Experimental

Apparent Ionization Constants.—All measurements on the acids and phenols were made in aqueous alcohol which was prepared from carbon dioxide-free water and Commercial Solvents Co. Gold Shield alcohol, mixed in equal parts by volume. Samples of about 30 μmoles of compound in 75 ml. of 50% alcohol were titrated with standard 0.05 *N* sodium hydroxide solution made up in the same solvent. The titrations were done under an atmosphere of purified nitrogen at 25 ± 1° using a Leeds and Northrup pH meter, Model 77664, equipped with glass and saturated calomel electrodes. The meter was standardized with aqueous buffers. The pK_a values were calculated from the Henderson equation[28] and are the average of two independent determinations at approximately 20, 40, and 60% neutralization. Tables I–II give the pK_a values measured for the acids and phenols.

The values of the apparent ionization constants of the anilinium ions were measured in 30% alcohol by a spectrophotometric method. The amine (about 50 μmoles) was dissolved in 50 ml. of 30% ethanol to give a stock solution. Aliquots of this stock solution (1 ml.) were diluted with 50 ml. of 30% alcohol and with 1 *N* hydrochloric acid in 30% alcohol to secure the amine in the forms of the free base and anilinium salt, respectively. Aliquots (1 ml.) of the amine solutions were also diluted to 50 ml. with a dilute hydrochloric acid solution having a pH within 0.5 units of the expected pK_a value. Absorption curves were then obtained using a Beckman DU spectrophotometer equipped with a Warren Spectrocord automatic recording attachment. The pH of the dilute acid solutions were determined at 25 ± 1° using a Leeds and Northrup pH meter standardized against a saturated solution of potassium hydrogen tartrate. The pK_a values were determined from the equation: $pK_a = pH + \log (RNH_3^+/RNH_2)$. The quantity $\log (RNH_3^+/RNH_2)$ was obtained from the relationship $RNH_3^+/RNH_2 = (A_b - A)/(A - A_a)$ where A_a, A_b, and A are the absorbancies of the acid, base, and dilute acid solutions at λ_{max} for the free amine. The pK_a values listed in Table III are the average of two determinations.

Ultraviolet Absorption Spectra.—The spectra for the compounds were determined in absolute ethanol using a Beckman Model DU spectrophotometer equipped with a Warren Spectrocord automatic recording attachment. The spectra of the phenols were also obtained in 0.1 *N* sodium hydroxide solution, and the spectra of the amines were also determined in 0.1 *N* hydrochloric acid solution. The results are tabulated in Table IV.

N.m.r. Shielding Parameters for the Fluorocyclanones.—The n.m.r. spectra were determined in dilute carbon tetrachloride solution using fluorobenzene as an internal standard, and the results are tabulated in Table VI. The spectrometer employed was a Varian Associates n.m.r. spectrometer, Model HR-60.

Acknowledgment.—The authors are indebted to Dr. L. A. Freiberg and to Mr. B. Shoulders (University of Illinois) for determining the spectra reported herein.

(28) F. G. Bordwell and G. D. Cooper, *J. Am. Chem. Soc.*, **74**, 1058 (1952).

The Synthesis of 11,12-Oxygenated Progesterones

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The rearrangement of 9α-bromo-11-ketoprogesterone with hydroxide ion gives 12α-hydroxy-11-ketoprogesterone. The syntheses of two other 11,12-ketols, *viz.*, 11α-hydroxy-12-ketoprogesterone and 12β-hydroxy-11-ketoprogesterone are also described, and their alkaline equilibration is discussed. The four possible 11,12-dihydroxyprogesterones have been prepared as well as the acetonides of the 11α,12α, 11β,12β, and 11α,12β isomers.

The reaction of 9α-halo-11-keto steroids with nucleophilic reagents leading to 12α-substituted 11-keto steroids has been the subject of a number of recent publications.[2] In 1961 the reaction of 9α-bromo-11-ketoprogesterone (I) with methoxide ion yielding 12α-methoxy-11-ketoprogesterone was reported[2b] from this laboratory. We would now like to report the reaction of I with hydroxide ion and the conversion of the product of this reaction to other 11,12-oxygenated progesterones.

The reaction of 9α-bromo-11-ketoprogesterone with sodium hydroxide under mild conditions gave a bromine-free compound which showed a correct analysis for $C_{21}H_{28}O_4$. That this compound was 12α-hydroxy-11-ketoprogesterone (II) and not one of the other isomeric 11,12-ketols which might have been formed under these alkaline conditions was confirmed by both chemical and physical methods. Reaction of 11β,12β-oxidoprogesterone[3] (III) with perchloric acid gave 11β,12α-dihydroxyprogesterone[4] (IV) which on acetylation gave only a monoacetate, the 12α-acetate (IVa). Oxidation of IVa with Jones reagent[5a] gave 12α-acetoxy-11-ketoprogesterone (IIa), identical with the acetylation product of II. That the structural assignments for these compounds were correct was also supported by the n.m.r. spectra of these compounds (*cf.* Table I) and the hydrogen bonding detectable in both the infrared and proton magnetic resonance spectra.[5b] The 11α and 12β protons of IV appeared at τ 5.75 ($W_{1/2}$ = 8.5 c.p.s.) and 6.10 ($W_{1/2}$ = 7.5 c.p.s.), respectively, and for IVa appeared at τ 5.77 ($W_{1/2}$ = 8 c.p.s.) and 4.96 (d, J = 2.5 c.p.s.). The doublet and small coupling constant of the 12β proton in the latter case indicated the diequatorial relationship of the C-12 proton to the C-11 proton. In II and IIa the 12β proton appeared at τ 6.10 (d, J = 3.5 c.p.s.) and 5.21 (s), respectively, the singlet of IIa confirming that no vicinal proton was present. That the carbonyl groups of II and IIa are at position 11 and not at 12 was evident by the resonance bands for the 18-methyl

(1) Deceased January 23, 1965.

(2) (a) J. S. G. Cox, *J. Chem. Soc.*, 4508 (1960); (b) P. A. Diassi and R. M. Palmere, *J. Org. Chem.*, **26**, 5240 (1961); (c) J. Fried, "Biological Activities of Steroids in Relation to Cancer," G. Pincus and E. Vollmer, Ed., Academic Press Inc., New York, N. Y., 1960, p. 9.

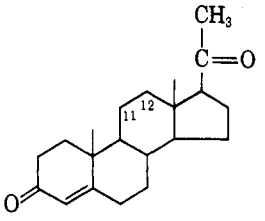
(3) J. E. Herz, J. Fried, and E. F. Sabo, *J. Am. Chem. Soc.*, **78**, 2017 (1956).

(4) The opening of 11β,12β-oxides by nucleophilic reagents of the type HX has been shown to lead to the *trans* diaxial (11β-OH, 12α-X) configuration: *cf.* (a) J. W. Cornforth, J. M. Osbond, and G. H. Phillips, *J. Chem. Soc.*, 907 (1954); (b) D. Taub, R. D. Hoffsommer, and N. L. Wendler, *J. Am. Chem. Soc.*, **78**, 452 (1957); (c) J. Elks, G. H. Phillipps, T. Walker, and L. J. Wyman, *J. Chem. Soc.*, 4330 (1956).

