characterized products. The infrared spectrum showed: ν_{max}^{KBr} 2940, 1695, 1495, 1450, 1410, 1285, 1215, 1180, 1160, 933, 740, 695, and 672 cm^{-1}. The nmr spectrum (in τ) showed: ν_{max}^{DSMO} −0.6, singlet (2 protons, COO*H*); 2.73, singlet (10 protons of 2 phenyl rings); and 5.32, slightly split singlet (2 protons, >C*H*).

Anal. Calcd for $C_{16}H_{14}O_4S_2$: C, 57.44; H, 4.25; S, 19.17. Found: C, 57.45; H, 4.48; S, 18.90.

From 2 g of 2-imino-5-(*p*-methoxyphenyl)-4-thiazolidinone under the same conditions, there was obtained 1.2 g (65% of theory) of dithiobis(*p*-methoxyphenylacetic acid), mp 201° dec.

Anal. Calcd for $C_{18}H_{18}O_6S_2$: C, 54.79; H, 4.60; S, 16.26. Found: C, 54.37; H, 4.85; S. 16.60.

Methyl α-Mercaptophenylacetate. An aqueous solution of potassium α-mercaptophenylacetate, prepared as previously described, was acidified to give α-mercaptophenylacetic acid as a yellow oil. After the crude acid was refluxed overnight with twenty volumes of methanol and a few drops of sulfuric acid, there was obtained 7 g (62% of theory) of **methyl α-mercaptophenylacetate**, bp 96–98° (0.8 mm). Analysis by glpc (2-m glycol succinate column programmed from 175 to 275°) showed the ester to be 80% pure.

Treatment of the crude ester in ethanol with ethanolic silver nitrate yielded a white precipitate which melted and then dissolved when the solution was warmed. The silver salt of **methyl α-mercaptophenylacetate** (IV) precipitated on cooling. Leaching with hot ethanol yielded an almost white material, mp 138°.

Anal. Calcd for $C_9H_9O_2SAg$: C, 37.38; H, 3.18; S, 11.09; OCH_3, 10.73. Found: C, 37.43; H, 3.20; S, 11.10; OCH_3, 10.58.

Disulfide Acid by the Xanthate Method. To 45 g (0.2 mole) of phenyl(trichloromethyl)carbinol and 23 g (0.3 mole) of freshly distilled carbon disulfide in 150 ml of methanol at 50° under a nitrogen atmosphere, there was added over a period of 75 min a solution of 104 g (1.6 moles) of potassium hydroxide pellets dissolved in 300 ml of methanol. The temperature was maintained near 50° during the addition; the reaction mixture was stirred 1 hr more at this temperature, and then allowed to cool to room temperature while standing overnight. After the solution was diluted with an equal volume of water and the negligible neutral fraction extracted with ether, the pH was adjusted to 1 and the acid fraction extracted with ether. There was obtained 29 g of crude α-mercaptophenylacetic acid, a yellow oil which gave a strong test for the mercapto group with sodium nitroprusside. Air oxidation of an aqueous solution of its sodium salt by the previously described procedure gave **dithiobis(phenylacetic acid)** (III), mp 197–201° dec, in 28% yield from the carbinol. Recrystallization from methanol–water raised the melting point to 210–212°.

Acknowledgments. This work was supported by fellowships from the National Science Foundation and from the Public Health Service (Grants GPM-18,638 and 5-Fl-18,638-02) to M. N.; this aid is gratefully acknowledged. The assistance of Dr. William McFarlane in obtaining the nmr spectra is deeply appreciated.

J. Chem. Soc. (Abstracts), **92** (I), 54 (1907); C. Ulpiani and U. Ciancarelli, *Atti Accad. Lincei*, [5] **12** (II), 226 (1903), from *J. Chem. Soc.* (Abstracts), **86** (I), 162 (1904).

Optical Rotatory Dispersion Studies. CVII.[1] Factors Governing the Relative Stability of Hydrindanones. Syntheses of 17-Alkyl-15-keto Steroids[2]

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Contribution from the Department of Chemistry, Stanford University, Stanford, California. *Received July 11, 1966*

Abstract: New syntheses of 17-alkyl-15-keto steroids from readily available 17-keto steroids are described, the key step being the base-catalyzed addition of benzyl alcohol to Δ^{15}-5α-androsten-17-one (VII). The pure 14α and 14β epimers were prepared, and the position of their base-catalyzed equilibrium was established by optical rotatory dispersion measurements yielding the results presented in Table I. The importance of nonbonded steric interaction between a 17β-alkyl substituent and the C-18 angular methyl group in 15-keto steroids is emphasized. A number of 14α- and 14β-Δ^{16}-15-ketones have been prepared, and their stereospecific catalytic hydrogenation is noted. Optical rotatory dispersion measurements on these α,β-unsaturated ketones demonstrated that the sign of their Cotton effect is controlled by the stereochemistry at C-14.

One of the complications in conformational analysis lies in the variation of the relative stabilities of *cis*- and *trans*-hydrindanone systems when incorporated into more complicated structures such as the steroids.[4] The contrast between 5α-cholestan-3β-ol-15-one[5] and 5α-androstan-15-one (XXXII)[4g] may be cited as an example, the former being more stable[6] with a *trans* C/D ring juncture while the latter is more stable (85–87% 14β) with a *cis* C/D ring fusion. The only variable responsible for this difference is the substituent at C-17.

The relative stabilities of *cis*- and *trans*-steroidal hydrindanone systems have been studied by numerous workers,[4a,7] and the variations observed had led to

(1) Paper CVI: C. Djerassi, R. Records, C. Ouannes, and J. Jacques, *Bull. Soc. Chim. France*, 2378 (1966).

(2) Financial assistance by the National Institute of Health (Grant No. CA-07195) of the U. S. Public Health Service is gratefully acknowledged.

(3) Taken from part of the Ph.D. dissertation of A. R. V., Stanford University, 1966.

(4) (a) For a detailed summary of literature citations see N. L. Allinger, R. B. Hermann, and C. Djerassi, *J. Org. Chem.*, **25**, 922 (1960); see also (b) H. Linde and K. Meyer, *Helv. Chim. Acta*, **42**, 807 (1959); (c) F. L. Weisenborn and H. E. Applegate, *J. Am. Chem. Soc.*, **81**, 1960 (1959); (d) N. L. Allinger and S. Greenberg, *J. Org. Chem.*, **25**, 1399 (1960); (e) H. Ishii, T. Tozyo, and D. Satoh, *Chem. Pharm. Bull.* Tokyo), **11**, 576 (1963); (f) T. Wada and D. Satoh, *ibid.*, **13**, 308 (1965); (g) C. Djerassi, G. von Mutzenbecher, J. Fajkos, D. H. Williams, and H. Budzikiewicz, *J. Am. Chem. Soc.*, 87, 817 (1965).

(5) C. S. Barnes, D. H. R. Barton, and G. F. Laws, *Chem. Ind.* (London), 616 (1953); D. H. R. Barton and G. F. Laws, *J. Chem. Soc.*, 52 (1954).

(6) This was later verified by optical rotatory dispersion measurements. See C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, 78, 6362 (1956).

considerable speculation. Existing rationalizations[4a,7] have suffered because of a general lack of adequate quantitative data. In fact, with the exception of our earlier study,[4a] the data which inspired these rationalizations were derived principally from product isolation and thus can at best be only qualitative.

The object of the present work was to investigate in detail the base-catalyzed equilibration of a single class of steroidal hydrindanones, namely 17β-alkyl-5α,14ξ-androstan-15-ones (XXXIV–XLI), in order to determine the role which the size of their C-17 alkyl substituents plays. In this paper the results of a quantitative study of the relative stabilities of such a related series of steroidal hydrindan-15-ones (XXXII–XLI) are presented. The simplest members of this series, namely 14α- (XXXII) and 14β- (XXXIII) 5α-androstan-15-one, have already been examined[4g] (Table I).

Table I. Position of Base-Catalyzed Equilibrium of 17ξ-R-5α-Androstan-15-one

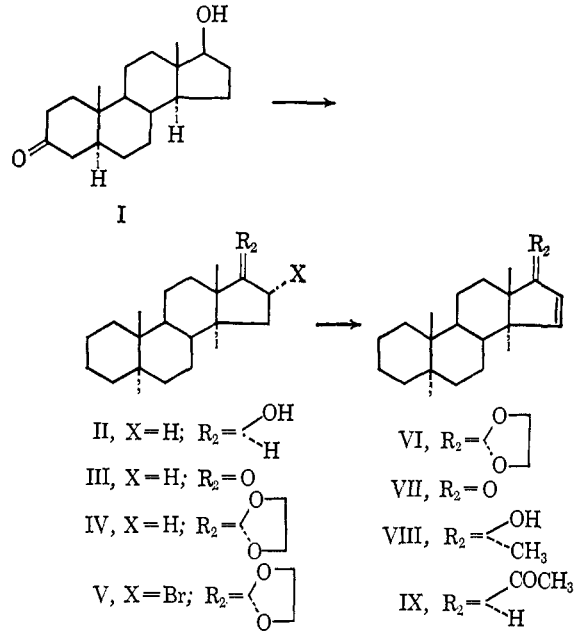
R	% 14β epimer
Hydrogen	85–87
17β-CH_3	59
17α-CH_3	>94
17β-C_2H_5	41
17β-$CH(CH_3)_2$	21
17β-C_9H_{19}	~20

Syntheses of 15-Keto Steroids

Since we wished to concentrate on the equilibrium of various 17β-alkyl-5α,14ξ-androstan-15-ones without complications arising from the presence of other functionalities, it was necessary to prepare the hitherto undescribed "naked" 17β-alkyl-15-keto steroids (XXXIV–XLI). Prior to our synthesis[4g] of 5α,14ξ-androstan-15-one (XXXII and XXXIII), most 15-keto steroids were obtained *via* microbiological hydroxylations[8] or transformations[8] of relatively rare naturally occurring steroids oxygenated at C-14 or C-15. The only previously known chemical method of potential applicability for introduction of a C-15 oxygen functionality into a 17-alkylandrostane was that of Barton and Laws[5] which started with steroidal $\Delta^{5,7}$-dienes.

Our earlier syntheses[4g] of 5α,14ξ-androstan-15-one (XXXII and XXXIII) utilized as its key step the hydrazine reduction of 15β,16β-oxido-5α-androstan-17-one (XLII) to give Δ^{16}-5α-androsten-15β-ol (XLIII). Initially it was hoped that a 1,4-Grignard[9] addition to Δ^{16}-5α-androsten-15-one (XXVIII)[4g] in the presence of cuprous acetate would give the desired 17β-methyl-5α-androstan-15-one (XXXIV). Failure to obtain any 1,4-addition product by this method necessitated the use of an alternate route to 15-keto steroids, and the introduction of a benzyloxy group at C-15[10] from readily prepared Δ^{15}-17-keto steroids (*e.g.*, VII) appeared promising. This method did provide the key intermediate, 15β-benzyloxy-5α-androstan-17-one (XI), used in the synthesis of the various 15-keto steroids described in this paper with the sole exception of 5α-ergostan-15-one (XL) which was prepared from Δ^{22}-5α-ergosten-3β-ol-15-one 3-acetate (LVI) and 3-benzoate (LV).[11]

Since testosterone is a commercially available steroid, synthesis of 15β-benzyloxy-5α-androstan-17-one (XI) was commenced with the readily accessible dihydrotestosterone (I).[12] Huang-Minlon reduction[13] to 5α-androstan-17β-ol (II) followed by oxidation with 8 *N* chromic acid reagent[14] of the 17β-hydroxyl group of II gave 5α-androstan-17-one (III) in excellent yield. Ketalization to IV and bromination with phenyltrimethylammonium bromide perbromide to the 16α-bromo ketal V followed by dehydrobromination with potassium *t*-butoxide in boiling xylene and subsequent cleavage of the Δ^{15}-ketal VI with *p*-toluenesulfonic acid in aqueous acetone to Δ^{15}-5α-androsten-17-one (VII) proceeded smoothly according to the literature directions.[4g] Treatment of the latter with powdered potassium hydroxide in benzyl alcohol afforded in 48% yield 15β-benzyloxy-5α-androstan-17-one (XI).



Cantrall, *et al.*,[10] presented arguments to support the configurational assignment to the various C-15 substituted estra-1,3,5(10)-trienes described in their work. Among the arguments presented by them,[10] the relatively large levorotatory shift in molecular rotation (Φ_D) reported[10,15] for a 15β-oxygenated substituent in comparison to a dextrorotatory shift of comparable magnitude observed[10,15] for a 15α-oxygenated substituent supports the assignment of a 15β configuration in 15β-hydroxy-5α-androstan-17-one (XII, $\Delta\Phi_D$ =

(7) For a detailed literature survey see the literature citations in (a) M. Hanack, "Conformational Theory," Academic Press Inc., New York, N. Y., 1965, pp 177–180 and 223–225; (b) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp 212–216; (c) D. H. R. Barton and G. Morrison, *Progr. Chem. Org. Nat. Prod.*, **19**, 179 (1961).

(8) For citations to these reactions see footnotes 15 and 16 in ref 4g.

(9) *Cf.* C. Beard, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, **86**, 269 (1964).

(10) E. W. Cantrall, R. Littell, and S. Bernstein, *J. Org. Chem.*, **29**, 64, 214 (1964).

