[Contribution from the Division of Steroid Research, the John Herr Musser Department of Research Medicine, University of Pennsylvania]

INVESTIGATIONS ON STEROIDS. XXI. 19-NORETIENIC ACIDS DERIVED FROM STROPHANTHIDIN*[1]

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The conversion of strophanthidin into a physiologically active, though amorphous, 19-norprogesterone and an apparently inactive, likewise amorphous, 19-nor-11-desoxycorticosterone was reported from this laboratory some time ago (1). In both preparations there was utilized as an intermediate a resinous product for which the composition of a 3-acetoxy-19-noretienic acid such as II was indicated by the analytical data. This material had been prepared by high-vacuum pyrolysis of the amorphous product resulting from the acetylation of 3β-5-dihydroxy-14β,17α,21-norpregnane-19,20-dioic acid with boiling acetic anhydride. The acetylation product was subsequently obtained in crystalline form and was identified as the 3,5-diacetate (I) (2).

The pyrolysis of I has now been reinvestigated, and crystalline 3β-acetoxy-14β,17α,19-nor-$\Delta^{5(10?)}$-etienic acid (II) has been isolated in moderate yield from the resinous distillate. This compound was hydrolyzed to give the crystalline 3β-hydroxy-14β,17α,19-nor-$\Delta^{5(10?)}$-etienic acid (III), and the non-crystalline ethyl ester (VI) was prepared with diazoethane and characterized as the crystalline 3,5-dinitrobenzoate (VII).

The behavior of 3β,5-dihydroxy-14β,17α,21-norpregnane-19,20-dioic acid 20-ethyl ester 3,5-diacetate (IV) and of the corresponding 19,20-diethyl ester 3,5-diacetate (2) under the conditions of pyrolysis have also been investigated. Although the latter compound distilled without change in a high vacuum, IV readily underwent decomposition, giving a good yield of an amorphous, neutral material which presumably was essentially pure ethyl 3β-acetoxy-14β,17α,19-nor-$\Delta^{5(10?)}$-etienate (V). Saponification of V under mild conditions consumed one equivalent of base and gave nearly quantitative yields of ethyl 3β-hydroxy-14β,17α,19-nor-$\Delta^{5(10?)}$-etienate (VI). This compound again resisted all attempts at crystallization, even after purification through the digitonide and by chromatography on alumina. The results of the latter procedure, however, indicated strongly that the product was homogeneous. The identity of VI obtained in this manner with the material obtained by esterification of the crystalline acid (III) was demonstrated by preparation of the same crystalline 3,5-dinitrobenzoate (VII).

Ethyl 3β-hydroxy-14β,17α,19-nor-$\Delta^{5(10?)}$-etienate (VI) and the 3-acetate (V) were both converted by vigorous saponification to 3β-hydroxy-14β,17α,19-

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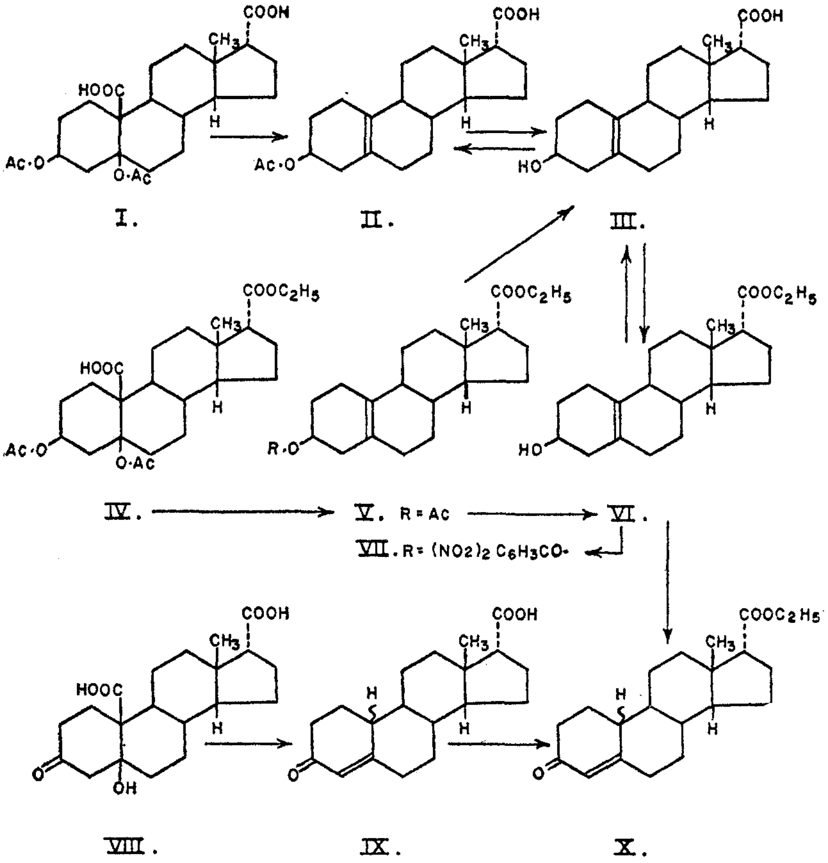
[1] The findings of this paper were incorporated in the Robert Gnehm Lecture delivered on July 7, 1952, at the Eidgenössische Technische Hochschule in Zurich [*cf.* M. Ehrenstein, *Chimia*, **6**, 287–289 (1952).]



