[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC., RAHWAY, N. J.]

Mechanism of Alkali-catalyzed D-Homoannulation of 16,17α-Dihydroxy-20-keto Steroids. A Contribution to the Mechanism of Dehydrobromination of α-Bromo Ketones[1]

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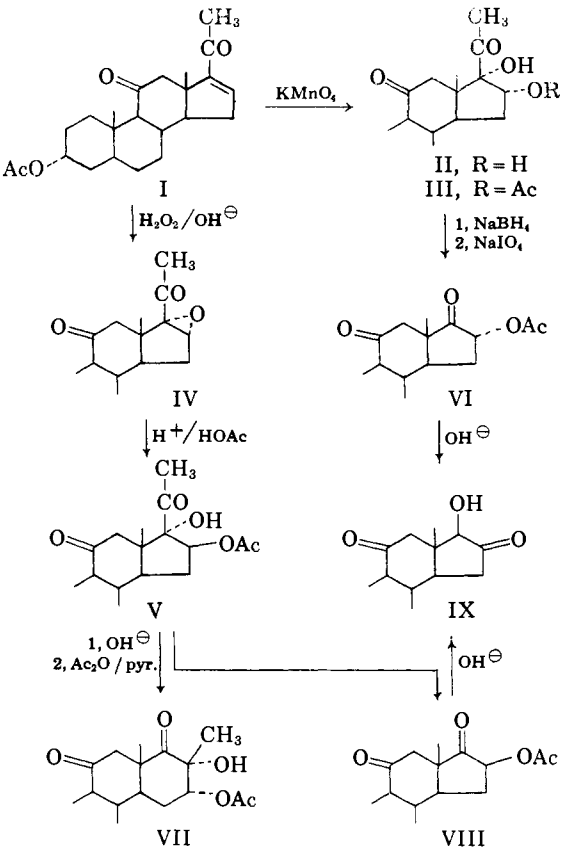
Treatment of 16β,17α-dihydroxy-20-ketopregnanes with alkali appears to invoke retroaldol opening of ring-D with subsequent reclosure to a D-homo system possessing a configurationally inverted C-16 hydroxyl function. The dehydrobromination of 3α-acetoxy-16α-deutero-17α-bromopregnane-11,20-dione by pyridine or lithium chloride in dimethylformamide has been found to proceed with deuterium retention, signifying an E_2 *trans*-elimination mechanism.

In the course of studies concerned with the D-ring expansion of 3α-acetoxy-16α,17α-dihydroxypregnane-11,20-dione (II),[2] we observed the unexpected formation of the 17a-ketone VII as major isolated product under conditions of alkaline as well as Lewis acid catalysis. The formation of a 17a-keto structure under alkaline conditions of D-homoannulation is contrary to previous experience with functionally less substituted derivatives. In view thereof, we undertook an examination of the behavior of the 16β-isomer V with the desire of relating possible dependence of reaction course on configuration.

The 16β-epimer of III, namely, 3α,16β-diacetoxy-17α-hydroxypregnane-11,20-dione (V), was prepared by acetolysis of the oxide IV by the well known procedure of Heusler and Wettstein.[3] Although the 3,16-diacetate product V was not obtained crystalline, its structure, nonetheless, was secured by oxidative cleavage to the 16β-acetoxy-17-ketone (VIII), m.p. 183–186°. The 3,16-diacetate derivative of the 16α-epimer III was correspondingly cleaved by reduction and oxidation to the epimeric 16α-acetoxy-17-ketone VI, m.p. 193–195°. Both epimeric acetoxyketones VI and VIII were converted by alkali to the 17β-hydroxy-16-ketone IX, m.p. 199–202°. This structure verification route had been employed earlier by Cooley, Ellis, Hartley and Petrow in another series.[4]

