The Transformation of 22,26-Oxido-$\Delta^{17(20)}$-cholestene-3β,16ξ-diol to 17-Iso,20-isocholestane Derivatives

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The reduction of 22,26-oxido-$\Delta^{17(20)}$-cholestene-3β,16ξ-diol in acidic media yields three 17-isocholestane derivatives. The major reduction product is a 17-iso,20-isocholestane-3β,16ξ-27-triol (IIIa). The conversion of IIIa to 17-iso,20-isocholestan-16ξ-ol (V), 17-iso,20-isocholestan-3β-ol (IXb), and 17-iso,20-isocholestane (IXa) is described.

In a previous publication[2] the structure of 22,26-oxido-$\Delta^{17(20)}$-cholestene-3β,16ξ-diol (I) was established. While ascertaining the structure of I, it was observed that the hydrogenation of I did not yield the expected 22,26-oxidocholestane-3β,16ξ-diol as the major product. Instead, three compounds were obtained, including a 22,26-oxido compound that was sterically different from the two epimeric 22,26-oxidocholestane-3β,16ξ-diols.[3] This paper is concerned with the hydrogenation of 22,26-oxido-$\Delta^{17(20)}$-cholestane-3β,16ξ-diol (I) and the proof of structure of the compounds so obtained. The transformation of the major reduction product, 17-iso,-20-isocholestane-3β,16ξ,27-triol (IIIa) to the formerly unknown 17-iso,20-isocholestan-3β-ol (IXb) and 17-iso,20-isocholestane (IXa) also is described.

Catalytic hydrogenation of I (PtO_2, 90% ethanol–acetic acid) gave II, IIIa, and IIIb in 23, 58, and 3% yields, respectively. Compound II obviously resulted from the saturation of the 17,20-double bond. It readily gave a diacetate indicating the presence of two hydroxyl groups and an inert ether oxygen. Oxidation of II with chromic acid gave the diketone XIII showing strong bands at 1712 and 1736 cm.$^{-1}$ of the 3- and 16-carbonyl bands. Since it may be assumed for steric reasons that the pyran ring in I is *trans* to the steroid skeleton, if hydrogen attacked from the back, II should be a 17-normal,20-isocholestane derivative.[4] The value of optical rotation of XIII indicates a 17-iso-compound (see Table I). The formation of such derivative (*i.e.*, 17-iso,20-normal) necessitates a front side attack of hydrogen on I. Compound II cannot be further reduced under the conditions employed. Furthermore XIII is sterically different from the two epimeric 22,26-oxidocholestane-3,16-diones[3] (see Table I). The mode of formation of these latter epimers demonstrated that they have the normal configuration at C-17 and C-20.

Our key compound IIIa, the major reduction product of I, is formulated as a 17-iso,20-isocholestane derivative because of its physical properties and a number of transformations elaborated later.[5] Acetylation of IIIa readily yielded a triacetate. Oxidation with chromic acid (acetone at 20°) gave 25-carboxy-17-iso,20-iso-26-norcholestane-3,16-dione (X), showing strong bands at 1709 (25-carboxy and 3-carbonyl groups) and 1733 (16-ketone), and the typical broad absorption of the carboxylic groups at 2500–2700 cm.$^{-1}$.

Apparently 16-keto steroids (see Table I) with a β-oriented side chain give high negative rotations. Therefore, the specific rotation +39° of XIII and +2° of X supports the assumption of the 17-iso configuration of these two compounds and consequently of II and IIIa.

Attempts to prepare the 17-iso,20-isocholestane-16ξ-ol derivative from IIIa *via* selective tosylation and subsequent lithium aluminum hydride reduction gave in good yields predominately the Δ^{16}-20-isocholestene (IVa). It should be remembered that under identical conditions, cholestane-3β,16β,27-triol gave cholestan-16β-ol.[6] When the tosylation of IIIa was carried out at 0°, subsequent reduction of the tosylate mixture with lithium aluminum hydride gave a mixture of at least four compounds. In order of their increasing adsorption on alumina Δ^{16}-20-isocholestene (IVa), 17-iso,-20-isocholestan-16ξ-ol (V), Δ^{16}-20-isocholesten-3β-ol (IVb), and 17-iso,20-isocholestane-3β,16ξ-diol (VI) were

TABLE I

Compound	$[\alpha]_D$, deg.	Compound	$[\alpha]_D$, deg.
17-Iso,20-isocholestan-16-one (VIIa)	+2	Cholestan-16-one	−117[a]
		Coprostan-16-one	−121[b]
		5-Cholestene-3β,27-diol-16-one	−156[c]
25-Carboxy-17-iso,20-iso-26-norcholestane-3,16-dione (X)	+2	25-Carboxycholestane-3,16-dione	−97[c]
22,26-Oxido-20ξ-methyl-17-isocholestane-3,16-dione (XIII)		22,26-Oxidocholestane-3,16-dione	−107[d]
	+39	22,26-Oxido-22-isocholestane-3,16-dione	−104[d]

[a] See ref. 9. [b] See ref. 6. [c] I. Scheer, M. J. Thompson, and E. Mosettig, *J. Am. Chem. Soc.*, **78**, 4733 (1956). [d] See ref. 3.

