chlorides were carried out under the conditions indicated in Table I. The reagents were mixed in the absence or in the presence of solvents, depending on the reactivity of the chlorides and on their physical state. The course of the reaction was followed by means of infrared spectrometry on small aliquots. At the end of the reaction, the solvent was evaporated under vacuum. When the products were liquids, purification was effected by vacuum distillation. When the products were solids, the crude phosphates, usually of an acceptable degree of purity, were obtained by addition of cold ether. The phosphates were crystallized from the solvents indicated in Table I.

Reaction of the Phospholene XIII with Phosgene.—The phosgene was condensed in a trap at −70° and was then passed[10] through anhydrous $CuSO_4$ and led into a 5 *M* solution of the biacetyl–trimethyl phosphite adduct, XIII, in methylene chloride at 0°. The addition of the phosgene was carried out over a 2-hr period; the chloride was used in excess (*ca.* 1.7 mol equiv). The solution was kept overnight at 20° and was then freed from solvent at 20° and 10 mm, with protection against moisture. The residue was analyzed by ^1H and ^{31}P nmr and infrared spectrometry. This material consisted of 95% acid chloride XXXI and 5% dimethyl phosphoacetoin. *The acid chloride should be handled with care since it may have a high degree of toxicity.*

The acid chloride XXXI (33 mmol) in benzene (80 ml) was treated at 0° with *p*-toluidine (67 mmol) in benzene (25 ml). The mixture was kept 1 hr at 25° and was then filtered. The filtrate was evaporated at 25° (10 mm) and the residue was washed with pentane. The crude *p*-toluide XXXII (76% yield) had mp 102–103°. The analytical sample had the same melting point (from benzene–hexane).

Anal. Calcd for $C_{14}H_{20}O_6NP$: C, 51.1; H, 6.1; N, 4.2. Found: C, 51.1; H, 6.2; N, 4.3.

The infrared spectrum in CH_2Cl_2 had bands at 3.00, 5.78, 5.95, and 7.80 μ. The ^1H nmr spectrum in $CDCl_3$ had singlets at τ 7.66 ($CH_3C_6H_4$–), 7.70 (CH_3CO), and 8.03 (CH_3C); it had doublets at 6.12 and 6.17, both with J_{HP} = 11 cps; it had aromatic protons near 2.7.

Hydrolysis of the Phosphate Esters of α-Hydroxy β-Diketones.—The procedure used and the properties of the resulting alcohols are given in Table III.

Acetyltrifluoroacetylmethylcarbinol dimethyl phosphate (XVII) was very sensitive to water, therefore, the following procedure was used. The phosphate (9.10 g) was dissolved in ether (30 ml) and the solution was cooled to 0°. One molar equivalent of water was added and the mixture was stirred for 30 min at 0° and for 30 min at 20°. The solution was submitted to fractional distillation and gave the hydroxy diketone, XXXIV, in 65% yield; *cf.* Table III.

Acetyltrifluoroacetylmethylcarbinyl Chloride (XX).—As stated in Table I, the reaction of the biacetyl–trimethyl phosphite adduct, XIII, with trifluoroacetyl chloride (XV) gave a by-product which was removed by distillation below 45° at 40 mm. This liquid was distilled and gave the chloro diketone, XX, bp 79–80° at 80 mm.

Anal. Calcd for $C_6H_6O_2F_3Cl$: C, 35.6; H, 3.0; F, 28.2; Cl, 17.3. Found: C, 35.9; H, 3.1.

The infrared spectrum in CH_2Cl_2 had bands at 5.62 and 5.80 with a shoulder at 5.70 μ. The ^1H nmr spectrum in $CDCl_3$ had singlets at τ 7.53 (acetyl) and 8.16 (methyl on C).

Registry No.—XIII, 1665-79-8; XVI, 15088-11-6; XVII, 15186-04-6; XVIII, 15088-10-5; XX, 15138-14-4; XXVII, 15138-15-5; XXVIII, 15138-16-6; XXIX, 15138-17-7; XXX, 15186-02-4; XXXI, 15138-18-8; XXXII, 15215-70-0; XXXIII, 7338-73-0; XXXIV, 15138-20-2; XXXV, 15138-21-3; XXXVI, 15138-22-4; XXXVII, 15186-03-5; XXXVIII, 15138-23-5.

Reaction of Hydriodic Acid with Tertiary Ketols[1]

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The reaction of hydriodic acid in refluxing acetic acid on tertiary ketols can bring about reduction to saturated ketones, rearrangements, and/or eliminations. Many ketols undergo these reactions whereby an intermediary carbonium ion can explain these reaction sequences. If the ketone cannot enolize no reaction takes place.

Recent publications[3–5] by Reusch, *et al.*, on the reduction of saturated and unsaturated α-diketones and secondary α-ketols with hydriodic acid in refluxing acetic acid prompted this publication on the reaction of the same reagent on tertiary ketols. *A priori*, we were interested in a versatile method for the reduction of 17α-hydroxy 20-keto steroids and also in the reduction of the 17,21-dihydroxy 20-keto side chain as an addition to already well-established methods[6–8] of reduction with zinc and acetic acid. Further examples for the study of tertiary ketol reduction by hydriodic acid were carried out in order to assess this method.

Most materials were allowed to react under the same conditions described by Reusch,[3–5] except in the case of 1-acetyl-1-hydroxycyclohexane which required increased temperature and duration of reaction. In all cases an immediate release of iodine was observed which rendered the solution dark. All conversions were free of tar formation[9] and gave in most cases readily separable mixtures.

Thus, 17α-hydroxyprogesterone (**1**) was first rearranged[10] to 17aα-methyl-17aβ-hydroxy-D-homoandrost-4-ene-3,17-dione[11] (**2**), which in turn was reduced to 17aβ-methyl-D-homoandrost-4-ene-3,17-dione (**3**) (see Scheme I). The isomerization[10] of 17α-hydroxyprogesterone with base and the isolation of the resulting isomeric hydroxymethyl-D-homo ketones is described in detail in the Experimental Section.

