Baeyer–Villiger Oxidation of 4-Methylated 3-Keto Steroids and the Facile Pyrolysis of 4,4-Dimethyl 3,4-Seco Lactones

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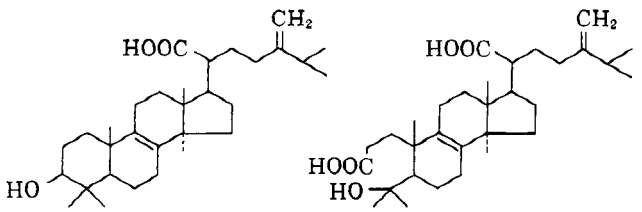
Received September 14, 1964

Oxidation of 4α- and 4β-methyl- and 4,4-dimethylcholestanone with *m*-chloroperbenzoic acid gave as the sole isolable products the lactones XI, XV, and XVIII, respectively, formed by migration of the more highly substituted carbon atom. The lactone XVIII was pyrolyzed at 200° in what is believed to be a stereospecific elimination reaction involving hydrogen abstraction from the 4α-methyl carbon to form the 4-methylene acid XXa. The selectivity of this reaction was demonstrated with the dilactone XXIII, which yielded the lactone acid XXIVa. The lactones were converted into the corresponding hydroxy acids and their methyl esters.

In a recent publication[2] we reported that incubation of the tetracyclic triterpene eburicoic acid (I) with the fungus *Glomerella fusarioides* resulted in cleavage of ring A with the formation of the 3,4-seco acid II, and



I II

that this acid and some of its derivatives possessed antibacterial activity against *Straphylococcus aureus* and BCG. In the interest of defining more closely the structural requirements for the antibacterial activity of steroid acids we have investigated the preparation of 3,4-seco-4-hydroxycholestan-3-oic acids possessing one or two methyl groups in the 4-position. Seco acids of this type should be readily available by Baeyer–Villiger oxidation of the requisite 3-ketones; in fact, the reaction brought about by fungal enzymes to furnish II may be termed the biochemical equivalent of the above reaction since it closely parallels it also with regard to its mechanism.[3,4]

The starting materials for these reactions were the known 4α- and 4β-methylcholestan-3-one and 4,4-dimethylcholestan-3-one. The preparation of the last-named substance according to the procedure of Chaudhry, Halsall, and Jones[5] proceeded without difficulty. On the other hand, the procedure for the preparation of the epimeric 4-methylcholestanones requires comment. Both epimers have been obtained by the direct monomethylation of 3-cholestanone-2-spiro-1′,3′-dithian followed by separation and Raney nickel desulfurization of the requisite 4-monomethyl derivatives.[6] We chose, however, to follow the alternative procedure, which derives the desired isomers from 4-methyl-Δ⁴-cholesten-3-one by stereospecific methods of reduction.[7,8] 4-Methyl-Δ⁴-cholestenone is prepared most conveniently by the general procedure of Kirk and Petrow,[9] in which cholestenone is subjected to a Mannich condensation with formaldehyde and thiophenol and the resulting 4-phenylthiomethyl-Δ⁴-cholesten-3-one is desulfurized with sponge nickel to 4-methylcholestenone. The reduction of 4-methylcholestenone with lithium in liquid ammonia to give 4α-methylcholestanone was unexceptional. However, the catalytic hydrogenation reported to yield the 4β-isomer occasioned some difficulty. Using the conditions specified by Mazur and Sondheimer, namely hydrogenation in absolute ethanol with a 10% palladium-on-charcoal catalyst, we were unable to obtain a pure sample of 4β-methylcholestanone. Thin layer chromatography revealed the presence of both 4α- and 4β-methylcholestanone even after repeated recrystallization.[10] Reproducible yields of 15–25% of 4β-methylcholestanone were obtained, however, when chromatographically purified 4-methyl-cholestenone was hydrogenated in absolute ethanol in the presence of 5% palladium on barium sulfate. This material was at least 95% pure by thin layer chromatography and by v.p.c. analysis of the derived lactone XV (*vide infra*).

The Baeyer–Villiger oxidation of cholestanone (and of coprostanone) has been investigated by Burckhardt and Reichstein[11] who reported the reaction to proceed with the formation of a single product, namely, the 3,4-seco lactone resulting by migration of the C-3–C-4 bond. In a recent communication Hara, Matsumoto, and Takeuchi[12] showed that Burckhardt and Reichstein's lactones were in fact mixtures of the 2,3- and 3,4-seco lactones, demonstrating that both the C-2–C-3 and C-3–C-4 bonds can migrate in this reaction. The fact that the mixed nature of the Burckhardt–Reichstein lactones was not readily apparent and has remained undetected for so long suggests that extreme care must be exercised in selecting the criteria to be used in the determination of purity of the lactones to be derived by Baeyer–Villiger oxidation of the 4-methylated cholestanones. Such precautionary measures were thought necessary even with the 4-methyl

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(2) A. I. Laskin, P. Grabowich, C. de L. Meyers, and J. Fried, *J. Med. Chem.*, **7**, 406 (1964).

(3) G. S. Fonken, H. C. Murray, and L. M. Reineke, *J. Am. Chem. Soc.*, **82**, 5507 (1960).

(4) R. L. Prairie and P. Talalay, *Biochemistry*, **2**, 203 (1963).

(5) G. R. Chaudhry, T. G. Halsall, and E. R. H. Jones, *J. Chem. Soc.*, 2725 (1961).

(6) J. L. Beaton, T. G. Halsall, E. R. H. Jones, and P. C. Phillips, *ibid.*, 753 (1957).

(7) Y. Mazur and F. Sondheimer, *J. Am. Chem. Soc.*, **80**, 5220 (1958).

(8) C. W. Shoppee, G. A. R. Johnston, and R. E. Lack, *J. Chem. Soc.*, 3604 (1962).

