Steroids and Related Natural Products. 66. Structural Modification of the Triterpene A Ring[1,2]

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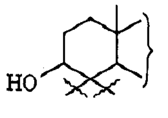
A new synthetic procedure has been developed for conversion of tetracyclic triterpenes to 14α-methyl or 4,14α-dimethyl steroids. Transformation of lanosterol to 3-oxo-14α-methylcholest-4-ene was used for illustration.

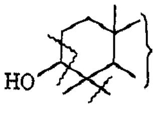
Naturally occurring steroids usually lack substituents at the C-4 position, but their biogenetic precursors usually possess a 4,4-dimethyl-substituted A ring.[3] A variety of new and potentially useful steroids can, in principle, be obtained by deletion of the 4,4-dimethyl substituents from the increasing number of readily available tetracyclic triterpenes. Therefore, it is important to have a selection of practical methods for reconstruction of the triterpene 3β-hydroxy-4,4-dimethyl system.

The classic procedure[4] for terpene → steroid transformation has been used, for example, for preparing 14α-methyl steroids[5] which might arise from a defect in the normal biosynthesis of cholesterol from squalene *via* lanosterol.[6,7] One of the early attempts to improve upon the method of Voser and colleagues for converting triterpene A rings to steroid 3-oxo-4-ene systems involved oxidizing the enol acetate of 3-oxo-14α-methyl-5α-A-norcholestane with perphthalic acid and adding methylmagnesium iodide to the rearranged product, 3-oxo-5-hydroxy-14α-methyl-5α-*A*-norcholestane, but the sequence proved impractical.[8] After our preliminary report of the present study,[9] three new methods for triterpene A-ring reconstruction were described. One has the advantage of not requiring a Grignard step,[10] another utilizes a "second-order" Beckmann cleavage,[11] and the third is based on the photochemical cleavage of a cyclopentyl nitrite.[12]

Discussion

Logical synthetic approaches to remove the 4,4-dimethyl substituents from the A ring of tetracyclic triterpenes would include a biosynthetic-type sequential elimination of the 30- and 31-methyl groups (i), or to expel either a 30- or 31-methyl group and then the C-3 carbon (ii),[13] or to remove the isopropyl group (iii) followed by readdition of a carbon atom, as accomplished by Voser and colleagues.[4] A successful approach employing the initial two steps of the Voser method (iii) as applied to 3β-hydroxy-5α-lanostane (Scheme I) will be first discussed, and then preliminary


i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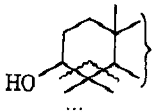
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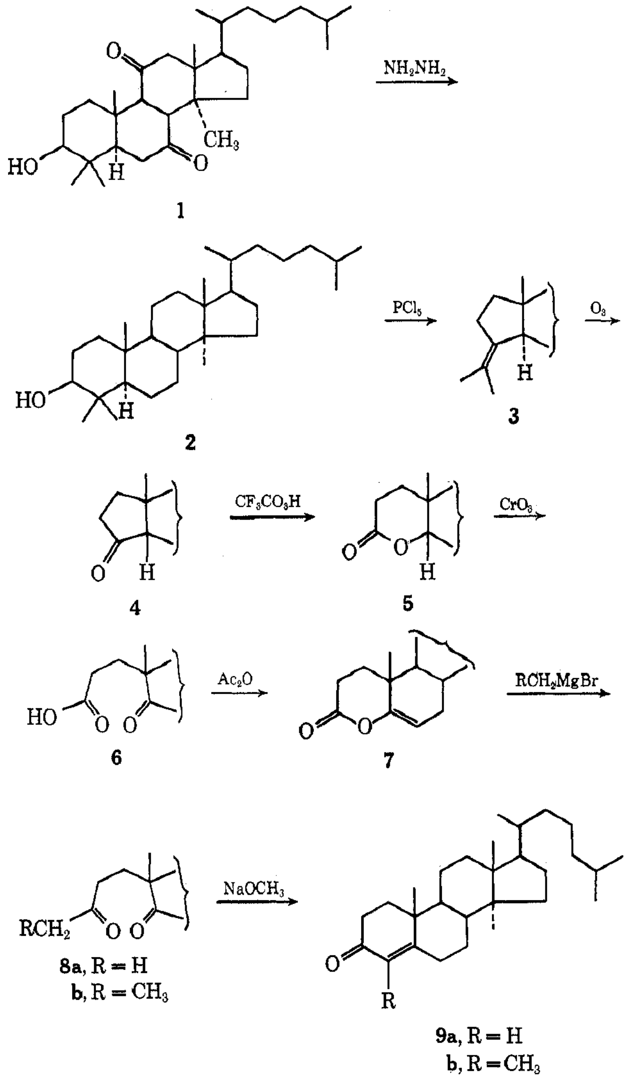
SCHEME I

CONVERSION OF TETRACYCLIC TRITERPENES TO STEROIDS



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[1] For Part 65 refer to G. R. Pettit, P. Brown, F. Bruschweiler, and L. Houghton, *Chem. Commun.*, 1566 (1971).

