1.4492, 68.5, 9.1; 3, 2.5, 41–42°, 17.9, 1.4632, 69.5, 9.0; 4, 2; 42–47°, 10.6, 1.4697, 69.5, 9.0; 5, 2, 47–58°, 1.9, 1.4670, —, —; 6, 2, 58–70°, 2.5, 1.4662, —, —; 7, 2, 70–84°, 4.1, 1.4700, —, —; 8, 2, 84–117°, 1.9, 1.4832, —, —; 9, 2, 117–124°, 7.9, 1.5035, —, —; residue, —, —, 32.6, 1.5150, 70.6, 8.7.

Fraction 4 on treatment with 2,4-DNP reagent yielded an orange-red DNP (recrystallized from absolute ethanol), m.p. 158–160°.

Anal. Calcd. for hexenone DNP ($C_{12}H_{14}N_4O_4$): C, 51.8; H, 5.07; N, 20.1. Found: C, 51.9, 52.1, 51.6; H, 4.9, 4.9, 5.0; N, 19.8, 19.8, 19.7. That fraction 4 was not pure hexenone also was indicated by its bromine number (137) and hydroxyl value (208).

Reaction of 2-Methylbutene-1 and Hexene-1 and Acetone with Sodium in Tetrahydrofuran.—A mixture of 30 g. of sodium wire and 400 ml. of tetrahydrofuran was chilled to −20° and 150 ml. of 2-methylbutene-1 was added. Acetone was added dropwise at such a rate to maintain the temperature at 30° (2.5 hr.). The clear homogeneous solution was quenched with 100 ml. of acetic acid and water and poured into an ice–water slurry. The mixture was extracted three times with ether and the ethereal solutions washed with sodium bicarbonate and dried over sodium sulfate. The distillation of the ethereal extracts yielded in addition to isopropyl alcohol, mesityl oxide, and isophorone. In addition there was formed a high boiling ketonic product(s) (b.p. 98–147° (1 mm.); $n^{25}\mathrm{D}$ 1.5053–1.5231; 7.1 g.) which showed hydroxyl absorption in the infrared spectrum (2.80, strong; 5.80, strong, 6.05, strong; 6.4, weak μ). The distillation pattern from the reaction of acetone with 2-methylbutene-1 is given below. Boiling range, $n^{25}\mathrm{D}$, weight (g.), C, H, hydroxyl value: 49.3–53.0°, 1.4705, 6.5, —, —, —; 53.0–53.5°, 1.4745, 8.5, 76.2, 10.2, —; 53.5–62.0°, —, 3.3, 77.5, 10.3, 0.624; 84–86°, 1.5089, 2.4, —, —, —; 86–88°, 1.5122, 3.0, —, —, —; 88–89°, 1.5158, 2.8, 79.9, 10.2, 0.500; 89–98°, 1.5156, 1.5, 79.2, 10.2, —; 98–128°, 1.5053, 3.3, —, —, —; 128–147°, 1.511, 3.0, —, —, —. A similar spectrum of products was obtained from the reaction of hexene-1 with acetone and sodium.

Reaction of Styrene and Methyl Propionate with Sodium in Ether.—To a mixture of 30 g. of sodium wire in 400 ml. of ether at −40° was added 10 ml. of methyl propionate and 150 ml. of styrene. Methyl propionate (150 ml.) was then added dropwise at 5–10° (0.5 hr.) and the reaction allowed to stir at 30–40° for 2 hr. (12 g. of unchanged sodium remained). The solution was decanted into a mixture of acetic acid and water and worked up in the usual manner. Distillation of the ether left approximately 100 g. of material which on distillation was primarily styrene. The reduction products although not isolated were probably monomeric products such as ethyl benzene and propanol. There was less than 3 g. of material boiling higher than styrene. It appeared thus that no condensation between methyl propionate and styrene occurred.

Acknowledgment.—The author wishes to thank Dr. Donald R. Whitman for illuminating discussions.

Steroids. CCXXI.[1] Syntheses of Some Steroid Dienes

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Novel syntheses are outlined of $\Delta^{1,3}$- and $\Delta^{2,4}$-androstadien-17β-ols, $\Delta^{2,4}$-pregnadien-20-one, and $\Delta^{2,5}$-pregnadien-17α-ol-20-one 17-acetate. $\Delta^{2,5}$-Pregnadiene-11β,17α,21-triol-20-one 21-acetate was obtained, but with the $\Delta^{3,5}$-isomer as a contaminant. Diagnostic features of ultraviolet absorption, infrared absorption, and nuclear magnetic resonance spectra, and optical rotatory dispersion are discussed.

Until very recently an oxygen atom at C-3 of the steroid nucleus was considered mandatory for biological activity. However, in 1959 biological activity was demonstrated for steroids carrying either no substituent at C-3[2] or a nitrogen substituent.[3] There rapidly followed reports of other active steroids devoid of a C-3 oxygen atom,[4–6] and further extensive investigations were initiated in the Syntex Laboratories. As a result there was discovered a new class of highly active androstenes, sp^2 hybridized at C-2 or C-3, or at both positions.[7] Substitution at the C-2 position of these steroid ring A olefins by methyl[8] or substituted methyl[9,10] led to further variations in activity, and some of these derivatives displayed an unusually favorable separation of androgenic and anabolic (myotrophic) activity. It was of distinct interest, therefore, to study the activity coincident upon the introduction of further unsaturation into the electron-rich ring A of these steroid olefins.

Accordingly, syntheses of such compounds have been developed by routes which also should prove applicable to other cyclic systems.

3β-Chloro-Δ^1-androsten-17β-ol acetate[7b] (Ia), from the reaction of the 3β-alcohol Ib with thionyl chloride, was converted smoothly in 80% yield into $\Delta^{1,3}$-androstadien-17β-ol acetate (IIa) by treatment with boiling dimethylformamide containing calcium carbonate or a little pyridine. Alternatively, boiling dimethyl sulfoxide alone, or in conjunction with a small quantity of pyridine, eliminated hydrogen chloride from Ia to give IIa. Earlier preparations of steroid $\Delta^{1,3}$-dienes proceeded in substantially inferior yields.[11] Hydrolysis of the acetate IIa furnished the corresponding 17β-alcohol IIb, which on oxidation with chromic acid[14]

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(1) (a) Steroids CCXX, J. A. Edwards, O. Halpern, and J. A. Zderic, *Chem. Ind.* (London), 1571 (1962); (b) a part of this work was presented (B. B.) at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962.

(2) M. S. de Winter, C. M. Siegmann, and S. A. Szpilfogel, *Chem. Ind.* (London), 905 (1959).

(3) R. O. Clinton, A. J. Manson, F. W. Stonner, A. L. Beyler, G. O. Potts, and A. J. Arnold, *J. Am. Chem. Soc.*, **81**, 1513 (1959); R. O. Clinton, *et al.*, *ibid.*, **83**, 1478 (1961).

(4) N. E. Borglin, *Acta Endocrinol.*, Supplementum LVIII (1960).

(5) J. A. Zderic, O. Halpern, H. Carpio, A. Ruiz, D. C. Limon, L. Magana, H. Jiménez, A. Bowers, and H. J. Ringold, *Chem. Ind.* (London), 1625 (1960).

(6) R. O. Clinton, A. J. Manson, F. W. Stonner, A. L. Beyler, R. G. Christiansen, G. O. Potts, and A. J. Arnold, *J. Org. Chem.*, **26**, 279 (1961).

(7) (a) J. A. Edwards and A. Bowers, *Chem. Ind.* (London), 1962 (1961); (b) A. Bowers, A. D. Cross, J. A. Edwards, H. Carpio, M. C. Calzada, and E. Denot, *J. Med. Chem.*, **6**, 156 (1963).

(8) A. D. Cross, J. A. Edwards, and A. Bowers, *ibid.*, **5**, 406 (1962); A. D. Cross, J. A. Edwards, J. C. Orr, B. Berkoz, M. C. Calzada, L. Cervantes, and A. Bowers, *ibid.*, **6**, 162 (1963).

(9) J. C. Orr, O. Halpern, and A. Bowers, *ibid.*, **5**, 409 (1962); J. C. Orr, O. Halpern, P. G. Holton, F. Alvarez, A. de la Roz, A. M. Ruiz, and A. Bowers, *ibid.*, **6**, 166 (1963).

