19-Nor and Aromatic Steroids. Part 1. The Cleavage of 3-Oxygenated-2β,19-ethers in the Cholestane Series

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Acetolysis of 2β,19-epoxy-5α-cholestan-3-one, catalysed by boron trifluoride, gave mainly 2α,19-diacetoxy-5α-cholestan-3-one which was partially hydrolysed with methanolic sodium hydroxide at 20° for 10 min. to 19-acetoxy-2α-hydroxy-5α-cholestan-3-one which resisted dehydration. Acetolysis of 2β,19-epoxycholest-4-en-3-one with acetic anhydride and boron trifluoride was complicated by enolacetylation of the 3-carbonyl group and subsequent addition of acetic anhydride to the Δ-5 double bond; however, 4α-bromo-2β,19-epoxy-5α-cholestan-3-one was slowly cleaved with acetic anhydride and boron trifluoride to give only 2α,19-diacetoxy-4α-bromo-5α-cholestan-3-one which was readily converted by treatment with calcium carbonate in dimethylacetamide into 2α,19-diacetoxycholest-4-en-3-one; the latter compound was hydrolysed with methanolic hydrochloric acid to give 3-hydroxy-19-norcholesta-1,3,5(10)-triene.

3α-Acetoxy-2β,19-epoxy-5α-cholestane was cleaved with boron trifluoride in acetic anhydride, probably involving an intermediate 2α,3α-acetoxonium ion, to give mainly 3α,19-diacetoxy-5α-cholestan-2α-ol which was readily dehydrated to 3α,19-diacetoxy-5α-cholest-1-ene; this was then hydrolysed, oxidised, and decarboxylated to give 19-nor-5α-cholest-1(10)-en-3-one.

SINCE the discovery that the removal of the angular methyl group at C-10 often results in enhanced activity,[1] interest has increased in methods of synthesis of 19-nor analogues of steroid hormones. Successful partial syntheses have been described *via* the Birch reduction [2,3] and catalytic hydrogenation [4] of aromatic steroids and by the functionalisation and removal of the C-10 methyl group by interaction with a 6β-hydroxy-substituent.[3,5] Here we describe the synthesis of 19-nor-5α-cholest-1(10)-en-3-one and 3-hydroxy-19-norcholesta-1,3,5(10)-triene by cleavage of 2β,19-ethers, thus providing a route to 19-nor and A-ring aromatic steroids without involving the B-ring.

3α-Acetoxy-2β,19-epoxy-5α-cholestane (Ia), prepared by the method of Kwok and Wolff,[6] was hydrolysed and oxidised to the ketone (IIa) which was converted into the bromo-ketone (IIb) [7] by hydrogen bromide-catalysed bromination in acetic acid. Although Wolff and his co-workers [7] were unable to eliminate hydrogen bromide

N.m.r. and i.r. spectra

Compound	C=O $\nu_{max.}$ (cm.$^{-1}$)	19-CH τ_A	19-CH τ_B	19-CH τ_{AB}	2H τ	2H J	1H	4H (J)	Acetate	3H τ	3H w_H	Acyl.	Misc.
(Ib)		6·33	6·23	9·5	5·79	5, 5			7·99	5·19	7		
(IIa)	1749	6·10	5·97	8·5	5·88	7·5	7·47						
(IIb)	1749	5·95	6·12	9·0	5·30	10		5·74(7)					
(III)	1693, 1608	6·54	5·96	7·3	5·74	1·8, 6	7·67	4·26					8·18 (1αH)
(IVa)	1761	6·29	6·21	8·2	5·10	6			7·96				
(Vb)	1751, 1739	5·61	5·52	12·0	4·61	7, 13			7·86, 7·84				
(VIIIb)	1789, 1745	5·96	5·80	10·0			7·52						6·30 (OMe)
(XIb)	1715, 1695 1615				3·82	10·5							0·01 (C*H*O)
(XIIa)	1680, 1655	6·00	5·92	11·5	5·26	*	3·0 *	4·03					
(XIIb)	1746, 1695 1622	5·75	5·27	12	4·22	6, 14		4·07	7·92, 7·82				
(XIV)	1760							4·31	7·87				4·61 (6H)
(XV)	1720, 1680 1610							3·93				7·80	6·73, w_H 9 c./sec. (6H)
(XVII)	1747	5·69		A_2	4·15			4·15	7·92, 7·95				4·15 (6H)
(XVIII)	1747, 1713	5·69			4·55			3·84	7·92	7·83			7·5 (6αH)
(XIX)	1745, 1713				5·45			3·82	7·92	7·83			7·3 (6αH)
(XX)	1745	5·65		A_2	5·45			4·15	7·92, 7·95				4·15 (6H)
(XXI)	1748	5·51		A_2	5·30	7, 12		5·08(12)	7·83, 7·86				
(XXIIa)					3·40	2, 8	3·05(8)	3·22(2)					7·21 ($6CH_2$, 9H)
(XXIIIa)	1740	5·88	5·68	12	6·15	*			7·88, 7·92	4·82	6		
(XXIIIb)	1747	5·84	5·70	12	5·09	*			7·91, 8·00	4·73	7		
(XXIIIc)	1745	5·83		A_2					7·89, 7·93	5·03	7		7·57 (*p*-Me)
(XXIVa)		6·32	6·19	11·5	3·95	*	3·95			5·87	9		
(XXIVb)	1733	5·86	5·68	12	4·22	*	3·88(10)		7·99, 7·94	4·8	*		
(XXVII)	1725				7·11	A_2	4·68	7·35 *					

* See Experimental for more details.

