[FROM THE SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH]

The D-Homoannulation of 17α-Hydroxy-20-ketosteroids[1]

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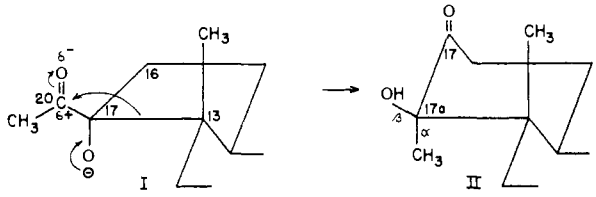
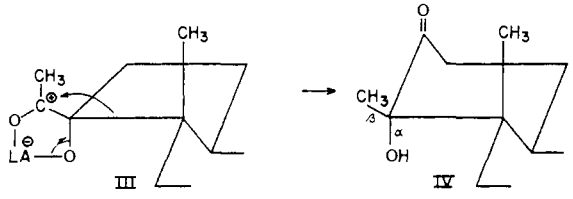
RECEIVED JUNE 20, 1955

The rearrangement of 3β,17α-dihydroxyallopregnane-20-one and 3α,17α-dihydroxypregnane-20-one to D-homosteroids by different methods has been studied. The 17aα- and 17aβ-hydroxy-17-keto-D-homo epimers were obtained with base. The major rearrangement product obtained with Lewis acids or by heating above the m.p. was the heretofore unknown 17α-hydroxy-17a-keto-D-homosteroid. The structure of the 17a-keto derivative was established by chemical and spectrophotometric evidence. The molecular rotation differences of these various isomers is discussed.

The rearrangement of 17α-hydroxy-20-ketosteroids to the D-homosteroids is effected with base as well as with Lewis acids and the stereospecific course of these rearrangements has been clarified by the mechanism proposed by Turner.[3] The base-catalyzed reaction is formulated to proceed by removal of a proton from the 17α-hydroxyl group to yield an intermediate I with the oxygens oriented by electrostatic repulsion. The migration of the C-13,17 bond in this intermediate will result in the formation of the 17aβ-hydroxyl-17aα-methyl-17-keto-D-homosteroid (II).

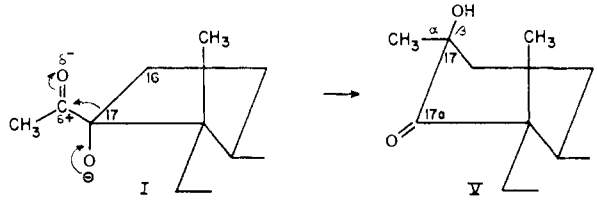


In the rearrangement with Lewis acids (LA), a coordinated cyclic intermediate III with orientation of the oxygen atoms has been indicated.

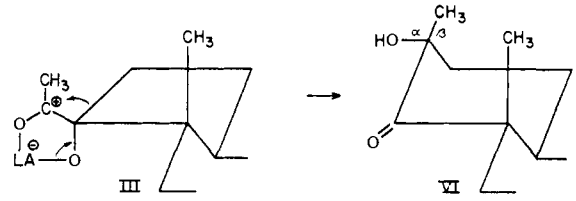


Migration of the C-13,17 bond will then result in formation of 17aα-hydroxy-17αβ-methyl-17-keto-D-homosteroid (IV).

The proposed mechanism depicts the formation of a single product from the base or Lewis acid catalyzed rearrangement of the 17α-hydroxy-20-ketosteroids. Further consideration, however, clearly indicates the possibility of the formation of more than one rearrangement product and this is confirmed by experimental results reported in the literature. In the base-catalyzed reaction, the C-20 carbonyl oxygen atom is not held rigidly in position as indicated in intermediate I so that a small amount of the 17aα-hydroxy-17aβ-methyl-17-keto-D-homosteroid will also be formed. Furthermore although migration of the C-16,17 bond has not been considered and there is no report of a product resulting from this rearrangement, the formation of a 17a-keto-D-homosteroid with the hydroxyl group at C-17 in the β-orientation V is a credible reaction.



In the Lewis acid-catalyzed D-homoannulation, the oxygen atoms in the cyclic intermediate III are held more rigidly in place than with the base-catalyzed reaction so that little or no epimeric 17aβ-hydroxy derivative should be formed. However, here again migration of the C-16,17 bond is possible and should result in the formation of 17a-keto-D-homosteroids with the hydroxyl group at C-17 in the α-orientation (VI).



The present investigation reports the isolation and characterization of the products obtained by the rearrangement of 3α,17α-dihydroxypregnane-20-one and 3β,17α-dihydroxyallopregnane-20-one with base and Lewis acids. The reaction conditions were those employed by other investigators; however, emphasis upon refinements of separation and identification permitted a more critical analysis of the products as a test of the considerations set forth above.

3β-Acetoxy-17α-hydroxyallopregnane-20-one (VIIb) was refluxed with aqueous ethanolic potassium hydroxide for 4 hours. Chromatography on a partition type silica gel column[4] and determination of infrared spectrum of the eluates showed that 3β,17aβ-dihydroxy-17aα-methyl-D-homoandrostane-17-one (VIIIa) was the principal product (71% yield). 3β,17aα-Hydroxy-17aβ-methyl-D-homoandrostane-17-one (IXa) was found to be

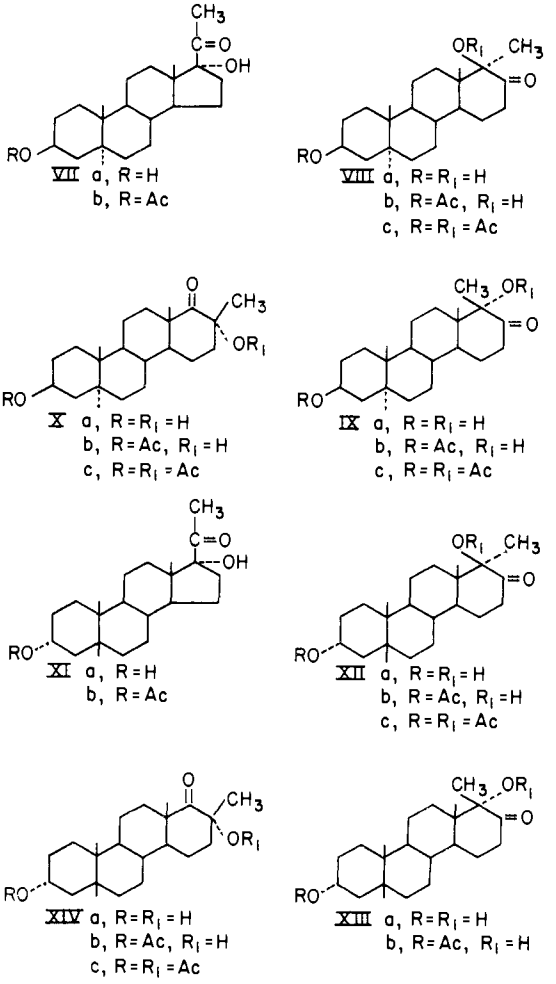
(1) This investigation was supported in part by an institutional research grant from the American Cancer Society, the Lillia Babbitt Hyde Foundation and in part by research grants (C-440 and C-2367) from the National Cancer Institute of the National Institutes of Health, United States Public Health Service. Deuterium oxide was obtained from the Stuart Oxygen Co., San Francisco, Calif., on allocation from the Atomic Energy Commission.

