STEREOCHEMICAL STUDIES

III. REACTIONS OF 4-OXA-5α-CHOLESTAN-3α-OL, A CARBOHYDRATE MODEL[1]

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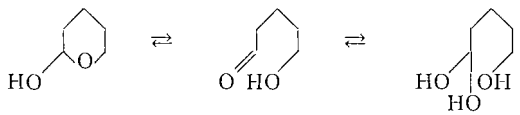
ABSTRACT

4-Oxa-5α-cholestan-3α-ol was prepared by reduction of 4-oxa-5α-cholestan-3-one with lithium aluminum hydride. It showed several typical carbohydrate reactions, such as mutarotation in aqueous tetrahydrofuran and condensation with alcohols in the presence of hydrogen chloride to give 3-alkoxy-4-oxa-5α-cholestanes. These compounds were also prepared by the reaction of alcohols with 3α-chloro-4-oxa-5α-cholestane in the presence of base. Factors governing the proportions of 3α and 3β isomers formed in these reactions are discussed.

The study of the pyranose ring system in simple compounds (e.g. I), devoid of the many hydroxyl groups and asymmetric carbon atoms of the common sugars, has attracted some interest (1, 2, 3, 4). Hurd and Saunders (5) showed that tetrahydropyran-2-ol (I) (6) in 75% aqueous dioxan had an ultraviolet absorption peak at 287 mμ, indicating the presence of the open-chain tautomer, 5-hydroxypentanal (II). From a comparison of the intensity of this peak with that of 5-methoxypentanal, they estimated that 5-hydroxypentanal made up 6% of the equilibrium mixture. They assumed the remaining 94% to be entirely in the lactol form I, but it is likely that about 2–3% is present as the hydrated aldehyde III (7, 8).



I II III

Substitution of the lactol stabilizes it with respect to the open-chain tautomer, which at equilibrium is present to only a very minor extent in solutions of the common pentoses and hexoses (9), perhaps because of conformational effects (10).

There appear to be advantages in studying the reactions of the lactol fused to a rigid polycyclic system, as in V. The use of optically active compounds makes it possible to determine the stereochemical course of reactions from the optical rotations of products, while the interpretation of results is simplified by the fact that the pyranose ring is locked into the C-1 conformation, the more stable conformation of glucose and many other pyranoses (11).

To obtain the desired lactol (V), 4-oxa-5α-cholestan-3-one (IV) (12, 13) in tetrahydrofuran was reduced with one-quarter of a mole of lithium aluminum hydride (14). A crystalline product, $C_{26}H_{46}O_2$, was obtained which possessed a potential carbonyl group, as shown by its reaction with 2,4-dinitrophenylhydrazine to form a derivative, $C_{32}H_{50}O_5N_4$. The infrared spectrum of this derivative had no hydroxyl peak, indicating that it had the cyclic structure VIII rather than the structure VII. Such cyclic structures have been postulated for the phenylhydrazones of some pyranoses, although the evidence for them is equivocal (15).

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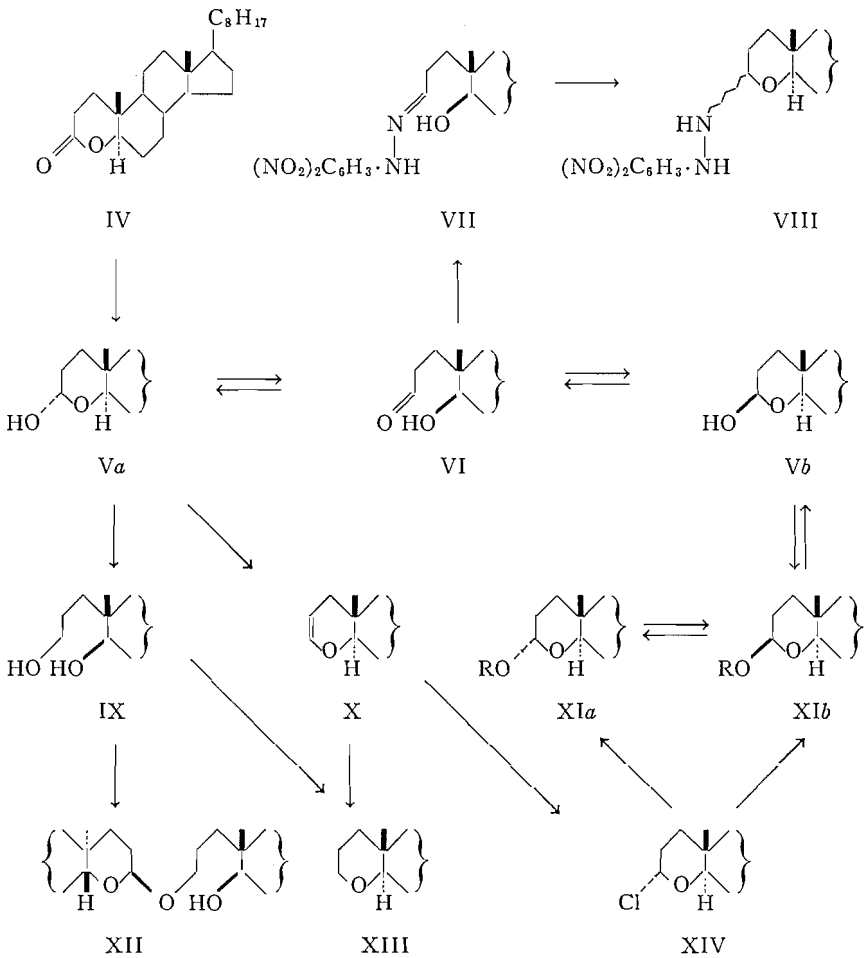


The reduction product itself is also in a cyclic form (V), since no carbonyl peak characteristic of the hydroxyaldehyde VI could be detected in the ultraviolet absorption spectrum of the compound in 90% aqueous dioxan or 85–90% aqueous tetrahydrofuran, or in the infrared absorption spectrum of the compound as a solid or in solution in chloroform, carbon tetrachloride, or tetrahydrofuran. Evidently fusing the lactol I to the rigid BCD ring system of cholesterol stabilizes the cyclic form.

The α-configuration (V*a*) of the 3-hydroxyl group of the crystalline lactone V is shown by the molecular rotation of the lactol, given in Table I along with the values calculated for the 3α (V*a*) and 3β (V*b*) compounds (using the known value for the parent compound (XIII)) by the elegant and powerful method of Brewster (16). Calculation by Whiffen's method (17) gives almost the same values; however, Whiffen's parameters are considered to be slightly less reliable in the present application, since for the most part they are derived from rotations of compounds dissolved in water rather than in organic solvents. The effect of solvent on rotation, not taken in account in Whiffen's or Brewster's treatments, is appreciable for our compounds (cf. Table I), but not so large as to invalidate the use of these treatments for assigning configurations.