Both 3β-methyl-3α-hydroxy-5α-androstane-2,17-dione[12] (**7**) and 2β-hydroxy-2α-acetyl-A-nor-5α-androstan-17-one[12] (**10**) gave the identical product, 3β-methyl-5α-androstane-2,17-dione (**6**) (see Scheme II).

(1) Supported, in part by grants AM-01934 and AM-07280 from the National Institute of Arthritis and Metabolic Diseases.

(2) Ayerst Laboratories, Montreal, Que.

(3) W. Reusch and R. LeMahieu, *J. Amer. Chem. Soc.*, **85**, 1669 (1963).

(4) W. Reusch and R. LeMahieu, *ibid.*, **86**, 3068 (1964).

(5) W. Reusch, R. LeMahieu, and R. Guynn, *Steroids*, **5**, 110 (1965).

(6) J. K. Norymberski, *J. Chem. Soc.*, 517 (1956).

(7) H. L. Slates and N. L. Wendler, *J. Org. Chem.*, **22**, 498 (1957).

(8) R. S. Rosenfeld, *J. Amer. Chem. Soc.*, **79**, 5540 (1957).

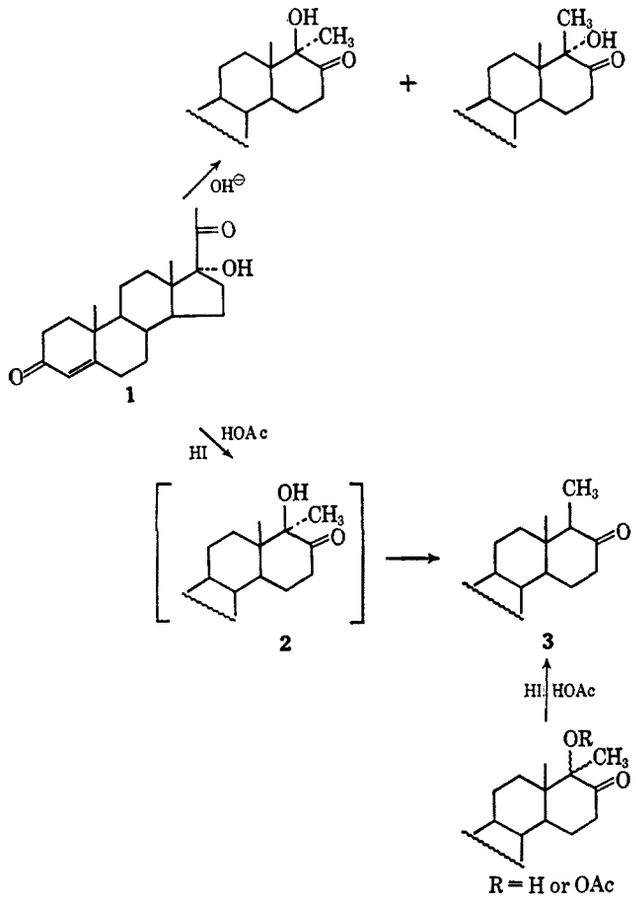
(9) Additional hydroxyls (besides the ketol itself) lead to extensive tar formation.

(10) For pertinent discussion of this rearrangement, see N. L. Wendler in "Molecular Rearrangements II," de la Mare, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, pp 1114–1121, and references therein.

(11) C. W. Shoppee and D. A. Prins, *Helv. Chim. Acta*, **26**, 201 (1943).

(12) The synthesis of this compound is described in the experimental part.

SCHEME I



Compounds **7** and **10** were prepared as follows. 2α-Ethynyl-A-nor-5α-androstane-2β,17β-diol[13] (**4**) was hydrated and the product acetylated by treating[14] it with acetic anhydride, acetic acid, boron trifluoride etherate, and mercuric oxide. The resulting 2α-acetyl-A-nor-5α-androstane-2β,17β-diol diacetate (**5**) was hydrolyzed with a 1.1 equiv of base to a mixture of 2α-acetyl-A-nor-5α-androstane-2β,17β-diol (**9**) and of the rearranged 3α,17β-dihydroxy-3β-methyl-5α-androstan-2-one (**8**). The relative configuration of hydroxyl and methyl at carbon 3 follows from reagent control of the reaction and from the bathochromic shift[15] of the optical rotatory dispersion curves of this hydroxy ketone from the corresponding 3-methyl-5α-androstane-2,17-dione (**6**). Both **8** and **9** were oxidized with chromic acid in acetone to their respective 17-ketones **7** and **10**.

Treatment of 5α-hydroxyandrostane-6,17-dione[12] (**14**) with hydriodic acid gave 5α-androstane-6,17-dione (**17**). **14** was prepared in the following fashion. Treatment of 3β-hydroxyandrost-5-en-17-one (**11**) with thionyl chloride gave the known 3β-chloroandrost-5-en-17-one[16] (**12**) (see Scheme III). This product was reduced with lithium in liquid ammonia and the androst-5-en-17β-ol (**13**) was epoxidized with *m*-chloroperbenzoic acid. The resulting 5α,6α-epoxyandrostan-17β-ol (**16**) was treated with acid, and the triol **15** then oxidized with chromic oxide to give the desired 5α-hydroxyandrostane-6,17-dione (**14**).

17α,21-Dihydroxypregn-4-ene-3,20-dione (**18**) was reduced (*via* Mattox rearrangement)[17] to deoxycorticosterone (**19**) (see Scheme IV). Some time ago Slates and Wendler[7] suggested that the reduction of the dihydroxyacetone side chain with zinc and acetic acid must proceed through an enol aldehyde intermediate **20**, and H. L. Herzog, *et al.*,[18] have shown that by treatment of this intermediate with zinc and acetic acid the corresponding 21-hydroxy 20-ketone could be obtained. Upon reduction of the dihydroxyacetone side chain with hydriodic acid the enol aldehyde intermediate could be isolated from the reaction mixture. This compound was reduced further to progesterone or was esterified to deoxycorticosterone acetate. Deoxycorticosterone (**19**) gave as reaction product in good yield progesterone (**21**) and a small amount of deoxycorticosterone acetate (**22**). The latter could be reduced further to furnish progesterone exclusively. 17α,21-Dihydroxypregn-4-ene-3,20-dione 21-acetate (**23**) gave a mixture of 80% deoxycorticosterone acetate (**22**), 5% deoxycorticosterone (**19**), and 15% progesterone (**21**).