(2) Ninol Laboratories, 17 S. Clinton Street, Chicago, Ill.

(3) R. B. Turner, THIS JOURNAL, **75**, 3484 (1953).

(4) E. R. Katzenellenbogen, K. Dobriner and T. H. Kritchevsky, *J. Biol. Chem.*, **207**, 315 (1954).

present in 13% yield. The physical constants of these compounds agree with those reported in the literature. Only a very small amount of the unchanged starting material was recovered; an unknown product, possibly the 17a-ketone resulting from 16,17-bond migration, was obtained in small yield.



When 3α,17α-dihydroxypregnane-20-one (XIa) was refluxed with base and chromatographed in the same way, infrared spectrometric study of the eluates showed a 67% yield of 3α,17aβ-dihydroxy-17aα-methyl-D-homoetiocholane-17-one (XIIa) and 16% yield of 3α,17aα-dihydroxy-17aβ-methyl-D-homoetiocholane-17-one (XIIIa). The assignment of structure was based on the relative yields of the two isomers by analogy with the results reported above and from other studies,[5] from infrared data and from the optical rotatory results described later. There was no indication by infrared spectrometry of the eluates for the presence of other isomers.

In order to investigate the rearrangement products obtained with Lewis acids, the D-homoannulation of 17α-hydroxy-20-ketosteroids was accomplished with aluminum *t*-butylate. 3β-Acetoxy-17α-hydroxyallopregnane-20-one (VIIb) was refluxed with aluminum *t*-butylate in benzene for 27 hours. The reaction products were reacetylated at room temperature for 3 hours and then separated by chromatography on a partition-type silica gel column. The eluates were examined by infrared spectrometry and the compounds were futher purified by recrystallization. In this reaction, Turner[3] isolated only 3β-acetoxy-17aα-hydroxy-17aβ-methyl-D-homoandrostane-17-one (IXb) in 30% yield of crude product. However, in this present investigation, IXb was obtained in only 15% yield. The major product, an isomer of IX and its 17aβ-hydroxy epimer VIII, was obtained in 52% yield. This third isomer proved to be 3β-acetoxy-17α-hydroxy-17β-methyl-D-homoandrostane-17a-one (Xb), a result of the migration of the C-16,17-bond during D-homoannulation.

Although in early investigation 17α-keto-17-hydroxy-D-homosteroid was formulated as the rearrangement product of 3β,17β-diacetoxyallopregnane-20-one with base,[6a] subsequent work has proved that the product had the 17-keto-17α-hydroxy structure.[6b] The evidence for the 17a-keto structure of Xb will be presented below.

A small amount of a diacetate which had the infrared spectrum of 3β,17α-diacetoxy-17β-methyl-D-homoandrostane-17a-one (Xc) was obtained from the early portion of the chromatogram. This diacetate Xc was also found to be the rearrangement product of 3β-acetoxy-17α-hydroxyallopregnane-20-one with boron trifluoride and acetic acid. The diacetate thus obtained had m.p. 239–240°, $[\alpha]^{24}D$ +64.5° (acetone), and was identical with that obtained by Turner from the same reaction by mixed m.p. determination and infrared spectrometry. The evidence from the present investigation clearly demonstrates the 17a-keto-D-homo structure for this diacetate, although Turner had assigned the structure, 3β,17aα-diacetoxy-17aβ-methyl-D-homoandrostane-17-one (VIIIc).[3] The latter diacetate VIIIc was obtained by Shoppee and Prins[7] by a different route and had m.p. 232–235° and $[\alpha]^{15}D$ 0 (acetone). Although the m.p. of the present diacetate Xc is close to that of VIIIc, the specific rotation, +64.5° (acetone), is very different. Furthermore, the hydrolysis of the diacetate Xc obtained with boron trifluoride gave a diol Xa, m.p. 182–182.5°, $[\alpha]^{33}D$ +32.9° ($CHCl_3$), whereas the m.p. reported for 3β,17aα-dihydroxy-17aβ-methyl-D-homoandrostane-17-one (VIIIa) is 305–306°[6a] and 295–300°.[6b] Acetylation of the diol with acetic anhydride and pyridine at room temperature afforded 3β-acetoxy-17α-hydroxy-17β-methyl-D-homoandrostane-17a-one (Xb) and a small amount of the diacetate Xc. In order to demonstrate that no rearrangement of the diacetate Xc occurred during hydrolysis, the monoacetate Xb was acetylated further by heating with pyridine and acetic anhydride for one hour to give 3β,17α-diacetoxy-17β-methyl-D-homoandrostane-17a-one (Xc) identical in all respects with the diacetate obtained from 3β,-17α-dihydroxyallopregnane-20-one with boron tri-

(5) J. von Euw and T. Reichstein, *Helv. Chim. Acta*, **24**, 879 (1941), obtained 17aβ-hydroxy-17aα-methyl-Δ⁴-D-homoandrostene-3,17-dione in 40% yield and the 17aα-hydroxy epimer in 18% yield from the rearrangement of 17α-hydroxyprogesterone with base.

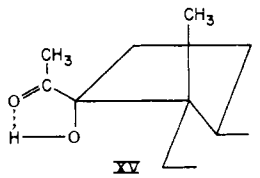
(6) (a) L. Ruzicka, K. Gätzi and T. Reichstein, *Helv. Chim. Acta*, **22**, 626 (1939); (b) C. W. Shoppee and D. A. Prins, *ibid.*, **26**, 185 (1943).