TABLE I

Molecular rotation $[M]_D$ values of 3-substituted 4-oxa-5α-cholestanes

3-Substituent	Compound	$[M]_{D,\ calc}$ (deg)	$[M]_{D,\ obs}$ (deg)	Solvent*
(Hydrogen)	XIII	(+186)	+180†	$CHCl_3$
			+189	CCl_4
			+190	THF
α-Hydroxy	V*a*	+286	+250	$CHCl_3$
			+256	CCl_4
			+344	THF
			+356	THF–H_2O (9:1, v/v)
β-Hydroxy	V*b*	+186	—	
α-Methoxy	XI*a*, R = Me	+391	+442	$CHCl_3$
			+410	CCl_4
			+460	THF–MeOH (1:1, v/v)
β-Methoxy	XI*b*, R = Me	+81	—	
α-Benzyloxy	XI*a*, R = CH_2Ph	+477‡	+466	$CHCl_3$
			+436	THF–$PhCH_2OH$ (2:3, v/v)
β-Benzyloxy	XI*b*, R = CH_2Ph	−5‡	−115	$CHCl_3$
			−19.2	THF–$PhCH_2OH$ (2:3, v/v)
α-Chloro	XIV	(ca. +686)	+672	$CHCl_3$
			+666	CCl_4
			+666	THF
β-Chloro		+186	—	

*THF = tetrahydrofuran.
†Fieser *et al.* (18) report the same value.
‡Calculated from the average increment in molecular rotation (+191° and −191°) in forming α- and β-benzyl-D-glycosides from the respective anomers (19).

While the optical rotation of the lactol V*a* dissolved in chloroform, carbon tetrachloride, or tetrahydrofuran showed no change on standing, it dropped rapidly for solutions in 85–90% aqueous tetrahydrofuran (Fig. 1), and with 1% hydrochloric acid

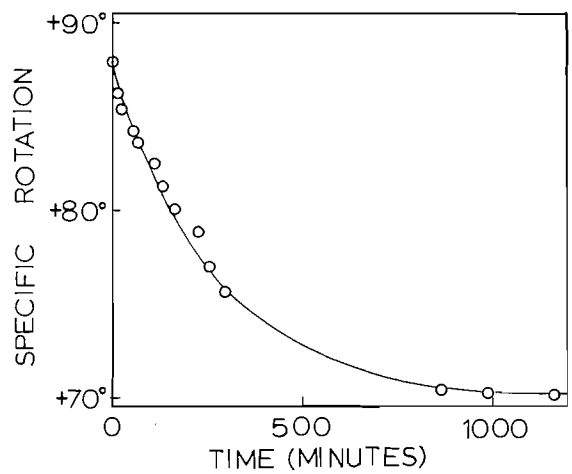


FIG. 1. Change in specific rotation of 4-oxa-5α-cholestan-3α-ol in 90% aqueous tetrahydrofuran (v/v) at 21° C. Theoretical curve for a first-order reaction having a rate constant of 0.0038 min^{-1} (natural logarithms).

in this solvent it had dropped to a steady value in less than 5 minutes. This change in rotation indicated the formation of the β isomer V*b*; such mutarotation is known to be catalyzed by acid (20). Assuming for the 3β isomer V*b* the molecular rotation shown in Table I, the lactol in 90% aqueous tetrahydrofuran is made up of 55% of the α isomer and 45% of the β isomer. However, all attempts to isolate the β isomer by crystallization from different solvents failed, only the α isomer being obtained.

Treatment of the lactol V*a* with hot acetic anhydride – sodium acetate gave 4-oxa-5α-cholest-2-ene (X), more conveniently prepared by the action of phosphorus oxychloride in pyridine. The acetate (XI, R = CH_3CO) could be prepared by the action of acetic anhydride in pyridine at 20° C, but proved reactive and difficult to purify; attempts to crystallize it from methanol afforded 3α-methoxy-4-oxa-5α-cholestane (XI*a*, R = Me), described below. Hydrogenation of the unsaturated ether X gave 4-oxa-5α-cholestane (XIII), previously obtained by dehydration of the diol IX (13).

Like dihydropyran (21), 4-oxa-5α-cholest-2-ene (X) in ether added hydrogen chloride to give a reactive chloro ether, which in the present instance must be 3α-chloro-4-oxa-5α-cholestane (XIV). This addition reaction may be reversible, like that of dihydropyran (21), because infrared studies showed the chloro ether always to be contaminated with small amounts of the unsaturated ether X, and attempts to purify it by crystallization from inert solvents always led to a drop in melting point. However, when a solution of the chloro ether in carbon tetrachloride ($[\alpha]_D$ +153°), shown by quantitative infrared measurements to contain 4% of the unsaturated ether, was saturated with hydrogen chloride, the specific rotation rose to +163° and the infrared peaks due to the unsaturated ether disappeared. The molecular rotations recorded in Table I for this compound are all for solutions saturated with hydrogen chloride.

The α-configuration at the 3-position of the chloro ether is probable from its molecular rotation (Table I). The molecular rotation of 3β-chloro-4-oxa-5α-cholestane should, according to the treatments of Whiffen and Brewster, be about the same as that of the parent compound (XIII); the molecular rotation of the 3α-chloro compound should be different, but the parameters which enable one to calculate it are not available. However, it is evident from Table II that the introduction of an α-chlorine atom at the 1-position

TABLE II

Molecular rotation values $[M]_D$ (deg) of sugar derivatives

Parent compound	Derivatives				
	1-Deoxy	1α-Chloro	$\Delta[M]_D$	1β-Chloro	$\Delta[M]_D$
3,4,6-Tri-*O*-acetyl-D-glucopyranose	+129 (22)	+608 (23)	+479	−48 (24)	−177
2,3,4,6-Tetra-*O*-acetyl-D-glucopyranose	+25 (25)	+600 (26)	+575	+62 (27)	+ 37
2,3,4,6-Tetra-*O*-acetyl-D-mannopyranose	−140 (28)	+331 (29)	+471		

of a pyranose ring in the C-1 conformation (11) causes a shift in molecular rotation of about +500°, the nature and configuration of the adjoining asymmetric center having a comparatively minor effect, so that the molecular rotation of 3α-chloro-4-oxa-5α-cholestane (XIV) should be about +686°, in good agreement with the values found for our chloro ether.

This argument by itself cannot be considered completely conclusive because the

evidence for the configurations assigned to the glycosyl halides is generally indirect and dependent on an interpretation of the stereochemical course of reactions (30). However, the configurations assigned to the stable glycosyl halides (30) and to 3α-chloro-4-oxa-5α-cholestane are those to be expected from the "anomeric effect" (31, 32, 33), discussed further below, which predicts that in dihydropyran rings a halogen atom on the carbon atom adjacent to the ring oxygen will be more stable in the axial orientation.

The lactol V*a* in methanol containing 3% hydrogen chloride gave an 88% yield of a crystalline methoxy derivative, shown by its rotation (Table I) to be 3α-methoxy-4-oxa-5α-cholestane (XI*a*, R = Me). This compound was stable in alkaline solution, but in aqueous acid was readily hydrolyzed to the lactol. Second crops from the preparation of the ether (XI*a*, R = Me), when obtained by rapid evaporation of the solvent at a low temperature (i.e. under non-equilibrating conditions (see below)), had a shoulder at 1068 cm^{-1}, absent in the infrared spectrum of the pure 3α isomer, which is probably due to the 3β isomer (XI*b*, R = Me). However, the latter could not be isolated in a pure state.