[2] Abstracted in part from the dissertation of J. R. Dias, Arizona State University, 1970; NIH predoctoral fellow, 1968–1970.

[3] For example, see G. Ourisson, P. Crabbé, and O. Rodig, "Tetracyclic Triterpenes," E. Lederer, Ed., Holden-Day, San Francisco, Calif., 1964.

[4] W. Voser, H. Heusser, O. Jeger, and L. Ruzicka, *Helv. Chem. Acta*, **36**, 299 (1953).

[5] G R. Pettit and P. Hofer, *ibid.*, **46**, 2142 (1963); *J. Chem. Soc.*, 4439 (1963).

[6] E. E. van Tamelen, *Accounts Chem. Res.*, **1**, 111 (1968).

[7] Since *in vivo* demethylation of the 14α-methyl group in lanosterol is activated by the 8,9 double bond, such a defect might arise from accidental reduction or premature isomerization of this double bond: P. Crabbé, *Rec. Chem. Progr.*, **20**, 180 (1959).

[8] D. H. R. Barton, D. A. J. Ives, and B. R. Thomas, *J. Chem. Soc.*, 903 (1954).

[9] G. R. Pettit and J. R. Dias, *Can. J. Chem.*, **47**, 1091 (1969).

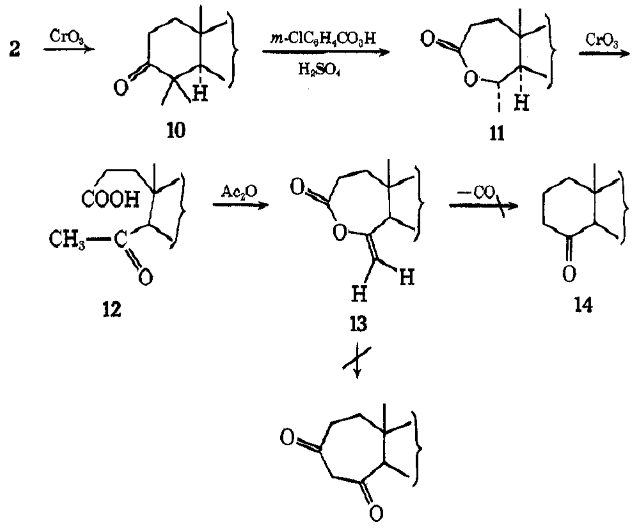
[10] R. Kazlauskas, J. Pinhey, J. Simes, and T. Watson, *Chem. Commun.*, 945 (1969).

[11] C. W. Shoppee, N. W. Hughes, R. E. Lack, and J. T. Pinhey, *J. Chem. Soc. C*, 1443 (1970).

[12] D. H. R. Barton and D. Kumari, *Justus Liebigs Ann. Chem.*, **737**, 108 (1970).

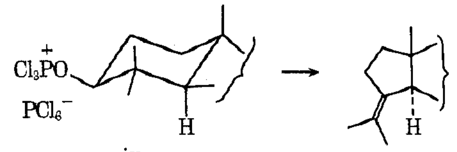
[13] The method used by the authors in footnote 10 embodies a combination of i and ii.

SCHEME II
ATTEMPTED CONVERSION OF TETRACYCLIC TRITERPENES TO STEROIDS



attempts to achieve this transformation *via* approach ii (Scheme II) will be described.

The key step in the Voser method for elimination of the 4,4-dimethyl groups utilizes a 1,3-Wagner-Meerwein rearrangement to transform the 3β-hydroxy-4,4-dimethyl system into an isopropylidene group (**2** to **3**). Stereoelectronic requirements make it imperative that the 3-hydroxy group has a β configuration so that the C-O bond is trans to the approaching 4,5 bond; otherwise, olefins resulting from hydrogen and methyl migrations are obtained (1,2-Nametkin rearrangement). When we allowed 1:1 mole ratios of phosphorus pentachloride to triterpene alcohol **2** to react (ice bath temperature, 1 hr, in benzene-toluene), only a 10% conversion of alcohol to olefin **3** occurred, whereas, with a 2:1 mole ratio, a 100% conversion was realized. Apparently the first mole of phosphorus pentachloride is rapidly consumed to form the tetrachlorophosphate of alcohol **2**, and the second mole forms a dimer ion pair, $PCl_6PCl_3{}^+O{-}R$, in which $PCl_3{}^+O{-}$ is a better leaving group than $PCl_4O{-}$ (iv → v).