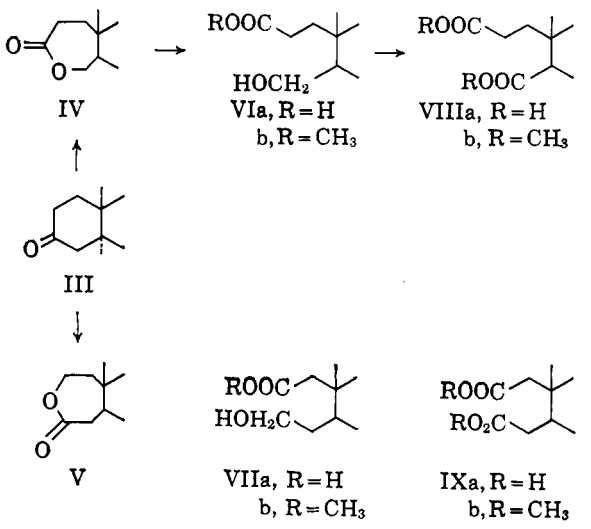
(9) D. N. Kirk and V. Petrow, *ibid.*, 1091 (1962).

(10) Vapor phase chromatography of authentic 4α- and 4β-methylcholestanone showed identical retention times, very probably as a result of epimerization of the 4β- to the 4α-isomer at the operating temperature of the column (205–210°).

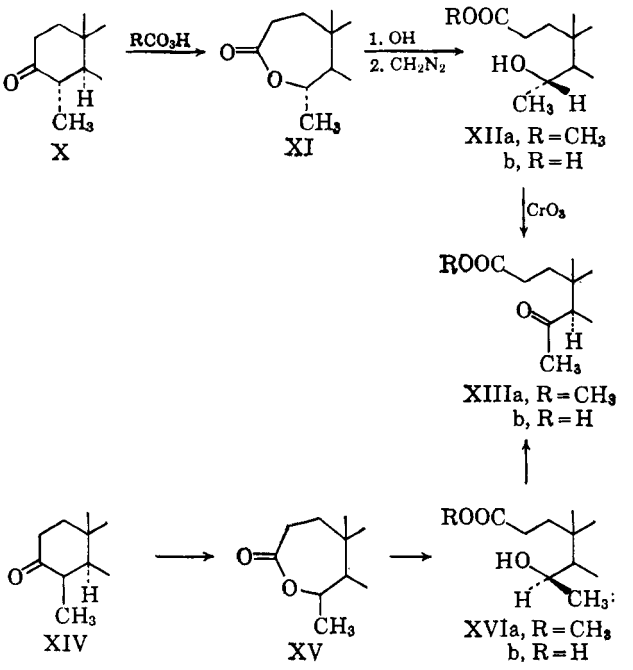
(11) V. Burckhardt and T. Reichstein, *Helv. Chim. Acta*, **25**, 821, 1434 (1942).

(12) S. Hara, N. Matsumoto, and M. Takeuchi, *Chem. Ind.* (London), 2086 (1962).

derivatives where the greater migratory aptitude of the secondary and tertiary alkyl group would clearly favor the 3,4-seco lactones over their 2,3-isomers.[13] In addition to thin layer chromatography the most reliable method for distinguishing between such closely related isomers was found to be vapor phase chromatography, though even this discriminating technique was not always capable of achieving the desired separation. When successful, however, it provided a ready means of quantitation of the components present. This was demonstrated with the mixture obtained on oxidation of cholestanone with *m*-chloroperbenzoic acid.[14] When the beautifully crystalline "lactone of m.p. 186–187°" described by Burckhardt and Reichstein was subjected to the procedure employed by Hara, *et al.*, namely, saponification to the hydroxy acids and oxidation of the latter to the diacids followed by methylation, and the resulting material, without isolation of intermediates, was subjected to vapor phase chromatography, two peaks were observed in the ratio of 7:3 which showed retention times equal to those of authentic dimethyl 3,4-secocholestane-3,4-dioate (VIIIb) and of its 2,3-isomer (IXb), respectively. When this same sequence of reactions followed by v.p.c. analysis was performed with the total crude peracid oxidation mixture rather than with the crystalline material the ratio of seco esters VIIIb and IXb was 55:45. These results are in agreement with those reported by the Japanese investigators who employed a chemical separation method. The chromatograms showed the presence of less than 2% of material other than VIIIb and IXb. It is interesting to note that the mixtures of the original lactones IV and V as well as the hydroxy ester mixtures VIb and VIIb could not be separated by our v.p.c. column and behaved as single substances.



The peracid oxidation of 4α- and 4β-methylcholestanone afforded the crystalline lactones XI[15] and XV in 82 and 75% yield, respectively, which gave single peaks on v.p.c. The two lactones were readily distinguishable in the system used, a fact which permitted the quantitative estimation of mixtures of 4α- and 4β-methylcholestanone,[10] and particularly the recognition of about 5% of the 4α-isomer X in our best preparations of XIV. The mother liquors from the respective oxidations were analyzed by v.p.c. and showed only two peaks, namely those for the lactones



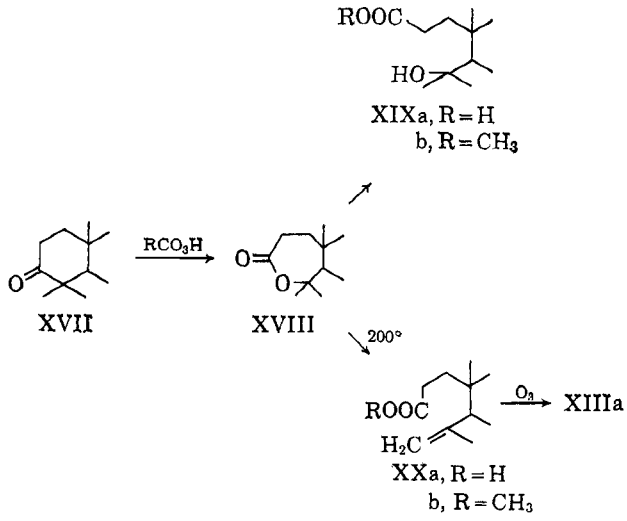
and for unchanged starting material. The n.m.r. spectra of the lactones XI and XV showed methyl signals as doublets at τ 8.71 and 8.53 (J = 7 c.p.s.), respectively, indicating methyl attached to carbon bearing an acyloxy substituent. Hydrolysis of the epimeric lactones followed by methylation gave the hydroxy methyl esters XIIa and XVIa, which on chromic acid oxidation afforded a single keto ester XIIIa (n.m.r. peak at τ 7.86), which was hydrolyzed to the corresponding acid XIIIb. From the foregoing it may already be concluded that the major if not the sole products in the peracid oxidation of the two methylcholestanones are the 3,4-seco lactones. Had cleavage also occurred between C-2 and C-3 the monomethyl ester of the 2,3-seco diacid should have resulted from the above sequence of reactions. Separation of the total chromic acid oxidation mixtures into neutral and acidic products revealed less than 10% of material in the acidic fractions. The conclusion is therefore warranted that the reaction in both the 4α- and 4β-methyl case proceeds to more than 90% with migration of the more highly substituted C-4.

