N, 2.91; Cl, 7.36. Found: C, 64.96; H, 5.19; N, 3.01; Cl, 7.68.

4,5-(*p*-Chlorobenzoyl)imino-9,10-dihydro-7-methoxy-2-methylphenanthrene-1-acetic Acid (6a).—To a solution of 50 mg (0.104 mmole) of the diacid **5** in 10 ml of methylene chloride was added 2 equiv (47 mg, 0.207 mmole) of DDQ in 5 ml of methylene chloride and the mixture stirred at room temperature for 1.5 hr.

The mixture was filtered and the filtrate was purified by preparative tlc using benzene–dioxane–acetic acid 90:25:6 as the developing solvent. Three main components were isolated: 21 mg (50% yield) of product (R_f 0.54), 5 mg of starting material (R_f 0.39), and 12 mg of a slightly more polar by-product (R_f 0.31).

The main product (R_f 0.54) had mp 195–220°; λ_{max} 232, 290 mμ (ε 38,600, 18,200); ν_{max}^{KBr} 2941 (carboxyl OH), 1695 (carboxyl CO), 1667 cm^{-1} (amide CO); nmr (in DMSO-d_6), 7.65 (s, *p*-chlorobenzoyl protons), 6.81 (s, C-3 H), 6.73 (m, C-6 H), 6.38 (m, C-8 H), 3.63 (s, OCH_3 + CH_2COO), 3.12 (s, C-9 H_2 + C-110 H_2), 2.25 ppm (s, C-2 CH_3); mass spectrum, *m/e* 433 [M$^+$, calcd for $C_{25}H_{20}ClNO_4$, 433], 389 [M − CO_2], 139 [base peak, *p*-ClC_6H_4CO].

Methyl 4,5-(*p*-Chlorobenzoyl)imino-9,10-dihydro-7-methoxy-2-methylphenanthrene 1-Acetate (6b).—To a suspension of 40 mg (0.092 mmole) of the acid **6a** in 8 ml of methanol were added several portions of ethereal diazomethane. The solution was acidified with acetic acid, washed with water, and evaporated.

The crude product was purified by preparative tlc using cyclohexane–ethyl acetate (70:30) as the developing solvent to give 37 mg (90%) of the methyl ester: mp 173–177°; λ_{max} (neutral) 231, 270 (sh) 290 mμ (ε 44,600, 17,800, 20,800); λ_{max} (basic) 244, 260 (sh), 305, 317 mμ (sh) (ε 56,400, 25,100, 11,700, 10,400); ν_{max}^{KBr} 1733 (carbomethoxyl CO), 1675 cm^{-1} (amide CO); nmr 7.33–7.67 (m, *p*-chlorobenzoyl protons), 6.90 (s, C-3 H), 6.61 (s, C-6 H + C-8 H), 3.68 (s, CH_2COOCH_3), 3.63 (s, OCH_3), 3.17 (s, C-9 H_2 + C-10 H_2), 2.30 ppm (s, C-2 CH_3); mass spectrum, *m/e* 447 [M$^+$, calcd for $C_{25}H_{20}ClNO_4$, 447], 388 [M − $COOCH_3$], 374 [M − CH_2COOCH_3], 249 [M − ($COOCH_3$ + *p*-ClC_6H_4CO)], 235 [M − (CH_2COOCH_3 + *p*-ClC_6H_4CO)].

Methyl 9,10-Dihydro-4,5-imino-7-methoxy-2-methylphenanthrene 1-Acetate (7).—To a solution of the methyl ester (**6b**, 21 mg, 0.048 mmole) in 10 ml of methylene chloride was added 84 mg (1.5 mmoles) of potassium hydroxide dissolved in 25 ml of methanol. The solution was allowed to stand at room temperature for 1 hr, then acidified with acetic acid, and evaporated in the presence of toluene. The resulting residue was dissolved in methylene chloride, filtered through Celite, and evaporated to a glass (19 mg) which was purified by preparative tlc (cyclohexane–ethyl acetate 70:30) to give 13 mg (91%) of pale tan crystals: mp 130–140°; λ_{max} 244, 260 (sh), 305, 317 mμ (sh) (ε 31,500, 17,300, 8300, 7100); $\nu_{max}^{CHCl_3}$ 3448 (NH), 1724 (carbomethoxyl CO), 1139 cm^{-1} (OCH_3); nmr (in DMSO-d_6), 10.4 (m, NH), 6.95 (s, C-3 H), 6.67 (m, C-6 H), 6.50 (m, C-8 H), 3.75, 3.70 (s, s, CH_2COOCH_3), 3.55 (s, OCH_3), 3.14 (s, C-9 H_2 + C-10 H_2), 2.35 ppm (s, C-2 CH_3).

