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# Synthesis and Reactions of Ring A Methylated Saturated Steroids[1]

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Methylation of cholestan-3-one (I) gives mainly 2α-methylcholestan-3-one (II) or 2,2-dimethylcholestan-3-one (III), depending on conditions. 2α-Methylcholestan-3-one (II) also can be obtained from I through conversion to the ethoxyoxalate IV, methylation and base treatment. The same sequence with Δ⁴-cholesten-3-one (V) produces 2α-methyl-Δ⁴-cholesten-3-one (VII), which on reduction with lithium in ammonia is converted to a mixture of 2α-methylcholestan-3-one (II) and 2α-methylcholestan-3β-ol (VIIIa). Catalytic hydrogenation of VII leads to a mixture of 2α-methylcholestan-3-one (II) and 2β-methylcoprostan-3-one (X). Lithium aluminum hydride reduction of the ketones II, III and X yields 2α-methylcholestan-3β-ol (VIIIa), 2,2-dimethylcholestan-3β-ol (IXa) and 2β-methylcoprostan-3α-ol (XIa), respectively. Bromination of 2α-methylcholestan-3-one (II) gives 2α-methyl-2β-bromocholestan-3-one (XIII) which can be dehydrobrominated to 2-methyl-Δ¹-cholestan-3-one (XIV). Catalytic hydrogenation of the latter yields 2β-methyl-cholestan-3-one (XV), isomerized to the 2α-isomer II with acids. Bromination of 2β-methylcoprostan-3-one (X) appears to take place at C-2 as well as at C-4 and after dehydrobromination a mixture of 2-methyl-Δ¹-coprosten-3-one (XVIII) and 2α-methyl-Δ⁴-cholesten-3-one (VII) is obtained in which the former predominates. Reduction of 4-methyl-Δ⁴-cholesten-3-one (XIX) with lithium in ammonia produces 4α-methylcholestan-3-one (XX). Catalytic hydrogenation of XIX leads to a mixture of 4β-methylcholestan-3-one (XXI) (epimerized to XX with acids), 4α-methylcholestan-3-one (XX) and 4β-methylcoprostan-3-one (XXII). Reduction of the ketones XX, XXVII and XXII yields 4α-methylcholestan-3β-ol (XXVIa), 4,4-dimethylcholestan-3β-ol (XXVIIIa) and 4β-methylcoprostan-3α-ol (XXXIIIa), respectively. Enol acetylation of 4α-methylcholestan-3-one (XX) leads to the acetate XXIX, which on bromination is converted to 2α-bromo-4α-methylcholestan-3-one (XXX) and then by dehydrobromination to 4α-methyl-Δ¹-cholesten-3-one (XXXI). Coprostan-3-one (XXXII) on methylation furnishes mainly 4β-methylcoprostan-3-one (XXII) which on successive bromination and dehydrobromination yields 4-methyl-Δ⁴-cholesten-3-one (XIX). The infrared spectra and molecular rotations of some of the methylated steroids are tabulated and various aspects of the data are discussed.

Citrostadienol, a substance isolated from citrus oil in these laboratories, showed properties which indicated it to be a ring A methyl-3β-hydroxy steroid.[2] It was mainly in this connection that we became interested in preparing and studying the properties of ring A methylated steroids. We have already reported on the synthesis of 4-methyl-Δ⁴-3-keto steroids.[3] In the present paper we describe the preparation of the various 2- and 4-methylated saturated 3-keto and 3-hydroxy steroids of the cholestane and coprostane series. A study also has been made of certain reactions of these compounds in order to determine whether the extra alkyl substituents change the normal course of such reactions. When our work was started nearly three years ago, no hydroaromatic steroid with additional alkyl groups at C-2 or at C-4 had been described, excepting for the 4,4-dimethyl steroids; the numerous naturally occurring tetracyclic triterpenes (4,4,14-trimethyl steroids) are to be included in this class and 4,4-dimethyl steroids lacking the 14-methyl group had been prepared in connection with the synthesis of lanosterol.[4] While the work described in this paper was in progress, a number of other research groups reported on the synthesis of various 2- and 4-methylated steroids as will be indicated later where relevant to our own work.

The direct methylation of cholestan-3-one (I) with methyl iodide and 1.4 molar equivalents of potassium *t*-butoxide in boiling *t*-butyl alcohol after 3 minutes yielded mainly 2α-methylcholestan-3-one (II), m.p. 120°. The structural assignment rests on the independent methods by which the same substance was prepared subsequently, on its behavior on bromination (see below) and on its stability toward both acids and bases. The reaction also produced smaller amounts of 2,2-dimethylcholestan-3-one (III), m.p. 113°, which proved to be the major product when the alkylation was carried out for a longer time with a large excess of potassium *t*-butoxide and methyl iodide.[5] The structure III follows from the analogous dimethylation of other 3-keto-5α-steroids as described recently.[6] The monomethylation at C-2 of cholestan-3-one (I) could alternatively be brought about by the sodium hydride catalyzed condensation of I with ethyl oxalate to give the 2-ethoxyoxalate IV, which on being methylated with methyl iodide over potassium carbonate in boiling acetone and then treated with sodium ethoxide in boiling ethanol, yielded the same 2α-methylcholestan-3-one (II) as had been obtained directly. The corresponding reaction in the androstane series has been reported.[6]

The direct monomethylation of Δ⁴-cholesten-3-one (V) at C-4 previously has been described by us.[3] Methylation at C-2 could be brought about by subjecting V to the sequence involving ethoxyoxalation (to give VI), and then methylation and treatment with sodium ethoxide.[5] The analogous reaction has been carried out with other Δ⁴-3-ketones.[6,7] This method of methylation was found to proceed rather better in the unsaturated than in the saturated series. The resulting 2α-methyl-Δ⁴-cholesten-3-one (VII), m.p. 127°, showed es-

(1) Presented in part (a) at the 19th Meeting of the Chemical Society of Israel, Rehovoth, June, 1956 (*Bull. Research Council Israel*, **5A**, 283 (1956)) and (b) at the 16th International Congress of Pure and Applied Chemistry, Paris, July, 1957 (Congress Handbook, Division of Organic Chemistry, p. 263).

(2) *Cf.* Y. Mazur, A. Welzmann and F. Sondheimer, THIS JOURNAL, **80**, 1007 (1958).

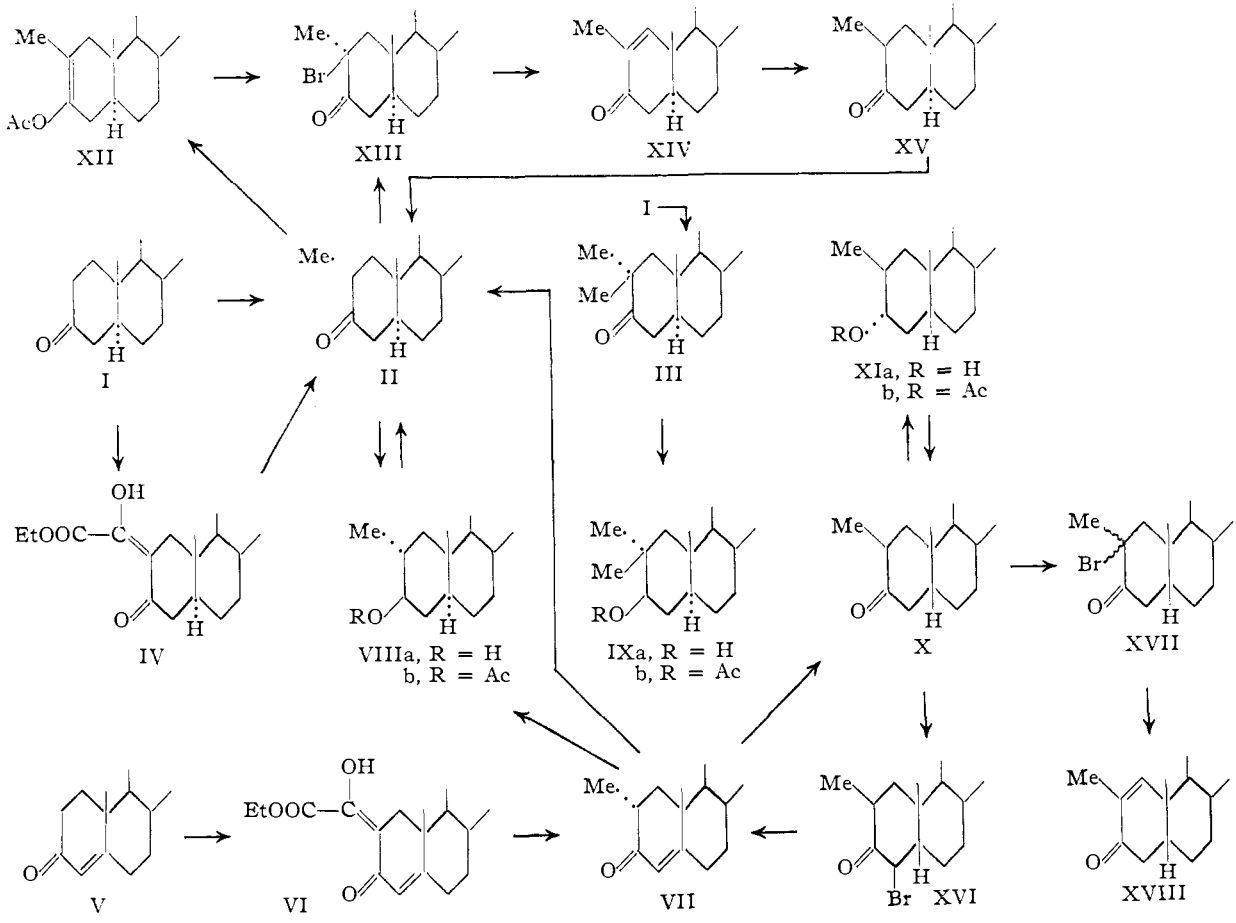
(3) F. Sondheimer and Y. Mazur, *ibid.*, **79**, 2906 (1957).

(4) *Cf.* R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives and R. B. Kelly, *ibid.*, **76**, 2852 (1954); *J. Chem. Soc.*, 1131 (1957).