(7) C. W. Shoppee and D. A. Prins, *ibid.*, **26**, 201 (1943).

fluoride and acetic anhydride or with aluminum *t*-butylate followed by acetylation. *Therefore the rearrangement of 17α-hydroxy-20-ketosteroids with boron trifluoride and other Lewis acids proceeds primarily with the migration of the C-16,17-bond to give 17a-keto-D-homosteroids.* Examination of models shows that in the Lewis acid complex III, there is considerably less interaction between the C-21 methyl group and other methyl and methylene groups during the migration of the C-16,17-bond (III → VI) than during the migration of the C-13,-17-bond (III → IV). Although electronic consideration would indicate that the migration of the C-13,17-bond would be favored, the products obtained demonstrate that the steric factors take precedence over the electronic effects. However, in the base-catalyzed rearrangement, the interaction of the C-21 methyl group is negligible so that the electronic factors overcome any steric effects and the products obtained are exclusively those of the C-13,17-bond migration.

The reaction of 3α,17α-dihydroxypregnane-20-one (XIa) with aluminum *t*-butylate gave a 68% yield of the C-16,17-bond migration product 3α,-17α-dihydroxy-17β-methyl-D-homoetiocholane-17a-one (XIVa) and only a 3% yield of 3α,17aα-dihydroxy-17aβ-methyl-D-homoetiocholane-17-one (XIIIa). A number of less polar and more polar compounds were eluted from the chromatogram but were not identified. These products probably arose from internal oxidation–reduction catalyzed by the aluminum *t*-butylate.

It was found that when 3β-acetoxy-17α-hydroxyallopregnane-20-one was heated above its m.p. for 30 minutes in a Pyrex test-tube, two isomeric D-homosteroids, 3β-acetoxy-17α-hydroxy-17β-methyl-D-homoandrostane-17a-one (Xb) and 3β-acetoxy-17aα-hydroxy-17aβ-methyl-D-homoandrostane-17-one (IXb), were each obtained in about 15% yield. The same two pairs of isomers were also obtained in about the same yield when 3α,17α-dihydroxypregnane-20-one was heated above its m.p. In both cases, the rearrangement was incomplete and large amounts of starting material were recovered.[8] The stereospecific rearrangement to the α-hydroxy derivatives during heating above the m.p. is probably due to the orientation of the oxygen in the C-20 carbonyl group by hydrogen bonding with the 17α-hydroxyl group as in XV.

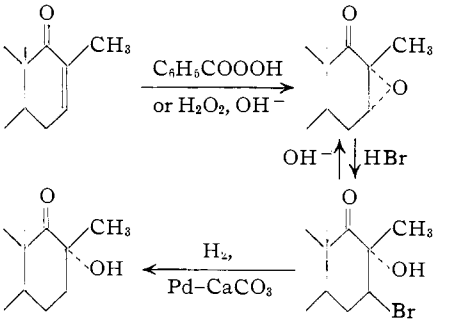


XV

Thus the rearrangement of 17α-hydroxy-20-ketosteroid by heating above its m.p. proceeds with the migration of the C-16,17-bond as well as with the migration of the C-13,17-bond. During the D-homoannulation of 17α-hydroxy-Δ⁴-pregnene-3,20-dione to 17aα-hydroxy-17aβ-methyl-D-homo-Δ⁴-androstene-3,17-dione with aluminum *t*-butylate, von Euw and Reichstein[5] obtained another compound, m.p. 162–164°, isomeric with the 17aα- and 17αβ-hydroxy-D-homosteroids. They also obtained the same pair of isomers when 17α-hydroxy-Δ⁴-pregnene-3,20-dione was heated above its m.p. Since in the present study it has been shown that the same pair of isomers is obtained from 17α-hydroxy-20-ketosteroids with aluminum *t*-butylate or heating above the m.p., there is little doubt that by analogy the isomer, m.p. 162–164°, obtained by von Euw and Reichstein is the 17a-keto derivative, 17α-hydroxy-17β-methyl-D-homo-Δ⁴-androstene-3,17a-dione.

The Evidence for the 17a-Ketone.[9]—The assignment of the 17a-keto-D-homo structure to the principal products X and XIV of the aluminum *t*-butylate rearrangement of 17α-hydroxy-20-ketones in both the normal and allo series is based on the following evidence. The quantitative Zimmermann determination of ketones with *m*-dinitrobenzene and alkali requires the grouping R-CO-CH_2–, for chromogenicity.[10] No color is obtained if there is no methylene group α to the carbonyl. All of the D-homosteroids obtained in the present study were analyzed by the modified Zimmermann reaction for 17-ketosteroids used routinely in this Laboratory.[11] The values, expressed in milligram equivalent of dehydroisoandrosterone (KS), are reported in Table I. In both the allo and normal series, the 17-keto-D-homosteroids which have a methylene group at C-16 gave the true Zimmermann magenta color. The 17aβ-hydroxy derivatives VIIIb and XIIb were more chromogenic, 0.56 KS, than their 17aα-hydroxy epimers IXb and XIIIb, 0.26 KS. The products Xb and XIVb obtained by the Lewis acid rearrangement gave no color and therefore did not contain any methylene group adjacent to a carbonyl. This fact is consistent with the 17a-keto-17-hydroxy-D-homosteroid structure assigned to these compounds.

Jones and Cole[12] have found that methylene



(8) In order to eliminate any catalytic effect due to the Pyrex glass, 3α,17α-dihydroxypregnane-20-one was heated in a quartz test-tube. In this case the compound was heated at a much higher temperature above its m.p. (235–240°) for 30 minutes and no starting material was recovered. The two D-homosteroids XIIIa and XIVa were obtained in almost equal amounts.

(9) ADDED IN PROOF.—Independent evidence for the 17α-hydroxy-17a-keto-D-homo structure of the rearrangement product of 17α-hydroxy-20-ketosteroids with Lewis acids has been obtained in another series by the following synthetic sequence (N. L. Wendler and D. Taub, *Chemistry & Industry*, 505 (1955). N. L. Wendler, D. Taub, D. K. Fukushima and S. Dobriner, *ibid.*, 1259 (1955)).

(10) W. Zimmermann, *Z. physiol. Chem.*, **245**, 47 (1936); N. H. Callow, R. K. Callow and C. W. Emmens, *Biochem. J.*, **32**, 1312 (1938).

(11) K. Dobriner, S. Lieberman and C. P. Rhoads, *J. Biol. Chem.*, **172**, 241 (1948).

(12) R. N. Jones and A. R. H. Cole, THIS JOURNAL, **74**, 5648 (1952).