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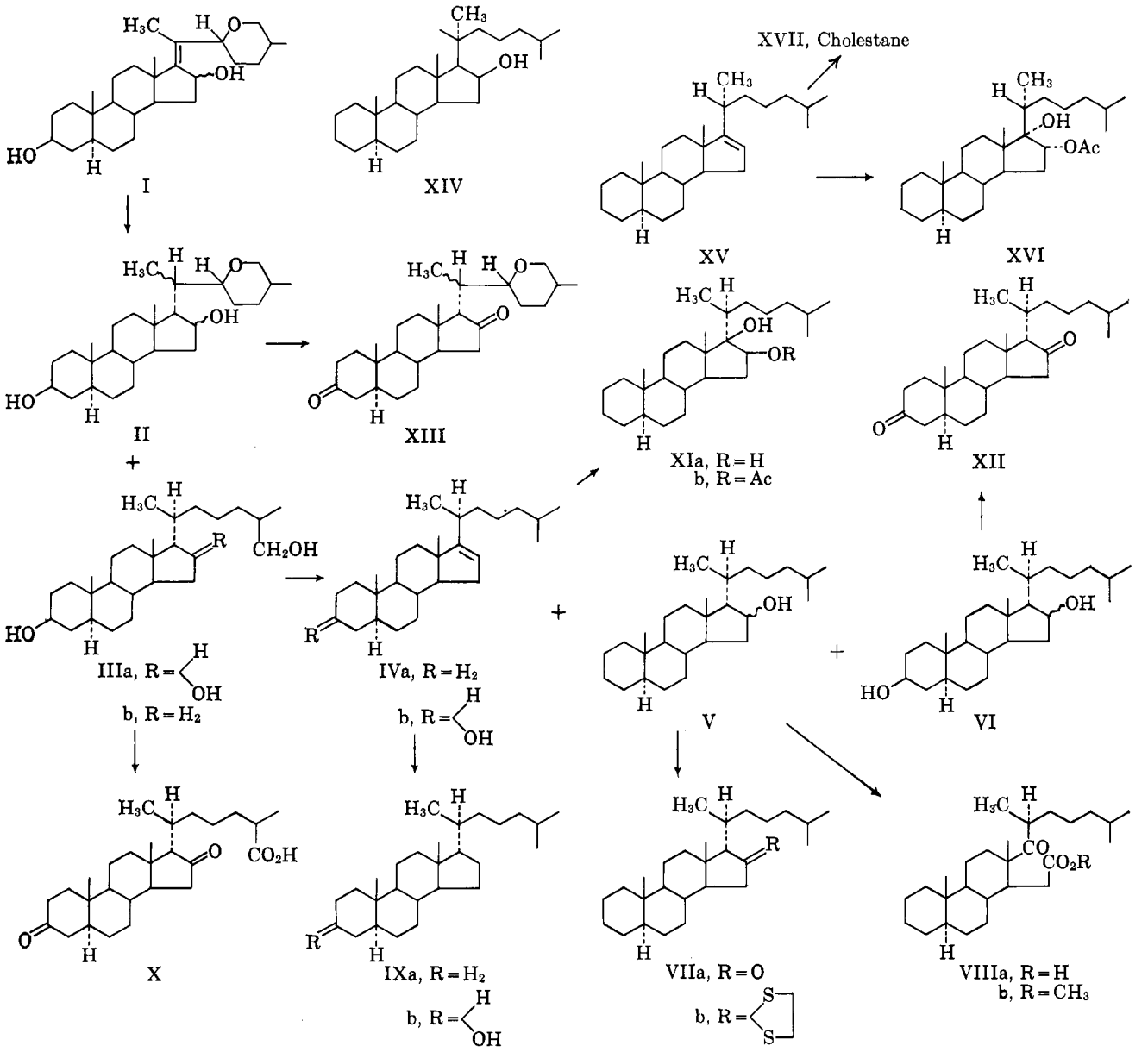
(2) M. J. Thompson, J. Moore, and E. Mosettig, *J. Org. Chem.*, **27**, 4108 (1962).

(3) I. Scheer, M. J. Thompson, and E. Mosettig, *J. Am. Chem. Soc.*, **79**, 3218 (1957).

(4) The configuration assignment at C-22 is arbitrary.