nor-$\Delta^{5(10?)}$-etienic acid (III) and thence by acetylation to the corresponding 3-acetate (II). The latter two products, as derived from IV, proved to be identical with the compounds derived from I. Furthermore, a much better yield of II is obtained in this way from IV, by omitting the purification of intermediates, than is obtained on pyrolysis of I.

The 5,10-position of the double bond in these compounds has been assigned arbitrarily, for the 5,6-position is also possible. The 4,5-position is most unlikely, however, because such compounds would not be expected to survive the conditions of pyrolysis or saponification. In any event, the double bond was readily rearranged to the 4,5-position when VI was subjected to Oppenauer oxidation, and a fair yield of the previously described (3) ethyl 3-oxo-14β,17α,19-nor-10ξ-Δ^4-etienate (X) was produced. The homogeneous nature of this product was indicated by its behavior on chromatography, and was verified by the preparation of identical material by treatment of the corresponding acid (IX) with diazoethane.

This 3-oxo-14β,17α,19-nor-10ξ-Δ^4-etienic acid (IX) was first prepared by Butenandt and Gallagher (4) by treatment of 3-oxo-5-hydroxy-14β,17α,21-norpregnane-19,20-dioic acid (VIII) with methanolic hydrogen chloride. These authors did not investigate the possibility that the product might consist of a mixture of stereoisomers epimeric at position 10. Treatment of VIII with Girard's Reagent T has now been found to result in a considerably improved yield of IX, and the stereochemical uniformity of this product has been demonstrated by comparison of the melting points, optical rotations and infrared absorption spectra[2] of the first five % and last ten % of IX eluted from a careful chromatogram which spread the material over 28 fractions.

The preliminary attempts to prepare a crystalline 19-norprogesterone by reaction of the acid chlorides of II and of IX with dimethylcadmium have been disappointing. Amorphous material similar to that previously reported (1) can be prepared readily, but only a trace has been obtained of a crystalline product having the expected analytical composition and ultraviolet absorption. (m.p. 109°; $\lambda_{\max}^{\text{alc}}$ 239 mμ, ϵ 17,100). This work is being continued and will be reported in a future communication.

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 according to Milner and Sherman (5). The percentage loss of weight on drying and gain of weight on exposure of the sample to the atmosphere are recorded. Optical rotations have not been corrected for crystal solvent. Solvents used for chromatography were Merck Reagent grade, dried and freshly distilled.

Ethyl 3β-acetoxy-14β,17α,19-nor-$\Delta^{5(10?)}$*-etienate* (V). The pyrolysis of 3β,5-dihydroxy-14β,17α,21-norpregnane-19,20-dioic acid 20-ethyl ester 3,5-diacetate (IV) (2) has been performed six times with quantities varying from 94 mg. to 1.494 g. with quite consistent results. In each experiment a glass retort containing the crystalline IV was evacuated on the mercury-vapor pump (approx. 1×10^{-4} mm.) and then was heated in a small electric oven. When the oven temperature reached 210–220° (30–45 minutes) the crystalline material melted, the pressure within the vacuum system rose to approximately 0.01 mm., and a colorless resin began to condense in the side-arm of the retort. The oven temperature was slowly raised to about 275° and was kept at this point until the distillation was complete, which was indicated by restoration of the original high vacuum. The duration of the distillation varied with the amount of starting material, averaging 1 minute per 10 mg. The distillate was returned to the bulb of the retort by rinsing with ether and the material was distilled a second time under the same conditions. The loss of weight ranged from 88% to 99% of the calculated amount after one distillation and was 96–100% of the calculated weight loss after the second distillation.