TABLE I

ZIMMERMANN COLOR VALUES OF D-HOMO KETOSTEROIDS

D-Homo ketosteroids	KS[a]
3β-Acetoxy-17aα-hydroxy-17aβ-methyl-D-homoandrostane-17-one	0.26
3α-Acetoxy-17aα-hydroxy-17aβ-methyl-D-homoetiocholane-17-one	.26
3β-Acetoxy-17aβ-hydroxy-17aα-methyl-D-homoandrostane-17-one	.56
3α-Acetoxy-17aβ-hydroxy-17aα-methyl-D-homoetiocholane-17-one	.57
3β-Acetoxy-17α-hydroxy-17β-methyl-D-homoandrostane-17a-one	0
3α-Acetoxy-17α-hydroxy-17β-methyl-D-homoetiocholane-17a-one	0
3β,17α-Diacetoxy-17β-methyl-D-homoandrostane-17a-one	0

[a] KS is milligram equivalent of dehydroisoandrosterone.

groups adjacent to a carbonyl group in the six-membered ring of the steroid nucleus have infrared absorption bands in the region 1438 to 1415 cm.$^{-1}$. The 17a-ketones X and XIV do not have any methylene groups adjacent to the carbonyl group and the infrared absorption spectra of these compounds show no characteristic absorption in the region 1438 to 1415 cm.$^{-1}$ for such methylene groups. However, the 17-keto-D-homosteroids VIII, IX, XII and XIII have a methylene group at C-16 and the infrared spectra of these compounds have bands at 1422, 1425, 1421 and 1427 cm.$^{-1}$, respectively. The methylene groups of the 17aβ-hydroxy epimer absorb at slightly higher wave number than those of the 17aα epimer. When the hydrogens on C-16 of the 17-keto-D-homosteroids VIII, IX, XII and XIII were replaced by deuterium, the absorption bands (1427–1421 cm.$^{-1}$) due to the $-CH_2-$ group adjacent to a carbonyl group disappeared from the spectrum.[13] Similar equilibration of 17a-keto-D-homosteroids X and XIV in a medium of deuterium resulted in no incorporation of isotope and there was no change in the infrared spectra

The infrared spectra of the 3-monoacetates of the D-homo isomers also point out further differences of the 17a- and 17-keto derivatives in the carbonyl region. The 17a-ketones X and XIV have the main carbonyl absorption band at 1697 cm.$^{-1}$ whereas the 17aβ- and 17aα-hydroxy-17-keto-D-homosteroids in both the normal and allo series have carbonyl absorption bands between 1722 and 1713 cm.$^{-1}$.

The α-orientation of the hydroxy group at C-17 in the 17a-ketones X and XIV has been assigned from the mechanism of formation from the 17α-hydroxy-20-ketosteroids and from conformational analysis. The mechanism proposed by Turner for the D-homoannulation with Lewis acid and extended in this present study to the formation of 17a-ketones leads to the α-orientation of the hydroxyl group at C-17 (*vide supra*). Furthermore, the hydroxyl group at C-17 was found to be acetylated readily at room temperature with pyridine and acetic anhydride. Consequently, the hydroxyl group must be in the less hindered equatorial conformation or the 17α-orientation.

(13) R. N. Jones, A. R. H. Cole and B. Nolin, THIS JOURNAL, **74**, 5662 (1952).

The study of the infrared spectra of the 3-monoacetates of the D-homosteroids in both the allo and normal series also gives indications for the equatorial nature of the C-17 hydroxyl group in the 17a-keto derivatives. Whereas the axial 17aα-hydroxyl group of the 3-acetoxy-17aα-hydroxy-17-keto-D-homosteroids IXb and XIIIb has a sharp absorption band in the usual place at about 3620 cm.$^{-1}$ and a broad band due to association at 3510 to 3440 cm.$^{-1}$, the equatorial 17aβ-hydroxyl group of VIIIb and XIIb has its absorption band shifted to about 3485 cm.$^{-1}$. In the 3-acetoxy-17-hydroxy-17a-keto-D-homosteroids, Xb and XIVb, the C-17 hydroxyl group also absorbs at 3500 to 3490 cm.$^{-1}$, respectively, pointing to an equatorial or α-oriented hydroxyl group at C-17.

The chemical and spectroscopic evidence for the 17a-keto-D-homo structure is corroborated by molecular rotation differences. It was found that the 17aα- and 17aβ hydroxy-17a-methyl-17-keto-D-homosteroids had the same specific rotation in both the normal and allopregnane series as well as in the 3β-hydroxy-Δ^5-pregnenes and 3-keto-Δ^4-pregnenes (*cf.* Table II). Consequently the molecular rotation differences for these D-homo epimers were the same. The ΔM_D (17α-OH, 20-C=O → 17α-OH, 17-C=O) was a low negative value, about −70. The molecular rotation difference to the 17a-acetoxy derivative was also the same for the two epimers, about +40. However, in one example, 3β,17aα-diacetoxy-17aβ-methyl-Δ^5-D-homoandrostene-17-one, the ΔM_D (17α-OH, 20-C=O → 17aα-OAc, 17-C=O) was +165. It is quite possible that the specific rotation of this compound is in error. In the conversion of the saturated 17α-hydroxy-20-ketosteroids to the 17α-hydroxy-17β-methyl-17a-keto-D-homosteroids, the ΔM_D (17α-OH, 20-C=O → 17α-OH, 17a-C=O) was a positive value (about +130) compared with the value −70 for the formation of the 17a-hydroxy-17-keto-D-homosteroids. The molecular rotation difference to the 17α-acetoxy-17a-keto-D-homosteroids was a much larger positive value (about +290).

Experimental[14]

Rearrangement of 3β-Acetoxy-17α-hydroxyallopregnane-20-one (VIIb, Reichsteins' Substance "L" Acetate). A. With Base.—A solution of 250 mg. of 3β-acetoxy-17α-hydroxyallopregnane-20-one in 200 ml. of ethanol and 200 ml. of 10% aqueous potassium hydroxide was refluxed for 4 hours. The alkaline solution was extracted with large volumes of ethyl acetate, the organic layer was washed with brine, dried and the solvent removed. The crystalline residue (223 mg.) was chromatographed on a column of 80 g. of silica gel containing 40 ml. of ethanol with methylene chloride–ethanol as the moving phase.[4] Elution with 2% ethanol in methylene chloride afforded 159 mg. of a product judged to be 3β,17aβ-dihydroxy-17aα-methyl-D-homoandrostane-17-one (VIIIa) by infrared spectrometry. Recrystallization from acetone gave 120 mg. of VIIIa, m.p. 199–200°. The analytical sample melted at 200–200.5°, $[\alpha]^{26}D$ −36.2°; reported[7] m.p. 200°.