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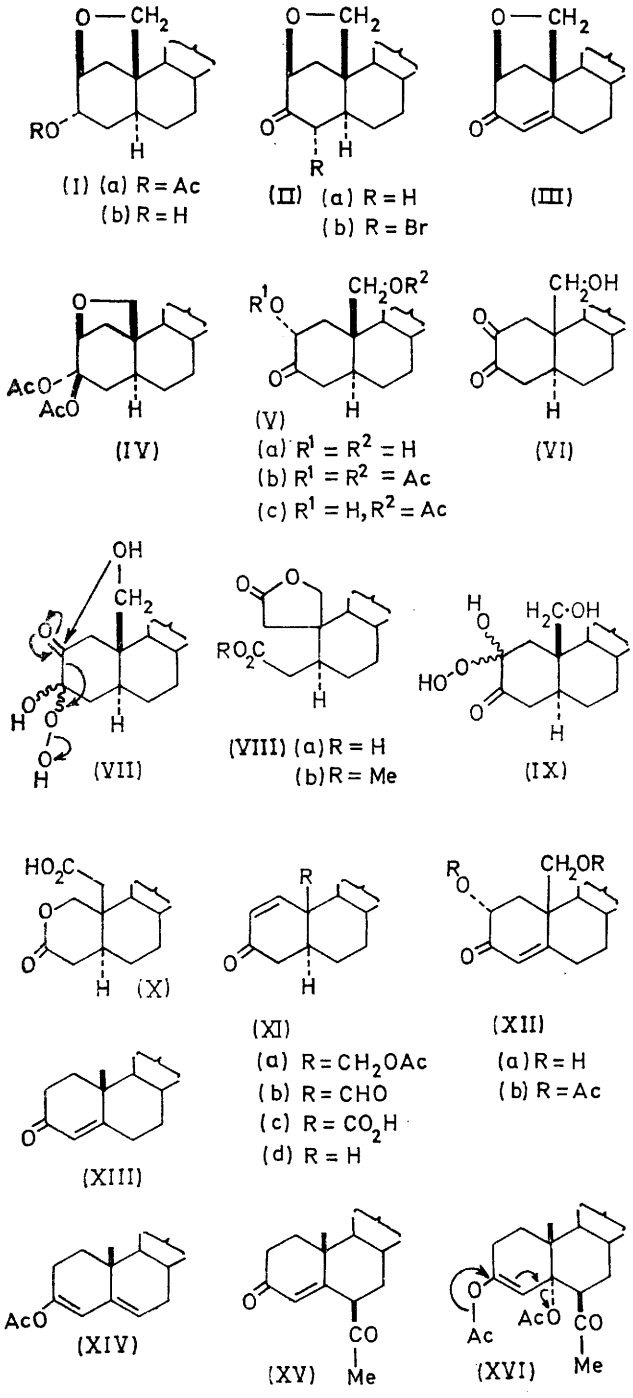
from this ketone (IIb) with a variety of reagents, treatment with calcium carbonate in dimethylacetamide gave



a good yield of the 4-en-3-one (III). Boron trifluoride-catalysed [8] acetolysis of the ethers (Ia), (IIa), (IIb), and (III) was examined since this reagent was found most successful in the cleavage of 2β,19-ethers without a 3-carbonyl group.[9] The ether (IIa) with boron trifluoride in acetic anhydride for 30 min., followed by preparative t.l.c. gave a low yield of a compound tentatively identified as the 3,3-diacetate * (IV) and mainly the 2α,19-diacetate (Vb). The i.r. absorption maxima in the i.r. spectrum of the gem diacetate (IV) occurred at 1761 cm.$^{-1}$. The n.m.r. spectrum of (IV) (Table) showed a signal equivalent to six protons at τ 7·96 for the two acetoxy-groups whilst the 2α-proton, coupled only to one of the protons at C-1 (J 6 c./sec.) appeared at τ 5·10, deshielded by the two acetoxy-groups at C-3. The ease of acid hydrolysis of the gem diacetate (IV) to the ether (IIa) supports the assignment.

The diacetate (Vb) would be expected by the mechanism proposed by Narayanan and Iyer.[8] Boron trifluoride complexing of the 2β,19-epoxide (IIa) followed by S_N2 attack at C-2 would give the diacetate (Vb). Due to steric hindrance no similar nucleophilic attack at C-19 occurs.[9]

Hydrolysis of the diacetate (Vb) with methanolic potassium hydroxide or with sodium carbonate solution at 20° overnight gave the lactone acid (VIIIa) which on treatment with diazomethane gave the methyl ester (VIIIb) with $\nu_{max.}$ 1789 (characteristic of a spirolactone [10]) and 1745 cm.$^{-1}$. It has been postulated [11] with 2α-hydroxy-5α-cholestan-3-one as a model, that autoxidation would be expected to occur under these conditions to give firstly the 2,3-dione (VI) and subsequently the hydroperoxide (VII). Intramolecular attack by the 19-hydroxy-group in preference to intermolecular attack by methanol,[11] would give the lactone (VIIIa). No sign of the alternative lactone (X) formed by way of the hydroperoxide (IX) was observed. When the hydrolysis was carried out with methanolic sodium hydroxide at 20° for 10 min., the optimum conditions found for the hydrolysis of 2α-acetoxy-5α-cholestan-3-one,[11] the major product was 19-acetoxy-2α-hydroxy-5α-cholestan-3-one (Vc).