4,4-Dimethylcholestanone reacted more slowly with *m*-chloroperbenzoic acid, some of the starting material always remaining unchanged under our reaction conditions. The resulting lactone, XVIII, was shown to have arisen by cleavage between C-3 and C-4, since the methyl ester XIXb, prepared by saponification of the lactone followed by methylation, was recovered unchanged from extended exposure to Jones reagent. The n.m.r. spectrum of the lactone showed a peak at τ 8.57, and the acid and its ester at 8.74, equivalent to 6 protons, confirmatory of this structural assignment.

(13) R. R. Sauers, *J. Am. Chem. Soc.*, **81**, 925 (1959); J. Meinwald and E. Frauenglass, *ibid.*, **82**, 5235 (1960).

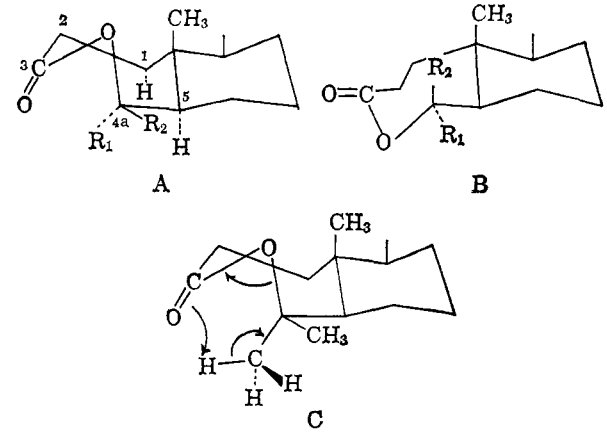
(14) *m*-Chloroperbenzoic acid was chosen as the oxidizing agent over other commonly used peracids because of its greater stability at room temperature and its commercial availability in solid form.

(15) In a recent paper [T. G. Halsall, D. W. Theobald, and K. B. Walshaw, *J. Chem. Soc.*, 1029 (1964)] the oxidation of 4α-methylcholestanone with perfluoroacetic acid to the lactone XI is described. However, no experimental details or physical constants are given.



When the lactone XVIII was subjected to v.p.c. no product could be detected among the gases emerging from the column. Such a behavior was suspected to be the result of pyrolytic cleavage of the lactone on the column giving rise to a polar, strongly held reaction product. This hypothesis was readily demonstrated to be correct. When the lactone XVIII was heated in a sealed evacuated vessel for 10 min. at 203–206°, the temperature of the v.p.c. column, a melt resulted which crystallized readily yielding as the sole product the unsaturated acid XXa. The structure of the acid followed from the presence of prominent bands at 6.10 and 11.10 μ in the infrared spectrum, and of vinyl proton absorption at τ 5.13 and 5.28 as well as low field methyl absorption at 8.25 in the n.m.r. spectrum. As expected, ozonolysis of its methyl ester XXb afforded the keto ester XIIIb. In contrast to the ready cleavage of the 4,4-dimethyl lactone XVIII the monomethyl lactones XI and XV remained unchanged even at 325°.[16] Simple tertiary esters, *e.g.*, *t*-butyl acetate, undergo elimination at 360°,[17] a temperature more than 150° higher than that observed in our case, suggesting that special stereochemical circumstances must be operative to explain this unusually facile elimination reaction.

There are two possible, readily interconvertible chair conformations for the ϵ-lactone system under consideration, which we shall call conformations A and B. In conformation B the 4β-substituent, R_2, is in a 1,3-diaxial relationship with regard to the 19-methyl group, whereas in conformation A, R_2 is equatorially situated. On the other hand, conformation A involves some interaction between the 4α-substituent, R_1, and the carbonyl group at position 3 as well as with the axial hydrogen atoms at C-1 and C-5. In the unsubstituted lactone IV and probably also in the 4α-methyl derivative XI it is likely that these latter factors combine to stabilize conformation B. However, the presence of a β-oriented methyl group at C-4 would be expected to overcome these interactions and force the lactone ring into conformation A, in which case the hydrogen atoms of the 4α-methyl group, R_1, are perfectly oriented for a facile intramolecular cyclic transition to the olefinic acid, XXa,[18] as shown in C. The above considerations receive support from the n.m.r. spectra of the various lactones. Examining the effect of substitution at C-4 on the 19-methyl signal we find that the mixture of lactones from cholestanone (IV and V) and the 4α-methyl lactone XI exhibit that signal at τ 9.11 and 9.09, respectively, while those lactones possessing 4β-methyl substituents (XV and XVIII) show the 19-methyl signal at significantly lower field, namely at τ 8.97 and 8.95, respectively. This is in full accord with our analysis, the deshielding of the C-19 methyl signal in the latter two lactones being an indication of the close proximity of that methyl group to the ring oxygen as demanded by A.



It is a consequence of the above considerations that the methylene group in the cleavage product XXa be derived exclusively from the 4α-methyl group, a conclusion, which, if proven correct, would enable us for the first time to distinguish chemically between triterpenoid methyl groups at C-4. The availability of such a stereospecific method would have considerable merit in permitting the design of experiments leading to a precise definition of the biogenetic origin of these methyl groups from their mevalonic acid precursor. Experiments to establish this latter point and to ascertain the steric course of the reaction are in progress.[19]

A striking demonstration of the expected selectivity of this pyrolytic elimination reaction was provided by the conversion of the dilactone XXIII prepared by Baeyer–Villiger oxidation of the known trisnorlactone XXII[20] derived from dipterocarpol (XXI), into the unsaturated acid XXIVa without opening of the γ-lactone ring. The lactone methyl ester XXIVb had properties identical with those reported for the methyl ester of the same structure derived by chromic acid oxidation of methyl dammarenolate (XXV).[20,21]

The discovery of this facile elimination reaction provides added justification for the biogenetic sequence

(16) ϵ-Methylcaprolactone has been reported to be cleaved at 520°: *cf.* W. J. Bailey and C. N. Bird, Abstracts, 131st National Meeting of the American Chemical Society, Miami, Fla., 1957, p. 44.