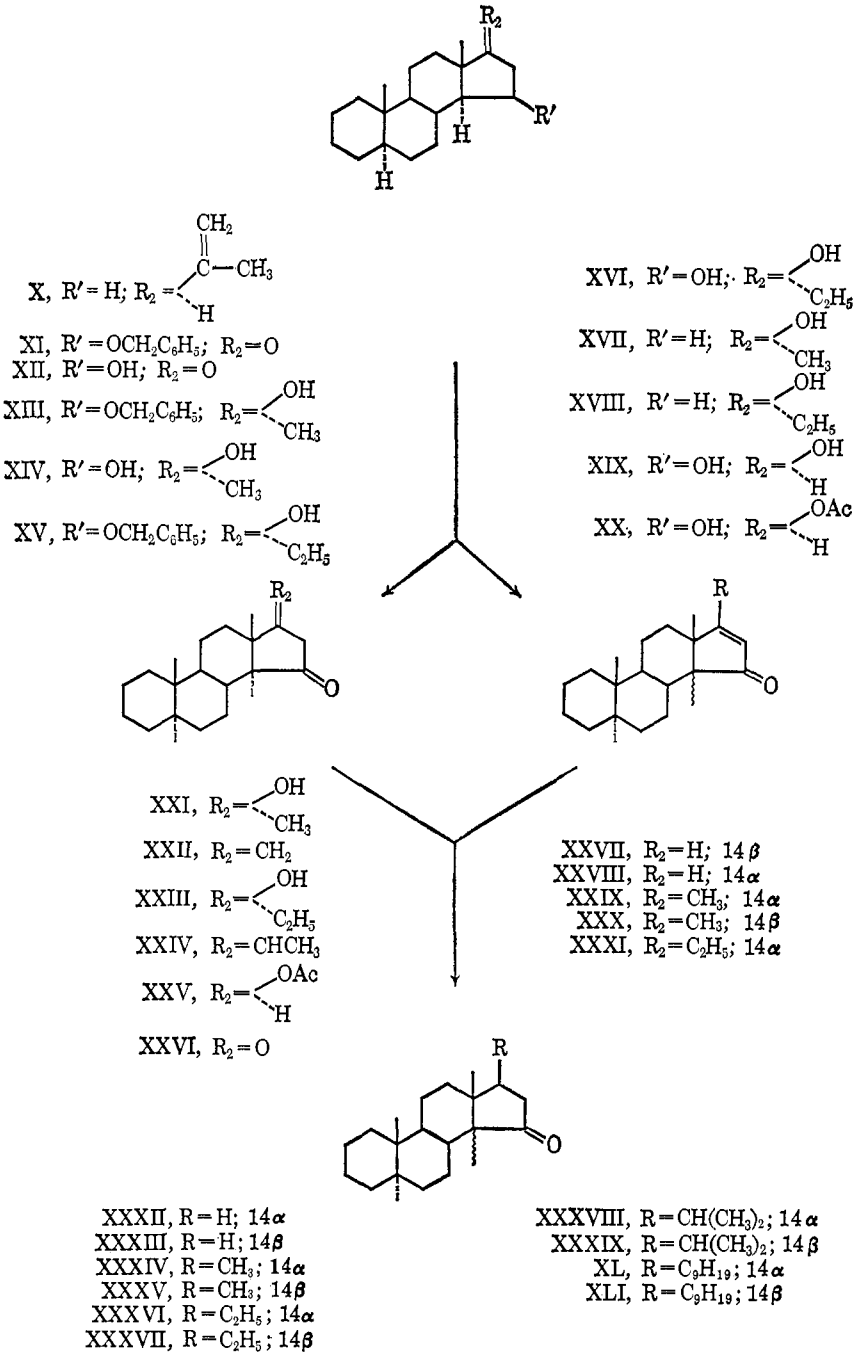
(11) The authors gratefully acknowledge a gift of Δ^{22}-5α-ergosten-3β-ol-15-one 3-acetate (LVI) and 3-benzoate (LV) from Professor D. H. R. Barton (Imperial College, London).

(12) We are indebted to Dr. Pierre Crabbé, Syntex, S. A., Mexico City, for a generous supply of dihydrotestosterone.

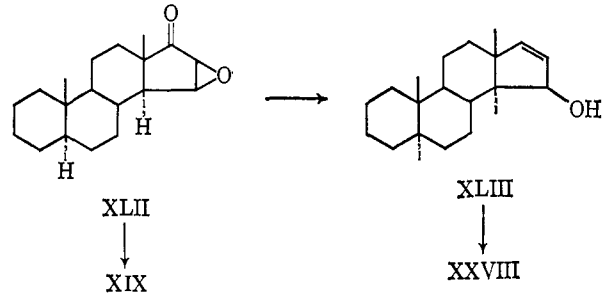
(13) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

(14) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(15) J. de Flines, W. F., van der Waard, W. J. Mijs, and S. A. Szpilfogel, *Rec. Trav. Chim.*, **82**, 143 (1963).



$-70°$) and in 15β-benzyloxy-5α-androstan-17-one (XI, $\Delta\Phi_D = -227°$). To establish more definitively that frontal (β face) approach of the benzyloxy nucleophile occurred, 15β-benzyloxy-5α-androstan-17-one (XI) was subjected to catalytic hydrogenolysis with 10% palladium-on-charcoal catalyst in acetic acid solution to give 5α-androstan-15β-ol-17-one (XII) which was further reduced with lithium aluminum hydride in ether to the diol XIX, identical in all respects with 5α-androstane-15β,17β-diol (XIX) prepared by lithium aluminum hydride reduction of 15β,16β-oxido-5α-androstan-17-one (XLII).[4g] A 17β-hydroxyl group would be expected from this reduction by analogy[16] with other 17-keto steroids. In view of the well-documented[17] course of diaxial opening of epoxides with lithium aluminum hydride, the stereochemistry of the second hydroxyl group must be 15β, since subsequent transformations of the diol XIX to 5α-androstan-15-one



(XXXII) firmly established the location of the hydroxyl group at C-15.

(16) W. Shoppee, *Nature*, **166**, 107 (1950); see also ref 7b, pp 467–468.

(17) For an extensive literature survey see J. G. Phillips and V. D. Parker in "Steroid Reactions," C. Djerassi, Ed., Holden-Day, Inc., San Francisco, Calif., 1963, Chapter 14.

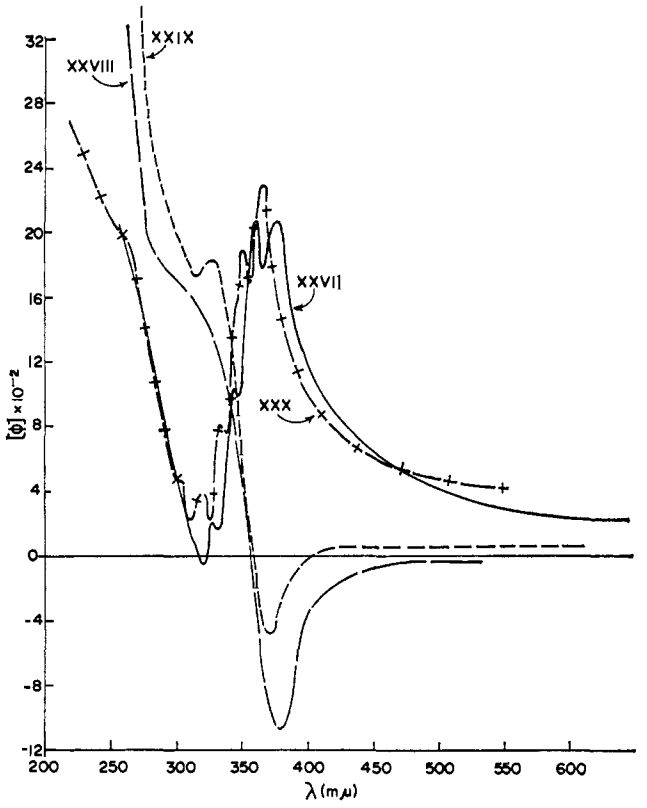
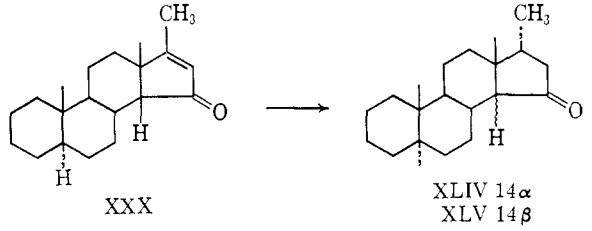


Figure 1. Optical rotatory dispersion curves (dioxane solution) of Δ^{16}-5α,14β-androsten-15-one (XXVII), Δ^{16}-5α-androsten-15-one (XXVIII), Δ^{16}-17-methyl-5α-androsten-15-one (XXIX), and Δ^{16}-17-methyl-5α,14β-androsten-15-one (XXX).

5α-Androstane-15β,17β-diol (XIX) served as a useful intermediate for still another route to 5α,14ξ-androstan-15-one (XXXII and XXXIII). Partial acetylation of the diol yielded principally[18] 5α-androstane-15β,17β-diol 17-acetate (XX) accompanied by some 15,17-diacetate but no starting material (XIX). Oxidation of the monoacetate XX by the Jones' procedure[14] followed by dehydroacetylation in refluxing acetic acid afforded Δ^{16}-5α,14β-androsten-15-one (XXVII), which was hydrogenated to 5α,14β-androstan-15-one (XXXIII). The assignment of the structure of the Δ^{16}-5α,14β-15-ketone (XXVII) was based on its ultraviolet absorption spectrum and method of synthesis. Establishment of the stereochemistry at C-14 in the saturated 14β-15-ketone XXXIV followed from its characteristic[6,19] negative ORD Cotton effect and *ipso facto* settles that of the precursor α,β-unsaturated ketone XXVII.

To prepare 17β-methyl-5α-androstan-15-one (XXXIV), 15β-benzyloxy-5α-androstan-17-one (XI) was treated with methylmagnesium iodide in ether solution and provided a chromatographically separable mixture of 15β-benzyloxy-17α-methyl-5α-androstan-17β-ol (XIII) and Δ^{15}-17α-methyl-5α-androsten-17β-ol (VIII). Catalytic hydrogenation of the latter led to the known 17α-methyl-5α-androstan-17β-ol (XVII). Hydrogenolysis of the other product, 15β-benzyloxy-17α-methyl-5α-androstan-17β-ol (XIII), provided entirely 17α-methyl-5α-androstane-15β,17β-diol (XIV), which was oxidized by the Jones' procedure[14] to the ketone XXI and then dehydrated with thionyl chloride in pyridine to a readily separable mixture of isomeric exocyclic (XXII) and endocyclic (XXIX) olefins. The ultraviolet and infrared spectra, as well as the characteristic negative ORD Cotton effect, observed for Δ^{16}-17-methyl-5α-androsten-15-one (XXIX) are consistent with the assigned structure. $\Delta^{17(20)}$-17-Methyl-5α-androsten-15-one (XXII) showed terminal double bond absorption in the infrared at 6.01 μ and an nmr multiplet, owing to the two olefinic protons, centered at δ 4.85. Catalytic hydrogenation of both Δ^{16}-(XXIX) and $\Delta^{17(20)}$-17-methyl-5α-androsten-15-one (XXII) proceeded in a stereospecific manner[16] in accordance with the rule[20] of "α-attack" to give 17β-methyl-5α-androstan-15-one (XXXIV). The 14α stereochemistry of the saturated 15-ketone XXXIV was established by its characteristic[6,19] positive ORD Cotton effect and by the fact that it was readily epimerized (see Table II) with base to its 14β-epimer XXXV with its expected[6,19] negative ORD Cotton effect.

Dehydration of 17α-methyl-5α-androstan-17β-ol-15-one (XXI), by heating in acetic acid solution, proceeded with inversion at C-14 to give Δ^{16}-17-methyl-5α,14β-androsten-15-one (XXX). A positive ORD Cotton effect with characteristic fine structure (see Figure 1) was obtained for this α,β-unsaturated ketone (XXX) and it is interesting to note its remarkable similarity to the rotatory dispersion curve of Δ^{16}-5α,14β-androsten-15-one (XXVII, see Figure 1). By contrast (see Figure 1), the 14α epimers XXVIII and XXIX exhibit a negative Cotton effect. Catalytic hydrogenation as well as chemical reduction with lithium–ammonia of Δ^{16}-17-methyl-5α,14β-androsten-15-one (XXX) led to 17α-methyl-5α,14β-androstan-15-one (XLV) with its expected[6,19] negative ORD Cotton effect. Catalytic hydrogenation of the α,β-unsaturated ketone XXX would be expected to occur from the β side giving 17α-methyl-5α,14β-androstan-15-one (XLV) since examination of Dreiding models[21] readily shows that the D ring folds under the molecule thereby greatly hindering hydrogenation from the α side.



XXX XLIV 14α XLV 14β

The preparation of C-14 epimeric 5α-pregnan-15-one (XXXVI and XXXVII) was carried out in the same manner as previously described for 17β-methyl-5α,14ξ-androstan-15-one (XXXIV and XXXV) with the sole exception that ethylmagnesium iodide was employed in the preparation of the tertiary carbinol XV. Analogous

(18) The 15β configuration of the C-15 hydroxyl group of the diol XIX also follows from its observed difficulty of acetylation. See J. Fried, R. W. Thomas, D. Perlman, J. E. Herz, and A. Borman, *Record Progr. Hormone Res.*, 11, 149 (1955); H. L. Herzog, M. J. Gentles, W. Charney, D. Sutter, E. Townley, M. Yudis, P. Kabasakalian, and E. B. Hershberg, *J. Org. Chem.*, 24, 691 (1959).

(19) (a) C. Djerassi, W. Closson, and A. E. Lippman, *J. Am. Chem. Soc.*, 78, 3163 (1956); (b) C. Djerassi, O. Halpern, V. Halpern, O. Schindler, and C. Tamm, *Helv. Chim. Acta*, 41, 250 (1958); (c) A. Lardon, H. P. Sigg, and T. Reichstein, *ibid.*, 42, 1457 (1959); (d) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1967, p 58.

(20) See ref 7b, pp 268 and 272; see also L. F. Fieser, *Experientia*, 6, 312 (1950); T. F. Gallagher and T. H. Kritchevsky, *J. Am. Chem. Soc.*, 72, 882 (1950).

(21) A. S. Dreiding, *Helv. Chim. Acta*, 42, 1339 (1959).