The Stereochemistry of the Cleavage of a Steroid 4,4-Dimethyl-3,4-seco Lactone

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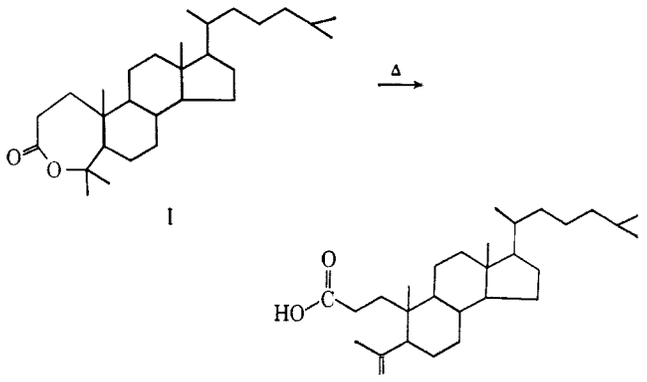
It has been reported recently[1] that the lactone I, obtained by the Baeyer–Villiger oxidation of 4,4-dimethylcholestanone, is readily pyrolized to the unsaturated acid II.



I

II

The recent interest in the detailed mechanism and stereochemistry of the biological synthetic pathways to steroids and terpenes[2] made us feel that this reaction, if stereospecific, could serve as the basis for the chemical degradation of steroid precursors, such as lanosterol, or of other triterpenes in order to verify the biogenesis of each C-4 methyl group in these substances. Accordingly we have carried out a series of reactions to determine to what extent each of the C-4 methyl groups in I are converted to the methylene and methyl portions of the isopropenyl group in II.

4-Methylcholestenone (III)[1,3] was alkylated with a slight excess of trideuteriomethyl iodide in the presence of potassium *t*-butoxide and *t*-butyl alcohol. It has been shown that when 4-methylcholesten-3-one is ethylated under basic conditions, the incoming alkyl group is nearly exclusively introduced into the 4α position.[4] Since the size of the alkylating agent does not materially effect the stereospecificity of the alkylation reaction,[5] the product of our trideuteriomethylation reaction was therefore 4β-methyl-4α-trideuteriomethyl-5-cholesten-3-one (IV).

Catalytic reduction of ketone IV with hydrogen on platinum in ethyl acetate containing a trace of perchloric acid smoothly gave 4β-methyl-4α-trideuteriomethyl-5α-cholestan-3β-ol (V). The 100-Mc nmr spectrum of this substance was identical with that of the unlabeled alcohol with the exception of the total absence[6] of the sharp signal at 96.5 cps (downfield from TMS) present in undeuterated V which can be assigned to the 4α-methyl group. This evidence proves that the original assignment[7] of the nmr signals for the 4α- and 4β-methyl groups in triterpene 3β alcohols was reversed and that the assignments made by Hemmert, *et al.*,[8] are correct.

Oxidation of the 3β alcohol V with chromium trioxide in acetone gave the deuterated 4,4-dimethylcholestan-3-one (VI) which was oxidized in chloroform solution with *m*-chloroperbenzoic acid to the 4aα-trideuteriomethyl lactone VII. Pyrolysis of this lactone at 205° was complete after 50 min and the

(1) D. Rosenthal, A. O. Niedermeyer, and J. Fried, *J. Org. Chem.*, **30**, 510 (1965).

(2) E. J. Corey, W. E. Russey, and P. R. Ortiz de Montellano, *J. Am. Chem. Soc.*, **88**, 4750 (1966); E. E. van Tamelen, J. D. Willett, R. B. Clayton, and K. E. Lord, **88**, *ibid.*, 4752 (1966); J. W. Cornforth, R. H. Cornforth, G. Popják, and L. Yengoyan, *J. Biol. Chem.*, **241**, 3970 (1966), and earlier papers in this series.