iv v

Cleavage of the isopropylidene group by ozone (**3** to **4**) introduces a 3-oxo group adjacent to the 5α hydrogen. The strained trans A-nor B ring junction undergoes facile acid isomerization to the more stable cis A-nor B ring system concurrently with zinc-acetic acid reduction of the ozonide.[14a] The positive Cotton effect curve observed for ketone **4** unequivocally established the 5β configuration.[14b,c]

A method for Baeyer-Villiger oxidation of ketone **4** to lactone **5** was not realized using *m*-chloroperbenzoic acid, but was easily effected by pertrifluoroacetic acid.[15] Only minor amounts of 3-oxa-4-oxo-14α-methyl-5β-cholestane, an isomer of lactone **5**, were detected. As Baeyer-Villiger oxidation is well known to proceed with retention of configuration (of the migrating group), the lactones would be expected to bear cis A/B ring junctions. Prolonged contact with chromium trioxide in concentrated sulfuric acid or with excess Jones reagent in acetone was found most effective for transforming lactone **5** directly to keto acid **6**. Since the milder Jones reagent proved quite adequate for this oxidation, the former oxidizing system was not further investigated.[16] Isolation of keto acid **6** in crystalline form was difficult if lactone **5** was contaminated by the isomeric lactone, 3-oxa-4-oxo-14α-methyl-5β-cholestane.

Enol-lactone **7** was obtained by brief contact of keto acid **6** with an acetic anhydride-perchloric acid reagent.[17] The enol exhibited an ability in methanol (containing a trace of pyridine) to readily form the corresponding methyl ester.

Slowly adding a methyl or ethyl Grignard reagent to an ice-cold solution of enol-lactone **7** led to good yields of 1,5-diketone **8a** or **8b**, respectively. Without further purification, the ketone was cyclized using 1% sodium hydroxide to give enone **9a** or **9b**.[18] The experiments just summarized, leading to ketones **9a** and **9b**, complete (Scheme I) a new and useful reconstruction of the tetracyclic triterpene A ring to yield 3-oxo-4-ene-type steroids.

The unique loss (in 65% yields) of a 31-methyl group has been observed when perbenzoic acid promoted Baeyer-Villiger oxidation of 3-oxo-4,4-dimethyl-5α-cholestane was explored in the presence of mineral acid.[19] Our alternative approach to triterpene → steroid conversion was based on this interesting reaction. A 3:1 molar ratio of *m*-chloroperbenzoic acid to 3-oxo-5α-lanostane (**10**) in the presence of 2% sulfuric acid was found to consistently give 29% yields of 3-oxo-4-oxa-4aα,14α-dimethyl-*A*-homo-5α-cholestane (**11**). Prolonged contact of lactone **11** with Jones reagent in acetone gave keto acid **12** in good yields, thereby further demonstrating the utility of this oxidizing system for direct conversion of lactones to keto acids. Brief contact of keto acid **12** with acetic anhydride-perchloric acid reagent gave enol-lactone **13** in which the double bond was exo, as demonstrated by the pair of doublets in a pmr spectrum at δ 5.0 and 4.6.

Since the thermodynamic favorability for transformation of enol-lactone **13** to ketone **14** or 1,3-diketone **15** was estimated to be -20 or -25 kcal, respectively, it was anticipated that either photolysis or thermolysis of enol-lactone **13** would effect one or both of these transformations. Further encouragement for transformation **13** to **14** was given by the observation of a $M^+ - 28$ peak in the mass spectrum of enol-lactone

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[14] (a) J. F. Biellmann and G. Ourisson, *Bull. Soc. Chim. Fr.*, 348 (1960); (b) N. L. Allinger, R. B. Hermann, and C. Djerassi, *J. Org. Chem.*, **25**, 922 (1960); (c) G. R. Pettit, B. Green, and W. J. Bowyer, *ibid.*, **26**, 2870 (1961).

[15] W. D. Emmons and G. B. Lucas, *J. Amer. Chem. Soc.*, **77**, 2287 (1955).

[16] To our knowledge, this is the first example of one-step oxidation of a lactone directly to a keto acid.

[17] B. E. Edwards and P. Narasima Rao, *J. Org. Chem.*, **31**, 324 (1966).

[18] A new method for converting enol lactones to enones with dimethyl methylphosphonate and *n*-butyllithium has been reported: C. A. Henrick, E. Bohme, J. A. Edwards, and J. A. Fried, *J. Amer. Chem. Soc.*, **90**, 5926 (1968).

[19] J. S. E. Holker, W. R. Jones, and P. J. Ramm, *Chem. Commun.*, 435 (1965).