(5) The formation of IIIa from I may take place through: (A) opening of the pyrano ring (facilitated by the 17,20-double bond), and subsequent saturation of the double bond of an intermediate $\Delta^{17(20)}$-cholestene derivative; (B) 1,4-addition of hydrogen to the allylic ether and subsequent saturation of an intermediary $\Delta^{17(22)}$-cholestene derivative. No intermediate compound in the reduction of I and II has been detected. Pathway A necessitates the assumption of a *cis* *n*-hexyl side-chain and frontal attack of hydrogen at the C-17,C-20 double bond. For pathway B again one has to assume (in the first step) a frontal attack of hydrogen at C-17. The saturation of the 20,22-double bond can lead then either to a 17-iso,20-normal, or 17-iso,20-iso configuration.

(6) I. Scheer and E. Mosettig, *J. Am. Chem. Soc.*, **77**, 1820 (1955).



obtained in respective yields of 13, 35, 13, and 11%.[7]

Compound V gave a monoacetate (acetic anhydride, pyridine, steam bath). Treatment with chromic acid in acetone for only 2 min. gave quantitatively 17-iso,20-isocholestan-16-one (VIIa). A strong band at 1736 cm.$^{-1}$ and the low specific rotation of +2° support the assigned structure. When V was treated with an excess of chromic acid for 30 min., the keto acid VIIIa was obtained. Its methyl ester VIIIb exhibited two sharp bands in the carbonyl region at 1739 (ester carbonyl) and 1712 cm.$^{-1}$ (ketone). Oxidation of 16β-hydroxycholestane under similar conditions gave cholestan-16-one.

The optical rotatory dispersion curve of VIIa exhibits a weak negative single Cotton effect (α_{310} −249°, $\alpha_{272.5}$ +241°).[8] The rotatory dispersion curve of cholestan-16-one exhibits a very strong negative single Cotton effect (α_{320} −2900°, α_{277} + 3100°). While the troughs and peaks are nearly at the same wave lengths, the amplitude of the latter curve is more than ten times that of the former.[9] Analogous relations prevail in regards to the 17α-epimeric methyl-D-homoanalones.[10]

Compound VI readily gave a diacetate and brief treatment with chromic acid gave in good yield the dione which showed strong absorption bands at 1712 and 1736 cm.$^{-1}$.

The location of the double bond in IVa was confirmed through n.m.r. spectra and integration of the olefinic proton area, as well as chemically by hydroxylation and subsequent acetylation. Chromatography of the reaction product yielded as the sole product the hydroxy acetoxy derivative XIb which was not attacked by chromic acid. The Δ^{16}-hydrocarbon also was obtained by heating under reflux the tosylate of V in collidine. We then converted under identical conditions cholestan-16β-ol (XIV)[6] to Δ^{16}-cholestene (XV).[11] Compounds XV and IVa proved to be different. The 17-normal,20-

(7) The ease of dehydration to Δ^{16}-compounds (IVa and IVb) suggests α-orientations in IIIa and consequently in V and VI.

(8) We are obliged to Professor Djerassi for providing these data.

(9) C. Djerassi, O. Galpern, G. R. Pettit, and G. H. Thomas, *J. Org. Chem.*, **24**, 1 (1959); see also C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p. 45.

(10) 17a,α-Methyl-D-homoandrostan-3β-ol-17-one, α_{320} −463°, α_{281} +195°; 17aβ-methyl-D-homoandrostan-3β-ol-17-one, α_{315} −1723°, α_{275} +1308: see C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6362 (1956).

(11) N.m.r. spectra and integration of the olefinic proton area showed only one proton indicating a trisubstituted double bond, *viz.* $\Delta^{16(17)}$.

normal configuration of XIV appears to be reasonably well established through its relation to cholestane.[6,12]

The C-20 in IVa must have an iso configuration, which consequently must be true for all compounds experimentally linked to it. Hydroxylation of XV and subsequent acetylation as applied in IVa, yielded after chromatography the hydroxy acetoxy derivative (XVI), $[\alpha]D$ −47°, differing considerably in the specific rotation from XIb, $[\alpha]D$ +35°. This difference suggests that the side chain of XIb is α-oriented[13] or, in other words, that hydroxylation of IVa has taken place at the front side, in contrast to the hydroxylation of XV.

Catalytic hydrogenation of IVa yields apparently as the only product a crystalline, saturated hydrocarbon IXa, m.p. 99.5–100.5°, $[\alpha]D$ −2°, which again means that hydrogen has entered from the front side; otherwise the 17-normal cholestane would have been formed.[14] Hydrogenation of the Δ^{16}-cholestene (XV) under identical conditions gave cholestane (XVII). The reduction of IVb gave the 17-iso,20-isocholestan-3β-ol (m.p. 165–166°, $[\alpha]D$ −7°). The structure of 17-iso,20-isocholestane is assigned to IXa and IXb. This is further supported by comparison with 20-isocholestane which was synthesized in this laboratory[15] (m.p. 67–68°, $[\alpha]D$ +7.6°). Mixture melting point of IXa and 20-isocholestane showed an appreciable depression.