Treatment of 3α,16β-diacetoxy-17α-hydroxypregnane-11,20-dione (V) with 0.5% aqueous potassium hydroxide in dioxane resulted, surprisingly, in its transformation to the known 16α-hydroxy-D-homo-17α-ketone isolated as its 3,16-diacetate VII[2]; the consequence of this rearrangement had been an inversion of configuration at C-16. Recently, Bernstein, Heller and Stolar[5] have reported the remarkable observation that in attempted hydrolyses of 16β-acetoxy-17α,hydroxycortical systems, the corresponding 16α-hydroxy epimers are produced. Our own observations on the formation of the D-homo system with inverted configuration led us to examine this transformation in greater detail. The occurrence of the inversion phenomenon at C-16 seemed reasonable



by only two pathways involving either: (1) Walden inversion or (2) formation of an intermediate species with trigonal planar symmetry about C-16. Of these two possibilities, a Walden inversion involving nucleophilic displacement of oxygen functionality at C-16 would seem highly unlikely; and were it to occur it should proceed intramolecularly to give the base stable oxide IV and not extramolecularly to produce an inverted diol. In this regard 16β-halo-17α-hydroxy-20-keto systems are converted completely to 16α,17-oxides with base.[6] On the other hand, the formation of an intermediate species with trigonal planar symmetry about C-16 could arise from either an oxidation–reduction sequence or, alternatively, from a retroaldol ring opening with subsequent reclosure. These two possibilities should be capable of differentiation by employing a system labeled

(1) For a preliminary communication of this work see: H. Kuo, D. Taub and N. L. Wendler, *Chemistry & Industry*, 1128 (1959).

(2) N. L. Wendler and D. Taub, *ibid.*, 1237 (1957); THIS JOURNAL, **82**, 2836 (1960).

(3) K. Heusler and A. Wettstein, *Chem. Ber.*, **87**, 1301 (1954).

(4) G. Cooley, B. Ellis, F. Hartley and V. Petrow, *J. Chem. Soc.*, 4373 (1955).

(5) S. Bernstein, N. Heller and S. Stolar, THIS JOURNAL, **81**, 1256 (1959).

(6) G. P. Mueller and L. L. Norton, *ibid.*, **77**, 143 (1955); P. L. Julian, W. Cole, E. W. Meyer and B. M. Regan, *ibid.*, **77**, 4601 (1955); and R. Beyler and F. Hoffman, *J. Org. Chem.*, **21**, 572 (1956).

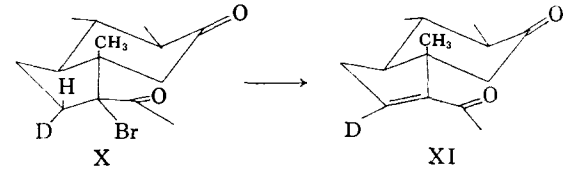
with deuterium at C-16; an oxidation–reduction sequence would be expected to result in loss of deuterium, whereas a process of dealdolization-realdolization should lead to retention of the tracer. In view thereof, synthesis of appropriate labeled systems was undertaken to establish this point.

Deuteration of 3α-acetoxy-Δ[16]-pregnene-11,20-dione (I) on 10% palladium–Nuchar catalyst provided the 16α,17α-dideuterio derivative which was found to have 1.64 atoms of deuterium per molecule. Bromination of the latter afforded 3α-acetoxy-16α-deuterio-17α-bromopregnane-11,-20-dione (X), identical by m.p. and infrared comparison with non-deuterated X,[7] and found by analysis to have 1.09 atoms of deuterium per molecule.

The deuterated bromo derivative X provided the opportunity of examining, by the method of Curtin and Kellom,[8] the mechanism of dehydrobromination of an α-bromoketone. The extensive studies on the mechanism of HX elimination of alkyl halides with bases have dealt to a negligible extent with the dehydrohalogenation of α-haloketones.[9] Displacement reactions of the latter class, in fact, are incompletely understood relative to their non-carbonyl containing counterparts.[10] The prevalent view, however, that dehydrohalogenation of α-haloketones pursues an E_2 *trans* elimination pathway is possibly best supported by the observation of Seebeck and Reichstein.[11] These authors observed that methyl 3α--acetoxy-11β-bromo-12-ketocholanate (11β-Br/9α-H *trans* axial) undergoes dehydrobromination to the corresponding Δ[α,β]-ketone more readily than the epimeric 3α-acetoxy-11α-bromo-12-ketocholanate (11α-Br/9α-H *cis*). On the other hand, more recently 4α- and 4β-bromo-3-ketopregnane derivatives have been dehydrobrominated by lithium chloride in dimethylformamide with certain experimental observations suggesting a *cis* elimination.[12]