(5) While this manuscript was in preparation, M. Mousseron, F. Winternitz and A. C. de Paulet (*Compt. rend.*, **245**, 1859 (1957)) in a preliminary communication independently reported on the direct methylation of cholestan-3-one (I) to give II and III. These workers also described the conversion of Δ⁴-cholesten-3-one (V) *via* the ethoxyoxalate VI to the 2α-methyl compound VII.

(6) H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, **21**, 1333 (1956).

(7) J. A. Hogg, F. H. Lincoln, R. W. Jackson and W. P. Schneider, THIS JOURNAL, **77**, 6411 (1955).




sentially the same ultraviolet spectrum as the unmethylated compound and acid treatment resulted in no change. These facts are consistent with the assigned structure.

Reduction of 2$\alpha$-methyl-$\Delta^4$-cholesten-3-one (VII) with lithium in liquid ammonia and decomposition with ammonium chloride yielded approximately equal amounts of a saturated ketone and a saturated alcohol. The first proved to be 2$\alpha$-methylcholestan-3-one (II) as was to be expected from the known course of such reductions.[8] The alcohol, m.p. 140°, was shown to be 2$\alpha$-methylcholestan-3$\beta$-ol (VIIIa) since it formed a precipitate with digitonin, since chromic acid oxidation furnished 2$\alpha$-methylcholestan-3-one (II) and since it was obtained by the reduction of the latter with lithium aluminum hydride. A similar reduction of 2,2-dimethylcholestan-3-one (III) produced 2,2-dimethylcholestan-3$\beta$-ol (IXa), m.p. 118°, likewise precipitated with digitonin.

Catalytic hydrogenation of 2$\alpha$-methyl-$\Delta^4$-cholesten-3-one (VII) in ethanol over palladium–charcoal gave a mixture which could be separated by chromatography on alumina into 2$\alpha$-methylcholestan-3-one (II) and a new saturated ketone, m.p. 112°. The latter substance was stable to acids and bases and the methyl group is therefore equatorial. The ketone must be 2$\beta$-methylcoprostan-3-one (X)[9] and this was confirmed since lithium aluminum hydride reduction gave in high yield an alcohol, m.p. 126°, which is a 3$\alpha$-ol as it gave no precipitate with digitonin. Chromic acid oxidation of this 2$\beta$-methylcoprostan-3$\alpha$-ol (XIa) regenerated 2$\beta$-methylcoprostan-3-one (X). The isolation of the saturated ketones II and X by chromatography was inefficient and a much superior separation method was to subject the total mixture from the hydrogenation of VII to lithium aluminum hydride reduction and then to treat the product with digitonin. The fraction which was precipitated on regeneration (pure 2$\alpha$-methylcholestan-3$\beta$-ol (VIIIa) could be obtained at this stage by crystallization) and chromic acid oxidation yielded 2$\alpha$-methylcholestan-3-one (II). The fraction not precipitated by digitonin (from which 2$\beta$-methylcoprostan-3$\alpha$-ol (XIa) could be obtained) on oxidation produced 2$\beta$-methylcoprostan-3-one (X). The ratio of II to X formed in the hydrogenation of VII is about 7:3 as judged by the digitonin precipitation. This conclusion is valid since lithium aluminum hydride reduction of pure II gave over 90% of material precipitated by digitonin, whereas pure X gave less than 10% .

Hydrogenation of $\Delta^4$-cholesten-3-one (V) under

(8) *Cf.* D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.*, 3045 (1954).

(9) In assigning the 2$\beta$-configuration to the methyl group in X and related substances, the assumption has been made that rings A and B both exist in the chair conformation as they do in coprostan-3-one itself (*cf.* D. H. R. Barton, *Experientia*, **6**, 316 (1950); D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.*, 1048 (1951)). That no unusual conformational effects are operative in X is shown by the fact that the rotatory dispersion curve is similar to that of coprostan-3-one (see footnote 28).

the conditions used with VII, followed by lithium aluminum hydride reduction and digitonin precipitation, indicated the ratio of 5α- to 5β-isomer formed to be about 9:1.[10] The presence of the 2α-methyl group in VII therefore results in an appreciable preference for attack of hydrogen from the α-side as compared with the unmethylated compound. It will be noted that the formation of 2β-methylcoprostan-3-one (X) by the hydrogenation of 2α-methyl-Δ⁴-cholesten-3-one (VII) involves an inversion at C-2. That inversion occurs during the hydrogenation and not during the subsequent chromatographic isolation of X follows from the conversion of the total reduction mixture to 2β-methylcoprostan-3α-ol (XIa) by lithium aluminum hydride reduction, a reagent which does not usually cause isomerization of epimerizable centers.[11]

Bromination of 2α-methylcholestan-3-one (II) with bromine in acetic acid yielded a bromoketone, m.p. 137°. The same substance was obtained by treating II with isopropenyl acetate and sulfuric acid to give the enol acetate XII, m.p. 94°, and then adding bromine to the latter dissolved in pyridine and acetic acid.[12] That bromination has occurred at C-2 as it does with cholestan-3-one was indicated by the fact that the bromo-substituent was axially oriented as shown by the location of the infrared carbonyl frequency at 1714 cm.$^{-1}$.[13] The compound was not epimerized by hydrogen bromide in acetic acid and the bromine is therefore attached to a fully substituted carbon atom, leading to the 2α-methyl-2β-bromocholestan-3-one structure XIII for the bromo-ketone. The presently described kinetically controlled bromination of II producing an axial bromo compound is in keeping with expectation[13b] and is in contrast to the thermodynamically controlled bromination of cholestan-3-one itself, resulting in the introduction of an equatorial bromo substituent.[13b,14]

Further evidence for structure XIII for the bromo-ketone from II was obtained through its dehydrobromination with lithium chloride in dimethylformamide.[15] The resulting unsaturated ketone, m.p. 74°, showed an ultraviolet maximum at 241 mμ consistent with the presence either of a 2-methyl-Δ¹-3-keto or of a Δ⁴-3-keto chromophore, since both have the same degree of substitution. The substance differed from 2α-methyl-Δ⁴-cholesten-3-one (VII) and could not be epimerized. It is therefore 2-methyl-Δ¹-cholesten-3-one (XIV). On hydrogenation in ethanol over palladium–charcoal, the unsaturated ketone XIV smoothly yielded a new saturated ketone, m.p. 97°. Absorption of hydrogen was expected to occur from the α-side to give 2β-methylcholestan-3-one (XV). That this is the structure of the hydrogenation product was demonstrated by its almost quantitative conversion to the 2α-methyl isomer II on acid treatment, the change involving epimerization of the methyl group from the axial to the equatorial configuration.

Bromination of 2β-methylcoprostan-3-one (X) with bromine in acetic acid yielded a product from which the expected 2β-methyl-4β-bromocoprostan-3-one (XVI), m.p. 128°, could be isolated only in low yield. The structure of this substance follows from the equatorial nature of the bromo-substituent ($\nu_{max}$ 1730 cm.$^{-1}$)[13] and from its dehydrobromination with lithium chloride in dimethylformamide,[15] whereby 2α-methyl-Δ⁴-cholesten-3-one (VII) was regenerated. The inversion of the 2β-methyl group to the more stable 2α-configuration may have been caused by the alkaline conditions under which the reaction was carried out or else it occurred during the chromatography used to isolate VII. Dehydrobromination of the total unpurified bromination mixture gave the 2α-methyl-Δ⁴-3-ketone (VII) only as a comparatively minor constituent, a new unsaturated ketone, m.p. 97°, being obtained in larger amount. The latter showed an ultraviolet maximum at 241 mμ (log ε 4.00) and was not epimerizable. It must consequently be 2-methyl-Δ¹-coprosten-3-one (XVIII), derived from 2-methyl-2-bromocoprostan-3-one (XVII) formed in the bromination step besides the 4-bromo isomer XVI. Attempts to isolate this second bromo ketone in the pure state were, however, unsuccessful. Whereas bromination of coprostan-3-one derivatives occurs mainly at C-4,[16] the extra methyl group in 2β-methylcoprostan-3-one (X) has therefore caused at least as much bromination to take place at C-2 as at C-4. This is due presumably to the preferred enolization toward C-2, attributable to the hyperconjugation effect of the 2-methyl group.

For the synthesis of 4-methylated saturated cholestane derivatives, the previously described 4-methyl-Δ⁴-cholesten-3-one (XIX)[3] was a suitable precursor. The reduction of this unsaturated ketone with lithium in liquid ammonia gave in high yield 4α-methylcholestan-3-one (XX), m.p. 123°, both of the new asymmetric centers at C-4 and C-5 being introduced so as to produce the most stable configuration.[8] On the other hand, hydrogenation of 4-methyl-Δ⁴-cholesten-3-one (XIX) in ethanol solution over palladium–charcoal followed by direct crystallization yielded 40% of a new saturated ketone, m.p. 127°. The latter must be 4β-methylcholestan-3-one (XXI), formally derived from XIX by normal *cis* addition of hydrogen from the α-side, since it was epimerized readily to 4α-

(10) This argument is based on the fact that the lithium aluminum hydride reduction of cholestan-3-one and coprostan-3-one yields over 90% of cholestan-3β-ol and coprostan-3α-ol, respectively (C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 687 (1950)). The present finding is in keeping with the previously reported formation of coprostan-3-one in at least 85% yield by the catalytic hydrogenation of Δ⁴-cholesten-3-one over palladium in ether (H. Grasshof, *Z. physiol. Chem.*, **223**, 249 (1934); L. Ruzicka, H. Brünger, E. Eichenberger and J. Meyer, *Helv. Chim. Acta*, **17**, 1407 (1934)).

(11) *Cf.* D. S. Noyce and D. B. Denney, THIS JOURNAL, **72**, 5743 (1950); D. N. Jones, J. R. Lewis, C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 2876 (1955).