13. By comparison, no such fragment was observed in the mass spectrum of enol-lactone **7**.

Photolysis of enol-lactone **13** in a quartz apparatus (carbon tetrachloride solution for 5 hr) gave a mixture with a distinct acid chloride odor. The product appeared to represent extensive chlorination of the steroid skeleton.[20]

Photolysis of enol-lactone **13** in tetrahydrofuran–ligroin (2:3) under nitrogen for 34 hr gave a yellow oil with a strong amine-like odor, and gave spectral data consistent with significant alteration of the olefin and ester functions. Such results combined with the consistently low yields of lactone **11**[21] discouraged further exploration of this superficially plausible approach.

Experimental Section

All routine reagents and solvents were Baker analyzed, Mallinckrodt AR, or Matheson Coleman and Bell. Jones reagent corresponds to a solution of chromium trioxide (8 *N* or 2.67 *M*) in aqueous sulfuric acid (4 *M*).[22] Acetic anhydride-perchloric acid reagent was prepared by adding 72% perchloric acid (0.05 ml) to ethyl acetate (50 ml), and 10 ml of this solution was added to ethyl acetate (30 ml) containing acetic anhydride (4.8 ml). More ethyl acetate was added to reach a final volume of 50 ml.[17] The Grignard reagents (approximately 0.5 *M*) were prepared in ether under a nitrogen atmosphere. Organic solutions were dried over anhydrous sodium sulfate and concentrated on a rotating evaporator.

Activated alumina (basic and acid washed, Merck, Rahway) and silica gel (E. Merck, Darmstadt, Germany, 0.2–0.5 mm) were used for column chromatography. Silica gel HF$_{254}$ (E. Merck) was used for analytical and preparative thin layer chromatography (tlc). The chromatograms were routinely prepared with benzene–ethyl acetate (5:1) and developed with iodine vapor or by heating with 2% ceric sulfate in 2 *N* sulfuric acid. The preparative thin layer plates were viewed under ultraviolet light.

Elemental microanalysis was performed by the laboratory of Dr. A. Bernhardt, Mikroanalytisches Laboratorium, 5251 Elbach Uber Engelskirchen, Fritz-Pregl-Strasse, West Germany. All samples submitted for analysis were colorless and exhibited a single spot on a tlc. Melting points were determined on a Kofler melting point apparatus. All spectra were recorded by J. R. D. or Miss K. Reimer as follows: infrared, Beckman IR-12 (potassium bromide or chloroform solution); rotatory dispersion (RD), Jasco (ORD/UV, in dioxane at room temperature); pmr, Varian A-60 (60 MHz, in deuteriochloroform, TMS internal standard). The mass spectra were determined (by E. Bebee and R. Scott) using an Atlas CH-4B (low resolution) or Atlas SM-1B (high resolution) instrument equipped with molecular beam inlet system.

3-Isopropylidene-14α-methyl-*A*-nor-5α-cholestane (**3**).[8]—To a cold (ice bath) solution of alcohol **2** (4.8 g, 0.011 mol) in benzene (700 ml)-toluene (250 ml) was added phosphorus pentachloride (4.8 g, 0.024 mol, in 80 ml of methylene chloride). After the clear, cold mixture (5–10°) was stirred for 55 min, saturated sodium carbonate (50 ml) and water (200 ml) were added, and stirring was continued for another 0.5 hr. The upper phase was evaporated to dryness. The yellow residue in carbon tetrachloride was chromatographed on a column of basic alumina (200 g) to yield upon elution with ligroin 2.82 g of needles: mp 110–113°; ν_{max} (0.1 *M* in CHCl$_3$) 2970, 1480, and 1390 K; pmr δ 2.2 (broad, 3 p, C-2 and C-5), 1.7 and 1.6 Hz (broad singlets 3p each, isopropylidene), 0.93 (s, 19-methyl), 0.83 (s, 14- and 18-methyls), and 0.77 (d, *J* = 7 Hz, C-21, C-26, and C-27 methyls).