(10) J. A. Edwards, P. G. Holton, J. C. Orr, E. Necoechea, A. de la Roz, E. Segovia, R. Urquiza, and A. Bowers, *ibid.*, **6**, 174 (1963).

(11) Henbest and Wilson[12] reported $\Delta^{1,3}$-cholestadiene as a minor non-isolated contaminant of Δ^1-cholestene formed through reductive dehalogenation of 3β-chloro-Δ^1-cholestene. Our synthesis of Δ^1-androstenes by the same experimental method furnished no trace of a $\Delta^{1,3}$-diene elimination reaction product.[7b] $\Delta^{1,3}$-Cholestadiene was obtained in 4.3% yield by the action of alumina on, or pyrolysis of, Δ^1-cholestene-3β-ol benzoate.[13]

(12) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 3289 (1956).

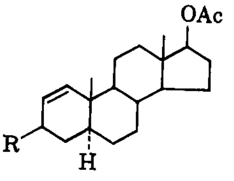
(13) Ch. Tamm and R. Albrecht, *Helv. Chim. Acta*, **42**, 2177 (1959).

yielded $\Delta^{1,3}$-androstadien-17-one (IIc). Treatment of the latter with methyl- or ethynylmagnesium bromide led to 17α-methyl-$\Delta^{1,3}$-androstadien-17β-ol (IId) or the 17α-ethynyl analog IIe, respectively. Brief treatment with 60% formic acid under reflux converted the $\Delta^{1,3}$-diene acetate IIa into a $\Delta^{3,5}$-diene, probably IIIa admixed with its 17-formate.

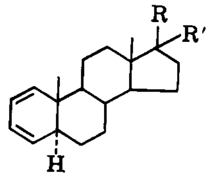
$\Delta^{2,4}$-Cholestadiene was prepared by Bergmann and his associates[15,16] by high temperature vacuum distillation of cholesterol from alumina, but the product is thermolabile, and it was considered essential, therefore, to develop a more attractive synthetic method. A synthesis of $\Delta^{2,4}$-estradienes from a 2α-acetoxy-Δ^{4}-3-ketone[17] was announced recently after the completion of our work.

Bromination of androstan-17β-ol-3-one acetate furnishes the 2α,4α-dibromo derivative IVa.[18,19] The latter when treated with sodium iodide in acetone afforded 2α-iodotestosterone acetate (Va)[20] in which the α-configuration of the iodine is equatorial as evidenced by the rotatory dispersion curve and infrared spectrum.[21] Reduction of the α-iodo ketone Va proceeded with sodium borohydride in aqueous dioxane to yield 2α-iodo-Δ^{4}-androstene-3,17β-diol 17-acetate (Vb).[22] A modified Cornforth reaction[23] on the iodohydrin Vb with a zinc–copper couple[24] in buffered acetic acid solution led to $\Delta^{2,4}$-androstadien-17β-ol acetate (VIa) in 35% over-all yield. This diene proved to be thermolabile, a hot solution in heptane developing ultraviolet absorption at 235 mμ characteristic of the isomeric $\Delta^{3,5}$-diene IIIb. Reductive cleavage of the acetate VIa furnished the corresponding 17β-alcohol VIb, from which the 17-ketone VIc was derived by oxidation in a two-phase system by the procedure of Brown and Garg.[25] Treatment of this ketone VIc with methylmagnesium iodide made available 17α-methyl-$\Delta^{2,4}$-androstadien-17β-ol (VId).

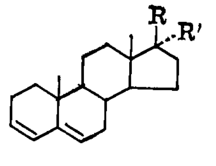
In a similar manner 5α-pregnan-20β-ol-3-one acetate[26] when brominated gave 2α,4α-dibromo-5α-pregnan-20β-ol-3-one acetate[26] (IVb), a crystalline compound, which upon treatment with sodium iodide furnished 2α-iodo-Δ^{4}-pregnen-20β-ol-3-one acetate (Vc). The latter was reduced by sodium borohydride in aqueous dioxane to afford the corresponding iodohydrin Vd[22] which, without further purification, was converted into $\Delta^{2,4}$-pregnadien-20β-ol acetate (VIe) by a modified Cornforth reaction.[23] Reductive cleavage of the 20β-acetate VIe with lithium aluminum hydride led to the derived 20β-alcohol VIf. Oxidation[25] of this alcohol VIf yielded the required $\Delta^{2,4}$-pregnadien-20-one (VIg). With hot acetic acid–hydrochloric acid the $\Delta^{2,4}$-diene VIe underwent conversion to a product showing ultraviolet maxima at 242, 235, and 227 mμ, which is considered to be mainly the isomeric $\Delta^{3,5}$-diene (IIId).



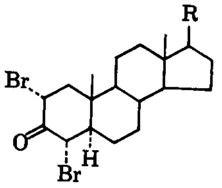
Ia, R = Cl
b, R = OH



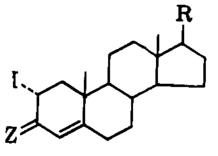
IIa, R = OAc; R' = H
b, R = OH; R' = H
c, R and R' = =O
d, R = OH; R' = Me
e, R = H; OR' = C≡CH



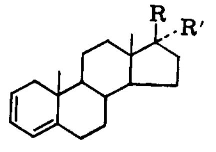
IIIa, R = OH; R' = H
b, R = OAc; R' = H
c, R = Ac; R' = OAc
d, R = CH(OAc)Me; R' = H



IVa, R = OAc
b, R = CH(OAc)Me



Va, Z = =O; R OAc
b, Z = H; R = OAc
c, Z = =O; R = CH(OAc)Me
d, Z = H, OH; R = CH(OAc)Me



VIa, R = OAc; R' = H
b, R =OH; R' = H
c, R and R' = =O
d, R = OH; H' = Me
e, R = CH(OAc)Me; R' = H
f, R = CHOH·Me; R' = H
g, R = Ac; R' = H

Pyrolysis of cholesteryl-2-naphthyl carbonate at 280° gives, besides conjugated dienes, a diene which shows no strong absorption in the ultraviolet spectrum and which is considered to be $\Delta^{2,5}$-cholestadiene in spite of the absence of any supporting evidence.[27] In view of this a more definitive synthesis was sought.

Epoxidation of Δ^{5}-pregnene-3β-17α-diol-20-one 17-acetate[28] with monoperphthalic acid furnished a mixture of α- and β-epoxides which proved separable by chromatography over alumina. The major product was assigned the α-configuration from a consideration of molecular rotation differences[29] and its nuclear magnetic resonance spectrum.[30] Tosylation of this α-epoxide VIIa gave the 3β-tosylate VIIb which underwent an elimination reaction when heated with lithium carbonate in dimethylacetamide to afford 5α,6α-epoxy-Δ^{2}-5α-pregnen-17α-ol-20-one acetate (VIIc). A Cornforth reaction[23,24] upon the Δ^{2}-5α,6α-epoxide VIIc furnished $\Delta^{2,5}$-pregnadien-17α-ol-20-one acetate (VIII).

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(14) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *ibid.*, 2548 (1953).

(15) H. E. Stavely and W. Bergmann, *J. Org. Chem.*, **1**, 575 (1936).

(16) E. L. Skau and W. Bergmann, *ibid.*, **3**, 166 (1938).

(17) P. N. Rao and H. R. Gollberg, *Chem. Ind.* (London), 1317 (1961).

(18) H. H. Inhoffen, G. Zuehlsdorff, and Huang-Minlon, *Chem. Ber.*, **73**, 451 (1960).

(19) C. Djerassi and C. R. Scholz, *J. Am. Chem. Soc.*, **69**, 2404 (1947).

(20) This type of elimination–substitution reaction was described earlier by G. Rosenkranz, O. Mancera, J. Gatica, and C. Djerassi, *ibid.*, **72**, 4077 (1950).

(21) *Cf.* L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Co., New York, N. Y., 1959, pp. 286–287.

(22) Previous examination[7b] of similar reductions showed that the reaction product is largely the 3β-alcohol with minor quantities of the 3α-epimer present.

(23) J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 112 (1959).

(24) D. H. R. Barton and P. T. Gilham, *ibid.*, 4596 (1960).

(25) H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.*, **83**, 2952 (1961).

(26) F. Sondheimer, M. Velasco, and G. Rosenkranz, *ibid.*, **77**, 5673 (1955).

(27) K. C. Tsou, *ibid.*, **76**, 6108 (1954).

