Synthetic Studies on C-19 Oxygenated Pregnanes

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Secondary and tertiary 6β-hydroxy-5α-pregnanes (IIIa–h) have been used as substrates to study the nature of products obtained on treatment with lead tetraacetate in an inert solvent. The effect of the presence of iodine in this reaction was also studied in some cases. 3β,20β-Diacetoxy-5α-chloro-6β,19-oxidopregnane (IVc) and 3β-acetoxy-5α-bromo-17α-methyl-6β,19-oxidopregnan-20-one (IVf) are converted *via* saponification and oxidation to 6β,19-oxidopregn-4-ene-3,20-dione (IXa) and 17α-methyl-6β,19-oxidopregn-4-ene-3,20-dione (IXb), respectively. 6α-Methyl-6β,19-oxidopregn-4-ene-3,20-dione (IXc) was synthesized by the oxidation of 5α-bromo derivatives Xa and Xb. Oppenauer oxidation of 3β,19,20β-trihydroxy-6-methylpregn-5-ene (VId) gave 19-hydroxy-6α-methylprogesterone (VIIIb) which was converted to 6α-methyl-19-norprogesterone (XVII). 6-Methyl-19-norpregna-4,6-diene-3,20-dione (XXI) was synthesized by ring opening of the oxidoprogesterone (IXc) followed by oxidation and elimination of C-19. The nature and reactivity of the Δ⁵-3β,19-dihydroxy system are discussed.

Intramolecular attack by an electron deficient group (oxygen in particular) on a suitably located non-activated C–H bond has been advantageously utilized[1] in recent years to synthesize C-18 and/or C-19 substituted steroids. The potentiality of 19-hydroxy-Δ⁴-3-ketones to generate[2] 19-norsteroids of biological importance has been demonstrated recently.[2c]

An investigation was initiated to study the scope and limitations of the reactions of 6β-hydroxypregnanes[3] with lead tetraacetate and to explore the transformations of 6β,19-oxides obtained therefrom to produce 19-norsteroids.

Readily available[4] 3β-hydroxy-Δ⁵-steroids were used to synthesize the substrates required for this work. Pregnenolone was converted to 3β,20β-diacetoxypregn-5-ene (Ia)[5] in excellent yields using sodium borohydride, followed by acetylation. Conventional routes such as (i) Δ⁵-steroid → 6-nitro derivative[6] → 6-ketone, and (ii) Δ⁵-steroid → 5α-bromo-6β-ol[7] → bromo ketone → 6-ketone gave 3β,20β-diacetoxy-5α-pregnan-6-one (IIa) in very poor yields (<20%). The latter compound as well as the ketones IIb and c were prepared in good yields using the hydroboration–oxidation method already described.[8] Ketones IIa and b were smoothly converted to the corresponding alcohols IIIa and d with sodium borohydride.[9] The carbinols IIIb, e, and g were synthesized by treating the corresponding ketones IIa, b, and c with methylmagnesium bromide.

Lead Tetraacetate Reaction.—The alcohols IIIa–h were treated[10] with excess lead tetraacetate and iodine (molar ratio 1:1) to yield the corresponding 6β,19-oxides IVa–h in satisfactory yields. In all the cases where comparative lead tetraacetate experiments were conducted, the yields of the 6β,19-oxides obtained when iodine was present were consistently superior to those obtained when iodine was excluded. Of particular interest are the results obtained with 3β,20β-diacetoxy-5α-pregnan-6β-ol (IIIa) and 3β,20β,diacetoxy-5α-chloropregnan-6β-ol (IIIc). Treatment of IIIa with lead tetraacetate in the absence of iodine gave a mixture of products from which 3β,20β-diacetoxy-5α-pregnan-6-one (IIa) was isolated by crystallization in 62% yield.[11] A chromatography of the residue obtained from the mother liquors afforded 3β,20β-diacetoxy-6β,19-oxido-5α-pregnane (IVa, *ca.* 6%). Treatment of IIIc with lead tetraacetate likewise yielded a mixture[12] of 3β,20β-diacetoxy-5α-chloropregnan-6-one (IId) and the corresponding oxide IVc. Attempts to separate these compounds either by crystallization or by column chromatography were unsuccessful. Treatment of the mixture with zinc and acetic acid gave, on crystallization of the crude product, ketone IIa as a major component. Chromatography of the residual material, followed by crystallization of the benzene–ether (19:1) eluate, yielded 3β,20β-diacetoxy-5α-chloro-6β,19-oxidopregnane (IVc). In contrast, when IIIa and c were treated with excess 1:1 molar lead tetraacetate–iodine, the oxides IVa and c were directly obtained by crystallization in 68 and 85% yields, respectively. The type of annulation described here can lead[10] to 19-iodinated or 19-hydroxy oxides. However, we were not able to isolate[13] any such derivatives.[14] The structures of the oxides IVa–h were established by their elemental analyses and by their infrared and nuclear magnetic resonance (n.m.r.) spectra.

Treatment of the diketal oxide (IVd) with sulfuric acid in acetone hydrolyzed the protective ketal groupings to give 6β,19-oxido-5α-pregnane-3,20-dione (Va). This compound was also obtained from IVa by saponification followed by oxidation with 8 *N* chromic acid

(1) (a) M. Wehrli, M. S. Heller, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **44**, 2162 (1961); (b) D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Am. Chem. Soc.*, **82**, 2640 (1960); (c) M. Akhtar and D. H. R. Barton, *ibid.*, **84**, 1496 (1962).

(2) (a) G. Barber and M. Ehrenstein, *J. Org. Chem.*, **20**, 1253 (1955); (b) M. Hagiwara, S. Noguchi, and M. Nishikawa, *Chem. Pharm. Bull. Japan*, **8**, 84 (1960); (c) A. Bowers, R. Villotti, J. A. Edwards, E. Denot, and O. Halpern, *J. Am. Chem. Soc.*, **84**, 3204 (1962).

(3) For references to similar studies in androstane series, see A. Bowers, *et al.*, *J. Org. Chem.*, **27**, 1862 (1962).

(4) Similar substrates are used in an anlogous study involving nitrite photolysis see ref. 1c.

(5) R. B. Turner and D. M. Voitle, *J. Am. Chem. Soc.*, **73**, 2283 (1951).

(6) C. E. Anagnostopoulos and L. F. Fieser, *ibid.*, **76**, 532 (1954).

(7) V. Grenville, D. K. Patel, V. Petrow, I. A. Stuart-Webb, and D. M. Williamson, *J. Chem. Soc.*, 4105 (1957).

(8) J. F. Bagli, P. F. Morand, and R. Gaudry, *J. Org. Chem.*, **27**, 2938 (1962).

(9) W. G. Dauben, E. J. Blanz, Jr., J. Jiu, and R. A. Micheli, *J. Am. Chem. Soc.*, **78**, 3752 (1956).

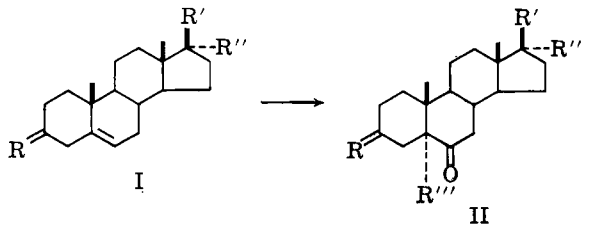
(10) Ch. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner, and A. Wettstein, *Experientia*, **17**, 475 (1961).

(11) These results present a marked contrast to those obtained when 3β,17β-diacetoxyandrostan-6β-ol was treated with lead tetraacetate under similar conditions (see ref. 3 and 10).

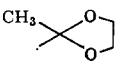
(12) The presence of 3β,20β-diacetoxy-5α-chloropregnan-6-one in the mixture was established by thin-layer chromatography and by its optical rotation (*vide.* Experimental).

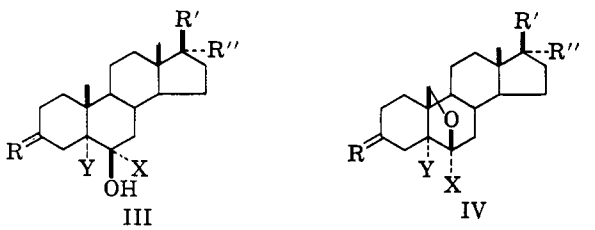
(13) Although no C-19 iodinated steroids were isolated, in some cases, *e.g.*, IVa and f after the work-up, the crude product slowly liberated some more iodine overnight. This was noted by production of brown color, odor, and by subsequent decolorization by thiosulfate extraction.

(14) Formation of such derivatives may involve C-19 diiodo compounds as intermediates (see ref. 10). An examination of models reveal severe 1,3 diaxial interaction between the C-19 diiodomethyl group and the C-2, C-4, C-6, and C-11 axial substituents.



I II

	R	R′	R″	R‴
a		—CH(OAc)CH$_3$	H	H
b			H	H
c)		—COOCH$_3$	CH$_3$	H
d		—CH(OAc)CH$_3$	H	Cl
e		—COOCH$_3$	CH$_3$	Br



III IV

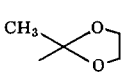
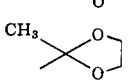
	R	R′	R″	X	Y
a		—CH(OAc)CH$_3$	H	H	H
b		—CH(OAc)CH$_3$	H	CH$_3$	H
c		—CH(OAc)CH$_3$	H	H	Cl
d			H	H	H
e			H	CH$_3$	H
f		—CO—CH$_3$	CH$_3$	H	Br
g		—COOCH$_3$	CH$_3$	CH$_3$	H
h		—COOCH$_3$	CH$_3$	H	Br

CHART 1

solution in acetone. 6α-Methyl-6β,19-oxido-5α-pregnane-3,20-dione (Vb) was similarly obtained from diketal oxide (IVe) and 3β,20β-diacetoxy-6α-methyl-6β,19-oxido-5α-pregnane (IVb), respectively.

Spectral Data.—An examination of the infrared spectra of the oxides described above revealed the presence of a low intensity band in the 1499–1488-cm.$^{-1}$ region. This band was generally well separated[15] from the envelope of bands representing the C–H bending modes of the methylenes in the rest of the molecule. It appears after annulation of the 6β-alcohols to the 6β,19-oxides and is absent in the products where the oxide ring is cleaved. The band may, therefore, be assigned to the C–H scissoring of the protons of the newly formed C-19 methylene. These bands together with another characteristic band in the 860–800-cm.$^{-1}$ region are listed in Table I.

(15) This band is slightly shifted towards the lower frequency and hence was not completely resolved in compounds IXa, b, and c.

TABLE I

CHARACTERISTIC INFRARED BANDS OF 6β,19-OXIDO DERIVATIVES

Compound no.	C-19 Methylene bending in cm.$^{-1}$	Other band in cm.$^{-1}$
IVa	1492	850
IVb	1496	829
IVc	1497	853
IVd	1490	827
IVe	1492	831
IVf	1495	860
IVg	1488	828
IVh	1499	852
Va	1494	858
Vb	1492	826
Xa	1496	832
Xb	1497	830
IXa	1487	881
IXb	1487	880
IXc	1485	880

Some observations on the n.m.r. spectra of the C-19 oxygenated compounds are worthy of mention. It is well established[16] that the nuclei of atoms of the same species bonded to a common carbon atom may behave as non-equivalent due to unsymmetrical electronic or steric environment. The n.m.r. spectra of the 6β,19-oxidoprogesterones (IXa, b, and c) exhibit a pair of doublets, having a pattern intermediate between A_2 and AB systems, ascribable to C-19 protons. Such a splitting of methylene protons α to the oxygen of a cyclic ether is not unprecedented.[17] The τ values for these signals are listed in Table II. The resonance signals of the C-19 protons of the oxides where the C-4 double bond is absent appears as a sharp singlet (A_2 system) in the region of 6.30 τ. In the case of the triacetates VIa and b, the signals due to C-19 protons appear as a pair of doublets (see Table II) of the type described above for oxidoprogesterones.