Table II. Optical Rotatory Dispersion Constants of Steroidal Hydrindan-15-one and Equilibrium Composition for Epimerization Reactions

Compound	Cotton effect extrema (methanol) [Φ], deg	λ, mμ	[Φ], deg	λ, mμ	Amplitude a,[32] deg	Equilibrium composition % 14β epimer
5α-Androstan-15-one (XXXII)[4g]	+6134	312	−7741	270	+139	
5α,14ξ-Androstan-15-one[a]	−2966	323	+3713	277	−67	85
5α,14β-Androstan-15-one (XXXIII)[4g]	−4553	322	+5801	275	−104	
5α,14ξ-Androstan-15-one[b]	−3183	323	+3979	278	−72	87
17β-Methyl-5α-androstan-15-one (XXXIV)[c]	+5814	315	−7038	275	+129	
17β-Methyl-5α,14ξ-androstan-15-one[a,d]	−618	332	+1236	297	−19	59
17β-Methyl-5α,14ξ-androstan-15-one[a,c]	−534	331	+1120	297	−17	59
17β-Methyl-5α,14β-androstan-15-one (XXXV)	−5021	326	+6944	284	−120	
17β-Methyl-5α,14ξ-androstan-15-one[b,e]	−374	332	+1215	302	−16	59
5α-Pregnan-15-one (XXXVI)[d]	+7159	314	−8369	275	+155	
5α,14ξ-Pregnan-15-one[a,d]	+2599	310	−1606	274	+42	41
5α,14ξ-Pregnan-15-one[a,c]	+2791	309	−1368	276	+42	41
5α,14β-Pregnan-15-one (XXXVII)	−4448	324	+7384	282	−118	
5α,14ξ-Pregnan-15-one[b]	+2655	309	−1499	272	+42	41
20-Methyl-5α-pregnan-15-one (XXXVIII)	+6502	315	−7784	275	+143	
20-Methyl-5α,14ξ-pregnan-15-one[a]	+4368	314	−5012	275	+94	21
20-Methyl-5α,14β-pregnan-15-one (XXXIX)	−3671	325	+5760	280	−94	
20-Methyl-5α,14ξ-pregnan-15-one[b]	+4386	315	−4740	276	+91	21
5α-Ergostan-15-one (XL)	+6828	314	−7739	278	+146	
5α,14ξ-Ergostan-15-one[a]	+4863	315	−5078	278	+99	~20
17α-Methyl-5α,14β-androstan-15-one (XLV)[e]	−4188	326	+6085	284	−103	
17α-Methyl-5α,14β-androstan-15-one[f]	−4247	326	+6250	284	−105	
17α-Methyl-5α,14ξ-androstan-15-one[b,f]	−3950	328	+5486	283	−94	>94
17α-Methyl-5α,14ξ-androstan-15-one[b,c]	−3818	325	+5725	283	−95	>94

[a] Base-catalyzed equilibration from the 14α epimer. [b] Base-catalyzed equilibration from the 14β epimer. [c] Prepared by catalytic hydrogenation of the corresponding Δ^{16}-15-ketone. [d] Prepared by catalytic hydrogenation of the corresponding $\Delta^{17(20)}$-15-ketone. [e] Isolation (preparative tlc) of the 14α and 14β epimers together after base-catalyzed equilibration of the 14β epimer. [f] Lithium–ammonia reduction of the α,β-unsaturated ketone XXX.

products were obtained in both synthetic sequences. Base-catalyzed equilibration of 5α-pregnan-15-one (XXXVI) gave an equilibrium mixture (see Table II) consisting of 41% of the 14β- (XXXVII) and 59% of the 14α- (XXXVI) epimers; separation was readily effected by preparative thin layer chromatography.

For the branched, 17β-isopropyl-substituted 15-keto steroids (XXXVIII and XXXIX) an alternate route had to be developed since isopropylmagnesium iodide failed to react with 17-keto steroids to give the corresponding tertiary carbinols. The classical method developed by Butenandt and Schmidt-Thomé[22] for transforming a 17-keto steroid into a 20-keto steroid was investigated and found to be applicable. 15β-Benzyloxy-5α-androstan-17-one (XI) was converted into a mixture of C-17 epimeric cyanohydrins (XLVI) by a modification[23] of Heusser's method. Dehydration of the epimeric cyanohydrins with phosphorus oxychloride in pyridine to 17-cyano-Δ^{16}-15β-benzyloxy-5α-androstene (XLVII) followed by Grignard reaction with methylmagnesium iodide afforded Δ^{16}-15β-benzyloxy-5α-pregnen-20-one (XLVIII). In agreement with its assigned structure, the 17-nitrile XLVII exhibited an ultraviolet maximum (ethanol) at 210 mμ (log ε 4.208) and absorption in the infrared at 4.50 μ (characteristic[24] of an α,β-unsaturated nitrile). The nmr spectrum in deuteriochloroform contained signals at δ 0.84 (C-18 methyl), 1.23 (C-19 methyl), 4.49 (benzylic methylene), and 7.29 (phenyl hydrogens). The C-16 proton is split by the neighboring pseudo-equatorial 15α-proton to give a slightly perturbed doublet centered at δ 6.58 (J = 2.6 cps) while the signal for the 15α proton, centered at δ 4.25, occurs as a quartet with coupling constants of approximately 2.8 and 5.0 cps, the latter coupling being attributed to splitting between the 14α and 15α protons. The chemical shifts and coupling constants for the 15α and 16 protons of XLVII are in good agreement with the nmr results observed[25] for the 15α proton (quartet with J = 2.8 and 5.0 cps) and the C-16 vinyl proton (doublet with J = 2.8 cps) of Δ^{16}-5α-androsten-15β-ol (XLIII).[4g] Exposure of the α,β-unsaturated ketone XLVIII to 10% palladized charcoal catalyst in ethanol in an atmosphere of hydrogen afforded 15β-benzyloxy-5α-pregnan-20-one (XLIX) and was accompanied by partial hydrogenolysis of the allylically activated 15β-benzyloxy substituent in Δ^{16}-15β-benzyloxy-5α-pregnen-20-one (XLVIII) to give 5α-pregnan-15β-ol-20-one (L). Further reduction of 15β-benzyloxy-5α-pregnan-20-one (XLIX) with 10% palladized charcoal catalyst in acetic acid solution rather than ethanol gave a mixture of 5α-pregnan-15β-ol-20-one (L) and a compound assumed to be its C-17 epimer, 17α-ethyl-5α-androstan-15β-ol-20-one. The positive ORD Cotton effect observed for L definitely established the stereochemistry of the acetyl group as 17β.[26]

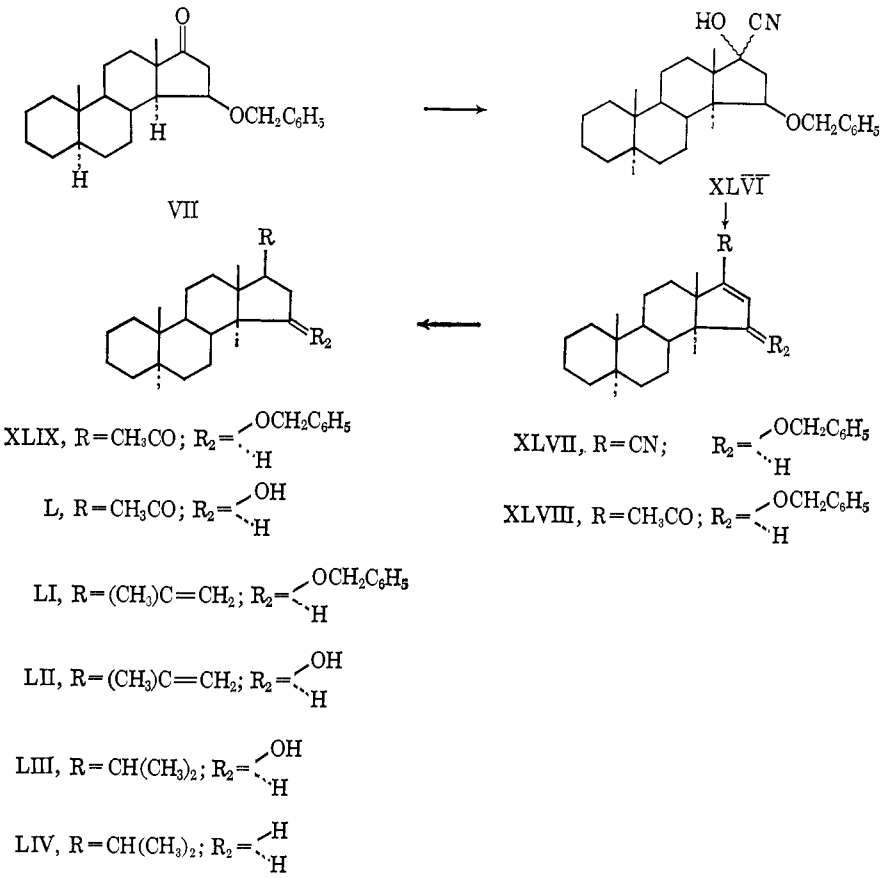
(22) A. Butenandt and J. Schmidt-Thomé, *Ber.*, 71, 1487 (1938); 72, 182 (1939).

(23) L. Miramontes, P. Aguinaco, and M. A. Romero, *J. Am. Chem. Soc.*, 82, 6153 (1960).

(24) (a) L. J. Bellamy, "The Infrared Spectra of Organic Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, Chapter 15; (b) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962, p 28.

(25) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry: Illustrations from the Steroid Field," Holden-Day, Inc., San Francisco, Calif., 1964, p 87.

(26) C. Djerassi, *Bull. Soc. Chim. France*, 741 (1957). For recent relevant reviews of 20-keto pregnanes see M. B. Rubin, *Steroids*, 2, 561 (1963); H. Mitsuhashi, T. Nomura, and M. Fukuoka, *ibid.*, 4, 483 (1964).



15β-Benzyloxy- (XLIX) and 15β-hydroxy- (L) 5α-pregnan-20-one when subjected together to the reaction conditions of Corey's modification[27] of the Wittig synthesis using triphenylmethylphosphonium bromide gave a chromatographically separable mixture of Δ^{20}-15β-benzyloxy- (LI) and Δ^{20}-15β-hydroxy- (LII) 20-methyl-5α-pregnene. The mixture of olefins LI and LII was not further characterized but directly subjected to catalytic reduction, first with 10% palladized charcoal catalyst in ethyl acetate to saturate the terminal methylene double bond, and then in acetic acid solution to effect hydrogenolysis of the C-15 benzyloxy substituent to give a mixture of known[28] 20-methyl-5α-pregnane (LIV)[29] and the desired 20-methyl-5α-pregnan-15β-ol (LIII). Catalytic hydrogenation was first carried out in ethyl acetate solution to prevent possible acid-catalyzed migration of the 20–22 double bond into the 17–20 tetrasubstituted position.

20-Methyl-5α-pregnan-15β-ol (LIII), homogeneous on thin layer chromatography, was not further characterized but directly oxidized by the Jones' procedure[14] to 20-methyl-5α-pregnan-15-one (XXXVIII) with its expected[6,19] positive ORD Cotton effect. Its nmr spectrum showed two sets of doublets centered at δ 1.01 and 0.88 (J_s = 7 cps) which definitely supports the presence of a C-17 isopropyl substituent. Hindered rotation of the isopropyl group presumably accounts for the different chemical shifts observed for these two otherwise similar C-21 and C-22 methyl substituents. Base-catalyzed epimerization of 20-methyl-5α-pregnan-15-one (XXXVIII) gave an equilibrium mixture (see Table II) which contained 21% of the chromatographically separable 14β-epimer XXXIX with its expected[6,19] negative Cotton effect.

Since the base-catalyzed equilibrium mixture of 20-methyl-5α-pregnan-15-one (XXXVIII) contained predominantly (79%) the *trans* epimer XXXVIII, further increments in the length of the C-17 side chain seemed unnecessary. We did however wish to examine the base-catalyzed epimerization of 5α-ergostan-15-one (XL) in order to check whether any 14β epimer is produced during base treatment.[30] Equilibration of Δ^{22}-5α-ergosten-3β-ol-15-one (LVII) gave a product which was homogeneous on thin layer chromatography, but since it is conceivable that the presence of the polar 3β-hydroxyl substituent might make separation of the 14α and 14β epimers very difficult, it was decided to remove the hydroxyl function in ring A.

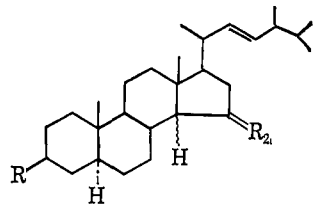
To prepare 5α-ergostan-15-one (XL), the acetate LVI and benzoate LV of Δ^{22}-5α-ergosten-3β-ol-15-one[11] were saponified to the corresponding alcohol LVII

(27) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, 28, 1128 (1963); E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 87, 1345 (1965).

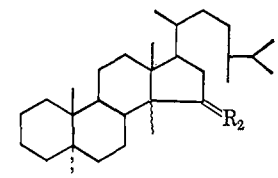
(28) J. P. Dusza and W. Bergmann, *J. Org. Chem.*, 25, 79 (1960).

(29) Δ^{16}-15β-Benzyloxy-5α-pregnen-20-one (XLVIII), although homogeneous on thin layer chromatography, presumably contained some Δ^{15}-5α-pregnen-20-one (IX) since infrared analysis of some of the chromatographic fractions (homogeneous on tlc) of XLVIII did show absorption at 13.2 μ which is characteristic for a *cis*-disubstituted cyclic olefin. The Δ^{15}-20-ketone IX presumably forms by β-elimination of the 15β-benzyloxy group during Grignard addition to Δ^{16}-17-cyano-15β-benzyloxy-5α-androstene (XLVII). It was not until hydrogenation of Δ^{20}-15β-benzyloxy-20-methyl-5α-pregnene (LI) was performed that the impurity was separable on thin layer chromatography. Catalytic hydrogenation of Δ^{15}-5α-pregnen-20-one (IX) followed by a Wittig reaction to give Δ^{20}-20-methyl-5α-pregnene (X) and further hydrogenation of X to 20-methyl-5α-pregnane (LIV) would account for the formation of this hydrocarbon.

(30) An equilibrium study has never been carried out; Barton and collaborators[5] have reported that lithium–ammonia reduction of $\Delta^{8(14)}$-15-ketostanols yields a single, alkali-stable 15-ketostanol, which upon Wolff–Kishner reduction is converted into the known stanol (*e.g.*, 5α-cholestan-3β-ol).



LV, R=OBz; R_2=O; 14α
LVI, R=OAc; R_2=O; 14α
LVII, R=OH; R_2=O
LVIII, R=OTs; R_2=O
LIX, R=H; R_2= 



LX, R_2=
LXI, R_2=O (XL=14α; XLI=14β)

(epimeric at C-14) which was then converted to its tosylate LVIII. Lithium aluminum hydride reduction of the tosylate LVIII produced the C-15 epimeric alcohols LIX. This mixture was catalytically hydrogenated to effect saturation of the 22–23 double bond and then oxidized by the Jones' procedure[14] to give 5α,14ξ-ergostan-15-one (LXI) which showed two spots on thin layer chromatography, a major spot corresponding to the 14α epimer XL and a less polar spot corresponding apparently to the 14β epimer XLI. While chromatographic methods do not define C-14 stereochemistry, they are useful for analysis and may be helpful in assigning configuration. The mixture of the less polar material on thin layer chromatography obtained after equilibration of 5α-ergostan-15-one (XL) was consistent with the results obtained after equilibration of the other "naked" 14ξ-15-keto steroids (XXXII–XXXIX) where the less polar material was definitely shown to be the 14β epimer. This observation coupled with the observed decrease in molecular amplitude observed in the optical rotatory dispersion curve for the equilibrium mixture resulting from base-catalyzed equilibration of 5α-ergostan-15-one (XL) strongly supports the presence of the 14β epimer in the equilibrium mixture. Separation of pure 5α-ergostan-15-one (XL) was effected by preparative thin layer chromatography but unfortunately the scarcity of XL precluded isolation of the 14β epimer XLI in quantity sufficient for analyses. Because of the very limited availability of starting material (LV and LVI),[5,11] none of the intermediates leading to 5α-ergostan-15-one (XL) were purified or characterized.