1-Acetyl-1-hydroxycyclohexane gave acetylcyclohexane and in addition a small amount of 1-acetylcyclohexene.

17α-Hydroxy-5β-D-homopregnane-3,11,20-trione (**24**) and 3β-hydroxy-3α-acetyl-5α-androstan-17-one (**25**) did not react (see Scheme V).

Discussion of Results

The reduction and/or rearrangement of tertiary ketols by hydriodic acid seems to be effected in several steps. This is evidenced in some examples by the isolation of intermediates. Most cases can be explained by initial protonation of the carbonyl function[19] to give a carbonium ion as common intermediate. This can be followed (loss of proton) by enolization, in analogy with the Mattox rearrangement.[17] The allylic alcohol can be attacked by a nucleophile as hydride or iodide ion which will then readily lead to the parent ketone (see Scheme VI).

Such a reaction sequence would explain the results obtained by reduction of 1-hydroxy-1-acetylcyclohexane to acetylcyclohexane, the reduction of 17α,21-dihydroxypregn-4-ene-3,20-dione (**18**) to 21-acetoxypregn-4-ene-3,20-dione (**22**), the reduction of deoxycorticosterone (**19**) to progesterone (**21**), the reduction of 5α-hydroxyandrostane-6,17-dione (**14**) to 5α-androstane-6,17-dione[20] (**7**), and others. Such a mechanism would also explain the recovery of starting material from a nonenolizable ketone as 17β-hydroxy-17α-methyl-D-homo-5α-androstane-3,17a-dione (**26**). The resistance to reduction of 3β-hydroxy-3α-acetyl-5α-androstan-17-one[21] (**25**) is most likely caused by the

(13) M. Minssen and J. Jacques, *Bull. Soc. Chim. Fr.*, 71 (1965).

(14) Compare L. Ruzicka and H. F. Meldahl, *Helv. Chim. Acta*, **21**, 1760 (1938).

(15) R. C. Cookson and S. H. Dandegaonker, *J. Chem. Soc.* 352 (1955); G. Baumgartner and C. Tamm, *Helv. Chim. Acta*, **38**, 441 (1955).

(16) E. S. Wallis and E. Fernholz, *J. Amer. Chem. Soc.*, **59**, 764 (1937).

(17) V. R. Mattox, *ibid.*, **74**, 4340 (1952).

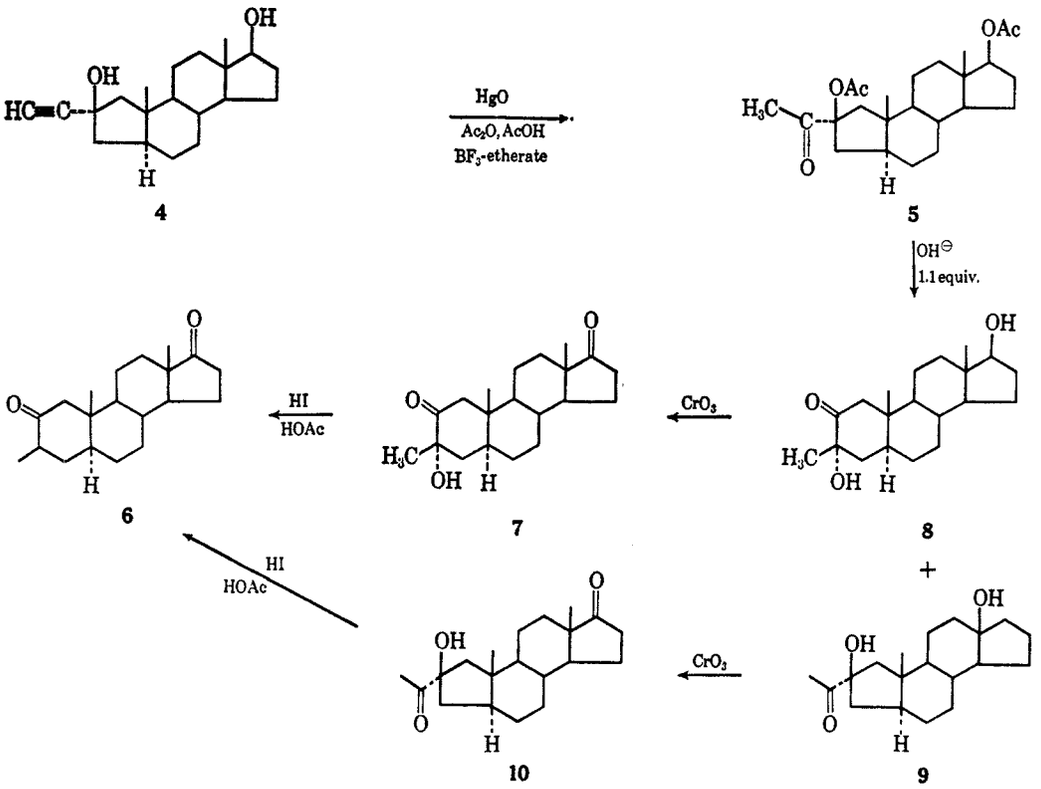
(18) Compare H. L. Herzog, M. J. Gentles, H. Marshall, and E. B. Hershberg, *ibid.*, **83**, 4073 (1961).

(19) This differs from the proposed protonation of the hydroxyl function; compare ref 4.