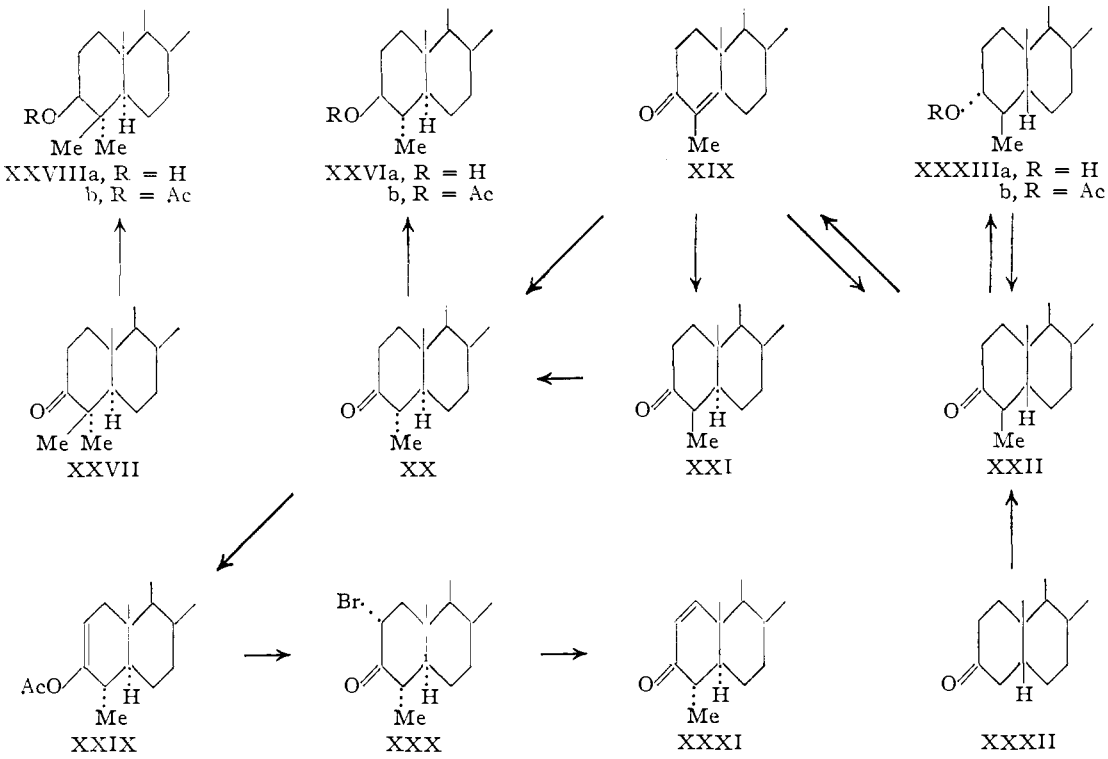
(12) This method of bromination was developed by Professor E. R. H. Jones and co-workers who kindly provided us with experimental details.

(13) *Cf.* (a) R. N. Jones, D. A. Ramsay, F. Herling and K. Dobriner, THIS JOURNAL, **74**, 2828 (1952); (b) E. J. Corey, *ibid.*, **75**, 2301, 4832 (1953); **76**, 175 (1954); *Experientia*, **9**, 329 (1953).

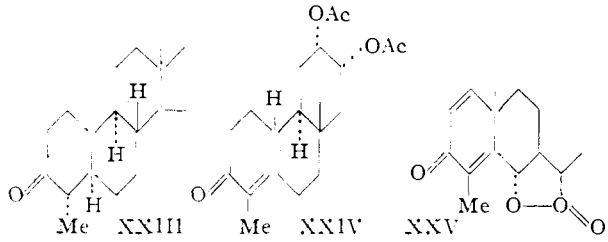
(14) L. F. Fieser and Wei-Yuan Huang, THIS JOURNAL, **75**, 4837 (1953).

(15) R. P. Holysz, *ibid.*, **75**, 4432 (1953).

(16) *Cf.* A. Butenandt, *et al.*, *Ber.*, **67**, 1901 (1934); **68**, 1854, 2091 (1935). The 2-bromo-3-ketone also has been obtained from the bromination of an unmethylated 3-keto-5β-steroid (*cf.* V. R. Mattox and E. C. Kendall, *J. Biol. Chem.*, **188**, 593 (1950)), but only in minor amounts.




methylcholestan-3-one (XX) by means of sulfuric acid in ethanol.[17] Chromatography of the hydrogenation product after removal of the crystalline XXI yielded 10% of 4β-methylcoprostan-3-one (XXII), m.p. 57°, the structure of which rests on its identity with XXII prepared from coprostan-3-one




(see below). Further elution of the column produced a mixture of 4α- and 4β-methylcholestan-3-one, which could not be resolved into its components but was converted on acid treatment smoothly to the pure 4α-methyl isomer XX. The axial 4β-methyl isomer XXI was found to be stable under the chromatography conditions used and the 4α-methylcholestan-3-one (XX) must therefore have been formed directly in the hydrogenation. The catalytic hydrogenation of 4-methyl-Δ⁴-cholesten-3-one (XIX) to give all of the possible isomers with the exception of 4α-methylcoprostan-3-one (XXIII) (to be expected formally from *cis* addition of hydrogen from the β-side) exactly parallels the hydrogenation results obtained with the analogous tricyclic unsaturated ketone XXIV[18] and with santonin (XXV).[19] The failure to obtain the isomer XXIII probably is due to the fact that the steric crowding of the axial 4α-methyl group in a 5β-compound such as XXIII is so severe as to prevent the formation or isolation without epimerization of this substance.[20]

The lithium aluminum hydride reduction of 4α-methylcholestan-3-one (XX) proceeded normally and yielded mainly 4α-methylcholestan-3β-ol (XXVIa), m.p. 164°, precipitated by digitonin. Similarly, the previously described 4,4-dimethylcholestan-3-one (XXVII)[17] produced mainly the corresponding 3β-ol XXVIIIa,[21] m.p. 158°, also precipitated with digitonin.

The enol acetylation of 4α-methylcholestan-3-one (XX) also proceeded as in the unmethylated series. Thus, isopropenyl acetate and sulfuric acid yielded an enol acetate, m.p. 104°, which on treatment with bromine in acetic acid and pyridine[12] produced a bromo ketone, m.p. 110°, dehydrobrominated by lithium chloride–dimethylformamide[15] to an unsaturated ketone, m.p. 83°. The latter differed from 4-methyl-Δ⁴-cholestene-3-one (XIX), and the observed ultraviolet maximum at 230 mμ (log ε 3.98) showed it to be 4α-methyl-Δ¹-cholesten-3-one (XXXI). The enol acetate is therefore

(17) After completion of these syntheses of the 4-methylated ketones XX and XXI (*cf.* footnote 1a), J. L. Beton, T. G. Halsall, E. R. H. Jones and P. C. Phillips (*J. Chem. Soc.*, 753 (1957)) reported independent preparations by different methods of the same substances with physical properties in excellent agreement with ours. Moreover G. D. Meakins and O. R. Rodig (*ibid.*, 4679 (1956)) described the lithium–ammonia reduction of 4-methyl-Δ⁴-cholesten-3-one (XIX) to 4α-methylcholestan-3-one (XX), the same saturated ketone also being obtained in poor yield by the catalytic hydrogenation of XIX over platinum in acetic acid and subsequent chromic acid oxidation.

(18) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, THIS JOURNAL, **74**, 4223 (1952).

(19) J. C. Banerji, D. H. R. Barton and R. C. Cookson, *J. Chem. Soc.*, 5041 (1957), and reference cited there.

(20) It is of interest that in the santonin series the isomer corresponding to XXIII has now been obtained (footnote 19), though not by hydrogenation of santonin.

(21) H. J. Ringold and G. Rosenkranz (*J. Org. Chem.*, **22**, 602 (1957)) have carried out the analogous reduction (with sodium borohydride) in the androstane series.

4α-methyl-Δ²-cholesten-3-ol acetate (XXIX) and the bromo ketone is 2α-bromo-4α-methylcholestan-3-one (XXX). The equatorial nature of the bromo substituent in the latter is indicated by the position of the infrared carbonyl band at 1733 cm.$^{-1}$,[13] which further confirms that bromination had occurred at C-2 and not at C-4.

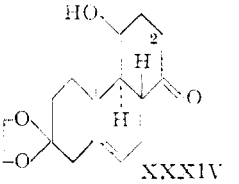
Treatment of coprostan-3-one (XXXII) with methyl iodide and potassium *t*-butoxide in *t*-butyl alcohol resulted mainly in methylation at C-4. Chromatographic purification gave 40% of a non-crystalline product consisting largely of 4β-methylcoprostan-3-one (XXII). The pure ketone, m.p. 59°, could be obtained through conversion to the semicarbazone, m.p. 208°, and regeneration with pyruvic acid.[22] Alternatively the non-crystalline ketone XXII was reduced with lithium aluminum hydride to give mainly 4β-methylcoprostan-3α-ol (XXXIIIa), the extra methyl group at C-4 not affecting the normal course of reduction. The small 3β-ol fraction was removed as the insoluble digitonide and acetylation then yielded pure 4β-methylcoprostan-3α-ol acetate (XXXIIIb), m.p. 89°. Saponification regenerated the alcohol XXXIIIa, m.p. 157°, which on chromic acid oxidation produced the crystalline ketone XXII. The latter could not be epimerized and the methyl group is therefore assigned the equatorial β-configuration. That monomethylation has occurred at C-4 follows from the fact that XXII had been obtained as a minor product from the hydrogenation of 4-methyl-Δ⁴-cholesten-3-one (XIX). Moreover the reverse process could be brought about. Thus, direct bromination of 4β-methylcoprostan-3-one (XXII) with bromine in acetic acid yielded an amorphous 4-bromo-ketone which on treatment with lithium chloride in boiling dimethylformamide[15] produced the same 4-methyl-Δ⁴-cholesten-3-one (XIX) as described previously.[3] Alternatively the unsaturated ketone XIX could be obtained by converting 4β-methylcoprostan-3-one (XXII) to its enol acetate, brominating the latter with bromine in pyridine and acetic acid[12] and finally dehydrobrominating the resulting bromo ketone as before. This incidentally completes a third route[3] to 4-methyl-Δ⁴-3-ketones, the starting material being the corresponding saturated 3-ketone of the 5β-configuration.