A solution of 3α-methoxy-4-oxa-5α-cholestane in methanol–tetrahydrofuran (1:1, v/v) having a low concentration (0.018 *M*) of hydrogen chloride showed a rapid drop in rotation (Fig. 2); with a 0.06 *M* concentration of hydrogen chloride the rotational drop

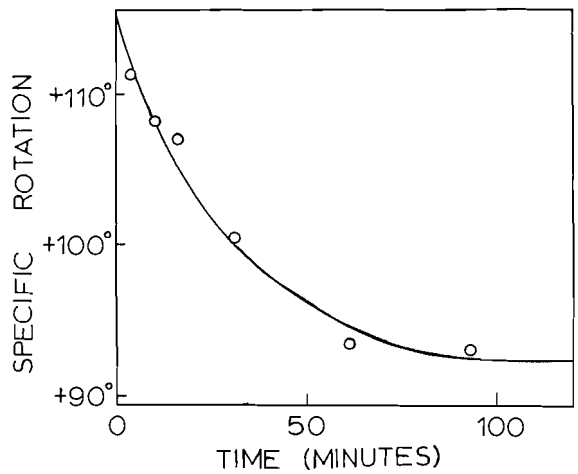
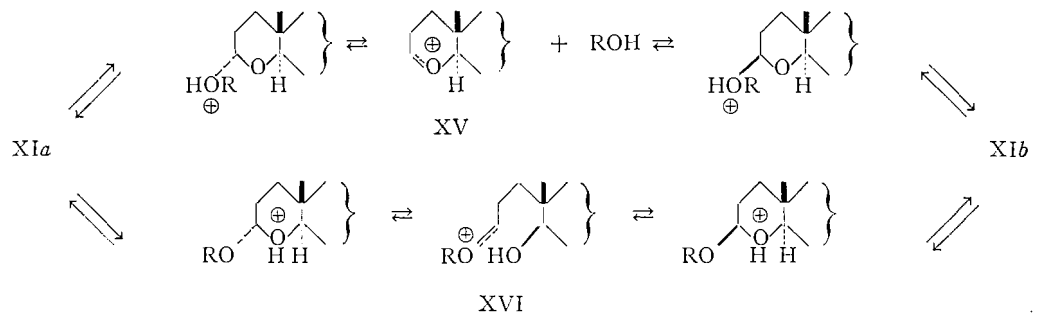


FIG. 2. Change in specific rotation of 3α-methoxy-4-oxa-5α-cholestane in tetrahydrofuran–methanol (1:1, v/v), 0.018 *M* with respect to hydrochloric acid, at 23° C. Theoretical curve for a first-order reaction having a rate constant of 0.040 min^{-1}.

was too fast to be measured. The solid recovered from the neutralized solution after equilibrium had been reached showed again a shoulder at 1068 cm^{-1}. These changes can be due only to the partial isomerization of the 3α (XI*a*, R = Me) to 3β (XI*b*, R = Me) compound. In methanol containing an acid these compounds would be expected to be in equilibrium via the intermediate cyclic (XV) (31) or acyclic carboxonium ion (XVI) (34).

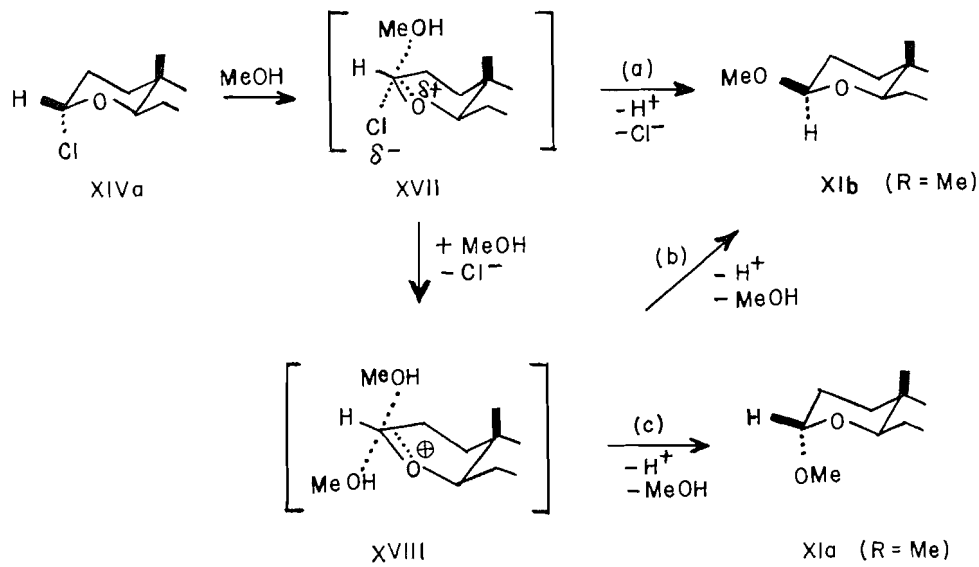
Accepting the calculated value (Table I) for the optical rotation of the 3β isomer, the change in rotation indicates a 24% conversion of the 3α to the 3β isomer.

The rate of this isomerization is considerably faster than that of α-methyl-2-deoxy-D-galactopyranoside (35), which in turn is faster than that of α-methyl-D-galactopyranoside (36). A progressive decrease in rate with the introduction of electron-attracting



groups is expected because of their effect in decreasing the basicity of the acetal oxygen, and hence the concentration of protonated intermediate, and also because of their effect in decreasing the stability, and hence probably the rate of formation, of the intermediate carboxonium ion (37, 38).

In an attempt to obtain a mixture rich in 3β-methoxy-4-oxa-5α-cholestane (XI*b*, R = Me), from which it might be isolated, the chloro ether XIV was solvolyzed in methanol containing methoxide ion or pyridine to neutralize the acid formed. With pyranosyl chlorides derived from methylated or acetylated sugars, such reactions take place with predominant inversion (30, 39, 40), provided that neighboring groups do not participate (41), and provided that steric hindrance to the entering group is not excessive (40). However, in the present instance the 3α-methoxy compound was the chief product, and no 3β-methoxy compound could be isolated, although its presence was indicated by a strong peak at 1068 cm^{-1}. The displacement of chlorine consequently takes place mainly with retention of configuration at the 3-position. The solvolysis of such a chloride in methanol is known to take place by an S_N1 mechanism (39, 40, 42, 43) and probably gives the solvated ion pair XVII (44). This ion pair would be more stable than the ion pairs formed from the chlorides of pyranose sugar derivatives because of the inductive effects of the many oxygen functions of the latter. Consequently, it would be relatively long lived, and not constrained to give an inverted product (XI*b*,



R = Me) by reacting with methanol before the chloride ion had diffused away (route (*a*)). The reaction of the symmetrically solvated carboxonium ion XVIII might seem equally likely to give the 3β (route (*b*)) and 3α product (route (*c*)); the preference for the latter probably arises from the steric effect of the angular methyl group at the 10-position, which generally favors the formation of α-substituted products in rings A and B of steroids (45). Very recently, Rhind-Tutt and Vernon (40) have observed a similar effect in the solvolysis of 2,3,4,6-tetra-*O*-methyl-α-D-mannopyranosyl chloride in methanol, which proceeded with 41–43% retention of configuration, while the corresponding glucose derivative gave almost complete inversion. This was attributed to steric hindrance in the mannopyranosyl chloride by the axial methoxyl group on the carbon adjacent to the reacting center, a far more severe hindrance than that offered by the angular methyl group of the chloro ether XIV. The fact that, even so, 57–59% inversion occurs in solvolysis of the mannopyranosyl chloride may be explained by the inductive effect mentioned above.*

Reaction of 3α-chloro-4-oxa-5α-cholestane with methanol in the presence of silver carbonate again gave mainly the 3α-methoxy compound, although under these conditions glycosyl halides generally give β-methoxy derivatives (46).