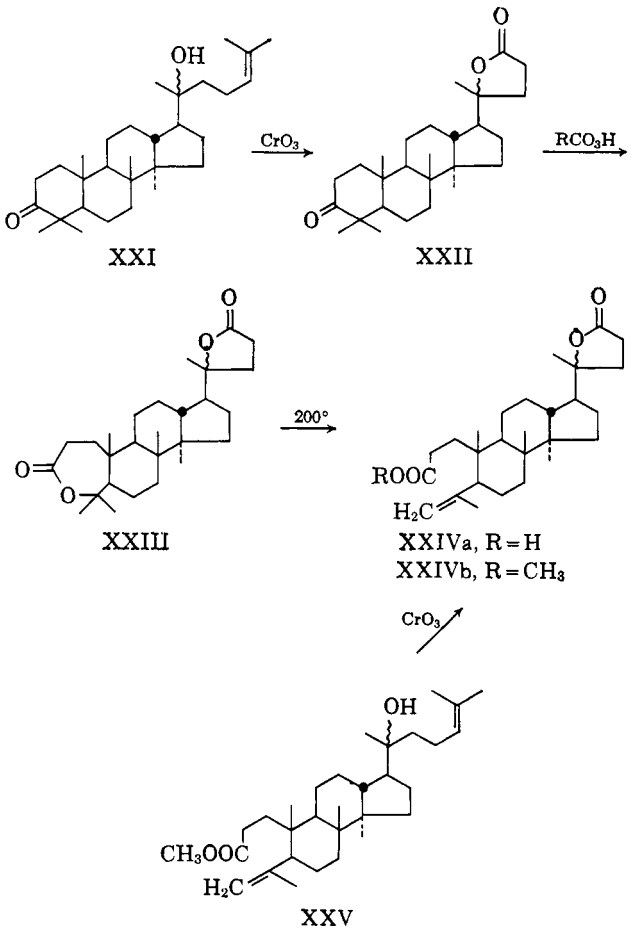
(17) C. D. Hurd and F. H. Blunck, *J. Am. Chem. Soc.*, **60**, 2419 (1938).

(18) C. H. DePuy and R. W. King, *Chem. Rev.*, **60**, 431 (1960).

(19) In a preliminary communication D. Arigoni [*Experientia*, **14**, 153 (1958)] showed that the pentacyclic triterpene soyasapogenol D derived from 2-^{14}C-mevalonolactone contained no significant amount of label in the 4β-hydroxymethyl group while the 4α-methyl group was labeled. In this case the 4α- and 4β-carbons are readily distinguishable chemically, since the 4β-methyl is hydroxylated.

(20) J. S. Mills and A. E. A. Werner, *J. Chem. Soc.*, 3132 (1955); *cf.*, also, P. Crabbé, G. Ourisson, and T. Takahashi, *Tetrahedron*, **3**, 279 (1958).

(21) D. Arigoni, D. H. R. Barton, R. Barnasconi, C. Djerassi, J. S. Mills, and R. E. Wolff, *J. Chem. Soc.*, 1900 (1960).



postulated by us[2] for the formation of naturally occurring seco acids *via* ϵ-lactones.

The antibacterial activity of the acids described in this paper and of other steroidal acids will be reported elsewhere.

Experimental

All melting points were taken on a Thomas–Hoover apparatus and are corrected for stem exposure. Ultraviolet spectra were measured on a Cary 11, infrared spectra on a Perkin-Elmer 21, and n.m.r. spectra on a Varian A-60 spectrometer in $CDCl_3$ solution with tetramethylsilane as internal standard. Rotations were taken in chloroform. V.p.c. analyses were carried out on an F and M gas chromatograph, Model 1609, using a 5.5-ft column, $^3/_{16}$-in. diameter, loaded with 70–80-mesh Anakrom ABS coated with 0.2% Carbowax 20M, at a helium flow of *ca.* 25 ml./min. The temperature was 225° unless otherwise indicated.

4-Methylcholestenone.—A solution of 21.7 g. of cholestenone, 18 ml. of thiophenol, 15 ml. of 40% formalin, and 15 ml. of triethylamine in 60 ml. of absolute ethanol was refluxed under nitrogen for 84 hr. The reaction mixture was taken up in benzene and washed three times with 2 *N* NaOH solution, then twice with saturated salt solution; the organic phase was dried over sodium sulfate; and the solvents were evaporated to give 28.7 g. of a clear yellow oil. This oil (27.7 g.) was added to a suspension of 200 ml. of commercial sponge nickel catalyst, which had been washed several times with acetone then refluxed with 1 l. of acetone for 1 hr. prior to the addition of the thio ether. The acetone suspension was stirred mechanically and refluxed for 5 hr., cooled, filtered, evaporated to a small volume, and allowed to crystallize overnight. The first two crops weighed 3.71 g. (m.p. 95–97°) and 4.29 g. (92–93°), respectively. Combination and recrystallization from methanol gave 6.51 g. (m.p. 98–99°). Additional material (3.3 g.) was obtained by chromatography of lower crop material. Total isolated yield was 48% based on cholestenone used. This material was not suitable for the subsequent hydrogenation step but had to be purified further by chromatography. In a typical run 7.2 g. of crude product was chromatographed on 250 g. of Woelm basic alumina, activity I, and the product was eluted with 1:1 benzene–hexane. After one crystallization of the eluted solids (5.4 g.) from methanol, 4.1 g., m.p. 99–100° (lit.[9] m.p. 101–103°), n.m.r. τ 8.24 (4-CH_3), was obtained.