(28) R. B. Turner, *ibid.*, **75**, 3489 (1953).

(29) A. Bowers, L. C. Ibáñez, and H. J. Ringold, *Tetrahedron*, **7**, 138 (1959).

(30) A. D. Cross, *J. Am. Chem. Soc.*, **84**, 3206 (1962).

Isomerization of this $\Delta^{2,5}$-diene VIII occurred on exposure to acetic acid containing hydrochloric acid, whereupon $\Delta^{3,5}$-pregnadien-17α-ol-20-one acetate (IIIc) was obtained with ultraviolet absorption spectrum resembling closely that of an authentic sample.[31]

By similar method 17,20:20,21-bismethylenedioxy-Δ^{5}-pregnen-3β-ol-11-one (IX)[33] was epoxidized and the α-epoxide Xa converted to the 3β-tosylate Xb which underwent elimination to afford the Δ^{2}-5α,6α-epoxide Xc. A Cornforth reaction then provided the $\Delta^{2,5}$-diene XIa. Lithium aluminum hydride reduced the corticoid 11-ketone XIa to the 11β-alcohol XIb. The free corticoid side chain was regenerated by brief acid hydrolysis of the bismethylenedioxy protecting group in XIb to furnish a mixture. This mixture was subjected to mild alkaline hydrolysis, acetylation, and chromatography over silica, but, in spite of repeated attempts, $\Delta^{2,5}$-pregnadiene-11β,17α,21-triol-20-one 21-acetate (XII) and its $\Delta^{3,5}$-isomer proved inseparable. Ultraviolet spectra analysis indicated that the mixture contained roughly equal proportions of the two isomers.

Physical Properties.—Ultraviolet absorption spectral data for some of the conjugated dienes and related compounds are collected in Table I. The molecular extinction coefficient of the $\Delta^{1,3}$-androstadienes (II) is less than one-half of that of $\Delta^{1,3}$-cyclohexadiene. Examination of Dreiding molecular models[34] suggests that this is due to the much greater difficulty in attainment of coplanarity of the double bonds in these $\Delta^{1,3}$-steroids than in the monocyclic compound. An unaccountable discrepancy exists between the ϵ values reported by Tamm and Albrecht[13] for $\Delta^{1,3}$-cholestadiene and the analogs described in this paper. Models[34] also reveal ring A of $\Delta^{2,4}$-steroid dienes to be more flexible than the $\Delta^{1,3}$-isomers, in keeping with their higher ϵ values.

TABLE I

ULTRAVIOLET ABSORPTION OF CYCLIC CONJUGATED DIENES

Compound	λ_{max}	ϵ
$\Delta^{1,3}$-Cyclohexadiene[a]	256.5	8000
$\Delta^{1,3}$-Cholestadiene[c]	262	5500
IIa	262	3800
IIb	262	3720
IIe	262	3800
$\Delta^{2,4}$-Estradien-17β-ol-3-one acetate[d]	259, 268, 279[b]	4450, 5270, 4620
VIa	266	6030
VIf	266	6450
VIg	266	6600

[a] V. Henri and L. W. Pickett, *J. Chem. Phys.*, **7**, 439 (1939). [b] Only a single maximum was observed for the $\Delta^{2,4}$-dienes prepared in the current work, though all showed a shoulder at 271–274 mμ. $\Delta^{2,4}$-Cholestadiene is reported as having maxima at 267 and 275 mμ [W. Bergmann and F. Hirschmann, *J. Org. Chem.*, **4**, 40 (1939)]. [c] See ref. 13. [d] See ref. 17.

In the infrared spectra all of the conjugated dienes show two absorption bonds characteristic for =C—H deformations of *cis*-disubstituted olefins. Both $\Delta^{1,3}$- and $\Delta^{2,4}$-dienes absorb strongly in the region 693–703 cm.$^{-1}$. For the $\Delta^{1,3}$-dienes the second absorption, of medium intensity, occurs at 735–740 cm.$^{-1}$, whereas in the $\Delta^{2,4}$-dienes this second absorption is observed in the range 719–728 cm.$^{-1}$.

The nuclear magnetic resonance (n.m.r.) spectra[35] clearly distinguish between the diene systems. Long range deshielding of the 19-angular methyl protons by the double bonds leads to characteristic shifts, $\Delta\delta$, relative to 5α-androstane (Table II), for each diene type. The olefinic proton resonance patterns (Fig. 1), though complex, are quite distinctive. For the $\Delta^{1,3}$-dienes, the only steroid nuclear conjugated dienes which carry four vinyl protons, the integrated areas are diagnostic. The $\Delta^{2,5}$-dienes show a two-proton absorption *ca.* 336 c.p.s. as a "hump," typical of the olefinic protons in a ring A unsubstituted Δ^{2}-steroid.[36]

TABLE II

N.M.R. FREQUENCIES OF THE ANGULAR METHYL PROTONS OF $\Delta^{1,3}$-, $\Delta^{2,4}$-, AND $\Delta^{2,5}$-STEROID DIENES[35]

Compound	Diene	19-H	$\Delta\delta$[a]	18-H
Androstane (in $CDCl_3$)[b]	. . .	46.5	0	40.4
IIb (in $CDCl_3$)	$\Delta^{1,3}$	47.5	+1.0	44.1
IIa (in CCl_4)[c]	$\Delta^{1,3}$	46.1	--0.4	46.1
VIII (in $CDCl_3$)	$\Delta^{2,5}$	59.2	+12.7	38.7
VIa (in CCl_4)[c]	$\Delta^{2,4}$	54.1	+7.6	46.6
VIe (in $CDCl_3$)[d]	$\Delta^{2,4}$	55.7	+9.2	39.7
VIf (in $CDCl_3$)[d]	$\Delta^{2,4}$	56.6	+10.1	47.0
VIg (in $CDCl_3$)[d]	$\Delta^{2,4}$	56.2	+9.7	39.2

[a] Positive values of $\Delta\delta$ indicate shifts downfield from the TMS reference and are caused by over-all deshielding. [b] R. F. Zürcher, *Helv. Chim. Acta*, **44**, 1380 (1961). [c] For steroids a change of solvent from carbon tetrachloride to deuteriochloroform generally causes small downfield frequency shifts. These shifts are largest for the resonances of protons which are part of, or adjacent to, polar groups (*e.g.*, acetate methyl). Values of $\Delta\delta$ should not be used for calculating angular methyl proton frequencies unless the solvent employed was the same for all $\Delta\delta$ determinations. [d] The small variations of the 19-H frequency in $\Delta^{2,4}$-dienes reflects small differences in the shielding contributions of substituents at C-17, as well as experimental error.

The rotatory dispersion curves (Fig. 2) of the $\Delta^{2,4}$-dienes VI (right-handed helices) all show a strong positive Cotton effect,[37] that of the 17-ketone VIc being the strongest due to the positive contribution of the cyclopentanone.[38] In the $\Delta^{1,3}$-dienes II the helicity of the diene is left-handed, and in consequence a negative Cotton effect curve is obtained.[37] The $\Delta^{1,3}$-17-ketone IIc, however, shows a positive Cotton effect curve since the amplitude of the cyclopentanone considerably outweighs that due to the diene.

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(31) Prepared by the following unambiguous route. Oppenauer oxidation of Δ^{5}-pregnene-3β,17α-diol-20-one ethylene ketal[32] gave Δ^{4}-pregnen-17α-ol-3,20-dione 20-ethylene ketal, which was treated successively with lithium aluminum hydride, then acid, to yield $\Delta^{3,5}$-pregnadien-17α-ol-20-one, acetylation of which gave the diene IIIc. O. Halpern and J. A. Zderic, *Chem. Ind.*, (London), 1540 (1962).

(32) P. L. Julian, E. W. Meyer, and I. Ryden, *J. Am. Chem. Soc.*, **72**, 367 (1950).

(33) Prepared from cortisone BMD by successive conversion to the $\Delta^{3,5}$-enol acetate, borohydride reduction to the Δ^{5}-3β,11β-diol, selective acetylation at C-3, and oxidation to the 11-ketone X. We thank J. Zderic and H. Carpio for this information in advance of their publication.

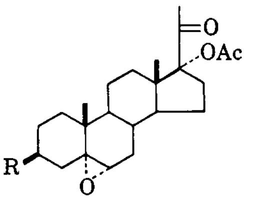
(34) A. Dreiding, *Helv. Chim. Acta*, **42**, 1339 (1959).