The reaction of 4-oxa-5α-cholestan-3α-ol with benzyl alcohol containing 3% hydrogen chloride gave a syrup from which was obtained, by chromatography on basic alumina (activity grade III), two compounds having the analysis and ultraviolet absorption spectra expected for the benzyl ethers (XI*a* and XI*b*, R = CH_2Ph). Their optical rotations (Table I) indicated one to be the 3α isomer (XI*a*, R = CH_2Ph) and the second to be the 3β isomer (XI*b*, R = CH_2Ph).

In a 0.005 *M* solution of hydrogen chloride in tetrahydrofuran – benzyl alcohol (2:3, v/v) both the 3α ($[\alpha]_D$ +91°) and 3β ($[\alpha]_D$ −4°) isomer underwent mutarotation to give a solution having $[\alpha]_D$ +66° (Fig. 3), and hence containing about 73% of the α and

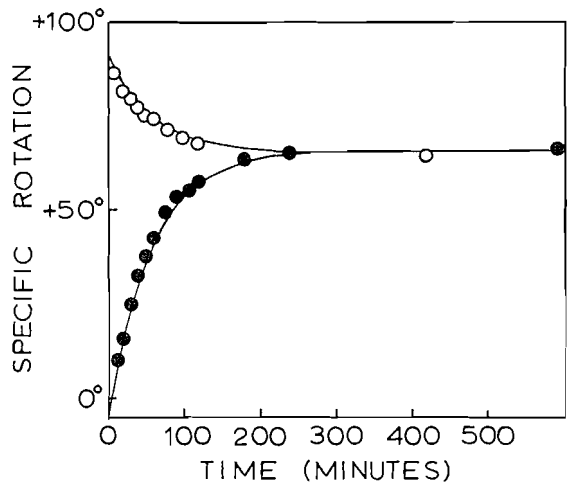


FIG. 3. Change in specific rotation of 3α- (○) and 3β-benzyloxy-4-oxa-5α-cholestane (●) in a 0.0032 *M* solution of hydrogen chloride in absolute tetrahydrofuran – benzyl alcohol (2:3, v/v) at 22.5° ± 0.5°C. Theoretical curves for first-order reactions having a rate constant of 0.0018 min^{-1}.

**Rhind-Tutt and Vernon (40) have claimed that the comparative unreactivity of pyranosyl chlorides derived from hexoses, as compared with simple α-chloro ethers, argues against a half-chair form of the carboxonium ion (31) being generated in solvolysis, with the positive charge localized chiefly on the oxygen. Such an argument ignores the inductive effects operating in derivatives of sugars.*

27% of the β isomer. This interpretation of the rotational changes was confirmed by starting with the pure 3α ether and isolating, after equilibration, 68% of the α and 12% of the β isomer. An attempt was made to catalyze this isomerization also by titanium tetrachloride in carbon tetrachloride, under conditions found successful for some carbohydrate derivatives (29). However, the only crystalline product to be isolated was 4-oxa-5α-cholestan-3α-ol (V*a*), probably formed from 3α-chloro-4-oxa-5α-cholestane when the mixture was treated with water at the end of the reaction.

Reaction of 3α-chloro-4-oxa-5α-cholestane (XIV) with benzyl alcohol in the presence of sodium acetate afforded the 3α and 3β benzyl ethers, isolated in 68% and 9% yields respectively. This is a further example of the solvolysis of the chloro ether proceeding mainly with retention of configuration at the 3-position.

While the benzyl ethers (XI*a* and XI*b*, R = CH_2Ph) would be expected to be fairly stable; in fact, on neutral and basic alumina of activity grade I, decomposition to 4-oxa-5α-cholest-2-ene (X) and 4-oxa-5α-cholestan-3α-ol (V*a*) took place. Consequently, all chromatographic separations were carried out with basic alumina, activity grade III, and even with this adsorbent there was evidence of slight decomposition.

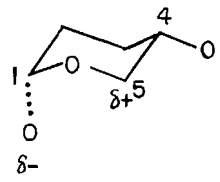
In Table III are summarized the results of the equilibrations of the 3-substituted

TABLE III

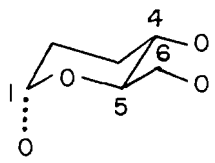
Thermodynamic constants for equilibrations of 3-substituted 4-oxa-5α-cholestanes at 22°±1° C

3-Substituent	Solvent	K	$-\Delta F_{obs}$ (cal/mole)	$-\Delta F_{calc}$ (cal/mole)
OH	Tetrahydrofuran–water (9:1, v/v)	1.2	110	170
OMe	Tetrahydrofuran–methanol (1:1, v/v)	3.1	670	710
OCH_2Ph	Tetrahydrofuran – benzyl alcohol (3:2, v/v)	2.7	590	710

4-oxa-5α-cholestanes expressed as equilibrium constants K (concentration of 3α isomer/concentration of 3β isomer). It is evident that in all cases the axial α isomer is more stable than the equatorial β isomer. This reversal of the usual order of stabilities found in cyclohexane derivatives is undoubtedly due to the ring oxygen, and has been variously explained (31, 32, 33). The most convincing explanation is due to Lemieux and Chu (32, 33), who showed that a consideration of bond lengths, bond angles, and dipoles in the structures XIX and XX indicated an attraction between C-5 and the anomeric oxygen (termed the "anomeric effect") large enough to overcome the steric repulsions from axial hydrogen atoms and hence to favor an axial orientation for the anomeric oxygen atom.



XIX



XX

Also shown in Table III are the free energy differences (ΔF_{obs}) between the 3α and 3β isomers given by the relation $\Delta F = -RT \ln K$. With some isomerizations and conformational changes such free energy differences have been successfully calculated by

additions of terms due to differences in non-bonded interactions in the two isomers (32, 33, 47) or conformers (48). In fact, the repulsion energies giving rise to these non-bonded interaction terms should affect only the enthalpy and not the entropy component of the free energy (49). However, Lemieux and Chu (32, 33) give reasons for believing that the entropy difference is negligible for the anomers of aldopentopyranose tetra-acetates and aldohexopyranose pentaacetates, and this may be true also for the isomeric forms of the ethers (XI, R = Me and CH_2Ph). It is less obviously true for the isomeric forms of the lactol V, as shown by the work of Kabayama, Patterson, and Piche (50) on the entropy differences between α and β forms of pyranose sugars in aqueous solution; however, their interpretation of these differences stresses the importance of the quasi-crystalline structure of water, and it is possible that the differences become less in organic solvents.