(3) G. D. Meakins and O. R. Rodig, *J. Chem. Soc.*, 4679 (1956); D. N. Kirk and V. Petrow, *ibid.*, 1091 (1962).

(4) G. Just and K. St. C. Richardson, *Can. J. Chem.*, **42**, 464 (1964).

(5) V. Permutti and Y. Mazur, *J. Org. Chem.*, **31**, 705 (1966).

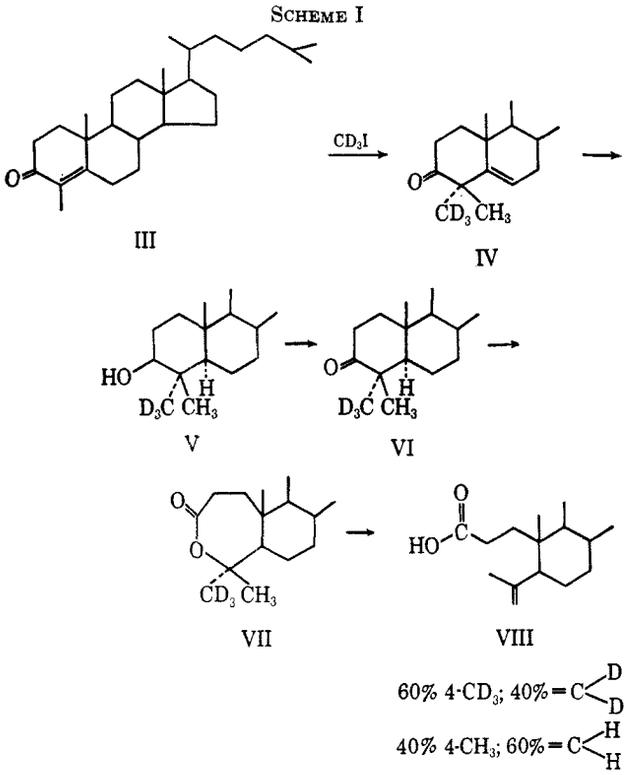
(6) In control experiments it was found that not more than 10% of the 4α-methyl epimer could have been present using this method of analysis.

(7) A. I. Cohen, D. Rosenthal, G. W. Krakower, and J. Fried, *Tetrahedron*, **21**, 3171 (1965).

(8) F. Hemmert, B. Lacoume, J. Levisalles, and G. R. Pettit, *Bull. Soc. Chim. France*, 976 (1966); F. Hemmert, A. Lablache-Combier, B. Lacoume, and J. Levisalles, *ibid.*, 982 (1966).

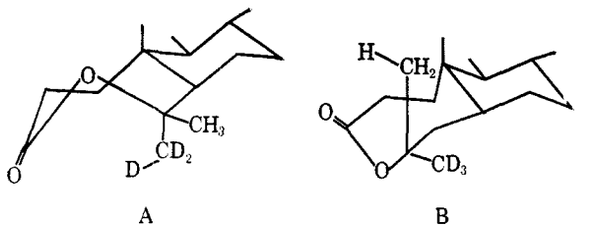
labeled seco acid VIII, mp 142–145°, was subjected to nmr analysis. Careful integration of the pertinent peaks in the nmr spectra of the labeled and the unlabeled seco acid showed that the methylene group of the product VIII was derived approximately 60% from the 4β-methyl group of VII and 40% from the 4α-methyl group (Scheme I).

SCHEME I



The shape of the pattern of the methylene protons in the labeled acid VIII was identical in every respect with that of the unlabeled acid. Had equilibration of the methyl and methylene groups occurred during or subsequent to the pyrolysis, species of the type =CHD would have been present in VII to the extent of approximately 50% which would result in the sharpening of the nmr pattern. Similarly the allylic methyl group showed no evidence of broadening due to $-CHD_2$ or $-CH_2D$ species. This evidence implies that no scrambling of label occurred in the isopropenyl group during the pyrolysis.