Acetylation with acetic anhydride and pyridine at room temperature for 3 hours gave 3β-acetoxy-17aβ-hydroxy-17aα-methyl-D-homoandrostane-17-one (VIIIb), m.p. 158.5–159°, $[\alpha]^{26}D$ −36.3°; reported[7] m.p. 159–160°, $[\alpha]^{15}D$ −34.8° (dioxane). The substance showed charac-

(14) All melting points are corrected. Optical rotations were determined in chloroform unless otherwise noted. The infrared spectra were determined on a Perkin–Elmer model 21 spectrophotometer in carbon tetrachloride unless otherwise specified.

TABLE II

MOLECULAR ROTATIONAL DIFFERENCE IN D-HOMOANNULATION

$\Delta_1 = \Delta M_D$ (17α-OH, 20-C=O → 17a-OH, 17-C=O) $\Delta_3 = \Delta M_D$ (17α-OH, 20-C=O → 17a-OAc, 17-C=O)
$\Delta_2 = \Delta M_D$ (17α-OH, 20-C=O → 17-OH, 17-C=O) $\Delta_4 = \Delta M_D$ 17α-OH, 20-C=O → 17-OAc, 17a-C=O)

	[α]ChlD,	M_D	Δ_1	Δ_2	Δ_3	Δ_4
3β-Acetoxy-17α-hydroxyallopregnane-20-one[a]	− 16.3°	− 60				
3β-Acetoxy-17aα-hydroxy-17aβ-methyl-D-homoandrostane-17-one[b]	− 35.6	−134	−74			
3β,17aα-Diacetoxy-17aβ-methyl-D-homoandrostane-17-one[c]	0[g]	0			+ 60	
3β-Acetoxy-17aβ-hydroxy-17aα-methyl-D-homoandrostane-17-one[b]	− 36.3	−136	−76			
3β,17aβ-Diacetoxy-17aα-methyl-D-homoandrostane-17-one[b]	− 6.4	− 27			+ 33	
3β-Acetoxy-17α-hydroxy-17β-methyl-D-homoandrostane-17a-one[b]	+ 21.2	+ 80		+140		
3β,17α-Diacetoxy-17β-methyl-D-homoandrostane-17a-one[b]	+ 53.5	+224				+284
3α-Acetoxy-17α-hydroxypregnane-20-one[a]	+ 27	+102				
3α-Acetoxy-17aα-hydroxy-17aβ-methyl-D-homoetiocholane-17-one[b]	+ 8.9	+ 33	−69			
3α-Acetoxy-17aβ-hydroxy-17aα-methyl-D-homoetiocholane-17-one[b]	+ 8.9	+ 33	−69			
3α,17aβ-Diacetoxy-17aα-methyl-D-homoetiocholane-17-one[b]	+ 34.8	+145			+ 43	
3α-Acetoxy-17α-hydroxy-17β-methyl-D-homoetiocholane-17a-one[b]	+ 61.2	+230		+128		
3α,17α-Diacetoxy-17β-methyl-D-homoetiocholane-17a-one[b]	+ 94.6	+396				+294
3β-Acetoxy-17α-hydroxy-Δ⁵-pregnene-20-one[a]	− 80.8	−302				
3β-Acetoxy-17aα-hydroxy-17aβ-methyl-Δ⁵-D-homoandrostene-17-one[c]	−101[h]	−376	−74			
3β,17aα-Diacetoxy-17aβ-methyl-Δ⁵-D-homoandrostene-17-one[c]	− 32.8	−137			+165	
3β-Acetoxy-17aβ-hydroxy-17aα-methyl-Δ⁵-D-homoandrostene-17-one[c,d]	− 98	−366	−65			
3β,17aβ-Diacetoxy-17aα-methyl-Δ⁵-D-homoandrostene-17-one[c]	− 68.4	−284			+ 18	
17α-Hydroxy-Δ⁴-pregnene-3,20-dione[a]	+ 90.4	+299				
17aα-Hydroxy-17aβ-methyl-Δ⁴-D-homoandrostene-3,17-dione[e]	+ 63.1	+208	−91			
17aβ-Hydroxy-17aα-methyl-Δ⁴-D-homoandrostene-3,17-dione[c]	+ 60.8	+201	−98			
17α-Acetoxy-17β-methyl-Δ⁴-D-homoandrostene-3,17a-dione[f]	+132[h]	+490				+192

[a] This Laboratory. [b] This investigation. [c] C. W. Shoppee and D. A. Prins, *Helv. Chim. Acta*, **26**, 201 (1943). [d] H. E. Stavely, THIS JOURNAL, **63**, 3127 (1941). [e] J. von Euw and T. Reichstein, *Helv. Chim. Acta*, **24**, 879 (1941). [f] R. B. Turner, THIS JOURNAL, **75**, 3484 (1953). This compound previously was assigned the structure 17aα-acetoxy-17aβ-methyl-Δ⁴-D-homoandrostene-3,17-dione, but from its characteristic infrared absorption bands and from the method of preparation with boron trifluoride, the 17a-keto structure is now assigned. [g] Acetone. [h] Dioxane.

teristic absorption bands in the infrared at 3485 cm.$^{-1}$ (shifted hydroxyl), 1736 and 1241 cm.$^{-1}$ (acetate), 1714 cm.$^{-1}$ (ketone) and 1425 cm.$^{-1}$ (α-methylene). The monoacetate was identical by infrared spectrometry and mixed m.p. determination with an authentic sample obtained from Dr. R. B. Turner and from Dr. C. W. Shoppee.

Acetylation of the 3-monoacetate VIIIb with boron trifluoride, acetic acid and acetic anhydride afforded 3β,17aβ-diacetoxy-17-aα-methyl-D-homoandrostane-17-one (VIIIc), m.p. 217–218°, $[\alpha]^{24}D$ −6.4°; reported[7] m.p. 221–222°, $[\alpha]^{18}D$ −6.1° (acetone). The diacetate was identical by infrared spectrometry and mixed m.p. determination with an authentic sample obtained from Dr. R. B. Turner and from Dr. C. W. Shoppee.

