[CONTRIBUTION FROM THE DIVISION OF STEROID RESEARCH, THE JOHN HERR MUSSER DEPARTMENT OF RESEARCH MEDICINE, UNIVERSITY OF PENNSYLVANIA]

Investigations on Steroids. XXVII. 19-Hydroxy-14β,17α-progesterone and 19-Hydroxy-11-desoxy-14β,17α-corticosterone[1,2]

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The conversion of strophanthidin, by way of the known 3β,5,14,19-tetrahydroxy-14β,17α-etianic acid (II), into 19-hydroxy-11-desoxy-14β,17α-progesterone (XIX) and 19-hydroxy-11-desoxy-14β,17α-corticosterone (XXI) is described. Treatment of II with 0.1 *N* ethanolic hydrogen chloride yielded mainly ethyl 3β,5,19-trihydroxy-17α-Δ^{14}-etienate (III) which, by catalytic hydrogenation, was transformed into ethyl 3β,5,19-trihydroxy-14β,17α-etianate (V) which in turn was saponified to the free 3β,5,19-trihydroxy-14β,17α-etianic acid (VII). Oxidation of VII with N-bromoacetamide gave 3-oxo-5,19-dihydroxy-14β,17α-etianic acid (X) which, on treatment with Girard's reagent T, underwent dehydration yielding 3-oxo-19-hydroxy-14β,17α-Δ^4-etienic acid (XI). Acetylation of XI gave 3-oxo-19-acetoxy-14β,17α-Δ^4-etienic acid (XIV) which, by treatment of its acid chloride with diazomethane, was converted into the amorphous 19-acetoxy-21-diazo-14β,17α-progesterone (XVII). Saponification of XVII gave the crystalline 19-hydroxy-21-diazo-14β,17α-progesterone (XVIII). By reacting XVIII with concentrated hydriodic acid, 19-hydroxy-14β,17α-progesterone (XIX) was obtained. On the other hand, treatment of XVIII with acetic acid gave 19-hydroxy-11-desoxy-14β,17α-corticosterone 21-monoacetate (XX) which was saponified to the free 19-hydroxy-11-desoxy-14β,17α-corticosterone (XXI). The mentioned compounds were characterized by suitable derivatives. The stereochemical configurations assigned to the compounds of this series (14β,17α) are supported by molecular rotation data.

The synthesis of 19-hydroxyprogesterone and 19-hydroxy-11-desoxycorticosterone, starting from strophanthidin, has been described.[3,4] Evidence in support of the normal configurations of these compounds has been presented[4,5] and the formation of 19-hydroxyl substituted steroid hormones by biological systems has been reviewed.[5] In the initial stage of the synthesis of these products, strophanthidol diacetate is oxidized, yielding mainly 3β,5,-14,19-tetrahydroxy-14β-etianic acid which has served as intermediate for the preparation of compounds of the normal series.[6] As the major by-product of this oxidation, 3β,19-diacetoxy-5,14-dihydroxy-20-oxo-14β-pregnan-21-oic acid 21 → 14-lactone (I) is obtained. The accumulation of substantial quantities of this substance made possible the synthesis of 19-hydroxy-14β,17α-progesterone (XIX) and 19-hydroxy-11-desoxy-14β,17α-corticosterone (XXI). The respective parent compounds, *viz.* 14β,17α-progesterone and the 21-acetate of 11-desoxy-14β,17α-corticosterone, are known.[7,8]

The conversion of the ketolactone I into 3β,5,14,-19-tetrahydroxy-14β,17α-etianic acid (II) was reported earlier.[9] The reaction involves opening of the lactone ring with aqueous alkali, causing epimerization at C_{17}, and subsequent oxidation of the acetyl-free α-keto acid with hydrogen peroxide. Although II has also been obtained by oxidation with periodic acid of 14β,17α-pregnane-3β,5,14,19,21-pentol-20-one,[10] it is most conveniently prepared from I.

Transformation of II into 19-hydroxy-14β,17α-progesterone (XIX) and 19-hydroxy-11-desoxy-14β,17α-corticosterone (XXI) followed in general the route worked out for the normal series.[6] In the reaction scheme the essential intermediates are connected by heavy arrows. The light arrows refer to the preparation of derivatives. Treatment of II with 0.1 *N* ethanolic hydrogen chloride resulted, in addition to esterification, mainly in selective dehydration, furnishing ethyl 3β,5,19-trihydroxy-17α-Δ^{14}-etienate (III). In analogy with the normal series[11] small amounts of an isomer, possibly ethyl 3β,5-dihydroxy-8,19-epoxy-14β,17α-etianate (IV),

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(2) The findings of this paper were incorporated in reports given on July 22, 1955, at the XIVth International Congress of Pure and Applied Chemistry Covering Organic Chemistry in Zürich (*cf.* M. R. Ehrenstein, *Analogs of Steroid Hormones Oxygenated in the 19-Position*, Congress Handbook, p. 173 [No. 264]) and on August 5, 1955, at the 3rd International Congress of Biochemistry in Brussels (*cf.* M. R. Ehrenstein, G. W. Barber, and M. Dünnenberger, *Analogs of Steroid Hormones Oxygenated in the 19-Position and Their Biological Significance*, Résumés des Communications, p. 4 [No. 1-26]).

(3) Barber and Ehrenstein, *J. Am. Chem. Soc.*, **76**, 2026 (1954).

(4) Barber and Ehrenstein, *J. Org. Chem.*, **19**, 1758 (1954).

(5) Barber and Ehrenstein, *J. Org. Chem.*, **20**, 1253 (1955).

(6) For general review of procedure, *cf.* Ehrenstein and Dünnenberger, *J. Org. Chem.*, **21**, 780 (1956).

