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THE CONTRACTION OF RING A IN 5α-CHOLESTANE DERIVATIVES

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Abstract—The β-keto-ester which is obtained by Dieckmann cyclization of the dimethyl ester (I) of the dicarboxylic acid obtained by oxidative opening of ring A in 5α-cholestan-3-one and related compounds has been shown to have the structure IIa, by its degradation, via the unsaturated acid (Va), to A-nor-5β-cholestan-3-one (VI) and to the dimethyl ester (VIIb). The stereochemistry of compound IIa and of related A-substituted A-nor-5α-cholestanes is discussed. A-nor-5α-Cholestan-1-one (XVIIb) has been synthesized, starting from 5α-cholest-1-en-3-one (XIV).

THIS work was designed to investigate the possibilities of contracting six-membered rings in steroids and D-homosteroids to five-membered rings bearing a suitably disposed functional group. It was prompted by the observation by one of us, while working with Prof. G. Stork at Columbia University, that the dimethyl ester (I) gave a single β-keto-ester upon Dieckmann cyclization with potassium t-butoxide or with sodium hydride in benzene. Reduction of this keto-ester (IIa) with sodium borohydride or with lithium aluminium tri-t-butoxy hydride gave in good yield a single hydroxy-ester (IIIa). On treatment with phosphorus oxychloride in pyridine this failed to dehydrate, giving instead a chloro-ester (IV), which in turn afforded the unsaturated acid (Va) upon alkaline hydrolysis.

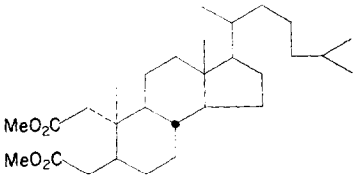
Alternatively the toluene *p*-sulphonyl derivative IIIc likewise gave the unsaturated ester (Vb) on treatment with potassium t-butoxide in t-butanol; it was unaffected by boiling collidine.

The position of the carboxyl group Va was established by Schmidt degradation. This gave a five-membered ring ketone, m.p. 79–80°; $[\alpha]_D$ +131°. Both these values are higher than those reported for A-nor-5β-cholestan-3-one.[1–3] Consequently we prepared the latter (VI) from Diels' acid as described by Windaus.[1] Careful purification of the product gave the desired pure ketone, identical with the product of degradation of compound Va.

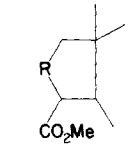
Further confirmation of the position of the ester group in the keto-ester (IIa) and of the double bond in acid Va was given by ozonolysis of the latter compound. This gave a dicarboxylic acid (VIIa); Fischer–Speyer esterification of this gave only neutral material in the form of the dimethyl ester (VIIb), showing that neither of the carboxyl groups in the ozonolysis product is attached at the tertiary C_{10} position.

Attempted catalytic hydrogenation of the unsaturated ester (Vb) at atmospheric pressure in either ether–methanol or in ethyl acetate in the presence of palladium–carbon led to rearrangement to a different α-β-unsaturated ester, whose formulation as shown in IX is supported by the expected bathochromic shift in its ultra-violet

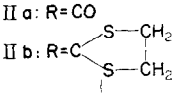
[1] A. Windaus, *Ber. Dtsch. Chem. Ges.* **52**, 170 (1919).
[2] D. E. Evans, A. C. de Paulet, C. W. Shoppee and F. Winternitz, *J. Chem. Soc.* 1451 (1957).
[3] B. B. Smith and H. R. Nace, *J. Amer. Chem. Soc.* **76**, 6119 (1954).

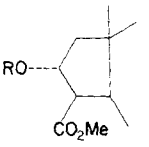


I



II a: R = CO

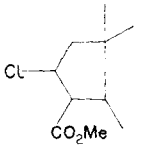
II b: R = 



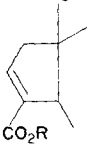
III a: R = H

III b: R = Ac

III c: R = $O_2SC_6H_4$-Me

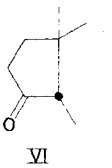


IV



V a: R = H

V b: R = Me



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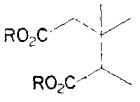
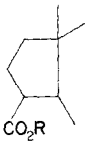


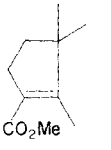
VII a: R = H

VII b: R = Me

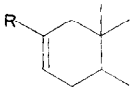


VIII a: R = H

VIII b: R = Me



IX

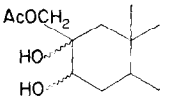


X a: R = CHO

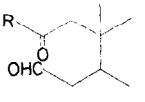
X b: R = CH_2OH

X c: R = CH_2OAc

X d: R = Me

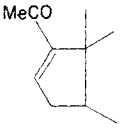


XI a, XI b

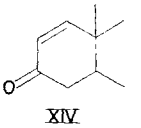


XII a: R = CH_2OAc

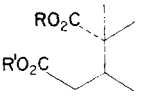
XII b: R = Me



XIII



XIV

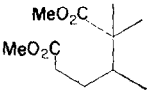


XV a: R = R' = H

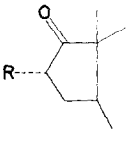
XV b: R = R' = Me

XV c: R = Me, R' = H

XV d: R' = Me; R = H



XVI



XVII a: R = CO_2Me

XVII b: R = H

spectrum. The saturated ester (VIIIb) was eventually obtained by desulphurization of the thioketal-ester (IIb).