Lactone VII may exist in two interconvertible chair conformations A and B. If one assumes that conformer A gives exclusively the product with a deuterium-



labeled methylene group and conformer B, the product with the protiated methylene group, two factors will determine the ratio of products: (1) the relative population of the two conformers and (2) the relative rate of reaction of each conformer. The latter factor can be further broken down into two parts: (1) the intrinsic difference in reactivities of the two conformers and (2) the fact that conformer A is subject to a deuterium isotope effect as compared with its protiated analog.

The evidence at hand cannot distinguish between these factors; however, the over-all reaction specificity is low and could readily be accounted for by an isotope effect alone,[9] assuming that the conformers A and B are of equal population[10] and of equal reactivity.[11]

The transformation of I to II has also been reported by means of 10% sulfuric acid in acetic acid at room temperature.[12] We repeated this reaction with our deuterium-labeled lactone. The ring opening was complete within 10 min. However, the product II which was isolated was completely *devoid* of deuterium label. This result implies that a rapid equilibration of II is occurring with the solvent, undoubtedly *via* a protonated carbonium ion, and that the product observed is more stable than the isopropylidene or the Δ^5 isomer, because of $A^{(1,3)}$ and $A^{(1,2)}$ strain[13] in the latter two isomers, respectively.

Experimental Section

Infrared spectra were run in Nujol mulls. Chromatography was on Woelm neutral alumina activity III. No attempt was made to optimize reaction conditions and therefore the yields reported are not maximal. Unless otherwise indicated, nmr spectra were determined in deuteriochloroform on a Varian A-60 spectrometer. The 100-Mc spectra were determined in deuteriochloroform on a Varian HA-100 spectrometer. We wish to thank Dr. C. Moreland and Mrs. M. Miller for these determinations.

4β-Methyl-4α-trideuteriomethyl-5-cholesten-3-one (IV).—To 20 ml of *t*-butyl alcohol which was freshly distilled from sodium was added 245 mg of potassium. The reaction vessel was rigorously dried before use and the reaction was kept dry with nitrogen. After the potassium had dissolved (15 min), 1.05 g of 4-methylcholestenone[1] was added. A solution of 0.4 ml of trideuteriomethyl iodide in 5 ml of *t*-butyl alcohol was then added dropwise to the refluxing steroid solution over a 45-min period. Reflux and stirring were then continued for 45 min more. The reaction mixture was cooled, a few drops of 2 *N* hydrochloric acid was added, and the reaction was concentrated *in vacuo* to a small volume. Water and benzene were added and the organic phase was washed twice with saturated sodium chloride solution, dried over sodium sulfate, filtered, and evaporated to yield 1.2 g of crude reaction product. The reaction product was chromatographed on 100 g of neutral activity III alumina, taking 60-ml fractions. The solvent system was 2.5 l. of a continuously varied mixture which began with 1:4 carbon tetrachloride–hexane and concluded with 1:99 isopropyl alcohol–benzene. A homogeneous fraction was eluted in tubes 25–41. Evaporation yielded 510 mg of crystalline product, showing a single spot on thin layer chromatography of identical R_f as the undeuterated product. Recrystallization from methanol furnished 419 mg of 4β-methyl-4α-trideuteriomethyl-5-cholesten-3-one: mp 176–176.5°; infrared peaks, 2217 (w), 2056 (w), 1707 (s), cm^{-1}; nmr, τ 8.75, 9.11, 9.30

Hydrogenation of Ketone IV.—Ketone IV (50 mg) was hydrogenated at atmospheric pressure in acetic acid (10 ml) containing 1 drop of 70% perchloric acid using 30 mg of prereduced Adams' catalyst. The hydrogenation was complete in 30 min and the product, 4β-methyl-4α-trideuteriomethyl-5α-cholestan-3β-ol (V), after usual work-up and crystallization from ethanol, weighed 30 mg, mp 140–145°. Recrystallization from methanol–

(9) K. B. Wiberg, *Chem. Rev.*, **55**, 713 (1955); C. H. DePuy and R. W. King, *ibid.*, **60**, 431 (1960).

(10) This assumption does not contradict the supposition advanced earlier[1] that based on room-temperature nmr studies lactone VII (undeuterated) exists primarily in conformation A. The assumption in the present work applies to the population at the pyrolysis temperature (205°).

