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

INVESTIGATIONS ON STEROIDS. XXIV. 19-HYDROXY-11-DESOXY-CORTICOSTERONE AND 19-HYDROXYPROGESTERONE*[1]

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The conversion of the readily available cardiac aglycone strophanthidin into analogs of steroid hormones having oxygen at position 19 has been one of the objectives of work being performed in this laboratory (*cf. e.g.* 2, 3). The inspection of models reveals that the location of a 19-hydroxyl group relative to the steroid nucleus can be very nearly the same as that of an 11β-hydroxyl group. It was therefore of some interest to determine whether such a compound as 19-hydroxy-11-desoxycorticosterone (IX) would possess physiological activity similar to that of the 11β-hydroxy analog, corticosterone. Additional impetus was given to this work by the suggestion, in the early reports of the isolation from adrenal extracts of "electrocortin," that this new crystalline hormone might be an isomer of corticosterone (4, 5).

The synthesis of 19-acetoxy-3-oxo-Δ^4-etienic acid (I) by degradation of strophanthidin has been reported (6). The acid chloride was prepared by reaction of the sodium salt of I with oxalyl chloride according to the procedure of Wilds and Shunk (7). Treatment of the acid chloride with diazomethane produced the amorphous 19-acetoxy-21-diazoprogesterone (II), accompanied by a more polar, likewise amorphous substance (III) which was undoubtedly 19-acetoxy-3-oxo-Δ^4-etienamide, since hydrolysis of III with potassium carbonate yielded the crystalline 19-hydroxy-3-oxo-Δ^4-etienamide (IV). The latter product proved to be identical with a sample prepared by reaction of the acid chloride of I with ammonia and subsequent hydrolysis. It seems likely that the compound which has been reported as a by-product of the preparation of 21-diazoprogesterone from the acid chloride of 3-oxo-Δ^4-etienic acid (8) is actually 3-oxo-Δ^4-etienamide (*i.e.* $C_{20}H_{29}NO_2$ rather than the reported $C_{21}H_{31}NO_2$),[2] the unambiguous preparation of which is recorded in the experimental section. These two instances of the isolation of the amide from the products of the reaction of an acid chloride with diazomethane are best explained by the assumption, a statement to the contrary (9) notwithstanding, that diazomethane as usually prepared contains ammonia as an impurity.

Heating II with acetic acid gave 19-hydroxy-11-desoxycorticosterone diacetate (V), and hydrolysis of V with potassium bicarbonate yielded the 19-monoacetate (VI). Potassium bicarbonate hydrolysis of the amorphous II gave the crystalline

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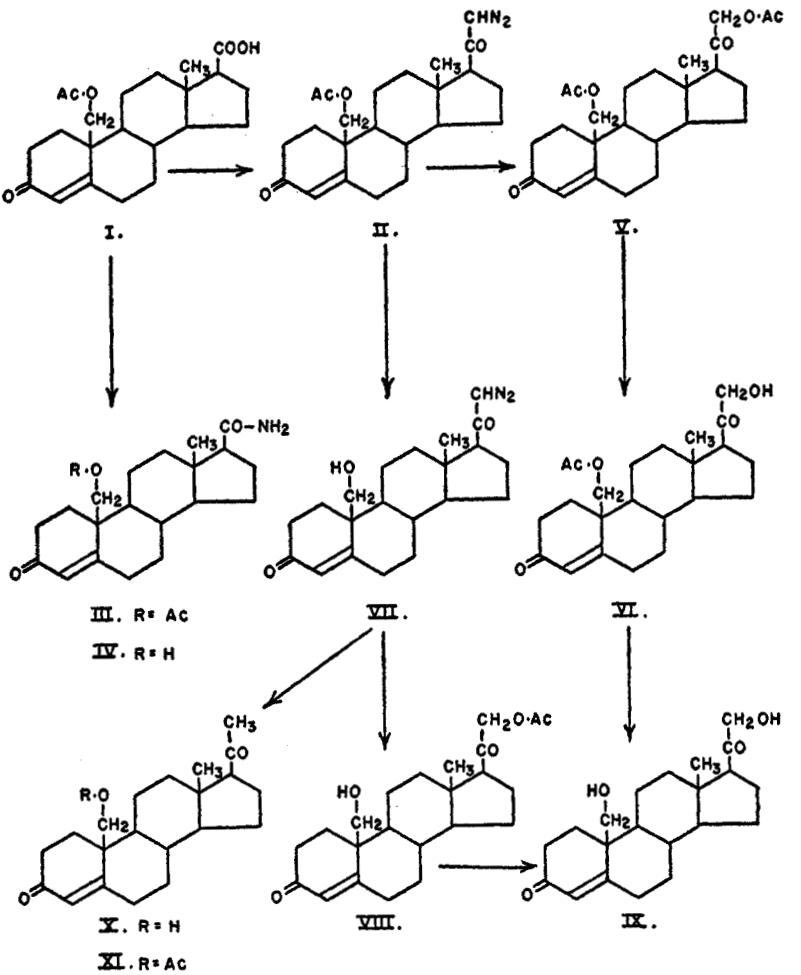
[1] *Cf.* the preliminary communication (1).