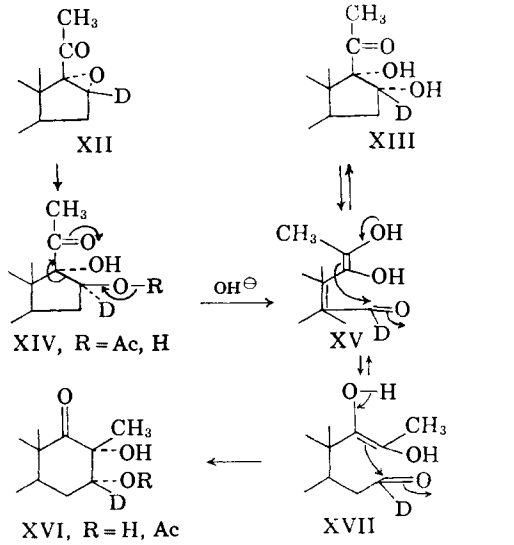
Dehydrobromination of the 16α-deuterio-17α-bromoketone (X) with refluxing pyridine yielded 3α-acetoxy-16-deuterio-Δ[16]-pregnene-11,20-dione (XI) containing 1.03 atoms of deuterium per molecule. Similarly, dehydrobromination of X with lithium chloride in dimethylformamide afforded XI possessing 0.98 atom of deuterium per molecule. Nuclear magnetic resonance spectra measurements on the 16-deuterio-Δ[16]-20-ketone XI obtained by both procedures indicated 15–20% of hydrogen at C-16, thereby indicating a corresponding amount of randomly distributed deuterium in XI as well as its precursor. The excess deuterium quite probably arose from equilibration with deuterium bromide formed in the bromination reaction giving X. This seems particularly indicated, inasmuch as the starting 3α-acetoxy-16α,17α-dideuteriopregnene-11,20-dione contained somewhat less than 2 atoms of deuterium expected by theory. Moreover, subsequent alkaline treatment in the further transformation of XI brought the level of deuterium content into coincidence with that indicated by n.m.r.

The deuterium orientation, 16α, in X is secured by the established rule of the rear mode of hydrogenation for Δ[16]-20-keto steroid systems.[13] The 17α-configuration of the bromine atom has also been established recently.[7] It follows, therefore, that the extent of deuterium retention in the dehydrobromination product XI becomes a measure of the degree of *trans* elimination. Consequently, the finding that retention of deuterium was the major consequence of dehydrobromination signifies the essential E_2 *trans* nature of the elimination process involved. If elimination had proceeded



to any great extent by an E_1 pathway[9a] or by preliminary reactions at the bromine-bearing carbon[14] or less likely at the highly hindered 20-carbonyl group,[7] substantially less deuterium would have been expected in the product XI.

Epoxidation of the 16-deuterio-Δ[16]-20-ketone XI with alkaline hydrogen peroxide yielded the deuterio oxide XII containing 0.93 atom of deuterium per molecule. This oxide was acetolyzed with sulfuric acid in acetic acid to the diolone acetate XIV; the latter was treated directly with 0.5% potassium hydroxide in aqueous dioxane followed by



(7) N. L. Wendler, R. P. Graber and C. G. Hazen, *Tetrahedron*, **8**, 144 (1958).

(8) D. Y. Curtin and D. B. Kellom, THIS JOURNAL, **75**, 6011 (1953).

(9) For leading references see: (a) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Chapter 8, Cornell Univ. Press, Ithaca, N. Y., 1953, p. 420; (b) D. J. Cram in Newman's "Steric Effects in Organic Chemistry," Chapter 6, John Wiley and Sons, Inc., New York, N. Y., 1956, p. 305; see also, N. H. Cromwell, R. P. Ayer, P. W. Foster and P. H. Hess, THIS JOURNAL, **82**, 130, 133, 138 (1960).

(10) See for example, E. L. Eliel, "Steric Effects in Organic Chemistry," Chapter 2, p. 103.

(11) E. Seebeck and T. Reichstein, *Helv. Chim. Acta*, **26**, 536 (1943).

(12) R. P. Holysz, THIS JOURNAL, **75**, 4432 (1953).