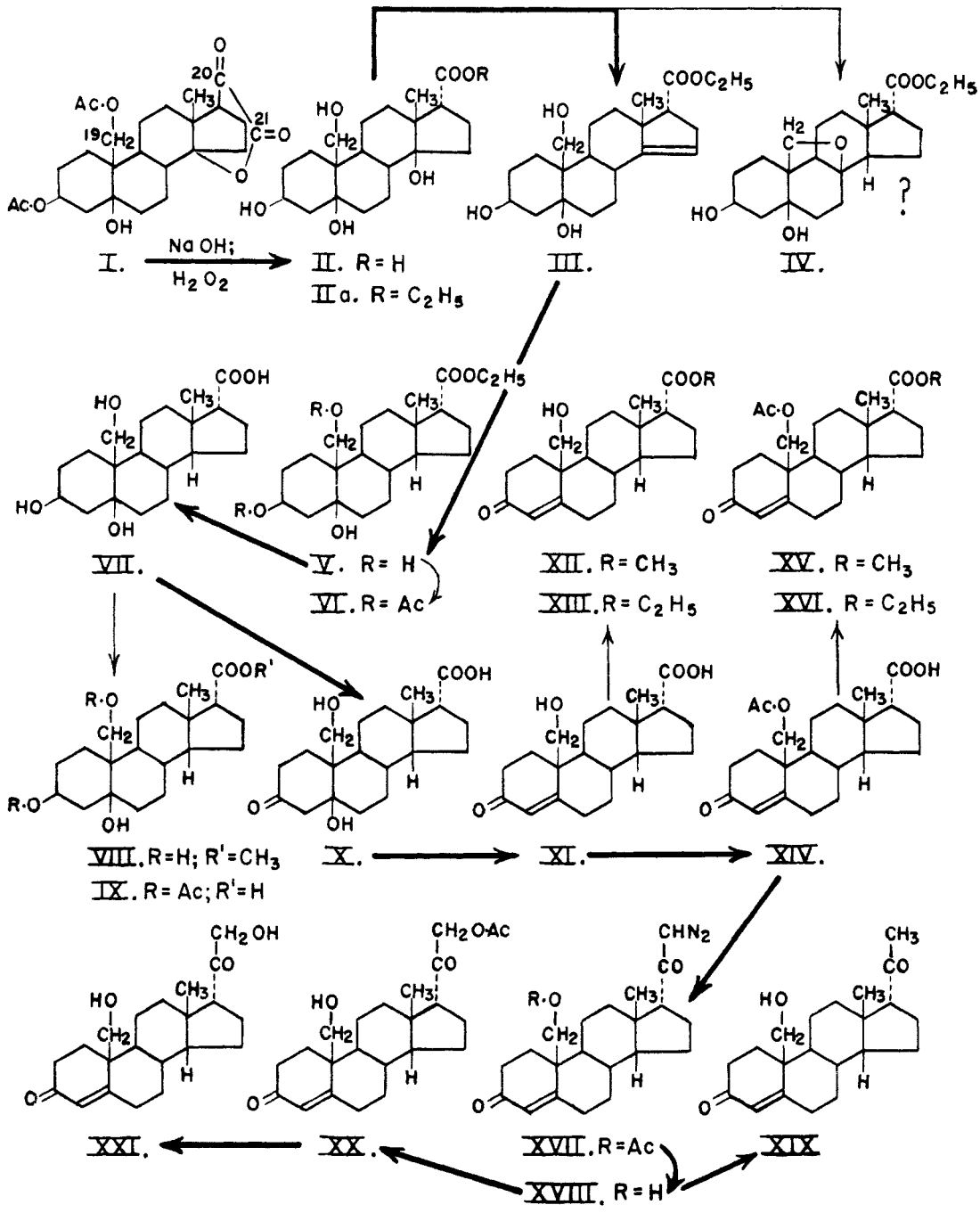
(7) Plattner, Heusser, and Segre, *Helv. Chim. Acta*, **31**, 249 (1948).

(8) Heusser, Frick, and Plattner, *Helv. Chim. Acta*, **33**, 1260 (1950).

(9) Barber and Ehrenstein, *J. Org. Chem.*, **16**, 1615 (1951).

(10) Balant and Ehrenstein, *J. Org. Chem.*, **17**, 1576 (1952).

(11) *Cf.* Ehrenstein and Neumann, *J. Org. Chem.*, **16**, 335 (1951).



were isolated.[12] As a variation, III was also prepared by treating ethyl 3β,5,14,19-tetrahydroxy-14β,17α-etianate (IIa)[10] with 0.1 *N* ethanolic hydrogen chloride. Catalytic hydrogenation of III resulted in the saturation of the double bond. The hydrogen atom at carbon atom 14 is assumed to have entered in the β-position, hence the resulting product should possess the structure of ethyl 3β,5,19-trihydroxy-14β,17α-etianate (V). This assumption is based on investigations by the Zurich school,[13] demonstrating that the stereochemical course of the catalytic hydrogenation of an isolated 14–15 double bond depends on the stereochemical configuration of the substituent at carbon atom 17. With the substituent in the α-configuration, as in the present instance, hydrogenation should lead to a 14β,17α-steroid. V

(12) In the present instance, the compound (IV) was isolated after hydrogenating crude III, probably containing IV, and subjecting the reaction product to chromatographic purification. The substance (IV) is clearly different from the compound of the normal series, *i.e.* ethyl 3β,5-dihydroxy-8,19-epoxyetianate (ref. 11).

(13) For a discussion of these aspects and the pertinent literature, *cf.* Heusser, Roth, Rohr, and Anliker, *Helv. Chim. Acta*, **38**, 1178 (1955).

TABLE I

COMPARISON OF MOLECULAR ROTATIONS

(Rotations measured in chloroform unless otherwise stated)

	Compound	Ref.	M_D	ΔM_D(a − b)
1.	(a) Methyl alloetianate	17	+155 (dioxane)	+285
	(b) Methyl 17α-alloetianate	17	−130 (dioxane)	
2.	(a) Methyl 3β-acetoxyalloetianate	17	+136	+275
	(b) Methyl 3β-acetoxy-17α-alloetianate	17	−139	
3.	(a) Methyl 3β-acetoxyetianate	17	+203 (acetone)	+308
	(b) Methyl 3β-acetoxy-17α-etianate	17	−105	
4.	(a) Δ⁵-Pregnen-3β-ol-20-one	7	+ 89 (alcohol)	+532
	(b) 17α-Δ⁵-Pregnen-3β-ol-20-one	7	−443 (alcohol)	
5.	(a) 3β-Acetoxy-Δ⁵-pregnen-20-one	7	+ 72 (alcohol)	+524
	(b) 3β-Acetoxy-17α-Δ⁵-pregnen-20-one	7	−452 (alcohol)	
6.	(a) Progesterone	18	+641	+641
	(b) 17α-Progesterone	19	0 (alcohol)	
7.	(a) 11-Desoxycorticosterone	20	+611	+631
	(b) 11-Desoxy-17α-corticosterone	21	− 20 (alcohol)	
8.	(a) 11-Desoxycorticosterone acetate	18	+693	+771
	(b) 11-Desoxy-17α-corticosterone acetate	21	− 78 (acetone)	
9.	(a) Methyl 17α-alloetianate	17	−130 (dioxane)	−212
	(b) Methyl 14β,17α-alloetianate	17	+ 82 (dioxane)	
10.	(a) Methyl 3β-acetoxy-17α-alloetianate	17	−139	−229
	(b) Methyl 3β-acetoxy-14β,17α-alloetianate	17	+ 90	
11.	(a) Methyl 3β-acetoxy-17α-etianate	17	−105	−224
	(b) Methyl 3β-acetoxy-14β,17α-etianate	17	+119	
12.	(a) 17α-Δ⁵-Pregnen-3β-ol-20-one	7	−443 (alcohol)	−399
	(b) 14β,17α-Δ⁵-Pregnen-3β-ol-20-one	7	− 44	
13.	(a) 3β-Acetoxy-17α-Δ⁵-pregnen-20-one	7	−452 (alcohol)	−389
	(b) 3β-Acetoxy-14β,17α-Δ⁵-pregnen-20-one	7	− 63	
14.	(a) 17α-Progesterone	19	0 (alcohol)	−437
	(b) 14β,17α-Progesterone	7	+437	
15.	(a) 11-Desoxy-17α-corticosterone acetate	21	− 78 (acetone)	−498
	(b) 11-Desoxy-14β,17α-corticosterone acetate	8	+420	
16.	(a) Methyl alloetianate	17	+170	+ 52
	(b) Methyl 14β,17α-alloetianate	17	+118	
17.	(a) Methyl 3β-acetoxyalloetianate	17	+136	+ 46
	(b) Methyl 3β-acetoxy-14β,17α-alloetianate	17	+ 90	
18.	(a) Methyl 3β-acetoxyetianate	17	+203 (acetone)	+ 84
	(b) Methyl 3β-acetoxy-14β,17α-etianate	17	+119	
19.	(a) Δ⁵-Pregnen-3β-ol-20-one	7	+ 73	+117
	(b) 14β,17α-Δ⁵-Pregnen-3β-ol-20-one	7	− 44	
20.	(a) 3β-Acetoxy-Δ⁵-pregnen-20-one	7	+ 61	+124
	(b) 3β-Acetoxy-14β,17α-Δ⁵-pregnen-20-one	7	− 63	
21.	(a) Progesterone	18	+641	+204
	(b) 14β,17α-Progesterone	7	+437	
22.	(a) 11-Desoxycorticosterone acetate	18	+693	+273
	(b) 11-Desoxy-14β,17α-corticosterone acetate	8	+420	