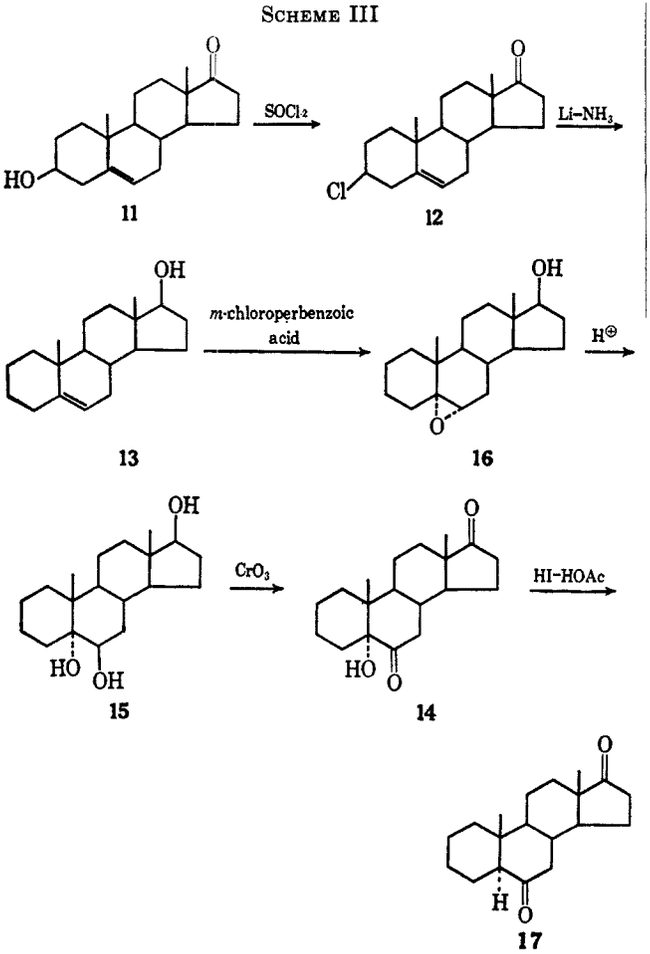
(20) A. Butenandt and L. A. Surang, *Chem. Ber.*, **75**, 591 (1942), and also G. Rosenkranz, M. Velasco, and F. Sondheimer, *J. Amer. Chem. Soc.*, **76**, 5024 (1954).

(21) 3β-Hydroxy-3α-acetyl-5α-androstan-17-one 17-ethylene ketal could not be brominated. Private communication of Dr. Andrée Marquet, Collège de France, Paris.

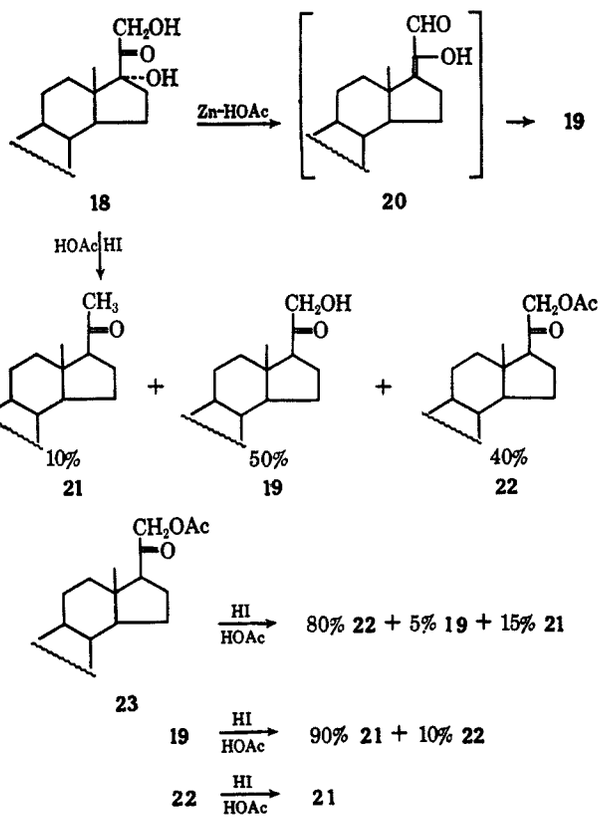
SCHEME II



SCHEME III



SCHEME IV

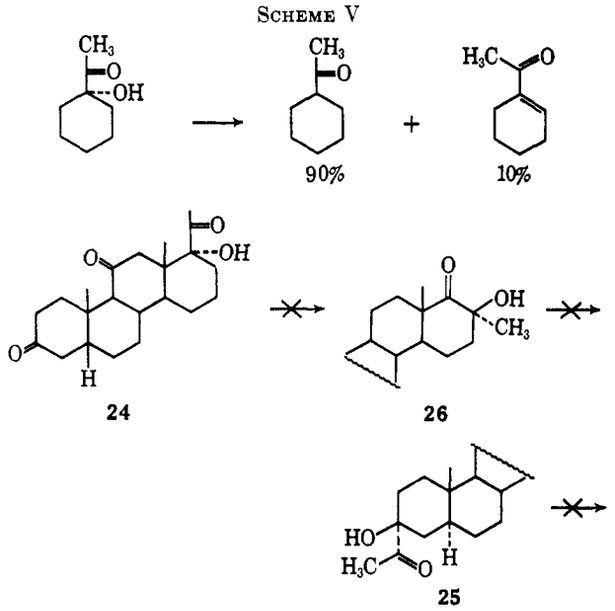


apparent inability of the ketone to enolize. The 17aα-hydroxy-D-homo-5β-pregnane-3,11,20-trione[22] (**24**) would give a 20-enol readily, but suffers from the interaction[23] between either OH group and C-12 or between the $-CH_2I$ moiety and C-12 of this hypothetical enolic intermediate.