4β-Methylcholestanone (XIV).—A solution of 200 mg. of 4-methylcholestenone in 40 ml. of 95% ethanol was hydrogenated over 80 mg. of 5% Pd–$BaSO_4$ catalyst (Engelhardt Industries). Careful crystallization from methanol gave 90 mg. of material, m.p. 119–120°, which on recrystallization afforded 55 mg.: m.p. 124.5–125.5°, $[\alpha]^{23}D$ +20.4° (lit.[6] m.p. 125–127°, $[\alpha]D$ +36°). A sample kindly supplied by Professor E. R. H. Jones, Oxford, had m.p. 125–126° and showed an infrared spectrum indistinguishable from that of our sample. Thin layer chromatography showed a trace of the 4α-isomer in both samples. We have no explanation for the lower specific rotation of our material. Its purity was confirmed by conversion into the pure lactone XV.

4α-Methylcholestanone (X).—4α-Methylcholestanone (X) was prepared by the reduction of 4-methylcholestenone with lithium in liquid ammonia according to the procedure of Mazur and Sondheimer.[7] The product from a 200-mg. run showed strong hydroxyl absorption in the infrared and was therefore reoxidized with Jones reagent and chromatographed. The pure product melted at 121–122° (block) (lit. m.p. 122–122.5°,[6] 121–123°[7]).

Peracid Oxidation of Cholestanone.—A solution of 1.0 g. of cholestanone and 1.0 g. of *m*-chloroperbenzoic acid in 10 ml. of chloroform was allowed to remain at 25° for 8 hr. Benzene and water were then added followed by excess potassium iodide and sodium bisulfite solutions. The organic phase was washed three times with saturated sodium bicarbonate solution, then once with water. Evaporation of the dried extract left 969 mg. of solid material consisting of lactones IV and V, which on v.p.c. analysis showed a single band (retention time 13.9 min.). The product was crystallized from a large volume of ether–methanol yielding 418 mg. of very fine plates, m.p. 185–187° (lit.[11] m.p. 186–187°). V.p.c. showed a single band at 13.5 min.

Saponification and Chromic Acid Oxidation of Lactones.—Two separate samples, one of the crystalline lactone mixture (IV and V), m.p. 185–187°, the other of the total crude mixture of lactones IV and V, each weighing 100 mg., were suspended in 25 ml. of 1.5 *N* KOH in methanol and shaken overnight at room temperature. Both samples were treated identically as follows. The solutions were acidified carefully to pH 3 and extracted with methyl isobutyl ketone, and the extracts were washed with saturated salt solution, dried over sodium sulfate, and evaporated to dryness *in vacuo*. When a small portion of each of these products was methylated with diazomethane to mixtures of methyl esters VIb and VIIb, each showed only a single peak on v.p.c. (retention time 8.0 min.).

The remaining total crude hydroxy acids VIa and VIIa derived from both total crude and crystalline lactone mixtures were each oxidized in 25 ml. of glacial acetic acid with 100 mg. of chromic acid containing a trace of water. The excess chromic acid was reduced with methanol and the total crude mixtures evaporated to near dryness *in vacuo*. The acids were then taken up in methyl isobutyl ketone and water and the organic layers dried and evaporated to yield 100 mg. each of mixed diacids VIIIa and IXa. These were methylated with excess ethereal diazomethane and the total methyl esters subjected to v.p.c. The peaks observed were then compared with those shown by standard samples of dihydro Diels acid dimethyl ester VIIIb and dimethyl 2,3-secocholestane-2,3-dioate (IXb).

Dihydro Diels acid dimethyl ester VIIIb (m.p. 121–123°) had a retention time of 18.7 min. and dimethyl 2,3-secocholestane-2,3-dioate (IXb, m.p. 58–59°), of 17.1 min. The mixture of dimethyl esters derived from the crystalline lactone (m.p. 186–187°) showed peaks at 16.5 min. and 17.5 min. indicating a composition of 30% IXb and 70% VIIIb, respectively. The corresponding mixture of dimethyl esters derived from the total crude Baeyer–Villiger oxidation product showed peaks at 16.8 min. and 18.1 min. indicating a composition of 45% IXb and 55% VIIIb.

4-Oxa-4aα-methyl-A-homocholestan-3-one (XI).—A solution of 75 mg. of 4α-methylcholestanone (X) and 75 mg. of *m*-chloroperbenzoic acid in 1.0 ml. of chloroform was allowed to remain at 25° for 18 hr. The mixture was worked up as described above for the oxidation of cholestanone and the product was crystallized from methanol. The yield of crystalline lactone XI was 65 mg.: m.p. 191–191.5°; $[\alpha]^{25}D$ −6° (*c* 0.66); λ_{max}^{Nujol} 5.75, 7.93

μ; n.m.r. τ 8.71 (doublet, J = 7 c.p.s., 4-CH_3), 9.09 (19-CH_3); v.p.c. single peak at 11.4 min. at 220°. The mother liquors were analyzed by v.p.c. and shown to contain at least 65% XI. The isolated yield was 82%; the yield calculated on the basis of product present in the mother liquor was 93%.

Anal. Calcd. for $C_{28}H_{48}O_2 \cdot CH_3OH$: C, 77.62; H, 11.68. Found: C, 77.72; H, 11.18.

3,4-Seco-(4*S*)-4-methyl-4-hydroxy-3-cholestanoic Acid (XIIb). A suspension of 30 mg. of 4-oxa-4aα-methyl-A-homocholestan-3-one (XI) in 10 ml. of 1.2 *N* KOH in methanol was shaken at 25° for 18 hr. The clear solution was then acidified carefully with dilute hydrochloric acid to pH 3.5 and extracted with chloroform. The chloroform extract was washed with saturated sodium chloride solution, dried over sodium sulfate, and evaporated to give a white gel (30 mg.). The latter crystallized with difficulty and yielded 5 mg. of material after one recrystallization from ether–hexane. The crystals were washed with hexane and dried to give 3,4-seco-(4S)-4-methyl-4-hydroxy-3-cholestanoic acid (XIIb): m.p. 110–115°; λ_{max}^{KBr} 2.97, 5.85 μ.

Anal. Calcd. for $C_{28}H_{50}O_3$ (434.69): C, 77.36; H, 11.59. Found: C, 77.51; H, 11.53; neut. equiv., 439.