TABLE II

N.M.R. DATA FOR C-19 OXYGENATED DERIVATIVES IN CDCl$_3$[a]

Compound no.	C-19 protons (J)[b]
IXa	5.85 d (9.0)
	6.53 d (9.0)
IXb	5.82 d (9.0)
	6.55 d (9.0)
IXc	5.86 d (9.0)
	6.54 d (9.0)
IVa	6.30
IVb	6.31
IVc	6.16
VIa	5.58 d (12.6)
	6.10 d (12.6)
VIb	5.61 d (12.6)
	6.12 d (12.6)

[a] Values are given in τ units relative to tetramethylsilane as reference. Singlets are unmarked, doublets are described by d. The values of doublets represent the center of the doublet. [b] In cycles per second.

(16) W. D. Phillips, *J. Phys. Chem.*, **25**, 949 (1956).

(17) L. F. Fieser, T. Goto, and B. K. Bhattacharyya, *J. Am. Chem. Soc.*, **82**, 1700 (1960).

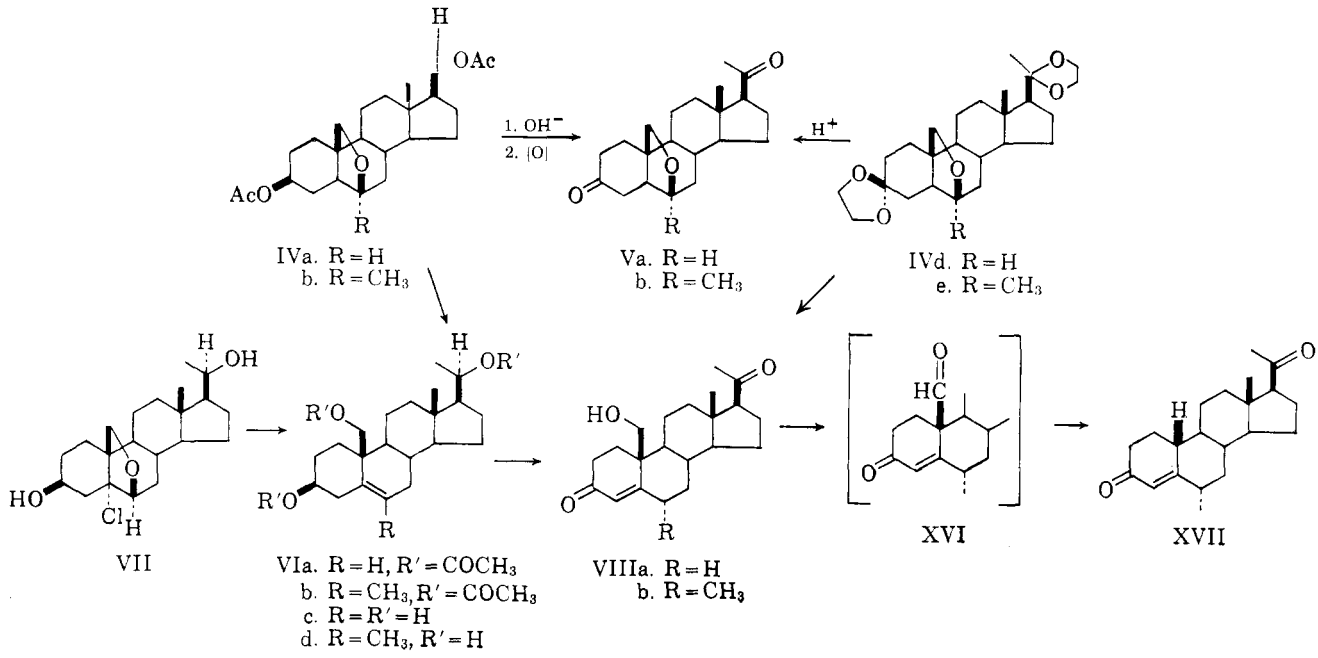


CHART 2

The appearance of "abnormal" ultraviolet spectra as a result of the interaction between non-adjacent chromophores has by now been amply exemplified.[18] These variations show up either as a charge transfer ($\pi \rightarrow \pi^*$) absorption band in some unsaturated ketones,[18c] or as intensified $n \rightarrow \pi^*$ absorption depending upon the value of the overlap integral between the olefinic π-orbitals and the p-orbitals of the carbonyl oxygen. We have observed the ultraviolet spectra of lactones XIIIa, b, and c. All three compounds exhibit an absorption band in the region of 230 mμ. The appropriate λ_{max} and ϵ values are listed in Table III. These lactones represent a novel class of chromophore exhibiting such $\pi \rightarrow \pi^*$ absorption. This absorption may be similar to that observed in some β,γ-unsaturated ketones not exhibiting intensification of $n \rightarrow \pi^*$ absorption.[18c] When the spectra of these compounds were recorded in alkaline medium, the absorption band disappeared and on treatment of the solution with acid the band reappeared. The above experiment clearly demonstrates that the absorption is associated with the stereoelectronic factors that are most favorable for $\pi \rightarrow \pi^*$ transition, due to the geometry of the system in the lactone form.

TABLE III

Compound no.	Max (mμ)	ϵ
XIIIa	231	3350
XIIIb	228	1330
XIIIc	228	2410

Cleavage of the Oxide Ring.—The opening of the 6β,19-oxides described above was achieved (i) by acid catalysis in the cases where a C-5 hydrogen was present and (ii) by reductive cleavage in the cases where a halogen atom was attached to C-5. The latter method involved the use of lithium–liquid ammonia or of zinc and acetic acid. 3β,20β-Diacetoxy-6β,19-oxido-5α-pregnane (IVa), when treated with a catalytic amount of *p*-toluenesulfonic acid in the presence of acetic acid and acetic anhydride, gave a mixture of products. An infrared spectrum of this mixture showed intense bands due to the acetate grouping (1720, 1250 cm.$^{-1}$), and absence of the 1492-cm.$^{-1}$ band present in the oxide. Saponification of the mixture, followed by chromatography of the crude alcohols, afforded 3β,19,20β-trihydroxypregn-5-ene (VIc) in *ca.* 27% yield. The structural assignment VIc follows from its n.m.r. spectrum (in deuterated methanol). The 6.07 τ signal attributed to the C-6 proton of the oxide IVa was absent, and a new singlet at 4.44 τ ascribable to the C-6 vinyl proton had appeared. Saponification of the oxide IVc gave 5α-chloro-6β,19-oxido-pregnane-3β,20β-diol (VII). On treatment with lithium–liquid ammonia, diol VII afforded a triol in 59% yield. This triol was shown by mixture melting point, t.l.c.,[19] and by comparison of the n.m.r. spectra to be identical with compound VIc obtained above from IVa *via* acid catalysis. A triacetate obtained by acetylation showed an n.m.r. spectrum in complete agreement with the structure VIa.

An acid-catalyzed ring opening of 3β,20β-diacetoxy-6α-methyl-6β,19-oxido-5α-pregnane (IVb) proceeded smoothly to give a triacetate (VIb), which on saponification, afforded 3β,19,20β-trihydroxy-6-methylpregn-5-ene (VId) in excellent yield. N.m.r. spectra of the triol VId (in deuterated methanol) and the triacetate VIb both exhibited the signals attributable to vinyl methyl protons at 8.35 and 8.38 τ, respectively. Acid-catalyzed cleavage of oxide IVd gave a crude product which was shown to contain an α,β-unsaturated ketone by infrared and ultraviolet spectra (λ_{max} 238 mμ, ϵ_{max} 8380). Alkaline hydrolysis followed by careful chromatography resulted in isolation of 19-hydroxyprogesterone (VIIIa) in a very low yield. Compound VIIIa was also isolated from an Oppenauer oxidation of triol

(18) (a) R. C. Cookson and N. S. Wariyar, *J. Chem. Soc.*, 2302 (1956); (b) H. Labhart and G. Wagniere, *Helv. Chim. Acta*, **42**, 2219 (1959); (c) S. Winstein, L. de Vries, and R. Orloski, *J. Am. Chem. Soc.*, **83**, 2020 (1961); R. C. Cookson and J. Hudec, *J. Chem. Soc.*, 429 (1962).

(19) The abbreviation "t.l.c." throughout this article refers to "thin-layer chromatography."

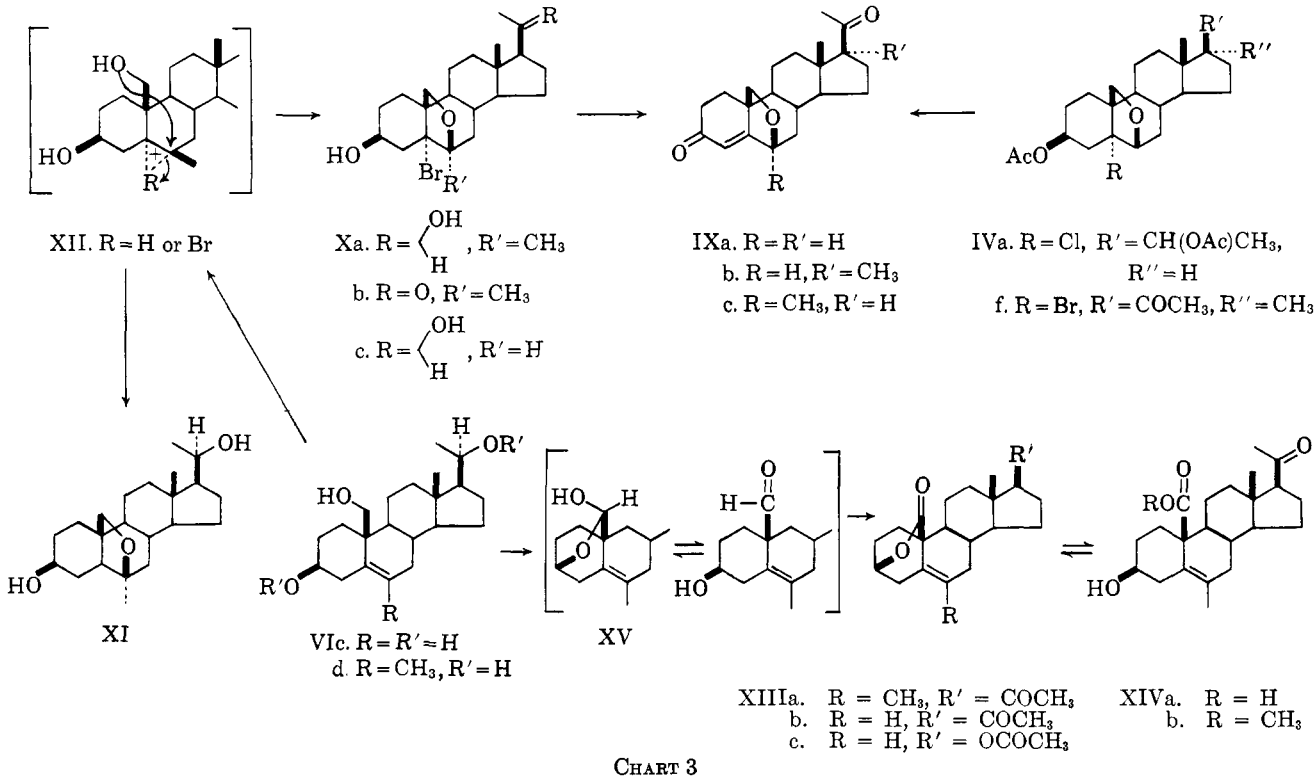


CHART 3

VIc. The infrared spectra and the R_f values by t.l.c. of the products obtained from both sources were identical.