In Table I the infrared carbonyl stretching frequencies are recorded for the various saturated 2- and 4-methylated 3-ketosteroids described in this paper. In the cholestane series it can be seen that introduction of one methyl group in the 2- or the 4-position causes a decrease of about 5 cm.$^{-1}$, irrespective of whether the methyl group is in the axial or in the equatorial configuration. Similarly in the coprostane series, introduction of an equatorial methyl group at C-2 or at C-4 lowers the carbonyl frequency, the decrease being *ca.* 4 cm.$^{-1}$. An analogous effect has been observed by Cherrier[23] for α-alkylcyclohexanones. The influence of α-monomethylation on the infrared spectrum of saturated ketones is in contrast to α-halogenation where an axial substituent has little effect while an equatorial one causes a considerable *increase* in the carbonyl frequency.[13] Our observations are in agreement with the report by Lukes, *et al.*,[24] that introduction of an equatorial methyl substituent at C-2 in the ketone XXXIV causes a *ca.* 8 cm.$^{-1}$ decrease in the carbonyl frequency, but not with the fact that introduction of an axial methyl group at C-2 results in a *ca.* 14 cm.$^{-1}$ *increase*. No generalizations can therefore be based on the latter phenomenon which must be due to special factors.

TABLE I

CARBONYL STRETCHING FREQUENCIES OF SATURATED 2- AND 4-METHYL-3-KETO-STEROIDS (IN $CS_2$ SOLUTION)

| Compound | Frequency, cm.$^{-1}$ |
|---|---|
| Cholestan-3-one (I) | 1715 |
| 2α-Methylcholestan-3-one (II) | 1711 |
| 2β-Methylcholestan-3-one (XV) | 1711 |
| 4α-Methylcholestan-3-one (XX) | 1709 |
| 4β-Methylcholestan-3-one (XXI) | 1708 |
| 2,2-Dimethylcholestan-3-one (III) | 1702 |
| 4,4-Dimethylcholestan-3-one (XXVII) | 1703 |
| Lanostan-3-one | 1704[25b] |
| 2,2,4,4-Tetramethylcholestan-3-one | 1698[25b] |
| Coprostan-3-one (XXXII) | 1713 |
| 2β-Methylcoprostan-3-one (X) | 1709 |
| 4β-Methylcoprostan-3-one (XXII) | 1709 |



XXXIV

Introduction of a *gem*-dimethyl group at C-2 or at C-4 of cholestan-3-one causes a carbonyl frequency decrease of *ca.* 12 cm.$^{-1}$ as is also observed with 4,4,14α-trimethylcholestan-3-one (lanostan-3-one) and the pentacyclic triterpene ketones containing the 4,4-dimethyl-3-one system.[25a] This effect caused by dimethylation at C-4 has been discussed recently by Cummins and Page[25b] who further reported that the carbonyl frequency of the hitherto undescribed fully methylated 2,2,4,4-tetramethylcholestan-3-one is lowered by *ca.* 17 cm.$^{-1}$ as compared with the unmethylated compound.

In the Δ⁴-3-ketone series, the introduction of a methyl group at C-2 or at C-4 also results in a lowering of the carbonyl frequency. Thus the values (measured in carbon tetrachloride) for Δ⁴-cholesten-3-one (V), 2α-methyl-Δ⁴-cholesten-3-one (VII) and 4α-methyl-Δ⁴-cholesten-3-one (XIX)[3] are 1675, 1671 and 1669 cm.$^{-1}$, respectively. Of interest also in the infrared spectra of the α,β-unsaturated ketones is the fact that whereas the comparatively small double bond band in the 1620 cm.$^{-1}$ region[26] in the Δ⁴-3-ketones V, VII and XIX is well-defined, it is so weak and badly-defined in the Δ¹-3-ketones XIV, XVIII and XXXI when measured under our conditions[31] as to be hardly recognizable.

(22) *Cf.* E. B. Hershberg, *J. Org. Chem.*, **13**, 542 (1948).

(23) C. Cherrier, *Compt. rend.*, **225**, 1063 (1947); see also H. Conroy and R. A. Firestone, THIS JOURNAL, **78**, 2290 (1956).

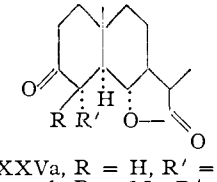
(24) R. M. Lukes, G. I. Poos, R. E. Beyler, W. F. Johns and L. H. Sarett, *ibid.*, **75**, 1707 (1953).

(25) (a) *Cf.* A. R. H. Cole and D. W. Thornton, *J. Chem. Soc.*, 1007 (1956); (b) E. G. Cummins and J. E. Page, *ibid.*, 3847 (1957).

(26) *Cf.* R. N. Jones, P. Humphries, E. Packard and K. Dobriner, THIS JOURNAL, **72**, 86 (1950).

In Table II the molecular rotations of the various saturated 2- and 4-methylated derivatives of cholestan-3$\beta$-ol and coprostan-3$\alpha$-ol are recorded and compared with those of the corresponding acetates. It has been observed previously that the shift in molecular rotation caused by acetylating the 3$\beta$-hydroxy group is generally negative with saturated steroids and positive with triterpenes and this fact has proved to be of value in distinguishing between the two classes of compounds.[27] Klyne and Stokes[27b] have attributed this reversal to the presence of the 4,4-dimethyl group in the triterpenes and have pointed out that the observed direction of the shift in the triterpenes (positive when a 3$\beta$-ol is acetylated, negative when a 3$\alpha$-ol is acetylated) is as expected from their known absolute configuration. The direction of the shift in molecular rotation ($\Delta_1$) observed on acetylating the methylated alcohols in Table II likewise is in keeping with expectation. Thus in the case of the 3$\beta$-hydroxy compounds, the $\Delta_1$ values of the 2-methyl and 2,2-dimethyl derivatives are more negative than that of the unmethylated 3$\beta$-ol, while the $\Delta_1$ values of the 4-methyl and 4,4-dimethyl derivatives are more positive. Conversely in the 3$\alpha$-hydroxy series, the $\Delta_1$ value of the 2-methyl compound is more positive than that of the unmethylated 3$\alpha$-ol and the $\Delta_1$ of the 4-methyl compound is more negative. The fact that the monomethyl alcohols exhibit larger $\Delta_1$ values than do the corresponding *gem*-dimethyl compounds is presumably ascribable to the presence of an extra asymmetric center adjacent to the alcohol group in the monomethyl compounds.

In Table III the specific rotations of the four monomethylcholestan-3-ones in chloroform solution are compared with the values determined in methanol.[28] It is of interest to note that whereas there is no appreciable solvent effect with 2$\alpha$-methyl- and 4$\alpha$-methylcholestan-3-one containing equatorial methyl groups, the $[\alpha]_D$ values in methanol for the corresponding axial 2$\beta$- and 4$\beta$-methyl compounds are considerably lower than in chloroform. This shift, which is in the opposite direction to that usually observed when passing from chloroform to methanol as a solvent,[29] occurs also with other axial $\alpha$-methyl ketones. Thus "$\alpha$"-tetrahydrosantonin (XXXVa) with the equatorial methyl group next to the ketone shows essentially



XXXVa, R = H, R′ = Me
b, R = Me, R′ = H

the same specific rotation in the two solvents, whereas "$\gamma$"-tetrahydrosantonin (XXXVb) with the methyl group axially orientated again exhibits a considerably lower $[\alpha]_D$ value in methanol than in chloroform. The same behavior is shown by the pair 30-nor-19$\alpha$(H)-taraxastan-20-one (XXXVIb) and 30-nortaraxastan-20-one (XXXVIa), except that in this case the shift occurs with the latter isomer which presumably is the equatorial methyl

TABLE II

MOLECULAR ROTATION DATA OF SATURATED 2- AND 4-METHYL-3-HYDROXY-STEROIDS AND THEIR ACETATES (IN $CHCl_3$)

| Compound | $[M]_D^{OH}$ | $[M]_D^{OAc}$ | $\Delta_1$ | $\Delta\Delta_1$[a] |
|---|---|---|---|---|
| Cholestan-3$\beta$-ol | + 89[29b] | + 60[29b] | − 29 | 0 |
| 2$\alpha$-Methylcholestan-3$\beta$-ol (VIIIa) | + 32 | −147 | −179 | −150 |
| 2,2-Dimethylcholestan-3$\beta$-ol (IXa) | +129 | + 87 | − 42 | − 13 |
| 4$\alpha$-Methylcholestan-3$\beta$-ol (XXVIa) | +109 | +182 | + 73 | +102 |
| 4,4-Dimethylcholestan-3$\beta$-ol (XXVIIIa) | + 46 | + 87 | + 41 | + 70 |
| 4,4,14$\alpha$-Trimethylcholestan-3$\beta$-ol[c] | +151[b] | +194[b] | + 43 | + 72 |
| Coprostan-3$\alpha$-ol | +124[29b] | +206[29b] | + 82 | 0 |
| 2$\beta$-Methylcoprostan-3$\alpha$-ol (XIa) | +100 | +346 | +246 | +164 |
| 4$\beta$-Methylcoprostan-3$\alpha$-ol (XXXIIIa) | + 60 | + 27 | − 33 | −115 |

[a] $\Delta\Delta_1$ refers to the difference in $\Delta_1$ between the methylated and the unmethylated compound. [b] W. Voser, M. Montavon, H. H. Günthard, O. Jeger and L. Ruzicka, *Helv. Chim. Acta*, **33**, 1893 (1950). [c] Lanostan-3$\beta$-ol.