was characterized as the 3,19-diacetate (VI) and was also saponified to the free 3β,5,19-trihydroxy-14β,17α-etianic acid (VII) which in turn was characterized as the methyl ester (VIII) and as the 3,19-diacetate (IX). Oxidation of VII with 1.6 equivalents of N-bromoacetamide gave 3-oxo-5,19-dihydroxy-14β,17α-etianic acid (X) which on treatment with Girard's reagent T underwent dehydration yielding 3-oxo-19-hydroxy-14β,17α-Δ⁴-etienic acid (XI). To prepare XI, it is not necessary to purify the intermediate X. XI was characterized as the methyl and ethyl esters (XII and XIII respectively). By acetylation, XI was converted into 3-oxo-19-acetoxy-14β,17α-Δ⁴-etienic acid (XIV). As derivatives of XIV, the methyl and ethyl esters (XV and XVI respectively) were prepared. Treatment of XIV with oxalyl chloride gave the acid chloride which was immediately reacted with di-

(14) Heard and Ziegler, *J. Am. Chem. Soc.*, **72**, 4328 (1950); *cf.* also ref. 4.

(15) *Cf.* also Fieser and Fieser, *The Chemistry of Natural Products Related to Phenanthrene*, 3rd ed., Reinhold Publishing Corporation, New York, 1949, p. 213.

(16) For ths listing of additional pairs of this type *cf. e.g.* Marshall and Gallagher, *J. Biol. Chem.*, **179**, 1265 (1949).

(17) Plattner, Ruzicka, Heusser, Pataki, and Meier, *Helv. Chim. Acta*, **29**, 949 (1946).

(18) Sondheimer, Kaufmann, Romo, Martinez, and Rosenkranz, *J. Am. Chem. Soc.*, **75**, 4712 (1953).

(19) Butenandt, Schmidt-Thomé, and Paul, *Ber.*, **72**, 1112 (1939).

(20) Eppstein, Meister, Leigh, Peterson, Murray, Reineke, and Weintraub, *J. Am. Chem. Soc.*, **76**, 3174 (1954).

(21) Shoppee, *Helv. Chim. Acta*, **23**, 925 (1940).

(22) *Cf.* ref. 5.

(23) Ehrenstein and Johnson, *J. Org. Chem.*, **11**, 823 (1946).

TABLE II

COMPARISON OF MOLECULAR ROTATIONS

(Rotations measured in chloroform unless otherwise stated.
* M_D values are corrected for crystal solvent)

Compound	Ref.	M.p.	M_D	ΔM_D(a − b)
1. (a) 3β,5,14,19-Tetrahydroxy-14β-etianic acid	23	217–218.5°	+143 (acetone)	+132
(b) 3β,5,14,19-Tetrahydroxy-14β,17α-etianic acid (II)	9	259–261°	+11* (ethanol)	
2. (a) Ethyl 3β,5,14,19-tetrahydroxy-14β-etianate	10	188–188.5°	+168	+133
(b) Ethyl 3β,5,14,19-tetrahydroxy-14β,17α-etianate (IIa)	10	231–232.5°	+35*	
3. (a) Ethyl 3β,5,19-trihydroxy-Δ^{14}-etienate	23	190–191.5°	+185	−216
(b) Ethyl 3β,5,19-trihydroxy-17α-Δ^{14}-etienate (III)	24	129–130°	+401	
4. (a) Ethyl 3β,5-dihydroxy-8,9-epoxyetianate	11	213–214.5°	+255	+29
(b) Ethyl 3β,5-dihydroxy-8,9-epoxy-14β,17α-etianate (IV)	24	211–213°	+226*	
5. (a) 3β,5,19-Trihydroxyetianic acid	23	259–260°	+245 (acetone)	+18
(b) 3β,5,19-Trihydroxy-14β,17α-etianic acid (VII)	24	184.5–185°	+227*	
6. (a) Methyl 3β,5,19-trihydroxyetianate	23	220–222.5°	+225	+27
(b) Methyl 3β,5,19-trihydroxy-14β,17α-etianate (VIII)	24	184–186°	+198	
7. (a) Ethyl 3β,5,19-trihydroxyetianate	23	188.5–190°	+239	+31
(b) Ethyl 3β,5,19-trihydroxy-14β,17α-etianate (V)	24	155°	+208*	
8. (a) 3β,19-Diacetoxy-5-hydroxyetianic acid	25	156–158°	+250*	
(b) 3β,19-Diacetoxy-5-hydroxy-14β,17α-etianic acid (IX)	24	197–197.5°	+240	+10
9. (a) Ethyl 3β,19-diacetoxy-5-hydroxyetianate	23	108–109.5°	+280	
(b) Ethyl 3β,19-diacetoxy-5-hydroxy-14β,17α-etianate (VI)	24	139.5–140.5°	+172	+108
10. (a) 3-Oxo-19-hydroxy-Δ^4-etienic acid	26	236–237°	+525*	
(b) 3-Oxo-19-hydroxy-14β,17α-Δ^4-etienic acid (XI)	24	216.5–217°	+555	−30
11. (a) Methyl 3-oxo-19-hydroxy-Δ^4-etienate	26	182°	+506	
(b) Methyl 3-oxo-19-hydroxy-14β,17α-Δ^4-etienate (XII)	24	191–192°	+478	+28
12. (a) Ethyl 3-oxo-19-hydroxy-Δ^4-etienate	27	182–185°	+495	
(b) Ethyl 3-oxo-19-hydroxy-14β,17α-Δ^4-etienate (XIII)	24	161.5–162°	+465	+30
13. (a) 3-Oxo-19-acetoxy-Δ^4-etienic acid	25	193–194°	+749	
(b) 3-Oxo-19-acetoxy-14β,17α-Δ^4-etienic acid (XIV)	24	196–197°	+749	0
14. (a) Ethyl 3-oxo-19-acetoxy-Δ^4-etienate	27	amorphous	+641	
(b) Ethyl 3-oxo-19-acetoxy-14β,17α-Δ^4-etienate (XVI)	24	116.5–117°	+737	−96
15. (a) 19-Hydroxyprogesterone	4	171–172°	+611	+243
(b) 19-Hydroxy-14β,17α-progesterone (XIX)	24	187–188°	+368*	
16. (a) 19-Hydroxy-11-desoxycorticosterone	4	163–165°	+640*	
(b) 19-Hydroxy-11-desoxy-14β,17α-corticosterone (XXI)	24	209–211°	+364	+276
17. (a) 19-Hydroxy-11-desoxycorticosterone 21-monoacetate	4	197–199°	+692	
(b) 19-Hydroxy-11-desoxy-14β,17α-corticosterone 21-monoacetate (XX)	24	172–173°	+401*	+291

(24) This paper.

(25) Herzig and Ehrenstein, *J. Org. Chem.*, **17**, 713 (1952).