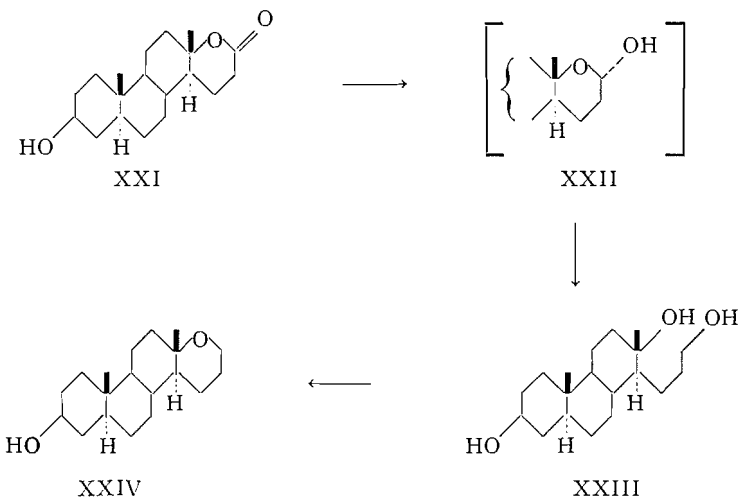
Lemieux and Chu (32, 33) found the free energies of sugar acetates to be additive functions of the following terms (among others): steric repulsion between axial hydrogen and axial oxygen, 180 cal/mole; anomeric effect for pentopyranose derivatives (XIX), 1290 cal/mole; anomeric effect for hexopyranose derivatives (XX), 1510 cal/mole. The first value seemed to be reasonably independent of the nature of the non-aqueous solvent (33), and is adopted here for the methyl and benzyl ethers (XI, R = Me and CH_2Ph), together with a value of 1070 cal/mole for the anomeric effect in these compounds. This latter value is derived on the assumption that the effect is due to the positive charge at C-5 caused by the ring oxygen atom. Addition of another oxygen atom at C-4 should increase the positive charge in the pentose derivatives XIX and give an anomeric effect of $1070+220 = 1290$ cal/mole, while addition of two oxygen atoms, at C-4 and C-6, should give an anomeric effect of $1070+2\times220 = 1510$ cal/mole in the hexose derivatives XX, on the assumption that the inductive effects of the C-4 and C-6 oxygens are the same, and that those of the C-2 and C-3 oxygens may be ignored. The free energy differences between α and β ethers (XI, R = Me and CH_2Ph) calculated using these terms are in reasonable agreement with the values found (Table III).

Chiurdoglu and Masschelein (51) have recently shown that the free energy of the axial hydroxyl – axial hydrogen interaction in cyclohexanol is 150–180 cal/mole, about the same as Lemieux and Chu's value for the axial acetoxyl – axial hydrogen interaction, and independent of the nature of the solvent. However, the most powerful hydrogen-donor solvent investigated by Chiurdoglu and Masschelein was chloroform. There is some evidence that the free energy of the axial hydroxyl – axial hydrogen interaction becomes considerably greater in aqueous or alcoholic solvents (33, 47), and Angyal and McHugh (48) calculated for it a value of 450 cal/mole from studies of the equilibria between cyclitols and their borate complexes in aqueous solution. The free energy difference between α and β forms of the lactol V calculated with this value and a value of 1070 cal/mole for the anomeric effect is again in reasonable agreement with the observed value (Table III), although this agreement may be fortuitous because of neglect of the entropy change.

While the reduction of the lactone IV with 0.25 mole of lithium aluminum hydride gave the lactol V*a*, with 1.2 mole of hydride it gave the diol IX (13), also obtained from the lactol V*a* by hydride reduction. In one experiment in which the lactone was reduced with 0.4 mole of hydride, a syrupy product was isolated, which, by chromatography on alumina, yielded 4-oxa-5α-cholest-2-ene, 4-oxa-5α-cholestan-3α-ol, a solid (product A), and 3,5-seco-A-norcholestan-3,5β-diol (IX). Product A was indicated by analysis to be composed of one molecule of 4-oxa-5α-cholestan-3α-ol and two molecules

of 3,5-seco-A-norcholestan-3,5β-diol, less one molecule of water; in agreement with this formulation, it gave, on treatment with methanolic hydrogen chloride, 3α-methoxy-4-oxa-5α-cholestane and the diol in about the expected proportions. It seems likely that it is a stable complex of one molecule of the structure XII with one molecule of diol, possibly formed when the eluent from the chromatogram containing the lactol V and diol was concentrated. The molecular rotation (+654°) supports this structure, being close to the value (+641°) calculated from the sum of the rotations of two molecules of diol and one molecule of 3α-alkoxy-4-oxa-5α-cholestane (assumed to have the same molecular rotation as the 3α-methoxy derivative). In camphor the complex is dissociated, a Rast determination of molecular weight indicating about half the theoretical value.

Attempts were made to prepare the lactol XXII, in which the steric repulsion of the angular methyl group would be expected to outweigh the anomeric effect, and which in consequence should have an equatorial hydroxyl group. However, reduction of the lactone XXI (52) with varying quantities of lithium aluminum hydride gave only starting material or the completely reduced diol XXIII. The latter was cyclized to 17α-oxa-D-homo-5α-androstan-3β-ol (XXIV) with benzenesulphonyl chloride in lutidine (cf. ref. 13).



EXPERIMENTAL

Where concentrations are not given, specific rotations are averages of 2–3 determinations using concentrations of 1.5–2.3 g/100 ml. Intensities of infrared absorption are indicated in parentheses after the frequencies either by the semiquantitative notation used previously (13), or as molecular extinction coefficients. Chromatography was on Woelm alumina; Brockmann activity grades shown.

4-Oxa-5α-cholestan-3α-ol (Va)

Lithium aluminum hydride (215 mg, 5.41 mmoles) in anhydrous, peroxide-free tetrahydrofuran (70 ml) was added under nitrogen to a stirred solution of 4-oxa-5α-cholestan-3-one (7.50 g, 19.33 mmoles) in the same solvent (75 ml), over a period of 10 minutes. During the addition, the reaction flask was cooled in an ice–salt bath; it was then allowed to warm up to room temperature while the stirring was continued for 1 hour. The reaction mixture was poured into cold 1 *N* sulphuric acid (150 ml). The white solid which precipitated was removed by filtration, washed with water, and dried. It was

taken up in anhydrous ethyl acetate and filtered through infusorial earth. Addition of petroleum ether to the filtrate resulted in the separation of colorless crystals (6.32 g, 84% yield), m.p. 184°–186° C. The melting point was raised, by recrystallization, to 188°–190° C (bath preheated to 180°, temperature rise 2° C per minute), but was dependent on the rate of heating. $[\alpha]_D^{25}$ +64° (in chloroform); $[\alpha]_D^{26}$ +88° (in tetrahydrofuran); $\nu_{max}^{CCl_4}$ in cm^{-1}: 3620 (55), 3385 (60), 2928 (495), 2853 (290), 1469 (152), 1449 (135), 1385 (115), 1368 (110), 1083 (285), 1045 (220), 947 (118). Calc. for $C_{26}H_{46}O_2$: C, 79.94; H, 11.87%. Found: C, 79.95; H, 12.02%.

