Stereochemistry of hydrogenation of 19-substituted 5α-cholestan-3-ones[1]

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The effect of 19-substituents on the stereochemistry of hydrogenation of 19-substituted 5α-cholestan-3-ones was examined. It has been shown that hydroxyl, acetoxyl, and methoxyl groups have some effect in increasing 3α-alcohols on hydrogenation over platinum in ethanol compared with the case of the unsubstituted ones.

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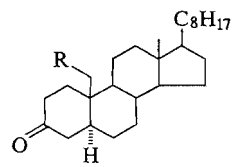
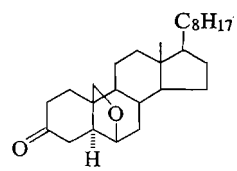
The stereochemistry of the alcohols resulting from the catalytic hydrogenation of steroidal ketones has been known to be very sensitive to the reaction medium (1–3), and the reason for this is a debated point (3, 4). On the other hand, the substituent effect on the stereochemistry of hydrogenation of ketones has not yet been well examined, and an investigation of the effect of some substituents in a rather rigid steroidal system seems to be of interest. Previously, we reported on the catalytic hydrogenation of 3β-acetoxy-19-hydroxy- and 3α,19-dihydroxycholest-5-enes and showed that the 19-hydroxyl group in the above compounds is effective in increasing the proportion of 5β-dihydro compounds (5, 6). It appeared that the lone paired electrons of the oxygen atom of the 19-hydroxyl group made it easier for the catalyst to approach the β-side of the molecule. As part of the investigation of the effect of 19-substituents on stereochemistry of hydrogenation we examined the influence of 19-substituents on the proportion of 3α- and 3β-alcohols obtained in the catalytic hydrogenation of 19-substituted 5α-cholestan-3-ones.

The proportion of the 3α-alcohol obtained in hydrogenation of 5α-cholestan-3-one over platinum has been reported to vary with acidity of the solvent used (1, 2), and the 3α-alcohol became the main product of hydrogenation by adding small amounts of hydrochloric acid to the solvent (3). As the stereochemistry of the hydrogenation of steroidal 3-ketones appears very susceptible to the influence of the condition of the reaction, for instance, the catalyst used, solvent, temperature and other factors, the proportion of 3α-alcohols obtained in hydrogenation of several ketones under the same condition was compared with that of 5α-cholestan-3-one in the present experiments.

We synthesized the 19-substituted 5α-cholestan-3-one derivatives listed below.



1*a* R = H
1*b* R = OH
1*c* R = OAc
1*d* R = OCH_3
1*e* R = Cl



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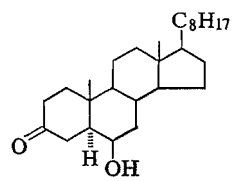

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Optical rotatory dispersion (o.r.d.) curves of the above ketones were measured and the results are shown in Table I. All 3-ketones measured showed

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TABLE I

Optical rotatory dispersion molecular amplitude (in dioxane)

Compound	Molecular amplitude
1*a*	+49
1*b*	+14
1*c*	+37
1*d*	+31
1*e*	+27
2	+114

positive Cotton effect curves such as that of 5α-cholestan-3-one, but some differences in amplitude were observed. Especially in 19-hydroxy-3-one (**1***b*) a considerable decrease of the positive amplitude was seen, and this phenomenon has been interpreted by Crabbé (7, 8) to be due to the possibility that the compound exists as the free and intramolecular hemiketal form. It has also been shown that the introduction of 6β,19-epoxide causes the considerable increase in molecular amplitude compared with that of 5α-cholestan-3-one.