(26) In discussing the rotatory contribution for the introduction of the 19-hydroxyl group in Δ^4-3-keto steroids, A. S. Meyer [*Experientia*, **11**, 99 (1955); *cf.* p. 101] pointed out that 3-oxo-19-hydroxy-Δ^4-etienic acid and its methyl ester [*cf.* ref. 25, pp. 719, 720] show an irregular behavior. On the assumption that in these instances an erroneous recording of the length of the polarimeter tube had occurred, we recalculated the figures on the basis of a 1.5 dm. (rather than the recorded 2 dm.) tube, inasmuch as a tube of such length was in use in our laboratory at that time. With the revised figures there is no more discrepancy. In order to prove this point, Dr. G. Winston Barber has azomethane yielding the non-crystalline 19-acetoxy-21-diazo-14β,17α-progesterone (XVII). By saponification with aqueous methanolic potassium carbonate, XVII was converted into the crystalline 19-hydroxy-21-diazo-14β,17α-progesterone (XVIII). By reacting XVIII with concentrated hydriodic acid,[14] 19-hydroxy-14β,17α-progesterone (XIX) resulted. On the other hand, heating of XVIII with acetic acid gave 19-hydroxy-11-desoxy-14β,17α-corticosterone 21-monoacetate (XX) which, by saponification with aqueous methanolic potassium bicarbonate, was converted into 19-hydroxy-11-desoxy-14β,17α-corticosterone (XXI). This product was possibly not quite pure.

It has been pointed out,[4] that, in the normal series, there is a hypsochromic shift in the ultraviolet absorption of the Δ^4-3-keto grouping on acetylation of the 19-hydroxyl group. The identical situation exists in the 14β,17α-series in that the compounds with a free 19-hydroxyl group (XI, XII, XIII, XVIII, XIX, XX, XXI) have the absorption maximum at 243 mμ, whereas in the 19-acetoxy compounds (XIV, XV, XVI) it is shifted to 239 mμ.

The assumptions made concerning the stereochemical configurations of the discussed compounds, especially regarding the asymmetric centers 14 and 17, are fully supported by an analysis of the molecular rotations.[15] Some previously established relationships are illustrated by the examples of Table I. Esters of etio acids as well as 20-keto compounds are considered. Transition from the $C_{17}\beta$- to the $C_{17}\alpha$-configuration produces a levorotatory effect (pairs 1–8) which is particularly exalted in the 20-keto compounds of this series (pairs 4–8).[16] On the other hand, inversion of the $C_{14}\alpha$ to the $C_{14}\beta$-configuration involves a dextrorotatory shift (pairs 9–15) which appears most pronounced in the 20-keto compounds (pairs 12–15). With an inversion of the natural configurations, both in positions 14 and 17, the individual effects upon the rotation compensate each other to the extent that in the listed 14β,17α-steroids (pairs 16–22) a moderate levorotatory shift is apparent. Also here the effect is more pronounced with the 20-keto compounds (pairs 19–22) than with the esters of the etio acids (pairs 16–18).

In Table II there are presented, for comparison of the molecular rotations, the available pairs of stereoisomers of the 19-hydroxy steroids prepared in this laboratory. The stereochemical configurations of the compounds listed under (a) can be considered established.[22] The first three pairs represent epimers differing only in the configuration at C_{17}. In the series of the saturated etio acids and their esters (pairs 4–14), the order of magnitude of the rotational differences is in agreement with the pairs 16 to 18 of Table I. In a like fashion, there is very good agreement between the 20-keto compounds of the 19-hydroxy series (Table II, pairs 15–17) and the analogous pairs of compounds of Table I (in particular 21 and 22). It is noted that in the pairs 9 and 14 of Table II the M_D increment deviates, although not decisively, from the other values. In these instances the possibility of errors in the determination of the optical rotation has to be considered.[28] Generally, the increments of the molecular rotations indicate that the compounds described in the present paper (Table II, b-series) actually possess the assigned configurations.

19-Hydroxy-14β,17α-progesterone (XIX) was examined for progestational activity by Dr. Roy Hertz of the National Cancer Institute. The Clauberg test was negative in each of two rabbits with a total dose of 2.5 mg. In this assay a maximal effect is obtained with 0.25 mg. of progesterone.

EXPERIMENTAL

Melting points. The m.p.'s were determined with the Fisher-Jones melting point apparatus and are uncorrected.

Absorption spectra. Ultraviolet spectra were determined in 95% ethanol with a Beckman Model DU spectrophotometer. The infrared studies pertaining to this paper were carried out on a Perkin-Elmer Model 21 double beam spectrometer in the Division of Steroid Metabolism of the Sloan-Kettering Institute for Cancer Research through the courtesy of Dr. Thomas F. Gallagher. The interpretation was done by Friederike Herling. The correlations are based upon those summarized in the publication of Jones and Herling.[29] Only those bands are mentioned which appear to have a direct bearing upon the structure of the particular compound. Details of other correlations between spectrum and structure will be summarized at a later time by the group at the Sloan-Kettering Institute.

Analyses. Unless stated otherwise, the microanalyses were performed by Dr. E. W. D. Huffman, Wheatridge, Colorado, on samples which were dried to constant weight *in vacuo* (P_2O_5; 80°) according to Milner and Sherman.[30] The percentage loss of weight on drying and gain of weight on exposure of the sample to the atmosphere are recorded.

Optical rotations. No corrections for crystal solvent have been made. Unless stated otherwise, the sample was dissolved in chloroform to make 2 cc. of solution and the rotation was determined in a 2-dm. semi-micro tube.

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prepared fresh supplies of the two compounds and has determined their optical rotations. The result confirms the explanation given above. Summary of findings: 3-Oxo-19-hydroxy-Δ^4-etienic acid. Previously reported (ref. 25): m.p. 228–230°; $[\alpha]_D^{23}$ +107°, corrected for tube length: $[\alpha]_D^{23}$ +142°. Redetermination by G. W. Barber: m.p. 236–237°; $[\alpha]_D^{22}$ +146° ± 2° (61.63 mg. in 10.0 cc. of chloroform containing 5 drops of ethanol; l, 2 dm.; α +1.80°). M_D^{22} +485° ± 5°. Laboratory records showed that on analyzing the original sample (ref. 25), a substantial amount of crystal solvent (7.61%) was found. In applying the appropriate correction to the molecular rotation, one obtains the value M_D^{22} +525° ± 5°.

Methyl 3-oxo-19-hydroxy-Δ^4-etienate. Previously reported (ref. 25): m.p. 176–177°; $[\alpha]_D^{23}$ +111°, corrected for tube length: $[\alpha]_D^{23}$ +147°. Redetermination by G. W. Barber: m.p. 182°; $[\alpha]_D^{22}$ +146° ± 2° (53.18 mg. in 10.0 cc. of chloroform; l, 2 dm.; α +1.55°). M_D^{22} +506° ± 6°.

(27) Ehrenstein, Barber, and Gordon, *J. Org. Chem.*, **16**, 349 (1951).

(28) Dr. G. Winston Barber kindly prepared fresh supplies of two additional compounds of this series and redetermined the optical rotations. Summary of findings: 3-oxo-19-acetoxy-Δ^4-etienic acid. Previously reported (ref. 25): m.p. 193–194°; $[\alpha]_D^{27}$ +193° ± 3°; M_D^{27} +749°. Redetermined: m.p. 195°; $[\alpha]_D^{21}$ +196° ± 2° (13.28 mg. in 2.0 cc. of chloroform; l, 2 dm.; α +2.60°); M_D^{21} +733° ± 6°. The figures are in good agreement. Ethyl 3-oxo-19-acetoxy-Δ^4-etienate. Previously reported (ref. 27): amorphous; $[\alpha]_D^{25}$ +159.2°; M_D^{25} +641°. Redetermined (substance prepared by treatment of the foregoing acid with diazoethane): resinous center fraction from chromatogram; $[\alpha]_D^{21}$ +176° ± 2° (12.47 mg. in 2.0 cc. of chloroform; l, 2 dm.; α +2.20°); M_D^{21} +710° ± 7°. On the basis of the latter value, the figure for ΔM_D(a − b), Table II, pair 14, becomes −27°. This is in better agreement with the expectations.