The colorless, resinous distillate was separated into neutral and acid fractions by partition between ether and *N* sodium carbonate. The neutral fraction amounted to 84–90% of the theoretical yield of V. It was transformed directly to VI or III without attempts at purification. A cursory investigation of the acid fraction in one experiment revealed the presence of a small amount of IV, but a redistillation of the combined acid fractions from three experiments gave predominantly acid material. This has not been investigated.

Ethyl 3β-hydroxy-14β,17α,19-nor-$\Delta^{5(10?)}$*-etienate* (VI). *A. By gentle hydrolysis of ethyl 3β-acetoxy-14β,17α,19-nor-*$\Delta^{5(10?)}$*-etienate* (V). A solution of 63.6 mg. (0.17 millimole) of

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[2] Kindly determined and interpreted by Dr. C. Roland Eddy of the Eastern Regional Laboratory, Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture, Philadelphia 18, Pa.

resinous V in 2.0 cc. of 0.0959 *N* ethanolic potassium hydroxide was allowed to stand at room temperature for 17 hours and then was titrated with 0.01 *N* hydrochloric acid, which revealed that 0.16 millimole of potassium hydroxide had been consumed. The reaction mixture was diluted with water and extracted with ether, and the ether was washed with *N* sodium carbonate, dried over sodium sulfate, and evaporated to dryness *in vacuo*. The residue of 54.2 mg. of resin was dissolved in 2 cc. of 50% ethanol to which was added a solution of 210 mg. of digitonin in 21 cc. of 50% ethanol. The slowly formed, flocculent precipitate was filtered, washed, and dried to give 235.6 mg. of white powder. This was dissolved in 2.5 cc. of pyridine and 25 cc. of ether was added. The precipitated digitonin was filtered and the filtrate was brought to dryness *in vacuo*. The residue was taken up in ether and the solution was washed with *N* hydrochloric acid and water. Drying over sodium sulfate and evaporation *in vacuo* gave 51.5 mg. of colorless resin. On chromatographing this product on 5 g. of alumina[3] (activity II, 6 × 170 mm.), 45.9 mg. of resin was eluted as a single peak by benzene-ether (4:1). A second chromatogram on 10 g. of alumina[3] (activity II, 12 × 115 mm.) gave 39.1 mg. of resinous material eluted as a single peak by benzene-ether (9:1). All attempts at crystallization were unsuccessful.

The resinous ethyl 3β-hydroxy-14β,17α,19-nor-$\Delta^{5(10?)}$-etienate (VI) was characterized as the 3,5-dinitrobenzoate (VII), prepared at room temperature by reaction with 3,5-dinitrobenzoyl chloride in dry benzene containing a trace of pyridine, and purified by chromatography on alumina[3] (activity II, eluted by benzene) and by crystallization from ether-petroleum ether and methanol-water; colorless needles, m.p. 112–113°. $[\alpha]_D^{20}$ +19° (5.39 mg. in 2.0 cc. of chloroform; l, 2 dm.; α +0.10° ± 0.01°). The melting point was not depressed on mixing withVII derived from III.

B. By esterification of 3β-hydroxy-14β,17α,19-nor-$\Delta^{5(10?)}$-etienic acid (III). To a solution of 20 mg. of III (obtained from IV) in 2 cc. of ether, freshly prepared ethereal diazoethane[4] was added until the yellow color persisted. After standing for 5 minutes, the reaction mixture was evaporated to dryness *in vacuo*, and the resinous residue was chromatographed on 8 g. of alumina[3] (activity II, 6 × 290 mm.). Benzene-ether (9:1) eluted 17.8 mg. of resinous VI which resisted all attempts at crystallization.

The *3,5-dinitrobenzoate*, prepared in dry benzene containing a trace of pyridine, was purified by chromatography on alumina[3] (activity II, eluted by benzene), and was recrystallized from ether-petroleum ether and then from methanol-water; long colorless needles, m.p. 113–114°. $[\alpha]_D^{20}$ +20° (5.58 mg. in 2.0 cc. of chloroform; l, 2 dm.; α +0.11° ± 0.01°).

Anal. Calc'd for $C_{28}H_{34}N_2O_8$ (526.57): N, 5.32. Found: N, 5.35. Special drying (5) proved to have been unnecessary.