(13) See for example: R. E. Marker, R. B. Wagner, P. R. Ulshafer, E. L. Wittbecker, D. P. Goldsmith and C. H. Ruof, THIS JOURNAL, **69** 2167 (1947).

(14) Compare: A. Butenandt and A. Wolff, *Ber.*, **68**, 2091 (1935).

acetylation to give the D-homo diolone XVI as its acetate derivative. The D-homo product was identical with undeuterated XVI by m.p. and infrared comparison and was found to contain 0.85 atom of deuterium per molecule. The retention of deuterium in the D-homo product XVI, of inverted C-16 configuration, clearly excludes the earlier discussed oxidation-reduction process as significantly responsible for the inversion phenomenon. By the same token confirmation is provided for a mechanism involving retroaldol ring opening *via* XV–XVII followed by recyclization to afford the D-homo system with thermodynamic control.[15] The intermediate formation of an acyclic enediol XV under the alkaline conditions of rearrangement derives support from the positive blue tetrazolium reaction produced by the diolone derivative XIV. In the transformation under discussion, the groups 16α-OH and 17β-CH_3 become pseudo-equatorially disposed to ring D where the latter has previously been shown very probably to possess the boat conformation.[16]

Experimental

3α,16β-Diacetoxy-17α-hydroxypregnane-11,20-dione (V).—To a stirred solution of 3.0 g. of 3α-hydroxy-16α,17α-oxidopregnane-11,20-dione (IV)[17] in 60 cc. of acetic acid at 15° was added slowly a cold solution of 6 cc. of concd. sulfuric acid in 60 cc. of acetic acid.[3] After 6 hours at 25°, 600 cc. of ice-water was added and the mixture extracted with chloroform. The chloroform extract was washed with aqueous potassium bicarbonate, water and saturated sodium chloride solution. It was dried over magnesium sulfate and concentrated to dryness to yield 3.1 g. of amorphous residue which was shown by paper chromatography to consist primarily of one mobile component, **3α,16β-diacetoxy-17α-hydroxypregnane-11,20-dione (V)**, as demonstrated by its degradation to the 16β-acetoxy-17-ketone VIII.

3α,16β-Diacetoxy-5β-androstane-11,17-dione (VIII).—To a stirred solution of 1 g. of the 3α,16β-diacetate V in 4 cc. of dimethylformamide was added 200 mg. of sodium borohydride in 10 cc. of water. The mixture was kept at 25° for 4 hours at which time a negative Zimmerman test indicated complete reduction of the 20-carbonyl group. Excess cold 10% acetic acid was added dropwise followed by additional water and the mixture was extracted with chloroform. The latter extract was washed with dilute potassium bicarbonate solution and water. It was dried over magnesium sulfate and taken to dryness to give 1.06 g. of crude **3α,16β-diacetoxy-17α,20-dihydroxypregnane-11,20-dione**. Without purification this intermediate was dissolved in 100 cc. of methanol and treated with 1.0 g. of sodium periodate in 40 cc. of water overnight at 25°. The precipitated sodium iodate was filtered, washed with ethyl acetate, and the filtrate and washings concentrated until the organic solvents were removed. The aqueous suspension was extracted with ethyl acetate, the latter extract washed with water, dried over magnesium sulfate and concentrated to dryness. Chromatography of the residue on neutral alumina gave 3α,16β-diacetoxy-5β-androstane-11,17-dione (VIII) from the benzene eluates. The analytical sample was crystallized from ether: m.p. 184–186°, $[\alpha]^{Chf}D$ +129°; λ_{max}^{Chf} 5.70, 5.75–5.80, 5.84, 8.0 μ; positive blue tetrazolium test.

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.30; H, 7.98. Found: C, 68.07; H, 7.77.

3α,16α-Diacetoxy-5β-androstane-11,17-dione (VI).—In the same manner as described above 400 mg. of 3α,16α-diacetoxy-17α-hydroxypregnane-11,20-dione (III) was treated successively with sodium borohydride and sodium periodate to give 3α,16α-diacetoxy-5β-androstane-11,17-dione (VI). The analytical sample was crystallized from ether: double m.p. 193–195°, 207–212°; $[\alpha]^{Chf}D$ +133° λ_{max}^{Chf} 5.69, 5.78–5.80, 5.84, 8.0 μ; noticeably slower tetrazolium test than the 16β-epimer VIII.