[2] Calc'd for $C_{21}H_{31}NO_2$: C, 76.55; H, 9.48; N, 4.25.
$C_{20}H_{29}NO_2$: C, 76.15; H, 9.27; N, 4.44.
Found (8): C, 76.19; H, 9.30; N, 4.82.

19-hydroxy-21-diazoprogesterone (VII), and heating the latter with acetic acid yielded 19-hydroxy-11-desoxycorticosterone 21-monoacetate (VIII). The first sample of 19-hydroxy-11-desoxycorticosterone (IX) was prepared by potassium carbonate hydrolysis of a mixture of the diacetate (V) and the 19-monoacetate (VI), but larger amounts of IX were later prepared more conveniently by potassium bicarbonate hydrolysis of the 21-monoacetate (VIII).



Heard and Ziegler have reported the facile preparation of progesterone by reaction of 21-diazoprogesterone with concentrated hydriodic acid (10). Application of this method to 19-hydroxy-21-diazoprogesterone (VII) gave 19-hydroxyprogesterone (X) in practically quantitative yield. Subsequent acetylation produced 19-acetoxyprogesterone (XI).

Infrared studies 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 infrared spectrum of 19-hydroxy-11-

desoxycorticosterone diacetate (V)[3] was determined in both carbon disulfide and chloroform solution. There was no evidence for hydroxyl absorption. Absorption bands at 1749 and 1731 cm.$^{-1}$ in carbon disulfide are due to the C=O stretching bands of a C-21-acetoxy-20-keto grouping. The increased intensity of the band at 1749 cm.$^{-1}$ (as compared with a compound such as 11-desoxycorticosterone acetate for instance) strongly suggests the presence of a second acetate group. Absorption at 1679 cm.$^{-1}$ in carbon disulfide and at 1666 and 1621 cm.$^{-1}$ in chloroform results from the presence of a Δ^4-3-ketone group. Strong absorption at 1230 cm.$^{-1}$ in carbon disulfide is ascribed to the C—O stretching vibration of the acetate groups.

19-Hydroxy-11-desoxycorticosterone (IX) was examined in the infrared in chloroform solution. There are hydroxyl stretching bands at about 3625 cm.$^{-1}$ and a broad absorption at about 3465 cm.$^{-1}$ ascribed to an associated hydroxyl group (C_{21}-OH, C_{20}-C=O). A band at 1707 cm.$^{-1}$ indicates the presence of a 20-ketone and bands at 1666 and 1620 cm.$^{-1}$ are the C=O stretching vibrations of a Δ^4-3-ketone group. Weak absorption at 1737 cm.$^{-1}$ was ascribed to contamination with some impurity.

19-Acetoxyprogesterone (XI) was measured in both chloroform and carbon disulfide solution. In chloroform there were bands at 1737 cm.$^{-1}$ indicative of the acetate group, a band at 1700 cm.$^{-1}$ indicative of the 20-ketone group, at 1666 cm.$^{-1}$ characteristic of the Δ^4-3-ketone system and a band at 1621 cm.$^{-1}$ indicative of the $\Delta^{4,5}$ unsaturation. The compound was only moderately soluble in carbon disulfide. In this solvent there were bands at 1747 cm.$^{-1}$, ascribed to the carbonyl stretching vibration of the acetate group; a band at 1707 cm.$^{-1}$ indicative of the 20-ketone group, a band at 1674 cm.$^{-1}$ characteristic of the Δ^4-3-ketone system and a band from 1229 to 1223 cm.$^{-1}$ indicative of the C—O stretching vibration of the acetate group.