Methyl 3,4-Seco-(4*S*)-4-hydroxy-4-methyl-3-cholestanoate (XIIa).—4-Oxa-4aα-methyl-A-homocholestan-3-one (XI, 46 mg.) was hydrolyzed with 20 ml. of 1.5 *N* KOH in methanol at 25° for 16 hr. The hydroxy acid obtained on acidification and extraction with chloroform was methylated with diazomethane in ether–methanol to furnish the crystalline methyl 3,4-seco-(4*S*)-4-hydroxy-4-methyl-3-cholestanoate in a yield of 49 mg. This substance was shown to be homogeneous by thin layer chromatography. After crystallization from methanol, 37 mg., m.p. 103–104°, was isolated: $[\alpha]^{25}D$ +14° (*c* 0.70); λ_{max}^{Nujol} 3.05, 5.75, 8.52 μ; n.m.r. τ 6.02 (quartet, J = 6 c.p.s., 4H), 8.87 (doublet, J = 6 c.p.s., 4-CH_3), 9.17 (19-CH_3); v.p.c. retention time 11.8 min.

Anal. Calcd. for $C_{29}H_{52}O_3$ (448.71): C, 77.62; H, 11.68. Found: C, 77.54; H, 11.67.

Methyl 3,4-Seco-4-keto-4-methyl-3-cholestanoate (XIIIa).—A solution of 27.5 mg. of methyl 3,4-seco-(4*S*)-4-hydroxy-4-methyl-3-cholestanoate (XIIa) in 20 ml. of acetone was oxidized with 0.05 ml. of Jones chromic acid reagent (200 mg. of CrO_3 and 320 mg. of H_2SO_4 in 1 ml. of H_2O). After reduction of excess oxidant with methanol, the mixture was taken up in chloroform and water, and the chloroform extract was washed with saturated sodium chloride solution and evaporated to give 22 mg. of an oil which crystallized on standing. Recrystallization from methanol gave methyl 3,4-seco-4-keto-4-methyl-3-cholestanoate (XIIIa): m.p. 74–75°; $[\alpha]^{25}D$ −5° (*c* 1.51); λ_{max}^{Nujol} 5.74, 5.85, 8.32 μ; n.m.r. τ 6.34 (OCH_3), 7.86 (4-CH_3), 8.98 (19-CH_3); v.p.c. retention time 5.0 min. at 225°, 12.0 min. at 205°.

Anal. Calcd. for $C_{29}H_{50}O_3$ (446.69): C, 77.97; H, 11.28. Found: C, 77.97; H, 11.33.

3,4-Seco-4-keto-4-methyl-3-cholestanoic Acid (XIIIb).—A suspension of 100 mg. of methyl 3,4-seco-4-keto-4-methyl-3-cholestanoate (XIIIa) in 35 ml. of 1.5 *N* KOH in methanol was stirred at room temperature overnight. On work-up as in previous hydrolyses 61 mg. of pure 3,4-seco-4-keto-4-methyl-3-cholestanoic acid (XIIIb) was obtained, which after recrystallization from methanol had m.p. 118–119°; $[\alpha]^{25}D$ +4° (*c* 0.74); λ_{max}^{Nujol} 3.70 (broad), 5.88 μ; n.m.r. τ 7.85 (4-CH_3), 8.98 (19-CH_3).

Anal. Calcd. for $C_{28}H_{48}O_3$ (432.66): C, 77.72; H, 11.18. Found: C, 77.62; H, 11.07.

4-Oxa-4aβ-methyl-A-homocholestan-3-one (XV).—A solution of 30 mg. of 4β-methylcholestanone (XIV) and 41 mg. of *m*-chloroperbenzoic acid in 0.4 ml. of chloroform was maintained at 32° for 16 hr. The mixture was then taken up in water and benzene and the benzene solution shaken successively with solutions of potassium iodide, sodium bisulfite, and finally sodium bicarbonate and sodium chloride. The combined benzene extracts were dried over sodium sulfate and evaporated to dryness *in vacuo*. Crystallization of the residue from methanol–ether gave two crops: 20 mg., m.p. 177–179°, and 6 mg., m.p. 171–173°; $[\alpha]^{23}D$ 0 ± 1.6°; λ_{max}^{KBr} 5.78, 8.45 μ; n.m.r. τ 5.63 (4-H), 8.53 (doublet, J = 7 c.p.s., 4-CH_3), 8.97 (19-CH_3); v.p.c. retention time 12.8 min. at 220°. Mixtures of the 4α- and 4β-methyl lactones were readily separated by v.p.c. The presence of about 5% of the 4α-isomer XI was clearly indicated by a peak at 11.6 min.

Anal. Calcd. for $C_{28}H_{48}O_2$ (416.66): C, 80.71; H, 11.61. Found: C, 80.69; H, 11.58.

3,4-Seco-(4*R*)-4-hydroxy-4-methyl-3-cholestanoic Acid (XVIb).—A suspension of 31 mg. of the lactone XV in 25 ml. of 1.5 *M* KOH in methanol was stirred at 25° for 18 hr. The clear solution was worked up as described above for the 4α-methyl isomer XI, yielding finally on crystallization from aqueous methanol 17 mg. of the hydroxy acid XVIb, m.p. 155–161°, and a second crop of 8 mg., m.p. 154–157°. The analytical sample had m.p. 161–163°, $[\alpha]^{23}D$ +1° (*c* 0.59).

Anal. Calcd. for $C_{28}H_{50}O_3$ (434.69): C, 77.36; H, 11.59. Found: C, 77.32; H, 11.51.

The methyl ester XVIa was prepared with diazomethane and recrystallized from methanol: m.p. 104–106°; $[\alpha]^{23}D$ +8° (*c* 0.35); v.p.c. retention time 13.3 min. This substance was easily separated from its 4*S*-epimer (11.8 min.).

Anal. Calcd. for $C_{29}H_{52}O_3$ (448.71): C, 77.62; H, 11.68. Found: C, 77.73; H, 11.65.

Oxidation of the ester XVIa with chromic acid as described above for XIIa yielded the keto ester XIIIa, m.p. 72–73°, identified by infrared and v.p.c. comparison.