TABLE III

SOLVENT EFFECT ON THE SPECIFIC ROTATIONS OF EQUATORIAL AND AXIAL $\alpha$-METHYL KETONES

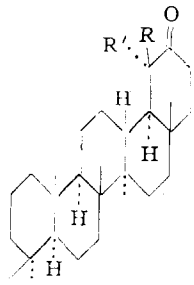
| Compound | $[\alpha]^{CHCl_3}D$ | $[\alpha]^{MeOH}D$ | $\Delta[\alpha]_D$ |
|---|---|---|---|
| 2$\alpha$-Methylcholestan-3-one (II) | +32 | +31[28] | − 1 |
| 2$\beta$-Methylcholestan-3-one (XV) | +86 | +67[28] | −19 |
| 4$\alpha$-Methylcholestan-3-one (XX) | +26 | +25[28] | − 1 |
| 4$\beta$-Methylcholestan-3-one (XXI) | +36 | +16[28] | −20 |
| "$\alpha$"-Tetrahydrosantonin (XXXVa) | +28[a] | +27[b] | − 1 |
| "$\gamma$"-Tetrahydrosantonin (XXXVb) | +72[a] | +52[b] | −20 |
| 30-Nor-19$\alpha$(H)-taraxastan-20-one (XXXVIb) | +15[30] | +20[28] | + 5 |
| 30-Nortaraxastan-20-one (XXXVIa) | +65[30] | +39[28] | −26 |
| 17a$\beta$-Methyl-D-homoandrostan-3$\beta$-ol-17-one (XXXVIIa) | −54[c] | −52[b,d] | + 2 |
| 17a$\alpha$-Methyl-D-homoandrostan-3$\beta$-ol-17-one (XXXVIIb) | −27[c] | −39[b,d] | −12 |

[a] W. Cocker and T. B. H. McMurry, *J. Chem. Soc.*, 4549 (1956). [b] C. Djerassi, R. Riniker and B. Riniker, THIS JOURNAL, **78**, 6362 (1956). [c] F. Ramirez and S. Stafiej, *ibid.*, **77**, 134 (1955); **78**, 644 (1956). [d] Rotation measured in dioxane.

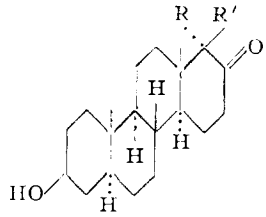
(27) *Inter al.* (a) D. H. R. Barton, *J. Chem. Soc.*, 813 (1945); (b) W. Klyne and W. M. Stokes, *ibid.*, 1979 (1954).

(28) The values in methanol were obtained by C. Djerassi, O. Halpern, V. Halpern and R. Riniker (THIS JOURNAL, **80**, 4001 (1958)) in the course of determining the rotatory dispersions.

(29) *Cf.* (a) P. A. Plattner and H. Heusser, *Helv. Chim. Acta*, **27**, 748 (1944); (b) D. H. R. Barton, *J. Chem. Soc.*, 1116 (1946); (c) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 3rd edition, 1949, p. 205.



XXXVI
a, R = H, R′ = Me
b, R = Me, R′ = H



XXXVII
a, R = H, R′ = Me
b, R = Me, R′ = H

compound.[30] However, with this pair the usual stability relationship is reversed, the equatorial isomer being the less stable due to interference with the C-12 methylene group. The presently described solvent shift is therefore operative with the less stable isomer XXXVIa, as is also the abnormality of the rotatory dispersion.[28] The last pair in Table III shows that the effect is also observed when comparing rotations measured in chloroform and dioxane. Thus whereas the equatorial methyl compound XXXVIIa shows almost the same rotation in the two solvents, the axial isomer XXXVIIb in dioxane has a markedly lower rotation than in chloroform, the direction of the shift again being opposite to the usual one.[29b,c] The magnitude is however less than in the other cases where chloroform was compared with methanol. The observation that the rotations of epimerizable α-methyl ketones are considerably lower in methanol or dioxane than in chloroform seems to be general.

**Acknowledgments.**—We would like to thank Professor E. R. H. Jones, F.R.S., for giving us advance information prior to publication about the bromination of enol acetates and Professor C. Djerassi for sending us a manuscript of the paper mentioned in footnote 28 before publication. We are also indebted to Dr. S. Pinchas of this Institute for determining the infrared spectra.

## Experimental[31]

**Direct Methylation of Cholestan-3-one (I). (a) To Give Mainly 2α-Methylcholestan-3-one (II).**—A solution of 700 mg. (18 millimoles) of potassium in 35 cc. of *t*-butyl alcohol was added to a boiling solution of 5 g. (13 millimoles) of cholestan-3-one (I) in 50 cc. of benzene and 25 cc. of *t*-butyl alcohol. Methyl iodide (5 cc.) in 5 cc. of benzene was then added and refluxing was continued for 3 minutes. The solution was cooled, ice was added and the product was isolated with ether. The crystalline residue was chromatographed in light petroleum solution on 300 g. of alumina. Elution with light petroleum yielded first 850 mg. of partially crystalline material (fraction A) enriched in 2,2-dimethylcholestan-3-one, then 1.01 g. of 2α-methylcholestan-3-one (fraction B), m.p. 117–119°, and then 482 mg. of material with m.p. 118–121° (fraction C) which by rechromatography was shown to be a mixture of cholestan-3-one and 2α-methylcholestan-3-one. Lastly light petroleum and light petroleum–benzene (9:1 and 4:1) yielded 2.11 g. of unchanged cholestan-3-one (fraction D), m.p. 125–129°.

Crystallization of fraction B from ether–methanol gave pure 2α-methylcholestan-3-one, m.p. 119–120°, $[\alpha]_D$ +32° (*c* 0.9).

*Anal.* Calcd. for $C_{28}H_{48}O$: C, 83.93; H, 12.08. Found: C, 84.20; H, 12.20.

Crystallization of fraction A from ether–methanol gave 0.55 g. of pure 2,2-dimethylcholestan-3-one, m.p. 111–113°, $[\alpha]_D$ +77° (*c* 0.87).

*Anal.* Calcd. for $C_{29}H_{50}O$: C, 83.99; H, 12.15. Found: C, 84.20; H, 12.33.

**(b) To Give Mainly 2,2-Dimethylcholestan-3-one (III).**—A solution of 2 g. (51 millimoles) of potassium in 50 cc. of *t*-butyl alcohol was added to a boiling solution of 2 g. (5 millimoles) of cholestan-3-one in 50 cc. of benzene and 25 cc. of *t*-butyl alcohol. Methyl iodide (15 cc.) in 50 cc. of benzene was added and the mixture was boiled under reflux for 1 hr. The product was isolated as previously and was chromatographed in pentane solution on 100 g. of alumina. The first fraction, eluted with pentane, on crystallization from ether–methanol yielded 1.02 g. of 2,2-dimethylcholestan-3-one, m.p. 111–113°. Identity with the sample prepared by method a was established by non-depression in m.p. on admixture and by infrared comparison. The next fraction, eluted with pentane and pentane–benzene (9:1) gave 120 mg. of 2α-methylcholestan-3-one, which after crystallization from methanol–ether showed m.p. 119–120°, undepressed with the previously described sample. Lastly, pentane–benzene (9:1 and 4:1) eluted 210 mg. of unchanged cholestan-3-one.

**Methylation of Cholestan-3-one (I) *via* the Ethoxyoxalate IV.**—A mixture containing 2 g. of cholestan-3-one, 120 mg. of sodium hydride and 0.68 cc. of ethyl oxalate in 20 cc. of benzene was stirred at room temperature in nitrogen for 76 hr. Ether and water were then added, the aqueous layer was separated, acidified with dilute hydrochloric acid and extracted with ether. This latter ether extract on being dried and evaporated yielded 1.9 g. of the crude ethoxyoxalate IV which was boiled for 16 hr. with 1 g. of anhydrous potassium carbonate and 2 cc. of methyl iodide in 20 cc. of dry acetone. The mixture was cooled and diluted with water and ether. The ether extract was washed with sodium hydroxide solution and water and was then dried and evaporated. The residue was boiled for 3 hr. under reflux with a solution of 5 g. of sodium in 100 cc. of ethanol. The neutral product was isolated with ether and was chromatographed in light petroleum solution on 100 g. of alumina. The fractions eluted with light petroleum and light petroleum–benzene (9:1) gave 203 mg. of 2α-methylcholestan-3-one, m.p. 118–119°. Identity with the above-described sample was established through mixture m.p. determination and infrared comparison.

**2α-Methyl-Δ⁴-cholesten-3-one (VII).**—A solution of 10 g. of Δ⁴-cholesten-3-one (V) in 50 cc. of benzene was treated with 3.75 cc. of ethyl oxalate and 0.6 g. of sodium hydride and the mixture was allowed to stand at room temperature in nitrogen for 72 hr. Methanol (5 cc.) was added to decompose the unreacted hydride and then ether and water. The aqueous extract was acidified, shaken with ether and the ether extract was dried and evaporated. The resulting crude ethoxyoxalate VI (8.2 g.) was boiled under reflux with 5 g. of anhydrous potassium carbonate and 5 cc. of methyl iodide in 50 cc. of dry acetone for 14 hr. The mixture was cooled, diluted with water and ether and the ether extract was washed with 5% sodium hydroxide solution and water. The oily residue obtained by evaporation of the ether was boiled for 3 hr. with a solution of 5 g. of sodium in 100 cc. of ethanol. Isolation of the neutral product with ether yielded 6.1 g. of a partially crystalline material which was dissolved in light petroleum–benzene (1:1) and chromatographed on 200 g. of alumina. The fractions eluted with light petroleum–benzene (1:1) on crystallization from ether–methanol gave 2.6 g. of 2α-methyl-Δ⁴-cholesten-3-one with m.p. 124–125°. The analytical sample, obtained by further crystallization from ether–methanol, showed m.p. 126–127°, $[\alpha]_D$ +92°, $\lambda_{max}$ 239 mμ (log ε 4.19). $\nu_{max}^{CCl_4}$ 1671 and 1622 cm.$^{-1}$.

*Anal.* Calcd. for $C_{28}H_{46}O$: C, 84.35; H, 11.63. Found: C, 84.20; H, 11.83.

**Lithium–Ammonia Reduction of 2α-Methyl-Δ⁴-cholesten-3-one (VII).**—A solution of 250 mg. of 2α-methyl-Δ⁴-

(30) T. R. Ames, J. L. Beton, A. Bowers, T. G. Halsall and E. R. H. Jones, *J. Chem. Soc.*, 1905 (1954).