(5) (a) K. Bowden, I. M. Heibron, E. R. H. Jones, and B. C. L. Weedon, *ibid.*, 39 (1946); (b) A. I. Cohen, B. T. Keeler, E. J. Becker, and P. A. Diassi, *J. Org. Chem.*, **30**, 2175 (1965).

TABLE I

N.M.R. CHEMICAL SHIFTS[a] OF 11,12-OXYGENATED PROGESTERONES



Compd.	Substituents C-11	C-12		Chemical shifts, τ C-4 H	C-11 H	C-12 H	OH	C-18 Me	C-19 Me	C-21 Me
VII	α-OH	=O		4.26	β 5.46 (d, d, 4.3, 11)[b]		6.07 (d, 4.3)	8.96	8.58	7.75
VIIa	α-OAc[c]	=O		4.21	β 4.41 (d, 11)			8.93	8.63	7.78
II	=O	α-OH		4.32		β 6.10 (d, 3.5)	5.67 (d, 3.5)[d]	9.41	8.59	7.89
IIa	=O	α-OAc[e]		4.28		β 5.21 (s)		9.30	8.53	7.94
V	=O	β-OH		4.27		α 5.90 (d, 4.7)	6.13 (d, 4.7)	9.45	8.56	7.66
Va	=O	β-OAc[f]		4.30		α 4.96 (s)		9.24	8.57	7.86
IV	β-OH	α-OH		4.33	α 5.75 ($W_{1/2}$ 8.5)	β 6.10 ($W_{1/2}$ 7.5)	6.92[g,h]	9.08	8.55	7.86
XIII	β-OH	β-OH		4.33	α 5.79 (d, d, 3, 3)[i]	α 6.77 (d, 3)	7.22, 4.41	9.07	8.52	7.80
XIV	α-OH	α-OH		4.28	β 5.94 ($W_{1/2}$ 20)	β 6.07 ($W_{1/2}$ 5.5)	7.29 (d, 8)[j] 6.78 (d, 3.5)[j]	9.27	8.68	7.86
VI	α-OH	β-OH		4.28	β 6.24 (d, d, 8.5, 9)	α 6.73 (d, 8.5)	7.07, 4.85	9.21	8.69	7.79
IVa	β-OH	α-OAc[k]		4.29	α 5.77 ($W_{1/2}$ 8)	β 4.96 (d, 2.5)		9.01	8.54	7.89
VIII	α-OH	β-OH	11,12-Acetonide[l]	4.26	β 6.31 (d, d, 8.5, 9)	α 6.54 (d, 8.5)[m]		9.27	8.73	7.69
XII	α-OH	α-OH	11,12-Acetonide[n]	4.28	β 5.71 (d, 7)	β 5.82 (d, 7)		9.30	8.76	7.84
XI	β-OH	β-OH	11,12-Acetonide[o]	4.31	α 5.56 (d, d, 6, 5.5)	α 5.90 (d, 6)		9.28	8.58	7.69
XV	β-OH	β-OH	11,12-Acetonide, 20β-OH[p]	4.32	α 5.56 (d, d, 6, 6)	α 6.18 (d, 6)	5.87 (s)	9.16	8.57	8.90 (d, 6)
XVI	β-OH	β-OH	11,12-Acetonide, 20α-OH[q]	4.31	α 5.62 (d, d, 6, 6)	α 6.24 (d, 6)		9.16	8.57	8.68 (d, 6)
XVII	β-OH	β-OH	11,12-Acetonide, 20α-OAc[r]	4.32	α 5.61 (m)	α 6.23 (d, 6)		9.21	8.57	~8.5

[a] Solvent $CDCl_3$ containing tetramethylsilane as an internal reference; coupling constants, J, in c.p.s.; m, multiplet; s, singlet; d, doublet; $W_{1/2}$, half-width, in c.p.s. [b] $J_{11,OH}$ = 4.3 c.p.s., $J_{9,11}$ = 11 c.p.s. [c] Acetoxyl methyl, τ 7.81. [d] Proton resonance concentration dependent at 0.23 M. [e] Acetoxyl methyl, τ 7.83. [f] Acetoxyl methyl, τ 7.86. [g] At 0.25 M concentration. [h] Not detected at 0.12 M. [i] $J_{9,11}$ = $J_{11,12}$ = 3 c.p.s. [j] Proton resonance concentration dependent at 0.21 M. [k] Acetoxyl methyl, τ 7.98. [l] Acetonide methyls, τ 8.63, 8.58. [m] ABX coupling pattern partially obscured; $J_{9,11}$ = 9 c.p.s. [n] Acetonide methyls, τ 8.62, 8.50. [o] Acetonide methyls, τ 8.64, 8.55. [p] Acetonide methyls, τ 8.63, 8.45; 20α-H, τ 6.33. [q] Acetonide methyls, τ 8.65, 8.48. [r] Acetonide methyls, τ 8.66, 8.52; acetate methyl, τ 8.00; 20β-H, τ 5.02.

protons in these compounds which are not deshielded significantly as would be expected for a 12-keto compound[6] and appeared at τ 9.41 and 9.30, respectively.

Of the many steroids known having an 11,12-ketol system equilibration with alkali leads predominately to the 12β-hydroxy 11-ketone.[4c,7] When 12α-hydroxy-11-ketoprogesterone (II) was refluxed with 0.9 N potassium hydroxide, two products could be separated by t.l.c. on alumina. The minor product (30%) was the starting compound and the major product (50%) was a new ketol which was shown to be 12β-hydroxy-11-ketoprogesterone (V). Compound V could be acetylated and the n.m.r. spectra of V and Va showed the 12α proton at τ 5.90 (d, J = 4.7 c.p.s.) and 4.96 (s), respectively, the singlet in Va ruling out an 11-acetoxy compound. Furthermore a 12-keto compound was excluded since the 18-methyl proton resonances again were not significantly deshielded and appeared at τ 9.45 and 9.24, respectively.

To prepare a ketol in the series with the ketone function at position 12, 12β-hydroxy-11-ketoprogesterone was ketalized to the 3,20-bisethylene ketal (Vb) which was reduced with sodium in butanol to give 3,20-bisethylenedioxy-11α,12β-dihydroxypregn-5-ene (VIb)[8] as the sole crystallizable product although other products were discernable by thin layer chromatography. Indeed, mild acid hydrolysis of a portion of the reaction product and chromatography yielded 11α-hydroxyprogesterone which represents the product of reductive scission of the C-12 oxygen function. Acid hydrolysis of VIb gave 11α,12β-dihydroxyprogesterone (VI). Acetylation of either VI or VIb gave the 11-monoacetates VIa and VIc, respectively,[9] the structures of which were assigned by hydrolysis of VIc to VIa and oxidation of VIa to an α-acetoxy ketone (VIIa) different from IIa and Va. Attempts to oxidize the ketal VIc with chromic acid were unsuccessful; however, 3,20-bisethylenedioxy-11α-acetoxypregn-5-en-12-one (VIIc) could be prepared by the ketalization of VIIa. Mild alkaline hydrolysis of VIIc gave VIIb, which on acid cleavage of ketal functions gave 11α-hydroxy-12-ketoprogesterone (VII).