4-Oxa-4a,4a-dimethyl-A-homocholestan-3-one (XVIII).—A solution of 100 mg. of 4,4-dimethylcholestan-3-one (XVII) and 150 mg. of *m*-chloroperbenzoic acid in 1 ml. of dichloromethane–chloroform (1:1) was kept at room temperature for 24 hr. The solution was diluted with chloroform and washed consecutively with 5% potassium iodide solution, 5% sodium bisulfite solution, water, 5% potassium bicarbonate solution, and water, dried, and evaporated to give 100 mg. of crude lactone (XVIII). Crystallization from methanol gave 83 mg. of material, m.p. 116–118°, which on recrystallization furnished analytically pure 4-oxa-4a,4a-dimethyl-A-homocholestan-3-one (XVIII): m.p. 123–124°; $[\alpha]^{20}D$ −1.7°; λ_{max}^{KBr} 5.79, 5.85 μ (sh); n.m.r. τ 8.57 (4,4-dimethyl), 8.95 (19-CH_3); v.p.c. no peak (pyrolysis *vide infra*).

Anal. Calcd. for $C_{29}H_{50}O_2$ (430.69): C, 80.87; H, 11.70. Found: C, 80.91; H, 11.71.

3,4-Seco-4,4-dimethylcholestan-4-ol-3-oic Acid (XIXa).—A solution of 100 mg. of the lactone XVIII in 10 ml. of 5% methanolic KOH was allowed to remain at 25° for 4.5 hr. The pH was then adjusted to 4.5 and, after dilution with water, the methanol was evaporated. The aqueous suspension was extracted with chloroform and the chloroform extract was washed with water, dried, and evaporated to give 99 mg. of the crude acid. Recrystallization from methanol gave 68 mg. of 3,4-seco-4,4-dimethylcholestan-4-ol-3-oic acid (XIXa): m.p. 137–139.5°; $[\alpha]^{25}D$ +27°; λ_{max}^{Nujol} 2.93, 3.04, 5.81 (sh), 5.84 μ; n.m.r. τ 8.73 (4,4-dimethyl), 8.98 (19-CH_3).

Anal. Calcd. for $C_{29}H_{52}O_3$ (448.71): C, 77.62; H, 11.68. Found: C, 77.88; H, 11.83.

The methyl ester XIXb was prepared with diazomethane and recrystallized from methanol: m.p. 87–88° and 111–112°; n.m.r. τ 6.33 (OCH_3), 8.74 (4,4-dimethyl), 8.98 (19-CH_3); v.p.c. 2 peaks at 6.9 min. (70%) and 8.2 min. (30%) at 205°. The less polar peak has the same retention time as the olefinic ester XXb (*vide infra*) and admixture of the latter causes enhancement of that peak, indicating dehydration on the column.

Anal. Calcd. for $C_{30}H_{54}O_3$ (462.73): C, 77.86; H, 11.76. Found: C, 77.64; H, 11.74.

The total crude methyl ester (XIXb) obtained by saponification and methylation of the crystallized lactone XVIII remained unchanged on Jones oxidation. It was, therefore, not a 2,3-seco lactone.

Methyl 3,4-Seco-4-methyl-4-methylenecholestan-3-oate (XXb).—4-Oxa-4a,4a-dimethyl-A-homocholestan-3-one (XVIII) (50 mg.) was placed into a small tube which was then evacuated and sealed under high vacuum. The contents of the tube were heated rapidly in a Woods metal bath to 200° and maintained at 200–210° for 10 min. The tube was then cooled and opened; the material on the bottom of the tube (45 mg.) (5 mg. of starting material had sublimed) was dissolved in 10 ml. of ether containing 1 drop of methanol and methylated with excess ethereal diazomethane. The crystalline residue gave fine crystals from methanol (22 mg.), m.p. 64–65°. From the mother liquor an additional 7 mg. of the methyl ester XXb, m.p. 67–68°, was recovered by chromatography on alumina (recrystallization of the first crop gave the raised m.p. 67–68.5°): $[\alpha]^{24}D$ +13.5° (*c* 0.75); λ_{max}^{Nujol} 5.71, 6.10, 11.17 μ; n.m.r. τ 5.12, 5.30 (4-CH_2=), 6.32 (OCH_3), 8.25 (4-CH_3), 9.09 (19-CH_3); v.p.c. retention time 6.9 min. at 205°.

Anal. Calcd. for $C_{30}H_{52}O_2$ (444.72): C, 81.02; H, 11.79. Found: C, 80.92; H, 11.61.

3,4-Seco-4-methyl-4-methylenecholestan-3-oic Acid (XXa).—4-Oxa-4a,4a-dimethyl-A-homocholestan-3-one (XVIII) (71 mg.) was pyrolyzed in a sealed tube as described in the previous experiment. Recrystallization of the reaction mixture from methanol furnished 28 mg. of the crystalline acid (XXa): m.p. 117–119°; $[\alpha]^{23}D$ +15° (*c* 0.99); $\lambda_{max}^{CHCl_3}$ 5.86, 6.10, 8.31, 11.10 μ; n.m.r. τ 5.13, 5.28 (4-CH_2=), 8.25 (4-CH_3), 9.09 (19-CH_3).

Anal. Calcd. for $C_{29}H_{50}O_2$ (430.69): C, 80.87; H, 11.70. Found: C, 80.81; H, 11.75.

Ozonolysis of Methyl 3,4-Seco-4-methyl-4-methylenecholestan-3-oate (XXb).—A solution of 10 mg. of methyl 3,4-seco-4-methyl-4-methylenecholestan-3-oate in 2 ml. of ethyl acetate was ozonized with an excess of ozonized oxygen at −40°. The solution was allowed to stand at −40° for 15 min., warmed to room temperature, and treated with 0.5 g. of zinc dust and 1 drop of glacial acetic acid. After stirring for 10 min., the reaction mixture was filtered, diluted with ethyl acetate, washed with water, dried over sodium sulfate, and evaporated to dryness. The reaction product was chromatographed on a thin layer of neutral alumina, activity V, and eluted with 1:1 benzene–hexane. The band corresponding to the known reaction product XIIIa (R_f 0.3) was isolated and rechromatographed in the same manner. Crystallization from methanol afforded 2 mg. of material, m.p. 74–76°, which on recrystallization from methanol had m.p. 75–76° (block). The infrared spectrum of this material was identical with that of an authentic sample of methyl 3,4-seco-4-keto-4-methyl-cholestan-3-oate (XIIIa).