The stereochemistry of these products is of interest, particularly in view of the appearance of a paper by Shoppee and Sly[4] which deals, *inter alia*, with the configuration of the two A-nor-5α-cholestan-2-ols which are obtained by reduction of A-nor-5α-cholestan-2-one, either catalytically or with sodium in ethanol or by the Meerwein–Ponndorf method.[5,6] One of these epimers, of m.p. 130°,[5] $[\alpha]_D$ +38°[4] (acetate: m.p. 80°,[4] $[\alpha]_D$ −1°[4]) gave a digitonide unlike the epimer of m.p. 155°,[5] $[\alpha]_D$ −28°[4] (acetate: m.p. 93°,[4] $[\alpha]_D$ +25°[4]), and hence these were originally designated as the β- and α-epimer respectively. Shoppee and Sly contend that Klyne's principle of enantiomeric types[7,8] cannot be used to correlate the configuration of these two epimers with those of 16β- and 16α-ols, since the latter give similar $[M]_D$ increments of the same sign. Alternatively they suggest that in view of the similar molecular rotation shown by A-nor-5α-cholestane (+90°) and 5α-cholestane (+91°) a direct correlation can be made between the above two A-nor-5α-cholestan-2-ols and between the epimeric 5α-cholestan-2-ols and their respective acetates. They come to the conclusion that the previously accepted configurations of the former pair should be reversed.

Against this, firstly, we have prepared A-nor-5α-cholestane by Wolff–Kischner reduction of A-nor-5α-cholestan-2-one, and have found the pure product to be higher in melting point and lower in specific rotation ($[M]_D$ +74°) than previously reported.[9] Secondly, it is not clear to us why, if corelation of A-nor-5α-cholestane derivatives with those of 5α-cholestane is at all valid, A-nor-5α-cholestan-2-ols should then be compared with 5α-cholestan-2-ols (and not with 5α-cholestan-3-ols, in which case incidentally Shoppee and Sly's conclusions would have to be reversed).

While it is true that $\Delta[M]_D$ values for 16β- and 16α-hydroxyl groups are not very much different, we wish to point out that those of 16β- and 16α-acetoxy groups differ considerably and consistently. From the wealth of examples now available from the literature it is clear that $\Delta[M]_D$ (16β-OAc) is either positive[8] or slightly negative,[10,11] while $\Delta[M]_D$ (16α-OAc) is always strongly negative,[8,10-12] so that $[M]_D$ (16β-OAc) − $[M]_D$ (16α-OAc) is always positive, ranging from +67°[9,13] to +410°.[14] If Klyne's theory is applicable then in nor-ring A, this being enantiomeric to ring D, $[M]_D$ (2β-OAc) − $[M]_D$ (2α-OAc) should be negative. Using Shoppee and Sly's data this is the case only if their conclusions are reversed and the heretofore accepted configurations for the two A-nor-5α-cholestan-2-ols retained (see Table 1.)

These arguments are pertinent presently when applied to the acetoxy-ester (IIIb). $[M]_D$ comparisons of methyl 3β,16α-diacetoxy-[11] and methyl 3β,16β-diacetoxy-5β-etianates[13] with methyl 3β-acetoxy-5β-etianate[11] show that here too $[M]_D$ (16β-OAc) -

[4] C. W. Shoppee and J. C. P. Sly, *J. Chem. Soc.* 345 (1959).
[5] R. E. Marker, O. Kamm, D. M. Jones and L. W. Mixon, *J. Amer. Chem. Soc.* **59**, 1363 (1937).
[6] K. Kawazaki, *Chem. Abstr.* **31**, 3060 (1937).
[7] W. Klyne, *J. Chem. Soc.* 2916 (1952).
[8] W. Klyne in Braude and Nachod, *Determination of Organic Structures by Physical Methods* p. 73. Academic Press, New York (1955).
[9] Lettre, *Z. physiol. Ch.* **221**, 73 (1933).
[10] J. Fajkos and F. Sorm, *Coll. Czech. Chem. Comm.* **21**, 1013 (1956).
[11] J. A. Moore, *Helv. Chim. Acta* **37**, 659 (1954); and refs. quoted there.
[12] V. Schwarz, V. Cerny and F. Sorm, *Coll. Czech. Chem. Comm.* **23**, 840 (1958).
[13] J. Fajkos and F. Sorm, *Coll. Czech. Chem. Comm.* **20**, 1464 (1955).
[14] D. K. Fukushima and T. F. Gallagher, *J. Amer. Chem. Soc.* **73**, 191 (1951); B. Ellis, F. Hartley, V. Petrow and D. Wedlake, *J. Chem. Soc.* 4383 (1955).

$[M]_D$ (16α-OAC) is positive (+206°) so that vicinal interference of the methoxycarbonyl group appears to be of no moment. Comparison (see Table 1) of the acetoxy-ester (IIIb) with the saturated ester (VIIIb) gives $\Delta[M]_D$ (OAc): +29° from which it can be deducted by comparison with the two 2-acetoxy-A-nor-5α-cholestanes that in IIIb the acetoxy group has the α-configuration. Since the properties of the hydroxy-ester IIIa (difficulty of ionic elimination, ease of acetylation,[15] no evidence of hydrogen bonding in its infra-red spectrum) indicate a *trans*-relationship between the two functional groups, the stereochemistry of compound IIIa must be assumed as shown, and hence that of compounds II, IV and VIII, since the reactions connecting these are such as to preclude epimerization of the methoxycarbonyl group.