(11) This supposition has been confirmed by Fried and Dudowitz who have carried out these reactions with C^{14}-labeled methyl groups and found nearly a 1:1 ratio of products. We wish to thank Dr. Fried for informing us of his results prior to publication.

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

(13) F. Johnson and S. K. Malhotra, *J. Am. Chem. Soc.*, **87**, 5492 (1965).

chloroform brought the melting point up to 149–150°. The nmr spectrum of this substance was identical in all respects with that of an authentic specimen of 4,4-dimethylcholestanol with the exception of the complete absence of a band at τ 9.04, present in the undeuterated sample; the infrared showed peaks at 3600, 3380, and 2217 cm^{-1} (w).

4β-Methyl-4α-trideuteriomethyl-5α-cholestan-3-one (VI).—A solution of 241 mg of the deuterated dimethylcholestenone IV in 25 ml of ethyl acetate containing 1 drop of 70% perchloric acid was hydrogenated at atmospheric pressure using 100 mg of platinum oxide as catalyst. The hydrogenation proceeded for 140 min. The reaction was filtered, 2 drops of pyridine was added, and the solution was taken to dryness. The crude product was dissolved in acetone (20 ml) and oxidized with 0.2 ml of a reagent prepared by dissolving 66.6 g of chromium trioxide in 57.5 ml of concentrated sulfuric acid and making the solution up to 250 ml with distilled water. Methanol was added to decompose the excess chromic acid and the mixture was filtered through Celite, evaporated, taken up in benzene, and chromatographed on a column of 15 ml of alumina in benzene. Fractions (5 ml) were taken. Fractions 3 and 4 were combined and evaporated to give 223 mg of a crystalline product, 95% pure by vpc analysis. Recrystallization from methanol–chloroform gave 173 mg of pure 4β-methyl-4α-trideuteriomethyl-5α-cholestan-3-one (VI): mp 98–100°; infrared peaks, 2230, 2065, 1708 cm^{-1}.

Deuterated 3,4-Seco-4-methyl-4-methylenecholestan-3-oic Acid (VIII).—Trideuterio-4,4-dimethylcholestanone (VI) was subjected to Baeyer–Villiger oxidation with *m*-chloroperbenzoic acid as has been described for the nondeuterated compound.[1] The lactone VII thus obtained (33 mg) was placed in a test tube which was flushed with nitrogen. The compound was heated in a Wood's metal bath at 205°. The course of the pyrolysis was followed by thin layer chromatography and the reaction was complete after 50 min. The reaction was cooled and the product dissolved in chloroform, reduced to a small volume, and taken up in a little methanol. After removal of a flocculent residue by filtration, the product, deuterated 3,4-seco-4-methyl-4-methylenecholestan-3-oic acid (VIII), crystallized slowly, mp 142–145°. The nmr spectrum of this sample was determined at 100 Mc and compared with a similar sample obtained from nondeuterated material. The shape of the signal corresponding to the methylene protons at τ 5.14 and 5.32 was identical in the two samples. There was no broadening of the τ 8.25 allylic methyl peak in the deuterated sample.

Integrating the intensity of methylene bands using the C-18 methyl band at τ 9.35 as an internal standard gave values of 60 ± 5% for the amount of $=CH_2$ methylene group present in the deuterated sample relative to the undeuterated acid. The allylic methyl group at τ 8.25 was less reliable and gave values of 35 ± 10% of allylic methyl relative to the undeuterated acid.

Treatment of Lactone VII with Strong Acid.—The deuterated lactone VII (33 mg) was dissolved in 4 ml of a solution of 10% sulfuric acid in glacial acetic acid. The reaction was shaken for 10 min and then poured into water. The sulfuric acid present was neutralized with a calculated amount of potassium bicarbonate and the product was extracted with chloroform. The organic phase was washed with saturated sodium chloride solution, dried over sodium sulfate, and evaporated. Crystallization from methanol gave 22 mg of acid VIII, mp 146–148°, whose infrared and nmr spectra were identical with those of the undeuterated acid.