(31) Melting points are uncorrected. All chromatograms were carried out with Merck "acid-washed" alumina. Rotations were determined at room temperature in chloroform solution. Ultraviolet spectra were measured in 95% ethanol solution on a Unicam Model S.P. 500 spectrophotometer. Infrared spectra were determined on a Perkin–Elmer model 12C single beam spectrophotometer with sodium chloride prism. Analyses were carried out in our microanalytical department under the direction of Mr. Erich Meier.

cholesten-3-one (VII) in 10 cc. of dry ether was added dropwise with stirring to a solution of 100 mg. of lithium in *ca.* 25 cc. of liquid ammonia during 5 minutes. The mixture was then stirred for another 20 minutes, when 2 g. of ammonium chloride was added. The product was then isolated with ether in the usual way and chromatographed in light petroleum solution on 6 g. of alumina. The fractions eluted with light petroleum and with light petroleum–benzene (9:1) gave 130 mg. of 2α-methylcholestan-3-one (II), which after crystallization from ether–methanol showed m.p. 118–119°. The substance was identical with that prepared previously (mixture m.p., infrared comparison). Further elution with benzene gave fractions which on crystallization from ether–methanol yielded 104 mg. of 2α-methylcholestan-3β-ol (VIIIa), m.p. 139–140°, $[\alpha]_D$ +8° (*c* 1.5).

*Anal.* Calcd. for $C_{28}H_{50}O$: C, 83.51; H, 12.52. Found: C, 83.84; H, 12.39.

**Catalytic Hydrogenation of 2α-Methyl-Δ⁴-cholesten-3-one (VII).**—A solution of 2 g. of 2α-methyl-Δ⁴-cholesten-3-one in 75 cc. of ethanol was shaken in hydrogen over 200 mg. of a 10% palladium–charcoal catalyst. Uptake of gas stopped after 1.03 molar equivalents of hydrogen had been absorbed. The catalyst and solvent were removed and the residue, dissolved in 50 cc. of absolute ether, was added dropwise to a stirred solution of 1 g. of lithium aluminum hydride in 50 cc. of ether. The mixture was boiled under reflux for 1 hr. and the excess hydride was then decomposed by the careful addition of ethyl acetate. Addition of dilute hydrochloric acid and isolation with ether in the usual way led to 1.98 g. of material which was treated with 4 g. of digitonin in 200 cc. of 90% ethanol. The precipitated digitonide was collected, dissolved in the minimum of pyridine and diluted with ether. The precipitated digitonin was removed by filtration, washed with ether and the ether filtrates were evaporated. The residual crystalline material (568 mg.) on crystallization from ether–methanol yielded 509 mg. of 2α-methylcholestan-3β-ol (VIIIa), m.p. 139–140°, identified with the above-described material through mixture m.p. determination and infrared comparison.

The filtrate obtained after removal of the digitonide was evaporated to dryness, the residue was treated with ether and the excess digitonin was removed by filtration. The ether solution was evaporated and yielded 1.42 g. of crude 2β-methylcoprostan-3α-ol (XIa). A sample on crystallization yielded the pure compound with m.p. 124–126°. The crude material (1.1 g.) dissolved in 50 cc. of acetic acid was oxidized by being allowed to stand for 16 hr. at room temperature with 0.4 g. of chromic acid in 20 cc. of 90% acetic acid. The excess of chromic acid was then decomposed by the careful addition of methanol, water was added and the product was isolated with ether. Crystallization from ether–methanol gave 720 mg. of 2β-methylcoprostan-3-one (X), m.p. 111–112°, $[\alpha]_D$ +30° (*c* 1.1).

*Anal.* Calcd. for $C_{28}H_{48}O$: C, 83.93; H, 12.08. Found: C, 83.75; H, 12.03.

The analogous oxidation of 500 mg. of the 2α-methylcholestan-3β-ol (VIIIa) obtained from the hydrogenation experiment led to 430 mg. of 2α-methylcholestan-3-one (II), m.p. 119–120°. Identity with the above-described samples was established in the usual way.

When the total hydrogenation product from 2 g. of 2α-methyl-Δ⁴-cholesten-3-one (VII) was chromatographed directly on 100 g. of alumina, the separation was incomplete. After rechromatography, a total of 245 mg. of 2β-methylcoprostan-3-one with m.p. 110–111° and 110 mg. of 2α-methylcholestan-3-one with m.p. 119–120° could be obtained, the former being eluted (with pentane) before the latter.

**Reduction of 2α-Methylcholestan-3-one (II) to 2α-Methylcholestan-3β-ol (VIIIa).**—A solution of 200 mg. of 2α-methylcholestan-3-one (II) in 20 cc. of ether was added dropwise to 500 mg. of lithium aluminum hydride in 20 cc. of ether. The mixture was boiled under reflux for 2 hr. and then decomposed by the addition of ice and dilute hydrochloric acid. Isolation with ether and crystallization from ether–methanol produced 174 mg. of 2α-methylcholestan-3β-ol (VIIIa), m.p. 139–140°, $[\alpha]_D$ +8° (*c* 1.4), identified with the above-described compound in the usual way. Acetylation (acetic anhydride, pyridine, room temperature, overnight) and subsequent crystallization from methanol yielded the acetate VIIIb with m.p. 107–108°, $[\alpha]_D$ −33° (*c* 1.7).

*Anal.* Calcd. for $C_{30}H_{52}O_2$: C, 81.02; H, 11.79. Found: C, 81.01; H, 11.95.

**Reduction of 2,2-Dimethylcholestan-3-one (III) to 2,2-Dimethylcholestan-3β-ol (IXa).**—The reduction of 1 g. of 2,2-dimethylcholestan-3-one with 1 g. of lithium aluminum hydride in 70 cc. of ether was carried out as described for the preceding experiment. Crystallization from methanol produced 850 mg. of 2,2-dimethylcholestan-3β-ol (IXa) with m.p. 116–118°, $[\alpha]_D$ +31° (*c* 0.8).

*Anal.* Calcd. for $C_{29}H_{52}O$: C, 83.58; H, 12.58. Found: C, 83.12; H, 12.59.

**The acetate IXb** (acetic anhydride, pyridine, room temperature, overnight) on crystallization from methanol showed m.p. 124–126°, $[\alpha]_D$ +19° (*c* 1.2).

*Anal.* Calcd. for $C_{31}H_{54}O_2$: C, 81.16; H, 11.87. Found: C, 81.06; H, 11.88.

**Reduction of 2β-Methylcoprostan-3-one (X) to 2β-Methylcoprostan-3α-ol (XIa).**—2β-Methylcoprostan-3-one (80 mg.) in 10 cc. of ether was reduced with 100 mg. of lithium aluminum hydride in 5 cc. of ether as previously. Crystallization of the product from ether–methanol yielded 66 mg. of 2β-methylcoprostan-3α-ol (XIa), m.p. 124–126°, $[\alpha]_D$ +25° (*c* 1.8).

*Anal.* Calcd. for $C_{28}H_{50}O$: C, 83.51; H, 12.52. Found: C, 83.09; H, 12.36.

**The acetate XIb** (acetic anhydride, pyridine, overnight at room temperature) on crystallization from methanol showed m.p. 86–87°, $[\alpha]_D$ +78° (*c* 1.1).

*Anal.* Calcd. for $C_{30}H_{52}O_2$: C, 81.02; H, 11.79. Found: C, 81.27; H, 11.81.

**2-Methyl-Δ²-cholesten-3-ol Acetate (XII).**—A solution of 150 mg. of 2α-methylcholestan-3-one (II) in 20 cc. of isopropenyl acetate was treated with 1 drop of concd. sulfuric acid and the solution was boiled under reflux for 3 hr. The product, isolated with ether in the usual way, was passed in pentane–benzene (9:1) solution through 6 g. of alumina. Crystallization of the eluates from ether–methanol gave 120 mg. of the enol acetate XII with m.p. 93–94°, $[\alpha]_D$ +50° (*c* 1.75), $\nu_{max}^{CCl_4}$ 1750 cm.$^{-1}$.

*Anal.* Calcd. for $C_{30}H_{50}O_2$: C, 81.39; H, 11.38. Found: C, 81.35; H, 11.46.

**2α-Methyl-2β-bromocholestan-3-one (XIII).** (a) **By Direct Bromination of 2α-Methylcholestan-3-one (II).**—A solution of 99 mg. of bromine in 3.3 cc. of glacial acetic acid was added dropwise during 10 minutes to a stirred solution of 225 mg. of 2α-methylcholestan-3-one (II) in 15 cc. of acetic acid at room temperature. The mixture was stirred for another 2 hr. and the resulting precipitate was then collected and washed with a little methanol. Crystallization from ether–methanol yielded 116 mg. of the bromo ketone XIII with m.p. 136–137°, $[\alpha]_D$ −20° (*c* 1.04), $\nu_{max}^{CCl_4}$ 1714 cm.$^{-1}$.

*Anal.* Calcd. for $C_{28}H_{47}BrO$: C, 70.11; H, 9.88. Found: C, 70.13; H, 9.89.

(b) **By Bromination of 2-Methyl-Δ²-cholesten-3-ol Acetate (XII).**—A solution of 40 mg. of bromine in 0.8 cc. of acetic acid was added to 100 mg. of the enol acetate XII dissolved in 18 cc. of acetic acid and 2 cc. of pyridine and the solution was allowed to stand overnight at room temperature. Water and ice were then added, the precipitate was collected, washed with water, dried and crystallized from ether–methanol. This procedure yielded 65 mg. of the 2β-bromo compound XIII, m.p. 136–137°, $[\alpha]_D$ −20° (*c* 0.8). Identity with the sample prepared by method a was established in the usual way.

**2-Methyl-Δ¹-cholesten-3-one (XIV).**—A solution of 165 mg. of 2α-methyl-2β-bromocholestan-3-one (XIII) in 10 cc. of dimethylformamide containing 1 g. of lithium chloride was boiled under reflux for 2 hr. The product, isolated by means of ether as usual, was triturated with 10 cc. of methanol. The insoluble material was removed by filtration and the filtrate was concentrated to small volume and cooled. The resulting 2-methyl-Δ¹-cholesten-3-one (72 mg.) was obtained as long needles with m.p. 73–74°, $[\alpha]_D$ +62° (*c* 0.9), $\lambda_{max}$ 241 mμ (log ε 4.02), $\nu_{max}^{CCl_4}$ 1675 cm.$^{-1}$.