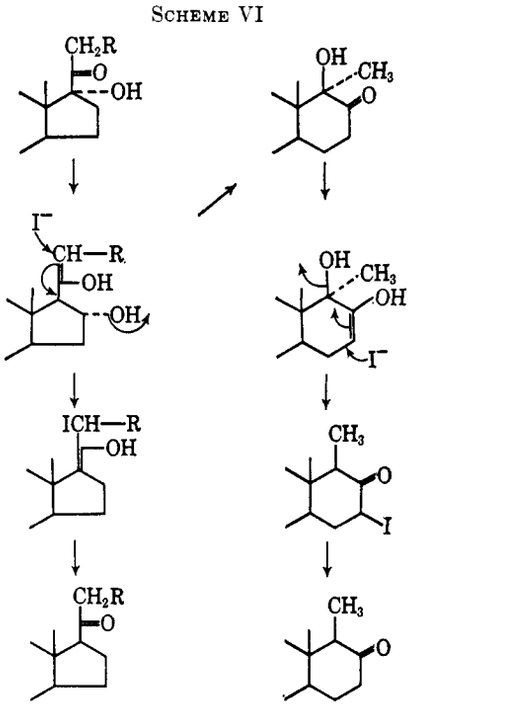
(22) R. O. Clinton, H. C. Neumann, A. J. Manson, S. C. Laskowski, and R. G. Christiansen, *J. Amer. Chem. Soc.*, **80**, 3395 (1958).

(23) Compare F. Johnson and S. K. Malhotra, *ibid.*, **87**, 5492 (1966); S. K. Malhotra and F. Johnson, *ibid.*, **87**, 5493 (1966).

SCHEME V



SCHEME VI



The reaction of 17α-hydroxyprogesterone (**1**) with hydriodic acid proceeds also through initial formation of a carbonium ion which is then followed by ring D expansion (migration of the C_{13-17} bond). The intermediate 17aβ-hydroxy-17aα-methyl-D-homopregn-4-ene-3,17-dione[24] (**2**) can then be reduced *via* formation of an allylic alcohol, as suggested above, to give 17aβ-methyl-D-homopregn-4-ene-3,17-dione (**3**). The transformation of 2β-hydroxy-2α-acetyl-A-nor-5α-androstan-17-one (**10**) to 3β-methyl-5α-androstane-2,17-dione (**6**) is analogous.

Experimental Section

Reaction of Hydriodic Acid on 17α-Hydroxyprogesterone.—A solution of 500 mg of 17α-hydroxyprogesterone (**1**) in 20 ml of glacial acetic acid and 1 ml of 47% hydriodic acid was heated on a steam bath. Samples were taken every 5 min and added to an aqueous sodium hydrogen sulfite solution. The precipitated solids were collected and dried. Then a 0.01-mg aliquot of each fraction was chromatographed on paper, using a Bush B_3 system [mobile phase Skellysolve C–benzene (2:1 v/v), stationary phase methanol–water (4:1 v/v)]. The results, obtained by inspection of the paper with an ultraviolet lamp, are tabulated in Table I.

TABLE I

Sample after x min	R_f values (relative amount of absorbance) I, 17α-Hydroxyprogesterone (**1**)	II, 17aβ-Hydroxy-17aα-methyl-D-homopregn-4-ene-3,17-dione (**2**)	III, 17aβ-Methyl-D-homopregn-4-ene-3,17-dione (**3**)
5	0.54 (faint)	(0)	(0)
10	0.54 (faint)	(0)	(0)
15	0.54 (++)	0.7 (++)	0.85 (+)
20	0.54 (+)	0.7 (++)	0.85 (++)
25	(0)	0.7 (++)	0.85 (+++)
30	(0)	(0)	0.85 (+++)

The solution of a 100-mg aliquot of the 25-min fraction in 5 ml of acetic acid was heated on a steam bath with 0.5 ml of 47% hydriodic acid for 30 min. The brown solution was poured into an aqueous sodium hydrogen sulfite solution and the precipitate collected by filtration. After washing and drying there was obtained 90 mg of crystalline material which was found to be a single compound and corresponded to spot III, judged by its migration on a Bush B_3 paper system. This fraction and the 30-min fraction were combined to give 190 mg of a substance which did not show any hydroxyl band in the infrared spectrum. The nmr spectrum showed the presence of two methyl peaks on tertiary carbon (46 and 74.5 cps corresponding to 18- and 19-CH_3 groups, respectively) and one methyl group on a secondary carbon (doublet centered at 61 cps, J_{AB} = 7.0 cps). No peak for a CH_3–CO– type methyl was present. A portion was crystallized for analysis from methylene chloride–ether: mp 210–212°; $\lambda_{max}^{methanol}$ 240 mμ (ϵ 12,500); ν_{max}^{KBr} 1700 (hexacyclic ketone), 1680, 1610 (conjugated ketone) cm^{-1}; nmr 46.0 (18-CH_3), 61 (d) (17α-CH_3, J_{AB} = 7 cps), 74.5 (19-CH_3) cps.

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.13; H, 9.83.

Isolation of the Intermediate from the Hydriodic Acid Reaction on 17α-Hydroxyprogesterone.—An aliquot of 60 mg of the 15-min and 20-min fractions from the hydriodic acid reaction product was chromatographed on celite using the Bush A system. After collecting 60 fractions the chromatography was stopped and identical fractions combined. Thus fractions 1 to 17 gave the 17aα-methyl-17-ketone **3**, fractions 20 to 25 gave 15 mg of the intermediate **2**, and fractions 28 to 60 yielded unreacted 17α-hydroxyprogesterone (**1**). The intermediate showed a hydroxyl band in the infrared and its nmr spectrum showed the absence of a CH_3C=O type methyl and the presence of three methyl groups on a tertiary carbon at 46.5, 70, and 80 cps. An aliquot was crystallized for analysis: mp 189–191°; $\lambda_{max}^{methanol}$ 240 mμ (ϵ 13,000); [α]D +40° (*c* 1.0 in $CHCl_3$); nmr, 46.5 (18-CH_3), 70.0 (19-CH_3), 80.0 (17a-CH_3) cps.

Anal. Calcd for $C_{21}H_{30}O_2$: C, 76.32; H, 9.15. Found: C, 76.36; H, 9.15.