6β,19-Oxidoprogesterone (IXa) and 6α-methyl-6β,19-oxidoprogesterone (IXc), when treated with zinc and acetic acid for varying periods of time and temperature, gave crude products whose infrared spectra indicated the cleavage of the oxide ring in varying degrees. When IXa was treated with zinc and acetic acid for thirty minutes at room temperature, essentially starting material was recovered together with a very small amount of hydroxylic material. The latter product had an R_f value by t.l.c. identical with that of 19-hydroxyprogesterone (VIIIa). When the experiment was conducted at reflux temperature for 2.5 hours, a mixture of products was obtained which showed in its infrared spectrum a complete absence of bands in the O—H stretching region, and a band of 1735 cm.$^{-1}$ attributable to an acetate carbonyl. Saponification of the crude product gave an oil whose infrared spectrum showed strong O—H bands and absence of the acetate absorption. Treatment of 17α-methyl-6β,19-oxidopregn-4-ene-3,20-dione (IXb) with zinc and acetic acid on a steam bath for twenty minutes yielded an oil which was shown to have hydroxyl and acetate groups from its infrared spectrum. The characteristic band at 1487 cm.$^{-1}$ (6β,19-oxide) in the starting material was absent.

C-19 Substituted and C-19 Norprogesterones.—The syntheses of 6β,19-oxidopregn-4-ene-3,20-dione (IXa) and the 17α-methyl derivative (IXb) were smoothly accomplished by saponification of the oxides IVc and f, respectively, followed by chromic acid oxidation.

The reaction of α-halo ketones with methylmagnesium bromide to give the corresponding dehalogenated ketones is well documented.[20] We found that 5α-halo-6-keto steroids likewise yielded 6-ketones instead of the desired carbinol on treatment with methylmagnesium bromide. When triol VId reacted with N-bromoacetamide in *t*-butyl alcohol, a crystalline solid was obtained in 69% yield. An infrared spectrum showed bands at 3450, 3619 (bonded and nonbonded O—H stretching), 1695 (C-20 ketone) cm.$^{-1}$, and a band at 1497 cm.$^{-1}$ indicative of 6β,19-oxide. An elemental analysis indicated the presence of one atom of bromine. The structure of this product was readily discerned to be 3β-hydroxy-5α-bromo-6β,19-oxido-6α-methylpregnan-20-one (Xb). That the carbonyl group was located at C-20 rather than at C-3 was established as follows. Compound Xb was recovered unchanged on treatment with acid or with alkali. Mild acid treatment however, preceeded by chromic acid oxidation gave 6α-methyl-6β,19-oxidopregn-4-ene-3,20-dione (IXc). The presence of a C-20 ketone in Xb was further confirmed by its n.m.r. spectrum (C-21 methyl, singlet at 7.94 τ). When a solution of bromine in acetic acid was added to a solution of the triols VIc or VId, they were quantitatively transformed to the diols Xc and Xa, respectively, characterized by their bromine analyses and by their infrared and n.m.r. spectra. Subsequent oxidation followed by acid-catalyzed dehydrobromination led to the corresponding oxidoprogesterones, IXa and c, respectively. Triol VId, when treated with methanolic hydrochloric acid, was quantitatively transformed into diol XI. Acetylation with pyridine and acetic anhydride afforded a diacetic identical in all respects with 3β,20β-diacetoxy-6α-methyl-6β,19-oxido-5α-pregnane (IVb). Similar acid treatment of VIc was abortive and gave only unchanged starting material. All the cyclization reactions of Δ^5-19-alcohols described above can be interpreted simply as being initiated by an electrophilic attack at the 5,6-double bond and terminated by an intramolecular nucleophilic

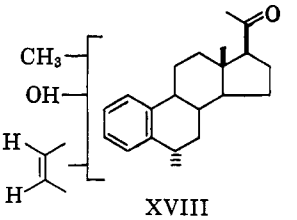
(20) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice Hall, New York, N. Y., 1954, p. 181.

ring closure by the C-19 oxygen on the intermediate cation (XII) thereby generating the products.

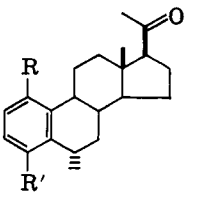
Oxidation of the triol VId with chromic acid in acetone at 0° resulted in isolation by crystallization[21] of a product in 32% yield. An infrared spectrum had a band at 1737 cm.$^{-1}$ suggesting the presence of a δ-lactone and one at 1698 (C-20 ketone) cm.$^{-1}$. An n.m.r. spectrum of this compound had a sharp singlet at 8.50 τ, characteristic of a vinyl methyl (at C-6) and an unresolved multiplet at 5.31 τ, ascribable to a proton on a carbon bearing an oxygen atom. Furthermore, it also exhibited sharp signals at 7.94 and 9.26 τ due to a C-21 methyl ketone and a C-18 angular methyl, respectively. We have assigned structure XIIIa to this lactone. This is further substantiated by the following experiments. Saponification of the lactone XIIIa yielded a carboxylic acid XIVa identified by its characteristic infrared spectrum. This acid was quantitatively transformed to its methyl ester XIVb whose infrared and n.m.r. spectra were in complete agreement with its assigned structure. The alcohol VIc on oxidation with chromic acid–acetone also yielded the corresponding lactone XIIIb.

The formation of lactones XIIIa and b under the above conditions of oxidation is particularly interesting. That the lactone results from the cyclization of the corresponding C-19 carboxylic acid during oxidation is highly improbable. The following arguments support this contention. In order to regenerate the lactone XIIIa from the acid XIVa, it was necessary to reflux the acid in methanolic hydrochloric acid for 2.5 to 3 hours. An analogous lactone XIIIc in the androstane series has been recently reported.[22] The lactonization in this case was effected by heating the corresponding C-19 acid with aqueous acetic acid in a sealed tube at 220–230° for two hours. Furthermore, lactone XIIIa was also isolated in low yields from a a pyridine–chromic acid oxidation of the triol VId. This reagent is known[24a] not to oxidize a primary alcohol to carboxylic acid. A mechanism for the genesis of the lactone XIIIa and b is readily envisaged by considering an equilibrium between the lactol XV and the corresponding aldehyde, followed by oxidation of XV.

Oppenauer oxidation of the triol VId yielded two crystalline products. One of these was shown by its infrared, ultraviolet, and n.m.r. spectra to be 19-hydroxy-6α-methylprogesterone (VIIIb). It was converted[2b] to 6α-methyl-19-norprogesterone (XVII) *via* aldehyde XVI. The second product of the Oppenauer oxidation showed in its infrared spectrum bands at 3420, 3622 (bonded and nonbonded O—H stretching), 1695 (C-20 ketone), and 1592 (aromatic C=C stretching) cm.$^{-1}$. The presence of the aromatic ring was confirmed by its characteristic ultraviolet spectrum (λ_{max} 284 mμ, ε 1570). Acetylation of this compound afforded an acetate, the infrared spectrum of which showed no hydroxyl group and a new carbonyl band at 1755 (phenolic acetate) cm.$^{-1}$. Saponification of this acetate regenerated the phenol. An n.m.r. spectrum of this phenol showed signals at 9.44 and 7.87 τ attributable to C-18 and C-21 methyls, respectively, and a doublet at 8.8 τ ascribable to a C-6 methyl group. The aromatic proton resonances appeared as a pair of doublets at 3.17 τ (J_{ab} = 9 c.p.s.) characteristic of two protons located *ortho* to each other. Furthermore, the spectrum exhibited a sharp signal at 7.83 τ. This phenol had a correct analysis for $C_{22}H_{30}O_2$, suggesting the presence of a fourth methyl group. In the absence of the signal due to the third proton on the aromatic ring, we have assigned the 7.83 τ peak to a methyl group on the aromatic ring. The above spectral and analytical data can be accommodated by six structural possibilities (XVIII), *viz.*, where the aromatic *ortho* hydrogen atoms are attached to (i) C-1 and C-2, (ii) C-3 and C-4, or (iii) C-2 and C-3.

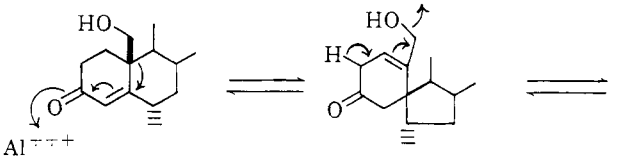


XVIII

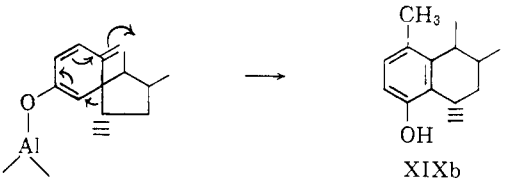


XIXa. R = OH, R′ = CH_3
b. R = CH_3, R′ = OH

The 'Oppenauer phenol' was isolated in about 2–3% yield from the triol VId. The same phenol was also isolated in *ca.* 6% yield when 6α-methyl-19-hydroxypregn-4-ene-3,20-dione (VIIIb) was subjected to the same Oppenauer conditions as triol VId, thus indicating VIIIb as a progenitor of the 'Oppenauer phenol.' The 'Oppenauer phenol' is best formulated by the expressions XIXa or b. Its formation from VIIIb may be rationalized by considering a Lewis acid[23] catalyzed rearrangement. One possible pathway to such a rearrangement is shown below.

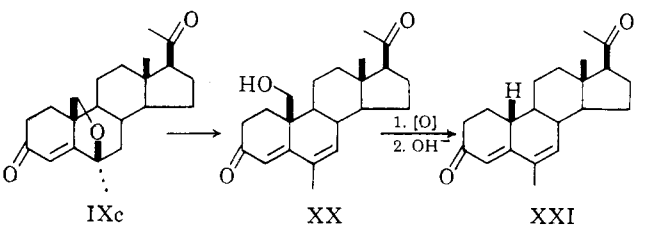


VIIIb



XIXb

An acid-catalyzed (*p*-toluenesulfonic acid in presence of acetic acid and acetic anhydride) opening of 6α-methyl-6β,19-oxidopregn-4-ene-3,20-dione (IXc) yielded a 19-acetoxy compound which was saponified to give 6-methyl-19-hydroxypregna-4,6-diene-3,20-dione (XX).



IXc XX XXI

(21) Attempts to isolate, by chromatography, any crystalline material from the residue obtained from the mother liquor were unsuccessful.

(22) R. Gardi and C. Pedrali, *Gazz. chim. ital.*, **91**, 1420 (1961). We with to thank Dr. R. Gardi for supplying us with a sample of lactone XIIIc for spectral purposes.

(23) R. B. Woodward and T. Singh, *J. Am. Chem. Soc.*, **72**, 494 (1950).

A pyridine–chromic acid oxidation followed by alkaline treatment of the crude product gave 6-methyl-19-norpregna-4,6-diene-3,20-dione (XXI).

Compounds IXa, b, and c were found inactive in Clauberg (subcutaneous and oral) assays.[24] They were also devoid of androgenic–anabolic activity. 6α-Methyl-19-norprogesterone (XVII) was found to be an active progestational agent, both orally and subcutaneously in preliminary tests.