3-Oxo-14α-methyl-*A*-nor-5β-cholestane (**4**).[8]—Olefin **3** (21.2 g) in chloroform (3.6 l.) was cooled to *ca.* −65° (Dry Ice–acetone bath). A slow stream of ozone in oxygen was passed through the reaction mixture until a deep blue color persisted for 30 min. Oxygen was passed into the solution until the blue color vanished. Zinc dust (20 g) and glacial acetic acid were added (800 ml), and the mixture was stirred 2 hr. The chloroform layer was washed with water (3 l. in two aliquots) and evaporated to dryness. The acetic-smelling, yellow oil was dissolved in benzene and chromatographed on a column of alumina (600 g of acid-washed grade). Elution with benzene–petroleum ether (1:4) yielded 10 g (50%) of colorless solid. Recrystallization from ethyl acetate gave an analytical sample: mp 126.5–127.5° (lath shaped crystals); ν_{max} (0.1 *M* in CHCl$_3$) 2970, 1740 (str C=O stretch), 1475, 1390, and 1240 K; pmr δ 2.2 (m, C-2 and C-5), 1.3 (s), 0.92 (s), 0.82 (s), and 0.72 (s); RD in chloroform (*c* 0.196), $[\alpha]_{589}$ +126°, $[\alpha]_{500}$ +175°, $[\alpha]$ +385°, $[\alpha]_{350}$ +740°, $[\alpha]_{314}$ +2430° (peak), $[\alpha]_{306}$ +1900° (shoulder), $[\alpha]_{292}$ 0.00°, $[\alpha]_{275}$ −1330° (trough), and $[\alpha]_{250}$ −4670°; mass spectrum 231 (100%), M$^+$ − 15 (1.5%), and M$^+$ 386 (9%).

Anal. Calcd for $C_{27}H_{46}O$ (386): C, 83.87; H, 11.99; O, 4.14. Found: C, 83.82; H, 11.75; O, 4.43.

3-Oxo-4-oxa-14α-methyl-5β-cholestane (**5**).—To ketone **4** (5.24 g, 0.0135 mol) in methylene chloride (*ca.* 30 ml) was added pertrifluoroacetic acid (13 ml from 8.47 ml of trifluoroacetic anhydride, 1.37 ml of 90% hydrogen peroxide, and 10.5 ml of methylene chloride).[15] After remaining in a refrigerator 24 hr, the amber mixture was heated at reflux for 2 min. Chloroform (50 ml) was added to the cooled mixture, and washing was performed with water (300 ml in three aliquots), 1 *M* sodium carbonate (50 ml), and saturated sodium chloride (25 ml). The residue on column chromatography through silica gel (100 g) and elution with benzene-ethyl acetate (5:1) yielded 4.24 g (78%) of solid. Recrystallization from methanol gave an analytical sample as plates: mp 172–177° (plates to needles at 163°); ν_{max} (0.1 *M* in CHCl$_3$) 2970, 1730 (str C=O stretch), 1470, 1380, and 1270 K (med C–O stretch); pmr δ 4.2 (1p, C-5 proton), 2.5 (quartet, 2p, C-2 protons), 1.0 (s, 19-methyl), 0.87 (d, *J* = 6 Hz, 21-, 26- and 27-methyls), and 0.82 (s, 14 α and 18-methyls); mass spectrum M$^+$ 402.

Anal. Calcd for $C_{27}H_{46}O_2$ (402): C, 80.54; H, 11.52; O, 7.95. Found: C, 80.53; H, 11.78; O, 8.20.

5-Oxo-14α-methyl-3,5-seco-*A*-norcholestane-3-carboxylic Acid (**6**).—To lactone **5** (0.33 g, 0.82 mmol) in aqueous acetone (50 ml containing 2 ml of water) was added Jones reagent (0.40 ml). After magnetically stirring for 12 hr 2-propanol (5.0 ml) was added to the yellow solution containing a green precipitate; the yellow color was discharged. The acetone was concentrated and the green residue extracted with ether (28 ml in four aliquots). The ethereal solution was extracted with 1 *N* potassium hydroxide (45 ml in five aliquots). To the cool basic solution of the potassium salt was added concentrated hydrochloric acid (5.0 ml): yield, 0.32 g of colorless solid. The solid was triturated with acetone (*ca.* 5 ml), and evaporation of the acetone yielded 0.31 g (91%) of needles, mp 115–120°. Recrystallization from ether–ligroin gave 0.23 g of needles, mp 121.4–122.8°, and 0.08 g of cruder material. The pure keto acid gave the following spectra: ν_{max} (KBr) 3400, (broad CO$_2$–H stretch, wk), 3100 (broad CO$_2$–H hydrogen-bonded stretch, med), 2970, 1710 (broad, str C=O stretch, shoulder at 1650), 1460, 1380, and 1225 K (med C–O stretch); pmr δ 10.0 (s, 1p, removed by D_2O), 2.3 (m, 4p, C-2 and C-5 protons), 1.1 (s, 19-methyl), 0.88 (d, *J* = 6 Hz, 21-, 26-, and 27-methyls), and 0.88 (s, 14 and 18 methyls); RD (*c* 0.521), $[\alpha]_{589}$ +53°, $[\alpha]_{500}$ +77°, $[\alpha]_{400}$ +135°, $[\alpha]_{350}$ +213°, $[\alpha]_{314}$ +380° (peak), $[\alpha]_{290}$ +246°, $[\alpha]_{271}$ +146° (trough), and $[\alpha]_{250}$ +295°; mass spectrum 346 (100%), M$^+$ −18 (38%), M$^+$ −15 (24%), and M$^+$ 418 (13%).