Isomerization of 17α-Hydroxyprogesterone with Base.—To a solution of 1 g of 17α-hydroxyprogesterone (**1**) in 95 ml of methanol, 5 g of potassium hydroxide in 5 ml water was added and the solution was refluxed under nitrogen. Samples were withdrawn from the reaction mixture after 30 min, 1 hr, 2 hr, 4 hr, and 20 hr of reaction. They were worked up by pouring them into water and extracting with ethyl acetate. After washing, drying, and evaporation, each fraction was chromatographed on paper using a Bush B_3 system. The results are tabulated in Table II.

Isolation of the Isomeric Hydroxymethyl Ketones.—A portion of fraction 5 weighing 50 mg was distributed between two phases of a Bush B_3 system in a countercurrent apparatus equipped with 99 tubes. After countercurrent extraction the solvents from each tube were removed by evaporation and the fractions were combined according to their R_f values, in the following manner: tubes 2 to 20 (15 mg, mp 284–286°, R_f 0.32),

(24) J. von Euw and T. Reichstein, *Helv. Chim. Acta*, **24**, 879 (1941).

TABLE II

Fraction	Time of withdrawal, hr	Spots and their R_f value
1	0.5	0.54
2	1	0.54
3	2	0.54; 0.71
4	4	0.54, 0.71; 0.33
5	20	0.71; 0.33

tubes 21 to 23 (mixture, 9 mg, R_f 0.32, 0.71), tubes 24 to 35 (25 mg, mp 185–186°, R_f 0.71).

The more polar fraction of mp 284–286° was identified as 17aα-hydroxy-17aβ-methyl-D-homoandrost-4-ene-3,17-dione.[22]

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.49; H, 9.21.

The nmr spectrum showed signals at 45.0 (18-CH_3), 70.0 (19-CH_3), 72.5 (17a-CH_3) cps.

The less polar major fraction was identified as 17aβ-hydroxy-17aα-methyl-D-homoandrost-4-ene-3,17-dione:[11,22] mp 189–191°; $[\alpha]D$ +40° (*c* 1.0 in $CHCl_3$); nmr 46.5 (18-CH_3), 70.0 (19-CH_3), 80.0 (17a-CH_3) cps. This product was identical in all respect with the intermediate of the hydriodic acid reaction product of 17α-hydroxyprogesterone.

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.36; H, 9.15.

2α-Acetyl-A-nor-5α-androstane-2β,17β-diol.—To a solution of 400 mg of 2β,17β-diacetoxy-2α-acetyl-A-nor-5α-androstane in 15 ml of methanol, 2.2 ml of 1 *N* sodium hydroxide solution was added during a period of 15 min and the solution heated on a steam bath for another 40 min. Then the solution was cooled, poured into ice, and neutralized with acetic acid. The precipitate was collected, washed, and dried to yield 350 mg of a substance showing no acetate band in the infrared. A silica gel, thin layer chromatogram using 30% ethyl acetate in benzene showed two spots with R_f values of 0.7 and 0.6, respectively. The product was chromatographed on a silica gel column. Elution with 12% ethyl acetate in benzene yielded fractions melting between 172–176°. Elution with 15% ethyl acetate yielded fractions melting between 165–170° and then fractions melting between 200–203°. Investigation of the chromatographic fractions by thin layer chromatography indicated that the fractions melting at 172–176° were one single component, the fractions melting at 165–170° were a mixture, and those melting at 200–203° were one single component. The fractions with mp 172–176° were combined to give 250 mg of 2α-acetyl-A-nor-5α-androstane-2β,17β-diol. A portion was crystallized three times from ether for analysis: mp 182–184°; ν_{max}^{KBr} 3700, 3500 (-OH), 1705 cm^{-1}; nmr, 45.5 (18-CH_3), 62.0 (19-CH_3), 135.0 (-C=OCH_3) cps.

Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 75.02; H, 10.21.

The fractions melting at 200–206° were combined to give 25 mg of 3α,17β-dihydroxy-3β-methyl-5α-androstan-2-one (**8**). A portion was recrystallized from ether–hexane to give an analytical sample: mp 206–208°; ν_{max}^{KBr} 3400, 3510 (-OH), 1700 (ketone) cm^{-1}; nmr, 45.0 (18-CH_3), 52.5 (19-CH_3, $W_{1/2}$ = 0.9 cps), 79.0 (3β-CH_3) cps; ORD, λ in mμ ([ϕ] in degrees); 450, (+293), 425, (+378), 400, (+506), 375, (+685), 350, (+1083), 325, (+2698), 300, (−135), 321, (+2881, peak).

Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 74.76; H, 9.94.

2β-Hydroxy-2α-acetyl-A-nor-5α-androstan-17-one (**10**).—To a cooled solution of 200 mg of 2α-acetyl-A-nor-5α-androstane-2β,17β-diol (**9**) in 20 ml of acetone was added 0.2 ml of 8 *N* chromic oxide (Jones reagent) solution and the mixture stirred at 0–5° for 5 min. Then the excess of chromic acid was decomposed by methanol and the solution poured into water. The crystalline precipitate was collected, washed, and dried to give 192 mg of 2β-hydroxy-2α-acetyl-A-nor-5α-androstan-17-one (**10**), mp 146–148°. A portion was crystallized from ether–hexane for analysis: mp 148–150°; ν_{max}^{KBr} 3500 (-OH), 1705 (ketone), 1740 (pentacyclic ketone) cm^{-1}; nmr, 53.5 (18-CH_3), 62.5 (19-CH_3), 134 (-COCH_3) cps.

Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.20; H, 9.63.