(35) N.m.r. spectra were taken with dilute deuteriochloroform or carbon tetrachloride solutions and a tetramethylsilane (TMS) internal reference on a Varian A-60 spectrometer. Calibration was checked against a Varian HR60 spectrometer suitably equipped for calibration by the standard sideband technique. Chemical shifts, δ, are quoted as c.p.s. downfield from the TMS reference and are accurate to ±1 c.p.s.

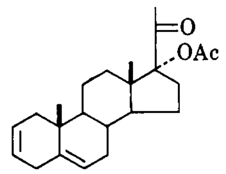
(36) A. D. Cross, forthcoming publication.

(37) *Cf.* A. W. Burgstahler, H. Ziffer, and U. Weiss, *J. Am. Chem. Soc.*, **83**, 4660 (1961); A. Moscowitz, E. Charney, U. Weiss, and H. Ziffer, *ibid.*, **83**, 4661 (1961).

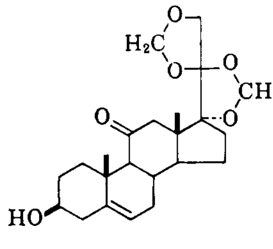
(38) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., New York, N. Y., 1960, p. 45.



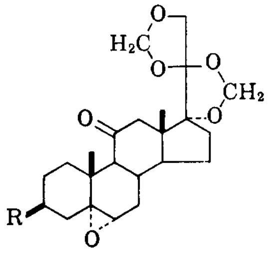
VIIa, R = OH
b, R = OTs
c, R = H; Δ²



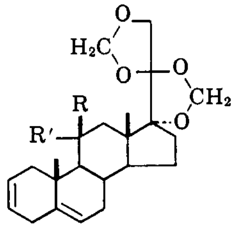
VIII



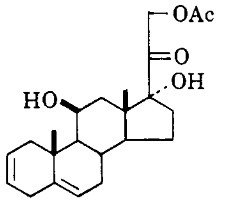
IX



Xa, R = OH
b, R = OTc
c, R = H; Δ²



XIa, R and R' = =O
b, R = OH; R' = H



XII

Experimental[39]

$\Delta^{1,3}$-Androstadien-17β-ol Acetate (**IIa**).—(a) 3β-Chloro-Δ^1-androsten-17β-ol acetate[7b] (Ia) (1 g.) was dissolved in 40 ml. of dimethylformamide and 2 ml. of pyridine, and the solution was boiled under reflux during 16 hr. Dilution with water was followed by extraction with ethyl acetate, and the latter solution was washed well with dilute hydrochloric acid, water, sodium bicarbonate solution, with water to neutrality, and dried. Filtration, then evaporation to dryness, afforded 810 mg. of solid residue which was recrystallized from aqueous methanol to furnish 730 mg. of $\Delta^{1,3}$-androstadien-17β-ol acetate (IIa), m.p. 115–118°. Further recrystallizations from the same solvent pair yielded a pure specimen, m.p. 124–125°; $[\alpha]_D$ +62°; λ_{max} 262 mμ, log ϵ 3.58; ν_{max} 3020 (w), 1738 (s), 1655 (w), 1250 (s), 738 (m), and 703 (s) cm.$^{-1}$; R.D., $[\alpha]_{589}$ +179°, $[\alpha]_{320}$ −24°, $[\alpha]_{295}$ −153°, $[\alpha]_{290}$ −82° (*c* 0.034 in dioxane).

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62; O, 10.18. Found: C, 80.11; H, 9.21; O, 10.53.

On a 7.5-g. scale the yield was 80%.

(b) A solution of 0.3 g. of 3β-chloro-Δ^1-androsten-17β-ol acetate (Ia) in 5 ml. of dimethylformamide was heated under reflux for 4 hr. together with 0.60 g. of calcium carbonate and then poured cautiously into 5% hydrochloric acid. Extraction with ethyl acetate led to the $\Delta^{1,3}$-diene IIa, λ_{max} 262 mμ, log ϵ 3.56, for the crude product. Recrystallization from methanol afforded 110 mg. of sample indistinguishable from the compound described previously.

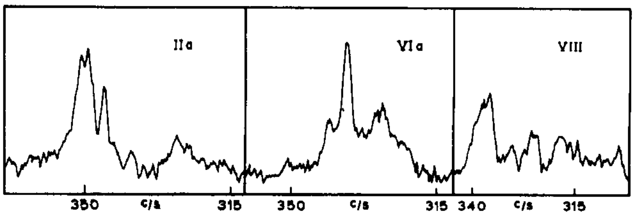
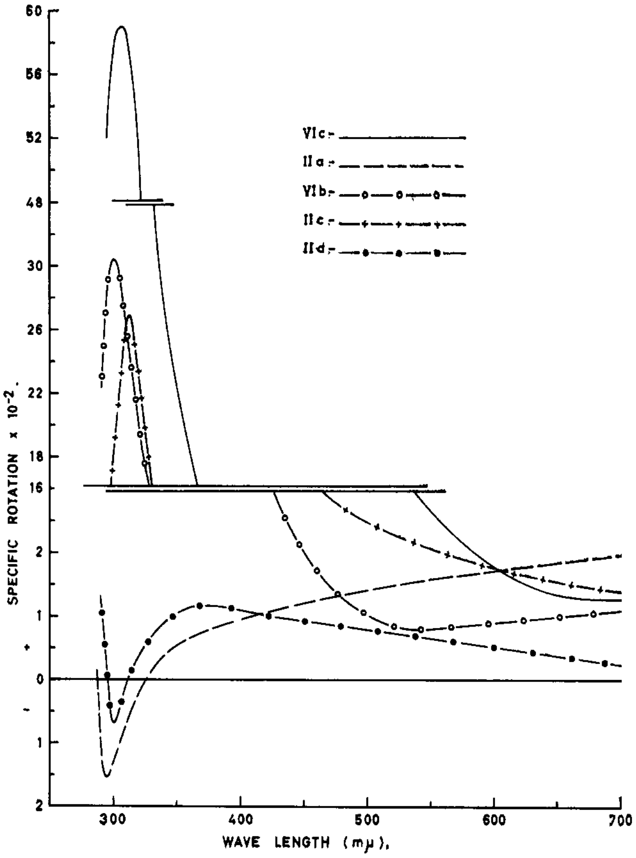


Fig. 1.—N.m.r. olefinic proton resonance patterns.



Fig' 2.—Optical rotatory dispersion curves of $\Delta^{1,3}$- and $\Delta^{2,4}$-androstenes.

(c) Replacement of dimethylformamide in method a by dimethyl sulfoxide gave the $\Delta^{1,3}$-diene IIa in 60% yield.

(d) Repetition of method c, but omitting the pyridine, again furnished the diene IIa in 60% yield.

$\Delta^{1,3}$-Androstadien-17β-ol (**IIb**).—The acetate IIa (2 g.) and 2 g. of sodium hydroxide were dissolved in 100 ml. of methanol, the solution kept 1.5 hr. under reflux, and then poured into ice–water. Ethyl acetate extracts were washed with hydrochloric acid and with water, dried, and evaporated to afford 1.57 g. of $\Delta^{1,3}$-androstadien-17β-ol (IIb) (91%), m.p. 143–145°. Several recrystallizations from methanol–water furnished a pure specimen, m.p. 147–148°; $[\alpha]_D$ +79°; λ_{max} 262 mμ, log ϵ 3.57; ν_{max} 3300 (s), 3025 (w), 1640 (w), 735 (m), and 700 (s) cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{28}O \cdot 1/2H_2O$: C, 81.09; H, 10.39; O, 8.53. Found: C, 81.33; H, 10.25; O, 8.30.