3ξ-2′,4′-Dinitrophenylhydrazo-4-oxa-5α-cholestane (VIII)

A solution of 4-oxa-5α-cholestan-3α-ol (78 mg) in 96% ethanol (6 ml) was added to a solution of 2,4-dinitrophenylhydrazine (39.6 mg) in 96% ethanol (2 ml) containing concentrated hydrochloric acid (0.8 ml). The mixture was boiled for 10 minutes. When the solution was cooled, yellow crystals (71 mg) separated, which after two recrystallizations from ethanol–benzene (9:1, v/v) melted at 154.5°–155.5° C. $[\alpha]_D^{25}$ +3.2° (*c*, 2.36 in chloroform); $[\alpha]_D^{23}$ +7.6° (*c*, 1.58 in pyridine–methanol (1:1, v/v); $\lambda\lambda_{max}$ 262, 347 mμ, $\epsilon\epsilon_{max}$ 11,900, 22,800 (in chloroform); $\lambda\lambda_{max}$ 248–255 (flat peak), 328 mμ (shoulder at 367 mμ), $\epsilon\epsilon_{max}$ 10,900, 18,500 (in cyclohexane); $\nu_{max}^{CCl_4}$ in cm^{-1}: 3350 (95), 3092 (39), 2930 (370), 2850 (200), 1620 (510), 1470 (140), 1430 (195), 1338 (610), 1313 (340), 1280 (160), 1137 (180), 1072 (235), 1062 (220), 1050 (187), 926 (130). Calc. for $C_{32}H_{50}O_5N_4$: C, 67.34; H, 8.83; N, 9.82%. Found: C, 67.45; H, 8.75; N, 10.04%.

3,5-Seco-A-norcholestan-3,5β-diol (IX)

A solution of 4-oxa-5α-cholestan-3α-ol (200 mg) in tetrahydrofuran (5 ml) was added dropwise, with stirring, under nitrogen, to a solution of lithium aluminum hydride (13 mg) in tetrahydrofuran (3 ml). The mixture was stirred a further 1.5 hours, and then the excess hydride decomposed by slowly adding aqueous tetrahydrofuran. The reaction mixture was added to ice-cold 1 *N* sulphuric acid solution. An oil separated which soon solidified (176 mg, 86%), and was identified as 3,5-seco-A-norcholestan-3,5β-diol (IX) (13) by melting point, mixed melting point, and infrared spectrum.

Reduction Product A

4-Oxa–5α-cholestan-3-one (4.33 g) in diethyl ether (75 ml) was reduced with a slurry of lithium aluminum hydride (175 mg) in diethyl ether (30 ml), following the procedure described above for 4-oxa-5α-cholestan-3α-ol. Instead of a white solid, a syrup was obtained, which was chromatographed on alumina (Merck). Elution with the solvents indicated gave the following fractions: (1) a syrup (2.22 g), shown by infrared analysis to contain no hydroxyl group (ligroin); (2) 4-oxa-5α-cholest-2-ene (23 mg), identified by infrared spectrum (ligroin); (3) 4-oxa-5α-cholestan-3α-ol, isolated after several recrystallizations from ethyl acetate as needles (280 mg), m.p. 184–186°, and identified by mixed melting point and infrared spectrum (benzene–ether (1:1, v/v)); (4) product A (ether); (5) 3,5-seco-A-norcholestan-3,5β-diol, isolated after several recrystallizations from ethyl acetate as needles (65 mg), m.p. 133–134°, and identified by mixed melting point and infrared spectrum (ether–ethanol (1:1, v/v)).

Product A crystallized from anhydrous ethyl acetate as colorless needles (309 mg), m.p. 139.5°–140.5° C. $[\alpha]_D^{26}$ +56.5 (*c*, 2.66 in chloroform); $[\alpha]_D^{27}$ +54.9 (*c*, 1.98 in tetrahydrofuran); $\nu_{max}^{CCl_4}$ in cm^{-1}: 3580 (m), 3470 (m), 2960 (s), 2885 (s), 1473 (s), 1452 (s), 1387 (s), 1371 (m), 1347 (w), 1127 (m), 1036 (s), 933 (w). Calc. for $C_{78}H_{140}O_5$: C, 80.90; H, 12.18%; molecular weight, 1158. Found: C, 80.75; H, 12.17%; molecular weight (Rast, camphor), 590.

Reaction of Product A with Methanolic Hydrogen Chloride

Acetyl chloride (0.6 ml) was added to absolute methanol (15 ml) to give an approximately 3% solution of hydrogen chloride. Product A (150 mg) was dissolved in this solution, and the mixture refluxed for 1 hour and then concentrated by distillation to 7 ml. The solution, on cooling, deposited plates (44 mg), m.p. 86°–88° C, raised to 98°–99.5° by recrystallization from methanol, which were identified as 3α-methoxy-4-oxa-5α-cholestane (see below) by mixed melting point, specific rotation, and infrared spectrum.

The mother liquors from the first crystallization were taken to dryness *in vacuo*, and the solid thus obtained was washed with water and dried. The crude solid (97 mg, m.p. 115°–121° C), after recrystallization from ligroin, melted at 134°–134.5° C, and was identified as 3,5-seco-A-norcholestan-3,5β-diol (IX) (13) by mixed melting point and infrared spectrum.

4-Oxa-5α-cholest-2-ene (X)

(*a*) A solution of 4-oxa-5α-cholestan-3α-ol (900 mg) and phosphorus oxychloride (2.3 ml) in pyridine (7 ml) was refluxed for 1 hour. The cooled solution was diluted with water and extracted with ether. The ether solution was washed with aqueous bicarbonate, dried (sodium sulphate), concentrated, and diluted with methanol (10 ml). On standing, the solution deposited colorless prisms of 4-oxa-5α-cholest-2-ene (686 mg, 80% yield), m.p. 68–70° C, raised by recrystallization from ethanol to 70°–72° C. $[\alpha]_D^{25}$ +88.8° (chloroform); ϵ_{210} 5500 (in cyclohexane, end absorption only); $\nu_{max}^{CCl_4}$ in cm^{-1}: 3050 (40), 2930 (510), 1647 (133), 1470 (150), 1448 (120), 1386 (110), 1370 (79), 1243 (95), 1204 (82), 1080 (420), 945 (82), 914 (40). Calc. for $C_{26}H_{44}O$: C, 83.82; H, 11.91%. Found: C, 83.83; H, 12.00%.

(*b*) A solution of 4-oxa-5α-cholestan-3α-ol (300 mg) and fused sodium acetate (150 mg) in acetic anhydride (2.0 ml) was refluxed for 5 hours, and then poured into ice water. The brown oil separating slowly solidified, and was purified by several crystallizations from methanol, giving white plates, m.p. 67–68°, and shown by mixed melting point and infrared spectrum to be identical with 4-oxa-5α-cholest-2-ene obtained above.

4-Oxa-5α-cholestane (XIII)

4-Oxa-5α-cholest-2-ene (510 mg) in glacial acetic acid (20 ml) was hydrogenated over platinum oxide (140 mg). After 3 hours, 95% of the theoretical volume of hydrogen had been absorbed. The catalyst was removed by filtration, the solution diluted with ether and washed with water, aqueous bicarbonate, and water, and dried (sodium sulphate). Evaporation of the ether left a white solid (0.48 g), which after one crystallization from methanol had m.p. 89°–90° C, undepressed by admixture with 4-oxa-5α-cholestane prepared from 3,5-seco-A-norcholestan-3,5β-diol (13), and having the same infrared spectrum. Fieser *et al.* (18) have reported a melting point of 93°–94° C for this compound prepared by a different route.