Experimental[25]

3β,20β-Diacetoxy-5α-pregnan-6β-ol (IIIa).—To a solution of ketone IIa (0.085 g.) in methanol (5 ml.) was added a solution of sodium borohydride (0.035 g.) in methanol (2 ml.). After stirring overnight at room temperature, acetic acid (2 ml.) was added to destroy the excess hydride. The solution was evaporated to dryness and the residue was taken up in chloroform. This solution was washed with sodium bicarbonate solution and water and then dried. The removal of solvent left a crystalline solid (0.078 g.), which after one crystallization from acetone–hexane, gave alcohol IIIa (0.050 g.), m.p. 165–167°. An analytical sample[26] had m.p. 173–174°; [α] +2°; ν 3650 (nonbonded O–H), 3500 (bonded O–H), 1725 (acetate carbonyl) cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{40}O_5$ (420.57): C, 71.39; H, 9.59. Found: C, 71.58; H, 9.80.

3,20-Diethylenedioxy-5α-pregnan-6β-ol (IIId).—To a refluxing solution of ketone IIb (0.58 g.) in methanol (30 ml.) was added a solution of sodium borohydride (0.24 g.) in methanol (6 ml.) over a period of 5 min. Refluxing was continued for 1 hr., the solution was cooled, and excess hydride was destroyed by acetone (2 ml.). After removing the solvents, the residue was taken up in chloroform and the latter solution was washed with sodium bicarbonate solution and water and then dried. Evaporation of the solvent left a white solid (0.56 g.), m.p. 193–196°. Crystallization from methanol (containing a trace of pyridine) afforded needles, m.p. 200–202°; [α] +3°; ν 3640 (nonbonded O–H), 3520 (bonded O–H) cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{40}O_5$ (420.57): C, 71.39; H, 9.59. Found: C, 71.61; H, 9.59.

6β-Hydroxy-5α-pregnane-3,20-dione.—A solution of alcohol IIId (0.40 g.) in methanol (20 ml.) containing a drop of perchloric acid was heated on a steam bath for 15 min. The solution was cooled, diluted with water, and extracted with ether. Working up in the usual way gave a white solid, m.p. 234–237°. An analytical sample obtained from acetone–hexane melted at 236–239°; [α] +84°; ν 3630 (nonbonded O–H), 3500 (bonded O–H), 1700 (carbonyl stretching) cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{32}O_3$ (332.47): C, 75.88; H, 9.70. Found: C, 75.67; H, 9.77.

3β,20β-Diacetoxy-6α-methyl-5α-pregnan-6β-ol (IIIb).—To a solution of ketone IIa (6.0 g.) in dry benzene (570 ml.) was added a solution[25] (180 ml.) of methylmagnesium bromide. The solvent was distilled until the vapor temperature reached 75°. The reaction mixture was refluxed for 2 hr., cooled, and ethyl acetate (140 ml.) was added followed by 10% hydrochloric acid (187 ml.). After separating the layers, the aqueous layer was extracted with ethyl acetate; the combined extracts were washed with sodium bicarbonate solution and water and then dried. The crude product (6.5 g.) obtained after removal of the solvent was acetylated with pyridine (42 ml.) and acetic anhydride (23 ml.) at room temperature overnight. Working up in the usual manner and crystallization of the crude acetate from aqueous methanol gave IIIb (4.5 g.), m.p. 197–199°. Several recrystallizations from chloroform–methanol afforded an analytical sample, m.p. 199–200°; [α] +10°; ν 3630 (nonbonded O–H), 1722 (acetate carbonyl) cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{42}O_5$ (434.60): C, 71.85; H, 9.74. Found: C, 72.05; H, 9.91.

3,20-Diethylenedioxy-6α-methyl-5α-pregnan-6β-ol (IIIe).—Crude ketone[8] IIb (5.0 g., m.p. 163–166°) was dissolved in tetrahydrofuran (125 ml., freshly distilled over lithium aluminum hydride). A solution (25 ml.) of methylmagnesium bromide[25] was slowly added in an atmosphere of nitrogen, and the reaction mixture was stirred at room temperature overnight. Addition of a saturated ammonium chloride solution was followed by extraction of the mixture with ethyl acetate. The combined extracts were washed to neutrality and dried. Removal of the solvent and one crystallization of the residue from methanol gave colorless crystals (3.76 g.), m.p. 187–189°. Recrystallization from the same solvent afforded an analytical sample, m.p. 188–191°; [α] +10°; ν 3640 (nonbonded O–H), 3520 (bonded O–H), 1103 (C–3 ketal), 1052 (C–20 ketal) cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{42}O_5$ (434.60): C, 71.85; H, 9.74. Found: C, 71.73; H, 9.82.

6β-Hydroxy-6α-methyl-5α-pregnane-3,20-dione.—A solution of alcohol IIIe (0.21 g.) in acetone (15 ml.) containing a drop of concentrated sulfuric acid was refluxed for 1 hr. After cooling, the solution was diluted with water and extracted with ether. The combined ether extracts were washed free of acid, dried, and evaporated to dryness. An infrared spectrum of the crude product (0.18 g.) showed the presence of some Δ^4-3-ketone (1660 cm.$^{-1}$). Elution with benzene from an alumina[25] column (9.0 g.) gave 6β-hydroxy-6α-methyl-5α-pregnane-3,20-dione (0.075 g.). Two crystallizations from acetone–hexane gave fluffy needles, m.p. 214–215°; [α] +78°; ν 3628 (nonbonded O–H), 3500 (bonded O–H), 1710–1697 (broad band, C–3 and C–20 ketone) cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{34}O_3$ (346.49): C, 76.26; H, 9.89. Found: C, 76.15; H, 9.69.

3β,20β-Diacetoxy-5α-chloropregnan-6β-ol (IIIc). A. From 5β,6β-Epoxide.—Dry hydrogen chloride gas was bubbled through a solution of 3β,20β-diacetoxy-5β,6β-epoxypregnane (5.0 g.) in chloroform (200 ml.) for 1 hr. Removal of the solvent, followed by crystallization of the residue from ethyl acetate–hexane, gave prisms (4.35 g.), m.p. 199–200°. An analytical sample had m.p. 203–204°; [α] −20°; ν 3630 (nonbonded O–H), 3480 (bonded O–H), 1720 (acetate carbonyl) cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{39}O_5Cl$ (455.02): C, 66.13; H, 8.65; Cl, 7.81. Found: C, 65.95; H, 8.79; Cl, 7.86.

B. From 3β,20β-Diacetoxypregn-5-ene (Ia).—To a solution of olefin Ia (50 g.) in ether (600 ml.) were added acetic acid (40 ml.) and a solution of calcium hypochlorite (50 g.) in water (3000 ml.). The reaction[27] mixture was stirred at 35° for 40 min. The organic layer was then separated and the aqueous layer was extracted with ether. The combined ether extracts were washed with sodium bicarbonate solution and water and then dried. Removal of the solvent and crystallization of the residue from ethyl acetate–hexane gave crystalline chlorohydrin IIIc (20 g.), m.p. 193–196°.

3β-Acetoxy-5α-bromo-17α-methyl-17β-carbomethoxyandrostan-6β-ol (IIIh).—To a stirred solution of olefin[28] Ic (1.0 g.) in dioxane (20 ml.) and water (5 ml.) was added N-bromosuccinimide (0.7 g.) followed by 70% perchloric acid (0.2 ml.) in water (1.0 ml.). Stirring was continued at room temperature for 35 min. Sodium bicarbonate was added to decolorize the solution which was then poured into an excess of water. The resulting oily precipitate was extracted with ether, and the combined ether extracts were washed with sodium bicarbonate solution and water and then dried. Crystallization from acetone–hexane of the residue obtained on removal of the solvent gave colorless needles (0.46 g.), m.p. 164–166° dec. Two recrystallizations from chloroform–

(24) (a) We wish to thank Dr. C. Revesz of our laboratories for pharmacological testing. (b) J. R. Holum, *J. Org. Chem.*, **26**, 4814 (1961).

(25) All melting points are uncorrected. Unless otherwise mentioned the following holds. Rotations were determined in chloroform (~1% solution) with a sodium lamp at room temperature. Infrared spectra were recorded in chloroform, on a Perkin–Elmer (Model 21) spectrophotometer equipped with sodium chloride optics. Ultraviolet spectra were taken in ethanol with a Beckman (Model DK) recording instrument. N.m.r. spectra were recorded on a Varian 60-Mc. spectrometer. Florisil (60–100 mesh, Floridin Co.), alumina (Woelm activity III), and silica gel (Davison grade 923, 100–200 mesh) were used for column chromatography. Silica gel G (acc. to Stahl, E. Merck Co., Germany) was used for thin- and thick-layer chromatography. Lead tetraacetate and calcium carbonate were dried over phosphorus pentoxide under vacuum for 48 hr. Petroleum ether refers to that fraction with b.p. 30–60°. Organic extracts were dried over anhydrous magnesium sulfate and the solvents were removed under vacuum. Acetone used for oxidation was distilled over potassium permanganate. Benzene and cyclohexane used for lead tetraacetate reactions were dried over sodium. Dry pyridine was used for acetylations. Grignard solution was 3 *M* in ethyl ether (Arapahoe Chemicals, Inc.).

The authors wish to thank Dr. G. Papineau-Couture and his associates for analytical and spectral data. Assistance from Dr. G. Myers and his group in large scale preparations is gratefully acknowledged.

(26) This alcohol was recently reported by D. H. R. Barton, *et al.*, *J. Am. Chem. Soc.*, **83**, 4076 (1961).

(27) S. Mori, *J. Chem. Soc. Japan*, **64**, 981 (1943).

(28) R. Deghenghi and R. Gaudry, *J. Am. Chem. Soc.*, **83**, 46, 68 (1961).

hexane yielded an analytical specimen, m.p. 171.5–172.5°; [α] −50°; ν 3635 (nonbonded O–H), 3520 (bonded O–H), 1722 (acetate carbonyl) cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{37}O_5Br$ (485.46): C, 59.39; H, 7.68; Br, 16.47. Found: C, 59.29; H, 7.77; Br, 16.59.

3β-Acetoxy-5α-bromo-17α-methyl-17β-carbomethoxyandrostan-6-one (IIe).—Crude bromohydrin IIIh (5.7 g.), obtained as above, was dissolved in acetone[25] (100 ml.) and the solution was cooled to 0°. An 8 *N* chromic acid[29] solution (2.5 ml.) was added and stirring was continued for 4 min. The reaction mixture was diluted with water and extracted with ether. Working up in the usual manner afforded a white solid (5.27 g.), m.p. 168–170° dec. Two crystallizations from acetone gave prisms, m.p. 183.5–184° dec.; [α] −149°.

Anal. Calcd. for $C_{24}H_{35}O_5Br$ (483.44): Br, 16.54. Found: Br, 16.73.

3β-Acetoxy-17α-methyl-17β-carbomethoxy-5α-androstan-6-one (IIc).—Bromo ketone IIe (32.0 g.), prepared as above, was dissolved in acetic acid (1040 ml.) and zinc dust (128 g.) was added. The reaction mixture was refluxed with vigorous stirring for 3 hr., filtered while hot, and the residue washed with ether. The filtrate was evaporated and a solution of the residue in ether was washed free of acid and dried. Removal of the solvent, followed by crystallization of the residue from aqueous methanol, afforded needles (21.0 g.), m.p. 147–150°. This compound was identical in all respects with ketone IIc described before.[8]

3β-Acetoxy-6α,17α-dimethyl-17β-carbomethoxy-5α-androstan-6β-ol (IIIg).—To a solution of ketone IIc (3.7 g., m.p. 150–157°) in anhydrous benzene (150 ml.) was added a solution[25] (37 ml.) of methylmagnesium bromide. The resulting precipitate was dissolved by adding dry tetrahydrofuran (5 ml.). The reaction solution was stirred at room temperature overnight and excess Grignard reagent was destroyed with saturated ammonium chloride solution. After extracting the aqueous phase with ethyl acetate, the organic extracts were washed with water and dried. The removal of solvent yielded an oil (3.4 g.). This oil was acetylated in the usual manner with pyridine (26 ml.) and acetic anhydride (14 ml.). One crystallization of the crude acetate from aqueous methanol gave colorless crystals (2.8 g.), m.p. 165–175°. An analytical sample obtained by more recrystallizations from the same solvent had m.p. 178–180°; [α] −12.5°; ν 3635 (nonbonded O–H), 1720 (acetate carbonyl) cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{40}O_5$ (420.57): C, 71.39; H, 9.59. Found: C, 71.09; H, 9.55.