Discussion of Optical Rotatory Dispersion Results

In the past optical rotatory dispersion has served as a useful tool in the elucidation of the stereochemistry of many of the compounds discussed in this paper. Our earlier studies[4a] demonstrated the accuracy and the ease of determining the equilibrium composition by means of optical rotation measurements in the ultraviolet region. The steroidal hydrindan-15-ones investigated in this paper possess much greater rotations in the ultraviolet than at the D line, and in the present case many of the compounds were prepared in limited amounts, so that quantitative studies at the D line would have been very uncertain. The percentages of the 14α and 14β epimers contained in the equilibrium mixture of the C-14 epimeric 17β-alkyl-5α-androstan-15-ones were obtained by first determining the rotatory dispersion curves for both pure 14α and 14β epimers[31] and then repeating the measurements on the total product obtained after base-catalyzed equilibration of each of the pure C-14 epimers. The calculations obtained from these results and a summary of the optical rotatory dispersion data in terms of molecular amplitudes (a)[32] and wavelengths are given in Table II.

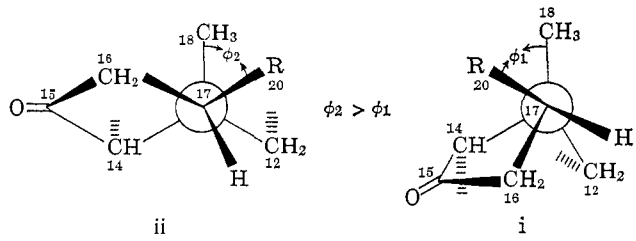
The percentages of the 14α and 14β epimers present in the equilibrium mixture resulting from the base-catalyzed equilibration of 5α-ergostan-15-one (XL) were calculated by assuming that the molecular amplitude[32] of unknown 5α,14β-ergostan-15-one (XLI) is approximately the same as that observed for 20-methyl-5α,14β-pregnan-15-one (XXXVIII). It is interesting to note (see Table II) that the 14α epimer XL has a molecular amplitude[32] very close (+146° *vs.* +143°) to that observed for 20-methyl-5α-pregnan-15-one (XXXVIII). A variation in molecular amplitude of ±30° for 5α,14β-ergostan-15-one (XLI), relative to 20-methyl-5α,14β-pregnan-15-one (XXXIX, −94°), gives a calculated difference of ∓2% for the relative stability of the C-14 epimers present in the equilibrium mixture. Variation in the molecular amplitude greater than ±30° for 5α,14β-ergostan-15-one (XLI) would seem unlikely based upon the variation in molecular amplitude observed for the other 5α,14β-15-keto steroids. The similarity in relative stability between 20-methyl-5α-pregnan-15-one (XXXVIII) and that approximated for 5α-ergostan-15-one (XL) is also supported by the similarity of the relative color intensity of the spots observed in qualitative thin layer chromatographic analyses of the equilibrium mixture from XL and XXXVIII.

The ability to assign the correct stereochemistry at C-14 was essential to our study of the epimerization of 15-keto steroids. The stereochemistry at C-14 controls the Cotton effect of 15-keto steroids since 14β-15-ketones exhibit a negative ORD Cotton effect and 14α-15-keto steroids a positive dispersion curve.[33] Such observed differences[6,19] in the Cotton effects of 15-keto steroids have permitted assignment of correct stereochemistry at C-14 in all of the saturated 15-keto steroids prepared in this study. Furthermore, the Cotton effects observed for the 14α and 14β epimers of 15-keto steroids are in complete agreement with the

(31) 5α,14β-Ergostan-15-one (XLI) was not isolated (see Discussion).

(32) For a definition of molecular amplitude see C. Djerassi and W. Klyne, *J. Chem. Soc.*, 4929 (1962).

(33) 14α- and 14β-bromo-5α-androstan-15-one are exceptions to this statement since the 14β-bromo-15-ketone gives a positive Cotton effect and the 14α-bromo-15-ketone a negative Cotton effect. This is however what would be predicted based upon the conclusions reached from the axial halo ketone rule. For further details see C. Djerassi, J. Fajkos, and A. R. Van Horn, *Steroids*, 6, 239 (1965).



17β-alkyl-5α-androstan-15-one 17β-alkyl-5α,14β-androstan-15-one

Figure 2.

sign predicted from consideration of the octant rule[34] to cyclopentanones.[35]

The optical rotatory dispersion curves (Figure 1) obtained for the C-14 epimeric Δ^{16}-15-ketones are interesting and deserve brief mention. The fact that the ORD Cotton effect of α,β-unsaturated keto chromophores are extremely sensitive to conformational changes occurring within the ring containing the chromophore or in an adjacent ring[36] is nicely illustrated by the positive Cotton effects observed for the Δ^{16}-5α,14β-15-ketones XXVII and XXX and the negative Cotton effects observed for the Δ^{16}-5α-15-ketones XXVIII, XXIX, and XXXI. The rotatory dispersion curves for Δ^{16}-5α,14β-androsten-15-one (XXVII) and Δ^{16}-17-methyl-5α,14β-androsten-15-one (XXX) are very reminiscent of the dispersion curve reported[37] for Δ^{15}-5α,14β-androsten-3β-ol-17-one; Δ^{15}-5α-androsten-3β-ol-17-one[37] and the various Δ^{16}-5α-15-ketones XXVIII, XXIX, and XXXI also have similar rotatory dispersion curves. In an important paper by Klyne,[38] dealing with molecular rotation at the D line, it was pointed out that 17-keto and 15-keto steroids with a 14α configuration are of the same enantiomeric type—a concept which was subsequently shown by Djerassi and co-workers[6] to be fundamental to the use of optical rotatory dispersion for assigning absolute configuration. Δ^{16}-5α,14β-Androsten-15-one (XXVII) and Δ^{15}-5α,14β-androsten-3β-ol-17-one and their corresponding C-14 epimers are apparently examples of such enantiomeric terminal rings, but this is purely a *post facto* conclusion, based on the observed ORD curves, and could not have been predicted *a priori* as noted elsewhere.[36a]

Stereochemical Conclusions

In the absence of intramolecular forces owing to hydrogen bonding or electrostatic effects—factors which are absent in the steroidal hydrindan-15-ones presently under discussion—the most stable conformation of a molecule is the one in which nonbonded repulsive interactions are at a minimum. The only difference between 17β-alkyl-5α-androstan-15-one and 5α-androstan-15-one (XXXII) is the presence of a C-17 alkyl substituent. Thus for 17β-alkyl-5α,14ξ-androstan-15-ones, the most stable conformation is the one in which nonbonded interactions owing to the 17β-alkyl group are at a minimum. The steric factors contributing to the conformational stability of the 14α and 14β epimers of 15-ketoandrostane XXXII and XXXIII are essentially all present in the 17β-alkyl-5α,14ξ-androstan-15-ones (XXXIV–XLI); consequently it is not necessary to calculate the nonbonded interactions responsible for the observed preference (85–87%, see Table II) of the *cis* epimer XXXIII over the *trans* epimer XXXII in the C-17 unsubstituted 5α-androstan-15-one.

Steric interaction between vicinal groups has been shown to be an important factor in determining conformer distribution especially in the absence of dipole–dipole repulsive forces and hydrogen bonding. The Newman projection formulas for the C-14 epimeric 17β-alkyl-5α-androstan-15-ones as viewed from C-17 toward C-13 are given in Figure 2. Examination of Dreiding models[21] of the steroidal hydrindan-15-ones reveals that a *cis* C/D ring juncture forces the 17β-alkyl group to be very nearly eclipsed with the C-18 angular methyl group. This interaction is somewhat relieved in the *trans* epimer.[39]

The results described herein demonstrate unambiguously that as the effective size of the alkyl group in 17β-alkyl-5α,14β-androstan-15-ones increases, the steric factors determining the relative stability of 17β-alkyl-15-keto steroids in base-catalyzed epimerization favor ii over i (see Figure 2). Simply stated, the conformer with the C-17 alkyl group more nearly eclipsed with the C-18 angular methyl is destabilized.

The energetically important vicinal eclipsing effect between a C-18 angular methyl and a C-17 substituent occurs only if the C-17 substituent is of the β configuration since an α configuration moves the substituent out of the immediate vicinity of the C-18 angular methyl group thereby preventing steric interaction. Therefore, the absence of a 17β substituent in 17α-methyl-5α,14β-androstan-15-one (XLV) leads to the prediction of an equilibrium value close to that obtained (see Table II) for the unsubstituted parent 5α-androstan-15-one (85% 14β). In point of fact, the 14β epimer is even more favored (>94%, see Table II) during base-catalyzed epimerization of 17α-methyl-5α,14β-androstan-15-one (XLV).[40] This is probably due, at least in part, to a 1,3-pseudo-diaxial steric interaction between the 17α-methyl group and the 14α-hydrogen atom.

(34) W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Am. Chem. Soc.*, 83, 4013 (1961).

(35) W. Klyne, *Bull. Soc. Chim. France*, 1396 (1960); W. Klyne, *Tetrahedron*, 13, 29 (1961).

(36) (a) C. Djerassi and J. E. Gurst, *J. Am. Chem. Soc.*, 86, 1755 (1964); (b) P. Crabbé, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1965, Chapter 5.

(37) F. Sondheimer, S. Burstein, and R. Mechoulam, *J. Am. Chem. Soc.*, 82, 3209 (1960); see also ref 19d, p 70, and 36b, p 215.

(38) W. Klyne, *J. Chem. Soc.*, 2916 (1952).

(39) F. V. Brutcher, Jr., and E. J. Leopold, *J. Am. Chem. Soc.*, 88, 3156 (1966), examined the X-ray data of several steroids, including two C/D *trans* fused cholestane derivatives in which $\theta_{13,17}$ ranged from 45° 31′ to 39° 3′. This shows that the C-18–C-20 interaction is of a *gauche* butane type, which is even tighter than that (θ = 60°) found normally in butane. It is not obvious, however, to what extent these data are applicable to steroids possessing a keto function at C-15. A referee has pointed out that no mention has been made of "a conceivably determining nonbonded interaction" between the 14β-hydrogen atom and the 17β-alkyl group in C/D *cis* 15-keto steroids. We consider it unlikely that such an interaction can be solely responsible for the great difference observed in the 17β-methyl and 17β-isopropyl compounds.

(40) Base-catalyzed equilibration of 17α-methyl-5α,14β-androstan-15-one (XLV), prepared by catalytic as well as chemical reduction of Δ^{16}-17-methyl-5α,14β-androsten-15-one (XXX), gave an equilibrium mixture which showed very little difference in the molecular amplitude of its ORD curve in comparison with the rotatory dispersion curve of pure 17α-methyl-5α,14β-androstan-15-one (XLV); in fact only the 14β epimer could be detected on thin-layer chromatographic analysis. It was therefore estimated that the equilibrium mixture contains more than 94% of the 14β epimer XLV under the conditions employed for epimerization.

The equilibrium value (see Table II) calculated for 5α-ergostan-15-one (XL) shows that increments in the length of the C-17 alkyl side chain starting from the C-22 carbon atom result in an equilibrium value (see Table II) very close to that determined for 20-methyl-5α-pregnan-15-one (XXXVIII). Apparently, alkyl side-chain substituents further removed than the C-21 and C-22 carbon atoms are too far away to cause any serious interaction with the C-18 angular methyl group. The relative stability observed for 3β-acetoxy-15-keto-5α-methyletiocholanate (87% 14β[4a]) emphasizes the importance of the nature of the C-17 substituent and its interaction with the adjacent C-18 angular methyl group. The "A" values[41] for methyl *vs.* methoxycarbonyl constitute evidence for the smaller effective size of the methoxycarbonyl group. In fact, the methoxycarbonyl substituent does not exert an energetically important eclipsing effect with the C-18 angular methyl group.

The actual energy differences ($\Delta G_{65}°$) responsible for the variation in equilibrium composition of the various 17β-alkyl-15-ketone pairs are very small. For the unsubstituted parent XXXII and XXXIII, this difference amounts to *ca.* +1.4 kcal/mole in favor of the 14β epimer XXXIII while in the methyl (XXXV), ethyl (XXXVII), and isopropyl (XXXIX) compounds the respective energy differences are +0.245, −0.244, and −0.89 kcal/mole.

Experimental Section[42]

Δ[16]-5α-Androsten-15-one (XXVIII). A sample, mp 75–77°, prepared by the previously[4g] described method exhibited the following ORD (Figure 1) in dioxane (*c* 0.077): $[\Phi]_{589}$ −93°, $[\Phi]_{376}$ −1085°, $[\Phi]_{355}$ 0°, $[\Phi]_{310}$ +1595°, $[\Phi]_{300}$ +1705°, $[\Phi]_{290}$ +1770°, $[\Phi]_{280}$ +1955°.

15β-Benzyloxy-5α-androstan-17-one (XI). To a solution of 1.00 g of Δ[15]-5α-androsten-17-one (VII)[4g] in 31 cc of distilled benzyl alcohol was added 0.80 g of powdered potassium hydroxide, and the resulting mixture was stirred under an atmosphere of nitrogen at room temperature for 5 hr. Addition of ethyl acetate resulted in the precipitation of a salt which was filtered. Concentration of the filtrate under reduced pressure followed by steam distillation of the concentrate removed unreacted benzyl alcohol. The aqueous residue, worked up in the usual manner,[42] afforded 1.340 g of dark brown oil. Chromatography on 40 g of neutral alumina (activity III) starting with hexane and proceeding to 15% benzene in hexane provided, after recrystallization from hexane, 647 mg (48%) of chromatographically (tlc, benzene developer) pure ketone XI, mp 114.5–115.5°; $[\alpha]^{27}D$ +4.5° (*c* 1.34); λ_{max}^{Nujol} 3.27 w and 3.31 vw (aromatic CH), 5.78 (C=O), and 13.52 and 14.44 μ (unsubstituted phenyl ring).

Anal. Calcd for $C_{26}H_{36}O_2$: C, 82.06; H, 9.54. Found: C, 81.93; H, 9.59.