*Anal.* Calcd. for $C_{28}H_{46}O$: C, 84.35; H, 11.63. Found: C, 84.39; H, 11.56.

**2β-Methylcholestan-3-one (XV).**—A solution of 100 mg. of 2-methyl-Δ¹-cholesten-3-one (XIV) in 20 cc. of ethanol

was shaken in hydrogen with 50 mg. of a 10% palladium–charcoal catalyst. Uptake stopped after 1.05 molar equivalents of hydrogen had been absorbed. The catalyst was removed and the filtrate was concentrated to small volume and cooled. The resulting 2β-methylcholestan-3-one (62 mg.) with m.p. 90–92° on further crystallization from ether–methanol yielded the analytical sample with m.p. 96–97°, $[\alpha]_D$ +86° (*c* 0.88). The m.p. was depressed by *ca.* 10° on admixture with a sample of 2α-methylcholestan-3-one.

*Anal.* Calcd. for $C_{28}H_{48}O$: C, 83.93; H, 12.08. Found: C, 84.13; H, 12.16.

**Isomerization of 2β-Methylcholestan-3-one (XV) to 2α-Methylcholestan-3-one (II).**—A solution containing 35 mg. of 2β-methylcholestan-3-one and 0.1 cc. of 20% sulfuric acid in 5 cc. of ethanol was boiled under reflux for 2 hr. Water was added and the product was isolated with ether. One crystallization from ether–methanol gave 2α-methylcholestan-3-one as needles with m.p. 117–119°, undepressed on admixture with an authentic sample (m.p. 119–120°).

**2-Methyl-Δ¹-coprosten-3-one (XVIII) and 2α-Methyl-Δ⁴-cholesten-3-one (VII) from 2β-Methylcoprostan-3-one (X).**—A solution of 80 mg. of bromine in 1.1 cc. of acetic acid containing a drop of hydrobromic acid (72%) was added to 200 mg. of 2β-methylcoprostan-3-one (X) in 30 cc. of acetic acid. After being allowed to stand at room temperature for 1 hr., the solution was diluted with water and ice and the product was isolated with ether in the usual way. The resulting total brominated product then was dissolved in 10 cc. of dimethylformamide, 1 g. of lithium chloride was added and the solution was boiled for 2 hr. The product, isolated with ether, was dissolved in pentane and chromatographed on 10 g. of alumina. The fractions eluted with pentane–benzene (4:1) on crystallization from methanol gave 43 mg. of 2-methyl-Δ¹-coprosten-3-one (XVIII) as needles with m.p. 96–97°, $[\alpha]_D$ +104° (*c* 0.76), $\lambda_{max}$ 241 mμ (log ε 4.00), $\nu_{max}^{CCl_4}$ 1671 cm.$^{-1}$.

*Anal.* Calcd. for $C_{28}H_{46}O$: C, 84.35; H, 11.63. Found: C, 84.69; H, 11.80.

The fractions eluted with pentane–benzene (1:1) on crystallization from methanol yielded 24 mg. of 2α-methyl-Δ⁴-cholesten-3-one (VII) with m.p. 125–127°, undepressed on admixture with the sample (m.p. 126–127°) described above.

When the bromination of 200 mg. of 2β-methylcoprostan-3-one (X) was carried out as above and the brominated product was crystallized from methanol containing a drop of acetic acid, 45 mg. of 2β-methyl-4β-bromocoprostan-3-one (XVI) with m.p. 126–128°, $[\alpha]_D$ +49° (*c* 0.8), $\nu_{max}^{CCl_4}$ 1730 cm.$^{-1}$, was obtained.

*Anal.* Calcd. for $C_{28}H_{47}BrO$: C, 70.11; H, 9.88. Found: C, 70.24; H, 9.91.

The pure bromo ketone XVI (30 mg.) was dehydrobrominated by being boiled under reflux for 2 hr. with 0.5 g. of lithium chloride in 5 cc. of dimethylformamide. Isolation with ether as usual, followed by chromatography on 6 g. of alumina and crystallization of the fractions eluted with pentane–benzene (1:1) from methanol yielded 12 mg. of 2α-methyl-Δ⁴-cholesten-3-one (VII) with m.p. 124–126°. There was no depression on admixture with an authentic sample. No indications of the formation of the Δ¹-isomer XVIII were obtained.

**Lithium–Ammonia Reduction of 4-Methyl-Δ⁴-cholesten-3-one (XIX).**—A solution of 100 mg. of 4-methyl-Δ⁴-cholesten-3-one (XIX)[3] in 10 cc. of dry ether was added dropwise with stirring to a solution of 100 mg. of lithium in *ca.* 25 cc. of liquid ammonia during 5 minutes. The mixture was then stirred for another 15 minutes, when ice and dilute hydrochloric acid were added and the product was isolated with ether as usual. Crystallization from ether–methanol yielded 71 mg. of 4α-methylcholestan-3-one (XX) with m.p. 121–123°, $[\alpha]_D$ +26° (*c* 1.4); reported[17] m.p. 122–122.5°, 123–124°, $[\alpha]_D$ +25°, +26°.

*Anal.* Calcd. for $C_{28}H_{48}O$: C, 83.93; H, 12.08. Found: C, 83.83; H, 12.27.

**Catalytic Hydrogenation of 4-Methyl-Δ⁴-cholesten-3-one (XIX).**—A solution of 250 mg. of 4-methyl-Δ⁴-cholesten-3-one (XIX)[3] in 50 cc. of ethanol was shaken in hydrogen with 100 mg. of a 10% palladium–charcoal catalyst until uptake ceased, 1.02 molar equivalents of gas being absorbed. The catalyst was removed by filtration and the filtrate was evaporated to small volume and cooled. The precipitate (156 mg., m.p. 87–93°) after three crystallizations from ether–methanol gave 101 mg. of 4β-methylcholestan-3-one (XXI) with m.p. 122–124°. A further purified sample showed m.p. 126–127°, $[\alpha]_D$ +36° (*c* 1.0); reported[17] m.p. 125–127°, $[\alpha]_D$ +36°. There was a *ca.* 20° depression in m.p. on admixture with the 4α-isomer XX.

*Anal.* Calcd. for $C_{28}H_{48}O$: C, 83.93; H, 12.08. Found: C, 84.02; H, 12.01.

The combined mother liquors were evaporated, dissolved in light petroleum and chromatographed on 10 g. of alumina. The first fractions, eluted with light petroleum, on being seeded and crystallized from ether–methanol gave 25 mg. of 4β-methylcoprostan-3-one (XXII) with m.p. 55–57°, undepressed on admixture with a sample prepared from coprostan-3-one (see below). The later fractions, eluted with light petroleum and light petroleum–benzene, had m.p. 108–118° and could not be purified by crystallization. This material was therefore boiled under reflux for 2 hr. with 25 cc. of ethanol and 0.25 cc. of 20% sulfuric acid. Isolation by means of ether and crystallization from ether–methanol gave 98 mg. of 4α-methylcholestan-3-one (XX) with m.p. 120–122°, undepressed on admixture with the sample obtained by the lithium–ammonia reduction of 4α-methyl-Δ⁴-cholesten-3-one (XIX).

**Isomerization of 4β-Methylcholestan-3-one (XXI) to 4α-Methylcholestan-3-one (XX).**—A solution of 500 mg. of 4β-methylcholestan-3-one (XXI) in 50 cc. of ethanol containing 0.5 cc. of 20% sulfuric acid was boiled under reflux for 2 hr. Isolation with ether and crystallization from ether–methanol yielded 384 mg. of 4α-methylcholestan-3-one (XX) with m.p. 120–122°, undepressed on admixture with the sample obtained by the lithium–ammonia reduction of 4-methyl-Δ⁴-cholesten-3-one.

**4α-Methylcholestan-3β-ol (XXVIa).**—A solution of 200 mg. of 4α-methylcholestan-3-one (XX) in 5 cc. of ether was added dropwise to a solution of 200 mg. of lithium aluminum hydride in 10 cc. of ether and the mixture was boiled under reflux for 2 hr. Ice and dilute hydrochloric acid were added and the product was isolated with ether as usual. The resulting material was dissolved in 20 cc. of ethanol and added to 50 cc. of a 2% solution of digitonin in 90% ethanol. The mixture was allowed to stand for 2 hr., the precipitated digitonide was collected, washed with 90% ethanol, dried and dissolved in a few drops of pyridine. Ether (200 cc.) was added, the digitonin was removed and the filtrate was evaporated. Crystallization of the residue from ether–methanol furnished 175 mg. of 4α-methylcholestan-3β-ol (XXVIa) with m.p. 160–163°. The analytical sample showed m.p. 163–164°, $[\alpha]_D$ +27° (*c* 0.8).

*Anal.* Calcd. for $C_{28}H_{50}O$: C, 83.51; H, 12.52. Found: C, 83.13; H, 12.37.

**The acetate XXVIb** (acetic anhydride, pyridine, overnight at room temperature) after crystallization from methanol showed m.p. 128–129°, $[\alpha]_D$ +41° (*c* 0.8).

*Anal.* Calcd. for $C_{30}H_{52}O_2$: C, 81.02; H, 11.79. Found: C, 81.35; H, 11.67.

**4,4-Dimethylcholestan-3β-ol (XXVIIIa).**—The reduction was carried out with 500 mg. of 4,4-dimethylcholestan-3-one (XXVII)[17] and 500 mg. of lithium aluminum hydride in 75 cc. of ether as described in the preceding experiment. Separation *via* the digitonide as before, regeneration and crystallization from methanol yielded 4,4-dimethylcholestan-3β-ol with m.p. 157–158°, $[\alpha]_D$ +11° (*c* 1.45).

*Anal.* Calcd. for $C_{29}H_{52}O$: C, 83.58; H, 12.58. Found: C, 83.02; H, 12.45.

**The acetate XXVIIIb** (acetic anhydride, pyridine, overnight at room temperature) after crystallization from methanol showed m.p. 138–139°, $[\alpha]_D$ +19° (*c* 1.33).