Anal. Calcd for $C_{27}H_{46}O_3$ (346): C, 77.46; H, 11.07; O, 11.46. Found: C, 77.54; H, 11.01; O, 11.34.

3-Oxo-4-oxa-14α-methylcholest-4-ene (**7**).—A solution of keto acid **6** (0.13 g) in acetic anhydride perchloric acid reagent (20 ml) was allowed to stand at room temperature for 5 min. Saturated sodium bicarbonate (20 ml) was added and stirring continued for 1.5 hr. The ethyl acetate phase was evaporated to dryness. The 0.13 g residue of yellow needles was dissolved in ethyl acetate and passed through Celite. Recrystallization from methanol afforded 74 mg of colorless needles, mp 124.2–125.2°. Preparative thin layer separation of mother liquor residue led to an additional 19 mg (total yield 74%). The following spectra were

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[20] For another example of unanticipated chlorination by photolysis in carbon tetrachloride solution, see R. Breslow and S. Baldwin, *J. Amer. Chem. Soc.*, **92**, 733 (1970).

[21] More recently we learned that *m*-perchlorobenzoic acid is much less effective than perbenzoic acid: J. S. E. Holker, W. R. Jones, and P. J. Ramm, *J. Chem. Soc. C*, 357 (1969). Thus, the Holker procedure with perbenzoic acid is recommended for obtaining lactone **11**.

[22] A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *ibid.*, 2548 (1953).

obtained for the pure product: ν_{max} (KBr) 2970, 1745 (str C═O stretch), 1675 (med C═C stretch), 1460, 1390, and 1260 K; pmr δ 5.3 (1p, C-5 protons), 2.3 (q, 2p, C-2 protons), 2.0 (m, 2p, C-7 protons), 1.2 (s, 19-methyl), 0.90 (d, J = 4 Hz, 21-, 26-, and 27-methyls), and 0.87 (s, 14α- and 18-methyls); λ_{max}^{EtOH} 205 (log ϵ 3.7); mass spectrum M^+ 400 (100%).

Anal. Calcd for $C_{27}H_{44}O_2$ (400): C, 80.94; H, 11.07; O, 7.99. Found: C, 81.22; H, 10.84; O, 7.94.

3-Oxo-14α-methylcholest-4-ene (9a).—Enol-lactone **7** (0.25 g) was dissolved in benzene (10 ml)–ether (10 ml) and cooled (ice salt bath). A clear solution of methylmagnesium iodide was slowly added to the stirred reaction mixture (under nitrogen). Progress of the reaction was monitored by tlc. After 3 hr, the tlc barely detected enol-lactone **7** but showed an intense lower R_f spot corresponding to the product. Hydrochloric acid (5 ml) and ether (10 ml) were added, and the ethereal phase was washed with saturated sodium bicarbonate (10 ml), sodium thiosulfate solution, water, and saturated sodium chloride. Solvent was evaporated and to the residue in methanol (20 ml) was added 10% sodium hydroxide (2.0 ml). After heating (steam bath) for 1.5 hr the methanolic solution was poured into water (40 ml), saturated sodium chloride (40 ml) was added, and the aqueous mixture was extracted with ether (50 ml in three aliquots). Evaporation of solvent gave a yellow solid which upon preparative thin layer chromatography (5:1 benzene–ethyl acetate), yielded 0.145 g (58%) of colorless plates: mp 113.5–115.0°;[8] λ_{max}^{EtOH} 242 (log ϵ 4.19); ν_{max} (0.1 M in $CHCl_3$) 2960, 1670 (conjugated C═O), 1620 (med C═C stretch), 1470, 1390, 1240, and 800 K; pmr δ 5.7 (s, 1p, C-4 proton), 2.3 (m, 4p, C-2 and C-6 protons), 1.2 (s, 3p, 19-methyl), 0.88 (d, J = 6 Hz, 21-, 26-, and 27-protons) and 0.87. (s, 14α- and 18-methyls); mass spectrum M^+ − 15 (34%) and M^+ 398 (100%).

Anal. Calcd for $C_{28}H_{46}O$ (398): C, 84.35; H, 11.63; O, 4.02. Found: C, 84.19; H, 11.83; O, 3.98.