5α-Androstan-15β-ol-17-one (XII). A solution of 1.00 g of 15α-benzyloxy-5α-androstan-17-one (XI) in 20 cc of acetic acid was hydrogenated overnight at room temperature and atmospheric pressure in the presence of 450 mg of 10% palladium–charcoal catalyst. The catalyst was separated by filtration and washed with ether. The filtrate was poured into water and extracted several times with ether. The combined ethereal extracts were washed successively with water, 10% sodium bicarbonate solution, and then with water. Evaporation of the dried solution under reduced pressure followed by recrystallization from hexane–benzene gave 530 mg of the pure 15β-hydroxy-17-ketone XII, mp 172.5–173.5°; $[\alpha]^{28}D$ +60° (*c* 1.80); λ_{max}^{Nujol} 2.91 and 5.81 μ; ORD in methanol (*c* 0.125): $[\Phi]_{589}$ +139°, $[\Phi]_{315}$ +6616°, $[\Phi]_{277}$ −6616°.

Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.66; H, 10.46.

5α-Androstane-15β,17β-diol (XIX). a. By Lithium Aluminum Hydride Reduction of 15β,16β-Oxido-5α-androstan-17-one (XLII). Reduction was effected by heating under reflux for 3 hr 822 mg of epoxy ketone XLII in 40 cc of dry ether and 500 mg of lithium aluminum hydride and then stirring at room temperature overnight. The mixture was decomposed with ethyl acetate followed by saturated sodium sulfate solution and anhydrous sodium sulfate. Work-up in the usual manner provided 799 mg of crystalline diol XIX. Chromatography on 100 g of neutral alumina (activity III) using 50% ether–benzene as eluent followed by recrystallization from chloroform–hexane provided 660 mg of 5α-androstane-15β,17β-diol (XIX), mp 148–149°; $[\alpha]^{27}D$ −21.5° (*c* 1.03); λ_{max}^{Nujol} 3.01 (broad) μ.

Anal. Calcd for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 77.81; H, 10.97.

b. By Lithium Aluminum Hydride Reduction of 5α-Androstan-15β-ol-17-one (XII). 15β-Hydroxy-17-ketone XII was reduced in the same way as the above epoxy ketone XLII. Column chromatography on neutral alumina (activity III) and recrystallization from chloroform–hexane gave a diol (82%), indistinguishable by melting point, mixture melting point, infrared, and thin layer chromatography comparison, from that described above (part a).

Oxidation of 5α-androstane-15β,17β-diol (XIX) by the Jones' procedure[14] afforded **5α-androstane-15,17-dione (XXVI)** in an almost quantitative yield. Recrystallization from chloroform–hexane provided crystals, mp 189–190°; $[\alpha]^{27}D$ −11.5° (*c* 2.10); ORD in methanol (*c* 0.093): $[\Phi]_{589}$ 0°, $[\Phi]_{321}$ +2015°, $[\Phi]_{312}$ +1767° (shoulder), $[\Phi]_{272}$ −1984°; $\lambda_{max}^{ethanol}$ 253 mμ (log ε 3.083) shifted to 277 mμ (log ε 3.898) in ethanolic alkali.

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.03; H, 9.65.

5α-Androstane-15β,17β-diol 17-Acetate (XX). A solution of 1.17 g of diol XIX in 4.8 cc of pyridine and 2.1 cc of acetic anhydride was set aside at room temperature for 13 hr and worked up in the usual manner to give 1.42 g of colorless oil. Thin layer chromatography (10% ether in benzene as developer) demonstrated the presence of monoacetate XX (less mobile) and of 5α-androstane-15β,17β-diol 15,17-diacetate (more mobile), but not starting diol XIX. Separation of the two acetates was achieved on 40 g of neutral alumina (activity III) starting with hexane and proceeding to 30% benzene in hexane. Elution provided, first, the less polar **5α-androstane-15β,-17β-diol 15,17-diacetate** (534 mg), which upon recrystallization from methanol afforded crystals with mp 141–142°, $[\alpha]^{27}D$ −32.1° (*c* 1.15); λ_{max}^{Nujol} 5.73, 5.77 (shoulder), 7.91, 7.99, and 8.06 μ.

Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.28; H, 9.57.

After a mixture of 37 mg of monoacetate XX and diacetate, there was eluted 793 mg of chromatographically homogeneous (tlc) monoacetate XX. The analytical sample of **5α-androstane-15β,17β-diol 17-acetate** (XX), after recrystallization from ethanol, exhibited mp 110–111°; $[\alpha]^{25}D$ −20° (*c* 1.51); λ_{max}^{Nujol} 2.89, 5.84, 5.87 (shoulder), and 7.94 μ (acetate C–O stretch).

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.18; H, 10.17.

(41) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," John Wiley and Sons, Inc., New York, N. Y., 1965, p 44; *cf.* also ref 7a, p 103.

(42) Melting points are uncorrected and were determined on a Kofler block. Optical rotations were measured in chloroform and ultraviolet absorption spectra in 95% ethanol solution with a Zeiss Model 50-370 polarimeter and a Cary Applied Physics Model 14 spectrophotometer, respectively. Unless otherwise noted, the infrared spectra were obtained with a Perkin-Elmer Model 237 B grating infrared spectrophotometer. We gratefully acknowledge the help of Mrs. R. Records who recorded the optical rotatory dispersion curves with a Durrum-JASCO Model ORD-5 spectropolarimeter. Nmr results are due to Dr. L. J. Durham and were recorded with Varian 60 or 100 Mc spectrophotometers, employing deuteriochloroform with tetramethylsilane as internal standard (δ = 0.00 ppm). The mass spectra were determined by Dr. A. M. Duffield and Mr. John Smith with a CEC mass spectrometer No. 21-103C using an all-glass inlet system heated to 200° (isatron temperature 270°) with an ionization energy of 70 ev and the ionizing current at 50 μa. Analytical thin-layer chromatoplates with a thickness of 0.25 mm of silica gel H (E. Merck A.G., Darmstadt) were used and the spots were detected by spraying with a 2% solution of ceric sulfate in 2 *N* sulfuric acid followed by heating for optimum development of the colored spots. Preparative thin-layer chromatoplates had a thickness of 0.50 mm of silica gel HF_{254} (E. Merck A.G., Darmstadt) and the bands were detected either visually or by viewing under ultraviolet light. We are indebted to Messrs. E. Meier and J. Consul for the microanalyses.

The phrase "in the usual manner" may be taken to mean the following procedure. The reaction mixture was diluted with water and extracted with three portions of ether. The combined ethereal extracts were washed with 5% hydrochloric acid solution and water, then with 5% sodium bicarbonate solution, and again with water until neutral. The washed ethereal extract was then dried over anhydrous magnesium sulfate, filtered through a cotton plug, and finally evaporated under reduced pressure using a rotary evaporator.

The fractions containing the diacetate were quantitatively converted to the starting diol XIX by lithium aluminum hydride reduction in ether solution (see preparation of XIX).

5α-Androstan-17β-ol-15-one 17-Acetate (XXV). 5α-Androstane-15β,17β-diol 17-acetate (XX, 328 mg) in 11 cc of pure acetone was oxidized in the usual way with 8 *N* chromic acid reagent[14] at 0°. This gave 325 mg (99%) of chromatographically pure keto acetate XXV. Recrystallization from methanol provided an analytical sample exhibiting mp 109–112°; $[\alpha]^{27}D$ +47° (*c* 1.04); λ_{max}^{Nujol} 5.73, 5.77 (shoulder), and 8.11 μ; ORD in methanol (*c* 0.225): $[\Phi]_{589}$ +99°, $[\Phi]_{300}$ +3320°, $[\Phi]_{274}$ −2891°.

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.89; H, 9.66.

Preparation and Hydrogenation of Δ[16]-5α,14β-Androsten-15-one (XXVII). A solution of 340 mg of the above keto acetate XXV in 30 cc of acetic acid was heated under reflux in an atmosphere of nitrogen for 14 hr. The slightly yellow acetic acid solution was cooled, poured into water, and extracted with three portions of ether. The combined ethereal extracts were washed with water, 10% sodium bicarbonate solution, and then with water. Drying over anhydrous magnesium sulfate and evaporation under reduced pressure afforded 280 mg of pale yellow crystalline material. Preparative tlc on four 20 × 20 cm plates using 10% ether in benzene as developing solvent gave 242 mg (87%) of chromatographically pure **Δ[16]-5α,14β-androsten-15-one** (XXVII). Recrystallization from hexane provided an analytical specimen exhibiting mp 79–80.5°; $[\alpha]^{24}D$ +120° (*c* 1.83); $\lambda_{max}^{ethanol}$ 222.5 mμ (log ε 3.87); λ_{max}^{Nujol} 5.86 and 6.26 μ; ORD (Figure 1) in dioxane (*c* 0.122): $[\Phi]_{589}$ +267°, $[\Phi]_{376}$ +2095°, $[\Phi]_{367}$ +1783°, $[\Phi]_{360}$ +2051°, $[\Phi]_{348}$ +981°, $[\Phi]_{345}$ +1025°, $[\Phi]_{330}$ +178°, $[\Phi]_{328}$ +200°, $[\Phi]_{323}$ 0°, $[\Phi]_{320}$ −45°, $[\Phi]_{318}$ 0°, $[\Phi]_{315}$ +89°, $[\Phi]_{310}$ +156°, $[\Phi]_{300}$ +446°.

Anal. Calcd for $C_{19}H_{28}O$: C, 83.77; H, 10.36. Found: C, 84.54; H, 10.15.

Catalytic reduction of freshly prepared α,β-unsaturated ketone XXVII in ethyl acetate solution with 10% palladized charcoal catalyst led to **5α,14β-androstan-15-one** (XXXIII) in 96% yield which was indistinguishable by melting point, mixture melting point, infrared, ORD, nmr (C-18 methyl 1.15, and C-19 methyl 0.73 ppm; calcd[43] 1.18 (C-18) and 0.725 (C-19) ppm), and thin-layer chromatographic comparison from that prepared by base-catalyzed epimerization of 5α-androstan-15-one (XXXII).[4g]

15β-Benzyloxy-17α-methyl-5α-androstan-17β-ol (XIII). A solution of 400 mg of 15β-benzyloxy-5α-androstan-17-one (XI) in 5 cc of dry ether was added over a period of 10 min to the Grignard reagent prepared from 428 mg of magnesium and 2.51 g of methyl iodide in 5 cc of dry ether solution. The mixture was heated under reflux for 10 hr, left overnight at room temperature, and decomposed with ice-cold 5% hydrochloric acid solution. The reaction mixture was extracted with three portions of ether, and the combined ethereal solutions were washed successively with 5% hydrochloric acid solution, 5% sodium thiosulfate solution, water, 5% sodium bicarbonate solution, and finally with water until neutral. Drying over anhydrous magnesium sulfate and evaporation under reduced pressure afforded 422 mg of colorless oil. A thin-layer chromatogram of the oily residue developed in ether exhibited one major spot (R_f 0.6) and one minor spot with an R_f value (0.7) identical with that of the starting material XI, and also two very minor spots (R_f 0.4 and 0.2). Careful gradient-elution chromatography using hexane and benzene on 45 g of neutral alumina (activity II) provided two compounds which exhibited identical R_f values on a thin-layer chromatogram developed in ether (R_f 0.6) or in 5 or 10% benzene in ether. First, there was eluted 32 mg (15%) of crystalline **Δ[15]-17α-methyl-5α-androsten-17β-ol** (VIII), which gave the following constants after recrystallization from methanol: mp 155.5–156.5°; $[\alpha]^{26}D$ −100° (*c* 0.33); λ_{max}^{Nujol} 2.88 (OH) and 3.29, 13.46, 13.99, and 14.31 μ (olefinic absorption).

Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18; mol wt, 288. Found: C, 83.21; H, 11.04; mol wt (mass spectroscopy), 288.

The structure of the allylic alcohol VIII was confirmed by hydrogenation in ethyl acetate over 10% palladium–charcoal catalyst, giving, after removal of catalyst and evaporation, 17α-methyl-5α-androstan-17β-ol (XVII) identical (melting point, mixture melting point, infrared, and tlc mobility) with authentic material prepared[9] by addition of methylmagnesium iodide to 5α-androstan-17-one (III).

Shortly after elution of the allylic alcohol VIII, 271 mg (65%) of oily 15β-benzyloxy-17α-methyl-5α-androstan-17β-ol (XIII) was obtained with $[\alpha]^{25}D$ −64.5° (*c* 0.76) and λ_{max}^{film} 2.94 (OH), 3.25, 3.28, 3.32, 6.25, 6.67, 13.21, 13.64, and 14.39 μ (phenyl absorption). This material could not be crystallized but its structure and purity were assured since catalytic hydrogenolysis provided entirely 17α-methyl-5α-androstane-15β,17β-diol (XIV) and not any 17α-methyl-5α-androstan-17β-ol (XVII) which would be formed if any allylic alcohol VIII were contaminating XIII.

Three additional Grignard additions to 15β-benzyloxy-5α-androstan-17-one (XI) in a manner identical with that described above provided the saturated alcohol XIII and allylic alcohol VIII in yields varying from 5.7 to 63.6% and 17.4 to 15.4%, respectively.

17α-Methyl-5α-androstane-15β,17β-diol (XIV). Catalytic hydrogenolysis of 15β-benzyloxy-17α-methyl-5α-androstan-17β-ol (XIII) was carried out in a manner directly analogous to that previously described in the preparation of 5α-androstan-15β-ol-17-one (XII) and provided in 93% yield the desired diol XIV, which proved to be homogeneous on thin layer chromatography. Recrystallization from methanol gave analytically pure material, mp 172.5–173°; $[\alpha]^{33}D$ −39° (*c* 0.62); λ_{max}^{Nujol} 2.94 μ; nmr signals at 1.12 and 0.84 ppm (calcd[43] C-18 methyl 1.11 and C-19 methyl 0.83 ppm).

Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.38; H, 11.18. Found: C, 78.52; H, 10.92.

17α-Methyl-5α-androstan-17β-ol-15-one (XXI). To a stirred solution of 96 mg of the above diol XIV in 15 cc of pure acetone at 0° was added 8 *N* chromic acid reagent[14] until the solution had a faint orange tinge. After an additional 3 min of stirring, methanol was added and the resulting green solution was worked up in the usual manner to yield 94 mg of chromatographically homogeneous 17β-hydroxy-15-ketone XXI. Recrystallization from ethanol provided fine needles exhibiting mp 177.5–178.5°; $[\alpha]^{27}D$ +12° (*c* 0.89); λ_{max}^{Nujol} 2.83, 3.02 (dimeric and polymeric H bands, respectively), and 5.76 μ; ORD in methanol (*c* 0.10): $[\Phi]_{589}$ 0°, $[\Phi]_{315}$ +4875°, $[\Phi]_{275}$ −6550°.