It is interesting, at this stage to confirm the observations made by Sondheimer and Mechoulam[13] and Plattner and Pataki[16] in their 20-iso series; the trend of optical rotation is towards negative values as epimerization proceeds *via* >20-iso, >17-iso, 20-iso series (see Table II).

TABLE II

Compound	M.p., °C.	$[\alpha]D$, deg.	MD, deg.
5α-Cholestane (17-*n*,20-*n*)	80	+25.9	+96.5
5α-Cholestane (17-*n*,20-iso)	68–69	+7.6[15]	+28.3
5α-Cholestane (17-iso,20-iso) IXa	99–100	−2.0	−7.5
5α-Cholestan-3β-ol (17-*n*,20-*n*)	144–145	+25.0	+97.7
5α-Cholestan-3β-ol (17-*n*,20-iso)	160–161	+6.0	+23.3
5α-Cholestan-3β-ol (17-iso,20-iso) IXb	165–166	−6.6	−28.8

[a] See ref. 15.

The physical properties and a number of transformations elaborated in the manuscript demonstrate that our key compound IIIa and the various compounds derived from IIIa are 17-iso,20-isocholestane derivatives and are structurally presented as the same in the scheme. The specific rotation +39° of XIII supports the assignment of the 17-iso configuration of XIII and consequently of II. Since the configuration at C-20 of these two compounds was not proven and could not be arrived at solely on mechanistic grounds, the configuration at C-20 is given the uncertain designation, namely "20ξ-methyl."

The physical properties, especially the $[\alpha]D$ of 17-iso,-20-isocholestane derivatives should be of significant help in determining the correct stereochemistry at C-17 of naturally occurring C_{27} sterols and steroids. It should be mentioned that the synthesis of the 17-iso,20-isocholestane derivatives leaves only one of the four possible isomers of the cholestane side chain to be synthesized, namely, the 17-iso,20-normal cholestane.

Experimental[17]

Reduction of 22,26-Oxido-$\Delta^{17(20)}$-cholestene-3β,16ξ-diol (I).—A mixture of 2.0 g. of 22,26-oxido-$\Delta^{17(20)}$-cholestene-3β,16ξ-diol (I), 0.5 g. of Adams catalyst, 275 ml. of 95% ethanol, and 25 ml. of glacial acetic acid was shaken with hydrogen at room temperature and atmospheric pressure for 24 hr. Approximately 2.2 molecular equivalents of hydrogen was absorbed. The catalyst was removed by filtration and the solution was concentrated to dryness *in vacuo*. The residue recrystallized from ethyl acetate–methanol to give 1.16 g. of **17-iso,20-isocholestane-3β,16ξ,27-triol (IIIa)** as rods, m.p. 243–247°. A second recrystallization raised the melting point to 246–248°, $[\alpha]D$ +20°.

Anal. Calcd. for $C_{27}H_{48}O_3$: C, 77.09; H, 11.50. Found: C, 76.92; H, 11.22.

The triacetate of IIIa (acetic anhydride–pyridine, steam bath, 2 hr.) was obtained as rectangular plates from dilute methanol, m.p. 119–120°, $[\alpha]D$ +6°.

Anal. Calcd. for $C_{33}H_{54}O_6$: C, 72.59; H, 9.96; acetyl, 23.6. Found: C, 72.53; H, 9.67; acetyl, 23.1.

20ξ-Methyl,22,26-oxido-17-isocholestane-3β,16ξ-diol (II).—The mother liquor from the catalytic hydrogenation of the 22,26-oxido-$\Delta^{17(20)}$-cholestene-3β,16ξ-diol (I), described before, was concentrated to dryness *in vacuo* and the residue was chromatographed on benzene-washed alumina (activity grade II). The crystalline fractions eluted with benzene–chloroform (9:1) and (6:1) and exhibiting identical infrared spectra were combined and recrystallized from acetone to give 0.46 g. of II as spears, m.p. 191–194°, $[\alpha]D$ +25°. Prolonged drying under high vacuum at 140° was required to free II of solvent.

Anal. Calcd. for $C_{27}H_{46}O_3$: C, 77.46; H, 11.08. Found: C, 77.30; H, 10.82.

Further elution of the column with benzene–chloroform (3:1) yielded 60 mg. of **17-iso,20-isocholestane-3β,27-diol (IIIb)** as needles from acetone, m.p. 194–195°, $[\alpha]D$ +3°.

Anal. Calcd. for $C_{27}H_{48}O_2$: C, 80.13; H, 11.95. Found: C, 80.42; H, 11.84.

The diacetate of II (acetic anhydride–pyridine, 18 hr., 25°) was obtained as rectangular plates from dilute methanol, m.p. 171–173°, $[\alpha]D$ +5°.