Elimination of the 2α-hydroxy-group from the α-ketol (Vc) would give the 1-en-3-one (XIa) which could then be hydrolysed and decarboxylated to give 19-nor-5α-cholest-1-en-3-one. The elimination of the 2α-hydroxy-group in 2α-hydroxy-5α-cholestan-3-one [11-13] was investigated as a model for the ketol (Vc). No reaction occurred when 2α-hydroxy-5α-cholestan-3-one was treated with thionyl chloride in pyridine at 0° [14] whilst treatment with thionyl chloride at 20°, with phosphorus pentabromide,[15] or with phosphorus oxychloride in

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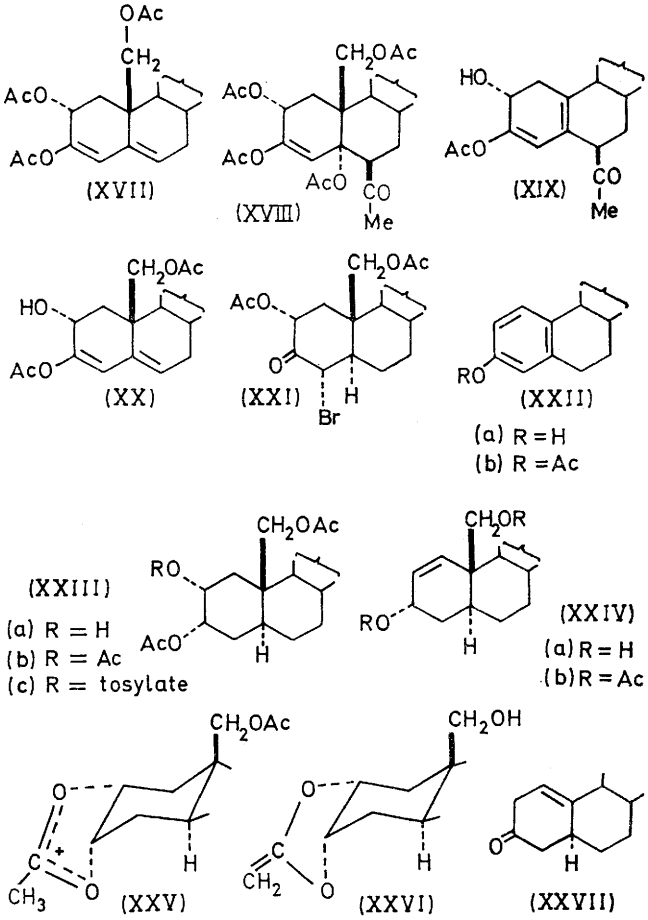
pyridine [16] gave only 5α-cholestan-2,3-dione.[11,17] A low yield of 5α-cholest-1-en-3-one [18] was obtained when the compound was heated with sulphuric acid in toluene whilst use of naphthalene β-sulphonic acid [19] gave a low yield of cholest-4-en-3-one. As a result of these unsuccessful reactions, the dehydration of the ketol (Vc) was not investigated.

The ether (III) was cleaved with boron trifluoride in acetic anhydride to give, after preparative t.l.c., a yellow oil ($\nu_{max.}$ 1747, 1713 cm.$^{-1}$) which was homogeneous on t.l.c. The n.m.r. spectrum, however, indicated it to be a mixture of compounds since it contained signals for at least three acetyl groups, τ 7·97, 7·93, 7·84 and many low-field protons of varying intensity. Since t.l.c. and the n.m.r. spectrum showed that 2α,19-diacetoxycholest-4-en-3-one (XIIb) was not one of the products, it was considered that ether cleavage was being complicated by enolisation of the 4-en-3-one system and a model compound was examined. Cholest-4-en-3-one (XIII) with boron trifluoride and acetic anhydride for 30 min. followed by the addition of ice gave 3-acetoxycholesta-3,5-diene [20] (XIV) after induced crystallisation. When the reaction mixture was allowed to stand several hours after the addition of ice, the product was mainly the diketone (XV). This diketone (XV) has previously been prepared by treatment of the enol acetate of cholest-4-en-3-one (XIII) with the same reagent.[21] The addition of acetic anhydride to 19-acetoxy-5α-cholest-2-ene under the same conditions has also been observed.[9]

By analogy with the results above, the products from the cleavage of the ether (III) with boron trifluoride in acetic anhydride appear to be a mixture of the enol acetate (XVII) and the acetic anhydride addition product (XVIII) which would account for complex signals for the acetoxy and acetyl groups between τ 8·0 and 7·8 and the complex pattern of low-field protons. The u.v. absorption at $\lambda_{max.}$ 237 mμ supports the presence of the enol acetate (XVII). Mild hydrolysis of this crude ether cleavage product with potassium hydroxide in methanol for 10 min., followed by preparative t.l.c. gave the 19-nor-enol acetate (XIX) $\lambda_{max.}$ 283 mμ (calc. 283 mμ) and the enol acetate (XX) $\lambda_{max.}$ 237 mμ (calc. 237 mμ). Since the Δ-4 double bond was complicating the ether cleavage, an indirect route, introducing the double bond after the ether cleavage, was investigated.

The 4α-bromo-ether (IIb) was slowly cleaved by boron trifluoride in acetic anhydride during five days to give only the 2α-acetate (XXI) which was converted into the enone (XIIb) with calcium carbonate in dimethylacetamide. Acid hydrolysis of the enone (XIIb) gave the diol (XIIa) which was readily converted into the diacetate (XIIb). Treatment of the latter with methanolic hydrochloric acid under reflux for 48 hr. gave the phenol (XXIIa) characterised as the phenyl acetate (XXIIb).[22]

Boron trifluoride-catalysed acetolysis of the acetoxy-ether (Ia) gave, after 2 hr., the 2α-ol (XXIIIa) as the major product together with a small amount of the triacetate (XXIIIb) expected from the S_N2 attack by the acetate ion from the α-side of the molecule. Since the 2α-ol (XXIIIa) was not formed by partial hydrolysis of



the corresponding triacetate (XXIIIb), or by the addition of water to the unsaturated diacetate (XXIVb), it was concluded that the 2α-ol (XXIIIa) was formed by participation of the neighbouring 3α-acetoxy-group in the favourable intramolecular S_N2 cleavage of the ether (Ia) to give the acetoxonium ion (XXV) which may be stabilised by mesomerism [23] or may form the keten acetal (XXVI). The keten acetal derived from 1,2-diacetoxycyclohexane reacted rapidly with aqueous acetic acid to give the *cis*-hydroxy-acetate.[24] The exclusive