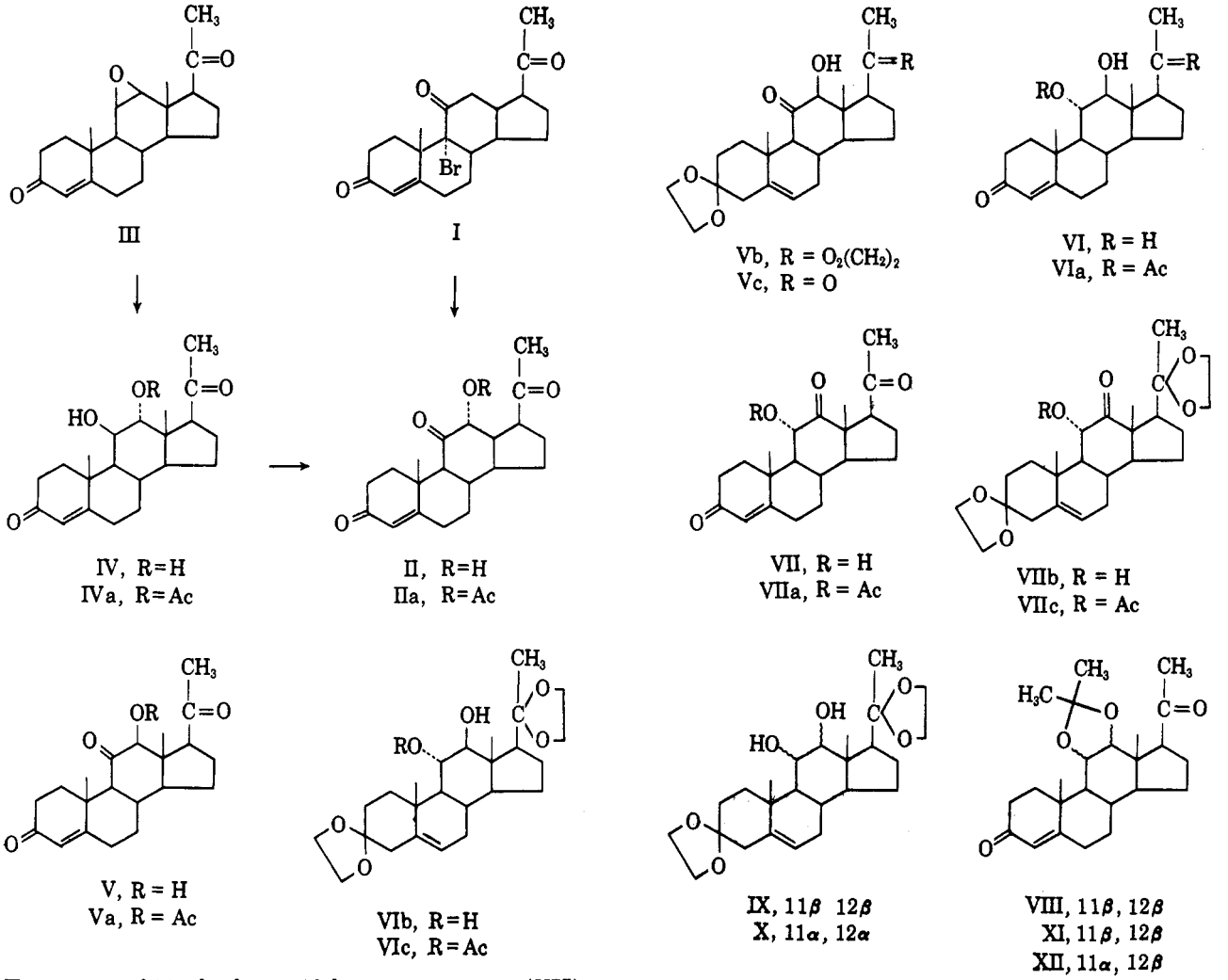
The n.m.r. spectra of the ketols VII–VIIc (the n.m.r. data concerning the diols VI–VIc will be discussed below) also supports their structural assignment. Thus the proton of the hydroxyl-bearing carbon of these compounds appeared (Table I) at τ 5.46 (d, d, $J_{11,OH}$ = 4.3 c.p.s., $J_{9,11}$ = 11 c.p.s.), 4.41 (d, $J_{9,11}$ = 11 c.p.s.), 5.35 (d, d, $J_{11,OH}$ = 4.5 c.p.s., $J_{9,11}$ = 9.5 c.p.s.), and 4.30 (d, $J_{9,11}$ = 8.5 c.p.s.), respectively, which is typical for the *trans* diaxial coupling of the 11β proton with the 9α proton, and the C-18 methyl protons resonated at τ 8.96, 8.93, 8.69, and 8.72, respectively, which are at lower field than II, IIa, V, or Va showing that the carbonyl group is at position 12.

(6) (a) A. I. Cohen and S. Rock, *Steroids*, **3**, 243 (1964); (b) R. F. Zürcher, *Helv. Chim. Acta*, **46**, 2054 (1963); **44**, 1380 (1961).

(7) (a) T. F. Gallagher, *J. Biol. Chem.*, **162**, 539 (1946); (b) O. Wintersteiner, M. Moore, and K. Reinhardt, *ibid.*, **162**, 707 (1946); (c) E. Borgstrom and T. F. Gallagher, *ibid.*, **177**, 951 (1949); (d) G. P. Mueller, L. L. Norton, R. E. Stobaugh, L. Tsai, and R. S. Winniford, *J. Am. Chem. Soc.*, **75**, 4892 (1953); (e) N. L. Wendler, R. F. Hirschmann, H. L. Slates, and R. W. Walker, *ibid.*, **77**, 1632 (1955).

(8) The reduction of 11-ketorockogenin under these conditions also gives an 11α,12β-diol.[7e]

(9) None of the 12β-acetate or 11α,12β-diacetate could be isolated as in the rockogenin series.[7e]



Treatment of 11α-hydroxy-12-ketoprogesterone (VII) or the 3,20-bisethylene ketal (VIIb) with refluxing alkali converted them in 70% yield to the corresponding 12β-hydroxy-11-keto derivatives V and Vb with no starting material recovered. This equilibrium which is so strongly in favor of 12β-hydroxy 11-ketone is in contrast to the epimerization of the 12α-hydroxy-11-ketoprogesterone (II) to V as discussed before. These results are in agreement with those found by Elks, *et al.*,[4c] and Wendler[7e] in the sapogenin series. The ease of epimerization of the 11α-hydroxy 12-ketone may be due to the fact that enolization in these compounds is only possible toward position 11 to give the symmetrical 11,12-enediolate ion which on axial protonation at position 12 gives the observed compound, whereas in the case of the 12α-hydroxy 11-ketone enolization is predominately toward position 9 in which case protonation would give back starting material.[10]

In contrast to findings of Gallagher,[7c] who found in the cholic acid series that the equilibration of the 12β-hydroxy 11-ketone in alkali produced all four possible 11,12-ketols, Vb under these conditions gave only starting material.