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.30; H, 7.98. Found: C, 67.87; H, 8.18.

3α,17β-Dihydroxy-5β-androstane-11,16-dione (IX).—To a solution of 30 mg. of the 16α-acetoxy-17-ketone VI in 1.5 cc. of methanol was added a solution of 50 mg. of sodium hydroxide in 0.5 cc. of water under nitrogen. After 1 hour at room temperature aqueous acetic acid was added to neutralize the alkali. Additional water was added and the mixture was extracted with chloroform. The chloroform extract was dried over magnesium sulfate and concentrated to dryness. Crystallization of the residue from acetone–ether gave 3α,17β-dihydroxy-5β-androstane-11,16-dione (IX), m.p. 199–201°; λ_{max}^{Chf} 2.75–2.95, 5.72, 5.84 μ.

Anal. Calcd. for $C_{19}H_{28}O_4$: C, 71.25; H, 8.81. Found: C, 71.15; H, 8.92.

Similar treatment of the 16β-acetoxy-17-ketone also produced the 17β-hydroxy-16-ketone IX.

Pyridine–acetic anhydride acetylation of IX gave **3α-17β-diacetoxy-5β-androstane-11,16-dione (IXa)** crystallized from acetone–ether, m.p. 185–187°, $[\alpha]^{Chf}D$ −54°; λ_{max}^{Chf} 5.68, 5.75, 5.83, 8.05 μ.

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.30; H, 7.98. Found: C, 68.62; H, 7.78.

Alkaline Rearrangement of 3α,16β-Diacetoxy-17α-hydroxypregnane-11,20-dione (V) to 3α,16α-Diacetoxy-17α-hydroxy-17β-methyl-D-homo-5β-androstane-11,17a-dione (VII).—A 2-g. sample of the oxide IV was converted to V in 40 cc. of acetic acid containing 4 cc. of concentrated sulfuric acid. The amorphous 3α,16β-diacetoxy-17α-hydroxypregnane-11,20-dione (V) produced was dissolved in 128 cc. of dioxane, treated with a solution of 1.2 g. of potassium hydroxide in 64 cc. of water and allowed to stand at 25° for 18 hours. At the end of this period the reaction mixture was treated with dilute aqueous hydrochloric acid and the dioxane removed *in vacuo* below 50°. The residue was extracted with ethyl acetate, dried and the solvents evaporated *in vacuo*. The residue was acetylated with 2 cc. each of pyridine and acetic anhydride and the product crystallized directly from ether to give 400 mg. of 3α,16α-diacetoxy-17α-hydroxy-17β-methyl-D-homo-5β-androstane-11,17a-dione (VII), m.p. 212–215°, identical in all respects with an authentic sample.[3]

Chromatography of the mother liquors yielded an additional 400 mg. of VII. The non-crystalline fractions combined exhibited $\lambda_{max}^{CH_3OH}$ 238 mμ, $E_{1cm}^{1\%}$ 46, indicating *ca.* 10% of diosphenol acetate[3] arising from VII. The latter was saponified with 20% methanolic potassium hydroxide and the product acetylated and crystallized to give authentic 3α,17-diacetoxy-17a-methyl-D-homo-5β-Δ[17]-androstene-11,16-dione, identical with a known sample.[3]

3α-Acetoxy-16α,17α-dideuteriopregnane-11,20-dione.[18]—A 37.2-g. (0.1 mole) sample of 3α-acetoxy-Δ[16]-pregnene-11,20-dione (I) in 370 cc. of ethyl acetate with 7.5 g. of 10% palladium-on-Nuchar catalyst was deuterated with deuterium gas at atmospheric pressure. The absorption of 1 mole equivalent of gas took place in 1.5–2 hours. The product was crystallized from acetone–hexane to give a first crop of 32.5 g., m.p. 166–168°; mixed m.p. with 3α-acetoxypregnane-11,20-dione was not depressed.

Anal. Calcd. for $C_{23}H_{34}O_4D_2$: D, 2 atoms/molecule. Found: D, 1.64 atoms/molecule.