Anal. Calcd. for $C_{31}H_{50}O_5$: C, 74.06; H, 10.02. Found: C, 74.21; H, 9.79.

20ξ-Methyl,22,26-oxido-17-isocholestane-3,16-dione (XIII).—To a stirred solution of 50 mg. of 20ξ-methyl,22,26-oxido-17-isocholestane-3β,16ξ-diol (II) in 5 ml. of acetone at 10° was added, dropwise, an 8 *N* solution of chromic acid in dilute sulfuric acid (*ca.* 40%) until a persistent orange-brown coloration indicated oxidation was completed.[18] The mixture was kept at 10° for 15 min., diluted with water, and the white crystalline precipitate was collected, washed with water, and dried to yield 40 mg. of XIII, m.p. 161–165°. Recrystallization from dilute acetone gave elongated needles, m.p. 173–175°, $[\alpha]D$ +39°, ν^{CHCl_3} 1736 (16-ketone) and 1712 (s, 3-ketone) cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21. Found: C, 78.42; H, 10.26.

(12) R. E. Marker and D. L. Turner, *J. Am. Chem. Soc.*, **63**, 767 (1941).

(13) The difference between cholesterol and 20-isocholesterol, *i.e.*, the contribution of the 20-methyl to optical rotation, is apparently quite small: see (a) F. Sondheimer and R. Mechoulam, *ibid.*, **80**, 3087 (1958); (b) R. Hayatsu, *ibid.*, **77**, 823 (1957); (c) K. Tsuda, R. Hayatsu, Y. Kishida, and S. Akagi, *ibid.*, **80**, 921 (1958).

(14) Attempts to arrive at IXa *via* VIIb failed, presumably because of partial inversion of VIIa during formation of the thioketal. The infrared spectra of IXa and the hydrocarbon mixture (m.p. 76–78°, $[\alpha]D$ +4°) obtained by desulfurization differed only slightly. Ketone VIIa, $[\alpha]D$ +2°, was isomerized by refluxing for 2 hr. with 5% methanolic potassium hydroxide to a product of m.p. 89° and $[\alpha]D$ −60°, which is either 20-isocholestan-16-one or a mixture of the latter and 17-iso,20-isocholestan-16-one (VIIa).

(15) G. V. Nair and E. Mosettig, *J. Org. Chem.*, **27**, 4659 (1962).

(16) P. A. Plattner and J. Pataki, *J. Chim. Acta*, **36**, 1241 (1943).

(17) All melting points were determined on the Kofler block. Rotations were determined in approximately 1% solutions in chloroform at 20°. Infrared spectra were obtained with a Perkin-Elmer Model 21 double beam spectrophotometer with sodium chloride prism and cells. N.m.r. spectra were obtained with a Varian HR-60 spectrometer. Deuteriochloroform was used as solvent and all data are reported in cycles per second referred to tetramethylsilane as an internal reference.

(18) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

25-Carboxy-17-iso,20-iso-26-norcholestane-3,16-dione (X).—To a stirred solution of 120 mg. of 17-iso,20-isocholestane,3β,16ξ,-27-triol (IIIa) in acetone at 20° was added a slight excess of an 8 *N* solution of chromic acid in dilute sulfuric acid and stirring was continued for 2 min. The mixture was diluted with water and the crystalline precipitate was collected, washed with water, and dried to yield 100 mg. of X, m.p. 194–196°. Recrystallization from dilute acetone gave rectangular plates, m.p. 195–197°, $[\alpha]_D$ +2°; ν^{CHCl_3} 2700–2500 (wb), 1709 (s, 3-ketone and carboxy carbonyl), and 1733 (s, 16-ketone) cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{42}O_4$: C, 75.30; H, 9.83. Found: C, 75.56; H, 9.66.

Tosylation and Subsequent Lithium Aluminum Hydride Reduction of 17-Iso,20-isocholestane-3β,16ξ,27-triol (IIIa).—To a solution of 2.2 g. of IIIa in 67 ml. of dry pyridine at 0° was added 3.4 g. of *p*-toluenesulfonyl chloride. The solution was allowed to stand overnight at 0°, was poured into ice and water, and the precipitate was extracted with ether. The ethereal solution was washed with cold 5% hydrochloric acid, water, 2% sodium bicarbonate solution, water, and dried over sodium sulfate. On evaporation *in vacuo* a semicrystalline residue was obtained. The residue was dissolved in 400 ml. of dry ether and 2.0 g. of solid lithium aluminum hydride was added. The mixture was refluxed overnight, cooled, treated with a few drops of ethyl acetate, water, and 20 ml. of 4 *N* hydrochloric acid. The ether layer was separated and washed with 5% bicarbonate solution and water, dried over sodium sulfate, and evaporated to dryness *in vacuo*. The semicrystalline residue was chromatographed over 9:1 benzene–petroleum ether (b.p. 60–70°) washed alumina (activity grade II). The first two fractions eluted with benzene–petroleum ether (9:1) crystallized from ether–methanol to give 0.25 g. of **$\Delta^{16(17)}$-20-isocholestene (IVa)** as spears, m.p. 87–90°, $[\alpha]_D$ −33°. This material gave a positive tetranitromethane test. N.m.r. intergration of the olefinic proton area showed only one proton indicating a trisubstituted double bond.