Further elution with 2% ethanol in methylene chloride gave 3 mg. of the saponified starting material VIIa and 16 mg. of an unknown substance. Acetylation and recrystallization from acetone–petroleum ether gave a product, m.p. 156.5–158.5°, which differed from VIIIb by mixed m.p. determination and infrared spectrometry. Following these compounds, 29 mg. of crystalline material was eluted which had the infrared spectrum of 3β,17aα-dihydroxy-17aβ-methyl-D-homoandrostane-17-one (IXa). Recrystallization from ethyl acetate gave the diol, m.p. 272–275°; the m.p. could not be raised on further recrystallization; reported[6b] m.p. 295–300°. Therefore all the material was acetylated with pyridine and acetic anhydride for 3 hours at room temperature. Chromatography on silica gel and elution with ethyl acetate–petroleum ether (1:4) gave 30 mg. of 3β-acetoxy-17aα-hydroxy-17aβ-methyl-D-homoandrostane-17-one (IXb). Recrystallization from acetone–cyclohexane afforded 18 mg. of needles, m.p. 234.5–235.5°, $[\alpha]^{25}D$ −35.6°, −31.1° (acetone); reported[6a] m.p. 244–244.5°, $[\alpha]^{25}D$ −31.3° (acetone). The substance showed characteristic absorption bands in the infrared at 3610 and 3500–3440 cm.$^{-1}$ (associated hydroxyl), 1734 and 1243 cm.$^{-1}$ (acetate), 1722 cm.$^{-1}$ (ketone) and 1422 cm.$^{-1}$ (α-methylene). The 3-monoacetate IXb was identical by mixed m.p. determination and infrared spectrometry with an authentic sample, m.p. 234–236°, obtained from Dr. R. B. Turner.

Saponification of the 3-monoacetate IXb afforded 3β,-17aα-dihydroxy-17aβ-methyl-D-homoandrostane-17-one (IXa). Repeated recrystallization from acetone and ethanol gave diol IXa, m.p. 281–284°, $[\alpha]^{25}D$ −30.4° (ethanol); reported m.p. 295–300°,[6b] 305–306° or in vacuum 274–275°.[6a] Acetylation of the diol with pyridine and acetic anhydride at room temperature yielded the 3-monoacetate IXb.

Acetylation of the 3-monoacetate IXb with boron trifluoride, acetic acid and acetic anhydride afforded a crude mixture from which only impure 3β,17aα-diacetoxy-17aβ-methyl-D-homoandrostane-17-one (IXc) and the starting material were isolated.

B. With Aluminum *t*-Butylate.—A solution of 150 mg. of 3β-acetoxy-17α-hydroxyallopregnane-20-one (VIIb) and 500 mg. of aluminum *t*-butylate in 30 ml. of dry benzene was refluxed for 27 hours. Ethyl acetate was added to the mixture and this solution was washed successively with dilute acid, water, dilute base and brine. After drying and removing the solvent, the residue was reacetylated with pyridine and acetic anhydride at room temperature for 3 hours. The semi-crystalline product, 129 mg., was chromatographed on 80 g. of silica gel containing 32 ml. of eth-

anol. Elution with 1% ethanol in methylene chloride–petroleum ether (1:1) gave 11 mg. of semi-crystalline 3β,17α-diacetoxy-17β-methyl-D-homoandrostane-17a-one (Xc). The infrared spectrum was identical with the diacetate obtained by the rearrangement of 3β-acetoxy-17α-hydroxyallopregnane-20-one (VIIb) with boron trifluoride, acetic acid and acetic anhydride. Further elution with 1% ethanol in methylene chloride–petroleum ether (1:1) gave 78 mg. of 3β-acetoxy-17α-hydroxy-17β-methyl-D-homoandrostane-17a-one (Xb). Recrystallization from benzene–cyclohexane gave 46 mg. of Xb, m.p. 106.5–109.5°. The analytical sample after recrystallization from ether–petroleum ether melted at 108.5–109.5°, $[\alpha]^{25}D$ +21.2°. The substance showed characteristic absorption bands in the infrared at 3490 cm.$^{-1}$ (shifted hydroxyl), 1736 and 1244 cm.$^{-1}$ (acetate) and 1697 cm.$^{-1}$ (ketone). There was no absorption band indicative of the α-methylene group.[12]

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.37; H, 9.64. Found: C, 73.26 H, 9.61.

Elution of the column with 1% ethanol in methylene chloride gave 15 mg. of 3β-acetoxy-17aα-hydroxy-17aβ-methyl-D-homoandrostane-17-one (IXb). Recrystallization from acetone–cyclohexane afforded 7 mg. of IXb, m.p. 235–236°. There was no depression in the m.p. when admixed with IXb obtained by treatment of Reichsteins' Substance "L" acetate VIIb with base and the infrared spectra were identical.

C. With Boron Trifluoride.—3β-Acetoxy-17α-hydroxyallopregnane-20-one (VIIb) was rearranged with boron trifluoride etherate, acetic anhydride and acetic acid according to the procedure of Turner.[3] 3β,17α-Diacetoxy-17β-methyl-D-homoandrostane-17a-one (Xa) was obtained with m.p. 239–240°, $[\alpha]^{26}D$ +53.5°, +64.5° (acetone), which was identical by mixed m.p. determination and infrared spectrometry with sample, m.p. 240–241°, prepared by Turner by the same reaction.[3] The substance showed characteristic absorption bands in the infrared at 1737 and 1243 cm.$^{-1}$ (acetate) and 1715 cm.$^{-1}$ (ketone). There was no absorption bands for the α-methylene and hydroxyl groups. The product from the boron trifluoride rearrangement had been previously assigned[3] the incorrect structure 3β,17aα-diacetoxy-17aβ-methyl-D-homoandrostane-17-one (IXc) which has the physical constants[7] m.p. 232–235°, $[\alpha]^{15}D$ 0° (acetone). Chromatography of the boron trifluoride reaction product and examination of the eluates by infrared spectrometry, however, has indicated the formation of 3β-acetoxy-17aα-hydroxy-17aβ-methyl-D-homoandrostane-17-one (IXb). The small quantity of this isomer present precluded further purification by recrystallization.

Saponification of 100 mg. of the diacetate Xc with 5% methanolic potassium hydroxide by reflux for 1 hour gave 85 mg. of diol Xa. Recrystallization from ethyl acetate and acetone afforded 3β,17α-dihydroxy-17β-methyl-D-homoandrostane-17a-one (Xa), m.p. 182–182.5°, $[\alpha]^{33}D$ +32.9°. The m.p. reported for 3β,17aα-dihydroxy-17aβ-methyl-D-homoandrostane-17a-one (IXa) is 295–300°,[6b] and 305–306°[6a]. In the present investigation m.p. 281–284° and $[\alpha]^{25}D$ −30.4° (ethanol) were obtained for the diol IXa.