3β-Acetoxy-5α-bromo-6β-hydroxy-17α-methylpregnan-20-one (IIIf).—To a solution 17α-methylpregnenolone acetate[28] (11.0 g.) in dioxane (176 ml.) and water (6.6 ml.) was added N-bromosuccinimide (7.7 g.) followed by 72% perchloric acid (2.2 ml.) in water (11 ml.). The mixture was stirred at room temperature for 30 min., solid sodium bisulfite was added, and the mixture was diluted with ice–water. The usual work-up with ether gave a residue, which, after one crystallization from acetone–hexane, yielded bromohydrin IIIf (5.1 g.), m.p. 166–168°. Several crystallizations from the same solvents gave an analytical sample, m.p. 175–176°; [α] −49°; ν 3635 (nonbonded O–H), 3490 (bonded O–H), 1725 (acetate carbonyl), 1692 (C–20 carbonyl) cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{37}O_4Br$ (469.46): C, 61.40; H, 7.94. Found: C, 61.62; H, 8.04.

Lead Tetraacetate Reaction. Method A (i).—To a solution of steroid in dry benzene was added lead tetraacetate[25] and the mixture was refluxed with stirring for 18–48 hr. The mixture was then cooled and an excess of 20% aqueous potassium iodide was added. The liberated iodine was neutralized with sodium thiosulfate solution. After separating the layers, the aqueous layer was extracted with benzene. The combined organic liquor was washed with water and then dried. Evaporation of the solvent gave the crude product.

Method A (ii).—In the cases where ketals were used, the above method was modified by pretreatment of the lead tetraacetate with anhydrous[25] calcium carbonate in the manner described by Kalvoda and co-workers.[30] The reaction was carried out in dry cyclohexane at reflux temperature and was worked up as described in method A (i).

Method B (i).—In this procedure, method A (i) was modified by adding iodine to the solution of the steroid, followed by lead tetraacetate.

Method B (ii).—Same procedure as method A (ii), except that the reaction was conducted in the presence of iodine.

Treatment of 3β,20β-Diacetoxy-5α-pregnan-6β-ol (IIIa) with Lead Tetraacetate. Method A (i).—To a solution of alcohol IIIa (3.14 g.) in benzene (300 ml.) was added lead tetraacetate (12.6 g.) and the reaction mixture was refluxed for 17 hr. The crude product (2.7 g.) obtained after the work-up gave, on crystallization from hexane, ketone IIa (2.0 g.). The residue from the mother liquor was chromatographed on Florisil[25] (28 g.) in benzene. Elution with ether–benzene (1:19) gave a solid, which on crystallization from acetone–hexane, afforded 3β,20β-diacetoxy-6β,19-oxido-5α-pregnane (IVa, 0.19 g.), m.p. 134–140°. An analytical sample obtained by recyrstallization from aqueous methanol had m.p. 147–147.5°; [α] +19°; ν 1719 (acetate carbonyl), 1492 (C-19 methylene) cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{38}O_5$ (418.55): C, 71.74; H, 9.15. Found: C, 71.61; H, 9.22.

Method B (i).—The above experiment was repeated with alcohol IIIa (0.80 g.) in the presence of iodine (0.92 g.). Crystallization of the crude product from hexane gave stout plates (0.54 g., 68%), m.p. 151–153°. This material was shown to be identical in all respects with 3β,20β-diacetoxy-6β,19-oxido-5α-pregnane (IVa) obtained above. A chromatography on Florisil[25] of the residue from the mother liquor afforded 0.12 g. more of the oxide IVa, m.p. 122–126°, whose infrared spectrum was essentially identical to that of the standard.

3,20-Diethylenedioxy-6β,19-oxido-5α-pregnane (IVd). Method A (ii).—Alcohol IIId (1.0 g.) was added to a stirred suspension of calcium carbonate (1.33 g.) and lead tetraacetate (4.5 g.) in cyclohexane (135 ml.). The reaction mixture was refluxed for 50 hr. An infrared spectrum of the crude product (0.91 g.), m.p. 175–179°, showed it to be a mixture of starting material (absorption band in the O—H stretching region), C-6 ketone (weak band at 1703 cm.$^{-1}$), and 6β,19-oxide (inflection at 1495 cm.$^{-1}$). Attempts to purify this material by column chromatography were unsuccessful. An analytical sample of 3,20-diethylenedioxy-6β,19-oxido-5α-pregnane (IVd) was successfully obtained by thick-layer chromatography[31] on silica gel,[25] m.p. 201–202°; [α] +16°; ν 1490 (C-19 methylene) cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{38}O_5$ (418.55): C, 71.74; H, 9.15. Found: C, 71.73; H, 9.25.

Method B (ii).—The above experiment was repeated with diketal alcohol IIId (2.0 g.) in the presence of iodine (2.24 g.). The reaction mixture was refluxed for 64 hr. and was worked up as described above. One crystallization from methanol gave oxide IVd (1.48 g.), m.p. 199–201°. A second crop (0.19 g.), m.p. 188–192°, was obtained on concentration of the mother liquor.

6β,19-Oxido-5α-pregnane-3,20-dione (Va). A. From Diketal IVd.—Crude 3,20-diethylenedioxy-6β,19-oxido-5α-pregnane (IVd, 2.0 g.) obtained by method A (ii) was dissolved in acetone (120 ml.) containing sulfuric acid (3 drops). This solution was heated on a steam bath for 20 min., cooled, and then diluted with water. Extraction with ether followed by the usual work-up gave a white solid (1.72 g.). A portion (1.68 g.) was dissolved in benzene and chromatographed on alumina[25] (75 g.). Elution with benzene gave a crystalline solid "A" (0.88 g.). Further elution with 2% ether–benzene gave 0.43 g. of material shown to be 6β,19-oxido-5α-pregnane-3,20-dione (Va).[32] Two crystallizations from acetone–hexane gave needles (0.12 g.), m.p. 214–218°; ν 1705 (C-3 and C-20 carbonyls), 1494 (C-19 methylene) cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{30}O_3$ (330.45): C, 76.32; H, 9.15. Found: C, 76.45; H, 9.02.

The solid "A" eluted with benzene was shown by its infrared spectrum to be the C-3 monoketal. Further treatment of this material with acid gave the diketone Va.

B. From Diacetate IVa.—Diacetate IVa (0.16 g., m.p. 125–132°) was dissolved in methanol (2.0 ml.) and a solution of potassium hydroxide (0.1 g.) in methanol (1.4 ml.) was added to it. The reaction solution was refluxed for 5 hr., cooled, and worked up in the usual way to give the corresponding diol (0.13 g.). This material was taken up in acetone[25] (10 ml.) and cooled to

(29) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

(30) J. Kalvoda, G. Anner, D. Arigoni, K. Heusler, H. Immer, O. Jeger, M. Lj. Mihailovic, K. Schaffner, and A. Wettstein, *Helv. Chim. Acta*, **44**, 186 (1961).

(31) We wish to thank Dr. G. Schilling of our laboratories for purification of compounds IVd, IVe, VIIIb, and XIIIb by thick-layer chromatography.

(32) An alternative synthetic route diketone Va has been recently described (see ref. 3).

0°. To this stirred solution was added 8 *N* chromic acid[29] solution (0.6 ml.) and stirring was continued for 5 min. Methanol was added and working up in the usual manner gave diketone Va (0.114 g.), m.p. 208–216°. The identity of this product was confirmed by mixture melting point and comparison of infrared spectra.

3β,20β-Diacetoxy-6α-methyl-6β,19-oxido-5α-pregnane (IVb). Method A (i).—To a solution of diacetate IIIb (1.0 g.) in benzene (60 ml.) was added lead tetraacetate (4.0 g.) and the suspension was refluxed for 48 hr. Crystallization of the crude product from acetone–hexane gave colorless plates (0.46 g.), m.p. 169–171°. Several recrystallizations afforded an analytical sample, m.p. 175–176°; [α] +18°; ν 1722 (acetate carbonyl), 1492 (C-19 methylene) cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{40}O_5$ (432.58): C, 72.19; H, 9.32. Found: C, 72.47; H, 9.23.

Method B (i).—To a solution of diacetate IIIb (4.7 g.) in benzene (284 ml.) were added iodine (5.3 g.) and lead tetraacetate (19.0 g.), and the reaction mixture was refluxed for 48 hr. Crystallization of the crude product from acetone–hexane gave oxide IVb (3.1 g., 72%), m.p. 171–173°.

3,20-Diethylenedioxy-6α-methyl-6β,19-oxido-5α-pregnane (IVe). Method A (ii).—Diketal alcohol IIIe (1.89 g.) was added to a suspension of calcium carbonate (2.6 g.) and lead tetraacetate (8.1 g.) in cyclohexane (250 ml.). The reaction mixture was refluxed for 40 hr. The crude product was purified by chromatography on alumina[25] (85 g.) in hexane. Elution with benzene–hexane (2:1) afforded a yellow sirup (0.58 g.) which was identified in infrared spectrum (characteristic band at 1492 cm.$^{-1}$) as oxide IVe. Further elution with ether–benzene of increasing polarity, followed by elution with pure ether, afforded a crystalline solid (0.73 g.) identified as unchanged starting alcohol (IIIe) by its infrared spectrum.

The crude oxide (IVe, 0.58 g.) obtained above was rechromatographed on alumina[25] (24 g.). Elution with benzene–hexane (2:1) followed by elution with benzene afforded a crystalline solid (0.22 g.). One crystallization from methanol gave needles, m.p. 138–141°. An analytical sample prepared by using thick-layer chromatography[31] had m.p. 138–140°; [α] −16°; ν 1492 (C-19 methylene) cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{40}O_5$ (432.60): C, 72.19; H, 9.32. Found: C, 71.88; H, 9.14.

Method B (ii).—Diketal alcohol IIIe (1.0 g.) and iodine (1.12 g.) were added to a suspension of calcium carbonate (1.3 g.) and lead tetraacetate (4.0 g.) in cyclohexane (120 ml.). The mixture was refluxed with stirring for 64 hr. and the crude product was purified by chromatography on alumina (40 g.). Elution with benzene–hexane (1:1), followed by benzene gave crystals (0.80 g.). One crystallization from hexane afforded needles (0.55 g.), m.p. 130–132°. An infrared spectrum of this solid was identical with that of oxide IVe obtained above.

6α-Methyl-6β,19-oxido-5α-pregnane-3,20-dione (Vb). A. From Diketal IVe.—The oxide IVe (0.23 g.) was dissolved in acetone (10 ml.) containing a drop of sulfuric acid. The solution was heated on a steam bath for 20 min., cooled, and diluted with water. Extraction with ether and working up in the usual way gave a white solid (0.18 g.). Two crystallizations from acetone gave needles, m.p. 211–212°; [α] +130°; ν 1702 (C-3 and C-20 carbonyls), 1492 (C-19 methylene) cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{32}O_3$ (344.48): C, 76.70; H, 9.36. Found: C, 76.72; H, 9.21.