Anal. Calcd. for $C_{27}H_{46}$: C, 87.49; H, 12.51. Found: C, 87.67; H, 12.08.

Further elution of the column with benzene–petroleum ether (9:1) afforded after crystallization from methanol 0.7 g. of **17-iso,20-isocholestan-16ξ-ol (V)**, m.p. 181–183°, $[\alpha]_D$ +19°.

Anal. Calcd. for $C_{27}H_{48}O$: C, 83.43; H, 12.44. Found: C, 83.70; H, 12.13.

The acetate of V (acetic anhydride–pyridine, 1 hr., steam bath) was obtained as plates, m.p. 141–142°, $[\alpha]_D$ +20°.

Anal. Calcd. for $C_{29}H_{50}O_2$: C, 80.87; H, 11.70. Found: C, 81.09; H, 11.31.

Elution of the column with benzene after the separation of V yielded, after crystallization from methanol, needles of **$\Delta^{16(17)}$-20-isocholesten-3β-ol (IVb)**, 0.26 g., m.p. 165–167°, $[\alpha]_D$ −26°. This compound gave a positive tetranitromethane test.

Anal. Calcd. for $C_{27}H_{46}O$: C, 83.86; H, 11.99. Found: C, 83.77; H, 11.85.

Continued elution of the column with benzene–chloroform (3:1) yielded 0.25 g. of **17-iso,20-isocholestane-3β,16ξ-diol (VI)**, m.p. 221–222°, $[\alpha]_D$ +21°.

Anal. Calcd. for $C_{27}H_{48}O_2$: C, 80.14; H, 11.96. Found: C, 80.07; H, 12.01.

The diacetate of VI (acetic anhydride–pyridine, 1 hr., steam bath) was obtained as needles from dilute methanol, m.p. 116–120°, with resolidification and remelting at 134–137°. After prolonged drying under high vacuum at 110°, the melting point was 137–139°, $[\alpha]_D$ +7°.

Anal. Calcd. for $C_{31}H_{52}O_4$: C, 76.18; H, 10.72. Found: C, 76.44; H, 10.31.

17-Iso,20-isocholestan-16-one (VIIa).—To a stirred solution of 0.3 g. of 17-iso,20-isocholestan-16ξ-ol (V) in 30 ml. of acetone at 15° was added a slight excess of 8 *N* solution of chromic acid in dilute sulfuric acid, and after 2 min. the mixture was diluted with water. The precipitate was collected, washed with water, and dried. The dried material (0.28 g.) was dissolved in benzene–petroleum ether (3:1) and filtered through a layer of Florisil. The solvent was removed *in vacuo* and the residue recrystallized from ethanol yielded as needles 0.25 g. of VIIa, m.p. 137–138°, $[\alpha]_D$ +2°; ν^{CS_2} 1736 (s, 16-ketone) cm.$^{-1}$; R.D. (*c* 0.09, methanol) trough at α_{310} −249°, peak at α_{272} +241°.

Anal. Calcd. for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found: C, 83.97; H, 11.73.

When the alcohol (V) in acetone at 25° was treated with an excess of 8 *N* solution of chromic acid in dilute sulfuric acid for 30 min., the **keto acid (VIIIa)** was obtained, m.p. 197–199°, $[\alpha]_D$ +90°.

Anal. Calcd. for $C_{27}H_{46}O_3$: C, 77.46; H, 11.08. Found: C, 77.25; H, 11.02.

Treatment of VIIIa with diazomethane in the usual manner gave the **methyl ester (VIIIb)**, m.p. 184–187°, $[\alpha]_D$ +96° ν^{CS_2} 1739 (ester carbonyl) and 1712 (ketone) cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{48}O_3$: C, 77.72; H, 11.19. Found: C, 77.34; H, 10.91.

17-Iso,20-isocholestan-16-one 16-Ethylenethioketal (VIIb).—To a solution of 70 mg. of 17-iso,20-isocholestan-16-one (VIIa) in 2 ml. of acetic acid was added 0.2 ml. of ethanedithiol and 0.2 ml. of boron fluoride in ether. The mixture was allowed to stand overnight at room temperature diluted with water and precipitate collected. Recrystallization from ether–methanol gave 50 mg. of VIIb as needles, m.p. 183–186° and 190–194°, $[\alpha]_D$ +8°.