The infrared spectrum of 19-hydroxyprogesterone (X) was determined in chloroform solution. There was a strong band in the hydroxyl region at 3640 cm.$^{-1}$; there were bands at 1700 cm.$^{-1}$ indicative of a 20-ketone group, a band at 1665 cm.$^{-1}$ indicative of a Δ^4-3-ketone system, and a band at 1619 cm.$^{-1}$ characteristic of the $\Delta^{4,5}$ unsaturation.

In bioassays kindly conducted by Dr. John A. Luetscher, Jr., Stanford University School of Medicine (*cf.* 11, 12) the effects of 19-hydroxy-11-desoxycorticosterone (IX) on the sodium excretion and on the potassium-sodium ratio were about 4% of those produced by DOCA. It is evident that the sodium-retaining activities of IX and of the 19-monoacetate (VI) are not of the same order as desoxycorticosterone. In the Ingle work test, performed by E. H. Morley, W. W. Byrnes, and K. J. Olson of the Research Division of the Upjohn Company, IX was found inactive at a level of 5 mg. per rat (2 animals), whereas hydrocortisone gives a significant response at a level of 100 μg. per rat. This means that in this bioassay IX possesses less than 2% of the activity of hydrocortisone. Broadly speaking the findings in the Ingle work test parallel those in the liver glycogen deposition test which was not done with IX.

19-Hydroxyprogesterone (X) was examined for progestational activity by Dr. Roy Hertz of the National Cancer Institute. The Corner-Allen test was negative with 1.0 mg. of this compound in two rabbits. In this test a maximal effect is obtained with 1.0 mg. of progesterone. 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. It may be concluded, therefore, that

[3] The fingerprint region of the spectrum of this compound is different from that of any steroid in the collection of the Sloan-Kettering Institute.

TABLE I

COMPARISON OF MOLECULAR ROTATIONS

Reference Compound	M_D			ΔM_D[a]		
	Not substituted I	21-Hydroxy II	21-Acetoxy III	II − I	III − I	III − II
19-Hydroxyprogesterone	+610°	+640°[b]	+692°	+30°	+82°	+52°
19-Acetoxyprogesterone	+829°[b]	+835°	+902°	+6°	+73°	+67°
Various substituted progesterones, pregnan-20-ones and allopregnan-20-ones				−3°[c],	+77°[d]	+89°[e]
17α-Progesterone	0° (17)	−20° (18)	−97° (18)	−20°	−97°	−77°
14β,17α-Progesterone	+437° (15)		+421° (19)		−16°	
14β,17α-Δ⁵-Pregnen-20-one	−45° (15)		−89° (19)		−44°	

[a] ΔM_D was calculated only for M_D values which had been determined in the same solvent. [b] M_D values are corrected for crystal solvent. [c] The mean of values calculated for 6 pairs of compounds; range, −19° to +27°. [d] The mean and median of values calculated for 27 pairs of compounds; standard deviation, $\sigma = 22°$; range, +29° to +112°. [e] The mean of values calculated for 7 pairs of compounds; range, +38° to +131°.

19-hydroxyprogesterone (X) is certainly less than one-tenth as active as progesterone.

Inasmuch as the preparation of I from strophanthidin involved the hydrogenation of a 14-15 double bond (13), it is not certain that the compounds here described have the hydrogen at carbon atom 14 in the normal α-position (*cf. e.g.* 14, p. 293), and consequently the orientation of the side chain is also open to question (*cf.* 15, 16). Comparison of the molecular rotations and molecular rotation differences with those of compounds of known configuration (Table I), however, lends support to the conclusion that the compounds described in this paper possess the normal configurations.