B. From Diacetate IVb.—The diacetate IVb (0.43 g.) was dissolved in methanol (20 ml.) containing potassium hydroxide (0.54 g.) and the solution was refluxed for 5.5 hr. Solvent was subsequently distilled from the solution until crystals began to appear and then the reaction mixture was cooled. Filtration of this mixture afforded 6α-methyl-6β,19-oxido-5α-pregnane-3β,-20β-diol (0.37 g.), m.p. 224–226°.

This diol was dissolved in acetone[25] (90 ml.) and oxidized with 8 *N* chromic acid[29] solution (1.5 ml.). Working up in the usual way gave a crystalline solid (0.30 g.), m.p. 205–208°. This material was shown to be 6α-methyl-6β,19-oxido-5α-pregnane-3,20-dione (Vb) by a mixture melting point and by comparison of its infrared spectrum with that of an authentic sample of Vb.

3β,20β-Diacetoxy-5α-chloropregnan-6-one (IId).—To a cooled solution (0°) of chlorohydrin IIIc (0.50 g.) in acetone[25] (60 ml.) was added 8 *N* chromic acid[29] solution (1.0 ml.), and the reaction mixture was stirred for 5 min. Methanol was added to destroy excess chromic acid and the solvent was removed. The residue was dissolved in chloroform and the solution was washed with sodium bicarbonate solution and water and then dried. Evaporation of the solvent afforded a crystalline material, which after one crystallization from acetone–hexane, gave a colorless solid (0.42 g.), m.p. 148–149°. An analytical sample from the same solvent had m.p. 149–150°; [α] −100°; ν 1720 (acetate and C-6 carbonyls) cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{37}O_5Cl$ (453.0): C, 66.28; H, 8.23. Found: C, 66.13; H, 8.08.

Lead Tetraacetate Reaction with 3β,20β-Diacetoxy-5α-chloropregnan-6β-ol (IIIc). Method A (i).—Lead tetraacetate (7.0 g.) was added to a solution of diacetate IIIc (1.8 g.) in benzene (75 ml.) and the reaction mixture was refluxed with stirring for 19 hr. The crude product (1.8 g.) obtained was refluxed with zinc (7.0 g.) and acetic acid (130 ml.) for 3 hr. and then filtered. After evaporating the filtrate to dryness, the residue was taken up in ether and the solution was washed free of acid and then dried. Removal of the solvent and crystallization of the residue from acetone–hexane gave 3β,20β-diacetoxy-5α-pregnan-6-one[8] (IIa, 0.69 g.), m.p. 180–182°. The residue (0.85 g.) from the mother liquor was chromatographed[25] on a column of Florisil (34 g.). Elution with benzene–ether (19:1) gave a solid (0.48 g.), which on crystallization from acetone–hexane, afforded 3β,20β-diacetoxy-5α-chloro-6β,19-oxidopregnane (IVc, 0.22 g.), m.p. 153–155°. An analytical sample from acetone–hexane had m.p. 155–156°; [α] +24°; ν 1721 (acetate carbonyl), 1497 (C-19 methylene) cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{37}O_5Cl$ (453.0): C, 66.28; H, 8.23; Cl, 7.82. Found: C, 66.36; H, 8.34; Cl, 7.92.

The crude product obtained from another reaction of diacetate IIIc (1.0 g.) with lead tetraacetate was chromatographed on Florisil (40 g.)[25] in benzene. The crystalline eluate obtained with ether–benzene (1:49) was crystallized from ether–hexane to give a solid (0.84 g.), m.p. 146–148°. The presence of chloro ketone IId and the oxide IVd in this mixture was established by comparison of the R_f values on a t.l.c.[19] with the authentic samples. The mixture was shown to contain 93.5% of chloro ketone IId and 6.5% of oxide IVc based on its optical rotation (−91.7°).

Method B (i).—To a solution of diacetate IIIc (15.0 g.) benzene (490 ml.) were added lead tetraacetate (60.0 g.) and iodine (16.8 g.), and the reaction mixture was refluxed for 18 hr. Crystallization of the crude product from acetone–hexane gave oxide IVc (11.9 g., 85%), m.p. 151–153°.

5α-Chloro-6β,19-oxidopregnane-3β,20β-diol (VII).—Diacetate IVc (5.0 g.) was dissolved in methanol (147 ml.), and a solution of potassium hydroxide (6.0 g.) in 50% aqueous methanol (96 ml.) was added to it. The reaction solution was refluxed for 5.5 hr. and concentrated under a stream of nitrogen until the product began to crystallize. The mixture was cooled and filtered to give stout plates (3.5 g.), m.p. 252–254°. One more crystallization did not alter the melting point.

Anal. Calcd. for $C_{21}H_{33}O_3Cl$ (368.93): Cl, 9.61. Found: Cl, 9.37.

6α,17α-Dimethyl-17β-carbomethoxy-6β,19-oxido-5α-androstan-3β-ol (IVg). Method B (i).—To a solution of alcohol IIIg (1.0 g.) in benzene (60 ml.) were added lead tetraacetate (4.0 g.) and iodine (1.12 g.), and the reaction mixture was refluxed for 48 hr. The crude product (1.06 g.), which failed to crystallize from solvents, was dissolved in methanol (10 ml.) and to this was added a solution of potassium hydroxide (0.48 g.) in 50% aqueous methanol (7.6 ml.). After keeping at room temperature overnight, the reaction mixture was diluted with water and extracted with ether. The usual work-up gave a crude product (0.80 g.), which after one crystallization from acetone–hexane, afforded colorless plates (0.62 g.), m.p. 158–160°. An analytical sample had m.p. 159–160°; [α] +2°; ν 3621 (nonbonded O–H), 3432 (bonded O–H), 1720 (ester carbonyl), 1494 (C-19 methylene) cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{36}O_4$ (376.52): C, 73.36; H, 9.64. Found: C, 73.00; H, 9.62.

3β-Acetoxy-5α-bromo-6β,19-oxido-17α-methylpregnan-20-one (IVf). Method B (i).—To a solution of alcohol IIIf (6.0 g.) in benzene (250 ml.) were added lead tetraacetate (24 g.) and iodine (6.72 g.), and the reaction mixture was refluxed for 18 hr. The usual work-up yielded a crude product (5.9 g.) which was chromatographed on a column of Florisil[25] (236 g.) in benzene. Elution with ether–benzene (1:19) followed by solvents of increasing polarity up to ether gave a semisolid (4.1 g.) which solidified over hexane, m.p. 145–158°. An analytical sample obtained by several crystallizations from acetone–hexane had m.p. 168–169°; [α] −1°; ν 1725 (acetate carbonyl), 1691 (C-20 ketone), 1498 (C-19 methylene) cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{35}O_4Br$ (467.42): C, 61.80; H, 7.35. Found: C, 61.93; H, 7.54.

3β-Acetoxy-5α-bromo-17α-methyl-17β-carbomethoxy-6β,19-oxidoandrostane (IVh). Method B (i).—Lead tetraacetate (8.0 g.) and iodine (2.24 g.) were added to a solution of bromohydrin IIIh (2.0 g.) in benzene (120 ml.), and the reaction mixture was refluxed for 19 hr. The crude product (1.95 g.) was crystallized from chloroform–methanol to yield colorless crystals (1.2 g.), m.p. 186–190°. An analytical sample from the same solvents had m.p. 213–214°; [α] −15°; ν 1499 (C-19 methylene) cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{35}O_5Br$ (483.42): C, 59.69; H, 7.29. Found: C, 59.97; H, 7.64.

6β,19-Oxidopregn-4-ene-3,20-dione (IXa).[33]—To a solution of diol VII (3.3 g.) in acetone,[25] cooled to 0°, was added an 8 *N* chromic acid[29] solution (15 ml.), and the mixture was stirred and allowed to reach room temperature. Excess chromic acid was destroyed with methanol then hydrochloric acid (0.5 ml.) was added and stirring was continued for 4 hr. at room temperature. The solvent was removed and the residue was dissolved in chloroform. The resulting solution was washed with sodium bicarbonate solution and water and then dried. Evaporation of the solvent gave an oily residue (2.96 g.) which crystallized to give oxidoprogesterone IXa (2.1 g.), m.p. 140–142°. An analytical sample, obtained by crystallization from hexane, had m.p. 142–143°; [α] −24°; ν 1699 (C-20 ketone), 1670 (C-3 ketone), 1487 (C-19 methylene) cm.$^{-1}$; λ_{max} 239 mμ (ε 12,500).

Anal. Calcd. for $C_{21}H_{28}O_3$ (328.43): C, 76.79; H, 8.59. Found: C, 76.93; H, 8.65.

6β,19-Oxido-17α-methylpregn-4-ene-3,20-dione (IXb).—To a solution of acetate IVf (0.52 g., m.p. 161–163°) in methanol (8 ml.) was added a solution of potassium hydroxide (0.2 g.) in methanol (3.0 ml.). After standing overnight the crystalline precipitate (0.32 g., m.p. 219–221°) was collected by filtration. A second crop (0.13 g., m.p. 213–216°) was obtained by concentration of the filtrate.

The crude diol (both crops, 0.43 g.) obtained above was dissolved in acetone.[25] To the stirred solution, at 0°, was added 8 *N* chromic acid[29] solution (1.7 ml.), and the reaction mixture was allowed to reach room temperature. After destroying excess chromic acid with methanol the solution was evaporated almost to dryness. The residue was taken up in chloroform, and the solution was washed with aqueous sodium bicarbonate solution and water and then dried. Removal of the solvent gave an oily solid (0.35 g.), λ_{max} 240 mμ (ε 12,300). One crystallization from acetone–hexane gave crystals (0.27 g.), m.p. 170–171°. An analytical sample from the same solvents had m.p. 170–171°; [α] −103°; ν 1687 (C-20 ketone), 1665 (C-3 ketone), 1620 (Δ^4 C=C), 1487 (C-19 methylene) cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{30}O_3$ (342.46): C, 77.15; H, 8.83. Found: C, 77.43; H, 9.05.

3β-Hydroxy-5α-bromo-6α-methyl-6β,19-oxidopregnan-20-one (Xb).—To a solution of triol VId (0.55 g.) in *t*-butyl alcohol (25 ml.) was added a solution of N-bromoacetamide (0.76 g.) in water (9.0 ml.). After stirring at room temperature for 18 hr., the reaction solution was decolorized by adding sodium bisulfite. Dilution with water, extraction with ether, and working up in the usual manner gave a crude product (0.63 g.). One crystallization from acetone–hexane gave colorless crystals (0.47 g., 69%), m.p. 180–182°. Several recrystallizations from chloroform–hexane gave an analytical sample, m.p. 188–189°; [α] +39°; ν 3620 (nonbonded O–H), 3455 (bonded O–H), 1696 (C-20 ketone), 1497 (C-19 methylene) cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{33}O_3Br$ (425.40): C, 62.11; H, 7.88. Found: C, 61.91; H, 8.10.

Acid Treatment of Xb.—To a solution of alcohol Xb (0.266 g.) in methanol (3.0 ml.) was added 3 drops of hydrochloric acid and the solution was left at room temperature overnight. Removal of the solvent gave a residue (0.245 g.) which was identical in all respects with the starting material.