$\Delta^{1,3}$-Androstadien-17-one (**IIc**).—A solution of 1.5 g. of the 17β-alcohol IIb in 15 ml. of pyridine was added to a stirred ice-cold slurry of 1.5 g. of chromic oxide in 15 ml. of pyridine. After being kept 18 hr. at room temperature, the mixture was diluted with 120 ml. of ethyl acetate and filtered through Celite, washing well with more ethyl acetate. The filtrate was passed quickly through an alumina column and evaporated to a solid mass. Upon further chromatographic separation hexane removed 770 mg. of $\Delta^{1,3}$-androstadien-17-one (IIc) (52%), and elution with benzene afforded unchanged alcohol. Several recrystallizations of the ketone from methanol yielded a pure sample, m.p. 129–130°; $[\alpha]_D$ +184°; λ_{max} 262 mμ, log ϵ 3.57; ν_{max} 3020 (w), 1745 (s), 735 (m), 712 (m), and 698 (s) cm.$^{-1}$; R.D.,

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[39] Except where stated otherwise rotations are for chloroform solutions, ultraviolet spectra are for ethanol solutions, and infrared spectra are for potassium bromide disks. Melting points were taken on the Fisher-Johns block and are uncorrected. Rotatory dispersion measurements were made on a Rudolph automatic spectropolarimeter. We are indebted to J. Matthews and his staff for these measurements. Microanalyses are by either Mid-West Microlaboratories, Indianapolis 20, Ind., or by A. Bernhardt, Mulheim (Ruhr), Germany. Alumina used for chromatography was neutralized by stirring with ethyl acetate and reactivated by heating at 120° for 72 hr. Unless stated otherwise the alumina had activity grade III, as defined by H. Brockmann and H. Schodder, *Ber.*, **74**, 73 (1941).

$[\alpha]_{589}$ +182°, $[\alpha]_{320}$ +2265°, $[\alpha]_{312.5}$ +2685°, $[\alpha]_{300}$ +1870°, (*c* 0.064 in methanol).

Anal. Calcd. for $C_{19}H_{26}O$: C, 84.39; H, 9.69; O, 5.92. Found: C, 84.36; H, 9.47; O, 5.92.

17α-Methyl-$\Delta^{1,3}$-androstadien-17β-ol (**IId**).—To a solution of the above 17-ketone IIc (250 mg.) in 30 ml. of anhydrous ether was added 5.9 ml. of 4 *N* methylmagnesium bromide in ether. The mixture was boiled under reflux during 15 hr. and then poured into aqueous ammonium chloride. Ethyl acetate extracts were washed to neutrality, dried, and evaporated. The resultant oil was subjected to chromatography over alumina. Hexane eluents furnished upon evaporation 120 mg. of 17α-methyl-$\Delta^{1,3}$-androstadien-17β-ol (IId) which, after several recrystallizations from aqueous acetone, had m.p. 118–119°; $[\alpha]_D$ +48°; λ_{max} 262 mμ, log ε 3.55; ν_{max} 3350 (s), 3020 (w), 1645 (w), 739 (m), and 698 (s) cm.$^{-1}$; R.D., $[\alpha]_{589}$ +48°, $[\alpha]_{320}$ +37°, $[\alpha]_{300}$ −67°, $[\alpha]_{297.5}$ −31°, $[\alpha]_{295}$ +31° (*c* 0.065 in methanol).

Anal. Calcd. for $C_{20}H_{30}O$: C, 83.86; H, 10.56; O, 5.59. Found: C, 83.62; H, 10.55; O, 5.85.

17α-Ethynyl-$\Delta^{1,3}$-androstadien-17β-ol (**IIe**).—A solution of $\Delta^{1,3}$-androstadien-17-one (660 mg.) in tetrahydrofuran (10 ml.) was added to an excess of ethynylmagnesium bromide in the same solvent. After being kept under reflux during 3.5 hr., the solution was stirred a further 18 hr. at room temperature and then poured into ice-cold aqueous ammonium chloride. Ethyl acetate extracts were washed with water to neutrality, dried, and evaporated, Chromatography of the residue over 26 g. of alumina (grade IV) afforded, by elution with 10:1 hexane–benzene, 17α-ethinyl-$\Delta^{1,3}$-androstadien-17β-ol (IIe) (330 mg.) which, after recrystallization from acetone–water, showed m.p. 142–143°; $[\alpha]_D$ +17°; λ_{max} 262 mμ, log ε 3.58; ν_{max} 3560 (m), 3280 (m), 3020 (m), 736 (m), 711 (s), 700 (s), and 668 cm.$^{-1}$; R.D., $[\alpha]_{589}$ +10°, $[\alpha]_{320}$ −148°, $[\alpha]_{298}$ −315°, $[\alpha]_{295}$ −271° (*c* 0.052 in dioxane).

Anal. Calcd. for $C_{21}H_{28}O$: C, 85.08; H, 9.52; O, 5.40. Found: C, 84.76; H, 9.60; O, 5.78.

Action of Acid on $\Delta^{1,3}$-Androstadien-17β-ol Acetate (**IIa**).—A solution of 20 mg. of $\Delta^{1,3}$-androstadien-17β-ol acetate (IIa) in 5 ml. of 60% aqueous formic acid was brought rapidly to reflux and 1-ml. aliquots were removed at intervals of 5 min. and added to aqueous sodium hydroxide. Ethyl acetate extracts of the alkaline solutions were washed, dried, and evaporated. The residual oils were examined for absorption in the ultraviolet. Substantial absorption at 235 mμ ($\Delta^{3,5}$-diene) was recorded for the second aliquot.

2α-Iodo-Δ^4-androsten-17β-ol Acetate (**Va**).—A solution of 30 g. of 2α,4α-dibromoandrostan-17β-ol-3-one acetate [18,19] and 30 g. of sodium iodide in 750 ml. of acetone was refluxed for 21 hr. Sodium bromide which precipitated from the dark-colored solution was filtered off and the color discharged from the filtrate by the addition of 5% sodium thiosulfate solution. Dilution with ice–water afforded a solid which was collected, washed with water, and crystallized from methylene chloride–heptane to furnish 20 g. of 2α-iodo-Δ^4-androsten-17β-ol acetate, m.p. 113–124° dec. Further recrystallization from the same solvent mixture gave the analytical sample, m.p. 126–130° dec.; $[\alpha]_D$ +80°; λ_{max} 244 mμ, log ε 4.15; ν_{max} 1732 (s), 1677 (s), and 1250 (s) cm.$^{-1}$; R.D., $[\alpha]_{589}$ −44°, $[\alpha]_{400}$ +171°, $[\alpha]_{362.5}$ +285°, $[\alpha]_{335}$ +117°, $[\alpha]_{320}$ +348°, $[\alpha]_{307.5}$ +629°, $[\alpha]_{290}$ +308° (*c* 0.06 in methanol).

Anal. Calcd. for $C_{21}H_{29}O_3I$: C, 55.26; H, 6.40; I, 27.80. Found: C, 55.56; H, 6.53; I, 27.77.

2α-Iodo-Δ^4-androstene-3,17β-diol 17β-Acetate (**Vb**).—A solution of 20 g. of previous 2α-iodo-3-ketone Va in 300 ml. of dioxane was mixed with a solution of 10 g. of sodium borohydride in 30 ml. of water and then kept for 18 hr. at 10° before diluting with ice–water. The solid which separated was collected (19 g.) and 3 g. subjected to chromatography over neutral alumina. Benzene eluted 1.3 g. of 2α-iodo-Δ^4-androstene-3,17β-diol 17β-acetate which was crystallized several times from methylene chloride–isopropyl alcohol to furnish the analytical sample, m.p. 105–110° dec.; $[\alpha]_D$ +19°; λ_{max} 258 mμ, log ε 2.94; ν_{max} 3320 (m), 1740 (s), and 1260 (s) cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{31}O_3I$: C, 55.02; H, 6.81; I, 27.68. Found: C, 55.40; H, 6.51; I, 27.26.

$\Delta^{2,4}$-Androstadien-17β-ol Acetate (**VIa**).—A mixture of 1.0 g. of the iodohydrin (Vb), 6.0 g. of copper–zinc couple,[24] and 2.5 g. of sodium acetate in 30 ml. of glacial acetic acid was stirred at or below room temperature for 6 hr. Temperature control was ensured by initial placement of the reaction vessel in a bath at 10°, the temperature of which slowly rose to 20°. Thereafter inorganic materials were removed by filtration and washed well with hexane. After being diluted with water the filtrate was extracted with hexane, and the extracts were washed to neutrality, dried, concentrated *in vacuo* at 40° to small volume, and passed through alumina. Elution with hexane furnished 610 mg. of product which after four recrystallizations from methylene chloride–pentane gave an analytical sample of $\Delta^{2,4}$-androstadien-17β-ol acetate (VIa), m.p. 102–104°; $[\alpha]_D$ +158°; λ_{max} 266 mμ, log ε 3.78, with a shoulder at 272–274 mμ, log ε 3.74; ν_{max} 1732 (s), 1250 (s), 725 (s), and 696 (s) cm.$^{-1}$; R.D., $[\alpha]_{589}$ +135°, $[\alpha]_{320}$ +1682°, $[\alpha]_{295}$ +3430°, $[\alpha]_{292.5}$ +3325° (*c* 0.052 in methanol).