TABLE 1

Compound	$[M]_D$	$\Delta[M]_D$
A-nor-5α-cholestane (present value)	+74°	
2β-acetoxy-A-nor-5α-cholestane, m.p. 80°[4]	+4	−70° } $\Delta\beta - \Delta\alpha$ = 100°
2α-acetoxy-A-nor-5α-cholestane, m.p. 93°[4]	+104	+30 }
3β-methoxycarbonyl-A-nor-5α-cholestane (VIIIb)	0	
2α-acetoxy-3β-methoxycarbonyl-A-nor-5α-cholestane (IIIb)	+29	Δ(2α-OAc): +29°

We now turned our attention to the possibility of contracting ring A in 5α-cholestan-3-one to give 1-substituted A-nor-5α-cholestane derivatives. It was hoped to achieve this by internal aldol cyclization of suitable dicarbonyl compounds derived from 2//3-seco-5α-cholestane, by analogy with the cyclization of 16,17-dicarbonyl-16//17-seco-D-homosteroids.[16,17] For example 2-formyl-5α-cholest-2-ene (Xa), obtained by metal hydride reduction of 2-isopropoxymethylene-5α-cholestan-3-one,[18] was converted into 2-acetoxymethyl-5α-cholest-2-ene (Xc), in which the double bond was cleaved, either by ozonolysis or by the action of lead tetra-acetate on the epimeric glycols XIa and XIb, to give a non-crystalline product which from its infra-red spectrum appeared to be the expected acetoxy-keto-aldehyde (XIIa).[19] Furthermore, 2-methyl-5α-cholest-2-ene (Xd) on ozonolysis gave what appeared to be the keto-aldehyde (XIIb). Attempted cyclization of either compounds XIIa or XIIb by a variety of methods failed to give any tangible product. Solely by passing a solution of compound XIIb through active acidic alumina a compound was isolated in low yield which may possibly be the unsaturated ketone XIII, but the amount obtained was insufficient for further characterization.

[15] H. Hirschmann and F. B. Hirschmann, *J. Amer. Chem. Soc.* **78**, 3755 (1956).
[16] J. W. Cornforth, in Cook, *Progress in Organic Chemistry* Vol. 3, p. 1. Butterworths, London (1955).
[17] W. F. Johns, *J. Amer. Chem. Soc.* **80**, 6456 (1958); G. Stork, H. N. Khastgir and A. J. Solo, *Ibid.* **80**, 6458 (1958).
[18] P. Seifert and H. Schinz, *Helv. Chem. Acta* **34**, 728 (1951); J. Fajkos and F. Sorm, *Chem. Listy* **47**, 418 (1953).
[19] The corresponding 16//17-seco-compound, A. Lardon, O. Schindler and T. Reichstein, *Helv. Chim. Acta* **40**, 666 (1957).

The failure of these reactions may be ascribed to the difficulty of carbanion formation at C_1 in these 2//3-seco compounds, presumably because of steric interference by the C_{10} angular methyl group and by ring C, and this of course would also explain the unidirectional cyclization of the diester I.[20] In the case of the 16//17-seco-D-homo-16,17-dialdehyde whose internal cyclization forms part of the total steroid synthesis by the Woodward group,[21] interference by the ring B methylene groups led, on the other hand, to preferential cyclization towards the formation of the 17-substituted steroid.[22]

TABLE 2

Compound	$[M]_D$	$\Delta[M]_D$
A-nor-5α-cholestane (present value)	+74°	
3β-methoxycarbonyl-A-nor-5α-cholestane (VIIIb)	0	(3β-CO_2Me) −74°
A-nor-5α-cholestan-2-one[8]	+525	
3β-methoxycarbonyl A-nor-5α-cholestan-2-one (IIa)	+468	(3β-CO_2Me) −57°
3β-acetoxy-5α-androstane[13]	+27	
3β-acetoxy-16β-methoxycarbonyl-5α-androstane[10]	−143	(16β-CO_2Me) +116
3β-acetoxy-16α-methoxycarbonyl-5α-androstane[10]	+17	(16α-CO_2Me) +44
A-nor-5α-cholestan-1-one (XVIIb)	+59°	
2α-methoxycarbonyl-A-nor-5α-cholestan-1-one (XVIIa)	+17	(2α-CO_2Me) −76

The unknown A-nor-5α-cholestan-1-one (XVIIb) was eventually synthesized by a method involving a C_3 carbanion. 5α-Cholest-1-en-3-one (XIV) on ozonolysis gave the dicarboxylic acid (XVa) whose monomethyl ester (XVc) was extended to the dimethyl ester (XVI). Dieckmann cyclization of the latter gave the β-keto-ester XVIIa (possible configuration of the ester group based on $[M]_D$ comparison with 3β-acetoxy-16α- and 3β-acetoxy-16β-methoxycarbonyl-5α-androstanes,[9] see Table 2), whose hydrolysis with acid gave the desired A-nor-1-ketone.

In principle it follows from the above work that a given *trans*-9-methyl-3-decalone might possibly be contractable towards either the 1- or the 3-hydrindanone, both involving the preferred 2 → 3 enolization of the former: starting either by formation of the 2-bromo-3-ketone or by oxidation of the Δ_2-enol or its equivalent.

EXPERIMENTAL

Infra-red spectra and rotations were determined in chloroform.

3β-Methoxycarbonyl-A-nor-5α-cholestan-2-one (IIa). Dimethyl 2//3-seco-5α-cholestane-2,3-dioate[23] (6·0 g, m.p. 63–64°) in dry benzene (400 ml) was refluxed with dry potassium t-butoxide (from

[20] The selective acyloin condensation of I to 3β-hydroxy-5α-cholestan-3-one, as reported by J. C. Sheehan and W. F. Erman, *J. Amer. Chem. Soc.* 79, 6050 (1957), is probably due to a different factor.

[21] R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, *J. Amer. Chem. Soc.* 74, 4223 (1952).

[22] A similar, though unsuccessful, approach to the contraction of ring A in allopregnanes was tried by H. Agahigian, Ph.D. Thesis, Brown Univ. (1957); *Dissertation Abstr.* 18, 390 (1958).

[23] A. Windaus and C. Uibrig, *Ber. Dtsch. Chem. Ges.* 47, 2384 (1914).