3-Oxo-4,14α-dimethylcholest-4-ene (9b).—Ethylmagnesium bromide was slowly added to a solution of enol-lactone **7** (0.14 g) in benzene (5 ml)–ether (5 ml). The reaction mixture was cooled (ice–salt bath), stirred under nitrogen, and monitored by tlc. After 1.5 hr, hydrochloric acid (5 ml) was added and the mixture allowed to stand at room temperature overnight. Solvent was evaporated from the ethereal layer. Methanol (10 ml) and 10% aqueous sodium hydroxide (1 ml) was added to the solid residue and the solution was heated on a steam bath 2 hr. The reaction mixture was diluted with water (40 ml) and extracted with ether (40 ml in four aliquots). The combined ether extract was washed with saturated sodium chloride solution and evaporated, and the solid residue was subjected to preparative thin layer chromatography using benzene–ethyl acetate (5:1) as the mobile phase: yield 94 mg (65%) of prisms for elution of the higher R_f zone with ether; mp 120.5–124.0°; λ_{max}^{EtOH} 251 (log ϵ 4.19); ν_{max} (KBr) 2970, 1660 (conjugated C═O stretch), 1600 (wk C═C stretch), 1460, 1370, and 1300 K; pmr δ 2.5 (m, 4p, C-2 and C-6 protons), 1.8 (s, 3p, 4-methyl), 1.2 (s, 19-methyl), 0.88 (d, J = 6 Hz, 21-, 26-, and 27-methyls), and 0.87 (s, 14α- and 18-methyls); mass spectrum M^+ 412.3724 (100%) (Beynon calcd mass 412.3705) and M^+ − 15 (35%).

Anal. Calcd for $C_{29}H_{48}O$: C, 84.40; H, 11.72; O, 3.88. Found: C, 84.37; H, 11.60; O, 4.03.

Elution of the lower R_f zone by ether led to 9 mg of needles, mp 198–202°, believed to be 3,3-diethyl-4-oxa-14α-methyl-5α-hydroxycholestane: ν_{max} (KBr) 3400 (broad), 2950, 1450, 1360, and 1015 K; mass spectrum 309 (100%), M^+ − 32 (16%) and M^+ − 18 (1.2%).

3-Oxo-5α-lanostane (10).—Jones reagent (23.0 ml) was added dropwise to alcohol **2** (20.0 g) dissolved in acetone (1.4 l.) containing enough ether (or tetrahydrofuran) to achieve solution. After standing for 10 min, 2-propanol (100 ml) was added to discharge the orange color. The green precipitate was collected and washed well with acetone. The acetone solution from the combined filtrates was concentrated and the residue in benzene was passed through basic alumina. The benzene solution was concentrated and the residue upon crystallization from ligroin afforded 10.3 g (98%) of colorless prisms: mp 131.5–132.0° (lit.[23] mp 127–128°); ν_{max} (KBr) 2970, 1700, 1455 (med), and 1370 K (med); pmr δ 2.4 (m, 2p, C-2), 1.1 (s, 19-, 31-, and 32-methyls), 0.87 (d, J = 6 Hz, 21-, 26-, and 27-methyls), and 0.82 (s, 14α- and 18-methyls); pmr (benzene) 2.3 (m) 1.1 (s, 19-methyl), 1.0 and 1.0 (s, 4α-and 4β-methyls), 0.90 (s), 0.87 (s), and 0.82 (s); RD in cyclohexane (c 0.56), $[\alpha]_{600}$ +18°, $[\alpha]_{589}$ +19°, $[\alpha]_{450}$ +36°, $[\alpha]_{380}$ +44° (hump), $[\alpha]_{350}$ +36°, $[\alpha]_{336}$ 0.0°, $[\alpha]_{324}$ + 17° (trough), $[\alpha]_{320}$ 0.0°, $[\alpha]_{300}$ +210°, and $[\alpha]_{280}$ +310°.[24]

3-Oxo-4-oxa-4α,14α-dimethyl-*A*-homo-5α-cholestane (11).—A cold (ice bath) solution prepared from ketone **10** (8.58 g, 0.02 mol), *m*-chloroperbenzoic acid (15.2 g, 0.06 M, 75% assay), chloroform (50 ml), glacial acetic acid (50 ml), and concentrated sulfuric acid (2 ml) was allowed to stand at room temperature in the dark for 5 days.[21] The amber solution was decanted from the precipitated *m*-chlorobenzoic acid and added to water (350 ml)–ether (100 ml). The aqueous layer was separated and extracted with ether (100 ml in three aliquots). The combined ether extract was washed with 1.5 M sodium hydrogen sulfite (900 ml in five aliquots) and saturated sodium bicarbonate (400 *ml in four aliquots*) which *removed most of the brown color*, and the emulsion was eliminated by filtration. The yellow etheral solution was dried and concentrated to dryness. Recrystallization of the yellow residue from ethyl acetate yielded 2.5 g (29%) of colorless needles: mp 185.5–186.2°; ν_{max} (0.1 M in $CHCl_3$) 2970 and 1730 K; pmr δ 4.5 (m, 1p, 4β-H), 2.6 (m, (m, 2p, C-2), 1.3 (d, J = 6.5 Hz, 4α-methyl) 1.0 (s, 19-methyl), 0.92 (s), and 0.80 (s); RD in chloroform (c 1.75), $[\alpha]_{650}$ +12°, $[\alpha]_{589}$ +15°, $[\alpha]_{500}$ +24°, $[\alpha]_{400}$ +42°, $[\alpha]_{300}$ +92°, $[\alpha]_{264}$ +114° (peak), $[\alpha]_{250}$ +71°, and $[\alpha]_{240}$ 0.0°; mass spectrum M^+ 430 (100%).