In another run 200 mg. of the diacetate Xc was saponified in the same manner as above. The product (158 mg.) containing no acetate group as judged by infrared spectroscopy was acetylated at room temperature for 3 hours with acetic anhydride and pyridine. The acetylation product was chromatographed on a partition column of 80 g. of silica gel impregnated with 40 ml. of *t*-butyl alcohol. The elution was started with 1% *t*-butyl alcohol in methylene chloride–petroleum ether (1:1). With 2% *t*-butyl alcohol in methylene chloride–petroleum ether (1:1), 10 mg. of crystalline product was eluted whose infrared spectrum was identical with the diacetate Xc.

Further elution with 2% *t*-butyl alcohol afforded 127 mg. of 3β-acetoxy-17α-hydroxy-17β-methyl-D-homoandrostane-17a-one (Xb). Recrystallization from benzene–cyclohexane gave 111 mg. of Xb, m.p. 108–110°. This compound was identical with the 17a-ketone Xb obtained by the rearrangement of Reichsteins' Substance "L" acetate (VIIb) with aluminum *t*-butylate by infrared spectroscopy and mixed m.p. determination.

Ten milligrams of the above monoacetate Xb was refluxed for 1 hour with 0.5 ml. of pyridine and 1 ml. of acetic anhydride. The crystalline acetylation product was principally 3β,17α-diacetoxy-17β-methyl-D-homoandrostane-17a-one from its infrared spectrum. Recrystallization from ether–petroleum ether yielded 4 mg. of 3β,17α-diacetoxy-17β-methyl-D-homoandrostane-17a-one (Xc), m.p. 238.5–239.5°, identical by infrared spectrometry and mixed m.p. determination with the rearrangement product obtained by boron trifluoride.

D. By Heating above Melting Point.—Three hundred mg. of 3β-acetoxy-17α-hydroxyallopregnane-20-one (VIIb) was melted completely and heated at 240° in an open Pyrex tube for 30 minutes. Chromatography on 150 g. of silica gel containing 60 ml. of ethanol and elution with 1% ethanol in methylene chloride–petroleum ether (1:1) gave fractions which by infrared spectrometry were judged to be 3β-acetoxy-17α-hydroxy-17β-methyl-D-homoandrostane-17a-one (Xb, 58 mg.), starting material (196 mg.) and 3β-acetoxy-17aα-hydroxy-17aβ-methyl-D-homoandrostane-17-one (IXb, 45 mg.). Recrystallization of the 17a-ketone fraction from petroleum ether gave 14 mg. of Xb, m.p. 109–110°. The fractions containing the 17aα-hydroxy-17-keto-D-homosteroid were recrystallized from acetone–cyclohexane to give 34 mg. of IXb, m.p. 235–238°.

Rearrangement of 3α,17α-Dihydroxypregnane-20-one (XIa). A. With Base.—A solution of 500 mg. of 3α,17α-dihydroxypregnane-20-one (XIa) in 250 ml. of ethanol and 250 ml. of 10% aqueous potassium hydroxide was refluxed for 4 hours. The alkaline solution was extracted with large volumes of ethyl acetate, the organic layer was washed with brine, dried and the solvent removed. The crystalline residue was chromatographed on a column of 190 g. of silica gel containing 76 ml. of ethanol with methylene chloride–ethanol as the moving phase. The elution was begun with 1% ethanol in methylene chloride and continued with increasing amounts of ethanol. From the 2 and 3% ethanol–methylene chloride eluates 335 mg. of **3α,17aβ-dihydroxy-17aα-methyl-D-homoetiocholane-17-one (XIIa)** was obtained. Recrystallization from acetone–petroleum ether gave 252 mg. of needles, m.p. 186–187°, $[\alpha]^{25}D$ −14.5°. An additional 41 mg., m.p. 183–186°, was obtained from the mother liquors.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.33; H, 10.16.

Acetylation with pyridine and acetic anhydride at room temperature for 4 hours and recrystallization from methanol gave 3α-acetoxy-17aβ-hydroxy-17aα-methyl-D-homoetiocholane-17-one (XIIb), m.p. 171–171.5°, $[\alpha]^{26}D$ +8.9°. The substance showed characteristic absorption bands in the infrared at 3480 cm.$^{-1}$ (shifted hydroxyl), 1736 and 1243 cm.$^{-1}$ (acetate), 1713 cm.$^{-1}$ (ketone) and 1427 cm.$^{-1}$ (α-methylene).

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.37; H, 9.64. Found: C, 73.41; H, 9.51.

Acetylation of XIIa with boron trifluoride etherate, acetic acid and acetic anhydride yielded 3α,17aβ-diacetoxy-17aα-methyl-D-homoetiocholane-17-one (XIIc), m.p. 187–190.5°, $[\alpha]^{23}D$ +34.9°.

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.70; H, 9.07.

From the 4% ethanol–methylene chloride eluates 77 mg. of 3α,17aα-dihydroxy-17aβ-methyl-D-homoetiocholane-17-one (XIIIa) was obtained. Recrystallization from acetone–petroleum ether gave 67 mg., m.p. 207–220°, which could not be improved by recrystallization from other solvents. The crystals and mother liquors were combined and acetylated with pyridine and acetic anhydride at room temperature for 4 hours. Recrystallization from acetone–petroleum ether gave 69 mg. of 3α-acetoxy-17aα-hydroxy-17aβ-methyl-D-homoetiocholane-17-one (XIIIb), m.p. 199–201°. The analytical sample melted at 201.5–202.5°, $[\alpha]^{26}D$ +8.9°. The substance showed characteristic absorption bands in the infrared at 3620 and 3510–3440 cm.$^{-1}$ (associated hydroxyl), 1738 and 1243 cm.$^{-1}$ (acetate), 1722 cm.$^{-1}$ (ketone) and 1421 cm.$^{-1}$ (α-methylene).

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.37; H, 9.64. Found: C, 73.27; H, 9.47.