The above ketones were hydrogenated over platinum in acetic acid and in ethanol solution, and the proportion of 3α- and 3β-alcohols was determined by gas–liquid chromatography. The results are reported in Table II. The experimental results of the reduction of the compound **1**, **2**, and **3** with sodium borohydride in methanol are also mentioned for comparison. The configurations of the epimeric alcohols obtained in the hydrogenation of **1***a*, **1***b*, **1***c*, **1***e*, **2**, and **3** have already been established (5, 6). The configurations of the products from the 19-methoxy derivative (**1***d*) have been assigned on the basis of nuclear magnetic resonance (n.m.r.) spectra. The differences in the chemical shift and in the half-widths of the peaks of the epimeric C-3 protons were used (3), namely, the 3α-alcohol had a C-3 proton peak centered at 5.05 p.p.m. (half-width 8 c.p.s.), while in the 3β-one it was centered at 4.7 p.p.m. (23 c.p.s.), as the 3-acetoxy derivative.

When reduced with sodium borohydride, all hydrogenated compounds gave about 10% of 3α-alcohols as in the case of 5α-cholestan-3-one and it was shown that 19-substituents have little effect on the steric course of the reaction. The catalytic hydrogenation in ethanol gave proportions of 3α-alcohols varying with the change of 19-substituent and it was observed that the presence of the 19-substituents such as hydroxyl, acetoxyl, and methoxyl groups caused the increase of the proportions of 3α-alcohols by 10–20% in ethanol. In acetic acid, the proportion of 3α-alcohol was shown to decrease a little in all 19-substituted derivatives compared with that in the unsubstituted one.

TABLE II

The proportions of 3α- and 3β-alcohols obtained in reduction*

Compound (19-substituent)	$NaBH_4$		H_2/Pt–EtOH		H_2/Pt–AcOH	
	3α-	3β-	3α-	3β-	3α-	3β-
1*a* (H)	13	87	17	83	16	84
1*b* (OH)	10	90	40	60	6	94
1*c* (OAc)	8	92	32	68	1	99
1*d* (OCH_3)	11	89	26	74	4	96
1*e* (Cl)	6	94	7	93	3	97
2	12	88	17	83	2	98
3	9	91	6	94	1	99

*Proportions expressed as percentages.

From the above experimental results, the effect of 19-substituents on hydrogenation in ethanol appears to be due to electronic interaction between substituents and catalyst rather than steric effect. In acetic acid, this interaction appears to be weakened by protonation, and the steric course of the hydrogenation seems to be more controlled by steric factors. On the hydrogenation of the 5,6-double bond, the effect of the 19-hydroxyl group in increasing the 5β-dihydro compound was shown to be weakened in acetic acid, but 3β-acetoxy-19-hydroxycholest-5-ene gave 36.5% of the 5β-dihydro compound even when it was hydrogenated over platinum in acetic acid, while 3β-acetoxycholest-5-ene afforded only 10% of the 5β-dihydro compound under the same conditions. On the other hand the effect of the 19-hydroxyl group completely disappeared in acetic acid on the reduction of the 3-keto group. On the basis of these results, it was supposed that the hydrogen bonding between the 19-hydroxyl group and the π-electrons of the 5,6-double bond contributed to the determination of the steric course of hydrogenation together with the lone paired-electrons of the oxygen atom. Not only hydroxyl but also acetoxyl and methoxyl groups appear to have some effect on the stereochemistry of hydrogenation of the 3-keto group in ethanol. Though the effect of acetoxyl and methoxyl groups as above has scarcely been reported, it

has been suggested that the lone paired-electrons of the oxygen atoms in these groups may play some role to promote the β-side hydrogenation. On the hydrogenation of the 5,6-double bond the 19-acetoxyl group has no effect in increasing the 5β-dihydro compound both in ethanol and in acetic acid. But in the case of the reduction of the 3-keto group an acetylation of the 19-hydroxyl group did not cause a large change in the proportion of the 3α-alcohol. This difference in the effect of the 19-acetoxyl group and the 3-keto group on the reduction of the 5,6-double bond seems to be related to the difference in the distance between the 19-substituent and the unsaturated bond to be hydrogenated, or may be due to a steric effect.

Numerous intramolecular reactions of A/B-*trans*- and Δ^5-steroids possessing functional groups at C-3 and C-19 have been reported (9–13). As the flexibility of ring A allows the interaction of the functional groups at C-3 and C-19, it is not clear that the larger effect of 19-hydroxyl group than that of others is partially attributed to the formation of the intramolecular hemi-ketal. From a consideration of the o.r.d. and n.m.r. results, it is suggested that the steric course of hydrogenation depends much more from the nature of the substituent at C-19 than from the possible changes of conformation occurring in ring A.