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62; O, 10.18. Found: C, 80.24; H, 9.74; O, 10.28.

$\Delta^{2,4}$-Androstadien-17β-ol (**VIb**).—To 300 mg. of lithium aluminum hydride in 80 ml. of anhydrous ether was added 1.0 g. of $\Delta^{2,4}$-androstadien-17β-ol acetate (VIa) in 70 ml. of the same solvent. Addition was complete in 2 min., and the mixture was then stirred at room temperature for 0.5 hr. Destruction of the excess of lithium aluminum hydride was effected with a saturated solution of sodium sulfate, and the ethereal layer was separated and dried (anhydrous sodium sulfate). Removal of the solvent under reduced pressure left a solid residue, m.p. 152–158°, which was chromatographed over neutral alumina (grade II). Methylene chloride–hexane (1:1) eluent afforded upon evaporation 620 mg. of $\Delta^{2,4}$-androstadien-17β-ol, further purified by crystallization from methylene chloride–hexane mixture and then sublimation, to give the analytical sample, m.p. 171–173°; $[\alpha]_D$ +209°; λ_{max} 266 mμ, log ε 3.77, with a shoulder at 271–275 mμ, log ε 3.72; ν_{max} 3260 (m), 721 (m), and 694 (s) cm.$^{-1}$; R.D., $[\alpha]_{589}$ +93°, $[\alpha]_{350}$ +1042°, $[\alpha]_{295}$ +3225°, $[\alpha]_{290}$ +2790° (*c* 0.0075 in methanol).

Anal. Calcd. for $C_{19}H_{28}O$: C, 83.77; H, 10.36; O, 5.87. Found: C, 84.00; H, 10.36; O, 6.21.

$\Delta^{2,4}$-Androstadien-17-one (**VIc**).—Concentrated sulfuric acid (1.87 ml.) was added to a solution of 2.6 g. of potassium dichromate in 50 ml. of water, and the resultant mixture was cooled to room temperature before the further addition of a solution of 700 mg. of $\Delta^{2,4}$-androstadien-17β-ol (VIb) in 200 ml. of ether. The two-phase system was stirred efficiently during 2 hr. at room temperature after which time the ether layer was separated and washed successively with water, aqueous sodium bicarbonate, and water, before being dried. Evaporation under reduced pressure led to a crystalline mass, m.p. 103–110°, which was purified by chromatography over neutral alumina. Methylene chloride–pentane (1:9) eluent on evaporation yielded $\Delta^{2,4}$-androstadien-17-one, further purified by recrystallization from methylene chloride–pentane to prisms, m.p. 134–136°; $[\alpha]_D$ +292°; λ_{max} 266 mμ, log ε 3.79, with a shoulder at 271–275 mμ; ν_{max} 1740 (s), 728 (m), and 698 (s) cm.$^{-1}$; R.D., $[\alpha]_{589}$ +182°, $[\alpha]_{350}$ +2170°, $[\alpha]_{307.5}$ +5900°, $[\alpha]_{290}$ +4330° (*c* 0.01 in methanol).

Anal. Calcd. for $C_{19}H_{26}O$: C, 84.39; H, 9.69; O, 5.92. Found: C, 84.40; H, 9.79; O, 5.81.

17α-Methyl-$\Delta^{2,4}$-androstadien-17β-ol (**VId**).—To a solution of methylmagnesium iodide (prepared from 540 mg. of magnesium) in 600 ml. of anhydrous ether was added, in one portion, 790 mg. of the 17-ketone VIc in 600 ml. of anhydrous ether, and the mixture was kept 1 hr. at room temperature. Destruction of the excess of Grignard reagent was achieved through the cautious addition of ammonium chloride solution to the stirred reaction mixture. After being washed with water and then dried, the ethereal solution was evaporated to dryness. The residual solid was subjected to chromatography over neutral alumina from which methylene chloride–hexane (1:1) removed 510 mg. of 17α-methyl-$\Delta^{2,4}$-androstadien-17β-ol. An analytical sample, prepared by four crystallizations from aqueous acetone, and sublimation, had m.p. 166–168°; $[\alpha]_D$ +128°; λ_{max} 266 mμ, log ε 3.75 with a shoulder at 271–275 mμ; ν_{max} 3300 (m), 722 (m), and 695 (s) cm.$^{-1}$; R.D., $[\alpha]_{589}$ +132°, $[\alpha]_{350}$ +1182°, $[\alpha]_{292.5}$ +4050°, $[\alpha]_{290}$ +3735° (*c* 0.009 in methanol).

Anal. Calcd. for $C_{20}H_{32}O$: C, 83.86; H, 10.56; O, 5.59. Found: C, 83.51; H, 10.42; O, 6.05.

2α,4α-Dibromopregnan-20β-ol-3-one Acetate (**IVb**).—To a solution of 5.52 g. of pregnane-20β-ol-3-one acetate[26] in 55 ml. of glacial acetic acid, 5.5 g. of bromine in 50 ml. of glacial acetic acid was added dropwise in 10 min. at room temperature. The mixture was kept at room temperature for 1 hr. and then poured into ice–water. The precipitate which formed was collected and washed with water. Crystallization from methylene chloride–isopropyl alcohol afforded 5.4 g. of the dibromopregnane, IVb, from which an analytical sample was obtained by recrystallization from the same solvent pair, m.p. 184–186° dec.; $[\alpha]_D$ +18°; λ_{max} 264–268 mμ, log ϵ 2.05; ν_{max} 1750 (s), 1735 (s), 1245 (s) cm.$^{-1}$; R.D., $[\alpha]_{589}$ +4°, $[\alpha]_{305}$ +454°, $[\alpha]_{300}$ +443° (*c* 0.001 in dioxane).

Anal. Calcd. for $C_{23}H_{34}O_3Br_2$: C, 53.28; H, 6.61; Br, 30.84. Found: C, 53.54; H, 6.59; Br, 31.22.

2α-Iodo-Δ^4-pregnen-20β-ol-3-one Acetate (Vc).—The mixture of 3.8 g. of the dibromopregnane, IVb, and 4.6 g. of sodium iodide in 160 ml. of acetone was refluxed for 7 hr. Sodium bromide was removed from the dark-colored solution by filtration and washed with acetone. The iodine color of the filtrate was discharged through the addition of 10% sodium thiosulfate solution. Addition of ice–water caused the precipitation of 2α-iodo-Δ^4-pregnen-20β-ol-3-one acetate (Vc), which was filtered, washed with water, and dried (yield, 3.8 g.), m.p. 124–128° dec. An analytical sample crystallized several times from methylene chloride–isopropyl alcohol exhibited m.p. 127–129° dec.; $[\alpha]_D$ +136°; λ_{max} 246 mμ, log ϵ 4.15; ν_{max} 1736 (s), 1683 (s), and 1612 (s) cm.$^{-1}$; R.D., $[\alpha]_{589}$ +110, $[\alpha]_{374}$ +579, $[\alpha]_{345}$ +267°, $[\alpha]_{341}$ +247°, $[\alpha]_{330}$ +380°, $[\alpha]_{295}$ +1328°, $[\alpha]_{290}$ +1019° (*c* 0.001 in dioxane).

Anal. Calcd. for $C_{23}H_{33}O_3I$: C, 57.02; H, 6.87; O, 9.91; I, 26.20. Found: C, 57.21; H, 7.13; O, 10.03; I, 26.47.