Finally, passing mention should be made of the hypsochromic shift in the ultraviolet absorption of the Δ⁴-3-keto grouping on acetylation of the 19-hydroxyl group, of which three examples are recorded here (VIII and V, IX and VI, X and XI). This shift has been noted before (20) and has also been observed with other hydroxyl groups in proximity to the Δ⁴-3-ketone group (*cf.* 21).

EXPERIMENTAL

The melting points were determined with the Fisher-Johns melting point apparatus and are uncorrected. Ultraviolet spectra were determined in 95% ethanol with a Beckmann Model DU spectrophotometer. All 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 (22). The percentage loss of weight on drying is recorded. Optical rotations have not been corrected for crystal solvent. 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. Solvents used for chromatography were Merck Reagent grade, dried and freshly distilled. The alumina (Alumina Adsorption, 80–200 mesh, Fisher Scientific Company) was washed with dilute acetic acid, methanol, and water, dried at

180° for 48 hours, and standardized according to Brockmann and Schodder (23). The silica gel (100–200 mesh, The Davison Chemical Corporation, Baltimore, Md.) was washed with methanol and water and dried at 180° for 48 hours.

19-Acetoxy-21-diazoprogesterone (II). A mixture of 233.4 mg. of 19-acetoxy-3-oxo-Δ^4-etienic acid (I) (4), m.p. 194–195°, in 10 cc. of ethanol and 6.23 cc. of 0.1001 *N* sodium hydroxide was frozen and evaporated to dryness *in vacuo*. The desiccated (vacuum; P_2O_5) residue was suspended in 10 cc. of dry benzene containing 6 drops of pyridine, and 1 cc. of oxalyl chloride was added. After 5 minutes at 0° the reaction mixture was frozen and evaporated to dryness *in vacuo*, and 2 cc. of dry benzene was added and evaporated in the same manner. After dissolving the powdery yellow product in 5 cc. of dry benzene, the suspension was filtered through sintered glass under dry nitrogen, and the residue was rinsed with 10 cc. of dry benzene. The filtrate was diluted with 10 cc. of dry ether and cooled to Dry Ice temperature, and 20 cc. of ethereal diazomethane, prepared from nitrosomethylurea and dried over potassium hydroxide, was added (approx. 20 millimoles). After standing at 0° for one hour, the solvent and excess diazomethane were removed *in vacuo* below room temperature. The residue was partitioned between ether and *N* aqueous sodium carbonate, giving 243.7 mg. of neutral material. Chromatography on 10 g. of alumina (activity I–II, 10 × 140 mm.) yielded 217 mg. (88%) of 19-acetoxy-21-diazoprogesterone (II), eluted as a single peak by benzene and benzene-ether mixtures. This amorphous but apparently homogeneous material resisted all attempts at crystallization.

19-Hydroxy-3-oxo-Δ^4-etienamide (IV). *A. Obtained from a by-product of II.* In a second preparation of II, starting with 372 mg. of I, m.p. 194–196°, and using 30 cc. of ethereal diazomethane which had been prepared from 5 g. of N-methyl-N-nitroso-N′-nitroguanidine (24)[4] (approx. 21 millimoles), the yield of II was only 66%, and the later, ether-methanol eluates from the chromatogram yielded 116 mg. of a second amorphous material (III). This was dissolved in 20 cc. of methanol to which was added 10 cc. of *N* aqueous potassium bicarbonate. After standing under nitrogen overnight, the mixture yielded 98.4 mg. of neutral material which still resisted all attempts at crystallization. It was subjected to more vigorous hydrolysis by dissolving in 10 cc. of methanol, adding 10 cc. of *N* aqueous potassium carbonate, and keeping the mixture under nitrogen for 18 hours. After concentrating *in vacuo* to about 5 cc. and diluting with water, a yellow precipitate resulted which was filtered and washed with water; 42.7 mg. of yellow powder. Crystallization from acetone-ether and methanol-water gave 27.0 mg. of IV as long, slender needles, m.p. 274–276°. $[\alpha]_D^{21.5}$ +117° (7.66 mg. in 2 cc. of chloroform containing 2 drops of ethanol; α +0.90° ±0.02°). λ_{max}^{alc} 242 mμ; ϵ 13,300. Extraction of the above aqueous filtrate with chloroform and repeated crystallization from methanol-water gave 16.8 mg. additional of IV with the same m.p.