Anal. Calcd for $C_{29}H_{50}O_2$ (430): C, 80.87; H, 11.70; O, 7.43. Found: C, 80.68; H, 11.83; O, 7.57.

4-Oxo-4,14α-dimethyl-3,4-seco-5α-cholestane-3-carboxylic Acid (12).—A solution of lactone **11** (0.12 g) in acetone (26 ml)–water (1 ml)–Jones' reagent (0.35 ml) was stirred for 15 hr. To the yellow mixture was added 2-propanol (5 ml). The green precipitate was collected and washed well with hot acetone and the filtrate evaporated to dryness. The residue was purified by preparative thin layer chromatography using benzene–ethyl acetate (5:1) as the mobile phase. Elution of the uppermost band with ether yielded 34 mg (27%) of recovered lactone as needles, mg 185.0–186.5°, and elution of the lower band with ether yielded 92 mg (72%) of keto acid as needles: mp 157.5–160.5°; ν_{max} (KBr) 3450 (broad shoulder appears at 3250) 2970, 1730 (str ketone C═O stretch), 1690 (str acid C═O stretch), and 1170 (med C–O stretch) K; pmr δ 9.3 (broad, 1p, removed by D_2O), 2.3 (m, 3p, C-2 and C-5), 2.2 (s, 3p, 4α-methyl), 1.1 (s, 19-methyl), 0.87 (d, J = 6 Hz, 21-, 26-, and 27-methyls), and 0.82 (s, 14α- and 18-methyls); mass spectrum 345 (100%), M^+ − 18 (82%), M^+ − 15 (88%) and M^+ 446 (59%).

Anal. Calcd for $C_{29}H_{50}O_3$ (446): C, 77.97; H, 11.28; O, 10.74. Found: C, 77.80; H, 11.28; O, 10.91.

3-Oxo-4-oxa-4a-methylidene-14α-methyl-*A*-homo-5α-cholestane (13).—After 15 min a solution of keto acid **12** (80 mg) in acetic anhydride–perchloric acid regent (10 ml) was treated and stirred with 1 M sodium carbonate solution (20 ml) for 40 min. The organic phase was evaporated to dryness. Separation of the residue by preparative thin layer chromatography, using benzene–ethyl acetate (10:1) as the mobile phase, and elution of the upper band with ether yielded 40 mg (52%) of prisms: mp 152–156°; ν_{max} (KBr) 2930, 1735, 1630, and 880 (2,2-disubstituted vinyl group), and 1100 K; pmr δ 5.0 (d, J = 1.5 Hz, 1p, 4a H cis to the ester), 4.6 (d, J = 1.5 Hz, 1p, 4a H trans to the ester), 2.5 (m, 2p, C-2), 1.0 (s, 19-methyl), 0.87 (d, J = 6 Hz, 21-, 26-, and 27-methyls), and 0.82 (s, 14α- and 18-methyls); RD in chloroform (c 0.159), $[\alpha]_{589}$ +118°, $[\alpha]_{600}$ +190°, $[\alpha]_{400}$ +330°, $[\alpha]_{350}$ +510°, $[\alpha]_{300}$ + 910°, $[\alpha]_{250}$ +3320°, $[\alpha]_{236}$ +4660° (peak), $[\alpha]_{230}$ +4010°, and $[\alpha]_{224}$ +2330°; mass spectrum 206 (100%), M^+ − 28 (8%) and M^+ 428 (35%).

Anal. Calcd for $C_{29}H_{48}O_2$ (428): C, 81.25; H, 11.29; O, 7.46. Found: C, 81.15; H, 11.24; O, 7.61.

Registry No.—**3,** 21857-87-4; **4,** 21857-88-5; **5,** 21857-89-6; **6,** 21857-90-9; **7,** 21857-91-0; **9a,** 21857-92-1; **9b,** 33495-90-8; **10,** 4639-29-6; **11,** 31656-58-3; **12,** 33495-93-1; **13,** 33487-95-5.

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