Experimental

All melting points are uncorrected. Nuclear magnetic resonance spectra were obtained at 60 Mc.p.s. on $CDCl_3$ solution containing TMS as an internal standard; the chemical shifts are expressed in p.p.m.; s = singlet, q = quartet.

3β-Acetoxy-19-benzoyloxy-5α-cholestane (4a)

Benzoylation of 3β-acetoxy-19-hydroxy-5α-cholestane (5) with pyridine and benzoyl chloride at room temperature gave **4a**, which was recrystallized from methanol, m.p. 125–126°; $[\alpha]_D^{26}$ +30.6° ($CHCl_3$, *c*, 1.625); ν_{max} (KBr) 1733, 1720, 1603, 1585, 1273, 1247, 1117, 1028, and 720 cm^{-1}; λ_{max} (EtOH) 231 mμ (ε 13 900), 274 mμ (ε 1 100).

Anal. Calcd. for $C_{36}H_{54}O_4$: C, 78.50; H, 9.88. Found: C, 78.62; H, 9.72.

3β-Hydroxy-19-benzoyloxy-5α-cholestane (4b)

Hydrolysis of **4a** with 0.5% KOH–ethanol gave **4b**, which was recrystallized from acetone–methanol, m.p. 154.5–155.2°; $[\alpha]_D^{26}$ +41.7° ($CHCl_3$, *c*, 1.440); ν_{max} (KBr) 3420, 1717, 1603, 1585, 1270, 1118, 1033, 1029, and 715 cm^{-1}; λ_{max} (EtOH) 231 mμ (ε 13 100), 274 mμ (ε 950).

Anal. Calcd. for $C_{34}H_{52}O_3$: C, 80.26; H, 10.30. Found: C, 79.96; H, 10.53.

19-Benzoyloxy-5α-cholestan-3-one (1f)

A solution of 300 mg of 3β-hydroxy compound (**4b**) in 30 ml of acetone was oxidized with 0.7 ml of 8 *N* chromic–sulfuric acid solution at 0° for 30 min. The crude product (270 mg) was recrystallized from acetone–methanol; yield, 230 mg, m.p. 152–152.5°; ν_{max} (KBr) 1718, 1603, 1585, 1273, 1115, 1030, and 719 cm^{-1}; λ_{max} (EtOH) 231 mμ (ε 13 600), 274 mμ (ε 910); n.m.r. (δ): 4.72 (s, 19-CH_2), 7.4–8.15 (aromatic H); o.r.d. (*c*, 0.0057, dioxane, 20°): $[\phi]_{450}$ +360°, $[\phi]_{315}$ +2430°, $[\phi]_{288}$ 0°, $[\phi]_{283}$ −320°.

Anal. Calcd. for $C_{34}H_{50}O_3$: C, 80.58; H, 9.95. Found: C, 80.78; H, 10.19.

19-Hydroxy-5α-cholestan-3-one (1b)

19-Benzoyloxy compound (**1f**) was hydrolyzed with 5% KOH–ethanol solution at room temperature. The crude product was recrystallized from methanol, m.p. 143.5–144.5°; ν_{max} (KBr) 3420, 1720 (weak), and 1045 cm^{-1}; n.m.r. (δ): 4.18 and 4.00 (AB type q, J = 10.5 c.p.s., 19-CH_2); o.r.d. (*c*, 0.0071, dioxane, 20°): $[\phi]_{450}$ +380°, $[\phi]_{313}$ +1730°, $[\phi]_{275}$ +330°, $[\phi]_{260}$ +590°.

Anal. Calcd. for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.67; H, 11.52.