3β-Hydroxy-14β,17α,19-nor-$\Delta^{5(10?)}$-etienic acid (III). *A. By saponification of ethyl 3β-hydroxy-14β,17α,19-nor-$\Delta^{5(10?)}$-etienate* (VI) *or the corresponding 3-acetate* (V). A solution of 871.4 mg. of resinous V in 90 cc. of *N* absolute ethanolic potassium hydroxide was refluxed for 7 hours and then was left for 16 hours at room temperature. Concentration *in vacuo* to about 5 cc. was followed by dilution with water and extraction with ether, from which 33.8 mg. of resinous neutral fraction was obtained. Acidification of the aqueous phase and extraction with ether yielded 693.1 mg. of acid fraction as white brittle foam. Crystallization from methanol-water gave 621.7 mg. (88%) of III as small round clusters of very small needles, m.p. 170–174°.

Saponification of 138 mg. of resinous VI under the same conditions produced 7.6 mg. of neutral material and 120 mg. of crude acid material. Crystallization of the latter from methanol-water gave 100.5 mg. of III as clusters of small needles, m.p. 173–176°.

Successive recrystallization of III from ether-petroleum ether and methanol-water

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[3] Alumina Adsorption, Fisher Scientific Co., washed with 5% acetic acid, distilled water, and methanol and dried for 48 hours at 180°, standardized according to Brockmann and Schodder (6).

[4] Prepared from ethylnitrosourea according to the *Organic Syntheses* directions for diazomethane (7).

raised the melting point to 174–175°; no depression on mixing with III obtained from I by pyrolysis and hydrolysis. [α_D^{25}] +97° (23.10 mg. in 2.0 cc. of chloroform containing 1 drop of ethanol; l, 2 dm.; α +2.23° ± 0.02°).

Anal. Calc'd for $C_{19}H_{28}O_3$ (304.41): C, 74.96; H, 9.27.

Found: C, 74.69, H, 9.13. Weight loss: 0.03. Weight gain: 0.25.

B. By hydrolysis of 3β-acetoxy-14β,17α,19-nor-$\Delta^{5(10?)}$*-etienic acid* (II). A 20-mg. sample of II, obtained by pyrolysis of I, was dissolved in 2 cc. of 0.1 *N* absolute ethanolic potassium hydroxide. After standing for 16 hours at room temperature, the solution was cooled in Dry Ice, concentrated *in vacuo* to about 0.5 cc., and diluted to 5 cc. with water. The curdy precipitate produced on acidification was filtered, washed with water, and dried (16.6 mg.). Recrystallization from methanol-water, ether-petroleum ether, and once more from methanol-water gave 12.6 mg. of 3β-hydroxy-14β,17α,19-nor-$\Delta^{5(10?)}$-etienic acid (III) as clusters of very small needles, m.p. 172–174°. $[\alpha]_D^{31}$ +100° (5.51 mg. in 2.0 cc. of chloroform containing 1 drop of ethanol; l, 2 dm.; α +0.55° ± 0.02°).

Anal. Calc'd for $C_{19}H_{28}O_3$ (304.41): C, 74.96; H, 9.27.

Found: C, 74.69; H, 9.29. Weight loss: 0.26. Weight gain: 0.24.

3β-Acetoxy-14β,17α,19-nor-$\Delta^{5(10?)}$*-etienic acid* (II). *A. By pyrolysis of 3β,5-dihydroxy-14β,17α,21-norpregnane-19,20-dioic acid 3,5-diacetate* (I). A glass retort containing 172.3 mg. of crystalline I (m.p. 189–190°) was evacuated on the mercury-vapor pump (approx. 1×10^{-4} mm.) and heated in a small electric oven. At an oven temperature of 200° the material began to melt, and at 210° the pressure within the system rose to approximately 0.01 mm. and distillation began. Distillation was complete in 10 minutes and the original high vacuum was restored. The loss of weight was 40.5 mg.; calculated, 39.8 mg. The resinous distillate was returned to the bulb of the retort and was redistilled under practically the same conditions with no significant additional loss of weight. The 130.7 mg. of resinous distillate was dissolved in benzene and chromatographed on 50 g. of silica gel[5] (32 × 100 mm.). Benzene, benzene-chloroform combinations, and the first 800 cc. of pure chloroform eluted practically nothing. The next eight 100-cc. portions of chloroform eluted a total of 100.9 mg. of white brittle foam, from which 60.4 mg. (46%) of II, m.p. 70–76°, was obtained by crystallization of the separate fractions from methanol-water. Recrystallization of the combined crystalline material from the same solvent mixture gave long, slender needles, m.p. 74–76°; no depression of the m.p. on admixture with II derived from IV. In another, similar experiment the yield of crystalline II was 39% of the theoretical.

