Chlorination of Cholesterol in Aqueous Solution: Isolation of a *trans*-Diequatorial Chlorohydrin

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In connection with a study of the reactions which wood extractives undergo during the bleaching of wood pulp, the chlorination of cholesterol in aqueous t-butanol solution was examined.[1] Besides the wellknown reaction products, 5α,6β-dichloro-cholestan-3β-ol,[2] 5α-chloro-cholestan-3β,6β-diol and 6β-chloro-cholestan-3β,5α-diol,[3] we obtained two ketonic oxidation products, 5α-chloro-cholestan-3β-ol-6-one and 6β-chloro-cholestan-5α-ol-3-one, as well as an unidentified compound with the formula $C_{27}H_{44}Cl_2O$ and a new chlorohydrin. The last compound was isolated as its acetate (*A*) in a yield of 15 %. The acetate *A* was also obtained by chlorination of cholesterol acetate. This communication describes its identification.

The compound *A* analysed for $C_{29}H_{49}ClO_3$. Its IR-spectrum showed the presence of acetate and hydroxyl groups. The mass spectrum indicated that it was a 5,6-substituted chlorohydrin as it showed great similarities with the spectra of other 5,6-substituted chlorohydrins. Alkaline saponification yielded 5β,6β-epoxy-cholestan-3β-ol. The hydroxyl group of the chlorohydrin was therefore in either the 5β or the 6β-position. As the compound did not react during attempted acetylation with acetic anhydride and pyridine the hydroxyl group was evidently tertiary and therefore linked to the 5β-position. Compound *A* is thus IIa or the isomer with a 6β-chloro group instead of the 6α-chloro group.

The NMR frequencies of *A* are shown in Table 1, which for comparison also includes those of 3β-acetoxy-5α-chloro-cholestan-6β-ol (IIIa). The half-band widths of the NMR signals are especially informative. The width is considerably larger for an axial proton than for the corresponding equatorial one.[4] Consequently, the signal width for the axial 3α-proton in IIIa (25 cps) is considerably larger than the width of the signal of compound *A* which is attributed to the equatorial 3α-proton (8 cps). The *A* proton which is geminal to the chloro atom gives a signal whose width is 20 cps. If compared with 6 cps for the equatorial 6α-proton of IIIa it is evident that the proton in *A* is axial, which agrees with a 6α-chloro group.

Table 1. The proton magnetic signals[a] from 3β-acetoxy-6α-chlorocholestan-5β-ol (IIa).

Shift (δ) ppm			Character[b]	Assignment
$CDCl_3$[c]		C_6H_6		
0.66	(0.68)	0.55	s	18-CH_3
0.88	(0.87)	0.97	d, $J_c = 5.5$	26,27-CH_3
1.00	(1.30)	0.97	s	19-CH_3
2.09	(2.03)	1.58	s	3β-CH_3COO
2.98		5.95	broad	5α-OH
4.4	(4.0[d])	4.4	m, $W = 20$	6α-H
5.35	(5.4[e])	5.3	m, $W = 8$	3α-H

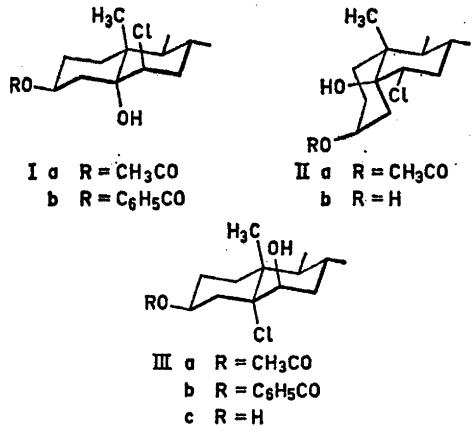
[a] 60 Mc.

[b] s is singlet: d, doublet: m, multiplet. J_c is the coupling constant and W, the half-band width, both in cps.