3α-Acetoxy-16α-deuterio-17α-bromopregnane-11,20-dione (X).—Bromination was effected by well-known procedure[7] on 10 g. of the above 3α-acetoxy-16α,17α-dideuteropregnane-11,20-dione. The product was crystallized several times from acetone–hexane to give 6.5 g. of X, m.p. 166–168°.

Anal. Calcd. for $C_{23}H_{33}O_4BrD$: C, 60.79; H(D), 7.49; Br, 17.62; D, 1 atom/molecule. Found: C, 60.97; H(D), 7.50; Br, 17.67; D, 1.09 atoms/molecule.

Dehydrobromination of the Bromoketone X. (A) By Pyridine.—A solution of 500 mg. of X in 15 cc. of pyridine

(15) A closely related retroaldol change has been suggested recently by Cornforth to account for the epimerization of the hydroxyl group in gibberellic acid; see B. E. Cross, *Chemistry & Industry*, 183 (1959).

(16) N. L. Wendler, *ibid.*, 1662 (1958).

(17) P. L. Julian, W. Cole, E. W. Meyer and B. M. Reagan, THIS JOURNAL, 77, 4601 (1955).

(18) The deuterium analyses were carried out through the courtesy of J. Nemeth, University of Illinois, and R. N. Boos and Ann Soha of these laboratories.

was refluxed for 2 hours. At the end of this period the pyridine was removed *in vacuo* and the residue extracted with ether. The ether solution was washed successively with dilute aqueous hydrochloric acid, water, and potassium bicarbonate solution. Evaporation of the dried ether solution and crystallization of the product from acetone–hexane ether afforded 3α-acetoxy-16-deuterio-Δ[16]-pregnene-11,20-dione (XI), m.p. 167–169°. An n.m.r. spectrum of this material revealed 15–20% of —C=C—H (Δ[16]-protonium) contamination.

Anal. Calcd. for $C_{23}H_{31}O_4D$: C, 73.99; H(D), 8.85; D, 1 atom/molecule. Found: C, 74.20; H(D), 8.65; D, 1.03 atoms/molecule.

(B) By Lithium Chloride in Dimethylformamide.—A solution of 500 mg. of bromoketone X and 0.13 g. of lithium chloride in 5 cc. of dimethylformamide was heated on the steam-bath for 6 hours. The product was watered out, extracted with ether and the residue obtained after evaporation of the ether was crystallized from acetone–hexane to give XI, m.p. 165–168°. This product was identical by mixed m.p. and infrared comparison with XI obtained in part A. Again an n.m.r. spectrum of this material showed the presence of 15–20% of —C=C—H.

Anal. Calcd. for $C_{23}H_{31}O_4D$: C. 73.99, H(D), 8.85; D, 1 atom/molecule. Found: C, 73.80; H(D), 8.78; D, 0.98 atom/molecule.

3α-Hydroxy-16α,17α-oxido-16β-deuteriopregnane-11,20-dione (XII).—To a cold stirred solution of 2.00 g. of the 16-deuterio-Δ[16]-pregnene XI in 60 ml. of methanol at 10° was added 3 cc. of cold 4 *N* aqueous sodium hydroxide and 6 cc. of cold 30% hydrogen peroxide (procedure of Julian, *et al.*[17]). After 40 hours at 5° and 1 hour at 25° the Δ[16]-20-keto ultraviolet absorption band was no longer present. The solution was concentrated to 30 cc., water was added and the mixture extracted with chloroform. The chloroform extract was washed with saturated aqueous sodium chloride, dried over magnesium sulfate and concentrated to dryness. Crystallization of the residue from methanol led to the 16α,17α-oxido-16β-deuteriopregnane XII as plates, m.p. 219–223°.

Anal. Calcd. for $C_{21}H_{29}O_4D$: C, 72.61; H(D), 9.00; D, 1.00. Found: C, 72.63; H(D), 8.71; D, 0.93.

An additional 0.37 g. of XII, m.p. 215–220° (total yield 86%), was obtained on concentration of the filtrate. Paper chromatography of the crystalline fractions as well as the crystalline residue (benzene–formamide system) showed each fraction to consist of a single component with the same mobility as an authentic sample of undeuterated oxide IV.