Anal. Calc'd for $C_{20}H_{29}NO_3$ (331.44): C, 72.47; H, 8.82; N, 4.23.

Found: C, 72.26; H, 8.87; N, 4.24; Residue, 0.20; Mol. wt. (cryoscopic; camphor), 506, 506.[5] Weight loss, 2.74.

B. By reaction of the acid chloride of I with ammonia. The acid chloride was prepared by suspending 20 mg. of I, m.p. 193–194°, in 2 cc. of dry benzene and adding a solution of 0.2 cc. of oxalyl chloride in 1 cc. of dry benzene. The crystals disappeared within 20 minutes and after 20 minutes more the reaction mixture was frozen and evaporated *in vacuo*, the last traces of oxalyl chloride being removed by adding and evaporating two 1-cc. portions of benzene. The residue was dissolved in 2 cc. of benzene and mixed with 10 cc. of ether which had been saturated with dry ammonia. After standing at room temperature for one hour the reaction mixture was evaporated *in vacuo*. The solid residue was dissolved in a mixture of 2 cc. of methanol and 2 cc. of *N* aqueous potassium carbonate, and the solution was allowed to stand overnight. Concentration *in vacuo* and dilution with water produced

[4] Purchased from the Aldrich Chemical Company, Inc., Milwaukee 3, Wis.

[5] Remarks of microanalyst: The molecular weight values are questionable. The sample dissolves slowly. After standing above the melting point the solution becomes cloudy. Although the results are precise, it is possible that there is a reaction with the solvent.

a mealy precipitate which was filtered and washed with water; 15.3 mg., m.p. 256–262° when placed on the block at 240°. Recrystallization from methanol-water gave 4.9 mg. of 19-hydroxy-3-oxo-Δ^4-etienamide (IV) as long flat needles, m.p. 278°. There was no depression of the melting point on admixture with the material obtained as a by-product of the diazoketone synthesis.[6]

3-Oxo-Δ^4-etienamide. A mixture of 50 mg. of 3-oxo-Δ^4-etienic acid (m.p. 259°), 5 cc. of dry benzene, and 0.5 cc. of oxalyl chloride was allowed to stand for one hour and then was frozen and evaporated to dryness *in vacuo*. After adding and evaporating two 2-cc. portions of dry benzene, the residue was dissolved in 5 cc. of benzene and 25 cc. of ammonia-saturated ether was added. After standing for one hour, the reaction mixture was evaporated *in vacuo* and the solid residue was triturated with *N* sodium carbonate. Filtering, washing with water, and drying gave 49.7 mg. of yellow powder. Crystallization from methanol yielded 23.2 mg. of 3-oxo-Δ^4-etienamide as pale yellow needles, m.p. 258–260°, and recrystallization from methanol-water gave colorless needles, m.p. 260–261°; $[\alpha]_D^{23}$ +127° (12.71 mg. in 2 cc. of chloroform containing 2 drops of ethanol; α +1.62° ±0.02°). [Reported for the by-product obtained in the preparation of 21-diazoprogesterone (8): m.p. 248–253°].

Anal. Calc'd for $C_{20}H_{29}NO_2$ (315.44): N, 4.44. Found: N, 4.51. Weight loss, 0.74.

19-Hydroxy-21-diazoprogesterone (VII). The amorphous II (108 mg.) was dissolved in 20 cc. of methanol, the air was replaced by nitrogen, and 10 cc. of nitrogen-saturated *N* aqueous potassium bicarbonate was added. After 19 hours at room temperature the reaction mixture was concentrated *in vacuo* to about 5 cc. and diluted to 15 cc. with water, yielding a crystalline precipitate which was filtered and washed with water; 87.8 mg., m.p. 156–160° with foaming. Repeated recrystallization from acetone-petroleum ether and methanol-water gave 62.1 mg. of VII as pale yellow needles melting sharply at 166° with foaming.

Anal. Calc'd for $C_{21}H_{28}N_2O_3$ (356.45): C, 70.76; H, 7.92.

Found: C, 70.22; H, 8.21; Residue, 0.94.