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formation of the equatorial 2α-ol on the addition of water involves preferential proton-transfer in the intermediate ortho ester to the C-2 equatorial oxygen atom. The 2α-ol (XXIIIa) was converted into the corresponding tosylate (XXIIIc) which, when heated under reflux with *s*-collidine for 3 days gave the allylic acetate (XXIVb); this was hydrolysed to the diol (XXIVa). Oxidation of the diol (XXIVa) with Jones reagent at 0° under nitrogen gave the 19-aldehyde (XIb) and traces of acidic products. Attempts to eliminate the 19-aldehyde group as formaldehyde by alkaline hydrolysis with 4% aqueous ethanolic sodium hydroxide [25] at 70° for 2 hr. gave only acidic products, possibly due to autoxidation. Oxidation of the diol (XXIVa) with an excess of Jones reagent gave the acid (XIc) contaminated with two other acidic products possibly involving cleavage of A ring. Decarboxylation of the crude acid (XIc) with methanolic hydrochloric acid followed by preparative t.l.c. gave 19-nor-5α-cholest-1(10)-en-3-one (XXVII).

The structures assigned above were confirmed by spectroscopic methods and the relevant data are shown in the Table. In particular, the ether (III) showed signals for the vinylic 4-proton at τ 4·26, the 1β-proton at τ 7·67 (J_{gem} 12 c./sec., $J_{1\beta H, 2\alpha H}$ 6 c./sec.) and for the 1α-proton at τ 8·18 (J_{gem} 12 c./sec.); while the signal for 2α-proton appeared as a quartet at τ 5·74 ($J_{2\alpha H, 1\beta H}$ 6 c./sec., $J_{2\alpha H, 4H}$ 1·8 c./sec.). The assignment of coupling constants was made since irradiation at the frequency of the 4-vinyl signal caused the signal for the 2α-proton to collapse to a doublet ($J_{2\alpha H, 1\beta H}$ 6 c./sec.). Furthermore, on irradiation at the frequency of the 2α-proton, the signals for the geminal 1 protons appeared as a clearly defined AB quartet.

The diacetate (Vb) showed i.r. absorption for the acetoxy-groups ($\nu_{max.}$ 1751 cm.$^{-1}$) and the 3-carbonyl group (1739 cm.$^{-1}$) whilst the n.m.r. spectrum revealed signals for the 19-methylene group at τ 5·61, 5·52 (J_{AB} 12·0 c./sec.), the two acetoxy-groups at τ 7·86, 7·84, and the 2β-proton at τ 4·61 ($J_{2\beta H, 1\beta H}$ 7 c./sec. and $J_{2\beta H, 1\alpha H}$ 13 c./sec.). The lactone (VIIIb) showed signals for the 19-methylene protons at τ 5·96 and 5·80 appearing as an AB quartet (J_{gem} 10 c./sec.), whilst the 1 protons appeared as an A_2 singlet at τ 7·52. The diketone (XV) showed i.r. absorption both for the 4-en-3-one ($\nu_{max.}$ 1680, 1610 cm.$^{-1}$) and for the 6β-methyl ketone ($\nu_{max.}$ 1720 cm.$^{-1}$), whilst the n.m.r. spectrum revealed a signal for the equatorial 6α-proton at τ 6·73 (W_H 9 c./sec.). The n.m.r. spectrum of the phenol (XXIIa) showed signals for three aromatic protons at τ 3·40, 3·22, and 3·05; in addition there was a broad signal at τ 7·21 assigned to the three benzylic protons at C-6 and C-9. The derived phenyl acetate showed u.v. absorption at 269 mμ (log ε 2·95) and 276 mμ (log ε 2·94) characteristic of a phenyl acetate.[22] 19-Nor-5α-cholest-1(10)-en-3-one (XXVII) showed i.r. absorption at 1725 cm.$^{-1}$, whilst the n.m.r. spectrum showed the 1-vinyl proton at τ 4·68 ($J_{1H, 2\alpha H}$ 3·5 c./sec. and $J_{1H, 2\beta H}$ 3·5 c./sec.).

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EXPERIMENTAL

M.p.s were determined with a Köfler hot-stage apparatus. U.v. absorption spectra (in ethanol) and i.r. absorption spectra (in carbon tetrachloride) were measured with Perkin-Elmer 4000A and 221 spectrophotometers respectively. N.m.r. spectra were measured with Varian A60 or HA100 instruments with deuteriochloroform as solvent and tetramethylsilane as internal reference. Mass spectra were measured with an MS9 double-focus mass spectrometer. Column chromatography was performed on alumina (Spence type H, Activity II) or on alumina deactivated by washing with 2N-acetic acid or on silica (Davison, 100—200 mesh). T.l.c. was carried out on silica plates in ether–hexane (1 : 4) and the plates were developed by spraying them with concentrated sulphuric acid and then heating them. Preparative t.l.c. was carried out on silica plates in ether–hexane (1 : 4); the plates were sprayed with berberine hydrochloride and examined in u.v. light. G.l.c. was performed in an F and M 400 instrument fitted with a disc integrator on a column (1·75 m. × 3 mm. diam.) packed with 1% silicone rubber (nitrile) XE60 on acid-washed silanised Gas Chrom P (100—140 mesh), or on a column (1·1 m. × 3 mm. diam.) packed with 3·8% SE30 on Diatoport (80—100 mesh); the injection port and detector were *ca.* 60° higher than the column temperature, and helium was used as the carrier gas at a flow rate of 75 ml./min.

2β,19-*Epoxy*-5α-*cholestan*-3-*one* (IIa).—The ether (IIa) prepared according to the method of Kwok and Wolff [6] had m.p. 111—113° (lit.,[6] 111—112°).