3,4-Seco-25,26,27-trisnordammarane-4,20ξ-diol-3,24-dioic Acid 3→4,24→20-Dilactone (XXIII).—A solution of 1.35 g. of 25-26,27-trisnordammaran-3-on-20ξ-ol-24-oic acid lactone (XXII)[20] and 1.35 g. of *m*-chloroperbenzoic acid in 8 ml. of chloroform was kept at 25° for 23 hr. After dilution with 25 ml. of chloroform to dissolve precipitated *m*-chlorobenzoic acid, the solution was washed consecutively with 5% potassium iodide, 5% sodium thiosulfate, water, 5% potassium bicarbonate, and water, dried over sodium sulfate, and evaporated to dryness *in vacuo*. The residual 3,4-seco-25,26,27-trisnordammarane-4,20ξ-diol-3,24-dioic acid 3→4,24→20-dilactone (XXIII, 1.3 g.) on recrystallization from methanol furnished in two crops a total of 865 mg. of material, m.p. 173–176°. Analytical material had m.p. 178–180° or 192–194° (polymorphic modifications): $[\alpha]^{23}D$ +104° (*c* 0.75); λ_{max}^{KBr} 5.65, 5.80 μ.

Anal. Calcd. for $C_{27}H_{42}O_4$ (430.61): C, 75.31; H, 9.83. Found: C, 75.33; H, 9.78.

3,4-Seco-25,26,27-trisnordammarane-4,20ξ-diol-3,24-dioic Acid and Its 24→20-Monolactone.—A solution of 40 mg. of the dilactone XXIII in 8 ml. of 6% KOH in methanol was allowed to remain at 25° for 18 hr. Water was then added; the mixture was acidified to pH 3.0 and extracted with methyl isobutyl ketone. The organic phase was washed with water and dried over sodium sulfate, and the solvent evaporated to dryness. The residue (48 mg.) on crystallization from methanol–ethyl acetate furnished 14 mg. of the diacid: m.p. 195–197° with sintering at 158°; λ_{max}^{KBr} 2.87, 5.85 μ; neut. equiv. 235 (calcd., 233).

The mother liquor from the above crystallization was recrystallized from acetone–hexane and furnished 25 mg. of the monolactone acid: m.p. 205–207°; $[\alpha]^{23}D$ +61° (*c* 0.64); λ_{max}^{KBr} 2.92, 5.70, 5.76 μ.

Anal. Calcd. for $C_{27}H_{44}O_5$ (448.62): C, 72.28; H, 9.89. Found: C, 72.21; H, 9.84.

3,4-Seco-25,26,27-trisnor-$\Delta^{4(30)}$-dammaren-20ξ-ol-3,24-dioic Acid 24→20-Lactone (XXIVa).—3,4-Seco-25,26,27-trisnordammarane-4,20ξ-diol-3,24-dioic acid 3→4,24→20-dilactone (XXIII) (252 mg.) was heated *in vacuo* at 202–204° for 8 min. Crystallization of the melt from methanol yielded 176 mg. of fine needles, m.p. 143–144°. The analytical sample (from 95% ethanol, dried at 80°) had m.p. 146–148°; $[\alpha]^{23}D$ +44.5° (*c* 0.83); λ_{max}^{Nujol} 2.86, 5.69, 5.86, 11.22 μ; n.m.r. τ 5.11, 5.29 (1 proton each, 4-CH_2=), 8.26 (4-CH_3), 8.63 (21-CH_3), and 8.97, 9.08 and 9.13 (8β-, 14α- and 19-CH_3).

Anal. Calcd. for $C_{27}H_{42}O_4 \cdot H_2O$ (448.63): C, 72.28; H, 9.89. Found: C, 72.43; H, 9.98.

The methyl ester XXIVb was prepared with diazomethane, purified by chromatography on neutral alumina, and recrystallized from methanol: m.p. 119–121°; $[\alpha]^{23}D$ +44° (*c* 1.2); λ_{max}^{Nujol} 5.66, 5.76, 6.08, and 11.27 μ; n.m.r. τ 5.14, 5.33 (1 proton each, 4-CH_2=), 6.34 (OCH_3), 8.26 (4-CH_3), 8.63 (21-CH_3), 8.98, 9.09, and 9.14 (8β-, 14α- and 19-CH_3); lit. m.p. 125–128°; $[\alpha]D$ +43°,[20] and m.p. 125–126°, $[\alpha]D$ +51°.[21]

Anal. Calcd. for $C_{28}H_{44}O_4$ (444.63): C, 75.63; H, 9.97. Found: C, 75.57; H, 9.98.

Acknowledgment.—The authors wish to thank Mr. J. Alicino and Mr. C. Sabo for the microanalyses, and Dr. A. I. Cohen for the n.m.r. spectra. We also wish to acknowledge the help of Dr. G. Krakower, P. Grabowich, and E. F. Sabo with some of the experiments.

Sulfonation of Acetone with Fuming Sulfuric Acid and Some Reactions of Propanone-1,3-disulfonic Acid

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Received September 2, 1964

Propanone-1,3-disulfonic acid can be prepared easily by sulfonation of acetone with fuming sulfuric acid. Its reactions are in many respects similar to those of β-keto carboxylic acid derivatives.

While β-keto carboxylic acids and their esters have been studied extensively, comparatively little work has been done on β-keto sulfonic acids. Until recently the only general method for the preparation of this class of compounds has been the reaction of α-halogenated ketones with alkali sulfite. Only recently it has been reported that some β-keto sulfonic acids can be obtained by treating ketones with SO_3–dioxane.[1]

It now has been found that acetone can be sulfonated conveniently and in high yield by reaction with fuming sulfuric acid. The solid propanone-1,3-disulfonic acid (I) formed can be obtained by filtration and may be purified by recrystallization from nitromethane.

The reactions of I resemble in many respects those of ethyl acetoacetate. The acidifying effect of the sulfonic acid group on the α-hydrogen atoms is actually stronger than that of a carboxylic acid group. This is evident from the fact that dimethyl propanone-1,3-disulfonate is a moderately strong acid. When titrated using a pH meter, a pH of 5.5 is obtained for 50% neutralization. Even in the case of disodium propanone-1,3-disulfonate one of the hydrogen atoms exhibits a certain degree of acidity, although, because of the presence of the two negative charges, to a much smaller degree. The corresponding salt crystallizes

(1) A. P. Terentev and L. A. Yanovskaya, *Zh. Obshch. Khim.*, **23**, 618, (1953).