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

Found: C, 73.02; H, 8.90. Weight loss: 3.99. Weight gain: 2.96.

B. By acetylation of 3β-hydroxy-14β,17α,19-nor-$\Delta^{5(10?)}$*-etienic acid* (III). To a solution of 51 mg. of III, m.p. 171–174°, (derived from IV) in 1 cc. of glacial acetic acid, the smallest possible drop of 60% perchloric acid was added. After 16 hours at room temperature, the reaction mixture was frozen in Dry Ice, and most of the acetic acid was evaporated *in vacuo* from the frozen mixture. The residue was taken up in *N* sodium carbonate and the solution was extracted with ether, which removed only a trace of neutral material. Acidification and extraction of the carbonate solution with ether yielded 52.4 mg. of white brittle foam. Crystallization from methanol-water gave 44.3 mg. of 3β-acetoxy-14β,17α,19-nor-$\Delta^{5(10?)}$-etienic acid (II) as slender needles, m.p. 77–78° (76%). The melting point was not raised by further recrystallization. $[\alpha]_D^{31}$ +74° (11.38 mg. in 2.0 cc. of chloroform; l, 2 dm.; α +0.84° ± 0.02°).

In one larger scale experiment (500 mg.) the crystalline product was found to be contaminated by about 30% of unchanged III, a fact which was overlooked at first because the melting point of II was not depressed by mixture with III, and the two compounds readily crystallized together. They were separated easily by chromatography on silica gel, how-

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[5] Davison Silica Gel, The Davison Chemical Corporation, Baltimore, Md., lot 923-08-08-226, 100–200 mesh, washed with methanol and with boiling water, and dried for 3 days at 180°.

ever, and the difficulty was avoided in subsequent experiments by allowing a much longer reaction time.

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

Found: C, 72.65; H, 8.60. Weight loss: 0.63. Weight gain: 0.59.

C. From 3β,5-dihydroxy-14β,17α,21-norpregnane-19,20-dioic acid 20-ethyl ester 3,5-diacetate (IV) *without purification of intermediates.* Vigorous saponification of the neutral fraction (V; 824 mg.) obtained by pyrolysis of 1.2092 g. of IV (m.p. 182–184°) gave 663 mg. of crude III, which was dissolved in 10 cc. of glacial acetic acid containing 5 drops of 60% perchloric acid. After 88 hours at room temperature the brown reaction mixture was frozen in Dry Ice and concentrated *in vacuo* to about 3 cc. Dilution with 100 cc. of water and prompt filtration of the precipitate gave 731 mg. of light brown powder. This was dissolved in benzene and chromatographed on 100 g. of silica gel[5] (32 × 200 mm.). Nothing was eluted by benzene, benzene-chloroform (1:1), or the first 1800 cc. of chloroform. The next 2200 cc. of chloroform eluted 584.9 mg. of resinous fractions which were combined and crystallized from methanol-water, giving 584.2 mg. of 3β-acetoxy-14β,17α,19-nor-$\Delta^{5(10?)}$-etienic acid (II) as colorless needles, m.p. 79°. This is 67% of the theoretical yield from IV.

Attempted pyrolysis of 3β,5-dihydroxy-14β,17α,21-norpregnane-19,20-dioic acid 19,20-diethyl ester 3,5-diacteate. A small retort containing 69.0 mg. of the diethyl ester diacetate (2), m.p. 123–124°, was evacuated to about 1×10^{-4} mm. and was heated in the electric oven. The material melted at an oven temperature of 150° and distilled completely in 30 minutes at 170–190°. The distillate then was redistilled under the same conditions. There was no impairment of the vacuum and no loss of weight during either distillation. Crystallization of the resinous distillate from methanol-water gave 66.1 mg. of glistening platelets, m.p. 123°; no depression of the m.p. on mixing with starting material.