The ultraviolet spectra of Vb and VIIb taken in alcohol have the weak maxima at 288 mμ (log ϵ 1.60) and 280 mμ (log ϵ 2.30), respectively, which is typical for equatorial α-hydroxy ketones.[4c,11]

(10) We have also found that 12α-methyl-11-ketoprogesterone[4c] is not epimerized to the 12β-methyl isomer by alkali. In this case steric factors as well as direction of enolization may influence the stability of 12α-methyl isomer.

The rotational changes associated with acetylation of the 11,12-ketols are given in Table II and are in agreement with those observed by Baumgartner and Tamm[11a] and Elks[4c] in that acetylation of an axial hydroxyl group changes the molecular rotation value in a positive direction, whereas acetylation of the equatorial hydroxyl resulted in a small positive or negative change.

TABLE II

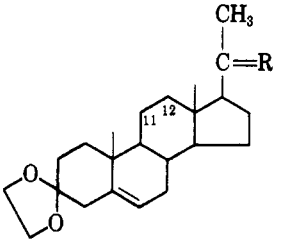
MOLECULAR ROTATIONS OF 11,12-KETOLS IN CHLOROFORM

Compd.	[M]D, deg.	Δ[M]D, deg.
12α-Hydroxy-11-ketoprogesterone (II)	+826	
		+168
12α-Acetoxy-11-ketoprogesterone (IIa)	+994	
11α-Hydroxy-12-ketoprogesterone (VII)	+645	
		+5
11α-Acetoxy-12-ketoprogesterone (VIIa)	+649	
3,20-Bisethylenedioxy-11α-hydroxypregn-5-en-12-one (VIIb)	+12	
		+107
3,20-Bisethylenedioxy-11α-acetoxypregn-5-en-12-one (VIIc)	+95	
12β-Hydroxy-11-ketoprogesterone (V)	+882	
		−178
12β-Acetoxy-11-ketoprogesterone (Va)	+704	

(11) (a) G. Baumgartner and Ch. Tamm, *Helv. Chim. Acta*, **38**, 441 (1955); (b) C. Djerassi, O. Halpern, V. Halpern, O. Schindle, and Ch. Tamm, *ibid.*, **41**, 250 (1958).

TABLE III

N.M.R. CHEMICAL SHIFTS[a] OF 11,12-OXYGENATED COMPOUNDS



Compd.	Substituents C-11	C-12	R	Chemical shifts, τ C-6 H	C-11 H	C-12 H	OH	C-18 Me	C-19 Me	C-21 Me
VIIb	α-OH	=O	$O_2(CH_2)_2$	4.60 (m)	β 5.35 (d, d, 4.5, 9.5)[b]		5.9–6.2[c]	8.69	8.83	8.69
VIIc	α-OAc[d]	=O	$O_2(CH_2)_2$	4.57 (m)	β 4.30 (d, 8.5)			8.72	8.76	8.72
Vb	=O	β-OH	$O_2(CH_2)_2$	4.67 (m)		α 5.8–6.1[c]	4.94 (s)	9.27	8.73	8.66
Vc	=O	β-OH	=O	4.65 (m)		α 5.8–6.1[c]	5.8–6.1[c]	9.47	8.75	7.65
X	α-OH	α-OH	$O_2(CH_2)_2$	4.58 (m)	β 5.8–6.2[c]	β 5.8–6.2[c]		9.17	8.81	8.73
IX	β-OH	β-OH	$O_2(CH_2)_2$	4.76 (m)	α 5.7 (m)	α 6.8 (m)	7.35 4.65	9.04	8.67	8.67
VIb	α-OH	β-OH	$O_2(CH_2)_2$	4.62 (m)	β 6.3 (m)	α 6.81 (d, 8.5)	7.18 4.99	9.19	8.81	8.69
VIc	α-OAc[e]	β-OH	$O_2(CH_2)_2$	4.62 (m)	β 4.75 (m)	α 6.66 (d, 9)	5.16	9.13	8.82	8.71

[a] Solvent $CDCl_3$ containing tetramethylsilane as an internal reference; coupling constants, J, in c.p.s.; m, multiplet; s, singlet; d, doublet. [b] $J_{11,OH}$ = 4.5 c.p.s., $J_{9,11}$ = 9.5 c.p.s. [c] Exact position obscured by ketal proton resonances. [d] Acetoxyl methyl, τ 7.84. [e] Acetoxyl methyl, τ 7.94.

Of the four possible isomeric 11,12-hydroxyprogesterones the two *trans* diols have already been described above. To prepare the *cis*-diols, 3,20-bisethylenedioxy-12β-hydroxypregn-5-en-11-one (Vb) and 3,20-bisethylenedioxy-11α-hydroxypregn-5-en-12-one (VIIb) were reduced with lithium aluminum hydride to the corresponding *cis*-diols, IX and X. Reaction of these diol bisketals as well as 3,20-bisethylenedioxy-11α,12β-dihydroxypregn-5-ene (VIb) with acetone and perchloric acid gave good yields of the corresponding 11,12-dihydroxyprogesterone acetonides[12] (XI, XII, and VIII).

Cleavage of IX and X with acid gave 11β,12β-dihydroxyprogesterone (XIII) and 11α,12α-dihydroxyprogesterone (XIV), respectively.

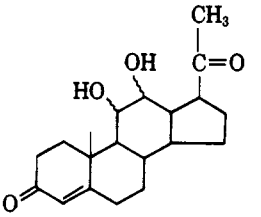
The structural assignments of the 11,12-dihydroxylated derivatives are also consistent with their n.m.r. spectra (Tables I and III); the coupling constants of the methine protons on the carbons bearing the oxygens to the protons on α carbons show explicitly their stereochemical relationship. In Table IV the magnitude of the coupling constant and the dihedral angle[13] measured from examination of Drieding models are tabulated. The coupling constants fall into two broad ranges: 8.5–11 c.p.s. for *trans* diaxial coupling, 2.5–3 c.p.s. for axial–equatorial coupling and in derivatives experiencing considerable C-ring distortions due to acetonide formation (XI and XII). Although the dihedral angle is only one parameter in determining the coupling constant,[13] it is not unexpected to observe a correlation between the measured dihedral angles and the experimentally observed coupling constants in compounds containing only oxygen.[14]

TABLE IV

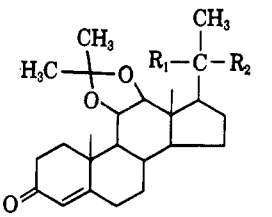
COMPARISON OF COUPLING CONSTANTS AND DIHEDRAL ANGLES

Compd.	Coupled protons	$J \pm 0.3$ c.p.s.	$\phi \pm 5°$
XII	11β,12β	7	25
XI	11α,12α	6	35
	9α,11α	5.5	45
XIII	9α,11α	3	60
	11α,12α	3	55
IVa	11β,12β	2.5	60
VII	9α,11β	11	175
VIIa	9α,11β	11	175
VIIb	9α,11β	9.5	175
VI	9α,11β	9	175
VIII	9α,11β	9	175
VIc	11β,12α	9	175
VIII	11β,12α	8.5	170
VI	11β,12α	8.5	175
VIb	11β,12α	8.5	175
VIIc	9α,11β	8.5	175

In connection with these studies the lability of the 20-ketal moiety to acid cleavage was observed. When Vb was treated with Jones reagent[5a] at room temperature, the only isolable product was the 3-monoketal which was assigned the structure Vc on the basis of the elemental analysis; the compound had no significant absorption in the ultraviolet and the n.m.r. showed the 21-methyl (τ 7.65) was adjacent to a carbonyl group. Ketalization of Vc gave back starting material and



XIII, 11β, 12β
XIV, 11α, 12α



XV, R_1=OH; R_2=H
XVI, R_1=H; R_2=OH
XVII, R_1=H; R_2=OAc

(12) J. A. Zderic, H. Carpio, and C. Djerassi [*J. Am. Chem. Soc.*, **82**, 446 (1960)] have prepared the 11β,12β-acetonide of 12β-hydroxyprednisolone.