1 g potassium) for 14 hr, during which time small portions of solvent were distilled off. The reaction mixture was cooled and dil hydrochloric acid was added. The organic layer was washed with water, dil $KHCO_3$ solution and again with water and dried ($MgSO_4$). The solvent was removed and the residue crystallized from methanol to give needles (4·50 g) of the *β-keto-ester*, double m.p. 110–111°, 121–122°, $[\alpha]_D$ + 109° (c, 0·69) (Found: C, 78·0; H, 10·5; O, 11·4. $C_{28}H_{44}O_3$ requires: C, 78·1; H, 10·75; O, 11·15%), bands at 5·70 μ and 5·79 μ. It gave a weak coloration with ferric chloride in methanol.[13]

Chromatography of the mother liquors gave another 1·0 g of the keto ester.

Hydrolysis by refluxing with a 3 : 1 mixture of acetic and conc hydrochloric acids gave A-nor-5α-cholestan-2-one, m.p. 105° (from methanol), $[\alpha]_D$ + 143° (c, 1) (reported: m.p. 100–100·5°,[24] $[\alpha]_D$ + 142°).[2]

3β-Methoxycarbonyl-A-nor-5α-cholestan-2α-ol (IIIa)

The above β-keto ester (3·0 g) was dissolved in tetrahydrofuran (12 ml) and methanol (12 ml) and sodium borohydride (0·4 g) was added at 0°. The solution was allowed to reach room temp during 4 hr and was then worked up in the usual manner. The crude product was chromatographed in hexane on neutral alumina (50 g). Elution with methylene chloride and then with chloroform gave the *hydroxy-ester* which crystallized from 90% methanol as felted needles, (2·0 g), m.p. 125·5–126°, $[\alpha]_D$ + 14° (c, 1) (Found: C, 77·9; H, 11·2; O, 10·85. $C_{28}H_{46}O_3$ requires: C, 77·7; H, 11·2; O, 11·1%) sharp bands at 2·76 μ and 5·79 μ.[13]

Similar results were obtained on reduction with lithium aluminium tri-t-butoxy hydride in dry tetrahydrofuran.

Acetylation of this hydroxy ester (100 mg) in pyridine (0·8 ml) with acetic anhydride (0·2 ml) at room temp for 15 hr gave the *acetate* (IIIb), m.p. 89–90° (from methanol), $[\alpha]_D$ + 29° (c, 1·30) (Found: C, 76·0; H, 10·4; O, 13·45. $C_{30}H_{48}O_4$ requires: C, 75·9; H, 10·6; O, 13·5%).

2β-Chloro-3β-methoxycarbonyl-A-nor-5α-cholestane (IV)

The above hydroxy ester (1·15 g) was dissolved in dry pyridine (10 ml) and phosphorus oxychloride (4 ml) was added at 0°. After standing overnight at room temp the reaction mixture was decomposed with ice and worked up in the usual manner. The crude product was chromatographed in hexane on alumina and crystallized from methanol to give the *chloro-ester* (0·9 g), needles, m.p. 125–126°, $[\alpha]_D$ −23° (c, 1) (Found: C, 74·1; H, 10·35; Cl, 7·85; $C_{28}H_{45}O_2Cl$ requires: C, 74·55; H, 10·5; Cl, 7·9%).

A-*nor*-5-*cholest*-2-*ene*-3-*carboxylic acid* (Va)

(a) The above chloroester (10 g) was heated under reflux for 6 hr with 20% methanolic potassium hydroxide (250 ml). Most of the methanol was removed, water was added and the resulting suspension acidified. The crude dry product (7·8 g) on crystallization from chloroform gave the *unsaturated acid*, m.p. 257–259°, $[\alpha]_D$ +78° (c, 0·3) (Found: C, 80·65; H, 10·8. $C_{27}H_{44}O_2$ requires: C, 80·95; H, 11·05%), λ_{max}^{EtOH} 226 mμ, ε 8000; bands at 5·98 μ and 6·25 μ.

Cautious esterification with diazomethane in ether methanol gave the *methyl ester* (Vb), needles from methanol, m.p. 112–113°, $[\alpha]_D$ +31·5 (c, 1·05) (Found: C, 81·1; H, 11·0. $C_{28}H_{46}O_2$ requires: C, 81·1; H, 11·2%), λ_{max}^{EtOH} 228 mμ, ε 12000,[25] bands at 5·86 μ and 6·25 μ.

Alkaline hydrolysis returned the acid Va, identified by m.p. and mixed m.p.

(b) The hydroxy-ester (IIIa, 230 mg), dissolved in pyridine (2 ml) was treated overnight at room temp with toluene *p*-sulphonyl chloride (170 mg). To the crude dry toluene *p*-sulphonate, obtained by working up in the usual manner, a solution of potassium (87 mg) in dry t-butanol (5 ml) was added and the solution was refluxed for 2 hr. The neutral product, obtained after adding saturated sodium chloride solution and extraction with ether, was purified by chromatography and crystallization from methanol to give the above methyl ester (211 mg), m.p. 108–110°, undepressed by admixture.

Schmidt degradation of (Va). The unsaturated acid (1·5 g) was dissolved in chloroform (40 ml) and conc sulphuric acid (10 ml) was added. With stirring sodium azide (2·0 g) was added in small portions, keeping the temp below 40°; stirring was then continued for another 30 min at room temp. Water

[24] A. Windaus and O. Dalmer, *Ber. Dtsch. Chem. Ges.* **52**, 162 (1919).

[25] Cf. with methyl 3β-acetoxy-5β-androst-16-ene 17-carboxylate: λ_{max} 225 mμ, log ε 4·1; K. Meyer, *Helv. Chim. Acta* **29**, 1580 (1946).