(29) Jones and Herling, *J. Org. Chem.*, **19**, 1252 (1954).

(30) Miner and Sherman, *Ind. Eng. Chem., Anal. Ed.*, **8**, 427 (1936).

Chromatography. The alumina used as adsorbent for chromatography has been described.[4] Unless stated otherwise, activity III was used.

Ethyl 3β,5,19-trihydroxy-17α-Δ¹⁴-etienate (III). *A. From ethyl 3β,5,14,19-tetrahydroxy-14β,17α-etianate* (IIa).[31] A solution of 200 mg. of IIa,[10] m.p. 219–222°, in 25 cc. of 0.1 *N* absolute ethanolic hydrogen chloride was refluxed on the steam-bath for one hour and then was distilled at atmospheric pressure for 1½ hours, thereby reducing the volume to 5 cc. After evaporating to dryness *in vacuo* and triturating the hydrogen chloride-free white brittle foam with ether, crystals separated. Repeated recrystallization from methanol-water and acetone-petroleum ether gave 23.9 mg. of unchanged IIa, m.p. 209–212°; no depression of m.p. with authentic sample; no color with tetranitromethane. The combined material obtained from the mother liquors was chromatographed on 20 g. of alumina (activity II, 22 × 65 mm.). Elution by chloroform-methanol combinations gave, in the order of polarity 86.4 mg. of crude III (*v. infra*) and 38.4 mg. of crude starting material (after recrystallization: 25.2 mg.; m.p. 212–217°; identified by mixture m.p. determination). Recrystallization of the crude ethyl 3β,5,19-trihydroxy-17α-Δ¹⁴-etienate (III) (86.4 mg.; 45.3%) from acetone-petroleum ether gave 51.6 mg. (27.0%) of clusters of needles, m.p. 126–132°. The analytical sample, bundles of colorless rods, m.p. 129–130°, was obtained by recrystallization from methanol-water; positive test with tetranitromethane. $[\alpha]_D^{30}$ +106° (12.21 mg.; α +1.29° ± 0.02°).

Anal. Calc'd for $C_{22}H_{34}O_5$ (378.49): C, 69.81; H, 9.05. Found: C, 69.80; H, 8.92.

Under slightly more vigorous conditions (846 mg. of IIa in 100 cc. of 0.1 *N* absolute ethanolic hydrogen chloride; refluxing for 3 hours; distilling during 2 hours to volume of 5 cc.) the yield of crude III was approximately the same. In addition, some more polar (starting material, IIa ?) and a fair amount of less polar material resulted. The latter may represent a polyene.

B. From 3β,5,14,19-tetrahydroxy-14β,17α-etianic acid (II). A solution of 1.45 g. of II, m.p. 261–262°, in 150 cc. of 0.1 *N* absolute ethanolic hydrogen chloride was concentrated by slow distillation at atmospheric pressure to ¼ of its original volume within a period of 5 hours. After the addition of an equal amount of water, the alcohol was removed by distilling *in vacuo* and the reaction mixture was then extracted with ethyl acetate. The acidic material was removed from the extract by shaking with a solution of 5% sodium carbonate and was isolated from the latter phase by acidification and subsequent extracting with ethyl acetate. Yield: neutral, 1.155 g.; acid, 0.255 g. In another experiment 2.45 g. of II, dissolved in 250 cc. of 0.1 *N* absolute ethanolic hydrogen chloride, was treated as described above. Yield: neutral, 2.150 g.; acid, 0.280 g.

The combined neutral material of both experiments, *i.e.* 3.305 g. resulting from 3.90 g. of II, was chromatographed over 63 g. of alumina (diam. of column: 1.8 cm.). The eluants used in this chromatogram contained 0.5% of water. Elution scheme: Benzene-ether, 3:1 (250 cc.) gave 0.998 g. of yellow resin; benzene-ether, 1:1 (250 cc.) and ether (1000 cc.) yielded 1.934 g. of crystalline material, m.p. 129–131°, representing crude ethyl 3β,5,19-trihydroxy-17α-Δ¹⁴-etienate (III) (yield: 48.3%); ether-methanol, 50:1 (150 cc.) gave 0.298 g. of yellow resin. Recrystallization of the crude III (1.934 g.) from acetone-hexane furnished 1.425 g. of the pure compound; white needles, m.p. 131–132° (yield: 35.6%); yellow color with tetranitromethane; no depression of m.p. when mixed with authentic sample of III described under *A*.

In another set of experiments, 3.31 g. and 3.65 g. of II, m.p. 260–262° (total: 6.96 g.), each dissolved in 350 cc. of 0.1 *N* absolute ethanolic hydrogen chloride, were separately subjected to the reaction described above. Weight of the resulting neutral material: 2.85 g. and 3.30 g. respectively (total: 6.15 g.); weight of the acid material: 0.35 g. and 0.38 g. respectively (total: 0.73 g.). Upon chromatography, the combined neutral material furnished 3.84 g. of crude crystalline III (yield: 53.7%), which upon recrystallization gave 3.05 g. of the pure compound, m.p. 127–129° (yield: 42.7%).

Ethyl 3β,5,19-trihydroxy-14β,17α-etianate (V) *by hydrogenation of ethyl 3β,5,19-trihydroxy-17α-Δ¹⁴-etienate* (III). The shaking of a solution of 1.40 g. of pure III, m.p. 131–132°, in 30 cc. of glacial acetic acid with 100 mg. of platinum oxide in an atmosphere of hydrogen for a period of two hours (room temperature; atmospheric pressure) resulted in the uptake of one equivalent of hydrogen. After filtering from the platinum, the solvent was removed *in vacuo*. The residue was repeatedly dissolved in a small volume of absolute ethanol and was taken to dryness in order to remove the last traces of acetic acid. One recrystallization from methanol-water gave 1.275 g. of ethyl 3β,5,19-trihydroxy-14β,17α-etianate (V) (yield: 90.6%); m.p. 153.5°. The analytical sample was repeatedly recrystallized from ether and from methanol-water; colorless plates; m.p. 155°. $[\alpha]_D^{23}$ +54.5° (14.68 mg.; α +0.80°).

Anal. Calc'd for $C_{22}H_{36}O_5$ (380.51): C, 69.44; H, 9.54. Found: C, 69.36; H, 9.46. Weight loss, 0.26; weight gain, 0.

In another experiment, the material contained in the mother liquors resulting from the recrystallization of the crude III (*cf.* preceding expt.; sect. *B*) was subjected to catalytic hydrogenation. The product obtained from the reduction of 1.35 g. of such mother-liquor material was chromatographed over 50 g. of alumina (diam. of column: 3.9 cm.). Elution scheme: (1) Benzene (700 cc.) yielded 0.38 g. of crystalline material, m.p. 100–170°; (2) ether (200 cc.), ether-chloroform, 1:1 (100 cc.), and chloroform (200 cc.) eluted 0.75 g. of uniform material, m.p. 140–148°, representing impure V (after 2 recrystallizations: 0.33 g.; m.p. 152–154°); (3) chloroform-methanol, 50:1 (300 cc.), yielded 0.21 g. of yellowish resin. The benzene eluates (0.38 g.) were rechromatographed over 12 g. of alumina (diam. of column: 1.2 cm.). Ether-methanol, 100:1 (150 cc.), eluted 0.19 g. of crystalline material, m.p. range 175–203° (*v. infra*). Ether methanol, 25:1 (150 cc.) eluted 0.11 g. of a crystalline product, m.p. range 140–146°; after recrystallization, m.p. 150–153°; identified as V by mixture m.p.