Base Treatment of Xb.—To a solution of Xb (0.060 g.) in methanol (5.0 ml.) was added a solution of potassium hydroxide (0.05 g.) in 50% aqueous methanol (1.0 ml.) and the reaction solution was refluxed for 1 hr. The solution was then neutralized with 10% hydrochloric acid, diluted with water, and extracted with ether. Working up in the usual way gave a solid (0.060 g.) whose infrared spectrum was identical with that of the starting material.

5α-Bromo-6α-methyl-6β,19-oxidopregnane-3β,20β-diol (Xa).—To a solution of triol VId (3.5 g.) in methanol (70 ml.) was added dropwise a solution of bromine (1.9 g., 1.1 mole) in acetic acid (4.0 ml.). The solution was then diluted with water and the precipitate (4.2 g.) thus obtained was collected by filtration, m.p. 213–215°. Two crystallizations raised the melting point to 228–230°. An infrared spectrum (saturated solution) had bands at 3620 (nonbonded O–H), 1496 (C-19 methylene) cm.$^{-1}$. Analysis of this sample indicated the presence of one atom of bromine (calcd. 18.69; found 18.05).

6α-Methyl-6β,19-oxidopregn-4-ene-3,20-dione (IXc). A. From Alcohol Xb.—A solution of Xb (0.35 g.) in acetone[25] was cooled to 0° and to it 8 *N* chromic acid[29] solution (1.0 ml.) was added. The reaction mixture was allowed to reach room temperature and then methanol was added. After removal of the solvent the residue was taken up in ether and worked up as usual to give a tarry residue (0.28 g.) which was chromatographed on a column of Florisil[25] (12 g.) in benzene. Elution with ether–benzene (3:7 and 1:1) gave crystalline material which after one crystallization from acetone–hexane afforded 6α-methyl-6β,19-oxidopregn-4-ene-3,20-dione (IXc, 0.066 g.), m.p. 172–174°. An analytical specimen had m.p. 175–176°; [α] −101°; ν 1698 (C-20 ketone), 1666 (C-3 ketone), 1485 (C-19 methylene) cm.$^{-1}$; λ_{max} 238 mμ (ε 13,600).

Anal. Calcd. for $C_{22}H_{30}O_3$ (342.46): C, 77.15; H, 8.83. Found: C, 77.09; H, 8.88.

B. From Diol Xa.—A solution of chromic anhydride (1.9 g.) in acetic acid (50 ml.) and water (2.0 ml.) was added to a solution of diol Xa (4.2 g., m.p. 213–215°) in acetic acid (100 ml.). The reaction solution was stirred for 2.5 hr. then diluted with water, and the solid (4.0 g.) which precipitated was collected by filtration. This solid was dissolved in methanol (90 ml.) containing 2 drops of concentrated hydrochloric acid. After standing overnight at room temperature, the solution was diluted with water, extracted with ethyl acetate, and worked up in the usual way. One crystallization of the crude product (2.8 g.) from acetone–hexane gave colorless prisms (2.2 g., 64% from triol VId), m.p. 173–175°. This compound was shown to be identical to 6α-methyl-6β,19-oxidopregn-4-ene-3,20-dione (IXc) in all respects.

Acid Treatment of Triol VId.—To a solution of triol VId (0.05 g.) in methanol (5.0 ml.) was added 3 drops of hydrochloric acid and this was heated for 1 hr. on a steam bath. The residue (0.05 g.) obtained on removal of the solvent was directly acetylated with pyridine and acetic anhydride and a crystalline solid (0.06 g.), m.p. 160–164°, was obtained on working up in the usual way. This diacetate was shown by comparison of its infrared spectrum and mixed melting point with an authentic sample to be identical with 3β,20β-diacetoxy-6α-methyl-6β,19-oxido-5α-pregnane (IVb).

3β,19,20β-Triacetoxypregn-5-ene (VIa).—A solution of crude diol VII (3.0 g., m.p. 253–255°) in dry tetrahydrofuran (110 ml.) was added over 25 min. to a solution of lithium (3.0 g.) in liquid ammonia (450 ml.). The reaction solution was stirred for 10 min., saturated ammonium chloride solution (17 ml.) was carefully added, and then the ammonia was removed. Water was added gradually and the layers were subsequently separated. The aqueous layer was further extracted with tetrahydrofuran, and the combined organic liquor was worked up in the usual way to give the crude product (3.2 g.). This was acetylated with pyridine (58 ml.) and acetic anhydride (29 ml.) to yield the crude triacetate VIa (3.7 g.). One crystallization from aqueous methanol gave colorless needles (2.32 g.), m.p. 137–138.5°. An analytical sample from methanol had m.p. 143–144°; [α] −60°; ν 1722 (acetate carbonyl) cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{40}O_6$ (460.59): C, 70.40; H, 8.75. Found: C, 70.23; H, 9.00.

Pregn-5-ene-3β,19,20β-triol (VIc). A. By Hydrolysis of Triacetate VIa.—Triacetate VIa (2.3 g., m.p. 137–138.5°) was dissolved in methanol (69 ml.) and a solution of potassium hydroxide (2.97 g.) in 50% aqueous methanol (46 ml.) was added to it. The reaction solution was refluxed for 5.5 hr., and the solvent was removed until crystallization set in. After cooling, the triol VIc (1.6 g.), m.p. 225–230°, was collected by filtration. An infrared spectrum of this material (in Nujol) showed strong hydroxylic absorption and the absence of acetate bands.

B. From Diacetate Oxide IVa.—The oxide IVa (0.47 g.) was dissolved in acetic acid (3.0 ml.) and acetic anhydride (0.84 ml.) and *p*-toluenesulfonic acid (0.005 g.) was then added. The reaction solution was refluxed for 2 hr., diluted with methanol,

(33) Since completion of this work a modified route to compound VIIIb [K. Heusler, *et al.*, *Helv. Chim. Acta*, **45**, 2161 (1962)] and the synthesis of compound IXa [K. Heusler, *et al.*, *Experientia*, **18**, 464 (1962)] have appeared in the literature.

and the solvents removed under reduced pressure. The residue was taken up in ether, the solution was washed with sodium bicarbonate solution and water, and then dried. Removal of the solvent left an oily material (0.527 g.) which was hydrolyzed as described above. The crude triol VIc (0.21 g.) was subsequently purified by chromatography on Florisil (8.0 g.). Elution with methanol–chloroform (1:49) gave a solid which after one crystallization from chloroform–hexane yielded a material (0.11 g.) with m.p. 185–191°. T.l.c.[19] of this substance showed it to be mainly triol VIc. An n.m.r. spectrum of this sample was identical with that of the authentic triol VIc.

Oxidation of Triol VIc with Chromic Acid.—To a stirred solution of triol VIc (1.0 g.) in acetone[25] (45 ml.) at 10° was added an excess of 8 *N* chromic acid[29] solution. The cooling bath was removed and stirring was continued for 10 min. After methanol had been added to destroy excess oxidant the reaction mixture was diluted with water, extracted with ethyl acetate, and worked up in the usual way to give a yellow oil (0.75 g.). Two crystallizations from methanol gave lactone XIIIb (0.074 g.), m.p. 175–178°. Thick-layer chromatography[31] of the mother liquors afforded a further 0.053 g. of lactone XIIIb, m.p. 183–184°. An analytical sample from methanol had m.p. 183–184°; $[\alpha]$ +2°; ν 1736 (lactone carbonyl), 1697 (C-20 ketone) cm.$^{-1}$; λ_{max} 228 mμ (ϵ 1330).

Anal. Calcd. for $C_{21}H_{28}O_3$ (328.44): C, 76.79; H, 8.59. Found: C, 76.83; H, 8.68.

5α-Bromo-6β,19-oxidopregnane-3β,20β-diol (Xc).—Bromine (1.46 g.) in acetic acid (13.5 ml.) was slowly added to a stirred solution of triol VIc (2.7 g.) in methanol (55 ml.) until a pale color persisted. Stirring was continued for 10 min. longer and dilution with water precipitated the crude product (2.85 g.), m.p. 205–216° dec. An analytical sample obtained after several crystallizations from methanol had m.p. 219–221° dec.; $[\alpha]$ −18°; ν 1497 (C-19 methylene) cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{33}O_3Br$ (413.39): C, 61.04; H, 8.04; Br, 19.32. Found: C, 60.93; H, 7.75; Br, 19.62.

Conversion of Diol Xc to 6β,19-Oxidoprogesterone (IXa).—Chromic anhydride (0.7 g.) was dissolved in acetic acid (16.0 ml.) and water (0.7 ml.) and this was added to a stirred solution of diol Xc (1.42 g.) in acetic acid (33.0 ml.). Stirring was continued at room temperature for 4 hr., and the solution was then poured into water. The solid (1.2 g.) which precipitated was collected by filtration, subsequently dissolved in methanol (25 ml.) containing concentrated hydrochloric acid (0.25 ml.), and left at room temperature overnight. Dilution with water, extraction with ether, and working up in the usual way gave a foam (0.7 g.). Crystallization from ether afforded crystals (0.17 g.), m.p. 136–138°; $[\alpha]$ −20°. This solid was shown by its ultraviolet and infrared spectra and by a mixture melting point to be 6β,19-oxidoprogesterone (IXa).

19-Hydroxypregn-4-ene-3,20-dione (VIIIa). A. From Diketal Oxide (IVd).—*p*-Toluenesulfonic acid (0.028 g.) was added to a solution of oxide IVd (0.28 g.) in acetic anhydride (28 ml.). The reaction solution was refluxed for 1.25 hr., cooled, and diluted with methanol. After removing the solvents under reduced pressure, the residue was taken up in ether and worked up in the usual way to give a brown sirup (0.425 g.), ν 1735 (acetate carbonyl), 1700 (C-20 ketone), 1665 (Δ^4-3-ketone) cm.$^{-1}$; λ_{max} 238 mμ (ϵ 8380).

The above product was dissolved in methanol (50 ml.) containing potassium hydroxide (1.0 g.) and the solution was refluxed for 45 min. The solution was concentrated under reduced pressure, diluted with water, and extracted with ether. Working up in the usual way gave an oil (0.215 g.) which was chromatographed on a column of Florisil (10.0 g.). Elution with methanol–ether (1:19) gave a solid (0.078 g.) which after two crystallizations from ether afforded 19-hydroxyprogesterone (VIIIa), m.p. 168–170°; ν 3640 (nonbonded O–H), 3460 (bonded O–H), 1700 (C-20 ketone), 1662 (Δ^4-3-ketone) cm.$^{-1}$; λ_{max} 243 mμ (ϵ 15,000). Reported[28a] m.p. 170–171°; λ_{max} 242 mμ (ϵ 12,900).

B. From Triol VIc.—To a solution of triol VIc (0.50 g.) in dry toluene (40 ml.) and cyclohexanone (8.0 ml.) was added a solution of aluminum isopropoxide (0.8 g.) in dry toluene (10 ml.). The reaction mixture was refluxed for 4 hr., cooled, and washed with dilute hydrochloric acid, sodium bicarbonate solution, and water. The organic liquor was steam distilled and the residue was extracted with ether and worked up in the usual way. Chromatography of the crude product on a column of Florisil[25] (20 g.) gave, on elution with methanol–ether (1:19), a solid (0.088 g.) which after crystallization from acetone–ether had m.p. 150–155°; λ_{max} 243 (ϵ 12,000). An infrared spectrum of this sample was essentially identical with that of VIIIa obtained by method A. T.l.c.[19] of this material with the product obtained by method A showed a major spot at the same R_f value as that of the latter substance.