[c] The figures in brackets refer to the signals from 3β-acetoxy-5α-chloro-cholestan-6β-ol (IIIa). If not otherwise stated, the signal characters and assignments are the same as those for (IIa).

[d] $W = 6$ cps. Assigned to the equatorial 6α-H.

[e] $W = 25$ cps. Assigned to 3α-H, which in this compound is axial.



I a R = CH_3CO
b R = C_6H_5CO

II a R = CH_3CO
b R = H

III a R = CH_3CO
b R = C_6H_5CO
c R = H

The compound *A* is then 3β-acetoxy-6α-chloro-cholestan-5β-ol (IIa) in which the 5,6-substituents are *trans*-diequatorial.

Chlorination of cholesterol thus yields 6α-chloro-cholestan-3β,5β-diol (IIb). The possibility that it is formed by rearrangement [5] of 5α-chloro-cholestan-3β,6β-diol (IIIc) was excluded by the finding that IIIc is stable under the reaction conditions.

Previously, Alt and Barton [6] had found that the chlorination and bromination of Δ^2- and Δ^3-cholestene formed small amounts of *trans*-diequatorial dihalo products together with the *trans*-diaxial compounds.

The 5β-hydroxyl and the 3β-acetate groups in IIa are suitably situated for the formation of a hydrogen bridge. Such an intermolecular bond explains why the stretching frequency for the acetate carbonyl is unusually low, 1707 cm^{-1} (in KBr), compared with that for other steroidal 3-acetates, 1719—1728 cm^{-1} (in $CHCl_3$).[7] It is well known that hydrogen bonding decreases the carbonyl frequency.[8] The hydrogen bond and the 5β-structure explain why IIa moved considerably faster on thin layer chromatography than the chlorohydrins Ia and IIIa and also cholesteryl acetate: its hydroxyl is masked by the hydrogen bridge and its acetate group is in the less exposed axial position.

The optical rotation of 3β-benzoxy-5α-chloro-cholestan-6β-ol (IIIb) was found to be $[\alpha]_{578}$ −21° (*c*, 0.1: $CHCl_3$) which differs considerably from that reported earlier, $[\alpha]_{Na} \pm 0$.[9]

Experimental. 3β-Acetoxy-6α-chloro-cholestan-5β-ol (IIa) was obtained from chlorination of cholesterol or its acetate as described in Ref. 1. Recrystallisations from ethanol yielded a chlorine-containing product with m.p. 127—129°C and $[\alpha]_{578}$ + 39°, $[\alpha]_{365}$ + 110° (*c*, 2.0: $CHCl_3$). (Found: C 72.6; H 10.3. Calc. for $C_{29}H_{49}ClO_3$: C 72.4; H 10.3). The proton magnetic signals are shown in Table 1. The mass spectrum gave the molecular peaks at *m/e* 480 and *m/e* 482, and peaks due to loss of HCl, H_2O, CH_3COOH, and combinations thereof. The spectra of Ia, IIa, Ib, and IIIb were identical below *m/e* 366 (the molecular ions minus HCl, H_2O, and AcOH). The IR spectrum showed peaks at 3430, 1707, 1265, and 1035 cm^{-1} (KBr).

The compound IIa (104 mg) was dissolved in a methanol solution of potassium hydroxide (0.5 N, 20 ml). The solution was left for 17 h at room temperature. Water was added and the crystals obtained (59 mg) were collected and recrystallised (methanol). The product, m.p. 132—133°C, $[\alpha]_{578}$ + 10° was indistinguishable from 5β,6β-epoxy-cholestan-3β-ol (mixed m.p., IR, and NMR).

A solution of 5α-chloro-cholestan-3β,6β-diol (IIIc) (0.2 g) in 0.2 M hydrochloric acid/t-butanol (20 ml/80 ml) was kept at room temperature. Thin layer chromatography, which was carried out under such conditions that IIb and IIIc should be separated, showed that IIIc did not react in 7 days.

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