(13) M. Karplus [*ibid.*, **85**, 2870 (1963)] has emphasized that the dihedral angle is only one parameter which determines the magnitude of the coupling constant.

(14) For the same dihedral angle, the 11α-hydroxy 12-ketone VII and its acetate VIIa has a somewhat larger coupling constant for the 9α and 11β protons than that of the 11α,12-diols VIa–c. The ketols may give rise to another set of parameters due to the added electronegativity of the ketone.

acid hydrolysis gave 12β-hydroxy-11-ketoprogesterone (V). Lithium aluminum hydride reduction of Vc followed by acetonation gave the epimeric 20-hydroxy-11β,12β-diol acetonides, XV and XVI. Both XV and XVI on oxidation gave 11β,12β-dihydroxyprogesterone 11,12-acetonide (XI). The assignment of the 20β-ol configuration to XV and the 20α-ol configuration could be made on hydrogen bonding evident in both the infrared and n.m.r.[5b] and the fact that XVI under mild conditions could be acetylated, whereas XV was recovered unchanged.

Experimental[15]

12α-Hydroxy-11-ketoprogesterone (II).—To a solution of 10 g. of 9α-bromo-11-ketoprogesterone in 500 ml. of dioxane a solution of 4.0 g. of sodium hydroxide in 300 ml. of water was added, and the mixture was left at room temperature for 15 min. It was then diluted with 1 l. of water and extracted three times with 400-ml. portions of chloroform which were combined, washed with water until neutral, dried over sodium sulfate, and evaporated *in vacuo*. The residue on crystallization from acetone–hexane gave 7.0 g. of II having m.p. 188–190°, $[\alpha]^{24}D$ +240° ($CHCl_3$), λ_{max}^{alc} 238 mμ (ε 15,600).

Anal. Calcd. for $C_{21}H_{28}O_4$ (344.43): C, 73.23; H, 8.19. Found: C, 73.16; H, 8.12.

11β,12α-Dihydroxyprogesterone (IV).—To a solution of 200 mg. of 11β,12β-oxidoprogesterone in 3.5 ml. of dioxane 1.7 ml. of 2 *M* perchloric acid was added, and the solution was left at room temperature for 24 hr. The solution was then diluted with 25 ml. of water and extracted three times with chloroform. The combined chloroform extracts were washed with water and evaporated to dryness *in vacuo*. The residue on crystallization from acetone–hexane gave 158 mg. of IV having m.p. 180–181°, $[\alpha]^{22}D$ +186° ($CHCl_3$), λ_{max}^{alc} 242 mμ (ε 14,800).

Anal. Calcd. for $C_{21}H_{30}O_4$ (346.45): C, 72.80; H, 8.73. Found: C, 72.76; H, 8.73.

11β,12α-Dihydroxyprogesterone 12-Acetate (IVa).—A solution of 25 mg. of 11β,12α-dihydroxyprogesterone in 3 ml. of dry pyridine and 1 ml. of acetic anhydride was kept at room temperature for 16 hr. The solution was then diluted with ice–water and extracted with chloroform. The chloroform extracts were washed with water, 2 *N* hydrochloric acid, and water again until neutral and evaporated to dryness *in vacuo*. The residue was plate chromatographed using alumina (activity V) as adsorbant and chloroform as the developing solvent. The band having R_f 0.4 on detection by ultraviolet was eluted with ethyl acetate, and, after evaporation of the solvent, the residue was crystallized from acetone–hexane to give 11.3 mg. of IVa having m.p. 238–240°, $[\alpha]^{22}D$ +203° ($CHCl_3$).

Anal. Calcd. for $C_{23}H_{32}O_5$ (388.49): C, 71.11; H, 8.30. Found: C, 70.91; H, 8.02.

12α-Acetoxy-11-ketoprogesterone (IIa). A. From II.—A solution of 117 mg. of 12α-hydroxy-11-ketoprogesterone in 2 ml. of pyridine and 1.5 ml. of acetic anhydride was left at room temperature overnight and then was slowly diluted with ice–water. The crystals which separated were filtered, washed with water, and dried. Recrystallization from acetone–hexane gave 100 mg. of IIa having m.p. 248–251°, $[\alpha]^{26}D$ +257° ($CHCl_3$).

Anal. Calcd. for $C_{23}H_{32}O_5$ (388.49): C, 71.11; H, 8.30. Found: C, 71.21; H, 8.34.

B. From IVa.—To a solution of 15 mg. of 12α-acetoxy-11β-hydroxyprogesterone in 1.5 ml. of reagent grade acetone 0.13 ml. of a solution containing 20 mg. of chromic anhydride/ml. and 32 mg. of sulfuric acid/ml. was added. After 5 min. a few drops of methanol was added, and the solution was diluted with water and extracted with chloroform. The chloroform extract was washed with water and evaporated *in vacuo*. The residue on crystallization from acetone–hexane gave IIa identical with that obtained from II.

(15) Melting points were taken on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Values of $[\alpha]D$ were taken in chloroform unless otherwise specified. Ultraviolet spectra were determined on a Cary 15 spectrophotometer in 95% ethanol; infrared spectra were taken on a Perkin-Elmer Model 237 Grating Infracord and n.m.r. spectra were taken using a Varian A-60 spectrometer in deuteriochloroform with tetramethylsilane as internal standard.

12β-Hydroxy-11-ketoprogesterone (V). A. From II.—A solution of 200 mg. of 12α-hydroxy-11-ketoprogesterone in 44 ml. of methanol and 6 ml. of water containing 2.5 g. of potassium hydroxide was refluxed for 3 hr. under nitrogen. After cooling, the solution was neutralized with 10% acetic acid, diluted with water, and extracted with chloroform. The chloroform extract was washed with water and evaporated *in vacuo*, and the residue was plate chromatographed on Woelm alumina (activity V) using chloroform as the developing solvent. Two bands were detectable by ultraviolet at R_f 0.5 and 0.3, respectively. Elution of each of these bands with ethyl acetate, removal of solvent *in vacuo*, and crystallization of the residue gave 60 mg. of starting material from the less polar band and 105 mg. of V having m.p. 179–180°, $[\alpha]^{22}D$ +256° ($CHCl_3$), λ_{max}^{alc} 238 mμ (ε 16,400) and 288 mμ (ε 40).