Ethyl 3β,5-dihydroxy-8,19-epoxy-14β,17α-etianate (IV) (?). The material eluted with ether-methanol, 100:1, m.p. range 175–203° (*v. supra*) was repeatedly recrystallized from methanol-water. This furnished white needles of constant m.p. 211–213°. When mixed with an authentic sample of ethyl 3β,5-dihydroxy-8,19-epoxyetianate (m.p. 214–215°),[11] the melting point was depressed (195–201°). $[\alpha]_D^{22}$ +59° (4.15 mg.; α +0.24°).

The infrared spectrum of IV was determined in chloroform solution. Because of the small amount of material at hand only a weak spectrum could be obtained. It shows O—H stretching bands at 3605 and at about 3500 cm.$^{-1}$. There is a weak carbonyl absorption at 1720 cm.$^{-1}$ which suggests the presence of the ethyl ester group. The fingerprint region shows a weak spectrum which differs from that of ethyl 3β,5-dihydroxy-8,19-epoxyetianate.[32]

Anal. Calc'd for $C_{22}H_{34}O_5$ (378.49): C, 69.81; H, 9.05. Found: C, 69.84; H, 9.33. Weight loss, 1.29.

Ethyl 3β,19-diacetoxy-5-hydroxy-14β,17α-etianate (VI). To

(31) These are orienting experiments carried out by Dr. G. Winston Barber.

(32) The infrared spectrum of ethyl 3β,5-dihydroxy-8,19-epoxyetianate was determined in chloroform solution. The spectrum shows O—H stretching bands at 3610 and at 3470 cm.$^{-1}$ Carbonyl absorption at 1722 cm.$^{-1}$ is due to C=O stretching vibration of the ethyl ester group. The fingerprint region is identical with that of another sample of this compound examined at the Sloan-Kettering Institute in June 1950.

19 mg. of ethyl 3β,5,19-trihydroxy-14β,17α-etianate (V), m.p. 151–153°, in 0.5 cc. of pyridine there was added 1 cc. of acetic anhydride. The mixture was allowed to stand overnight, and then was poured onto ice. Working up as usual gave 22.5 mg. of resin which refused to crystallize. Chromatography over 600 mg. of alumina and elution with benzene yielded 17 mg. of crystalline material; repeated recrystallization from methanol-water furnished needles, m.p. 139.5–140.5°. $[\alpha]_D^{23}$ +37° (10.77 mg.; α +0.40°).

Anal. Calc'd for $C_{26}H_{40}O_7$ (464.58): C, 67.21; H, 8.68. Found: C, 67.01; H, 8.62. Residue, 0.13.

3β,5,19-Trihydroxy-14β,17α-etianic acid (VII). A solution of 1.175 g. of ethyl 3β,5,19-trihydroxy-14β,17α-etianate (V) in 100 cc. of 2 *N* ethanolic potassium hydroxide was refluxed for one hour. After adding 100 cc. of water, the ethanol was evaporated *in vacuo*. The aqueous solution was extracted with three 150-cc. portions of ethyl acetate, yielding 0.047 g. of neutral material. The aqueous phase was made acidic to Congo Red by the addition of 10% sulfuric acid and then was extracted with three 250-cc. portions of ethyl acetate, furnishing 1.065 g. of acid material. Recrystallization from methanol-water gave 0.919 g. of crystals, m.p. 180–181° (yield: 84.4%; The yields in two analogous experiments were 76.6% and 78.8%. The m.p. of the analytical sample was 184.5–185°. $[\alpha]_D^{22}$ +62° (16.1 mg.; α +1.00°).

Anal. Calc'd for $C_{20}H_{32}O_5$ (352.50): C, 68.15; H, 9.15. Found: C, 68.13; H, 9.25. Residue, 0.14. Weight loss, 3.70; weight gain, 1.92.

Methyl 3β,5,19-trihydroxy-14β,17α-etianate (VIII). To 20 mg. of 3β,5,19-trihydroxy-14β,17α-etianic acid (VII), m.p. 183.5–184°, in 2 cc. of methanol was added a slight excess of ethereal diazomethane. After 15 minutes' standing, the working up of the solution furnished a product which, after repeated recrystallization from acetone-hexane, gave 15 mg. of colorless needles, m.p. 184–186°. $[\alpha]_D^{24}$ +54° (12.9 mg.; α +0.70°).

Anal. Calc'd for $C_{21}H_{34}O_5$ (366.48): C, 68.83; H, 9.35. Found: C, 68.96; H, 9.30. Residue, 0.23.

3β,19-Diacetoxy-5-hydroxy-14β,17α-etianic acid (IX). A solution of 21 mg. of 3β,5,19-trihydroxy-14β,17α-etianic acid (VII), m.p. 183.5–184°, in 1 cc. of pyridine and 1 cc. of acetic anhydride was allowed to stand overnight. The addition of 20 cc. of *N* hydrochloric acid produced a turbid solution from which colorless needles, m.p. 192–193°, separated. Repeated recrystallization from acetone-water yielded 16 mg. of fine needles, m.p. 197–197.5°. $[\alpha]_D^{24}$ +55° (13.1 mg.; α +0.72°).

Anal. Calc'd for $C_{24}H_{36}O_7$ (436.53): C, 66.03; H, 8.31. Found: C, 66.07; H, 8.41. Residue, 0.18.

3-Oxo-5,19-dihydroxy-14β,17α-etianic acid (X). To 55 mg. of 3β,5,19-trihydroxy-14β,17α-etianic acid (VII), m.p. 180–181°, in 1.5 cc. of *tert*-butyl alcohol, was added 35 mg. (1.6 equivalents) of N-bromoacetamide (recryst. before use; m.p. 108°) and 0.25 cc. of water. After keeping the mixture at room temperature for 16 hours, 20 cc. of water was added causing, within a few minutes, the separation of needles; 42.8 mg.; m.p. 143–146° (yield: 78.3%). In analogous experiments with 300 mg. and 560 mg. of VII, the yields of X were 76.5% and 67.4% respectively. Extraction of the aqueous filtrate, after the addition of sodium sulfite, with ethyl acetate furnished additional, though small amounts of rather impure X. Repeated recrystallization from methanol-water yielded stellate clusters of needles, m.p. 146–148° (decomp. above 160°); no ultraviolet absorption maximum in the range 220–300 mμ; $[\alpha]_D^{22}$ +66° (12.10 mg. in 2 cc. of absol. ethanol; α +0.80°).

Anal. Calc'd for $C_{20}H_{30}O_5$ (350.44): C, 68.54; H, 8.63. Found: C, 68.41; H, 8.61. Weight loss, 4.99; weight gain, 1.43.