3β-Methyl-5α-androstane-2,17-dione (**6**).—A solution of 200 mg of 2β-hydroxy-2α-acetyl-A-nor-3α-androstan-17-one (**10**) in 10 ml of acetic acid was heated on a steam bath with 2 ml of 47% hydriodic acid for 30 min. The dark brown solution was cooled and poured into a cold 10% solution of sodium bisulfite. The precipitate was collected, thoroughly washed, and dried to yield 180 mg of 3β-methyl-5α-androstane-2,17-dione (**6**), mp 145–147°. A portion was crystallized for analysis from ether–hexane: mp 148–150°; ν_{max}^{KBr} 1745 (17-ketone), 1700 (2-ketone) cm^{-1} (no -OH stretching); nmr, 45.0 (19-CH_3, $W_{1/2}$ = 0.9 cps), 53.0 (18-CH_3), 63 (3β-CH_3, $-J_{AB}$ = 6.0 cps); ORD, λ in mμ ([ϕ] in degrees), 450 (+640), 425 (+818), 400 (+1124), 375 (+1649), 350 (+2366), 325 (+7330), 300 (+1678), 290 (+526), 320.5 (+8778 shoulder), 316 (+9205 peak).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00 Found: C, 79.61: H, 9.81.

3α-Hydroxy-3β-methyl-5α-androstane-2,17-dione (**7**).—Precisely as described for 2α-acetyl-A-nor-5α-androstane-2β,17β-diol (**9**), 100 mg of 3α,17β-dihydroxy-3β-methyl-5α-androstan-2-one (**8**) were oxidized to give 90 mg of 3α-hydroxy-3β-methyl-5α-androstane-2,17-dione (**7**): mp 192–193°; ν_{max}^{KBr} 1750 (17-ketone), 1700 (2-ketone) cm^{-1}.

3β-Methyl-5α-androstane-2,17-dione (**6**) **from 3α-Hydroxy-3β-methyl-5α-androstane-2,17-dione** (**7**).—When 50 mg of 3α-hydroxy-3β-methyl-5α-androstane-2,17-dione (**7**) was treated with hydriodic acid as described in the case of 2β-hydroxy-2α-acetyl-A-nor-5α-androstan-17-one (**10**), 40 mg of a substance, mp 147–149°, was obtained which was proved to be identical with 3β-methyl-5α-androstane-2,17-dione (**6**), obtained previously, by its infrared and nmr spectrum.

5α,6α-Epoxyandrostan-17β-ol (**16**).—To a solution of 4.09 g of androst-5-en-17β-ol (**13**) in 40 ml of dichloromethane, was added during a period of 2 min a solution of 2.8 g of *m*-chloroperbenzoic acid (FMC, 85% assay) in 30 ml of dichloromethane. The mixture was stirred at 25° for a period of 45 min and then left at −15° for 2–3 hr. The *m*-chlorobenzoic acid, which started to precipitate after 20 min of stirring, was removed by filtration. The *m*-chlorobenzoic acid in solution and the excess peracid were removed by extraction with 2 *N* aqueous sodium hydroxide solution. The dichloromethane extract was dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. The residue was triturated with ether and the crystalline slurry filtered. The crystals were washed with little ether, collected, and dried. There was obtained 3.14 g of colorless prisms.

Recrystallization of this material with ether by means of a Soxhlet extraction apparatus furnished the analytical sample: mp 140–142°; ν_{max}^{KBr} 3280, 1180, 1075, 1050, 1025, 968, 958, and 920 cm^{-1}.

Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.78; H, 10.56.

Androstane-5α,6β,17β-triol (**15**).—To a suspension of 2.0 g of 5α,6α-epoxyandrostan-17β-ol (**16**) in 30 ml of acetone was added 2 ml of a 1.5 *N* aqueous perchloric acid solution. The mixture was stirred at 25° for a period of 45 min, after which time the clear solution was left for 18 hr at −15°. The product was precipitated by pouring the solution into a mixture of 600 g of ice and 150 ml of saturated saline solution and then the mixture was left standing until the ice had melted. The microcrystalline precipitate was filtered and washed with water to give 1.52 g of colorless crystals, mp 182–185°. The analytical sample was obtained by recrystallization from dichloromethane–acetone: mp 188–190°; ν_{max}^{KBr} 3450, 1075, 1052, 1010, 960, and 920 cm^{-1}.

Anal. Calcd for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46. Found: C, 73.64; H, 10.69.

5α-Hydroxyandrostane-6,17-dione (**14**).—A solution of 300 mg of androstane-5α,6β,17β-triol (**15**) in 10 ml of acetone was oxidized with 0.3 ml of Jones reagent in the usual fashion. Work-up yielded 270 mg of the dione, mp 230–234°. Recrystallization from ether gave the analytical sample: mp 236–238°; ν_{max}^{KBr} 3400 (-OH), 1750 (17-ketone), 1702 (6-ketone) cm^{-1}.

Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.94; H, 9.50.

5α-Androstane-6,17-dione (**17**).—A solution of 200 mg of 5α-hydroxyandrostane-6,17-dione (**14**) in 10 ml of acetic acid was heated on a steam bath with 2 ml of hydriodic acid. Work-up as described for 2β-hydroxy-2α-acetyl-A-nor-5α-androstan-17-one (**10**) yielded 180 mg of solids, mp 128–130°. Thin layer chromatography of the product in 30% ethyl acetate in benzene showed one spot, R_f 0.75. The crude product was recrystallized from hexane to give pure 5α-androstane-6,17-dione:[20] mp 132–135°; $[\alpha]^{23}D$ +96° (*c* 1.0 in chloroform); nmr 45.5 (19-CH_3, $W_{1/2}$ = 0.6), 52.5 (18-CH_3) cps.

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.20; H, 9.49.

Treatment of 17α,21-Dihydroxypregn-4-ene-3,20-dione with Zinc and Acetic Acid.[18]—A solution of 1 g of 17α,21-dihydroxypregn-4-ene-3,20-dione (**18**) in 100 ml of 50% aqueous acetic acid was refluxed with 10 g of zinc powder. Samples were collected every 10 min (for a total period of 90 min); the reaction product was worked up by filtering into water and collection of the resulting precipitate. Each fraction was chromatographed on a thin layer plate using 30% ethyl acetate in benzene, and the results are tabulated in Table III.