*Anal.* Calcd. for $C_{31}H_{54}O_2$: C, 81.16; H, 11.87. Found: C, 81.37; H, 11.92.

**4α-Methyl-Δ²-cholesten-3-ol Acetate (XXIX).**—A solution containing 300 mg. of 4α-methylcholestan-3-one (XX), 20 cc. of isopropenyl acetate and 1 drop of sulfuric acid was boiled under reflux for 3 hr. The product was isolated with ether, dissolved in pentane–benzene (9:1) and filtered through a column containing 10 g. of alumina. Two crystallizations from ether–methanol yielded 220 mg. of the enol acetate XXIX with m.p. 103–104°, $[\alpha]_D$ +9° (*c* 1.3), $\nu_{max}^{CCl_4}$ 1754 cm.$^{-1}$.

*Anal.* Calcd. for $C_{30}H_{50}O_2$: C, 81.39; H, 11.38. Found: C, 81.60; H, 11.28.

**2α-Bromo-4α-methylcholestan-3-one (XXX).**—A solution containing 56 mg. of bromine in 1 cc. of acetic acid was added to 140 mg. of the enol acetate XXIX previously dissolved in 18 cc. of acetic acid and 2 cc. of pyridine. The solution was then allowed to stand overnight at room temperature. Water and ice were added, the precipitate was collected, washed with water, dried and crystallized twice from ether–methanol. This procedure yielded 65 mg. of the bromo ketone XXX with m.p. 108–110°, $[\alpha]_D$ +49° (*c* 0.61), $\nu_{max}^{CCl_4}$ 1733 cm.$^{-1}$.

*Anal.* Calcd. for $C_{28}H_{47}BrO$: C, 70.11; H, 9.88. Found: C, 69.97; H, 9.55.

**4α-Methyl-Δ¹-cholesten-3-one (XXXI).**—A solution containing 50 mg. of the bromo ketone XXX and 500 mg. of lithium chloride in 7.5 cc. of dimethylformamide was boiled under reflux for 2 hr. Isolation with ether and crystallization from methanol afforded 32 mg. of 4α-methyl-Δ¹-cholesten-3-one as needles with m.p. 82–83°, $[\alpha]_D$ +47° (*c* 0.38), $\lambda_{max}$ 230 mμ (log ε 3.98), $\nu_{max}^{CCl_4}$ 1677 cm.$^{-1}$.

*Anal.* Calcd. for $C_{28}H_{46}O$: C, 84.35; H, 11.63. Found: C, 83.95; H, 11.37.

**4β-Methylcoprostan-3-one (XXII) by Methylation of Coprostan-3-one (XXXII).**—A solution of 1.65 g. (42 millimoles) of potassium in 75 cc. of *t*-butyl alcohol was added to a boiling solution of 11 g. (28 millimoles) of coprostan-3-one (XXXII) in 120 cc. of benzene and 60 cc. of *t*-butyl alcohol. Boiling was continued for 3 minutes and the mixture was then cooled and decomposed by the addition of ice. The product was isolated with ether, dissolved in 50 cc. of pentane and chromatographed on 500 g. of alumina. The first fractions (0.24 g.), eluted with pentane, were amorphous and were not investigated further. The next fractions (4.81 g.), eluted with pentane–benzene (99:1–9:1), were rich in 4β-methylcoprostan-3-one (XXII), but could not be obtained crystalline directly. Finally pentane–benzene (9:1–8:2) eluted 2.80 g. of unchanged coprostan-3-one with m.p. 61–62°, undepressed on admixture with the starting material.

The crude 4β-methylcoprostan-3-one (2.9 g.) from the column was dissolved in 100 cc. of methanol and treated with a solution of semicarbazide acetate (from 2.5 g. of semicarbazide hydrochloride and 4 g. of sodium acetate) in methanol. The mixture was allowed to stand overnight, and the resulting precipitate was collected, washed with water, methanol and a little ether and then dried. The 4β-methylcoprostan-3-one semicarbazone thus obtained weighed 2.76 g. (83% based on the crude ketone) and showed m.p. 204–206°. Crystallization from methylene chloride–ethanol yielded the analytical sample with m.p. 206–208°, $[\alpha]_D$ +43° (*c* 1.0).

*Anal.* Calcd. for $C_{29}H_{51}N_3O$: C, 76.09; H, 11.23. Found: C, 75.76; H, 11.35.

The free ketone was regenerated by adding 3 cc. of freshly distilled pyruvic acid and 4 cc. of water to a solution of 2.53 g. of the semicarbazone (m.p. 204–206°) in 45 cc. of acetic acid at 90°. The solution was kept at 90° for an additional 10 minutes and the neutral product was then isolated with ether in the usual way. Crystallization from a small volume of methanol produced 1.66 g. of 4β-methylcoprostan-3-one with m.p. 52–54°. Further crystallization from ether–methanol gave the analytical sample with m.p. 58–59°, $[\alpha]_D$ +34° (*c* 1.6).

*Anal.* Calcd. for $C_{28}H_{48}O$: C, 83.93; H, 12.08. Found: C, 84.15; H, 12.13.

The pure ketone yielded in nearly quantitative yield a semicarbazone of m.p. 203–205°, undepressed on admixture with the semicarbazone from which it was derived.

**4β-Methylcoprostan-3α-ol (XXXIIIa).**—A solution of 330 mg. of the crude oily 4β-methylcoprostan-3-one (XXII), as obtained by chromatography from the preceding experiment, in 10 cc. of ether was added to a solution of 500 mg. of lithium aluminum hydride in 10 cc. of ether. The mixture was boiled under reflux for 2 hr. Isolation with ether yielded a product which was dissolved in 50 cc. of ethanol and added to a solution of 1 g. of digitonin in 50 cc. of 90% aqueous ethanol. After 2 hr. at room temperature the small precipitate was removed and the filtrate was evaporated to dryness. Ether was added to the residue, the excess digitonin was removed, the filtrate was evaporated and the residue was acetylated (acetic anhydride, pyridine, overnight at room temperature). Crystallization from ether–methanol yielded 155 mg. of 4β-methylcoprostan-3α-ol acetate (XXXIIIb) with m.p. 88–89°, $[\alpha]_D$ +6° (*c* 1.4).

*Anal.* Calcd. for $C_{30}H_{52}O_2$: C, 81.02; H, 11.79. Found: C, 81.00; H, 11.76.

4β-Methylcoprostan-3α-ol (XXXIIIa) was obtained by boiling the acetate for 1 hr. with a 3% solution of potassium hydroxide in methanol. It was crystallized from methanol and showed m.p. 155–157°, $[\alpha]_D$ +15° (*c* 0.5).

*Anal.* Calcd. for $C_{28}H_{50}O$: C, 83.51; H, 12.52. Found: C, 83.53; H, 12.36.

**Oxidation of 4β-Methylcoprostan-3α-ol (XXXIIIa) to 4β-Methylcoprostan-3-one (XXII).**—A solution of 50 mg. of chromic acid in 10 cc. of 90% acetic acid was added to 50 mg. of 4β-methylcoprostan-3α-ol in 10 cc. of acetic acid. After being allowed to stand at room temperature for 16 hr., the solution was diluted with water. Isolation with ether and crystallization from ether–methanol yielded 35 mg. of 4β-methylcoprostan-3-one with m.p. 58–59°, undepressed on admixture with the sample obtained by regeneration of the semicarbazone.

**4-Methyl-Δ³-coprosten-3-ol Acetate.**—4β-Methylcoprostan-3-one (XXII) (200 mg.) was boiled under reflux for 3 hr. with 15 cc. of isopropenyl acetate containing 1 drop of concd. sulfuric acid. The product, isolated with ether, was dissolved in pentane and filtered through a column of 10 g. of alumina. Crystallization from ether–methanol yielded 170 mg. of the enol acetate of XXII with m.p. 86–87°, $[\alpha]_D$ +103° (*c* 1.1), $\nu_{max}^{CCl_4}$ 1754 cm.$^{-1}$.

*Anal.* Calcd. for $C_{30}H_{50}O_2$: C, 81.39; H, 11.38. Found: C, 80.90; H, 11.34.

**4-Methyl-Δ⁴-cholesten-3-one (XIX). (a) Through Direct Bromination of 4β-Methylcoprostan-3-one (XXII).**—A solution containing 88 mg. of bromine in 5 cc. of acetic acid was added to a solution of 200 mg. of 4β-methylcoprostan-3-one in 60 cc. of acetic acid containing 1 drop of hydrobromic acid (72%). After being allowed to stand for 72 hr., the mixture was diluted with water and the product was isolated with ether. The resulting amorphous oily bromo ketone was boiled under reflux for 2 hr. with 500 mg. of lithium chloride in 10 cc. of dimethylformamide. The material isolated by means of ether was dissolved in 10 cc. of pentane and chromatographed on 10 g. of alumina. The fractions eluted with pentane–benzene (9:1) on crystallization from ether–methanol furnished 96 mg. of 4-methyl-Δ⁴-cholesten-3-one, m.p. 102–103°, $\lambda_{max}$ 251 mμ (log ε 4.18). Identity with a sample prepared as described previously[3] was shown through non-depression in m.p. on admixture and through infrared comparison.

**(b) Through Bromination of 4-Methyl-Δ³-coprosten-3-ol Acetate.**—A solution of 24 mg. of bromine in 0.5 cc. of acetic acid was added to 60 mg. of the above-described enol acetate of 4β-methylcoprostan-3-one in 9 cc. of acetic acid and 1 cc. of pyridine. After being allowed to stand overnight at room temperature, the solution was diluted with water and the product was isolated with ether. The resulting red oily bromo-ketone (66 mg.) showed $\lambda_{max}$ 251 mμ (log ε 3.60), indicating it to be contaminated with *ca.* 25% of the unsaturated ketone XIX. The product was boiled for 2 hr. with 1 g. of lithium chloride in 10 cc. of dimethylformamide. Isolation with ether, followed by purification through chromatography and crystallization as above, yielded 35 mg. of 4-methyl-Δ⁴-cholesten-3-one with m.p. 102–103°, undepressed on admixture with an authentic specimen[3] (m.p. 102–103°).

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