3-Oxo-19-hydroxy-14β,17α-Δ⁴-etienic acid (XI). *A. By dehydration of 3-oxo-5,19-dihydroxy-14β,17α-etianic acid* (X). A total of 488 mg. of crude X, m.p. range 136–142°, was dissolved in 15 cc. of absol. ethanol and, after the addition of 750 mg. of Girard's Reagent T and 0.5 cc. of glacial acetic acid, the mixture was refluxed for 1 hour. After reaching room temperature, it was poured into ice-water and the aqueous solution extracted with ethyl acetate. The extract yielded 59 mg. of non-ketonic material. The aqueous phase was acidified to Congo Red with *N* hydrochloric acid, and after standing for ½ hour at room temperature, was extracted with ethyl acetate. Evaporation of the solvent yielded 411 mg. of ketonic material which gave from acetone-hexane 335 mg. of 3-oxo-19-hydroxy-14β,17α-Δ⁴-etienic acid (XI), m.p. 214–215° (Yield: 72.4%). The analytical sample was recrystallized from acetone-hexane and methanol-water; m.p. 216.5–217°. $[\alpha]_D^{22}$ +167° (11.90 mg. in 2 cc. of chloroform containing 2 drops of ethanol; α +1.99°). λ_{max}^{alc} 243 mμ; ε 19,300.

Anal. Calc'd for $C_{20}H_{28}O_4$ (332.42): C, 72.26; H, 8.49. Found: C, 72.09; H, 8.40. Residue, 0.25.

B. Directly from 3β,5,19-trihydroxy-14β,17α-etianic acid (VII). A mixture of 2.28 g. of VII, m.p. 180–181°, in 40 cc. of *tert*-butyl alcohol, 8 cc. of water, and 1.60 g. of N-bromoacetamide was kept at room temperature overnight. After the addition of 20 cc. of water and 0.20 g. of sodium sulfite, the reaction product was isolated by extracting with ethyl acetate; 2.26 g. of brittle foam. This was dissolved in 60 cc. of absol. ethanol and, after the addition of 3.2 g. of Girard's Reagent T and 2 cc. of glacial acetic acid, the solution was treated as under *A*. Non-ketonic fraction: 0.35 g.; ketonic fraction: 1.75 g. The ketonic part was crystallized from acetone-water; first crop: 1.16 g., m.p. 214.5–216°, representing pure XI. Over-all yield (from VII): 54.0%.

Methyl 3-oxo-19-hydroxy-14β,17α-Δ⁴-etienate (XII). To 18 mg. of 3-oxo-19-hydroxy-14β,17α-Δ⁴-etienic acid (XI), m.p. 214.5–216°, in 2 cc. of methanol was added an excess of ethereal diazomethane. Working up as usual; neutral material: 16 mg., m.p. 189–190°. Repeated recrystallization from acetone-water gave colorless needles, m.p. 191–192°. $[\alpha]_D^{24}$ +138° (12.25 mg.; α +1.69°). λ_{max}^{alc} 243 mμ; ε 16,300.

Anal. Calc'd for $C_{21}H_{30}O_4$ (346.45): C, 72.80; H, 8.73. Found: C, 72.79; H, 8.77. Residue, 0.1.

Ethyl 3-oxo-19-hydroxy-14β,17α-Δ⁴-etienate (XIII). To 17 mg. of 3-oxo-19-hydroxy-14β,17α-Δ⁴-etienic acid (XI), m.p. 214.5–216°, in 2 cc. of absol. ethanol was added an excess of an ethereal solution of diazoethane.[33] Working up as usual the neutral fraction (17 mg.) was recrystallized from acetone-hexane; white needles, m.p. 161.5–162° $[\alpha]_D^{24}$ +129° (12.0 mg.; α +1.55°). λ_{max}^{alc} 243 mμ; ε 19,100.

Anal. Calc'd for $C_{22}H_{32}O_4$ (360.48): C, 73.70; H, 8.95. Found: C, 73.12; H, 8.86. Residue, 0.1.

3-Oxo-19-acetoxy-14β,17α-Δ⁴-etienic acid (XIV). A solution of 1.110 g. of 3-oxo-19-hydroxy-14β,17α-Δ⁴-etienic acid (XI), m.p 214.5–216°, in 10 cc. of pyridine and 6 cc. of acetic anhydride was kept at room temperature overnight. The addition of 120 cc. of *N* hydrochloric acid produced a turbid solution from which white needles began to separate after about five minutes. Finally, the crystalline compound was filtered and washed with water; 1.120 g.; m.p. 196–197° (yield: 89.6%). The analytical sample was recrystallized from acetone-hexane; m.p. 198–199°. $[\alpha]_D^{22}$ +200° (10.40 mg.; α +2.08°). λ_{max}^{alc} 239 mμ; ε 15,100.

Anal. Calc'd for $C_{22}H_{30}O_5$ (374.46): C, 70.56; H, 8.08. Found: C, 70.44; H, 8.04.

Methyl 3-oxo-19-acetoxy-14β,17α-Δ⁴-etienate (XV). A solution of 20 mg. of 3-oxo-19-acetoxy-14β,17α-Δ⁴-etienic acid (XIV), m.p. 196–197°, in 2 cc. of methanol was treated with ethereal diazomethane. The resulting neutral product (20 mg.) was difficult to crystallize. Finally, crystals were obtained by dissolving the material in 2 cc. of methanol, adding 3 drops of water, and slowly concentrating *in vacuo*. After a few minutes a crystal was formed on the wall. The subsequent addition of 2 cc. of water produced a turbid solution from which long needles separated overnight.

(33) Prepared from ethylnitrosourea according to the *Organic Syntheses* directions for diazomethane. Blatt, *Org. Syntheses*, Coll. Vol. 2, 165, 461 (1943).

Repeated recrystallization gave the analytical sample, m.p. 78.5–79°. $[\alpha]_D^{24}$ +179° (9.93 mg.; α +1.77°). λ_{max}^{alc} 239 mμ; ϵ 16,900.

Anal. Calc'd for $C_{23}H_{32}O_5$ (388.49): C, 71.10; H, 8.30. Found: C, 70.85; H, 8.20. (Dried at 50°.)

Ethyl 3-oxo-19-acetoxy-14β,17α-Δ⁴-etienate (XVI). To 19 mg. of 3-oxo-19-acetoxy-14β,17α-Δ⁴-etienic acid (XIV), m.p. 196–197°, in 2 cc. of absol. ethanol was added a slight excess of ethereal diazoethane.[33] Working up as usual gave 19.5 mg. of neutral product. Crystalline material was obtained by applying the technique used in crystallizing the methyl ester (preceding expt.). Recrystallization from acetone-water gave colorless needles, m.p. 116.5–117°. $[\alpha]_D^{24}$ +183° (9.61 mg.; α +1.76°). λ_{max}^{alc} 239 mμ; ϵ 18,100.

Anal. Calc'd for $C_{24}H_{34}O_5$ (402.51): C, 71.61; H, 8.51. Found: C, 71.51; H, 8.46. (Dried at 70°.)

19-Acetoxy-21-diazo-14β,17α-progesterone (XVII) *and 19-hydroxy-21-diazo-14β,17α-progesterone* (XVIII). To 360 mg. of 3-oxo-19-acetoxy-14β,17α-Δ⁴-etienic acid (XIV), m.p. 196–197°, suspended in 14.4 cc. of dry benzene (distilled over sodium before use), was added 1.5 cc. of oxalyl chloride at 0°. The mixture was kept at room temperature for 1 hour, and the clear solution then was evaporated to complete dryness *in vacuo*. The resinous residue was dissolved in 14.4 cc. of dry benzene and the solution was added to ethereal diazomethane (prepared from 6.3 g. of nitrosomethylurea; successively dried over potassium hydroxide and sodium) at −10°. The mixture was allowed to stand at room temperature for ½ hour and then was evaporated to dryness *in vacuo*. The residue (approx. 390 mg.) was chromatographed over 11 g. of alumina (diam. of column: 1.2 cm.). Elution with benzene gave a single peak of yellow resinous material which did not crystallize; wt. 331 mg.; representing crude 19-acetoxy-21-diazo-14β,17α-progesterone (XVII).