3-Acetoxy-4-oxa-5α-cholestane (XI, R = MeCO)

4-Oxa-5α-cholestan-3α-ol (204 mg) was dissolved in pyridine (3 ml) with gentle warming, and acetic anhydride (0.3 ml) was added to the cooled solution. After 2 days, the solution was poured into ice water to give a solid which was washed free from acid with water and dried. The crude product (203 mg), m.p. 90°–101° C, was probably a mixture of the isomeric 3-acetoxy compounds (XI*a* and XI*b*, R = MeCO); $\nu_{max}^{CCl_4}$ in cm^{-1}: 2940 (s), 2860 (s), 1755 (s), 1473 (m), 1463 (sh), 1450 (m), 1385 (m), 1374 (m), 1222 (s), 1158 (m),

1142 (m), 1046 (s), 939 (m), 891 (m). Recrystallization from methanol afforded a mixture (164 mg), m.p. 65–80° C, as shown by chromatography on neutral alumina (5 g, grade III). The following fractions were eluted: (*a*) with hexane (30 ml), 3α-methoxy-4-oxa-5α-cholestane (72 mg), m.p. and mixed m.p. 93°–94° and 94°–95°; (*b*) with hexane–benzene, 1:1 (30 ml), a fraction (62 mg), m.p. 74°–85° C, having the same infrared spectrum as the crude acetate described above; (*c*) with ether (50 ml), 4-oxa-5α-cholestan-3α-ol (20 mg) identified by infrared spectrum. Attempts to recrystallize the acetate from anhydrous ether, tetrahydrofuran, benzene, or petroleum ether failed.

3α-Chloro-4-oxa-5α-cholestane (XIV)

A solution of 4-oxa-5α-cholest-2-ene (140 mg) in anhydrous ether (10 ml) saturated with hydrogen chloride was kept under nitrogen for 2 hours. Evaporation of the ether by a jet of dry nitrogen left crystals which sintered at 95° C, m.p. 104°–107° C. $[\alpha]_D^{20}$ +156° (*c*, 1.56 in absolute chloroform); $\nu_{max}^{CCl_4}$ in cm^{-1}: 2925 (585), 2855 (330), 1469 (150), 1448 (135), 1384 (110), 1367 (92), 1330 (47), 1155 (272), 1130 (292), 1119 (sh, 197), 1033 (258), 928 (82), 908 (56). Calc. for $C_{26}H_{45}OCl$: C, 76.34; H, 11.09%. Found: C, 76.16; H, 10.89%. Quantitative infrared measurements showed that this material, in different preparations, contained 3–6% of starting material; however, all attempts at recrystallization led to a lowering of the melting point.

3α-Methoxy-4-oxa-5α-cholestane (XI, R = Me)

(a) From 4-Oxa-5α-cholestan-3α-ol

Acetyl chloride (1.2 ml) was added to absolute methanol (30 ml) to give an approximately 3% solution of hydrogen chloride. A solution of 4-oxa-5α-cholestan-3α-ol (333 mg) in this solvent was refluxed for 30 minutes. When concentrated to 10 ml, the solution deposited glistening white plates (302 mg), m.p. 91–93° C. These were washed with water to remove traces of acid, dried, and recrystallized from methanol, giving crystals melting at 98°–99.5° C. $[\alpha]_D^{26}$ +109° (*c*, 1.43 in chloroform); $[\alpha]_D^{22}$ +113.5° (*c*, 1.49 in methanol–tetrahydrofuran (1:1, v/v)); $\nu_{max}^{CCl_4}$ in cm^{-1}: 2930 (580), 2860 (340), 1470 (170), 1457 (138), 1448 (148), 1382 (124), 1368 (134), 1132 (360), 1058 (360), 1039 (412), 934 (105), 893 (178). Calc. for $C_{27}H_{48}O_2$: C, 80.20; H, 11.95; OMe, 7.68%. Found: C, 80.25; H, 12.00; OMe, 7.92%.

Fieser *et al.* (18) have recently reported preparing, by a different route, a compound, m.p. 89°–92° C, having the structure of our compound but undefined stereochemistry; it is probably identical with our compound.

(b) From 3α-Chloro-4-oxa-5α-cholestane

Sodium (60 mg) was dissolved in absolute methanol (12 ml), followed by 3α-chloro-4-oxa-5α-cholestane (153 mg), dissolution of the latter requiring that the solution be warmed. The solution was refluxed for 40 minutes, and the solvent then removed under reduced pressure. The residue was treated with water (12 ml) and ether (12 ml), and the ether layer was washed, dried, and diluted with methanol (8 ml). On standing for 2 days, with partial evaporation of the ether, the solution deposited long plates of 3α-methoxy-4-oxa-5α-cholestane (110 mg), m.p. 98.5–99.5, undepressed by admixture with authentic material. Further concentration of the solution gave a brownish semisolid mass (48 mg), which in carbon tetrachloride solution had an infrared spectrum similar to that of pure 3α-methoxy-4-oxa-5α-cholestane, with the addition of a peak at 1068 cm^{-1} and a shoulder at 1126 cm^{-1}. This material resisted all attempts at purification.

(c) From 3α-Chloro-4-oxa-5α-cholestane in the Presence of Silver Carbonate

To a suspension of powdered calcium chloride (500 mg) and freshly prepared silver carbonate (53) (230 mg) in absolute chloroform (15 ml) was added a solution of 3α-chloro-4-oxa-5α-cholestane (287 mg) in absolute chloroform (15 ml), followed by the slow addition, with vigorous stirring, of methanol (0.12 ml) in absolute chloroform (3 ml). The mixture was stirred for 30 minutes at room temperature and 30 minutes at 50° C. Then water was added, the mixture was filtered through infusorial earth, and the organic layer was separated, washed with water, and dried. Concentration of this solution afforded a syrup which in contact with a little methanol solidified. The solid, crystallized from ether–methanol, gave a first crop (226 mg), m.p. 86°–94° C, $[\alpha]_D^{20}$ +110° (*c*, 1.15 in chloroform); second crop (15 mg), m.p. 79°–85° C, $[\alpha]_D^{20}$ +98.5° (*c*, 1.16 in chloroform); third crop (7 mg), m.p. 62°–68° C; and a brownish semisolid residue (28 mg). Infrared examination showed the first crop to be 3α-methoxy-4-oxa-5α-cholestane contaminated with a small amount of 4-oxa-5α-cholest-2-ene, and the third crop to have the spectrum of 3α-methoxy-4-oxa-5α-cholestane, with the addition of a weak shoulder at 1068 cm^{-1}.

Hydrolysis of 3α-Methoxy-4-oxa-5α-cholestane

A solution of 3α-methoxy-4-oxa-5α-cholestane (150 mg) in tetrahydrofuran (10 ml) – 15% aqueous hydrochloric acid (3.5 ml) was refluxed for 10 minutes, then poured into ice water. A solid was removed by filtration, washed with water, and dried; this crude product (125 mg), m.p. 154°–158° C, was recrystallized from methanol and identified as 4-oxa-5α-cholestan-3α-ol by melting point, mixed melting point, and infrared spectrum.

3α- and 3β-Benzyloxy-4-oxa-5α-cholestane (XIa and XIb, R = CH_2Ph)

(a) From 4-Oxa-5α-cholestan-3α-ol

Acetyl chloride (0.4 ml) was added to benzyl alcohol (10 ml), then 4-oxa-5α-cholestan-3α-ol (100 mg) was dissolved in this solution. The solution, after 24 hours at room temperature, was concentrated at 0.5 mm; removal of the dibenzyl ether formed in this reaction required that the flask be heated to 100°. The residual syrup, which partially crystallized, was chromatographed on basic alumina (25 g, grade III), and the fractions eluted from the column were examined by infrared spectroscopy. The fractions fell into the following groups: (*a*) with ligroin (b.p. 65–75°; 60 ml), 4-oxa-5α-cholest-2-ene, obtained as crystals (10 mg), m.p. 63–66°, having the characteristic infrared spectrum; (*b*) with more ligroin (110 ml), a syrup (65 mg) identified as 3α-benzyloxy-4-oxa-5α-cholestane (see below); (*c*) with ligroin–benzene (4:1, v/v) (30 ml), a syrup (25 mg) shown by infrared spectroscopy to be a slightly impure mixture of 3α- and 3β-benzyloxy-4-oxa-5α-cholestane; (*d*) with more ligroin–benzene (4:1, v/v) (50 ml), impure crystals of 3β-benzyloxy-4-oxa-5α-cholestane.