4α-*Bromo*-2β,19-*epoxy*-5α-*cholestan*-3-*one* (IIb).—The ether (IIa) (810 mg.) in carbon tetrachloride (80 ml.) containing a drop of hydrogen bromide in acetic acid was treated with bromine according to the method of Wolff and his co-workers [7] to give the 4α-bromo-ketone (IIb) m.p. 117° from ether–methanol (lit.,[7] 122—123°); *M* (mass spectrometry) 478·2448. Calc. for $C_{27}H_{43}BrO_2$, 478·2447; isotope abundance: *P*: 478 (100%); *P* + 1: 479 (31%); *P* + 2: 480 (97%).

2β,19-*Epoxycholest*-4-*en*-3-*one* (III).—The bromo-ketone (IIb) (380 mg.) in dimethylacetamide (8 ml.) was added dropwise to calcium carbonate (300 mg.) in boiling dimethylacetamide (4 ml.) during 3 min.; the mixture was heated under reflux for 15 min. Isolation and chromatography on silica gel in ether–hexane (1 : 10) of the product gave the *enone* (III) (172 mg.), m.p. 133—135° (from acetonitrile); *M* (mass spectrometry), 398·3184; $C_{27}H_{42}O_2$ requires *M*, 398·3184; $\lambda_{max.}$ 243·5 mμ (log ε 4·04); $\nu_{max.}$ 1693, 1608 cm.$^{-1}$; τ 9·30 (C-18), 5·96, 6·54 (J_{gem} 7·3 c./sec., 19-CH_2), 5·74 ($J_{2\alpha H, 4H}$ 1·8 c./sec., $J_{2\alpha H, 1\beta H}$ 6·1 c./sec., 2α-H), 4·26 ($J_{4H, 2\alpha H}$ 1·8 c./sec., 4H).

Acetolysis of the Ether (IIa) *with Boron Trifluoride in Acetic Anhydride*.—The ether (IIa) (200 mg.) in acetic anhydride (20 ml.) and ether (4 ml.) was treated dropwise with boron trifluoride (16 drops) and left for 30 min. Ice was added and the mixture was set aside for several hours before it was extracted with ether. Preparative t.l.c. gave 2α,19-*diacetoxy*-5α-*cholestan*-3-*one* (Vb) (129 mg.) as an oil, *M* (mass spectrometry), 502·3659; $C_{31}H_{50}O_5$ requires *M*, 502·3658; $\nu_{max.}$ 1751, 1739 cm.$^{-1}$; τ 9·32 (18-Me), 7·86, 7·84 (OAc), 5·61, 5·52 (J_{gem} 12·5 c./sec., 19-CH_2), 4·61 ($J_{2\beta H, 1\beta H}$ 7 c./sec., $J_{2\beta H, 1\alpha H}$ 13 c./sec., 2βH). A second product isolated by preparative t.l.c. was 3,3-*diacetoxy*-2β,19-*epoxy*-5α-*cholestane* (IV) (20 mg.), m.p. 143—146° (from acetone), *M* (mass spectrometry) 502·3659; $C_{31}H_{50}O_5$ requires *M*,

502·3658; $\nu_{max.}$ 1761 cm.$^{-1}$; τ 9·40 (18-Me), 7·96 (OAc), 6·29, 6·21 (J_{gem} 8·2 c./sec., 19-CH_2), 5·10 ($J_{1\beta H, 2\beta H}$ 6 c./sec.).

Hydrolysis of the Diacetate (Vb).—(*a*) The diacetate (Vb) (25 mg.) in methanol (4 ml.) was treated with potassium hydroxide (60 mg.) in methanol (4 ml.) at 20° for 16 hr. Ether extraction gave the crude lactone acid (VIIIa) as an oil (22 mg.) which was treated with ethereal diazomethane and purified by preparative t.l.c. in ether–hexane (1 : 1) to give the *methyl ester* (VIIIb) (24 mg.), m.p. 119—121° (from methanol); *M* (mass spectrometry) 446·3390; $C_{28}H_{46}O_4$ requires 446·3396; $\nu_{max.}$ 1789, 1745 cm.$^{-1}$; τ 9·32 (18-Me), 6·30 (OMe), 5·96, 5·80 (J_{gem} 10 c./sec., 19-CH_2), 7·52 (1-CH_2).

(*b*) The diacetate (Vb) (40 mg.) in methanol (10 ml.) was added to a solution of potassium hydroxide (85 mg.) in methanol (20 ml.) under nitrogen. After 10 min., the mixture was neutralised at 0° with dilute hydrochloric acid and the solvent was evaporated off. Preparative t.l.c. on silica in ether–hexane (1 : 1) gave 19-*acetoxy*-2α-*hydroxy*-5α-*cholestan*-3-*one* (Vc) (23 mg.) as an oil (Found: C, 75·5; H, 10·3. $C_{29}H_{48}O_4$ requires C, 75·6; H, 10·5%); $\nu_{max.}$ 3500, 1735, 1711 cm.$^{-1}$; τ 9·34 (18-Me), 7·89 (OAc) 5·60, 5·52 (J_{gem} 12 c./sec., 19-CH_2), 5·72 ($J_{2\beta H, 1\beta H}$ 6·5 c./sec., $J_{2\beta H, 1\alpha H}$ 12·0 c./sec., 2-H), 7·16 ($J_{1\beta H, 2\beta H}$ 6·5 c./sec., J_{gem} 12·0 c./sec.).

Hydrolysis of the Diacetate (IVa).—(*a*) The diacetate (IVa) (26 mg.) in ethanol (10 ml.) was heated under reflux with hydrochloric acid (10N) (0·5 ml.) for 2 hr. The usual isolation gave the ether (IIa) (20 mg.) m.p. and mixed m.p. 113—115° (from acetonitrile).