3-Oxo-14β,17α,19-nor-10ξ-Δ^4-etienic acid (IX). 3-Oxo-5-hydroxy-14β,17α,21-norpregnane-19,20-dioic acid (VIII) was prepared by oxidation of 1.1730 g. of 3β,5-dihydroxy-14β,17α,21-norpregnane-19,20-dioic acid with chromium trioxide in acetic acid as described previously (3). The crude oxidation product, 1.0813 g. of white brittle foam (93%), was dissolved in 30 cc. of absolute ethanol, and 2.4 g. of Girard's Reagent T and 1.8 cc. of glacial acetic acid were added. After refluxing for one hour, the reaction mixture was cooled and diluted to 100 cc. with ice-water. This solution was extracted with three 150-cc. portions of ice-cold ethyl acetate which were combined and washed with water. Drying and evaporation of the ethyl acetate gave 225.9 mg. of resinous non-ketonic material. The aqueous phase was made acid to Congo Red and allowed to stand for 3 hours. The yellow oil which separated was extracted with ethyl acetate which was dried and evaporated to give 674.3 mg. of ketonic material as yellow brittle foam. Evaporation of the remaining aqueous phase and trituration of the dry residue with acetone yielded 84.3 mg. of amorphous material which was insoluble in ether or ethyl acetate but was soluble in methanol and in water. This was not investigated.

The ketonic fraction was dissolved in benzene and chromatographed on 200 g. of silica gel[5] (40 × 255 mm.). The column was developed with 42 successive 500-cc. portions of chloroform, followed by various chloroform-ether combinations. Evaporation of the first 4 fractions left no residues and the fifth fraction yielded only 2.5 mg. of resin. The next 2 fractions eluted 36.9 mg. of crystalline ethyl 3-oxo-14β,17α,19-nor-10ξ-Δ^4-etienate (X), identified by mixture m.p. of the recrystallized material (m.p. 85–86°) with an authentic sample. This compound may have been formed as a by-product of the reaction of VIII with Girard's Reagent T in ethanol, or may have arisen from a trace of 20-ethyl ester in the starting material. Fractions 8–14 eluted only traces of resin.

Evaporation of the remaining 28 chloroform fractions (15–42) left crystalline residues of 3-oxo-14β,17α,19-nor-10ξ-Δ^4-etienic acid (IX) totaling 502.9 mg. and eluted as a single peak, the largest fraction being number 26 (44.3 mg.). Successive recrystallization of (a) fractions 15–16 combined (25.3 mg.) and (b) fractions 33–41 combined (46.8 mg.) from ether-petroleum ether and methanol-water gave in each case feathery clusters of needles: (a) 15.7 mg., m.p. 188°, $[\alpha]_D^{26}$ +107°; (b) 32.5 mg., m.p. 189°, $[\alpha]_D^{26}$ +109°. Infrared spectra determined on these two samples in bromoform solution[2] showed no significant difference, so the balance of the material (fractions 17–32) was combined and recrystallized, giving 407.7 mg. additional of IX, m.p. 187–188°.

The first 10 chloroform-ether combinations (99:1, 19:1, 9:1) eluted an additional peak of partly crystalline material (52.3 mg.), from which 25.8 mg. of IX, m.p. 184–186°, was obtained by recrystallization. The total yield of 481.7 mg. of crystalline IX from 3β,5-dihydroxy-14β,17α,21-norpregnane-19,20-dioic acid is 50% of the theoretical. The most carefully purified sample of 3-oxo-14β,17α,19-nor-10ξ-Δ^4-etienic acid melted at 189°. $[\alpha]_D^{24}$ +109° (10.19 mg. in 2.0 cc. of chloroform; l, 2 dm.; α +1.11° ± 0.02°). λ_{max}^{alc} 240 mμ; ϵ 18,360. Reported (4): m.p. 186°; $[\alpha]_D^{23}$ +83° (ethanol); λ_{max}^{alc} 240 mμ, ϵ 17,200.

Methyl ester of IX. Addition of an excess of ethereal diazomethane to a solution of 14.3 mg. of IX in ether, evaporation of the solvent, and two recrystallizations from methanol-water gave 8.6 mg. of slender needles, m.p. 98°. $[\alpha]_D^{31}$ +80° (7.49 mg. in 2.0 cc. of chloroform; l, 2 dm.; α +0.60° ± 0.02°). λ_{max}^{alc} 239 mμ; ϵ 14,900.