Fractions (*b*) were dissolved in hot methanol and filtered through charcoal–celite. The syrup (62 mg) which separated on being cooled was dried at 100° C at 0.5 mm. The syrup from some runs crystallized to a solid, m.p. 42–51° C, when cooled to 15° and rubbed; the syrup from other runs could not be crystallized, but was indistinguishable with respect to specific rotation and infrared spectrum. Attempts to recrystallize the solid at low temperatures with seeding afforded always a syrup without change in specific rotation or infrared spectrum: $[\alpha]_D^{26}$ +99° (*c*, 2.23 in chloroform); $[\alpha]_D^{22}$ +91° (*c*, 1.46 in 3:2 benzyl alcohol – tetrahydrofuran, v/v); $\lambda\lambda_{max}^{EtOH}$ 248, 252.5, 258, 264, 268 mμ; $\epsilon\epsilon_{max}$ 165, 234, 272, 217, 148; $\nu_{max}^{CCl_4}$ in cm^{-1}: 3060 (40), 3020 (55), 2920 (540), 2855 (355),

1470 (175), 1457 (175), 1382 (128), 1342 (88), 1164 (100), 1130 (250), 1052 (215), 1037 (380), 1027 (360), 945 (110), 935 (125), 889 (90), 696 (81). Calc. for $C_{33}H_{52}O_2$: C, 82.45; H, 10.91%. Found: C, 82.37; H, 10.84%.

Chromatographic fractions (*d*) were dissolved in ligroin and treated with charcoal. Evaporation of the solvent afforded well-formed prisms, which were washed on the filter with ligroin (cooled to −10° C) and then recrystallized from ligroin or methanol to give pure 3β-benzyloxy-4-oxa-5α-cholestane (12 mg), melting at 131°–132° C. $[\alpha]_D^{22}$ −22° (*c*, 2.02 in chloroform; $[\alpha]_D^{22}$ −3.8 (*c*, 1.46 in tetrahydrofuran – benzyl alcohol (2:3, v/v)); $\lambda\lambda_{max}$ 248, 252.5, 258.5, 264.5, 268 mμ; $\epsilon\epsilon_{max}$ 171, 218, 252, 210, 151 (in cyclohexane); $\nu_{max}^{CCl_4}$ in cm^{-1}: 3060 (40), 3028 (57), 2930 (575), 2850 (340), 1497 (40), 1469 (174), 1457 (180), 1450 (155), 1387 (134), 1370 (126), 1344 (102), 1166 (224), 1141 (210), 1120 (215), 1094 (190), 1070 (510), 1047 (335), 935 (122), 902 (66), 695 (88). Calc. for $C_{33}H_{52}O_2$: C, 82.45; H, 10.91%. Found: C, 82.38, H, 10.98%.

(b) From 3α-Chloro-4-oxa-5α-cholestane

A suspension of 3α-chloro-4-oxa-5α-cholestane (265 mg) and finely powdered anhydrous sodium acetate (150 mg) in anhydrous benzyl alcohol (5 ml) was heated on a steam bath for 1 hour. The solvent was then removed at reduced pressure, the residue dissolved in ether and water, and the ether layer dried and then taken to dryness. The residue was dissolved in hexane and chromatographed on basic alumina (grade III), as described above, to give slightly impure 3α-benzyloxy-4-oxa-5α-cholestane (239 mg, 76%) and 3β-benzyloxy-4-oxa-5α-cholestane (70 mg, 22%), identified by melting point and infrared spectra.

Isomerization of 3α-Benzyloxy-4-oxa-5α-cholestane (XIa, R = CH_2Ph)

Acetyl chloride (4 drops) was added to benzyl alcohol (0.4 ml) to generate hydrogen chloride, and the solution was diluted with anhydrous ether (3 ml). 3α-Benzyloxy-4-oxa-5α-cholestane (110 mg) was dissolved in this solution. After 4 hours at room temperature, the solvents were removed at reduced pressure (0.5 mm at 80° C) and the residual syrup was chromatographed on basic alumina (grade III) as described above to give starting material (71 mg) and 3β-benzyloxy-4-oxa-5α-cholestane (13 mg), identified by melting point, mixed melting point, and infrared spectrum.

For preparative purposes, the yield of β isomer was increased by allowing a syrupy mixture of isomers containing a trace of acid to stand for several weeks, after which time a certain amount of the β isomer had crystallized out. The whole mixture was then neutralized and chromatographed to give a 25% yield of β isomer.

Action of Titanium Tetrachloride on 3α-Benzyloxy-4-oxa-5α-cholestane

Titanium tetrachloride was purified by standard vacuum-line techniques, and an estimated 100–150 mg was distilled into a frozen solution of 3α-benzyloxy-4-oxa-5α-cholestane (120 mg) in carbon tetrachloride (5 ml). The mixture was allowed to melt under vacuum, refluxed for 5 hours with rigid exclusion of moisture, and then poured into ice water. More carbon tetrachloride was added and the organic layer was separated, washed with bicarbonate and water, and dried over magnesium sulphate. Removal of the solvent at reduced pressure left a yellowish solid (125 mg) which was treated with cold ligroin. The undissolved fraction (35 mg) proved by melting point and mixed melting point to be slightly impure 4-oxa-5α-cholestan-3α-ol. The ligroin solution, on chromatography on basic alumina (grade III), gave only glassy, unidentifiable materials, followed by a small quantity of impure 4-oxa-5α-cholestan-3α-ol (18 mg).

*17α-Oxa-*D*-homo-5α-androstan-3β-ol (XXIV) (40)*

13,17-Seco-5α-androstan-3β,13α-17-triol (54) (510 mg) was treated with benzenesulphonyl chloride in lutidine under conditions already described (13). The product, isolated in the usual way, was an oil (427 mg) which was chromatographed on alumina (activity II–III). Elution with ether–acetone, 9:1, gave 17α-oxa-D-homo-5α-androstan-3β-ol (114 mg), m.p. 171°–174° C, raised by one crystallization from methanol to 174°–175° C. $\nu_{max}^{CCl_4}$ in cm^{-1}: 3635 (m), 2940 (s), 2860 (sh), 2708 (w), 1462 (sh), 1451 (s), 1440 (sh), 1375 (s), 1282 (m), 1212 (w), 1155 (m), 1132 (sh), 1120 (s), 1080 (s), 1075 (sh), 1064 (sh), 1044 (s), 1032 (s), 973 (w), 955 (w), 945 (w), 935 (m), 923 (w), 895 (w), 877 (w), 848 (w), 840 (w). Calc. for $C_{19}H_{32}O_2$: C, 78.02; H, 11.03%. Found: C, 77.84; H, 10.79%.

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