19-Hydroxy-11-desoxycorticosterone diacetate (V). A solution of 108 mg. of amorphous II in 5 cc. of glacial acetic acid was heated on the steam-bath for one-half hour and then was evaporated to dryness *in vacuo*. The residue, which crystallized on the addition of a few drops of ether, was chromatographed on 10 g. of alumina (activity I–II; 10 × 135 mm.). A total of 83.5 mg. of V was eluted by benzene-ether mixtures as 8 crystalline fractions with melting points in the range 125–129°. Recrystallization of the peak fraction (18.2 mg.) from ether-petroleum ether and methanol-water gave 14.7 mg. of V as colorless rods melting sharply at 127°, which was used for characterization. The remainder of the material was combined and recrystallized from ether-petroleum ether and methanol-water to give additional V; 52.5 mg., m.p. 126–127°, and 5.8 mg., m.p. 119–120°. $[\alpha]_D^{25}$ +210° (10.21 mg.; α +2.14° ±0.02°), λ_{max}^{alc} 239 mμ; ϵ13,400.

Anal. Calc'd for $C_{25}H_{34}O_6$ (430.52): C, 69.74; H, 7.96.

Found: C, 70.16; H, 8.12.

19-Acetoxy-11-desoxycorticosterone (VI). A flask containing 58.3 mg. of the diacetate (V) (m.p. 126–127° and 119–120°) in 10 cc. of methanol was evacuated until the solvent boiled and then oxygen-free nitrogen (*cf.* 25, p. 1058) was admitted. This was repeated several times and 10 cc. of nitrogen-saturated *N* aqueous potassium bicarbonate was added. After 19 hours at room temperature under nitrogen, the reaction mixture was concentrated *in vacuo* to about 2 cc., yielding a crystalline precipitate which was filtered and washed with water; 41.4 mg., m.p. 167–170°. Chromatography over 10 g. of silica gel (10 × 165 mm.) yielded a total of 25.8 mg. of crystalline residues eluted by chloroform and chloroform-ether mixtures. Combination of those residues melting above 185° (20.6 mg.) and recrystallization from methanol-water gave 17.2 mg. of VI as colorless, shining plates, m.p. 189–190°. $[\alpha]_D^{25}$

[6] Except for minor differences in the fingerprint region, ascribed to slight differences in purity, the infrared spectra of the samples obtained under A and B were identical (Measured through the courtesy of Dr. Thomas F. Gallagher in the Sloan-Kettering Institute for Cancer Research on a Perkin-Elmer single beam instrument in potassium bromide discs).

+215° (7.89 mg.; α +1.70° ±0.02°). λ_{max}^{alc} 239 mμ; ε16,000. From the ether-methanol eluates of the chromatogram 12.9 mg. of impure IX was obtained.

Anal. Calc'd for $C_{23}H_{32}O_5$ (388.49): C, 71.10; H, 8.30.

Found: C, 71.06; H, 8.65.

19-Hydroxy-11-desoxycorticosterone 21-monoacetate (VIII). A solution of 18 mg. of 19-hydroxy-21-diazoprogesterone (VII), m.p. 166°, in 1 cc. of glacial acetic acid was heated for one-half hour on the steam-bath and then was evaporated *in vacuo*, leaving 19.0 mg. of crystalline residue, m.p. 185–190°. Successive recrystallization from acetone-petroleum ether and methanol-water gave 13.5 mg. of VIII as colorless rods, m.p. 197–199°. $[\alpha]_D^{24}$ +178° (9.04 mg.; α +1.61° ±0.02°). λ_{max}^{alc} 242 mμ; ε13,500.

Anal. Calc'd for $C_{23}H_{32}O_5$ (388.49): C, 71.10; H, 8.30.

Found: C, 70.86; H, 8.01.