(100 ml) was then added and the mixture heated under reflux for 4 hr. After cooling the chloroform layer was washed with water, 5% potassium hydroxide solution, again with water and dried ($MgSO_4$) and the solvent removed. The residue was chromatographed in pentane on alumina (Fisher, 25 g). Hexane eluted A-nor-5β-cholestan-3-one (VI), needles from methanol, m.p. 79–80° (corr), $[\alpha]_D$ + 131° (*c*, 1·1), band at 5·77 μ. The 2,4-*dinitrophenylhydrazone* had m.p. 162–164° from ethyl acetate–ethanol; reported[2] m.p. 166–167° (Found: N, 10·1. $C_{32}H_{48}O_4N_4$ requires: N, 9·75%).

This ketone, prepared from Diels' acid as described by Windaus[1], had m.p. 72–74°, $[\alpha]_D$ + 105° as reported. On chromatography in pentane on active alumina this solvent eluted a small amount of non-polar material; hexane eluted the pure ketone, m.p. 77–79°, undepressed by admixture with the above product. The infra-red spectra were identical.

Ozonolysis of (Va). Excess ozonized oxygen was passed through a solution of the unsaturated acid (1·0 g) in ethyl acetate–acetic acid (1 : 1) cooled to −15°; 30% hydrogen peroxide (15 ml) was then added and the solution left at room temp overnight. It was then concentrated *in vacuo* at room temp and the residue was taken up in ether. The ether layer was washed with water, dried ($MgSO_4$) and the ether removed. The residue was triturated with pentane to give 2′/3-*seco*-5α-*cholestane*-2,4-*dioic acid* (VIIa), which after crystallization from chloroform had m.p. 221–223° (Found: C, 74·05; H, 10·65; O, 15·45. $C_{26}H_{44}O_4$ requires: C, 74·25; H, 10·55; O, 15·2%).

Esterification of this dicarboxylic acid by the Fischer Speyer method gave only neutral material which could not be induced to crystallize. A sample of this *dimethyl ester* (VIIb) was evaporatively distilled *in vacuo* (145–150°/10⁻³ mm); it had $[\alpha]_D$ + 9° (*c*, 1) (Found: C, 74·9; H, 10·7; O, 14·2. $C_{28}H_{48}O_4$ requires: C, 74·95; H, 10·8; O, 14·2%), band at 5·79 μ.

3β-*Methoxycarbonyl*-2,2-*ethylenedithio*-A-*nor*-5α-*cholestane* (IIb)

The β-keto-ester (IIa, 0·30 g) was dissolved in ethanedithiol (1·5 ml) in the presence of zinc chloride (0·30 g, fused *in vacuo*) and anhydrous sodium sulphate (0·20 g). After standing overnight ether and 10% sodium hydroxide solution were added; the ether layer was washed repeatedly with water, dried ($MgSO_4$) and the solvent removed. The residue was purified by chromatography in hexane on neutral alumina and crystallization from methanol to give the *thio-ketal*, small needles, m.p. 121–122° (Found. C, 71·0; H, 9·8; S, 12·75. $C_{30}H_{50}O_2S_2$ requires: C, 71·1; H, 9·95; S, 12·65%), band at 5·80 μ.

A-*nor*-5α-*Cholestane*-3β-*carboxylic acid* (VIIIa)

The above thio-ketal (0·22 g) was dissolved in dioxan (5 ml) and a suspension of Raney nickel (ca. 2 g, W5) in methanol (5 ml) was added. The suspension was refluxed for 4 hr, after which it was filtered and the filtrate concentrated *in vacuo*. The residue was purified by chromatography in pentane on neutral alumina and crystallization from methanol to give the *methyl ester* (VIIIb) leaflets, m.p. 78·5–79°, $[\alpha]_D$ 0° (*c*, 1·76) (Found: C, 80·55; H, 11·4. $C_{28}H_{46}O_2$ requires: C, 80·7; H, 11·6%), band at 5·80 μ.

Alkaline hydrolysis gave the *acid*, m.p. 170° from pentane. (Found: C, 80·5; H, 11·45. $C_{27}H_{44}O_2$ requires: C, 80·55; H, 11·5%), band at 5·88 μ.

Esterification with diazomethane returned the above methyl ester, identified by m.p. and mixed m.p.

3-*Methoxycarbonyl*-A-*nor*-*cholest*-3-*ene* (XI)

The methyl ester (Vb, 150 mg) was shaken under hydrogen in either methanol–ether or in ethyl acetate in the presence of palladium–carbon (10%, 100 mg) at room temp and atm press for 5 hr. No hydrogen uptake was observed. The residue obtained after filtration and removal of the solvents was chromatographed in pentane on neutral active alumina (4 g). Hexane eluted the *unsaturated ester* (XI), long needles from methanol, m.p. 84–84·5°, $[\alpha]_D$ + 66° (*c*, 1·79) (Found: C, 81·05; H, 11·2. $C_{28}H_{44}O_2$ requires: C, 81·1; H, 11·2%), λ_{max}^{EtOH} 237 mμ, ε 12000; bands at 5·90 μ and 6·09 μ.

2-*Isopropoxymethylene*-5α-*cholestan*-3-*one*

2-Hydroxymethylene-5α-cholestan-3-one, m.p. 180–182°, $[\alpha]_D$ + 50° (*c*, 1; reported:[26] m.p. 176–178°; 6·0 g) was dissolved in dry 2-butanone (120 ml); isopropyl iodide (25 ml) and anhydrous potassium carbonate (12·0 g) were added and the suspension was refluxed with stirring for 18 hr.

[26] M. W. Goldberg and H. Kirchensteiner, *Helv. Chim. Acta* **26**, 288 (1943).