Ethyl 3-oxo-14β,17α,19-nor-10ξ-Δ^4-etienate (X). *A. By esterification of* IX. Freshly prepared ethereal diazoethane[4] was added to a solution of 51 mg. of IX (m.p. 182–185°) in 5 cc. of ether until the yellow color persisted. The solvent was evaporated immediately and the crystalline residue was chromatographed on 10 g. of alumina[3] (activity I–II, 10 × 140 mm.). Nothing was eluted by petroleum ether-benzene combinations, but 5 successive 100-cc. portions of benzene eluted a total of 48.6 mg. of crystalline X. Recrystallization of the second and largest of these residues (19.8 mg.) from methanol-water yielded 19.5 mg. of long needles, m.p. 88°. $[\alpha]_D^{31}$ +83° (12.71 mg. in 2.0 cc. of chloroform, l, 2 dm.; α +1.06° ± 0.02°). λ_{max}^{alc} 239 mμ; ϵ 16,900. Combination and recrystallization of the remaining fractions from methanol-water gave 27.1 mg. of needles, m.p. 84–87°.

B. By Oppenauer oxidation of ethyl 3β-hydroxy-14β,17α,19-nor-$\Delta^{5(10?)}$-etienate (VI). The crystalline acid III, 50 mg., m.p. 170–174°, in 2 cc. of ether was treated with excess ethereal diazoethane.[4] After 15 minutes the solvent was evaporated and to the resinous residue (VI) there were added 2.5 cc. of dry acetone and a solution of 160 mg. of aluminum *tert*-butoxide in 4 cc. of dry benzene. After refluxing for 16 hours, the mixture was diluted with ether and extracted with *N* sulfuric acid, water and *N* sodium carbonate. The ether phase was dried over sodium sulfate and evaporated, leaving 62.6 mg. of odoriferous yellow resin. To this residue there were added 1.5 cc. of absolute ethanol, 135 mg. of Girard's Reagent T, and 0.09 cc. of glacial acetic acid. The mixture was refluxed for one hour and then was cooled in ice. After the addition of 2 g. of ice and an ice-cold solution of 75 mg. of sodium carbonate in 10 cc. of water, the mixture was quickly extracted with three 10-cc. portions of ether. The combined ether extract was washed with water, dried over sodium sulfate, and evaporated, leaving 19.5 mg. of resinous non-ketonic material. The aqueous phase was made acid to Congo Red and allowed to stand one hour at room temperature. The yellow oil which separated was extracted with ether. Drying over sodium sulfate and evaporation of the solvent left 31.5 mg. of yellow, resinous ketonic material.

The ketonic fraction was purified by chromatography on 5 g. of alumina[3] (activity II, 6 × 180 mm.). Only traces of resin were eluted by petroleum ether-benzene combinations, but a total of 19.7 mg. of crystalline material was eluted as a single peak by 5 successive 50-cc. fractions of benzene. Two recrystallizations of these combined residues from methanol-water gave 13.7 mg. of ethyl 3-oxo-14β,17α,19-nor-10ξ-Δ^4-etienate (X) as shining needles, m.p. 86°. $[\alpha]_D^{30}$ +89° (11.18 mg. in 2.0 cc. of chloroform; l, 2 dm.; α +1.00° ± 0.02°). λ_{max}^{alc} 239 mμ; ϵ 17,700.

SUMMARY

1. Reinvestigation of the high-vacuum pyrolysis of 3β,5-dihydroxy-14β,17α,21-norpregnane-19,20-dioic acid 3,5-diacetate (I) using crystalline material has resulted in the isolation of crystalline 3β-acetoxy-14β,17α,19-nor-$\Delta^{5(10?)}$-etienic acid (II) in fair yields.

2. Better yields of II were obtained from 3β,5-dihydroxy-14β,17α,21-nor-pregnane-19,20-dioic acid 20-ethyl ester 3,5-diacetate (IV) by saponification and reacetylation of the pyrolysis product, ethyl 3β-acetoxy-14β,17α,19-nor-$\Delta^{5(10?)}$-etienate (V).

3. Improved yields of the known 3-oxo-14β,17α,19-nor-10ξ-Δ^4-etienic acid (IX) (4) were obtained by treatment of 3-oxo-5-hydroxy-14β,17α,19-nor-pregnane-19,20-dioic acid (VIII) with Girard's Reagent T, and the product was shown to be stereochemically uniform.

4. The identical ethyl 3-oxo-14β,17α,19-nor-10ξ-Δ^4-etienate (X) has been obtained by esterification of IX and by esterification and Oppenauer oxidation of II.

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