19-Hydroxy-11-desoxycorticosterone (IX). *A. By hydrolysis of a mixture of the 19-monoacetate* (VI) *and the diacetate* (V). A mixture of 8 mg. of VI, m.p. 189–190°, and 8 mg. of V, m.p. 127°, was dissolved in 3 cc. of methanol, the air was replaced by nitrogen, and 2 cc. of nitrogen-saturated *N* aqueous potassium carbonate was added. After standing at room temperature for 16 hours, the reaction mixture was concentrated *in vacuo* below 0° to about 2 cc., diluted to 10 cc. with water, and extracted with chloroform. Evaporation of the dried chloroform left 8.5 mg. of amorphous solid. This was combined with 10 mg. of similar material obtained by potassium carbonate hydrolysis of impure mother liquor residues of V and VI, and the total was chromatographed on 5 g. of silica gel (10 × 105 mm.). A total of 9.3 mg. of crystalline material was eluted by ether. Recrystallization from ethanol-water gave 5.8 mg. of IX as flat needles or blades, m.p. 163–165° with a gradual change in appearance from 120° to 145° and sintering at 153–158°. $[\alpha]_D^{25}$ +180° (2.00 mg.; α +0.36° ±0.02°). λ_{max}^{alc} 242 mμ; ε18,500. This product reduces ammoniacal silver nitrate rapidly at room temperature and gives an instant deep blue color with triphenyltetrazolium chloride.

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

Found: C, 72.56; H, 8.70; Residue, 0.10. Weight loss, 2.44.

B. By hydrolysis of the 21-monoacetate (VIII). A mixture of 75 mg. of VIII, m.p. 193–194°, in 5 cc. of methanol and 5 cc. of nitrogen-saturated *N* aqueous potassium bicarbonate was left under nitrogen at room temperature for 18 hours and then was concentrated *in vacuo* below 0° to about 5 cc. Dilution with water to 25 cc. produced a mealy precipitate which was filtered and washed with water, giving 50.7 mg. of yellow powder. Extraction of the filtrate with chloroform yielded 13.7 mg. of colorless resin which crystallized on adding a few drops of ether. Recrystallization of the combined material from acetone-ether and then from methanol-water gave 45 mg. of blades, m.p. 165–168° with sintering at 154–156°. There was no depression of the m.p. on mixing with IX as obtained under A.

19-Hydroxyprogesterone (X). A solution of 40 mg. of 19-hydroxy-21-diazoprogesterone (VII), m.p. 166°, in 10 cc. of chloroform was shaken with 2 cc. of 48% hydriodic acid (Baker's Analyzed Reagent) for 2 minutes. The chloroform layer was then successively shaken with concentrated aqueous potassium iodide, water, and *N* aqueous sodium thiosulfate. After drying over sodium sulfate, evaporation of the chloroform left 37.4 mg. of colorless crystals. Recrystallization from acetone-petroleum ether and methanol-water gave 29.0 mg. of 19-hydroxyprogesterone (X) as shining plates, m.p. 171–172°. $[\alpha]_D^{24}$ +185° (11.97 mg.; α +2.21° ±0.02°). λ_{max}^{alc} 242 mμ; ε12,900.

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

Found: C, 75.88; H, 9.11.

19-Acetoxyprogesterone (XI). This compound was prepared by acetylation of 12 mg. of X, m.p. 171–172°, with acetic anhydride and pyridine, and was recrystallized from methanol-water; yield: 12.2 mg.; double melting point, melting first at 89–95°, resolidifying above 100° and melting again at 125–126°. $[\alpha]_D^{25}$ +212° (7.63 mg.; α +1.62° ±0.02°), λ_{max}^{alc} 239 mμ; ε17,300.

Anal. Calc'd for $C_{23}H_{32}O_4$ (372.49): C, 74.16; H, 8.66.

Found: C, 73.45; H, 8.69. Weight loss, 4.26. (Dried at 70°). Calc'd for one mole of crystal water: 4.61.

SUMMARY

1. 19-Acetoxy-3-oxo-Δ^4-etienic acid (I), obtainable by degradation of strophanthidin (6), has been converted by way of the diazoketone (II) into 19-hydroxy-11-desoxycorticosterone (IX) and 19-hydroxyprogesterone (X) respectively. The 19-monoacetate (VI), the 21-monoacetate (VIII), and the 19,21-diacetate (V) of IX have been described. X was characterized by the acetate (XI).

2. The bioassays of 19-hydroxy-11-desoxycorticosterone (IX) and of 19-hydroxyprogesterone (X) are reported.

3. The preparations of 19-hydroxy-3-oxo-Δ^4-etienamide (IV) and of 3-oxo-Δ^4-etienamide are discussed.

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