Anal. Calcd. for $C_{29}H_{50}S_2$: C, 75.25; H, 10.85. Found: C, 75.05; H, 10.84.

Isomerization of VIIa.—A mixture of 53 mg. of 17-iso,20-isocholestan-16-one (VIIa, $[\alpha]_D$ +2°) and 10 ml. of 5% methanolic potassium hydroxide was refluxed for 2 hr. The mixture was diluted with water and extracted with ether. The ethereal solution was washed with water and dried over sodium sulfate. The solution was concentrated to dryness *in vacuo*. Crystallization from methanol gave 40 mg. of plates, m.p. 88–91°, $[\alpha]_D$ −60°; ν^{CS_2} 1736 (s, 16-ketone) cm.$^{-1}$.

17-Iso,20-isocholestane-3,16-dione (XII).—Oxidation of 100 mg. of 17-iso,20-isocholestane-3β,16ξ-diol (VI) as was described for the preparation of VIIa gave 95 mg. of XII as needles, m.p. 170–175°. Two recrystallizations from ethanol gave 70 mg. of material, m.p. 174–176°, $[\alpha]_D$ +18°; ν^{CS_2} 1712 (s, 3-ketone) and 1736 (s, 16-ketone) cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.68; H, 10.81.

Hydroxylation and Subsequent Acetylation of $\Delta^{16(17)}$-20-Isocholestene (IVa).—A mixture of 100 mg. of $\Delta^{16(17)}$-20-isocholestene (IVa), 10 ml. of dry ether, 100 mg. of osmium tetroxide, and two drops of pyridine was allowed to stand for 24 hr. at room temperature. Hydrogen sulfide was passed through the mixture and the black precipitate of osmium sulfide was collected. The ether was evaporated *in vacuo* to a crystalline residue, which was dissolved in 10 ml. of benzene and chromatographed over Florisil. The first 25-ml. fraction of benzene yielded 30 mg. of starting material IVa. The column was then eluted with benzene–chloroform (1:1) to yield crystalline material. This material was acetylated (acetic anhydride–pyridine, steam bath, 2 hr.). The crystalline material was chromatographed over neutral alumina (activity grade II). The fraction eluted with 6:1 benzene–petroleum ether (b.p. 60–70°) upon recrystallization from dilute methanol yielded 65 mg. of XIb as elongated needles, m.p. 167–169°; after drying at 100° under high vacuum, m.p. 179–180°, $[\alpha]_D$ +35°; ν^{CS_2} 1745 (s, acetate) and 3571 (hydroxyl) cm.$^{-1}$. This material was not attacked by chromic acid solution under mild conditions.

Anal. Calcd. for $C_{29}H_{50}O_3$: C, 77.97; H, 11.28. Found: C, 78.19; H, 11.18.

The Glycol (XIa).—Saponification of XIb with 2% methanolic potassium hydroxide solution gave the glycol XIa in 90% yield, needles from dilute methanol, m.p. 201–203°, $[\alpha]_D$ +10°.

Anal. Calcd. for $C_{27}H_{48}O_2$: C, 80.13; H, 11.96. Found: C, 80.36; H, 12.09.

$\Delta^{16(17)}$-Cholestene (XV).—A mixture of 650 mg. of cholestan-16β-ol (XIV) and 1.1 g. of *p*-toluenesulfonyl chloride was allowed to stand overnight at room temperature. The mixture was poured into ice and water, and extracted with ether. The ethereal solution was washed with water, 2% sodium bicarbonate solution, water, dried over sodium sulfate, and concentrated to dryness *in vacuo*. To the oily tosylate was added 50 ml. of dry collidine and the mixture was refluxed for 30 min. The collidine was removed *in vacuo* and the residue was treated with petroleum ether. The insoluble residue was removed by filtration and the petroleum ether filtrate was passed through a column of activity grade II alumina. The first two fractions eluted with petroleum ether yielded 418 mg. of an oily hydrocarbon. Crystallization from acetone gave 206 mg. of $\Delta^{16(17)}$-cholestene (XV), m.p. 65–66°, $[\alpha]_D$ +6°. The infrared spectra of XV and IVa were different. N.m.r. integration of the olefinic proton area showed one olefinic proton, indicating a trisubstituted double bond, *viz.*, $\Delta^{16(17)}$.

Anal. Calcd. for $C_{27}H_{46}$: C, 87.49; H, 12.51. Found: C, 87.65; H, 12.34.

Hydroxylation and Subsequent Acetylation of $\Delta^{16(17)}$-Cholestene (XV).—As in the prior preparation of XIb, 50 mg. of $\Delta^{16(17)}$-cholestene and 100 mg. of osmium tetroxide were allowed to stand at room temperature overnight. The crystalline glycol thus obtained was acetylated (acetic anhydride–pyridine, steam bath, 2 hr.). Careful chromatography of the crystalline acetate yielded 44 mg. of the **hydroxy acetate (XVI)** as the only product, m.p. 174–175°, $[\alpha]D$ −47°; ν^{CS_2} 1745 (s, acetate) and 3571 (hydroxyl) cm.$^{-1}$. The infrared spectra of XIb and XVI were different.