19-Acetoxy-5α-cholestan-3-one (1c)

Acetylation of **1b** with pyridine and acetic anhydride overnight at room temperature gave the acetate (**1c**). Recrystallization of the crude product from methanol gave a pure product, m.p. 99.5–100.5°; ν_{max} (KBr) 1735, 1710, 1249, 1240, and 1050 cm^{-1}; n.m.r. (δ): 4.49 (s, 19-CH_2), 2.10 ($OCOCH_3$); o.r.d. (*c*, 0.006, dioxane, 20°): $[\phi]_{450}$ +270°, $[\phi]_{315}$ +2180°, $[\phi]_{293}$ 0°, $[\phi]_{274}$ −1560°, $[\phi]_{260}$ −1250°.

Anal. Calcd. for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88. Found: C, 78.49; H, 10.96.

3-Ethylenedioxy-19-benzoyloxy-5α-cholestane (5a)

19-Benzoyloxy-3-ketone (**1f**) was converted into the ethylenedioxy derivative by exchange dioxolonation (14). The mixture of 250 mg of 3-ketone (**1f**) and 7 mg of *p*-toluenesulfonic acid in 4 ml of 2-methyl-2-ethyl-1,3-dioxolane was refluxed for 6 h. After cooling, the reaction mixture was diluted with benzene and the resulting solution was washed with sodium bicarbonate solution and with water, and dried over sodium sulfate. Evaporation of the solvent *in vacuo* gave the crude product, which was recrystallized from acetone–methanol; yield, 200 mg, m.p. 138.5–139.5°; $[\alpha]_D^{26}$ +42.9° ($CHCl_3$, *c*, 1.625); ν_{max} (KBr) 1715, 1274, 1115, 1104, 1073, 1028, 946, and 710 cm^{-1}; λ_{max} (EtOH) 231 mμ (ε 13 600), 274 mμ (ε 910); n.m.r. (δ): 3.95 (s, 3-ethylenedioxy), 4.52 (s, 19-CH_2), 7.4–8.15 (aromatic H).

Anal. Calcd. for $C_{36}H_{54}O_4$: C, 78.50; H, 9.88. Found: C, 78.37; H, 9.79.

3-Ethylenedioxy-19-hydroxy-5α-cholestane (5b)

19-Benzoyloxy compound (**5a**) was hydrolyzed with 5% KOH–ethanol under reflux for 45 min. The crude product was recrystallized from *n*-hexane, m.p. 146.1–146.7°; $[\alpha]_D^{26}$ +48.1° ($CHCl_3$, *c*, 2.075); ν_{max} (KBr) 3530, 1112, 1103, 1097, 1040, and 946 cm^{-1}; n.m.r. (δ):

3.95 (s, 3-ethylenedioxy), 3.75, and 4.00 (AB type q, J = 12 c.p.s., 19-CH_2).

Anal. Calcd. for $C_{29}H_{50}O_3$: C, 77.97; H, 11.28. Found: C, 77.74; H, 11.16.

3-Ethylenedioxy-19-methoxy-5α-cholestane (5c)

Potassium metal (55 mg) was added to a solution of 100 mg of 19-hydroxy compound (**5b**) in 5 ml of dry benzene, and the mixture was refluxed for 2 h with vigorous stirring. Then methyl iodide (2 ml) was added and the refluxing was continued for 3 h (15). After cooling, methanol was added, the reaction mixture was diluted with ether, and the solution was washed with water and dried over sodium sulfate. Evaporation of the solvent gave the crude product (92 mg), which was purified by chromatography on alumina eluting with *n*-hexane–chloroform (10:1). Recrystallization of the product purified by chromatography gave 70 mg of the pure methoxy compound (**5c**), m.p. 128–129°; $[\alpha]_D^{26}$ +30.0° ($CHCl_3$, *c*, 1.340); ν_{max} (KBr) 1110, 1096, 1070, 978, and 810 cm^{-1}; n.m.r. (δ): 3.32 (s, OCH_3), 3.51 (s, 19-CH_2), 3.97 (s, 3-ethylenedioxy).

Anal. Calcd. for $C_{30}H_{52}O_3$: C, 78.20; H, 11.38. Found: C, 78.38; H, 11.52.