Registry No.—I, 2202-04-2; IV, 14128-48-4; V, 14154-63-3; VI, 14154-64-4; VIII, 14128-49-5.

17-Acetyl-13β-etiojerv-16-en-3β-ol *via* Performic Acid Oxidation of the Sapogenin Side Chain

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Although the Baeyer–Villiger degradation of the sapogenin side chain has been known for many years,[1] its applications have been severely limited by the absence of a route for converting the 16,20-dihydroxypregnane produced to the more tractable pregn-16-en-20-one. The problems posed in this last transformation were investigated when the classical pseudomerization and chromic acid degradation[2] failed in the 18-substituted C-nor-D-homo sapogenins.[3] The initial study reported here was made in the 18-unsubstituted derivatives.[4]

Performic acid oxidation of the rearranged sapogenin **3** followed by saponification provided as the chief product the triol **4**. The stereochemistry of the 16- and 20-hydroxyl groups of this compound is assigned by analogy to that determined in the pregnanes.[4,5] Attempts to convert this triol to the unsaturated ketone **9a** *via* selective esterification (benzoylation) led mainly to the 3,20-dibenzoate. The structure of this diester was demonstrated by oxidation to the corresponding 16-ketone (**8**-dibenzoate), which lacked an acetyl signal in the nmr; on treatment with base, β elimination of the ester group occurred, yielding an amorphous mixture of isomeric unsaturated (Δ^{17}) ketones (λ_{max} 238 mμ) in accord with the assigned structure. Selective hydrolysis of the triacetate of **4** also failed to yield the desired 20-monohydroxy compound in a reasonable yield.

The conversion of the sapogenin **3** to the unsaturated ketone **9a** was realized by use of the mixed ester obtained directly from the performic acid oxidation. The structure of this material, hitherto unexplored, was expected to be that resulting from oxidation of the tertiary carbon at position 20 adjacent to the latent 22-carbonyl, leaving a 20-valerate; the 16- and 26-hydroxyls would be esterified by the formic acid present (see **2**). Accordingly, the formate esters in the crude Baeyer–Villiger product were hydrolyzed by contact with alumina[6] and the resulting diol was etherified (presumably at 16 and 26) with dihydropyran. Saponification of the remaining ester functions (at 3, and, presumably, 20) followed by oxidation and base treatment led to a mixture lacking an appreciable acetyl signal in the nmr. This result suggested that the actual structure of the Baeyer–Villiger product was the reverse of that expected, and that in fact the valerate ester was at position 16 (**5**). The amorphous alcohol **6a**, obtained by the alumina treatment, was therefore oxidized directly; the resulting material, after base treatment, afforded the desired unsaturated ketone **9a**. The over-all yield (50%) from the sapogenin **3** compares favorably with that from the alternate pseudomerization procedure (45%).[4a]

The most probably mechanistic course of the Baeyer–Villiger oxidation is attack of peroxide at C-22 of a protonated hemiketal such as i. A subsequent bond shift would produce the symmetrical dioxolane intermediate ii[7] which is then preferentially solvolyzed at the 20-oxygen.

(1) R. E. Marker, E. Rohrmann, H. M. Crooks, E. L. Whittle, E. M. Jones, and D. L. Turner, *J. Am. Chem. Soc.*, **62**, 525 (1940). For a more recent publication modifying the original method, see K. Morita, S. Noguchi, H. Kono, and T. Miki, *Chem. Pharm. Bull.* (Tokyo), **11**, 90 (1963), and following papers. Brief mention of this reaction in the C-nor-D-homo steroids appeared here, after completion of the present work.

(2) See, for example, M. E. Wall and S. Serota, *Tetrahedron*, **10**, 238 (1960).

(3) Work to be published in a forthcoming communication.

(4) (a) W. F. Johns, *J. Org. Chem.*, **29**, 2545 (1964); (b) H. Mitsuhasi, K. Shibata, T. Sato, and Y. Shimizu, *Chem. Pharm. Bull.* (Tokyo), **12**, 1 (1964).

(5) C. H. Halsall, *Org. Reactions*, **9**, 79 (1957).

(6) F. C. Chang and R. T. Blickenstaff, *J. Am. Chem. Soc.*, **80**, 2906 (1958).