The reaction mixture was diluted with ether and water was added. The organic layer was washed 3 times with ice-cold 10% potassium hydroxide solution, then with water and dried ($MgSO_4$). The residue obtained on removal of solvents *in vacuo* (6·1 g) was used directly for the next step; a sample of the *ketone* was recrystallized from cyclohexane-isopropanol, m.p. 162–164° (Found: C, 81·4; H, 11·35. $C_{31}H_{52}O_2$ requires: C, 81·5; H, 11·5%), bands at 5·99 μ, 6·16 and 6·32 μ.

2-*Formyl*-5α-*cholest*-2-*ene* (Xa)

The above crude ketone (1·0 g) was dissolved in a 1 : 1 mixture of ether and methanol (20 ml) and sodium borohydride (250 mg) was added in small portions with stirring at room temp. After 3 hr most of the solvents were removed *in vacuo* at room temp, water (5 ml) was added and the mixture acidified at 0° with 10% sulphuric acid. The product was extracted with ether, the extract was washed with water, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was chromatographed in hexane on neutral active alumina (30 g). Methylene chloride–hexane (1 : 9) eluted the unsaturated aldehyde (0·35 g) which after repeated crystallization from methanol formed long needles, m.p. 130–132°, $[\alpha]_D$ + 57° (*c*, 1; reported[27]: m.p. 130–132°, $[\alpha]_D$ + 75°), bands at 5·95 μ, 6·06 μ.

More erratic results were obtained on reduction with lithium aluminium hydride in tetrahydrofuran.

2-*Hydroxymethyl*-5α-*cholest*-2-*ene* (Xb)

The above unsaturated aldehyde (650 mg) was dissolved in ether-methanol (20 ml) and sodium borohydride (300 mg) was added in small portions. After stirring for 4 hr the solvents were removed *in vacuo* at room temp and the product isolated as described for obtaining the aldehyde Xa. The crude *unsaturated alcohol* was crystallized from pentane to give needles, m.p. 140–142°, $[\alpha]_D$ +63° (*c*, 0·5) (Found: C, 83·95; H, 11·85. $C_{28}H_{48}O$ requires: C, 83·95; H, 12·1%), band at 2·76 μ.

Acetylation of this acetic anhydride–pyridine at room temp overnight gave the *acetate* (Xc), needles from methanol, m.p. 82 83° (Found: C, 81·45; H, 11·2; O, 7·3. $C_{30}H_{50}O_2$ requires: C, 81·4; H, 11·4; O, 7·25%), band at 5·79 μ.

2-*Methyl*-5α-*cholest*-2-*ene* (Xd)

2α-Methyl-5α-cholestan-3-one was prepared both by methylation of 2-hydroxymethylene-5α-cholestan-3-one with methyl iodide in acetone in the presence of anhydrous potassium carbonate, and by methylation of 5α-cholestan-3-one with methyl iodide via the enamine; it had m.p. 120–122·5° (reported[28]: m.p. 119–120°) undepressed on admixture with an authentic specimen.[28]

Reduction of this ketone with lithium aluminium hydride in ether gave 2α-methyl-5α-cholestan-3β-ol, m.p. 136–137° (reported[28]: m.p. 139 140°).

The latter alcohol (2·2 g) was treated in pyridine (10 ml) with toluene *p*-sulphonyl chloride (1·7 g) at room temp. The customary working-up gave the crude toluene *p*-sulphonate (m.p. 152–153°). This (3·0 g) was dissolved in dry 2,4,6-trimethylpyridine (15 ml) and the solution was refluxed under nitrogen for 2 hr. The usual working-up gave a crystalline residue which on recrystallization from ether–methanol gave long needles of the olefin (Xd, 1·55 g), m.p. 100–101°, $[\alpha]_D$ + 68° (*c*, 1) (reported[28] m.p. 96°, $[\alpha]_D$ +77) (Found: C, 87·3; H, 12·55. Calc. for $C_{28}H_{48}$: C, 87·45; H, 12·55%).

Ring opening of Xc

(a) The unsaturated acetoxy compound (1·01 g) was dissolved in ethyl acetate and the solution was treated at −40° with 91 ml of a solution of ozone in the same solvent, found to contain 119 mg O_3/100 ml. The solution was allowed to reach room temp and was then stirred with 10% ferrous sulphate solution. It was then washed with water, dried ($MgSO_4$), and the solvent removed at room temp *in vacuo*, leaving a residue (1·15 g), probably XIIa which showed a band at 3·69 μ (aldehyde) and a broad carbonyl band.

(b) The unsaturated acetoxy compound (250 mg) in pure dioxan (25 ml) was added to osmium tetroxide (250 mg) in dioxan (5 ml). The resulting dark suspension of the osmate was left at room temp overnight. Hydrogen sulphide (previously passed through barium hydroxide solution) was

[27] Pl. A. Plattner and L. M. Jampolsky, *Helv. Chim. Acta* **24**, 1459 (1941).
[28] Y. Mazur and F. Sondheimer, *J. Amer. Chem. Soc.* **80**, 5220 (1958).
[28] E. Wettstein, Ph.D. Thesis, ETH, Zurich (1959).

passed through the suspension for 1/2 hr, which was then filtered through a column of celite. The filtrate was concentrated at room temp *in vacuo* and the residue crystallized from methanol, to give one *epimer* of *2-acetoxy-2ξ,3ξ-dihydroxy-5α-cholestane* (XIa, 60 mg), of m.p. 130–133° (Found: C, 75·35; H, 10·95; O, 13·5. $C_{30}H_{54}O_4$ requires: C, 75·6; H, 11·0; O, 13·4%). From the mother liquors an *epimer* (XIb) was isolated (40 mg), which after 4 recrystallizations from methanol had m.p. 166° (Found: C, 75·55; H, 11·0; O, 13·5%).