Anal. Calcd. for $C_{21}H_{28}O_4$ (344.44): C, 73.22; H, 8.19. Found: C, 73.41; H, 8.06.

B. From Vb.—To a solution of 500 mg. of 3,20-bisethylenedioxy-12β-hydroxypregn-5-en-11-one in 200 ml. of reagent grade methanol, 7.0 ml. of an 8% solution of sulfuric acid was added, and the resulting solution was refluxed for 40 min. After cooling, the solution was neutralized carefully with 5% aqueous sodium bicarbonate diluted with 400 ml. of water and extracted with chloroform. The chloroform extracts were washed with water, dried over sodium sulfate, and evaporated to dryness *in vacuo*. Crystallization of the residue from acetone–hexane gave 329 mg. of V.

C. From VII.—A solution of 103 mg. of 11α-hydroxy-12-ketoprogesterone was refluxed in methanolic potassium hydroxide as described in part A. Plate chromatography of the reaction product gave 71 mg. of V.

3,20-Bisethylenedioxy-12β-hydroxypregn-5-en-11-one (Vb). A. From V.—To a solution of 102 mg. of 12β-hydroxy-11-ketoprogesterone in 90 ml. of benzene and 20 ml. of ethylene glycol 50 mg. of *p*-toluenesulfonic acid was added, and the mixture refluxed for 40 hr. using a Dean–Stark separation containing a calcium carbide tube for removing the water. The solution was then diluted with chloroform, washed successively with 5% sodium bicarbonate and water until neutral, dried over sodium sulfate, and evaporated to dryness *in vacuo*. Crystallization of the residue from acetone–hexane gave 80 mg. of Vb having m.p. 182–184°, $[\alpha]^{26}D$ +62.0° ($CHCl_3$).

Anal. Calcd. for $C_{25}H_{36}O_6$ (432.54): C, 69.42; H, 8.39. Found: C, 69.49; H, 8.29.

B. From VIIb.—A solution of 5.0 g. of 3,20-bisethylenedioxy-11α-hydroxypregn-5-en-12-one in 875 ml. of methanol and 125 ml. of water containing 50 g. of potassium hydroxide was refluxed for 3 hr., then cooled, diluted with water, and extracted with ethyl acetate which was washed well with water, dried over sodium sulfate, and evaporated to dryness *in vacuo*. Crystallization from acetone–hexane gave 4.1 g. of Vb.

3,20-Bisethylenedioxypregn-5-ene-11α,12β-diol (VIb).—Thirty grams of sodium was added in small portions to a refluxing solution of 3.0 g. of 3,20-bisethylenedioxy-12β-hydroxypregn-5-en-11-one in 500 ml. of *n*-butyl alcohol over a 3-hr. period. The resulting solution was then refluxed for 3 hr., during which time the sodium dissolved completely. The orange solution was then slowly diluted with 50 ml. of water whereupon crystals slowly separated. An additional 100 ml. of water were then added slowly, and the mixture was filtered and dried to give 1.07 g. of VIb having m.p. 185–187°, $[\alpha]^{27}D$ −26.2° ($CHCl_3$).

Anal. Calcd. for $C_{25}H_{38}O_6$ (434.55): C, 69.09; H, 8.81. Found: C, 68.85; H, 8.63.

The filtrate was diluted further with water and extracted with chloroform, and the chloroform extract was washed with water and evaporated to dryness. Plate chromatography of the residue using neutral alumina (activity V) as adsorbent and chloroform–ethyl acetate (4:1, v./v.) as the developing solvent gave two bands detectable by ultraviolet at R_f 0.4 and 0.7, respectively. Elution of the more polar band and crystallization gave an additional 300 mg. of VIb and elution of the less polar band followed by cleavage of the ketals with 8% sulfuric acid gave 56 mg. of 11α-hydroxyprogesterone, m.p. 153–154°.

3,20-Bisethylenedioxypregn-5-ene-11α,12β-diol 11-Acetate (VIc).—3,20-Bisethylenedioxypregn-5-ene-11α,12β-diol (500 mg.) was acetylated as described for IIa to give on crystallization from acetone–hexane 493 mg. of VIc having m.p. 180–182°, $[\alpha]^{22}D$ −1.1° ($CHCl_3$).

Anal. Calcd. for $C_{27}H_{40}O_7$ (476.59): C, 67.04; H, 8.46. Found: C, 67.25; H, 8.28.

11α,12β-Dihydroxyprogesterone (VI).—Following the procedure described for the hydrolysis of Vb, 100 mg. of 3,20-bisethylenedioxypregn-5-en-11α,12β-diol gave on crystallization from acetone–hexane 54.3 mg. of VI having m.p. 152–154°, $[\alpha]^{27}D$ +108° ($CHCl_3$), λ_{max}^{alc} 241 mμ (ε 14,600).

Anal. Calcd. for $C_{21}H_{30}O_4$ (346.45): C, 72.80; H, 8.73. Found: C, 72.71; H, 8.88.

11α-Acetoxy-12β-hydroxyprogesterone (VIa). A. From VI.—11α,12β-Dihydroxyprogesterone (312 mg.) was acetylated as described for IIa to give 200 mg. of VIa having m.p. 173–175°, $[\alpha]^{27}D$ +142° ($CHCl_3$), λ_{max}^{alc} 238 (ε 17,000) and 310 mμ (ε 355).

Anal. Calcd. for $C_{23}H_{32}O_5$ (388.49): C, 71.10; H, 8.30. Found: C, 71.12; H, 8.28.

B. From VIc.—A solution of 852 mg. of VIc in 340 ml. of methanol containing 12 ml. of 8% sulfuric acid was refluxed for 40 min., then cooled, neutralized with 5% sodium bicarbonate, diluted with water, and extracted with chloroform. The chloroform extract was washed with water and evaporated *in vacuo*. The residue on crystallization from acetone–hexane gave 480 mg. of VIa.

11α-Acetoxy-12-ketoprogesterone (VIIa). A. From VIa.—To a solution of 104 mg. of 11α-acetoxy-12β-hydroxyprogesterone in 4 ml. of glacial acetic acid 18 mg. of chromic anhydride was added, and the mixture was stirred at room temperature overnight. A few drops of methanol was then added, and the mixture was evaporated to dryness *in vacuo*. The residue was dissolved in ether, washed successively with 5% sodium bicarbonate and water, dried over sodium sulfate, and evaporated to dryness. Plate chromatography of the residue using Woelm neutral alumina (activity V) as adsorbant and chloroform as the developing solvent gave a band at R_f 0.6 which on elution with ethyl acetate, evaporation, and crystallization from acetone–hexane gave 41 mg. of VIIa having m.p. 226–228°, $[\alpha]^{26}D$ +170° ($CHCl_3$), λ_{max}^{alc} 238 mμ (ε 17,100).

Anal. Calcd. for $C_{23}H_{30}O_5$ (386.47): C, 71.48; H, 7.82. Found: C, 71.71; H, 7.60.