To a solution of this product in 60 cc. of methanol (saturated with N_2) was added 25 cc. of *N* potassium carbonate[34] (saturated with N_2). The mixture then was kept under an atmosphere of nitrogen at room temperature for 17 hours. After the addition of 20 cc. of water, the methanol was taken off *in vacuo* at room temperature. The remaining aqueous phase was extracted with methylene chloride-ether, 1:2. After washing with water and drying over sodium sulfate, evaporation of the solvent furnished 291 mg. of a resinous residue. This was chromatographed over 10 g. of alumina (diam. of column: 1.2 cm.). Elution with ether-methanol, 100:1 (1000 cc.) yielded a total of 212 mg. of crystalline fractions, m.p. range 136–137°, representing 19-hydroxy-21-diazo-14β,17α-progesterone (XVIII) (Yield, from XIV: 61.9%. In preliminary, orienting, experiments with 200 mg. and 400 mg. of XIV, the yields were 48.9% and 42.0% respectively). Recrystallization from methylene chloride-hexane gave 176 mg. of yellowish needles m.p. 141–142°; m.p. of analytical sample, obtained after further recrystallizations, 142–144° (effervescence). Recrystallization of the pure compound sometimes gave a product, m.p. range 158–161° which upon additional recrystallization reverted to the lower m.p. $[\alpha]_D^{27}$ +115° (11.0 mg.; α +1.26°). λ_{max}^{alc} 243 mμ; ϵ 14,800.

Anal. Calc'd for $C_{21}H_{28}N_2O_3$ (365.45): C, 70.76; H, 7.92. Found: C, 71.02; H, 7.86. Weight loss, 0.56.

19-Hydroxy-14β,17α-progesterone (XIX). A solution of 21.5 mg. of 19-hydroxy-21-diazo-14β,17α-progesterone (XVIII), m.p. 139–141°, in 10 cc. of chloroform was shaken with 1 cc. of 48% hydriodic acid (Baker's Analyzed Reagent) for 2 minutes. The chloroform layer then was successively shaken with concentrated aqueous potassium iodide, water, *N* aqueous sodium thiosulfate, and water. After drying, evaporation of the solvent left 20 mg. of yellowish resin which crystallized from methylene chloride-hexane; 15.5 mg.; m.p. 182–185° (Yield: 79.7%). In two analogous expts. the yields were 72.3% and 99.2%). Repeated recrystallization from methanol-water gave the analytical sample; white shining plates; m.p. 187–188°. $[\alpha]_D^{22}$ +111° (10.30 mg.; α +1.14°). λ_{max}^{alc} 243 mμ; ϵ 18,100.

The infrared spectrum of XIX[35] was determined in chloroform solution. It shows hydroxyl absorption at 3620 cm.$^{-1}$ and weak associated hydroxyl absorption at 3500–3380 cm.$^{-1}$. Carbonyl absorption at 1701 cm.$^{-1}$ is due to the 20-ketone group. Bands at 1665 and 1619 cm.$^{-1}$ are due to the presence of the Δ⁴-3-ketone system. The fingerprint region differs from the spectrum of 19-hydroxyprogesterone.[4]

Anal. Calc'd for $C_{21}H_{30}O_3$ (330.45): C, 76.32; H, 9.15. Found: C, 76.06; H, 9.02. Weight loss, 0.21.

19-Hydroxy-11-desoxy-14β,17α-corticosterone 21-monoacetate (XX). To 95 mg. of 19-hydroxy-21-diazo-14β,17α-progesterone (XVIII), m.p. 140–141°, was added 10 cc. of glacial acetic acid. The solution was heated on the steam-bath for 20 minutes and then was evaporated to dryness *in vacuo*. The yellowish residue resisted all attempts at crystallization. Chromatography over 6 g. of alumina (diam. of column: 1.2 cm.) and elution with ether-methanol, 250:1 (700 cc.) gave 70 mg. of colorless crystalline fractions; m.p. 166–167°; representing fairly pure XX (Yield: 69.3%). The analytical sample was recrystallized from acetone-water and methylene chloride-hexane; colorless needles; m.p. 172–173°. $[\alpha]_D^{27}$ +103° (10.65 mg.; α +1.10°). λ_{max}^{alc} 243 mμ; ϵ 17,600.

The infrared spectrum of XX[35] was determined in chloroform solution. It shows hydroxyl absorption at 3620 cm.$^{-1}$ and weak associated hydroxyl absorption at 3480–3420 cm.$^{-1}$. Carbonyl bands at 1749 and 1725 cm.$^{-1}$ are evidence for the presence of the 21-acetoxy-20-ketone group. Bands at 1665 and 1619 cm.$^{-1}$ are due to the Δ⁴-3-ketone system. The fingerprint region is different from that of 19-hydroxy-11-desoxycorticosterone 21-monoacetate.[36]

Anal. Calc'd for $C_{23}H_{32}O_5$ (388.49): C, 71.10; H, 8.30. Found: C, 71.07; H, 8.32. Residue, 0.36; weight loss, 0.19.

19-Hydroxy-11-desoxy-14β,17α-corticosterone (XXI). To 25 mg. of 19-hydroxy-11-desoxy-14β,17α-corticosterone 21-monoacetate (XX), m.p. 171–172°, in 5 cc. of methanol was added 5 cc. of *N* aqueous potassium bicarbonate. The mixture was kept under an atmosphere of nitrogen at room temperature for 17 hours and, after subsequently adding 10 cc. of water, was extracted with methylene chloride-ether, 1:2. The extract was washed to neutrality, dried, and evaporated to dryness *in vacuo*. The yellowish resinous residue, 22 mg., crystallized on spraying it with hexane; needles; m.p. 200–202°. The product was decolorized by dissolving it in 5 cc. of methylene chloride and shaking the solution with Norit. After filtering, the colorless solution was evaporated to dryness and the residue was recrystallized three times from acetone-hexane; 10 mg. of shiny needles; m.p. 206–207°. $[\alpha]_D^{22}$ +105° (7.45 mg.; α +0.78°). λ_{max}^{alc} 243 mμ; ϵ 18,300. In another experiment the crude reaction product was purified by chromatography (alumina; elution with ether-methanol, 100:1). The chromatographed product was recrystallized from methylene chloride-hexane yielding colorless shiny plates, m.p. 209–211°. Analyses were performed with the reaction product of both runs.

Anal. Calc'd for $C_{21}H_{30}O_4$ (346.45): C, 72.80; H, 8.73. Found: C, 72.09, 72.15; H, 8.87, 8.56. Residue, 0.3, 0.

PHILADELPHIA 4, PENNA.

(34) In orienting experiments hydrolysis by potassium bicarbonate was attempted at room temperature and under reflux. A mixture of XVIII and unchanged XVII resulted.

(35) The fingerprint region is different from any spectrum in the collection of the Sloan-Kettering Institute.

(36) The infrared spectrum of 19-hydroxy-11-desoxy-corticosterone 21-monoacetate (references 4, 35) was determined in chloroform solution. It shows hydroxyl absorption at 3620 cm.$^{-1}$ and weak associated hydroxyl absorption at 3500–3420 cm.$^{-1}$ Carbonyl bands at 1748 and 1725 cm.$^{-1}$ are evidence for the presence of the 21-acetoxy-20-ketone group. Bands at 1664 and 1618 cm.$^{-1}$ are due to the Δ⁴-3-ketone system.