Anal. Calcd. for $C_{29}H_{50}O_3$: C, 77.97; H, 11.28. Found: C, 78.26; H, 11.33.

17-Iso,20-isocholestane (IXa).—A mixture of 0.3 g. of $\Delta^{16(17)}$-20-isocholestene (IVa), 1.0 g. of 10% palladium on charcoal, 25 ml. of ethyl acetate, and 10 ml. of acetic acid was shaken with hydrogen at room temperature and pressure for 2 hr. The crystalline residue obtained from the reaction gave 250 mg. of plates, m.p. 98–99°. A second recrystallization from ether–methanol gave 235 mg. of IXa, m.p. 99.5–100.5°, $[\alpha]D$ −2°, negative tetranitromethane test.

Anal. Calcd. for $C_{27}H_{48}$: C, 87.02; H, 12.98. Found: C, 87.10; H, 12.71.

Hydrogenation of $\Delta^{16(17)}$-cholestene (XV) under similar conditions gave cholestane (XVII), m.p. 78–79°. Mixture melting point with an authentic sample of cholestane showed no depression. The compounds had identical infrared spectra.

The Raney nickel reduction of the 17-iso,20-isocholestan-16-one 16-ethylenethioketal (VIIb) afforded plates from ether–methanol, m.p. 76–78°, $[\alpha]D$ +4°. The infrared spectra of this material and the substance obta ned from catalytic hydrogenation of IVa were different.

17-Iso,20-isocholestan-3β-ol (IXb).—A mixture of 100 mg. of $\Delta^{16(17)}$-20-isocholesten-3β-ol (IVb), 50 ml. of ethyl acetate, 5 ml. of acetic acid, and 50 mg. of platinum oxide was shaken with hydrogen at room temperature and pressure. The crystalline residue crystallized from ethanol gave needles, m.p. 160–163°. The material recrystallized twice from ethanol gave 60 mg. of needles, m.p. 165–166°, $[\alpha]D$ −6.6°. Mixture melting point with 20-isocholestan-3β-ol (m.p. 160–161°)[15] showed a depression, m.p. 130–137°.

Anal. Calcd. for $C_{27}H_{48}O$: C, 83.43; H, 12.45. Found: C, 83.70; H, 12.22.

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Telomerization by Free-Radical Mercaptan Chain Transfer. II. Telomers of Acrylate Esters with Simple Thiols[1,2]

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Preparation and characterization of ten telomers formed from acrylate esters in reactions with methyl and ethyl mercaptans are reported. Determination of the first three telomerization chain transfer constants and the polymerization chain transfer constant for the methyl acrylate–ethanethiol system is also described. The two-unit transfer constant is about equal to the polymerization constant, but the three-unit constant is substantially higher than either. This suggests that a reactivity minimum exists for the three-unit radical such as has been reported for bromotrichloromethane telomers. A possible explanation is suggested.

Studies of telomerization of several monomers with bromotrichloromethane[3] have yielded evidence for an unexplained reactivity minimum in radical chains three or four units long. Propagation rate constants (k_p) are reported to be significantly lower for these lengths than for shorter or longer chains. Rate constants for chain transfer (k_d) are much less reduced; hence the Mayo chain transfer constants ($C_n = k_d/k_p$) show a corresponding maximum.

Some exchange reaction or interaction involving the chain end seems implied by these findings, but its nature is still obscure. Kirkham and Robb[3b] suggested a "semibond" interaction between a terminal chlorine atom and the radical-bearing carbon. In three- and four-unit chains these are eight and ten atoms apart respectively, which are usually considered improbable intervals for maximum direct interaction. However, there is some uncertainty about the chain sizes involved since the experiments on which these results are based do not involve quantitative separation of telomer products.

Kharasch and Fuchs[4] showed that methyl acrylate yields mixtures of volatile telomers when it reacts with ethanethiol in the presence of a free-radical initiator; hence acrylate esters and low molecular weight thiols appear to be promising systems for telomerization studies involving discrete separations of products by gas chromatography. This paper reports identification and characterization of ten acrylate ester telomers with methyl and ethyl mercaptans. Determination of several chain transfer constants in the methyl acrylate–ethanethiol system, which show some evidence for a reactivity minimum, also are described.

A procedure for obtaining telomer chain transfer constants similar to that described by Scott and Wang[2] was employed. This has the advantage that only ratios of successive telomer concentrations formed at low conversion and varying monomer to thiol ratios need to be measured. Chances for experimental errors are thereby minimized. The polymerization chain transfer

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