B. From VII.—11α-Hydroxy-12-ketoprogesterone (56 mg.) was dissolved in 1 ml. of dry pyridine and 1 ml. of acetic anhydride. After 16 hr. at room temperature, the mixture was diluted with water, and the crystals which separated were filtered, washed with water, and dried to give 50 mg. of VIIa.

3,20-Bisethylenedioxy-11α-hydroxypregn-5-en-12-one 11-Acetate (VIIc).—A solution of 93 mg. of 12α-acetoxy-11-ketoprogesterone in 90 ml. of benzene and 20 ml. of ethylene glycol containing 50 mg. of *p*-toluenesulfonic acid was refluxed for 40 hr. using a calcium carbide trap to remove water. The solution was then partially evaporated *in vacuo*, diluted with chloroform which was washed successively with 5% sodium bicarbonate and water and evaporated to dryness *in vacuo*. Crystallization of the residue from acetone–hexane gave 87 mg. of the bisethylene ketal VIIc having m.p. 224–226°, $[\alpha]^{22}D$ −22° ($CHCl_3$).

Anal. Calcd. for $C_{27}H_{38}O_7$ (474.57): C, 68.33; H, 8.07. Found: C, 68.26; H, 8.11.

3,20-Bisethylenedioxy-11α-hydroxypregn-5-en-12-one (VIIb).—A mixture of 102 mg. of 3,20-bisethylenedioxy-11α-hydroxypregn-5-en-12-one 11-acetate in 20 ml. of methanol and 2 ml. of 10% potassium carbonate was warmed on a steam bath until the steroid had dissolved and then left at room temperature for 2 hr., during which time crystals separated. These were filtered, washed with aqueous methanol, and dried to give 50 mg. of VIIb having m.p. 224–226°, $[\alpha]^{22}D$ +2.90° ($CHCl_3$).

Anal. Calcd. for $C_{25}H_{36}O_6$ (432.54): C, 69.42; H, 8.39. Found: C, 69.45; H, 8.58.

11α-Hydroxy-12-ketoprogesterone (VII).—Following the procedure for the hydrolysis of Vb, 500 mg. of VIIc gave on crystallization from acetone–hexane 305 mg. of VII having m.p. 165–168°, $[\alpha]^{24}D$ +187° ($CHCl_3$), λ_{max}^{alc} 240 mμ (ε 16,300) and 280 mμ (ε 200).

Anal. Calcd. for $C_{21}H_{28}O_4$ (344.43): C, 73.23; H, 8.19. Found: C, 73.25; H, 8.24.

3,20-Bisethylenedioxypregn-5-ene-11β,12β-diol (IX).—To a solution of 101.6 mg. of 3,20-bisethylenedioxy-12β-hydroxypregn-5-ene-11-one in 25 ml. of tetrahydrofuran, freshly distilled from lithium aluminum hydride, 103.6 mg. of lithium aluminum hydride was added in small portions over a 5-min. period. The mixture was then refluxed for 3.5 hr. and cooled, and the excess reagent was decomposed by the careful addition of ethyl acetate. The mixture was then diluted with water and extracted with chloroform, and the chloroform extracts were combined, washed with water, and evaporated to dryness *in vacuo*. Crystallization of the residue from acetone–hexane gave 72.3 mg. of IX having m.p. 208–210°, $[\alpha]^{22}D$ −35.3° ($CHCl_3$).

Anal. Calcd. for $C_{25}H_{38}O_6$ (434.55): C, 69.09; H, 8.81. Found: C, 69.04; H, 8.84.

3,20-Bisethylenedioxypregn-5-ene-11β,12β-diol (X).—To a solution of 1.0 g. of 3,20-bisethylenedioxy-11α-hydroxypregn-5-en-12-one in 75 ml. of tetrahydrofuran, freshly distilled from lithium aluminum hydride, 1.0 g. of lithium aluminum hydride was added in small portions over a 5-min. period. Then, following the procedure for the preparation of IX, there was obtained by crystallization from acetone–hexane 900 mg. of IX having m.p. 222–224°, $[\alpha]^{22}D$ −26.1° ($CHCl_3$).

Anal. Calcd. for $C_{25}H_{38}O_6$ (434.55): C, 69.09; H, 8.81. Found: C, 69.03; H, 8.86.

11α,12β-Dihydroxyprogesterone 11,12-Acetonide (VIII).—A solution of 700 mg. of 3,20-bisethylenedioxypregn-5-ene-11α,-12β-diol in 100 ml. of reagent grade acetone containing 0.1 ml. of perchloric acid was kept at room temperature for 18 hr. It was then neutralized with 5% sodium bicarbonate and diluted carefully with water whereupon crystals separated. The crystals were filtered, washed with water, and dried to give 11α,12β-dihydroxyprogesterone 11,12-acetonide having m.p. 199–201°, $[\alpha]^{22}D$ +222° ($CHCl_3$), λ_{max}^{alc} 239 mμ (ε 16,000).

Anal. Calcd. for $C_{24}H_{34}O_4$ (386.57): C, 74.57; H, 8.87. Found: C, 74.57; H, 8.85.

11β,12β-Dihydroxyprogesterone 11,12-Acetonide (XI).—A solution of 107 mg. of 3,20-bisethylenedioxypregn-5-ene-11β,12β-diol in 20 ml. of acetone containing 0.02 ml. of perchloric acid was kept at room temperature for 16 hr. It was then neutralized with dilute sodium bicarbonate solution, diluted with water, and extracted with chloroform. The chloroform extracts were combined, washed with water, and evaporated to dryness *in vacuo*. Crystallization of the residue from acetone–hexane gave XI having m.p. 224–226°, $[\alpha]^{22}D$ +224° ($CHCl_3$), λ_{max}^{alc} 238 mμ (ε 17,000).

Anal. Calcd. for $C_{24}H_{34}O_4$ (386.51): C, 74.57; H, 8.87. Found: C, 74.64; H, 8.77.

11α,12α-Dihydroxyprogesterone 11,12-Acetonide (XII).—A solution of 50 mg. of 3,20-bisethylenedioxypregn-5-ene-11α,-12α-diol in 10 ml. of acetone containing 0.01 ml. of perchloric acid was kept at room temperature for 18 hr. It was then diluted with water, neutralized with 5% sodium bicarbonate, and extracted with chloroform. The chloroform was washed with water and evaporated to dryness *in vacuo* to give a residue which on crystallization from acetone–hexane gave 30 mg. of XII having m.p. 162–164°, $[\alpha]^{22}D$ +88.9° ($CHCl_3$), λ_{max}^{alc} 239 (ε 17,000).

Anal. Calcd. for $C_{24}H_{34}O_4$ (386.51): C, 74.57; H, 8.87. Found: C, 75.12; H, 9.08.

11α,12α-Dihydroxyprogesterone (XIV).—A solution of 500 mg. of 3,20-bisethylenedioxypregn-5-ene-11α,12α-diol in 200 ml. of reagent grade methanol and 7 ml. of a solution of 8 ml. of sulfuric acid in 92 ml. of water was refluxed for 40 min. It was then cooled, neutralized carefully with 5% sodium bicarbonate, diluted with water, and extracted with chloroform. The chloroform extract was then washed with water and evaporated to dryness *in vacuo*. The residue on plate chromatography using alumina(V) as adsorbant and chloroform–ethyl acetate (4:1 v./v.) as developing solvent gave a band at R_f 0.5 detectable by ultraviolet, which on separation and elution with ethyl acetate gave a residue which on crystallization from acetone–hexane yielded 150 mg. of XIV having m.p. 158–160°, $[\alpha]^{27}D$ +142° ($CHCl_3$), λ_{max}^{alc} 242 mμ (ε 16,100).