Anal. Calcd for $C_{20}H_{32}O_2$ + $0.75C_2H_5OH$: C, 76.17; H, 10.85. Found: C, 76.16; H, 10.61.

Δ[16]-17-Methyl-5α,14β-androsten-15-one (XXX). A solution of 42 mg of 17α-methyl-5α-androstan-17β-ol-15-one (XXI) in 11 cc of acetic acid was heated under reflux in an atmosphere of nitrogen for 14 hr and worked up as described for XXVII to give 40 mg of crystalline residue. Chromatography on 10 g of silica gel (Merck, <0.08 mm) using 20% ether in hexane afforded 34.6 mg (88%) of the α,β-unsaturated ketone XXX. The analytical sample after recrystallization from methanol exhibited mp 97.5–99.5°; $[\alpha]^{25}D$ +124° (*c* 0.36); λ_{max}^{Nujol} 5.89 and 6.16 μ; $\lambda_{max}^{ethanol}$ 229 mμ (log ε 4.039); ORD (Figure 1) in dioxane (*c* 0.10): $[\Phi]_{365}$ +2280°, $[\Phi]_{346}$ +1685°, $[\Phi]_{330}$ +1900°, $[\Phi]_{339}$ +698°, $[\Phi]_{334}$ +815°, $[\Phi]_{325}$ +217°, $[\Phi]_{320}$ +488°, $[\Phi]_{312}$ +217°, $[\Phi]_{305}$ +434°, $[\Phi]_{300}$ +488°, $[\Phi]_{285}$ +1465°, $[\Phi]_{270}$ +1790°, $[\Phi]_{260}$ +2005°.

Anal. Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.95; H, 10.34.

17α-Methyl-5α,14β-androstan-15-one (XLV). a. By Catalytic Hydrogenation of Δ[16]-17-Methyl-5α,14β-androsten-15-one (XXX). Catalytic hydrogenation of the freshly prepared α,β-unsaturated ketone XXX in ethyl acetate solution with 10% palladized charcoal catalyst provided 17α-methyl-5α,14β-androstan-15-one (XLV) in 95% yield. Two recrystallizations from methanol furnished the analytical specimen, mp 102.5–103.5°; $[\alpha]^{24}D$ −30° (*c* 0.79); λ_{max}^{Nujol} 5.74 μ; nmr ($CDCl_3$) showed methyl signals at 1.1 (C-18), 0.73 (C-19), and 0.96 (C-17, doublet, *J* = 6 cps) ppm; nmr (benzene) showed methyl signals at 0.85 (C-18), 0.71 (C-19), and 0.70 (C-17, doublet, *J* = 6 cps) ppm. The optical rotatory dispersion properties are summarized in Table II.

Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18; mol wt, 288. Found: C, 83.39; H, 11.12; mol wt (mass spectroscopy), 288.

Epimerization of 17α-methyl-5α,14β-androstan-15-one (XLV) was effected by heating a 5-mg sample under reflux for 2.5 hr in a solution of 5 cc of 2.4% methanolic potassium hydroxide solution and 0.7 cc of water. Dilution with water, extraction with ether, and washing with water afforded 4.9 mg of crystalline material. Optical rotatory dispersion measurements on the total crude residue exhibited little difference in its molecular amplitude[32] (Δa = 9) when compared with the pure 14β epimer XLV (see Table II). The equilibrium mixture showed only one spot on a thin-layer chromatogram corresponding in R_f value to that of the 14β epimer XLV. A difference in the ORD molecular amplitude[32] between 80 and 160° for the unknown 17α-methyl-5α-androstan-15-one (XLIV) only corresponds to a variation of 94 to 97%, respectively, for the amount of 14β epimer XLV present in the equilibrium mixture.

(43) The effect of substituents on the chemical shift of the C-18 and C-19 tertiary methyl groups at 60 Mc were calculated using the tables given in chapter 2 of ref 25.

It can therefore be estimated that the total crude residue contains more than 94% of the 14β epimer XLV under the conditions employed for epimerization.

b. By Birch Reduction of Δ^{16}-17-Methyl-5α,14β-androsten-15-one (XXX). A solution of 10 mg of α,β-unsaturated ketone XXX in 1.5 cc of dry ether and 1.5 cc of dry dioxane was added dropwise to 9 cc of refluxing liquid ammonia containing 12 mg of lithium. After stirring for 15 min, ammonium chloride was carefully added until the blue color was discharged, and the ammonia was then allowed to evaporate. The product (9.9 mg) was isolated in the usual way and since infrared and tlc examination demonstrated the presence of hydroxyl-containing material, oxidation by the conventional Jones' procedure[14] was effected to regenerate the saturated ketone XLV. Column chromatography on 5 g of silica gel (Merck, <0.08 mm) using 5% benzene in hexane as eluent gave material, mp 102–104° (material melting at 105.5–106.5° was encountered once) after two recrystallizations from methanol; its melting point was not depressed (102–104°) on admixture with the catalytic reduction product (102.5–103.5°) described above (part a). The R_f values (tlc, benzene as developer) of 17α-methyl-5α,14β-androstan-15-one (XLV), obtained by catalytic and chemical reduction of the corresponding α,β-unsaturated ketone XXX, were identical. The optical rotatory dispersion properties of ketone XLV and its base-catalyzed equilibrium mixture are collected in Table II.

$\Delta^{17(20)}$- (XXII) and Δ^{16}- (XXIX) 17-Methyl-5α-androsten-15-one. Thionyl chloride (0.3 cc) was added to 53 mg of 17α-methyl-5α-androstan-17β-ol-15-one (XXI) in 3 cc of dry pyridine, and the solution was stirred at ice bath temperature for 30 min, whereupon it was poured onto crushed ice and processed in the usual manner to give 50 mg of oil which crystallized within a few minutes. Thin layer chromatography indicated the absence of starting material XXI and demonstrated that the product was primarily a mixture of two components, β,γ-unsaturated ketone XXII (more mobile) and α,β-unsaturated ketone XXIX (less mobile). Separation of the isomeric olefins was achieved on a column of 7 g of silica gel (Merck, <0.08 mm).

Elution with 10% benzene in hexane afforded 22.6 mg (45%) of **$\Delta^{17(20)}$-17-methyl-5α-androsten-15-one** (XXII), which after recrystallization from hexane exhibited mp 102.5–104°; $[\alpha]^{24}D$ +25° (*c* 0.72); λ_{max}^{Nujol} 5.69, 6.01, 11.19, and 11.30 μ; ORD in methanol (*c* 0.056): $[\Phi]_{589}$ +173°, $[\Phi]_{316}$ +6747°, $[\Phi]_{280}$ −8650°. The nmr spectrum showed methyl signals for C-18 and C-19 of 0.90 and 0.82 ppm, respectively, as well as the presence of a methylene group (multiplet at 4.85 ppm).

Anal. Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.56; H, 10.43.

Finally, elution with 30% benzene in hexane provided 14 mg (28%) of **Δ^{16}-17-methyl-5α-androsten-15-one** (XXIX), which after recrystallization from hexane gave an analytically pure sample, mp 142.5–143.5°; $[\alpha]^{25}D$ +14° (*c* 0.57); λ_{max}^{Nujol} 5.89 and 6.23 μ; $\lambda_{max}^{ethanol}$ 232.5 mμ (log ϵ 3.994); ORD (Figure 1) in dioxane (*c* 0.113): $[\Phi]_{589}$ +74°, $[\Phi]_{370}$ −493°, $[\Phi]_{360}$ 0°, $[\Phi]_{325}$ +1833°, $[\Phi]_{310}$ +1721°.

Anal. Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56; mol wt, 286. Found: C, 83.77; H, 10.27; mol wt (mass spectroscopy), 286.

17β-Methyl-5α-androstan-15-one (XXXIV). a. By Catalytic Hydrogenation of Δ^{16}-17-Methyl-5α-androsten-15-one (XXIX). Δ^{16}-17-Methyl-5α-androsten-15-one (XXIX, 12 mg) was hydrogenated at room temperature and atmospheric pressure over a period of 40 min in 5 cc of ethyl acetate with 135 mg of 10% palladized charcoal catalyst. Filtration of the reaction mixture and evaporation to dryness of the filtrate left 11.5 mg (96%) of crystalline ketone XXXIV which showed one spot on a thin-layer chromatogram. Two recrystallizations from methanol gave thin plates exhibiting mp 133.5–135°; $[\alpha]^{25}D$ +24° (*c* 0.41); λ_{max}^{Nujol} 5.75 μ; nmr methyl signals at 0.65 (C-18), 0.80 (C-19), and 0.97 (C-17, doublet, J = 6 cps) ppm; for optical rotatory dispersion data, see Table II.

Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18; mol wt, 288. Found: C, 83.04; H, 11.00; mol wt (mass spectroscopy), 288.

b. By Catalytic Hydrogenation of $\Delta^{17(20)}$-17-Methyl-5α-androsten-15-one (XXII). Catalytic hydrogenation of 13 mg of β,γ-unsaturated ketone XXII, performed in a manner identical with that described above (part a), provided 13 mg of crystalline residue which on thin-layer chromatography showed the presence of a small amount of material corresponding in R_f value to starting material XXII. Chromatography on 7 g of silica gel (Merck, <0.08 mm) and elution with 10% benzene in hexane provided, after recrystallization from methanol, thin plates, mp 133.5–135.5°, which were identified by mixture melting point, infrared, and thin layer chromatography comparison with the catalytic reduction product XXXIV described above (part a).

Base-Catalyzed Epimerization of 17β-Methyl-5α-androstan-15-one (XXXIV). Isolation of 17β-Methyl-5α,14β-androstan-15-one (XXXV). A mixture of 37 mg of 17β-methyl-5α-androstan-15-one (XXXIV) in 16 cc of 2.5% methanolic potassium hydroxide solution, and 2 cc of water was heated under reflux for 2.5 hr. The solution was poured into water and the product extracted with ether. After washing the latter with water and drying, the solvent was evaporated under reduced pressure and afforded 36 mg of semicrystalline residue containing approximately equal quantities of the 14β (XXXV, R_f 0.41) and 14α (XXXIV, R_f 0.32) epimers as judged by thin layer chromatography (benzene as developer). Preparative chromatography on one silica gel plate (20 × 20 cm) in benzene gave 19.9 mg of 14β epimer XXXV, which exhibited a single spot on a thin-layer chromatogram. The analytical specimen crystallized from methanol as needles, mp 83–85°; λ_{max}^{Nujol} 5.76 μ; nmr ($CDCl_3$) showed methyl signals at 0.75 (C-19), 1.05 (C-18), and 0.99 (C-17, doublet, J = 6 cps) ppm; nmr (benzene) methyl signals at 0.70 (C-19), 0.81 (C-18), and 0.66 (C-17, doublet, J = 6 cps) ppm. The optical rotatory dispersion data are presented in Table II.

Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18; mol wt, 288. Found: C, 83.07; H, 10.97; mol wt (mass spectroscopy), 288.

In order to determine spectropolarimetrically (see Table II) the composition of the equilibrium mixture, 10 mg each of the 14α (XXXIV)[44] and 14β (XXXV) epimers was dissolved in 3.5 cc of methanol containing a few drops of water and 21 mg of sodium and heated under reflux for 2.5 hr. The solution was poured into water and extracted with ether, and the total residue submitted to optical rotatory dispersion measurements. Using the molecular amplitudes from the rotatory dispersion curves of the pure 14α (XXXIV) and 14β (XXXV) ketones it is possible to calculate the composition (see Table II) of the equilibrium mixture. Equilibration of the saturated ketones XXXIV and XXXV normally resulted in a very small amount of extremely polar material located near the origin of a thin-layer chromatogram. In order to determine whether this material would effect the per cent composition of the equilibrium mixture, the crude residue obtained from base-catalyzed epimerization of the 14β epimer XXXV was purified by preparative thin-layer chromatography with benzene as the eluting solvent and the 14α (XXXIV) and 14β (XXXV) ketones isolated together. The rotatory dispersion data are given in Table II and the composition of the equilibrium mixture was found to be identical with that determined from optical rotatory dispersion measurements carried out on nonchromatographed material.

17α-Ethyl-5α-androstane-15β,17β-diol (XVI). A solution of 733 mg of 15β-benzyloxy-5α-androstan-17-one (XI) in 15 cc of dry ether was added dropwide to the Grignard solution prepared from 5.90 g of ethyl iodide and 919 mg of magnesium in 15 cc of dry ether. The reaction mixture was heated under reflux for 13 hr, followed by stirring at room temperature for 3.5 hr, and then poured into ice–ammonium chloride solution. The reaction mixture was worked up in the usual manner to give 775 mg of colorless oil. Thin layer chromatography using 10% ether in benzene showed the presence of material possessing the same R_f value (0.58) as the starting material XI, two very minor components with R_f values of 0.20 and 0.26, and a major component with a R_f value of 0.40. Gradient elution chromatography on 25 g of neutral alumina (activity III) using benzene–ether mixtures provided, in addition to 95 mg of starting material XI, 440 mg of oil, which showed only one spot on thin layer chromatography. Although this material was chromatographically homogeneous, infrared analysis, as well as the results obtained from catalytic hydrogenation described below, and analogy to the reaction between 15β-benzyloxy-5α-androstan-17-one (XI) and methylmagnesium iodide previously described, strongly suggest that this oily material is a mixture of Δ^{16}-17α-ethyl-5α-androsten-17β-ol and 15β-benzyloxy-17α-ethyl-5α-androstan-17β-ol (XV). This mixture (355 mg) was not further separated but subjected directly to catalytic hydrogenolysis (room temperature and atmospheric pressure) in 20 cc of acetic acid solution with 190 mg of 10% palladized charcoal catalyst. The catalyst was collected and the filtrate diluted with water. The aqueous mixture was extracted with ether, and the combined organic layers were washed successively with water, 5% sodium bicarbonate solution, and water. Evaporation of the dried solution afforded 267 mg of semicrystalline residue. Column chromatography on 20 g of neutral alumina

(44) Samples of 17β-methyl-5α-androstan-15-one (XXXIV) obtained by catalytic hydrogenation of Δ^{16}- (XXIX) as well as $\Delta^{17(20)}$- (XXII) 17-methyl-5α-androsten-15-one were both subjected to the epimerization reaction.