(*b*) The diacetate (IVa) (22 mg.) in methanol (5 ml.) was treated with potassium hydroxide (80 mg.) in methanol (3 ml.) at 20° for 16 hr. The crude product was shown by g.l.c. and t.l.c. to be a mixture of at least four compounds and was not further investigated.

Attempted Dehydration of 2α-*Hydroxy*-5α-*cholestan*-3-*one*.—(a) *Thionyl chloride*. 2α-Hydroxy-5α-cholestan-3-one [11–13] (50 mg.) was heated under reflux for 10 min. with thionyl chloride (0·5 ml.).[26] After ether extraction, preparative t.l.c. gave unchanged starting material (10 mg.) m.p. 122—125° (from methanol) [11–13] and 5α-cholestan-2,3-dione (15 mg.) identical with an authentic sample.[11,17]

(b) *Phosphorus oxychloride–pyridine*. 2α-Hydroxy-5α-cholestan-3-one (50 mg.) in dry pyridine (3 ml.) was treated with phosphorus oxychloride at 0° for 16 hr. Preparative t.l.c. gave 5α-cholestan-2,3-dione (20 mg.) identical with the sample in (*a*) and 2,3-seco-5α-cholestane-2,3-dioic acid (9 mg.) m.p. and mixed [27] m.p. 195—197° (from ether–hexane).

(c) *Phosphorus pentabromide*. 2α-Hydroxy-5α-cholestan-3-one (100 mg.) was ground with freshly sublimed phosphorus pentabromide (200 mg.); addition of chloroform (3 drops) followed by ether extraction gave, after preparative t.l.c., only 5α-cholestan-2,3-dione (58 mg.) identical with samples prepared in (a).

(d) *Sulphuric acid*. 2α-Hydroxy-5α-cholestan-3-one (50 mg.) was treated with concentrated sulphuric acid (1 ml.) for 2 hr. at 20° before dilution with water. The crude product, after extraction with ether, was shown by t.l.c. to contain at least four compounds. Preparative t.l.c. gave 5α-cholest-1-en-3-one (3 mg.) m.p. and mixed [18] m.p. 97°.

(e) *Naphthalene*-β-*sulphonic acid*.[21] Naphthalene-β-sulphonic acid (400 mg.) in dry toluene (500 ml.) was distilled to remove 450 ml. of distillate. 2α-Hydroxy-5α-cholestan-3-one (200 mg.) was added and the mixture was heated under reflux for 2 hr. Preparative t.l.c. of the crude product after ether extraction gave cholest-4-en-3-one (39 mg.), m.p. and mixed m.p. 80—82°.

Acetolysis of the Ether (III) *with Boron Trifluoride in Acetic Anhydride*.—The ether (III) (200 mg.) in acetic anhydride (20 ml.) and ether (4 ml.) was treated dropwise with boron trifluoride (16 drops) and then set aside for 30 min. Ice was added and the mixture was left for several hours before it was extracted with ether. Preparative t.l.c. on silica, in addition to unidentified oils, gave an oil (100 mg.) thought to be a mixture of the enol acetate (XVII) $\lambda_{max.}$ 237 mμ, $\nu_{max.}$ 1747 cm.$^{-1}$; τ 5·69 (19-CH_2), 7·92, 7·95 (OAc), 4·15 (2-vinyl protons), and the enol acetate (XVIII), $\nu_{max.}$ 1747, 1713 cm.$^{-1}$; τ 5·69 (19-CH_2), 7·92 (OAc), 7·83 (Ac), 4·55 (2β-H), 3·84 (4-H) and 7·5 (w_H 9 c./sec., 6α-H). This mixture of enol acetates (50 mg.) in methanol (10 ml.) was treated with potassium hydroxide (100 mg.) in methanol (15 ml.) under nitrogen at 20° for 10 min. After neutralisation at 0° with dilute hydrochloric acid and removal of the methanol *in vacuo*, the product was separated by preparative t.l.c. to give the *enol acetate* (XIX) as an oil (Found: C, 76·3; H, 9·6. $C_{30}H_{46}O_4$ requires C, 76·5; H, 9·85%); $\lambda_{max.}$ 283 mμ (log ε 4·10); $\nu_{max.}$ 1745, 1713 cm.$^{-1}$; τ 7·92 (OAc), 7·83 (Ac), 7·3 (w_H 9 c./sec., 6α-H), 5·45 (2β-H), 3·82 (4-H). A further product isolated was the *enol acetate* (XX) as an oil (15 mg.) (Found: C, 74·2; H, 9·4%; $C_{31}H_{48}O_5$ requires C, 74·35; H, 9·65%); $\lambda_{max.}$ 237 mμ (log ε 3·99), $\nu_{max.}$ 1745 cm.$^{-1}$; τ 5·65 (19-CH_2), 7·92, 7·95 (OAc), 5·45 (2β-H), 4·15 (4 and 6-H's).

Treatment of Cholest-4-*en*-3-*one* (XIII) *with Boron Trifluoride*.—The enone (XIII) (200 mg.) in acetic anhydride (20 ml.) and ether (1 ml.) was treated dropwise with boron trifluoride (16 drops). Ice was added and crystallisation was induced by scratching the flask to give the enol acetate (XIV) (115 mg.), m.p. 79—80° (lit.,[22] 80°); $\nu_{max.}$ 1760 cm.$^{-1}$ τ 9·31 (18-Me), 7·87 (OAc), 4·31 ($J_{4H, 6H}$ 1·8 c./sec., 4-H), and 4·61 (w_H 9 c./sec., 6-H).

A repeat of the reaction in which the mixture was set aside for several hours to allow hydrolysis of the acetic anhydride, gave the diketone (XV) (207 mg.) m.p. 141° (lit.,[21] m.p. 141—142°) (Found: C, 81·2; H, 10·8. Calc. for $C_{29}H_{46}O_2$: C, 81·5; H, 10·9%), $\nu_{max.}$ 1720, 1680, 1610 cm.$^{-1}$; τ 9·28 (18-Me), 7·80 (Ac), 3·93 (4-H), 6·73 (w_H 9 c./sec., 6α-H).