Anal. Calcd. for $C_{21}H_{30}O_4$ (346.45): C, 72.80; H, 8.73. Found: C, 72.86; H, 8.76.

11β,12β-Dihydroxyprogesterone (XIII).—Following the procedure for the preparation of XIV but substituting 3,20-bisethylenedioxyprogen-5-ene-11β,12β-diol for the 3,20-bisethylenedioxypregn-5-ene-11α,12α-diol there was obtained by crystallization from acetone–hexane 260 mg. of XIII having m.p. 188–189°, $[\alpha]^{26}D$ +116° ($CHCl_3$), λ_{max}^{alc} 240 mμ (ε 17,800).

Anal. Calcd. for $C_{21}H_{30}O_4$ (346.45): C, 72.80; H, 8.73. Found: C, 72.74; H, 8.82.

3-Ethylenedioxy-12β-hydroxypregn-5-ene-11,20-dione (Vc).—To a solution of 216 mg. of Vb in 15 ml. of reagent grade acetone 2.0 ml. of an aqueous solution containing 20 mg. of chromic anhydride/ml. and 32 mg. of sulfuric acid/ml. was added dropwise with stirring. After 5 min. a few drops of methanol were added,

and the mixture was diluted with water and extracted with chloroform. The chloroform was washed with water and evaporated to dryness *in vacuo*. Crystallization of the residue from acetone–hexane gave 129 mg. of Vc having m.p. 198–200°, $[\alpha]^{28}D$ +28° ($CHCl_3$).

Anal. Calcd. for $C_{23}H_{32}O_5$ (388.49): C, 71.10; H, 8.30. Found: C, 71.20; H, 8.08.

Following the procedure for obtaining 12β-hydroxy-11-ketoprogesterone (V) from Vb, acid hydrolysis of Vc also gave V. Similarly Vb could be obtained from Vc by ketalization following the same procedure described for V.

11β,12β,20β-Trihydroxypregn-4-en-3-one 11,12-Acetonide (XV) and 11β,12β,20α-Trihydroxypregn-4-en-3-one 11,12-Acetonide (XVI).—A mixture of 1.0 g. of 3-ethylenedioxy-12β-hydroxypregn-5-ene-11,20-dione and 1.0 g. of lithium aluminum hydride in 75 ml. of tetrahydrofuran freshly distilled from lithium aluminum hydride was refluxed for 3.5 hr. with stirring, then cooled, and the excess lithium aluminum hydride was decomposed by the dropwise addition of ethyl acetate. The mixture was then diluted with water and extracted with chloroform which was washed with water and evaporated to dryness *in vacuo*. The residue was dissolved in 200 ml. of acetone, 0.2 ml. of 70% perchloric acid was added, and the solution was left at room temperature for 2 hr. It was then neutralized with dilute sodium bicarbonate, diluted with water, and extracted with chloroform. The chloroform was washed with water and evaporated to dryness *in vacuo*. Plate chromatography of the residue using Woelm neutral alumina (activity V) as adsorbant and chloroform as the developing solvent gave two bands detectable by ultraviolet at R_f 0.7 and 0.5 which were separated, eluted with ethyl acetate, evaporated, and crystallized from acetone–hexane. The less polar band gave 270 mg. of XVI having m.p. 152–154°, $[\alpha]^{26}D$ +123° ($CHCl_3$), λ_{max}^{alc} 239 mμ (ε 16,200).

Anal. Calcd. for $C_{24}H_{36}O_4$ (388.53): C, 74.19; H, 9.34. Found: C, 74.26; H, 9.35.

From the more polar band 330 mg. of XV was obtained having m.p. 178–180°, $[\alpha]^{26}D$ +112° ($CHCl_3$), λ_{max}^{alc} 238 mμ (ε 19,100).

Anal. Calcd. for $C_{24}H_{36}O_4$ (388.53): C, 74.19; H, 9.34. Found: C, 74.33; H, 9.42.

Acetylation of XVI at room temperature for 16 hr. using acetic anhydride and pyridine gave the 20α-acetate XVII having m.p. 116–118°, $[\alpha]^{26}D$ +109° ($CHCl_3$), λ_{max}^{alc} 238 mμ (ε 18,800).

Anal. Calcd. for $C_{26}H_{38}O_5$ (430.56): C, 72.52; H, 8.90. Found: C, 72.72; H, 8.93.

Reaction of XV with acetic anhydride and pyridine under these conditions gave only starting material.

Jones oxidation[5a] of either XV or XVI gave 11β,12β-dihydroxyprogesterone 11,12-acetonide (XI).

The Chemistry of 11,12-Oxygenated Progesterones. II. Hydrogen-Bonding Studies

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The relationships between structure and hydrogen bonding of 11,12-oxygenated derivatives have been determined by n.m.r. and infrared spectroscopy. In the intramolecular hydrogen-bonding studies, a general correlation is found between the hydroxyl frequency and the proton chemical shift.

Hydrogen bonding in cyclic and acyclic diols has been systematically investigated by high-resolution infrared spectroscopy.[2] Jones, *et al.*,[3a] in their definitive survey, applied infrared spectroscopy to the determination of hydrogen bonding of steroidal ketols and diols. Subsequent investigations have been concerned with various aspects of hydrogen bonding in steroids[3b-d] and triterpenes.[4] The detection and identification of hydrogen bonding by infrared spectroscopy have been instrumental in the assignment of partial structures.[5]

Hydrogen-bonding studies of steroids by n.m.r. spectroscopy have, however, received little attention. In their survey of the n.m.r. of steroids, Shoolery and Rogers[6] presented spectral evidence for hydrogen bonding in a number of steroids which include the ketols, 17α-hydroxyprogesterone and 11-dehydrocorticosterone. Subsequently, there have been only scattered reports of the proton resonance of steroidal hydroxyl groups.[5b,7]

Although solution infrared and n.m.r. spectra are obtained under different conditions, the spectral results are complementary. N.m.r. spectroscopy was used extensively to assign the structure of related 11,12-oxygenated progesterones.[8] Since hydrogen bonding was encountered in these compounds, high-resolution infrared spectra of carbon tetrachloride or deuteriochloroform solutions were also obtained. The interpretation of the hydrogen-bonding phenomena which aided in the subsequent structural assignment of the derivatives is the subject of this report.

Experimental

The method of preparation and the chemical and physical properties of these compounds have been described in the preceding paper.[8] Testosterone and 17α-hydroxyprogesterone were obtained from the Squibb collection. The n.m.r. spectra were obtained by transferring a known quantity of steroid to a 1-ml. volumetric flask and diluting to mark with deuteriochloroform containing 0.5 % (v./v.) tetramethylsilane as an internal refer-

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