(activity III) using 50% benzene–ether gave, first, 38 mg of crystalline 17α-ethyl-5α-androstan-17β-ol (XVIII), which after recrystallization from methanol exhibited mp 102–104°; $[\alpha]^{26}D$ −3.3° (*c* 0.60); λ_{max}^{Nujol} 3.03 (broad) μ [lit.[45] mp 116–117.5° (cor) (recrystallized from hexane); $[\alpha]^{20}D$ −3° ($CHCl_3$)].

Anal. Calcd for $C_{21}H_{36}O$: mol wt, 304. Found: mol wt (mass spectroscopy), 304.

Elution with ether gave 183 mg of **17α-ethyl-5α-androstane-15β,-17β-diol** (XVI) which was homogeneous on a thin-layer chromatogram. Recrystallization from methanol gave an analytical sample, which exhibited mp 144–145°; $[\alpha]^{27}D$ −38° (*c* 2.12); λ_{max}^{Nujol} 2.89 and 2.96 (shoulder) μ.

Anal. Calcd for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32. Found: C, 78.41; H, 11.28.

17α-Ethyl-5α-androstan-17β-ol-15-one (XXIII). The 15β,17β-diol XVI was oxidized in 98% yield by the Jones' procedure[14] at ice-bath temperature to the desired 17β-hydroxy-15-ketone XXIII, which was shown to be homogeneous on thin layer chromatography. The analytical sample, after recrystallization from methanol, melted at 176.5–177.5° and exhibited $[\alpha]^{25}D$ +27.7° (*c* 2.75); λ_{max}^{Nujol} 2.94 and 5.81 μ.

Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 78.95; H, 10.51.

Δ16- (XXXI) and Δ17(20)- (XXIV) 5α-Pregnen-15-one. A solution of 140 mg of 17α-ethyl-5α-androstan-17β-ol-15-one (XXIII) in 9 cc of dry pyridine and 0.9 cc of thionyl chloride was stirred at ice-bath temperature for 40 min and processed in the usual manner to give 118 mg of pale yellow oil, which slowly crystallized upon standing at room temperature. This semicrystalline mixture was separated into two components by thin layer chromatography on two 20 × 10 cm plates using benzene as the eluting solvent. Isolation of the less mobile **Δ16-5α-pregnen-15-one** (XXXI, 16 mg, 12%), followed by recrystallization from hexane, provided material which exhibited the following physical constants: mp 118.5–120°; $[\alpha]^{27}D$ +10° (*c* 0.96); λ_{max}^{Nujol} 5.82 and 6.23 μ; $\lambda_{max}^{ethanol}$ 234 mμ (log ε 3.997); ORD (Figure 1) in dioxane (*c* 0.113): $[\Phi]_{589}$ +26°, $[\Phi]_{380}$ −212°, $[\Phi]_{370}$ −424°, $[\Phi]_{365}$ −266°, $[\Phi]_{340}$ +1325°, $[\Phi]_{335}$ +1396°, $[\Phi]_{330}$ +1435°, $[\Phi]_{325}$ +1409°, $[\Phi]_{320}$ +1299°.

Anal. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73; mol wt, 330. Found: C, 83.61; H, 10.43; mol wt (mass spectroscopy), 300.

The more mobile **Δ17(20)-5α-pregnen-15-one** (XXIV, 84 mg, 63%) was recrystallized from methanol and gave analytically pure material, mp 106.5–108°; $[\alpha]^{27}D$ +30.0° (*c* 2.31); λ_{max}^{Nujol} 5.71, 5.92, and 12.12 μ; ORD in methanol (*c* 0.033): $[\Phi]_{589}$ 0°, $[\Phi]_{312}$ +3780°, $[\Phi]_{273}$ −4511°.

Anal. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73; mol wt, 300. Found: C, 83.56; H, 10.60; mol wt (mass spectroscopy), 300.

5α-Pregnan-15-one (XXXVI). a. By Catalytic Hydrogenation of Δ17(20)-5α-Pregnen-15-one (XXIV). Pure Δ17(20)-5α-pregnen-15-one (XXIV, 70 mg) in 20 cc of ethyl acetate was hydrogenated (45 min) at room temperature and atmospheric pressure with 60 mg of 5% palladium–charcoal catalyst. The reaction mixture was filtered and the filtrate evaporated leaving 66 mg of crystalline ketone XXXVI which showed only one spot on a thin-layer chromatogram. Recrystallization from methanol afforded thin plates exhibiting mp 128.5–130°; $[\alpha]^{27}D$ +54° (*c* 1.64); λ_{max}^{Nujol} 5.72 μ; nmr showed methyl signals at 0.66 and 0.79 ppm (calcd[43] C-18, 0.63 and C-19, 0.79 ppm). The optical rotatory dispersion data are summarized in Table II.

Anal. Calcd for $C_{21}H_{34}O$: C, 83.38; H, 11.33; mol wt, 302. Found: C, 83.65; H, 11.17; mol wt (mass spectroscopy), 302.

b. By Catalytic Hydrogenation of Δ16-5α-Pregnen-15-one (XXXI). Catalytic hydrogenation of 8 mg of the α,β-unsaturated ketone XXXI was achieved in 23 min by using 8 mg of 5% palladized charcoal catalyst and 5 cc of ethyl acetate as described above (part a) and afforded 8 mg of chromatographically homogeneous ketone XXXVI, which after recrystallization from methanol exhibited mp 128–130°, not depressed on admixture with the catalytic reduction product (mp 128.5–130°) described above (part a). The R_f values of 5α-pregnan-15-one (XXXVI), obtained by catalytic hydrogenation of the α,β- (XXXI) and β,γ- (XXIV) unsaturated ketones, were identical.

Base-Catalyzed Epimerization of 5α-Pregnan-15-one (XXXVI). Isolation of 5α,14β-Pregnan-15-one (XXXVII). 5α-Pregnan-15-one (XXXVI, 27 mg) was dissolved in 11 cc of 2.5% methanolic potassium hydroxide solution and 0.9 cc of water and heated under reflux for 2.5 hr. After diluting with water and extracting with ether, the ethereal solution was washed with water until neutral. Evaporation of the dried solution afforded 27 mg of oil which quickly crystallized at room temperature. The semicrystalline residue contained approximately equal quantities of the 14α- (XXXVI, R_f 0.29) and 14β- (XXXVII, R_f 0.40) 15-ketones as judged by thin layer chromatography (30% hexane in benzene as developer). Preparative chromatography on one 20 × 20 cm plate using 30% hexane in benzene as eluting solvent afforded 10 mg (40%) of chromatographically homogeneous 5α,14β-pregnan-15-one- (XXXVII), which crystallized from methanol as needles, mp 105.5–107.5°; $[\alpha]^{27}D$ −15° (*c* 0.82); λ_{max}^{Nujol} 5.75 μ; for optical rotatory dispersion data, see Table II.

Anal. Calcd for $C_{21}H_{34}O$: C, 83.38; H, 11.33; mol wt, 302. Found: C, 83.32; H, 11.20; mol wt (mass spectroscopy), 302.

To determine the equilibrium composition, epimerization of 5α,14α- (XXXVI) and 5α,14β- (XXXVII) pregnan-15-one was effected separately by heating a 10-mg sample under reflux with 3.5 cc of 2.5% methanolic potassium hydroxide solution containing 5 drops of water. The product was extracted with ether and the rotatory dispersion curve determined on the total residue (see Table II).

Δ16-17-Cyano-15β-benzyloxy-5α-androstene (XLVII). A stirred mixture of 1.05 g of 15β-benzyloxy-5α-androstan-17-one (XI) and 6.33 g of potassium cyanide in 50 cc of 95% ethanol was treated over a period of 40 min with 6.73 cc of acetic acid while maintaining the reaction temperature at 10°. The mixture was stirred an additional hour at 10° and then for 7 hr at room temperature. After dilution with water, the precipitated product was collected on a filter, washed with 1 l. of 2% acetic acid solution, and dried at room temperature. The crude C-17 epimeric cyanohydrins XLVI (1.090 g) exhibited mp 63–65° dec; $[\alpha]^{27}D$ −60° (*c* 1.70); $\lambda_{max}^{CHCl_3}$ 2.89, 4.46 (nitrile),[24] and 5.77 μ (parent ketone). The crude cyanohydrin XLVI is very easily converted back to its parent ketone XI; attempts to purify it by column and thin layer chromatography readily effected partial conversion to the parent ketone XI.

A solution of 1.09 g of crude C-17 epimeric cyanohydrin XLVI in 48 cc of dry pyridine and 6 cc of freshly distilled phosphorus oxychloride was heated under reflux in an atmosphere of nitrogen for 7 hr, and then stirred at room temperature for an additional 1.5 hr. The dark brown solution was carefully poured onto ice–5% hydrochloric acid solution and the product isolated in the usual manner. The resulting dark yellow oil (1.038 g) was chromatographed on 30 g of silica gel (Davison, Grade 950, 60–200 mesh) and elution with benzene–hexane mixtures led to 713 mg of **Δ16-17-cyano-15β-benzyloxy-5α-androstene** (XLVII). A portion of this α,β-unsaturated nitrile upon recrystallization from methanol gave colorless crystals with the following constants: mp 89.5–90.5°; $[\alpha]^{27}D$ −142° (*c* 2.95); λ_{max}^{film} 4.50 (α,β-unsaturated nitrile)[24] and 3.24, 3.26, 3.30, 6.25, 6.67, 13.59, and 14.39 μ (phenyl absorption); $\lambda_{max}^{ethanol}$ 210 mμ (log ε 4.208); the nmr spectrum showed signals at 0.84 (C-18 methyl), 1.23 (C-19 methyl), 4.25 (quartet, J = 2.8 and 5.0 cps, C-15 hydrogen), 4.49 (benzylic methylene), 6.58 (slightly perturbed doublet, J = 2.6 cps, C-16 vinyl hydrogen), and 7.29 ppm (phenyl hydrogens). For interpretation of nmr see Discussion section.

Anal. Calcd for $C_{27}H_{35}ON$: C, 83.24; H, 9.06. Found: C, 83.20; H, 9.17.

5α-Pregnan-15β-ol-20-one (L). A solution of 325 mg of Δ16-17-cyano-15β-benzyloxy-5α-androstene (XLVII) in 20 cc of dry ether was added dropwise over a period of 13 min to the Grignard reagent[46] prepared from 1.73 g of magnesium and 4.45 cc of methyl iodide in 10 cc of dry ether. The mixture was heated under reflux for 8 hr and then cooled in an ice–water bath while 21 cc of acetic acid in 15 cc of ether was carefully added to the stirred solution. The ether was distilled from the reaction mixture and 14 cc of water was added; the resulting red solution was heated under reflux for 25 min, diluted with water, and extracted several times with ether. The combined organic phases were successively washed with water, 5% sodium bicarbonate solution, and finally with water until neutral. Drying over anhydrous magnesium sulfate and evaporation under reduced pressure provided 338 mg of thick yellow oil. Chromatography on 35 g of silica gel (Davison, Grade 950, 60–200 mesh) starting with hexane and proceeding to 45% benzene in hexane afforded 143 mg (42%) of chrom-

(45) C. Djerassi, R. Yashin, and G. Rosenkranz, *J. Am. Chem. Soc.*, 72, 5750 (1950).

(46) Using methylmagesium chloride in place of the corresponding iodide resulted in a smaller yield (38%) of Δ16-15β-benzyloxy-5α-pregnen-20-one (XLVIII). It is interesting to note that Butenandt and Schmidt-Thomé (see ref 2 and p 545 of ref 7b) reported that the Grignard reaction was unsatisfactory when methylmagnesium *iodide* was treated with Δ16-17-cyano-5α-androsten-3β-ol 3-acetate.

atographically homogeneous oily **Δ^{16}-15β-benzyloxy-5α-pregnen-20-one** (XLVIII). A sample obtained from a middle cut of its chromatographic fractions exhibited $[\alpha]^{28}D$ −87° (*c* 1.51); λ_{max}^{film} 5.98 and 6.28 μ, and typical phenyl absorption; $\lambda_{max}^{ethanol}$ 235 mμ (log ϵ 3.994). This material could not be crystallized but its structure was confirmed by its infrared and ultraviolet spectra.

Δ^{16}-15β-Benzyloxy-5α-pregnen-20-one (XLVIII, 175 mg) was not further analyzed but directly hydrogenated at room temperature and atmospheric pressure for 25 min in 15 cc of ethyl acetate solution with 145 mg of 10% palladized charcoal catalyst. Filtration and evaporation gave 164 mg of semicrystalline material, which was chromatographed on 45 g of silica gel (Davison, Grade 950, 60–200 mesh). First, elution starting with 10% benzene in hexane and proceeding to 100% benzene furnished 74 mg of oily **15β-benzyloxy-5α-pregnan-20-one** (XLIX) which showed a single spot on a thin-layer chromatogram. A spectrum obtained from a middle cut of its chromatographic fractions exhibited λ_{max}^{film} 5.86 μ and typical phenyl absorption; ORD in methanol (*c* 0.025): $[\Phi]_{589}$ −108°, $[\Phi]_{307}$ +4641°, $[\Phi]_{267}$ −8008°. Continued elution using 50% benzene–ether provided 53.4 mg of chromatographically homogeneous 5α-pregnan-15β-ol-20-one (L). Recrystallization from methanol furnished the analytical specimen, mp 198.5–200.5°; λ_{max}^{Nujol} 2.87 and 5.9 μ; ORD in methanol (*c* 0.102): $[\Phi]_{589}$ 0°, $[\Phi]_{305}$ +8993°, $[\Phi]_{266}$ −11,241°.

Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 78.94; H, 10.51.

Catalytic hydrogenolysis in the usual way (see preparation of XII) of a small amount of 15β-benzyloxy-5α-pregnan-20-one (XLIX) provided semicrystalline material. Thin-layer chromatography (50% benzene–ether as developer) indicated, in addition to 5α-pregnan-15β-ol-20-one (L, R_f 0.47), the presence of material (roughly 20% as judged from color intensity of the spots) which was slightly more mobile (R_f 0.54). Although the latter contaminant was not isolated and characterized, it must be the 17α-epimer of L, namely 17α-ethyl-5α-androstan-15β-ol-20-one, since C-17 epimerization would be expected to occur under the conditions (acetic acid solution) employed for catalytic hydrogenolysis. Preparative thin layer chromatography of this mixture using 50% benzene–ether as eluting solvent afforded crystalline material, which after recrystallization from methanol was indistinguishable by melting point (198.5–201°), mixture melting point, infrared, and thin layer chromatography comparison from the 15β-hydroxy-20-ketone L obtained by catalytic reduction of Δ^{16}-15β-benzyloxy-5α-pregnen-20-one (XLVIII). Qualitative rotatory dispersion analysis of the more mobile material contaminated with a small amount of 5α-pregnan-15β-ol-20-one (L) did show a negative Cotton effect which would be expected[26] for 17α-ethyl-5α-androstan-15β-ol-20-one.

