19-CH_3), 4.16 (1H, dd, J=5.0, 8.2 Hz, 3β-H), and 5.50 (2H, s, $W/2$=3.0 Hz). Found: C, 83.80; H, 12.05%. Calcd for $C_{27}H_{46}O$: C, 83.87; H, 11.99%.

Acetylation of **5a** with pyridine–acetic anhydride gave 3α-acetate (**5b**), melting at 113—115 °C. IR (KBr): 1735, 1240, 1025, 770, and 735 cm^{-1}; NMR δ: 0.66 (3H, s, 18-CH_3), 1.02 (3H, s, 19-CH_3), 1.98 (3H, s, 3α-OAc), 5.28 (1H, t, J=9.0 Hz, 3β-H), 5.39 (1H, d, J=9.5 Hz, 2-H), and 5.67 (1H, d, J=9.5 Hz, 1-H). Found: C, 80.66; H, 10.94%. Calcd for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29%.

5β-Cholest-1-en-3β-ol (**6a**, 60 mg) was obtained as plates from the mother liquor by repeated crystallization from ether–methanol. Mp 114—118 °C; IR (KBr): 3020, 1650, 1040, 1010, and 780 cm^{-1}; NMR δ: 0.65 (3H, s, 18-CH_3), 1.03 (3H, s, 19-CH_3), 3.98 (1H, m, $W/2$=8.5 Hz, 3α-H), and 5.63 (2H, s with shoulder). Found: C, 84.56; H, 12.65%. Calcd for $C_{27}H_{46}O$: C, 83.87; H, 11.99%.

Acetylation of **6a** with pyridine–acetic anhydride gave 3β-acetate (**6b**), melting at 67—69 °C. IR (KBr): 3020, 1720, 1250, 1020, 850, and 770 cm^{-1}; NMR δ: 0.67 (3H, s, 18-CH_3), 1.09 (3H, s, 19-CH_3), 1.98 (3H, s, 3β-OAc), and 4.92—5.92 (3H, complex signals). Found: C, 81.24; H, 10.65%. Calcd for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29%.

*Hydrogenation of 5β-Cholest-1-en-3α-ol (**5a**) and 3β-ol (**6a**).* A mixture of **5a** (100 mg), 5% palladium–charcoal (50 mg), and cyclohexane (20 ml) was stirred vigorously under hydrogen atmosphere at room temperature for 1 h. The solution was filtered and evaporated under reduced pressure. Crystallization of the residue from ether–methanol gave 5β-cholestan-3α-ol (**7**, 45 mg) as fine needles, melting at 108—111 °C (lit,[7] mp 107—109 °C).

Similar hydrogenation of **6a** (10 mg) gave 5β-cholestan-3β-ol **8**, 6 mg) as needles, melting at 100—102 °C (lit,[7] mp 96—98 °C).

*3α-Chloro-5β-cholest-1-ene (**9**).* Thionyl chloride (1.0 ml) was added to a solution of **5a** (313 mg) in benzene (10 ml), and the mixture was stirred at room temperature for 3 h, poured into water containing ice, and extracted with ether. The organic layer was washed with aq sodium hydrogencarbonate and saline, dried and evaporated. Crystallization of the oil from acetone afforded **9** (240 mg) as fine needles. Mp 74—76 °C; IR (KBr): 3020, 1640, 775, and 665 cm^{-1}; NMR δ: 0.65 (3H, s, 18-CH_3), 1.02 (3H, s, 19-CH_3), 4.50 (1H, dd, J=7.0, 10.0 Hz, 3β-H), and 5.50 (2H, s, $W/2$=4.5 Hz). Found: C, 80.12; H, 11.18%. Calcd for $C_{27}H_{45}Cl$: C, 80.05; H, 11.20%.

*5β-Cholest-1-ene (**1**).* Lithium aluminium hydride (3.0 g) was added to a solution of **9** (5.5 g) in dry ether (500 ml), and the mixture was refluxed for 22 h. After the excess hydride had been decomposed with dil sulfuric acid, the ethereal layer was washed with aq sodium hydrogencarbonate and water, dried and evaporated. Crystallization of the oil from acetone gave **1** (3.7 g) as needles, melting at 48—51 °C. IR (KBr): 3020, 1650, 718, and 706 cm^{-1}; NMR δ: 0.65 (3H, s, 18-CH_3), 0.99 (3H, s, 19-CH_3), and 5.47 (2H, s, $W/2$=2.0 Hz). Found: C, 87.15; H, 12.85%. Calcd for $C_{27}H_{46}$: C, 87.49; H, 12.51%.

*Sodium Borohydride Reduction of 2β-Bromo-5β-cholestan-3-one (**3**).* Sodium borohydride (0.36 g) was added with stirring to a suspension of **3** (4.0 g) in absolute ethanol (160 ml). The mixture was stirred for 60 min and then concentrated under reduced pressure. The residue was dissolved in ether, and the solution was washed with water repeatedly and dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure gave 2β-bromo-5β-cholestan-3ξ-ol (**10**, 4.0 g) as a colorless oil, which resisted crystallization from various solvents. IR (NaCl): 3420 cm^{-1}.

*5β-Cholest-2-ene (**2**).* Zinc dust (36.0 g) was added to a solution of the bromohydrin mixture (**10**, 3.7 g) in acetic acid (40 ml), and the mixture was refluxed for 90 min. After the zinc dust had been filtered off, the filtrate was diluted with water and extracted with ether. The organic layer was neutralized with aq sodium hydrogencarbonate, washed with saline, dried and evaporated. The product (3.2 g) was chromatographed over silica gel, and the fractions eluted with hexane were collected and crystallized from acetone, giving **2** as needles (1.3 g), melting at 46—48 °C (lit,[2] mp 47—48 °C). IR (KBr): 3020, 1655, and 660 cm^{-1}; NMR δ: 0.64 (3H, s, 18-CH_3), 0.95 (3H, s, 19-CH_3), and 5.49 (2H, s, $W/2$=4.5 Hz.)

*Gas Chromatography of the Oxygenation Products of 5β-Cholest-1-ene (**1**) and 2-ene (**2**).* A Hitachi Model 063 instrument was used for gas chromatography. Oxygenation products were analyzed with use of a 2 m×5 mm column packed with 5% OV-17 on Chromosorb W (80—100 mesh) operating at 250 °C. Olefins (**1**) and (**2**) in glass tubes equipped with a screw cap were preserved for *ca.* a year at room temperature and at temperature below 5 °C.

In both samples of **1** and **2** aged at room temperature, most of the olefins were converted into **4**. On the other hand, no oxygenated product was present in **1** or **2** aged at temperature below 5 °C.

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