TABLE III

Fractions	R_f values: **18** ("S")	**19** (DOC)	**20** intermediate
1	0.15	×	0.6
2	0.15	0.2	0.6
3	0.15	0.2	0.6
4	0.15	0.2	0.6
5	0.15	0.2	0.6
6	0.15	0.2	0.6
7	0.15	0.2	0.6
8	×	0.2	0.6
9	×	0.2	0.6

A 100-mg aliquot of the combined fractions was chromatographed on a thin layer plate. The fraction 3 (R_f 0.6) was isolated from the plate. Three such plates yielded 75 mg of this intermediate. It was crystallized from methanol–ether to give an analytical sample: mp 185–187°; ν_{max}^{KBr} 3500 (–OH), 1675, 1650, 1600 (Δ^4-3-ketone and $\Delta^{17(20)}$-21-aldehyde); λ_{max}^{EtOH} 242 mμ (ε 17,000), 285 mμ (ε 14,000); nmr 62.5 (18-CH_3), 73.5 (19-CH_3), 335.0 (enolic proton), 345.0 (>C=CH), 576.0 (–C(H)=O) cps.

Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.56; H, 8.47.

This intermediate was identified as 20-hydroxy-21-oxopregna-4,17(20)-dien-3-one (**20**).

Treatment of Deoxycorticosterone (19) with Hydriodic Acid.—A solution of 500 mg of 21-hydroxypregn-4-ene-3,20-dione (**19**) in 25 ml of acetic acid was heated on a steam bath for 1 hr with 5 ml of hydriodic acid. Usual work-up gave 450 mg of solids which showed two spots on a thin layer plate chromatography corresponding to progesterone (**21**) and to deoxycorticosterone acetate (**22**). The crude product was chromatographed on a silica gel column whereby elution with ethyl acetate–benzene mixtures (5:95 and 7:93) yielded 400 mg of progesterone (**21**). Elution with an ethyl acetate–benzene mixture (15:85) yielded 35 mg of deoxycorticosterone acetate (**22**).

Treatment of Deoxycorticosterone Acetate (22) with Hydriodic Acid.—A solution of 500 mg of deoxycorticosterone acetate (**22**) was treated similarly as in the case described for deoxycorticosterone, except that the reaction time was reduced to 30 min. Usual work-up yielded 480 mg of progesterone (**21**). No other compound was detected.

Treatment of 17α,21-Dihydroxypregn-4-ene-3,20-dione (18) with Hydriodic Acid.—The amount of 500 mg of 17α,21-dihydroxypregn-4-ene-3,20-dione (**18**) was treated in the same manner as described for deoxycorticosterone acetate. A thin layer plate chromatography of the crude product showed three spots corresponding to progesterone, deoxycorticosterone acetate, and deoxycorticosterone (R_f 0.6, 0.35, and 0.2), respectively. A 100-mg aliquot of the crude product was separated on a thin layer plate (30% ethyl acetate in benzene). The bands were visualized with an ultraviolet lamp and then the appropriate zones scraped off the plate. The elution of these fractions yielded 5 mg of progesterone (**21**), 29 mg of deoxycorticosterone acetate (**22**), and 35 mg of desoxycorticosterone (**19**).

Treatment of 17α,21-Dihydroxypregn-4-ene-3,20-dione 21-Acetate (23) with Hydriodic Acid.—The amount of 500 mg of 17α,21-dihydroxypregn-4-ene-3,20-dione 21-acetate was subjected to hydriodic acid treatment as described for the case of desoxycorticosterone acetate. Thin layer plate chromatography of the reaction product showed three spots corresponding to progesterone (**21**) (R_f 0.6), deoxycorticosterone acetate (**22**) (R_f 0.35), and deoxycorticosterone (**19**) (R_f 0.2). A 100-mg aliquot of the crude product, separated on a thin layer plate, yielded 60 mg of deoxycorticosterone acetate (**22**), 5 mg of deoxycorticosterone (**19**), and 12 mg of progesterone (**21**).

Reaction of 1-Hydroxy-1-acetylcyclohexane with Hydriodic Acid.—A solution of 100 mg of 1-hydroxy-1-acetyl-cyclohexane in 10 ml of acetic acid was refluxed for 2 hr with 2 ml of 47% hydriodic acid. This was poured into a solution of sodium bisulfite and sodium hydroxide and the mixture was extracted with ether. The ether extract was washed with a solution of sodium hydroxide and water and dried over anhydrous sodium sulfate. Removal of the solvent yielded 75 mg of an oil which, in its infrared spectrum, did not show any hydroxyl band, but had a strong band at 1700 cm^{-1} (saturated ketone) and less intense bands at 1680 and 1660 cm^{-1} for the unsaturated enone system.

The thin layer plate chromatogram of the crude oil showed the presence of two products and one spot absorbed in the ultraviolet.

The extinction (at 232 mμ) of the crude reaction product indicates 1-acetyl-cyclohexene to amount to approximately 10%.

The ultraviolet-absorbing zone was eluted from the silica gel and showed in the infrared bands at 1680 and 1660 cm^{-1}. The ultraviolet had a λ_{max}^{MeOH} 232 mμ (ε 12,000), in agreement with the literature value.[25] The infrared spectrum of the nonabsorbing product was identical with the one of authentic acetylcylohexane.

Registry No.—**1,** 68-96-2; hydriodic acid, 10034-85-2; **2,** 2328-80-5; **3,** 15296-76-1; 17aα-hydroxy-17aβ-methyl-D-homoandrost-4-ene-3,17-dione, 14510-23-7; **6,** 15313-99-2; **7,** 15314-00-8; **8,** 15296-62-5; **9,** 15296-63-6; **10,** 15296-64-7; **14,** 15296-65-8; **15,** 15296-66-9; **16,** 6197-92-8; **17,** 13713-89-8; **18,** 152-58-9; **19,** 64-85-7; **20,** 6762-52-3; **22,** 56-47-3; **23,** 640-87-9; 1-hydroxy-1-acetylcyclohexane, 1123-27-9.

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