2α,19-*Diacetoxy*-4α-*bromo*-5α-*cholestan*-3-*one* (XXI).—The bromo-ether (IIb) (100 mg.) in acetic anhydride (20 ml.) and ether (2 ml.) was treated dropwise with boron trifluoride (20 drops) for 5 days at 20°. Ice was added to the mixture and after 2 hours the product was extracted with ether to give the *diacetate* (XXI) as an oil (117 mg.); this was homogeneous on t.l.c. (Found: C, 63·5; H, 8·2%; $C_{31}H_{49}BrO_5$ requires C, 64·0; H, 8·5%); $\nu_{max.}$ 1748 cm.$^{-1}$ τ 9·35 (18-Me), 7·83, 7·86 (OAc), 5·51 (19-CH_2), 5·08 ($J_{4\beta H, 5\alpha H}$ 12 c./sec., 4-H), 5·30 ($J_{2\beta H, 1H}$ 7 c./sec., $J_{2\beta H, 1H}$ 13 c./sec., 2 β-H); isotope abundance *M* 580 (100%), 581 (41%), 582 (100%), 583 (41%).

2α,19-*Diacetoxycholest*-4-*en*-3-*one* (XIIb).—The bromo-ketone (XXI) (850 mg.) in dimethylacetamide (16 ml.) was slowly added to calcium carbonate (850 mg.) in dimethylacetamide (8 ml.) under reflux for 2 hr. The product was isolated and purified by preparative t.l.c. on silica to give 2α,19-*diacetoxycholest*-4-*en*-3-*one* (XIIb) (587 mg.), m.p. 112—115° (Found: C, 74·25; H, 9·65; $C_{31}H_{48}O_5$ requires C,

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74·35; H, 9·65%); $\lambda_{max.}$ 240·5 mμ (log ε 4·17); $\nu_{max.}$ 1746, 1695, 1622 cm.$^{-1}$; τ 9·28 (18-Me), 7·91, 7·82 (OAc), 5·75, 5·25 (J_{gem} 11·0 c./sec., 19-CH_2), 4·22 ($J_{2\beta H, 1\beta H}$ 6·0 c./sec., $J_{2\beta H, 1\alpha H}$ 14·0 c./sec., 2-H), 4·07 (4-H).

2α,19-*Dihydroxycholest*-4-*en*-3-*one* (XIIa).—The diacetate (XIIb) (50 mg.) in methanol (14 ml.) was heated under reflux with 3N-hydrochloric acid (7 ml.) for 2 hr. to give the *diol* (XIIa) (42 mg.), m.p. 169—170° (from ether–pentane); *M* (mass spectrometry) 416·3295; $C_{27}H_{44}O_3$ requires 416·3290; $\lambda_{max.}$ 245 mμ (log ε 4·08); $\nu_{max.}$ 3380, 1680, 1655 cm.$^{-1}$; τ 9·30 (18-Me), 6·00, 5·92 (J_{gem} 11·5 c./sec., 19-CH_2), 5·26 ($J_{2\beta H, 1\beta H}$ 6 c./sec., $J_{2\beta H, 1\alpha H}$ 13 c./sec., 2-H), 4·03 (4-H).

3-*Acetoxycholesta*-1,3,5(10)-*triene* (XXIIb).—The diacetate (XIIb) (50 mg.) in methanol (20 ml.) was heated under reflux with 3N-hydrochloric acid (7 ml.) for 48 hr. The crude oil (47 mg.) which was isolated was purified by preparative t.l.c. to give the 2α,19-diol (XIIa) (13 mg.), m.p. and mixed m.p. 169—170° (ether–pentane) and cholesta-1,3,5(10)-triene-3-ol (XXIIa) (9 mg.) as an oil, τ 9·30 (18-Me), 3·22 ($J_{4H, 2H}$ 2 c./sec., 4-H), 3·05 ($J_{2H, 1H}$ 8 c./sec., 1-H), 3·40 ($J_{4H, 2H}$ 2 c./sec., $J_{2H, 1H}$ 8 c./sec., 2-H), 9·21 (6-CH_2 and 9-H). The phenol (XXIIa) was treated with acetic anhydride (1 ml.) and pyridine (5 drops) for 4 hr. at 20° to give the phenyl acetate (XXIIb), m.p. 91—93° (from ether–methanol) (lit.,[28] 93·5—95°) $\lambda_{max.}$ 269 mμ (log ε 2·95) and 276 mμ (log ε 2·94).[22]

Acetolysis of the Ether (Ia) *with Boron Trifluoride in Acetic Anhydride*.—The ether (Ia) (200 mg.) in acetic anhydride (20 ml.) and ether (4 ml.) was treated dropwise with boron trifluoride (15 drops) and was then set aside for 2 hr. Ice was added to the mixture and after several hours the product was extracted with ether. Preparative t.l.c. on silica in ether–hexane (1 : 1) gave 3α,19-*diacetoxy*-5α-*cholestan* 2α-*ol* (XXIIIa) (147 mg.), m.p. 126—127° (from pentane); $\nu_{max.}$ 1740 cm.$^{-1}$ (Found: C, 73·35; H, 10·30. $C_{31}H_{52}O_5$ requires C, 73·75; H, 10·4%); τ 9·36 (18-Me), 7·92, 7·88 (OAc), 5·88, 5·68 (J_{gem} 12 c./sec., 19-CH_2), 6·15 ($J_{2\beta H, 1\alpha H}$ 12 c./sec., 2-H), 4·82 (w_H 6 c./sec., 3-H). A further product was 2α,3α,19-*triacetoxy*-5α-*cholestane* (XIIIb) (13 mg.), m.p. 129—130° (from acetone–methanol); $\nu_{max.}$ 1743 cm.$^{-1}$; *M* (mass spectrometry) 546·3917; $C_{33}H_{54}O_6$ requires 546·3919; τ 9·36 (18-Me), 8·0, 7·91 (OAc), 5·84, 5·70 (J_{gem} 12 c./sec., 19-CH_2), 5·09 ($J_{2\beta H, 3H}$ 3·5 c./sec., $J_{2\beta H, 1\beta H}$, 3·5 c./sec., $J_{2\beta H, 1\alpha H}$ 12 c./sec., 2 β-H), 4·73 (w_H 7 c./sec., 3-H).