B. With Aluminum *t*-Butylate.—A solution of 60 mg. of 3α,17α-dihydroxypregnane-20-one (XIa) and 300 mg. of aluminum *t*-butylate in 10 ml. of dry benzene was refluxed for 18 hours. Ethyl acetate was added to the mixture and this solution washed with dilute acid, water, dilute base and brine. After drying with sodium sulfate, the solvent was removed to give a semi-crystalline residue which was chro-

matographed on 40 g. of silica gel containing 16 g. of formamide.

Elution with cyclohexane–benzene (1:1) saturated with formamide afforded 4 mg. of unknown compound, m.p. 172–174°, $[\alpha]^{26}D$ +46.4°; the m.p. was depressed when admixed with 3α,17α-dihydroxy-17β-methyl-D-homoetiocholane-17a-one, m.p. 169–170°. From a later portion of the chromatogram, 2 mg. of 3α,17aα-dihydroxy-17aβ-methyl-D-homoetiocholane-17-one (XIIIa) was obtained. There was also 13 mg. of very polar material, not further characterized.

Elution with cyclohexane–benzene (1:1) yielded 41 mg. of **3α,17α-dihydroxy-17β-methyl-D-homoetiocholane-17a-one (XIVa)**. Recrystallization from acetone–petroleum ether yielded 16 mg. of needles, m.p. 169–170°, $[\alpha]^{25}D$ +48.4°.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.11; H, 10.22.

Acetylation with acetic anhydride and pyridine at room temperature overnight gave a mixture of the 3-monoacetate and 3,17-diacetate. Chromatography on silica gel and elution with ethyl acetate–petroleum ether (1:4) yielded the monoacetate. Recrystallization from acetone–petroleum ether gave 3α-acetoxy-17α-hydroxy-17β-methyl-D-homoetiocholane-17a-one (XIVb), m.p. 188–189.5°, $[\alpha]^{26}D$ +61.2°. The substance showed characteristic absorption bands in the infrared at 3500 $cm.^{-1}$ (shifted hydroxyl), 1738 and 1243 $cm.^{-1}$ (acetate) and 1698 $cm.^{-1}$ (ketone). There was no absorption band indicative of the α-methylene group.

Anal. Calcd. for $C_{25}H_{36}O_4$: C, 73.37; H, 9.64. Found: C, 73.32; H, 9.37.

C. With Boron Trifluoride.—Acetylation of 100 mg. of 3α,17α-dihydroxypregnane-20-one with acetic acid, acetic anhydride and boron trifluoride etherate gave 124 mg. of yellow oil which was chromatographed on 40 g. of silica gel containing 20 ml. of *t*-butyl alcohol. The eluates with the infrared spectra of 3α,17α-diacetoxy-17β-methyl-D-homoetiocholane-17a-one (XIVc) were combined (76 mg.). Recrystallization from petroleum ether gave 52 mg. of XIVc, m.p. 141.5–144°. The analytical sample melted at 144–144.5°, $[\alpha]^{23}D$ +94.6°.

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.98; H, 9.10.

D. By Heating above Melting Point.—One hundred mg. of 3α,17α-dihydroxypregnane-20-one (XIa) was melted completely in an open Pyrex tube and heated for 30 minutes at 220–225°. Chromatography on 40 g. of silica gel containing 16 ml. of ethanol and elution with 2% ethanol in methylene chloride afforded 46 mg. of a mixture of starting material and **3α,17α-dihydroxy-17β-methyl-D-homoetiocholane-17a-one (XIVa)**. Recrystallization of this mixture from acetone–petroleum ether gave 17 mg. of a product, m.p. 188–190°, which had an infrared spectrum identical with that of the starting material, 3α,17α-dihydroxypregnane-20-one (XIa). The mother liquors were rechromatographed on a formamide partition column. Elution with cyclohexane–benzene (1:1) saturated with formamide yielded 15 mg. of material with an infrared spectrum identical with that of 3α,17α-dihydroxy-17β-methyl-D-homoetiocholane-17a-one (XIVa) which was also obtained in the aluminum *t*-butylate reaction. Acetylation and recrystallization from petroleum ether gave 3α-acetoxy-17α-hydroxy-17β-methyl-D-homoetiocholane-17a-one (XIVb), m.p. 189–189.5°.

Further elution of the initial ethanol partition column with 3 and 4% ethanol in methylene chloride gave 31 mg. of product which had an infrared spectrum identical with that of **3α,17aα-dihydroxy-17aβ-methyl-D-homoetiocholane-17-one (XIIIa)**. Recrystallization from acetone and acetone–benzene gave 20 mg. of needles, m.p. 216–219°. The infrared spectrum was identical with that of the product isolated from reaction A with base. Acetylation with acetic anhydride and pyridine at room temperature for 3 hours and recrystallization from acetone–petroleum ether gave 3α-acetoxy-17aα-hydroxy-17aβ-methyl-D-homoetiocholane-17-one (XIIIb), m.p. 202–203.5°; the infrared spectrum was identical with that of the compound obtained from reaction A.

Zimmermann Color Reaction.—The Zimmermann color values of the D-homo derivatives were obtained by the macro method used routinely in these Laboratories[11] and are reported as mg. equivalent of dehydroisoandrosterone per mg. of compound (Table I).

Deuterium Exchange of D-Homosteroids.—The deuterium exchange in alkaline solution was carried out by the procedure of Jones and co-workers.[13] Fifteen to 25 mg. of steroid was refluxed with 5 mg. of anhydrous sodium carbonate in 0.5 ml. of deuterium oxide (99.8% D), and 5 ml. of CH_3OD for 20 minutes. The solvent was blown off under a stream of nitrogen and an additional 0.5 ml. of deuterium oxide and 5 ml. of CH_3OD added. The solution was refluxed again for 20 minutes and the solvent removed. The residue was dissolved in ethyl acetate and was washed with brine. The ethyl acetate extract was dried and the solvent evaporated. The recovered D-homosteroid was recrystallized from appropriate solvents and the infrared spectrum was measured in carbon tetrachloride solution or by the potassium bromide disk technique.[15] When the starting material was available only as the acetate, the product was reacetylated and the infrared spectra of the acetates were compared. The equilibrated 3β,17aβ-dihydroxy-17aα-methyl-D-homoandrostane-17-one was found to contain 4.60 atom % excess deuterium or 1.56 g. atom of deuterium.[16]

Acknowledgment.—The authors are grateful to Dr. T. F. Gallagher for his interest and encouragement throughout this investigation. We are indebted to Syntex, S. A., Mexico City, Mexico, D. F., and The Upjohn Co., Kalamazoo, Mich., for a generous supply of steroids.

NEW YORK 21, N. Y.

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