Alkaline Rearrangement of 3α,16β-Diacetoxy-17α-hydroxy-16α-deuteriopregnane-11,20-dione (XIV, R = Ac) to 3α,16α-Diacetoxy-17α-hydroxy-17β-methyl-16β-deuterio-D-homo-5β-androstane-11,17a-dione (XVI).—A 1-g. sample of the deuterated oxide XII was acetolyzed as previously described in 30 cc. of acetic acid containing 2 cc. of concentrated sulfuric acid. The product XIV (R = Ac) was dissolved in 64 cc. of dioxane, treated with 600 mg. of potassium hydroxide in 32 cc. of water and allowed to stand at room temperature for 18 hours. At the end of this period the reaction mixture was acidified, the dioxane removed *in vacuo* and the residue extracted with ethyl acetate. Evaporation of the ethyl acetate and crystallization of the residue from acetone–ether gave XVI in copious crystalline form, m.p. 212–215°, not depressed on mixed m.p. with authentic XVI. The infrared spectra of the two samples were identical.

Anal. Calcd. for $C_{25}H_{35}O_7D$: D, 1 atom/molecule; corrected for C_{16}–H contamination (n.m.r.) D, 0.8–0.85. Found: D, 0.85 atom/molecule.

In a like manner 3α-acetoxy-16α,17α-dihydroxypregnane-11,20-dione (XIII) under the same conditions of alkaline rearrangement gave XVI.

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Alkylated Adrenal Hormones. The Synthesis of 5α-Methylated Androstanes

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The synthesis of 5α-methyl-androstane-17β-ol-3-one *via* angular methylation of a suitable 6-ketone, IV, is described.

It is a well known fact that the double bond between carbons four and five in testosterone is not a necessary prerequisite for biological activity. For instance an A/B-*trans* saturated analog of testosterone, 5α-androstane-3α-ol-17-one, is a potent androgen.[1] On the other hand, the corresponding C-5 epimer, 5β-androstane-3α-ol-17-one, is inactive in this regard, but exhibits a pyrogenic[2] effect in humans. The introduction of α-methyl groups at positions 2[3a] and 6[3b] into C-19 steroids has the effect of increasing the ratio of anabolic to androgenic activity. One of these compounds, 2α-methyl-androstane-17β-ol-3-one has also found utility in the treatment of some cases of metastatic breast cancer.[4]

In order to study the effect of substitution, at the ring juncture of an A/B-*trans* steroid, on androgenic and anabolic activity, it was of interest to prepare a C-5α-methylated androstane derivative. This paper describes the synthesis of 5α-methyl-androstane-17β-ol-3-one (VII) from testosterone acetate.

No 5α-methylated derivative of the biologically active steroid hormones has been reported.[5] Modification of a recent synthesis[6] of 5β-methylated pregnanes by alkylation of 17α,20,20,21-bismethylenedioxy-3-ethylenedioxy-allopregnane-6,11-dione (A) offered a possible approach to the desired compound.

Examination of the factors responsible for the stereospecific introduction of methyl on the β-

(1) R. I. Dorfman and R. A. Shipley, "The Androgens," John Wiley and Sons, Inc., New York, N. Y., 1956.

(2) A. Kappas, L. Hellman, D. K. Fukushima and T. F. Gallagher, *J. Clin. Endocrinol. Metabolism*, **17**, 451 (1957).

(3) (a) H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, **21**, 1333 (1956); H. J. Ringold, E. Batres, O. Halpern and E. Necoechea, THIS JOURNAL, **81**, 427 (1959); (b) H. J. Ringold, E. Batres and G. Rosenkranz, *J. Org. Chem.*, **22**, 99 (1957); M. Ackroyd, W. J. Adams, B. Ellis, V. Petrow and I. A. Stuart-Webb, *J. Chem. Soc.*, 4099 (1957).

(4) C. M. Blackburn and D. S. Childs, *Proc. Staff Meet., Mayo Clinic*, **34**, 113 (1959).

(5) 5α-Methyl-cholestane-3β,6β-diol is the only reported example of a 5α-methylated steroid; M. Chuman, *J. Chem. Soc., Japan, Pure Chem. Section*, **70**, 253 (1949); see, however, ref. 6.

(6) J. H. Fried, G. E. Arth and L. H. Sarett, THIS JOURNAL, **82**, 1684 (1960).