The mixture of crude XIa and XIb (245 mg) was dissolved in dry chloroform (5 ml) and anhydrous potassium carbonate (500 mg) and recrystallized lead tetra-acetate (250 mg) were added. After shaking for 1 hr a few drops of ethylene glycol were added and the suspension was filtered. The filtrate was washed with water, dried ($MgSO_4$) and the solvent removed *in vacuo*, leaving a semi-crystalline residue (XIIa, 218 mg) which showed a band at 3·69 μ and a broad band at 5·70–5·82 μ (inflections at 5·70, 5·75 and 5·81 μ).

Ring opening of (Xd). The olefin (1·5 g) was dissolved in methylene chloride (60 ml) and the solution cooled to −15°. Ozonized oxygen (5–10%) was passed in until a blue colour persisted. Acetic acid (30 ml) was added, and then zinc powder (1·5 g) in small portions with stirring during 0·5 hr. After this (negative starch-iodide reaction) the suspension was filtered, ether was added and the organic layer was washed well with water, 5% potassium carbonate solution and again with water. Drying ($MgSO_4$) and removal of solvent *in vacuo* left an oily residue (1·60 g, probably XIIb), which showed an aldehyde band at 3·69 μ and a broad carbonyl band at 5·82–5·88 μ. This yielded the *bis-2,4-dinitrophenylhydrazone* of *2-methyl-2,3-dioxo-2′,3-seco-5α-cholestane*, m.p. 203–204° (decomp) from ethyl acetate ethanol. (Found: C, 62·0; H, 7·35; N, 14·2. $C_{40}H_{54}O_8N_8$ requires: C, 61·85; H, 7·25; N, 14·4%).

Attempted internal cyclization of XIIa *and* XIIb

(a) The following conditions were tried.

On XIIa: (i) refluxing with trimethylamine benzoate in xylene for 24 hr,[19] (ii) refluxing with toluene *p*-sulphonic acid in xylene containing a small amount of acetic anhydride.

On XIIb: (iii) as for (i), (iv) refluxing with piperidine acetate in xylene for 24 hr, (v) refluxing with potassium t-butoxide in t-butanol, (vi) refluxing with aqueous potassium hydroxide at 80° under reduced pressure.[20]

Only in the case of (iii) and (iv) the crude product showed a weak band at 6·03 μ, indicating the presence of traces of α,β-unsaturated carbonyl, but no crystalline product could be isolated.

(b) The crude keto-aldehyde (XIIb, 600 mg) was transferred in hexane to a column of active acidic alumina (Woelm, activity I, 30 g). After 48 hr a yellow band was eluted with benzene methylene chloride giving 250 mg of an oily impure product, which after a number of crystallizations from methanol gave a small amount of *1-acetyl-A-nor-5α-cholest-1-ene* (?) (XIII), m.p. 127–130° (Found: C, 83·7; H, 11·85. $C_{28}H_{48}O$ requires: C, 83·95; H, 12·1%), bands at 6·05 μ, 6·21 μ. This gave a red *2,4-dinitrophenylhydrazone*, m.p. 198–200° (decomp) (from ethyl acetate ethanol) (Found: N, 9·65. $C_{34}H_{52}O_4N_4$ requires: N, 9·65%).

1β/2-Seco-5α-cholestane-1,3-dioic acid (XVa)

5α-Cholest-1-en-3-one, (XIV), prepared by dehydrobromination of 2-bromo-5α-cholestan-3-one with lithium chloride and lithium carbonate in dimethyl formamide,[21] had m.p. 99–100°, $[\alpha]_D$ +57° (reported[22]: m.p. 98–100°, $[\alpha]_D$ +57·5°).

This (8·0 g) was dissolved in a 1 : 1 : 1 mixture of methylene chloride–ethyl acetate and acetic acid. Ozonized oxygen (5–10%) was passed at room temp through the solution until the latter became yellow (ca. 1 hr). More acetic acid and 30% hydrogen peroxide (30 ml) were then added and the mixture left overnight. The residue obtained after concentration *in vacuo* was taken up in ether; the ether layer was washed with dil acidic ferrous sulphate solution, then with water and finally with 20% potassium hydroxide solution. The acidic product was taken up in ether, the ether solution washed with water, dried ($MgSO_4$) and the ether removed. The crude residue (8·0 g) was dissolved in anhydrous methanol (200 ml) and the solution saturated with dry hydrogen chloride at 0°. After leaving the solution overnight at room temp the hydrogen chloride and methanol were removed *in vacuo* at

[20] G. I. Poos, W. F. Johns and L. H. Sarett, *J. Amer. Chem. Soc.* **77**, 1026 (1955).
[21] R. Joly, J. Warnant, G. Nominé and D. Bertin *Bull. Soc. Chim.* 366 (1958).
[22] C. Djerassi and C. R. Scholz, *J. Amer. Chem. Soc.* **69**, 2404 (1947).

room temp, the residue was taken up in ether and the ether solution extracted with several portions of 20% potassium hydroxide solution. Acidification of these extracts gave the crude monomethyl ester (XVd, 4·0 g) which was isolated with ether. A sample of this was hydrolysed by refluxing with 20% aqueous ethanolic potassium hydroxide to give the *dicarboxylic acid*, m.p. 227–230° from ether-hexane)[23] (Found: C, 73·6; H, 10·65; O, 15·4. $C_{28}H_{44}O_4$ requires: C, 74·25; H, 10·55; O, 15·2%).