19-Methoxy-5α-cholestan-3-one (1d)

A solution of 140 mg of **5c** and 14 mg of *p*-toluenesulfonic acid in 20 ml of anhydrous acetone was refluxed for 15 h. After cooling, the solution was diluted with ether and washed with sodium bicarbonate solution and water, and dried over sodium sulfate. The crude product obtained was recrystallized from acetone–methanol; yield, 90 mg, m.p. 104–105°; ν_{max} (KBr) 1723, 1110, and 960 cm^{-1}; n.m.r. (δ): 3.33 (s, OCH_3), 3.62 (s, 19-CH_2); o.r.d. (*c*, 0.0059, dioxane, 20°): $[\phi]_{450}$ +170°, $[\phi]_{315}$ +1970°, $[\phi]_{291}$ 0°, $[\phi]_{273}$ −1100°, $[\phi]_{260}$ −850°.

Anal. Calcd. for $C_{28}H_{48}O_2$: C, 80.71; H, 11.61. Found: C, 80.62; H, 11.92.

19-Chloro-5α-cholestan-3-one (1e)

Oxidation of 3β-hydroxy-19-chloro-5α-cholestane with 8 *N* chromic–sulfuric acid solution at 0–5° for 30 min gave **1e**, which was recrystallized from methanol, m.p. 107.2–108°; ν_{max} (KBr) 1717, 778, and 730 cm^{-1}; n.m.r. (δ): 3.86 and 4.02 (AB type q, J = 13 c.p.s., 19-CH_2); o.r.d. (*c*, 0.0053, dioxane, 20°): $[\phi]_{450}$ +240°, $[\phi]_{315}$ +1810°, $[\phi]_{291}$ 0°, $[\phi]_{273}$ −930°, $[\phi]_{260}$ −710°.

Anal. Calcd. for $C_{27}H_{45}OCl$: C, 77.01; H, 10.77. Found: C, 76.98; H, 11.05.

6β,19-Epoxy-5α-cholestan-3-one (2)

The epoxy compound (**2**) was synthesized by usual oxidative cyclization of 3β-acetoxy-6β-hydroxy-5α-cholestane with lead tetraacetate – iodine (16, 17) followed by hydrolysis and oxidation. Recrystallization of the crude product from methanol gave a pure product, m.p. 131–132.5°; ν_{max} (KBr) 1725, 1490, 1034, 1022, and 960 cm^{-1}; n.m.r. (δ): 3.95 (s, 19-CH_2); o.r.d. (*c*, 0.0019, dioxane, 20°): $[\phi]_{450}$ +760°, $[\phi]_{315}$ +6290°, $[\phi]_{307}$ +5650° (shoulder), $[\phi]_{292}$ 0°, $[\phi]_{270}$ −5140°, $[\phi]_{260}$ −4700°.

Anal. Calcd. for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 81.11; H, 11.13.

Reduction of 5α-Cholestan-3-one Derivatives with Sodium Borohydride

A solution of 20 mg of 5α-cholestan-3-one in 2 ml of methanol was treated with 20 mg of sodium borohydride at room temperature for 30 min. After addition of a small amount of acetic acid, the reaction mixture was treated with water and ether, and the ethereal extract was washed with water to neutrality. The reduction product was analyzed by gas–liquid chromatography (g.l.c.) as the trimethylsilyl ether.

Catalytic Hydrogenation of 5α-Cholestan-3-one Derivatives over Platinum Catalyst

(*A*) A solution of 10 mg of **1a** in 1 ml of acetic acid was hydrogenated in the presence of 3 mg of pre-reduced platinum oxide under atmospheric pressure at room temperature for 2 h. After the catalyst was removed by decantation, ether and water were added. The ethereal solution was washed with sodium bicarbonate solution and with water, dried, and evaporated. The residue was analyzed by g.l.c. as above.

(*B*) A solution of 10 mg of **1a** in 1 ml of ethanol was hydrogenated with 5 mg of pre-reduced platinum oxide for 2 h. After addition of ether, the catalyst was removed by filtration. Evaporation of the solvent *in vacuo* gave a product, which was analyzed by g.l.c. as above.

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