$\Delta^{2,4}$-Pregnadien-20β-ol Acetate (VIc).—To a solution of 14 g. of sodium borohydride in 42 ml. of water, 27.8 g. of 2α-iodo-Δ^4-pregnen-20β-ol-3-one acetate (Vc) dissolved in 43 ml. of dioxane was added and the two-phase mixture kept at 5° for 17 hr. Precipitation from the above mixture with ice–water and filtration afforded 23.9 g. of the iodohydrin, m.p. 113–117° dec. A mixture of 5 g. of this crude iodohydrin, 9.25 g. of sodium acetate, and 10 g. of zinc–copper couple[24] in 275 ml. of glacial acetic acid was stirred efficiently at room temperature for 6 hr. Filtration followed by addition of ice–water to the filtrate afforded a milky precipitate which was extracted with hexane. The hexane solution was washed with water, 5% sodium bicarbonate solution, and finally with water until the washings were neutral. After being dried, the hexane solution was filtered and evaporated to furnish a crystalline mixture. This was chromatographed over neutral alumina and the fractions eluted with benzene–hexane (1:4) were collected to afford 1.3 g. of $\Delta^{2,4}$-pregnadien-20β-ol acetate (VIe). An analytical sample was obtained by crystallization from acetone, m.p. 140–142°; $[\alpha]_D$ +209°; λ_{max} 266 mμ, log ϵ 3.80 (shoulder at 271–274 mμ); ν_{max} 1735 (s), 1245 (s), 721 (m), 695 (s) cm.$^{-1}$; R.D., $[\alpha]_{589}$ +255°, $[\alpha]_{292.5}$ + 4380°, $[\alpha]_{290}$ +4160° (*c* 0.04 in methanol).

Anal. Calcd. for $C_{23}H_{34}O_6$: C, 80.66; H, 9.92; O, 9.11. Found: C, 80.72; H, 10.10; O, 9.28.

$\Delta^{2,4}$-Pregnadien-20β-ol (VIIf).—To a suspension of 900 mg. of lithium aluminum hydride in 1500 ml. of ether 3.0 g. of $\Delta^{2,4}$-pregnadien-20β-ol acetate (VIe) was added, and the mixture was kept at room temperature for 2 hr. The excess of the hydride was destroyed with a saturated solution of sodium sulfate and the ethereal solution dried and filtered. Evaporation afforded 2.9 g., m.p. 110–116°, of $\Delta^{2,4}$-pregnadien-20β-ol (VIf), from which an analytical sample was obtained by recrystallization from methylene chloride–hexane, m.p. 121–122°; $[\alpha]_D$ +182°; λ_{max} 266 mμ, log ϵ 3.81 (shoulder at 271–274 mμ); ν_{max} 3400 (m), 719 (m), and 684 (s) cm.$^{-1}$; R.D., $[\alpha]_{589}$ +284°, $[\alpha]_{292.5}$ +4190°, $[\alpha]_{290}$ +3845° (*c* 0.04 in methanol).

Anal. Calcd. for $C_{21}H_{32}O$: C, 84.01; H, 10.75; O, 5.44. Found: C, 84.00; H, 10.78; O, 5.60.

$\Delta^{2,4}$-Pregnadien-20-one (VIg).—A two-phase system of 2000 ml. of ether containing 1.77 g. of $\Delta^{2,4}$-pregnadien-20β-ol (VIf) and 260 ml. of water containing 13.4 g. of potassium dichromate and 9.6 ml. of concentrated sulfuric acid was stirred efficiently for 24 hr. at room temperature. Thereafter the ether solution was washed with water, 5% sodium bicarbonate solution, and finally with water until the washings were neutral. The solution was dried over sodium sulfate and evaporated to give the crude diene, VIg, m.p. 99–107°, which was chromatographed over neutral alumina. Elution with chloroform–hexane (1:9) afforded 930 mg. of $\Delta^{2,4}$-pregnadien-20-one (VIg). An analytical sample crystallized from acetone–hexane had m.p. 116–118°; $[\alpha]_D$ +296°; λ_{max} 266 mμ, log ϵ 3.82 (shoulder at 271–274 mμ); ν_{max} 1700 (s), 728 (m), and 702 (s) cm.$^{-1}$; R.D., $[\alpha]_{589}$ +541°, $[\alpha]_{292.5}$ +7740° $[\alpha]_{290}$ +7230° (*c* 0.001 in methanol).

Anal. Calcd. for $C_{21}H_{30}O$: C, 84.51; H, 10.13; O, 5.36. Found: C, 84.48; H, 10.17; O, 5.48.

Action of Acid on $\Delta^{2,4}$-Pregnadien-20β-ol Acetate (VIe).—A solution of 26 mg. of $\Delta^{2,4}$-pregnadien-20β-ol acetate (VIe) in 5 ml. of acetic acid and one drop of 15% hydrochloric acid was refluxed for 2 hr. The mixture was then extracted with ethyl acetate and washed with water, 5% sodium bicarbonate solution, and finally with water. Evaporation of the solvent led to an oil which exhibited λ_{max} 242, 235, 227 mμ.

5α,6α-Epoxy-pregnane-3β,17α-diol-20-one 17-Acetate (VIIa).—To 50 g. of 17α-acetoxy-Δ^5-pregnen-3β-ol-20-one[28] in solution in 250 ml. of chloroform was added, in one portion, an excess (900 ml.) of monoperphthalic acid solution[40] and the mixture kept at 0° for 16 hr. Ethyl acetate was added and the solution washed successively with water (enough ethyl acetate was used to ensure a good separation into two layers with water), sodium bicarbonate solution, water, sodium thiosulfate solution, and water. Distillation of the washed and dried solution gave a crystalline mass which was delivered (in benzene solution) to a column of neutral alumina. Elution with chloroform–benzene (1:1) furnished 25 g. of the epoxide VIIa, which was purified through recrystallization from methylene chloride–heptane to obtain the analytical sample, m.p. 252–254°; $[\alpha]_D$ −57°; ν_{max} 3420 (m), 1735 (s), 1720 (s), and 1250 (s) cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78; O, 20.49. Found: C, 71.21; H, 8.56; O, 20.15.

5α,6α-Epoxypregnane-3β,17α-diol-20-one 3-Tosylate 17-Acetate (VIIb).—To a solution of 7.0 g. of previous epoxide VIIa in 200 ml. of dry pyridine was added 7.0 g. of *p*-toluenesulfonyl chloride, and the mixture was kept at room temperature for 20 hr. Work-up in the normal manner furnished the tosylate VIIb as a solid which was purified by chromatography over neutral alumina. Elution with benzene provided 6 g. of the tosylate which, after several recrystallizations from isopropyl alcohol, had m.p. 184–186° dec.; $[\alpha]_D$ −54°; λ_{max} 226, 262, and 274 mμ, log ϵ 4.10, 2.76, and 2.69, respectively; ν_{max} 1735 (s), 1712 (s), 1250 (s), and 668 (s) cm.$^{-1}$.

Anal. Calcd. for $C_{30}H_{40}O_7S$: S, 5.88. Found: S, 5.73.

5α,6α-Epoxy-Δ^2-pregnen-17α-ol-20-one Acetate (VIIc).—A mixture of 1 g. of the 5α,6α-epoxide 3β-tosylate VIIb and 1 g. of lithium carbonate in 50 ml. of dimethylacetamide was kept under reflux during 3.5 hr. Thereafter the inorganic salts were removed by filtration and washed well with ethyl acetate. The combined washings and filtrate were washed with water, dried, and evaporated. Chromatography of the residue over alumina and elution with benzene led to 200 mg. of the Δ^2-5α.6α-epoxide VIIc. Crystallization from methylene chloride–heptane followed by sublimation gave a sample with m.p. 214–216°; $[\alpha]_D$ −40°; ν_{max} 1735 (s), 1715 (s), 1250 (s), and 750 (s) cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66; O, 17.18. Found: C, 73.90; H, 8.77; O, 17.14.

$\Delta^{2,5}$-Pregnadien-17α-ol-20-one Acetate (VIII).—A mixture of 1.2 g. of 5α,6α-epoxy-Δ^2-pregnen-17α-ol-20-one acetate (VIIc), 1.5 g. of sodium iodide, 400 mg. of sodium acetate, and 280 mg. of zinc, in 20 ml. of acetic acid containing 0.25 ml. of water, was stirred at room temperature for 6 hr. Solid material was collected by filtration, and the filtrate was diluted with water and extracted with ethyl acetate. These extracts were washed with water, with 5% aqueous sodium bicarbonate, and with water again. Evaporation of the dried extracts and subsequent chromatography of the residual solid over neutral alumina gave from the benzene eluent 845 mg. of the $\Delta^{2,5}$-diene VIII, further purified by recrystallization from ethyl alcohol to obtain the analytical sample, m.p. 176–178°; $[\alpha]_D$ −47°; ν_{max} 1740 (s), 1715 (s), 1250 (s), and 798 (s) cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56; O, 13.39. Found: C, 77.25; H, 9.30; O, 13.54.