3α,19-*Diacetoxy*-5α-*cholestan*-2α-*yl* *Toluene*-p-*sulphonate* (XXIIIc).—The diacetate (XXIIIa) (80 mg.) in pyridine (4 ml.) was treated with *p*-tolylsulphonyl chloride (188 mg.) at 0° for 10 days to give the *tosylate* (XXIIIc) (59 mg.), m.p. 78—80°, 141—143° (from pentane); *M* (mass spectrometry) 658·3895; $C_{38}H_{58}O_7S$ requires 658·3903; τ 9·35 (18-Me), 7·93, 7·89 (OAc), 7·57 (*p*-Me), 5·83 (19-CH_2), 5·03 (w_H 7 c./sec., 3-H), 2·17—2·73 (ArH).

3α,19-*Diacetoxy*-5α-*cholest*-1-*ene* (XXIVb).—The tosylate (XXIIIc) (180 mg.) in collidine (30 ml.) was heated under reflux for 3 days. Preparative t.l.c. on silica in ether–hexane (1 : 1) of the product gave 3α,19-*diacetoxy*-5α-*cholest*-1-*ene* (XXIVb) (75 mg.) as an oil, $\nu_{max.}$ 1733 cm.$^{-1}$ (Found: C, 75·5; H, 9·8. $C_{31}H_{48}O_4$ requires C, 75·8; H, 10·0%); τ 9·32 (18-Me), 7·99, 7·94 (OAc), 5·68, 5·86 (J_{gem} 12·0 c./sec., 19-CH_2), 4·80 ($J_{3\beta H, 2H}$ 4·5 c./sec., $J_{3\beta H, 4\beta H}$ 4·5 c./sec., 3-H), 4·22 ($J_{2H, 3\beta H}$ 4·5 c./sec., $J_{2H, 1H}$ 10·0 c./sec., 2-H), 3·88 ($J_{1H, 2H}$ 10·0 c./sec., 1-H).

5α-*Cholest*-1-*ene*-3α,19-*diol* (XXIVa).—The diacetate (XXIVb) (47 mg.) was heated under reflux with 5% potassium hydroxide in methanol (2 ml.) for 1 hr. to give the *diol* (XXIVa) (37 mg.), m.p. 153—154° (from acetonitrile); $\nu_{max.}$ 3310 cm.$^{-1}$; *M* (mass spectrometry) 402·3499; $C_{27}H_{46}O_2$ requires 402·3498; τ 9·33 (18-Me), 6·32, 6·19 (J_{gem} 11·5 c./sec., 19-CH_2), 5·87 (w_H 9 c./sec., 3β-H), 3·95 (1-H and 2-H).

19-*Formyl*-5α-*cholest*-1-*en*-3-*one* (XIb).—The diol (XXIVa) (50 mg.) in acetone (5 ml.) was treated dropwise with Jones' reagent for 10 min. at 0°. Preparative t.l.c. of the product gave the *aldehyde* (XIb) which decomposed on attempted recrystallisation; *M* (mass spectrometry) 398·3190; $C_{27}H_{42}O_2$ requires 398·3185; $\nu_{max.}$ 1715, 1695, 1615 cm.$^{-1}$; τ 9·28 (18-Me), 3·00 ($J_{1H, 2H}$ 10·5 c./sec., 1-H), 3·82 ($J_{1H, 2H}$ 10·5 c./sec., 2-H), 0·01 (19-CHO).

19-*Nor*-5α-*cholest*-1(10)-*en*-3-*one* (XXVII).—The diol (XXIVa) (150 mg.) in acetone (15 ml.) was treated with an excess of Jones reagent (0·7 ml.) for 2 hr. T.l.c. of the crude product showed three polar products which were not further purified but were dissolved in ethanol (10 ml.) and treated with 2% aqueous hydrochloric acid (2 ml.) under reflux for 1 hr. T.l.c. showed that the major acidic compound had disappeared and preparative t.l.c. on silica gave 19-nor-5α-cholest-1(10)-en-3-one (XXVII) as an oil (40 mg.); $\nu_{max.}$ 1725, 1678 cm.$^{-1}$ (Found: C, 84·0; H, 11·5. $C_{26}H_{42}O$ requires C, 84·4; H, 11·45%); τ 9·32 (18-Me), 4·68 ($J_{1H, 2\alpha H}$ 3·5 c./sec., $J_{1H, 2\beta H}$ 3·5 c./sec., 1-H), 7·11 (w_H 4 c./sec., 2-CH_2), 7·35 (J_{gem} 11 c./sec., 4α-H), and 7·70 (J_{gem} 11 c./sec., $J_{4\beta H, 5\alpha H}$ 6 c./sec., 4β-H).

Attempted Isomerisation of 19-*Norcholest*-1(10)-*en*-3-*one*.—The ketone (XXVII) (15 mg.) in benzene (5 ml.) was treated with boron trifluoride (1 drop) at 20° for 3 days. The product was shown to be a mixture of conjugated en-one (XId), $\nu_{max.}$ 1687 cm.$^{-1}$ and the unconjugated ketone (XXVII), $\nu_{max.}$ 1725 cm.$^{-1}$.

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