20-Methyl-5α-pregnan-15-one (XXXVIII). Sodium methylsulfinylcarbanion was prepared in the usual way[27] from 162 mg of sodium hydride and 4 cc of dry dimethyl sulfoxide. A solution of 2.60 g of methyltriphenylphosphonium bromide[47] in 5.5 cc of dry dimethyl sulfoxide was then added at room temperature. After stirring the yellow-orange solution for 30 min, a solution of 65 mg of 15β-benzyloxy-5α-pregnan-20-one (XLIX) and 42 mg of 5α-pregnan-15β-ol-20-one (L) in 10 cc of dry tetrahydrofuran was added, followed immediately by the addition of 2 cc of tetrahydrofuran to redissolve any precipitated starting material. The resulting solution was stirred at 59° for 18 hr, and then poured into 1 l. of water. Isolation of the product in the usual manner afforded 244 mg of yellow oil which smelled strongly of sulfide. Chromatography on 18 g of silica gel (Davison, Grade 950, 60–200 mesh) using 30% benzene in hexane provided 47 mg of **Δ^{20}-15β-benzyloxy-20-methyl-5α-pregnene** (LI), which proved to be homogeneous as demonstrated by thin layer chromatography and exhibited λ_{max}^{film} 6.06, 11.26 (terminal methylene), and 6.68, 13.62, 14.38 μ (phenyl absorption). Continued elution proceeding to 80% benzene in hexane provided 38 mg of chromatographically homogeneous **Δ^{20}-20-methyl-5α-pregnen-15β-ol** (LII), mp 96.5–100°; λ_{max}^{Nujol} 2.82 (OH), 6.06, and 11.26 μ (terminal methylene).

Catalytic hydrogenation of a mixture of 47 mg of Δ^{20}-15β-benzyloxy-20-methyl-5α-pregnene (LI) and 34 mg of Δ^{20}-20-methyl-5α-pregnen-15β-ol (LII), first in ethyl acetate and then in acetic acid solution with 10% palladized charcoal catalyst led to 70 mg of slightly yellow oil. Thin layer chromatography using benzene as developer indicated that the product was primarily a mixture of two components with R_f values of 0.3 and 0.8. Separation of the two components was achieved on 18 g of silica gel (Davison, Grade 950, 60–200 mesh). Elution with 30% benzene in hexane provided 9 mg of **20-methyl-5α-pregnane** (LIV),[29] which could be recrystallized from methanol giving thin plates, mp 111–112°; $[\alpha]^{28}D$ +9° (*c* 0.74) (lit.[28] mp 111–112°; $[\alpha]^{25}D$ +8.9°).

Anal. Calcd for $C_{22}H_{38}$: mol wt, 302. Found: mol wt (mass spectroscopy), 302.

The polar component, **20-methyl-5α-pregnan-15β-ol** (LIII, 51 mg), was eluted using 50 to 80% benzene in hexane and was shown to be homogeneous by thin layer chromatography.

The alcohol LIII (47 mg) was not further characterized or purified but directly oxidized by the Jones' procedure[14] to give 45 mg of crystalline material. This product appeared to be homogeneous on thin layer chromatography with benzene but development with 30% hexane in benzene demonstrated the presence of a major (R_f 0.26) and minor (R_f 0.32) component. This mixture (35 mg) was chromatographed on one plate (20 × 20 cm) using 30% hexane in benzene and afforded 6.2 mg of 20-methyl-5α-pregnan-15-one (XXXVIII) contaminated with the less polar impurity and 26.8 mg of pure (tlc, 30% hexane in benzene developer) 20-methyl-5α-pregnan-15-one (XXXVIII), which after recrystallization from methanol exhibited mp 138.5–140.5°; $\lambda_{max}^{CHCl_3}$ 5.72 (C=O) and 7.16 and 7.25 μ[48] (*gem*-dimethyl group);[49] nmr (100 Mc) showed methyl signals at 0.74, 0.78 (angular methyl groups), and 0.88, 1.01 ppm (C-21 and C-22, J = 7 cps, doublets). The optical rotatory dispersion data are summarized in Table II.

Anal. Calcd for $C_{22}H_{36}O$: C, 83.48; H, 11.47; mol wt, 316. Found: C, 83.26; H, 11.38; mol wt (mass spectroscopy), 316.

Base-Catalyzed Epimerization of 20-Methyl-5α-pregnan-15-one (XXXVIII). Isolation of 20-Methyl-5α,14β-pregnan-15-one (XXXIX). Base-catalyzed epimerization in the usual manner (see preparation of XXXVII) of 20 mg of 20-methyl-5α-pregnan-15-one (XXXVIII) afforded 19.5 mg of semicrystalline residue which was judged by thin layer chromatography (30% hexane in benzene as eluting solvent) to consist of approximately 20% 14β- (XXXIX, R_f 0.30) and 80% 14α- (XXXVIII, R_f 0.20) 15-ketones. Careful chromatography on one 20 × 20 cm plate using 30% hexane in benzene as eluting solvent provided 2 mg of chromatographically homogeneous 14β-ketone XXXIX and 16.5 mg of a mixture of the 14α- (XXXVIII) and 14β- (XXXIX) ketones. Four more base-catalyzed epimerizations, each followed by chromatographic separation of the 14β-ketone XXXIX, gave a total of 7.5 mg of 20-methyl-5α,14β-pregnan-15-one (XXXIX) which proved to be chromatographically homogeneous. Recrystallization from a small amount of methanol gave an analytical sample, exhibiting mp 99–101°; λ_{max}^{Nujol} 5.75 μ; for rotatory dispersion constants, see Table II.

Anal. Calcd for $C_{22}H_{36}O$: mol wt, 316. Found: mol wt (mass spectroscopy), 316.

In order to determine spectropolarimetrically the composition of the base-catalyzed equilibrium mixture, 5 mg of the 14β-ketone (XXXIX) and 10 mg of the 14α-ketone (XXXVIII) each were epimerized in methanolic potassium hydroxide solution as previously described (see preparation of XXXVII). The rotatory dispersion data and equilibrium composition are listed in Table II.

5α-Ergostan-15-one (XL). *p*-Toluenesulfonyl chloride (185 mg) was added to a solution of 18 mg of Δ^{22}-5α,14ξ-ergosten-3β-ol-15-one (LVII), prepared by alkaline saponification of LV and LVI,[5,11] in 0.5 cc of dry pyridine. The solution was stirred for 21 hr at room temperature and the product (22 mg) isolated in the usual manner. Preparative chromatography on one 20 × 20 cm plate with 20% ether in benzene as eluting solvent provided 20 mg of tosylate LVIII which was homogeneous on thin layer chromatography and did not show hydroxyl absorption in the infrared.

The tosylate LVIII (20 mg) was reduced (21 hr, room temperature) with 100 mg of lithium aluminum hydride in 8 cc of dry ether. Isolation of 15 mg of alcohol LIX by thin layer chromatography (20% ether in benzene) was followed by hydrogenation with 10% palladium–charcoal catalyst (25 mg) in 5 cc of ethyl acetate overnight and then platinum oxide catalyst (30 mg) in 5 cc of acetic acid for 5 hr. Hydrogenation of the *trans*-disubstituted 22–23 double bond in the side chain of the alcohol LIX was confirmed by the absence of absorption at 10.3 μ[50] in the infrared. Jones' oxidation[14] of the saturated alcohol LX afforded 13 mg of semicrystalline residue. Thin layer chromatography (50% benzene–hexane as developer) demonstrated, in addition to very polar

(47) G. Wittig and U. Schoellkopf, *Org. Syn.*, 40, 66 (1960).

(48) Infrared spectrum recorded on a Perkin-Elmer 421 grating spectrophotometer.

(49) See ref 24b, pp 20 and 130.

(50) See ref 7b, p 172.

material (R_f 0.02), the presence of a major (XL, R_f 0.35) and a minor (XLI, R_f 0.39) spot. Separation of this mixture on one chromatoplate (20 × 20 cm) using 50% benzene–hexane provided: (1) 3 mg of a very polar contaminant, which remained unchanged in its R_f value upon further oxidation with Jones' reagent;[14] (2) 6 mg of chromatographically homogeneous 14α-ketone XL; (3) 2.8 mg of a mixture of the 14α-ketone XL with slightly more mobile material, presumably the 14β-ketone XLI. Recrystallization of 5α-ergostan-15-one (XL) from a small amount of methanol afforded an analytical specimen which exhibited mp 143–144°; λ_{max}^{Nujol} 5.73 μ. The optical rotatory dispersion data are presented in Table II.

Anal. Calcd for $C_{28}H_{48}O$: C, 83.93; H, 12.08; mol wt, 400. Found: C, 83.70; H, 11.81; mol wt (mass spectroscopy), 400.

A 5-mg sample of 5α-ergostan-15-one (XL) was epimerized in 2.5% methanolic potassium hydroxide solution as previously described (see preparation of XXXVII). For the rotatory dispersion data of the crude residue, see Table II.

An insufficient amount of 15-keto steroid coupled with the observed similarity[51] in R_f values between the 14α epimer XL and the 14β epimer XLI precluded isolation of pure 5α,14β-ergostan-15-one (XLI) sufficient for analysis. Base-catalyzed epimerization of 5α,14β-ergostan-15-one (XLI), containing a little of its 14α epimer (XL), gave a semicrystalline residue identical on thin-layer chromatographic comparsion with that obtained from an identical epimerization reaction with pure 5α-ergostan-15-one (XL); this comparison further supports the fact that the more mobile spot (tlc) obtained during equilibration of 5α-ergostan-15-one (XL) in basic medium is, indeed, 5α,14β-ergostan-15-one (XLI).

A difference in molecular amplitude between −64 and −124° for unknown 5α,14β-ergostan-15-one (XLI) only corresponds to a variation of 22–18%, respectively, for the amount of 14β epimer XLI present in the equilibrium mixture. These values for the equilibrium composition are very close to that determined (see Table II) for 20-methyl-5α-pregnan-15-one (XXXVIII). The value (20% 14β) expressed in Table II assumes an amplitude of −95° for the unknown 5α,14β-ergostan-15-one (XLI).

(51) Closer here than for the other C-14 epimeric 17β-alkyl-5α-androstan-15-ones (XXXIV–XXXIX) described in this paper.

The Biosynthesis of Nicotine in *Nicotiana glutinosa* from Carbon-14 Dioxide. Labeling Pattern in the Pyrrolidine Rings[1,2]

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Received September 1, 1966

Abstract: A systematic degradation has been developed which permits isolation of each carbon atom of the pyrrolidine ring of nicotine. The independent synthesis of specifically labeled intermediates obtained during this sequence and their degradation have confirmed the integrity of the entire process. This degradation has been applied to numerous samples of nicotine obtained from short-term $^{14}CO_2$ biosynthesis with *N. glutinosa*, and in each experiment the pyrrolidine ring showed an unsymmetrical labeling pattern, a condition contrary to the accepted symmetrical intermediate hypothesis of pyrrolidine ring formation. Ornithine feeding experiments, from which the symmetrical theory had evolved, were applied to *N. glutinosa* and results were identical with those in other species. These experiments establish a greatly different labeling pattern in the pyrrolidine ring from CO_2 than from preformed precursors such as ornithine.

The formation of the pyrrolidine ring of nicotine in various *Nicotiana* species has been studied extensively since the initial observation that ornithine-2-^{14}C was incorporated only into the pyrrolidine ring, and that carbon-14 was found exclusively, and equally, at positions 2′ and 5′, leading to the proposal of a symmetrical pyrroline intermediate.[4] Glutamic acid was found to act as a precursor of the pyrrolidine ring in a similar manner, but to a lesser extent.[5] These data were interpreted to mean that ornithine is a close or immediate precursor of the pyrrolidine ring of nicotine and, furthermore, that the relationship between glutamate, derived by the tricarboxylic acid cycle, and ornithine is very close *via* the intermediacy of glutamic semialdehyde.[6,7] This interpretation led to development of the generally accepted[8] glutamate symmetrical intermediate hypothesis for pyrrolidine ring biosynthesis.

Support for this hypothesis was obtained by feeding various labeled tricarboxylic acid cycle intermediates to intact plants or root cultures of *Nicotiana*,[7,9] and results were generally consistent with the predicted pyrrolidine ring labeling pattern. Several exceptions to the calculated labeling pattern were noted,[10] the most significant contradiction being found in the pyrrolidine ring derived from short-term administration of acetate-2-^{14}C.[7] Only under longer term, more equilibrating conditions did this precursor provide a labeling pattern in agreement with that predicted by the hypothe-

(1) Preliminary results of this work have been reported: A. A. Liebman, F. Morsingh, and H. Rapoport, *J. Am. Chem. Soc.*, 87, 4399 (1965).

(2) Sponsored in part by the United States Atomic Energy Commission and Grant MH 12797 from the National Institutes of Health, U. S. Public Health Service.

(3) Public Health Service Postdoctoral Research Fellow of the National Institute of General Medical Sciences.

(4) E. Leete, *Chem. Ind.* (London), 537 (1955); L. J. Dewey, R. U. Byerrum, and C. D. Ball, *Biochim. Biophys. Acta*, 18, 141 (1955).

(5) B. L. Lamberts and R. U. Byerrum, *J. Biol. Chem.*, 233, 939 (1958).

(6) E. Leete, *J. Am. Chem. Soc.*, 78, 3520 (1956).

(7) P. L. Wu, T. Griffith, and R. U. Byerrum, *J. Biol. Chem.*, 237, 887 (1962).

(8) (a) A. R. Battersby, *Quart. Rev.* (London), 15, 259 (1961); (b) K. Mothes and H. R. Schutte, *Angew. Chem.*, 75, 265 (1963); (c) E. Ramstad and S. Agurell, *Ann. Rev. Plant Physiol.*, 15, 143 (1964); (d) E. Leete, *Science*, 147, 1000 (1965).

(9) D. R. Christman and R. F. Dawson, *Biochemistry*, 2, 182 (1963).

(10) For a review of the labeling pattern produced in the pyrrolidine ring of nicotine after administration of various carbon-14 precursors see W. L. Alworth, A. A. Liebman, and H. Rapoport, *J. Am. Chem. Soc.*, 86, 3375 (1964).