The above crude monoester (XVd, 4·0 g) was treated in ether with diazomethane. The crude neutral product obtained after the usual working-up was chromatographed in hexane on alumina (Alcoa, 150 g). Prolonged elution with hexane gave a yellow by-product (300 mg); elution with methylene chloride–hexane (1 : 4) gave the *dimethyl ester* (XVb, 2·10 g) which, crystallized from methanol, had m.p. 57–58°, $[\alpha]_D$ + 29° (*c*, 10·7) (Found: C, 75·1; H, 10·65; O, 14·5. $C_{29}H_{46}O_4$ requires C, 74·95; H, 10·8; O, 14·25%), band with inflexions at 5·77 μ, 5·80 μ.

The above dimethyl ester (1·75 g) was heated under reflux with one equivalent of N sodium hydroxide (4 ml) in methanol (25 ml) for 3 hr. The solution was then concentrated *in vacuo*, water was added and the mixture extracted with hexane. The aqueous layer was acidified and the product extracted with ether. The extract was dried ($MgSO_4$) and the ether removed, giving the crude monomethyl ester, 1-*methoxycarbonyl*-1-1*nor*-2-*seco*-5α-*cholestan*-3-*oic acid* (XVc, 1·7 g), which could not be induced to crystallize even after chromatography on silica gel, it showed neutralization equivalent: 402 (Calc. for $C_{29}H_{46}O_4$, one CO_2H: 434). The S-*benzyl thiouronium salt* had m.p. 140–141° (from nitromethane) (Found: C, 70·1; H, 9·5; S, 5·05. $C_{37}H_{56}O_4N_2S$ requires: C, 69·95; H, 9·4; S, 5·35%).

Dimethyl 1*nor*-2-*seco*-5α-*cholestane*-1,2-*dioate* (XVI)

The above monomethyl ester (XVc, 1·7 g) in dry benzene (5 ml) was treated with thionyl chloride (2 ml) and a few drops of pyridine were added. The reaction mixture was left at room temp for 0·5 hr and at 40° for 10 min. The solvents were then removed *in vacuo*, benzene being added repeatedly to remove the last traces of thionyl chloride, leaving the crude ester-acid chloride which showed bands at 5·58 μ and at 5·81 μ. This was redissolved in dry benzene (15 ml) and the filtered solution was added dropwise with stirring to an excess of diazomethane in dry ether. After 20 min at room temp the solution was concentrated *in vacuo*; the yellow residue crystallized overnight, it showed bands at 4·75 μ, 5·81 μ and 6·12 μ. This crude diazoketone was dissolved in anhydrous methanol (60 ml) and a solution (4 ml) of silver benzoate in dry triethylamine (0·5 g in 5 ml) was added dropwise with stirring during 1 hr; during this time ca. 60% of the theoretical amount of nitrogen was evolved. The reaction mixture was refluxed for 1 hr, cooled, filtered (charcoal), and the filtrate concentrated *in vacuo*. The residue was chromatographed in hexane on alumina (Alcoa, 70 g). Methylene chloride–hexane (1 : 4) eluted the *dimethyl ester* (420 mg) which had m.p. 60° (from methanol), $[\alpha]_D$ 0° (*c*, 0·4) (Found: C, 75·45; H, 10·8; O, 14·0. $C_{29}H_{46}O_4$ requires: C, 75·3; H, 10·9; O, 13·85%).

2α-*Methoxycarbonyl*-A-*nor*-5α-*cholestan*-1-*one* (XVIIa)

The above dimethyl ester (400 mg) in dry benzene (15 ml) was refluxed with dry potassium t-butoxide (from 300 mg potassium) for 12 hr, during which small portions of solvent were distilled off. The reaction mixture was treated as described for the preparation of the keto ester (IIa). The crude product (200 mg) on crystallization from methanol gave the *keto-ester*, m.p. 121·5–122·5°, $[\alpha]_D$ −4° (*c*, 0·4) (Found: C, 77·9; H, 10·95. $C_{28}H_{44}O_3$ requires: C, 78·1; H, 10·75%), bands at 5·72 μ and 5·80 μ. It gave a dark green colour with ferric chloride.

A-*nor*-5α-*Cholestan*-1-*one* (XVIIb)

The above keto ester (96 mg) was heated under reflux in acetic acid (5 ml) and conc hydrochloric acid (2 ml) during 1 hr, after which the mixture was concentrated to half its volume. The neutral product obtained after ether extraction was chromatographed in hexane on alumina (Alcoa, 3 g). The crystalline fractions eluted by hexane were combined and recrystallized from methanol to give needles of the *ketone* (52 mg), m.p. 84–85°, $[\alpha]_D$ + 16° (*c*, 0·81) (Found: C, 83·95; H, 11·8. $C_{26}H_{44}O$ requires: C, 83·8; H, 11·9%), band at 5·80 μ, (5·78 μ in CS_2). The orange 2,4-*dinitrophenylhydrazone* had m.p. 130–131° (from ethanol) (Found: C, 69·9; H, 8·95. $C_{35}H_{48}O_4N_4$ requires: C, 69·55; H, 8·75%).

[23] Ch. Tamm and R. Albrecht, *Helv. Chim. Acta* **43**, 768 (1960) report m.p. 221–222° for this compound.

A-nor-5α-Cholestane

A-nor-5α-Cholestan-2-one (250 mg) was refluxed for 1 hr in ethylene glycol (6 ml) with 85% hydrazine hydrate (0·6 ml). To the cooled solution potassium hydroxide (0·5 g) was added and the mixture was distilled until the vapour temp reached 190°; after this reflux was continued for 3 hr. To the cooled mixture water was added and the product extracted with pentane. The washed and dried extract was concentrated and applied to basic active alumina. Pentane eluted the *hydrocarbon* which was recrystallized from ether–methanol; it had m.p. 85·5–86·0°, $[\alpha]_D$ +20·6° (*c*, 2·62) (Found: C, 87·05; H, 12·75. Calc. for $C_{26}H_{46}$: C, 87·05; H, 12·95%).

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