Acid-Catalyzed Isomerization of $\Delta^{2,5}$-Pregnadien-17α-ol-20-one Acetate (VIII).—(a) A solution of the $\Delta^{2,5}$-diene VIII in acetic acid containing 1% hydrochloric acid was kept at room temperature 24 hr. Isolation of the diene by dilution with water and extraction furnished a solid with weak ultraviolet absorption, λ_{max} 235 mμ, log ϵ 2.05.

(b) A solution of 20 mg. of the $\Delta^{2,5}$-diene VIII in 5 ml. of acetic acid containing 4 drops of concentrated hydrochloric acid and 3 drops of water was boiled under reflux during 3 hr. Dilution with water and ethyl acetate extraction led to a gum from which

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(40) E. E. Royals and L. L. Harrell, *J. Am. Chem. Soc.*, **77**, 3405 (1955).

was obtained by chromatographic separation over alumina and elution with benzene 15 mg. of a product, m.p. 130–145°.

Recrystallization from aqueous acetone furnished a sample, m.p. 155–163°; λ_{max} 235 mμ, log ϵ 4.24, with shoulders at 243 and 229 mμ. The infrared spectrum and chromatographic behavior were very similar to those of authentic $\Delta^{3,5}$-pregnadien-17α-ol-20-one acetate[31] (IIIc) (λ_{max} 228, 235, and 243 mμ, log ϵ 4.30, 4.35, and 4.15, respectively).

17α,20:20,21-Bismethylenedioxy-5α,6α-epoxy-pregnan-3β-ol-11-one (Xa).—To 10 g. of 17α,20:20,21-bismethylenedioxy-Δ^5-pregnen-3β-ol-11-one[33] (IX) in 150 ml. of chloroform was added an excess (1000 ml.) of monoperphthalic acid solution, and the mixture was kept at 0° for 18 hr. Some crystalline material separated and was collected (1.03 g.) by filtration. The filtrate was diluted with ethyl acetate, sufficient to ensure formation of a two-phase system, after which the organic solution was washed with water, 5% sodium bicarbonate solution, and water again. Traces of monoperphthalic acid which persisted in the ethyl acetate solution were destroyed with 5% sodium iodide solution, and the liberated iodine was then discharged with 5% sodium thiosulfate solution. Finally, the dried ethyl acetate solution was evaporated to dryness, and the crystalline residue was then combined with the precipitate obtained earlier and subjected to chromatography over neutral alumina. Benzene–chloroform (1:3) eluted 9.0 g. of the 5α,6α-epoxide (Xa) which, after several crystallizations from isopropyl alcohol, had m.p. 260–261°; $[\alpha]_D$ −116°; ν_{max} 3280 (m) and 1705 (s) cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{32}O_7$: C, 65.69; H, 7.67; O, 26.64. Found: C, 65.73; H, 7.75; O, 26.09.

17α,20:20,21-Bismethylenedioxy-5α,6α-epoxypregnan-3β-ol-20-one Tosylate (Xb).—p-Toluenesulfonyl chloride (5.0 g.) was added to a solution of 5 g. of preceding 5α,6α-epoxy 3β-alcohol Xa in 100 ml. of anhydrous pyridine, and the mixture was then kept 17 hr. at room temperature. When the mixture was poured into ice-water, a precipitate formed which was collected, washed with water, and purified by chromatography over alumina. Chloroform–benzene (3:7) eluent removed the tosylate Xb which was recrystallized from chloroform–isopropyl alcohol to furnish 3.9 g. of the pure material, m.p. 192–194°; $[\alpha]_D$ −96°; λ_{max} 226, 256, 262, 267, and 274 mμ, log ϵ 4.08, 265, 2.75, 2.70, and 2.61, respectively; ν_{max} 1699 (s), 1600 (m), 1500 (w), and 668 (s) cm.$^{-1}$.

Anal. Calcd. for $C_{30}H_{38}O_9S$: C, 62.69; H, 6.66; S, 5.57. Found: C, 63.02; H, 6.66; S, 5.62.

17α,20:20,21-Bismethylenedioxy-5α,6α-epoxy-Δ^2-pregnen-11-one (Xc).—A mixture of 3.8 g. of the tosylate Xb and 2.0 g. of lithium carbonate in 25 ml. of dimethylacetamide was boiled under reflux for 5 hr. After filtration the solution was poured into water, and the precipitate was collected and subjected to chromatographic purification over alumina. Benzene eluted 950 mg. of the Δ^2-5α,6α-epoxide Xc containing impurities which absorbed in the ultraviolet (λ_{max} 320, 308, and 297 mμ). Rechromatography over silica gel sequestered these impurities and ethyl acetate–benzene (1:4) eluted 780 mg. of the Δ^2-5α,6α-epoxide Xc. Further recrystallization from isopropyl alcohol and sublimation gave the analytical sample, m.p. 213–214°; $[\alpha]_D$ −76°; ν_{max} 1700 (s) cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51; O, 23.85. Found: C, 68.38; H, 7.47; O, 23.72.

17α,20:20,21-Bismethylenedioxy-$\Delta^{2,5}$-pregnadien-11-one (XIa).—A Cornforth reaction was carried out, as described before, on a mixture consisting of 700 mg. of the Δ^2-5α,6α-epoxide Xc, 400 mg. of sodium acetate, 1 g. of sodium iodide, and 320 mg. of zinc-copper couple[24] in 10 ml. of acetic acid containing 2 drops of water, for 1.5 hr. at room temperature. Work-up as before followed by chromatography of the crude product over alumina led to 530 mg. of the $\Delta^{2,5}$-diene XIa from evaporation of the benzene–hexane (1:1) eluent. Recrystallization from isopropyl alcohol afforded the analytical sample, m.p. 155–158°; $[\alpha]_D$ −113°; ν_{max} 1700 (s) and 803 (s) cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82; O, 20.70. Found: C, 71.39; H, 7.92; O, 20.42.

17α,20:20,21-Bismethylenedioxy-$\Delta^{5,2}$-pregnadien-11β-ol (XIb).—The $\Delta^{2,5}$-diene 11-ketone XIa (400 mg.) in 30 ml. of dry tetrahydrofuran was added during 5 min. to a suspension of 400 mg. of lithium aluminum hydride in 40 ml. of the same solvent. The mixture was then stirred for 1 hr. at room temperature before being worked up as described earlier for a similar reduction with this reagent. Chromatography of the crude product over silica gel gave 360 mg. of the $\Delta^{2,5}$-diene-11β-ol XIb in the chloroform–benzene (1:9) eluent. An analytical sample prepared by several recrystallizations from isopropyl alcohol had m.p. 219–220°; $[\alpha]_D$ −61°; ν_{max} 3450 (m) and 800 (s) cm.$^{-1}$; and no detectable absorption in the ultraviolet, at 235 mμ.

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30; O, 20.59. Found: C, 71.14; H, 8.45; O, 20.42.

Acid Hydrolysis of 17α,20:20,21-Bismethylenedioxy-$\Delta^{2,5}$-pregnadien-11β-ol (XIb).—The bismethylenedioxy compound XIb (200 mg.) in solution in 50 ml. of dioxane was added to a boiling solution of 70% aqueous formic acid, and the mixture was refluxed for 2 min. Thereafter the clear solution was poured into ice–water, and to the slightly turbid solution which resulted was added dropwise a cold solution of 20% sodium hydroxide to pH 7. The precipitate which formed was collected, washed with water, and dried (136 mg.; λ_{max} 236 mμ, log ϵ 3.10). A solution of this material in 5 ml. of dioxane was diluted with 10 ml. of methanol and then treated with 10 ml. of 2% methanolic potassium hydroxide at 0° for 1 hr., during which time dry nitrogen was slowly bubbled through the solution. When the solution was poured into ice–water a solid separated, which was collected, washed with water, and dried. To the dry product were added 5 ml. of pyridine and 2 ml. of acetic anhydride, and the mixture was kept for 16 hr. at room temperature then poured into ice–water. The solids which were precipitated were filtered off, washed with water, and dried (80 mg.), m.p. 100–210°. Paper chromatography revealed the presence of at least three products. Chromatography of the mixture over silica gel and elution with chloroform–hexane, chloroform, and acetone–chloroform afforded a succession of heterogeneous oily fractions all of which absorbed in the ultraviolet at 235 mμ and gave strong positive tests for the free corticoid side chain. Only traces of crystalline product resulted.