6-Methylpregn-5-ene-3β,19,20β-triol (VId).—To a solution of oxide IVb (18.5 g.) in acetic acid (500 ml. and acetic anhydride (250 ml.) was added *p*-toluenesulfonic acid (1.57 g.) and this was stirred at room temperature for 44 hr. The solution was then diluted with methanol and subsequently evaporated to dryness. The residue was taken up in ether and worked up in the usual way to give a sirup (20.6 g.) whose infrared spectrum indicated the absence of the characteristic oxide band (1496 cm.$^{-1}$). This sirup was dissolved in methanol (300 ml.), and a solution of potassium hydroxide (20 g.) in 50% aqueous methanol (240 ml.) was added to it. The solution was refluxed for 5 hr. and solvent was removed until crystallization set in. After cooling the mixture, the precipitated solid (13.15 g.), m.p. 202–204°, was collected by filtration. An analytical sample obtained from acetone–hexane had m.p. 203–204°; ν (saturated solution) 3630 (nonbonded O–H) cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{36}O_3$ (348.51): C, 75.81; H, 10.41. Found: C, 75.60; H, 10.20.

Reacetylation of triol VId (0.50 g.) with pyridine (4.0 ml.) and acetic anhydride (1.5 ml.) afforded a sirupy triacetate VIb whose infrared spectrum was identical with that of the triacetate obtained above by acid catalyzed cleavage of the oxide IVb. This sirup slowly crystallized over petroleum ether (b.p. 30–60°) and the crystals (0.40 g.), m.p. 102–105°, were collected by filtration. An n.m.r. spectrum of this solid was in complete agreement with the structure VIb.

Oxidation of Triol VId. A. With Chromic Acid.—To a solution of triol VId (0.80 g.) in acetone[25] (130 ml.) cooled to 0° was added 8 *N* chromic acid[29] solution (6.25 ml.). The reaction mixture was stirred and allowed to reach room temperature. Excess chromic acid was destroyed with methanol and the solvents were removed. The residue was taken up in chloroform and worked up in the usual way to give a sirup (0.70 g.), which crystallized from chloroform–methanol as colorless needles of lactone XIIIa (0.29 g.), m.p. 190–198°. An analytical specimen from the same solvents had m.p. 201–202°; $[\alpha]$ −70°; ν 1737 (lactone carbonyl), 1698 (C-20 ketone) cm.$^{-1}$; λ_{max} 231 mμ (ϵ 3350).

Anal. Calcd. for $C_{22}H_{30}O_3$ (342.46): C, 77.15; H, 8.83. Found: C, 77.14; H, 8.71.

B. With Pyridine–Chromic Acid.—A pyridine–chromic acid complex was prepared from pyridine (10.0 ml.) and chromic acid (1.0 g.). To it was added a solution of triol VId (0.50 g.) in pyridine (10 ml.), and the reaction mixture was stirred at room temperature overnight. After filtering the reaction mixture the filtrate was diluted with water and extracted with benzene. The combined extracts were washed with dilute hydrochloric acid, sodium bicarbonate solution, and water and then dried. Removal of solvent gave a brown oil (0.35 g.) whose infrared spectrum was essentially identical with that of lactone XIIIa. One crystallization from chloroform–methanol yielded a substance (0.15 g.), m.p. 189–196°, which was shown to be identical in all respects to the lactone XIIIa.

3β-Hydroxy-6-methylpregn-5-en-20-on-19-oic Acid (XIVa).—Lactone XIIIa (0.88 g.) was dissolved in a 0.1 *N* ethanolic sodium hydroxide solution (90 ml.) and refluxed for 2.5 hr. Ethanol was removed and the residue was taken up in water, cooled in an ice–water bath, and acidified with concentrated hydrochloric acid. The precipitated carboxylic acid XIVa (0.80 g.), m.p. 224–228°, was collected by filtration. An infrared spectrum (Nujol) showed the characteristic hydroxyl stretching band (3448 cm.$^{-1}$) of an acid and carbonyl bands at 1712 (carboxyl group) and 1684 (C-20 ketone) cm.$^{-1}$. The above material was repurified once through its sodium salt to give a crystalline solid (0.60 g.), m.p. 225–228°, and was used in the following experiment.

Methyl Ester of Carboxylic Acid XIVa.—To a solution of carboxylic acid XIVa (0.56 g.) in methanol, cooled to 0°, was added excess diazomethane solution in ether and the reaction solution was kept between 0–5° for 10 min. The solvents and excess diazomethane were removed under nitrogen atmosphere and the crude product crystallized from methanol to give colorless crystals of 3β-hydroxy-6-methylpregn-5-en-20-on-19-oic acid methyl ester (XIVb, 0.60 g.), m.p. 185–191°. Several crystallizations from the same solvent gave an analytical sample, m.p. 195–196°; $[\alpha]$ −60°; ν 3619 (nonbonded O–H), 3480 (bonded O–H), 1717 (ester carbonyl), 1700 (C-20 ketone) cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{34}O_4$ (374.50): C, 73.76; H, 9.15. Found: C, 74.01; H, 9.38.

6α-Methyl-19-hydroxypregn-4-ene-3,20-dione (VIIIb)[33].—To a solution of triol VId (15.0 g.) in dry toluene (1200 ml.) and cyclohexanone (240 ml.) was added a solution of aluminum isopropoxide (24 g.) in dry toluene (50 ml.), and the reaction mixture was refluxed for 3.75 hr. After cooling the reaction mixture it was washed with dilute hydrochloric acid, sodium carbonate solution, and water. The organic solution was steam distilled and the residue was extracted with ether and worked up in the usual way. The crude product (16.0 g.) was chromatographed on a column[25] of Florisil (450 g.) in benzene. Elution with benzene–ether (9:1) gave, as a first fraction, an oil (1.1 g.) which crystallized slowly. Two recrystallizations from acetone–hexane gave colorless needles (0.31 g.) of a phenol (XIXa or b), m.p. 210–212°. An analytical sample from the same solvents had m.p. 219–220°; [α] +76.5°; ν 3625 (nonbonded O–H), 3420 (bonded O–H), 1696 (C-20 ketone), 1592 (aromatic C=C stretching) cm.$^{-1}$; λ_{max} 284 mμ (ε 1570).

Anal. Calcd. for $C_{22}H_{30}O_2$ (326.46): C, 80.93; H, 9.26. Found: C, 81.20; H, 9.26.

Further elution with benzene–ether (1:1), ether, and ether–methanol (9:1) afforded a semisolid which, on trituration with ether, gave 6α-methyl-19-hydroxypregn-4-ene-3,20-dione (VIIIb, 2.65 g.), m.p. 159–161°. An analytical sample[31] from ether had m.p. 178–180°; [α] +150°; ν 3640 (nonbonded O–H), 3440 (bonded O–H), 1696 (C-20 ketone), 1660 (Δ^4-3-ketone) cm.$^{-1}$; λ_{max} 242 mμ (ε 14,400).

Anal. Calcd. for $C_{22}H_{32}O_3$ (344.48): C, 76.70; H, 9.36. Found: C, 76.84; H, 9.03.

6α-Methyl-19-norpregn-4-ene-3,20-dione (XVII).—To a solution of chromic anhydride (2.1 g.) in pyridine (50 ml.) and water (25 ml.) was added a solution of alcohol VIIIb (1.0 g.) in pyridine (30 ml.), and the reaction solution was stirred at 60–65° for 1.5 hr. The solution was then poured into ice–water, extracted with ether, and worked up in the usual way to give a sirup (0.80 g.). An infrared spectrum of this material had an absorption band at 2730 (aldehydic C—H stretching) and another new band (shoulder) at 1717 (aldehyde carbonyl) cm.$^{-1}$.

The above material was dissolved in methanol (40 ml.) and poured into 4% aqueous sodium hydroxide solution (380 ml.), and this was stirred at 50–55° for 45 min. The reaction mixture was cooled, extracted with ether, and worked up in the usual way to give the crude product (0.69 g.). One crystallization from acetone–hexane gave a substance (0.35 g.) with m.p. 108–110°. An analytical specimen obtained by several recrystallizations from the same solvents had m.p. 113.5–114.5°; [α] +97°; ν 1700 (C-20 carbonyl), 1665 (Δ^4-3-ketone) cm.$^{-1}$; λ_{max} 241 mμ (ε 16,000).

Anal. Calcd. for $C_{21}H_{30}O_2$ (314.45): C, 80.21; H, 9.62. Found: C, 80.31; H, 9.49.

6-Methyl-19-hydroxypregna-4,6-diene-3,20-dione (XX).—A solution of 6α-methyl-6β,19-oxidoprogesterone (IXb, 2.7 g.) in acetic acid (80 ml.) and acetic anhydride (40 ml.) containing *p*-toluenesulfonic acid (0.26 g.) was stirred at room temperature for 40 hr. After dilution with methanol the solvents were removed and the residue was taken up in ether and worked up in the usual way to give a pale brown sirup (2.8 g.). An infrared spectrum showed bands at 1732 (acetate carbonyl), 1700–1660 (C-20 ketone and Δ^{4,6}-3-ketone), 1627, 1585 (Δ^4 and Δ^6 double bonds) cm.$^{-1}$.

To a solution of the crude product obtained above in methanol (70 ml.) was added a solution of potassium carbonate (6.3 g.) in water (50 ml.) and this was kept at room temperature under nitrogen overnight. Dilution with water, extraction with ether, and working up in the usual way yielded a pale yellow sirup (2.32 g.). This was chromatographed on a column[25] of Florisil (80 g.) in benzene. Elution with benzene–ether (8:2 and 1:1) gave a colorless oil (1.5 g.) which crystallized over ether to give prisms (0.88 g.), m.p. 114–116°. An analytical sample from acetone–hexane had m.p. 116–117°; [α] +160°; ν 3640 (nonbonded O–H), 3465 (bonded O–H), 1697 (C-20 ketone), 1655 (Δ^{4,6}-3-ketone), 1623 and 1581 (Δ^4 and Δ^6 double bonds) cm.$^{-1}$; λ_{max} 290 mμ (ε 27,550).

Anal. Calcd. for $C_{22}H_{30}O_2$ (342.46): C, 77.15; H, 8.83. Found: C, 77.29; H, 8.84.

6-Methyl-19-norpregna-4,6-diene-3,20-dione (XXI).—A solution of alcohol XX (0.68 g., m.p. 114–116°) in pyridine (10 ml.) was added to a solution of chromic anhydride (1.5 g.) in water (16 ml.) and pyridine (33 ml.) and this was stirred at 74° (bath temperature) for 1.5 hr. The reaction solution was cooled and poured into 10% hydrochloric acid (208 ml.) containing crushed ice. Extraction with ether and working up in the usual way gave an oil (0.63 g.) whose infrared spectrum showed absorption at 2750 (aldehydic C—H stretching), and 1720 (shoulder, aldehyde carbonyl) cm.$^{-1}$.

The oil was dissolved in methanol (14 ml.) and added to a 4% sodium hydroxide solution (153 ml.). After stirring at 66° (bath temperature) for 1 hr., the crude product (0.30 g.) was isolated by extraction with chloroform and working up in the usual way. This material was chromatographed on a column of silica gel[25] (15 g.) in benzene. Elution with benzene–ether (9:1) gave a solid material (0.18 g.) which after two crystallizations from acetone–hexane afforded 0.083 g. of substance, m.p. 149–155°. An analytical sample from the same solvent pair had m.p. 155–156°; [α] +115°; ν 1697 (C-20 ketone), 1655–1650 (Δ^{4,6}-3-ketone), 1622, 1581 (Δ^4 and Δ^6 double bonds) cm.$^{-1}$; λ_{max} 289 mμ (ε 24,600).

Anal. Calcd. for $C_{21}H_{28}O_2$ (312.44): C, 80.73; H, 9.03. Found: C, 80.97; H, 8.88.

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