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Preparation and Reactions of 11-Substituted 1,3,5(10)-Estratrienes. II. Synthesis of 19-Norhydrocortisone[1]

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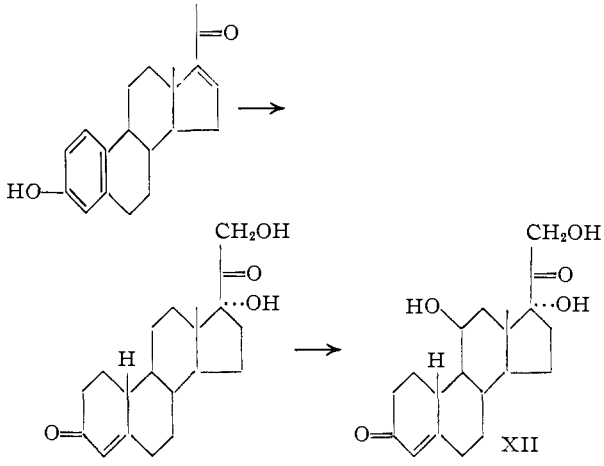
The synthesis of 19-norhydrocortisone, its ring A aromatized counterpart 3,11β,17α,21-tetrahydroxy-19-nor-1,3,5(10)-pregnatrien-20-one, and intermediates is described.

The enhanced and varied activity of such 19-norsteroids as 19-norprogesterone,[2a] 19-nordesoxycorticosterone[2b] and 17α-ethinyl-19-nortestosterone[2c] stimulated interest in a synthesis of 19-norhydrocortisone (XII). The Syntex group has described a synthesis of 19-norhydrocortisone (XII) employing a tissue homogenate method to introduce the 11β-hydroxyl group into 19-nor-Reichstein's Substance S which was prepared from 3-hydroxy-19-nor-1,3,5(10),16(17)-pregnatetraen-20-one by a multi-step process.[3]



In our synthesis of 19-norhydrocortisone the 11β-hydroxyl group was introduced prior to the modification of the A ring. This route also makes available aromatic hydrocortisone (XX) [3,11β,17α,21-tetrahydroxy-19-nor-1,3,5(10)-pregnatrien-20-one] a biologically interesting compound.

The successful aromatization of 3-keto-1,4-dienes containing varied substituents at C-11,[4] encouraged us to attempt this reaction with 11β,21-dihydroxy-1,4,17(20)-[*cis*]-pregnatrien-3-one (I).[5] This compound, which contains both the unstable 11β-hydroxyl and an allylic alcohol side chain, when pyrolyzed in a mineral oil suspension, yields about 10–15% of the desired phenol II. The latter compound, in contrast to phenols containing the 21-carbomethoxy group[4] was soluble in dilute alkali. Successive methylation and acylation of II formed IV which when ozonized yielded 3-methoxy-11β-acetoxy-1,3,5(10)-estratrien-17-one (XV). Since the conversion of XV to 11β-hydroxy-19-nortestosterone has been described,[4] the structure of II was thus established.[6] When treated with osmium tetroxide and N-methylmorpholine oxide peroxide,[7] IV is converted to V in 65% yield. Saponification with potassium bicarbonate removed the 21-acetate, but left the 11β-acetate intact. The 20-ketone was blocked by ketal formation yielding VII in 50% yield. Reduction of VII with sodium–liquid ammonia and alcohol failed to give the desired product IX, apparently due to influence of the 11β-acetoxy group.[4] Therefore, VII was treated with lithium aluminum hydride and then reduced by the Birch method to yield IX.

Mild acidic hydrolysis of the enol ether IX gave X,[8] which readily isomerized to XI in the presence of alkali. Hydrolysis with 50% acetic acid yielded 19-norhydrocortisone XII. The direct hydrolysis of IX to 19-norhydrocortisone (XII), using boiling 50% acetic acid, proceeded in 30% yield, about twice that obtained by the alternate method. The physical constants of 19-norhydrocortisone (XII) compared favorably with the published values.[3] Sodium bismuthate oxidation of XII yielded 11β-hydroxy-4-estrene-3,17-dione (XIII).[3]

Acylation of II with excess acetic anhydride–pyridine gave the triacetate XVIII. When the quantity of anhydride was restricted to two moles, the 3,21-diacetate XVII was isolated. 11β-Hydroxyestradiol (XVI)[4] was prepared from the triacetate XVIII by ozonization and reduction. The diacetate XVII was treated with osmium tetroxide–hydrogen peroxide to form XIX, which when saponified with potassium bicarbonate in dilute methanol yielded 3,11β,17α,21-tetrahydroxy-19-nor-1,3,5(10)-pregnatrien-20-one (XX).

Using similar procedures the triacetate XVIII was converted to 11β-acetoxy-3,17α,21-trihydroxy-19-nor-1,3,5(10)-pregnatrien-20-one (XXII).

The endocrine activity of 19-norhydrocortisone (XII) and 3,11β,17α,21-tetrahydroxy-19-nor-1,3,5-(10)-pregnatrien-20-one (XX) is summarized in Table I.

Acknowledgment.—The spectral data included

(1) A preliminary announcement of this work was reported in a Communication to the Editor, THIS JOURNAL, **79**, 1508 (1957).

(2) (a) C. Djerassi, L. Miramontes and G. Rosenkranz, *ibid.*, **75**, 440 (1953); (b) A. Sandoval, L. Miramontes, G. Rosenkranz, C. Djerassi and F. Sondheimer, *ibid.*, **75**, 4117 (1953); (c) C. Djerassi, L. Miramontes, G. Rosenkranz and F. Sondheimer, *ibid.*, **76**, 4092 (1954).

(3) A. Zaffaroni, H. J. Ringold, G. Rosenkranz, F. Sondheimer, G. H. Thomas and C. Djerassi, *ibid.*, **76**, 6210 (1954).

(4) B. J. Magerlein and J. A. Hogg, *ibid.*, **80**, 2220 (1958).

(5) J. A. Hogg, F. H. Lincoln, A. H. Nathan, A. R. Hanze, B. J. Magerlein, W. P. Schneider, P. F. Beal and J. Korman, *ibid.*, **77**, 4436 (1955).

(6) The configuration at 17(20) was not definitely determined, though introduction of the dihydroxyacetone side chain (IV → V) in good yield is strong evidence in favor of the *cis* configuration, since in the *trans* series this reaction gives inferior yields (private communication, P. F. Beal of these laboratories).

(7) W. P. Schneider and A. R. Hanze, U. S. Patent 2,769,823 (1956).

(8) Compound X, as well as 11β-hydroxy-19-nor-5-androsten-3-one, gave a strong test with Tollens reagent, presumably due to β-oxidation in the A ring.

SCHEME I

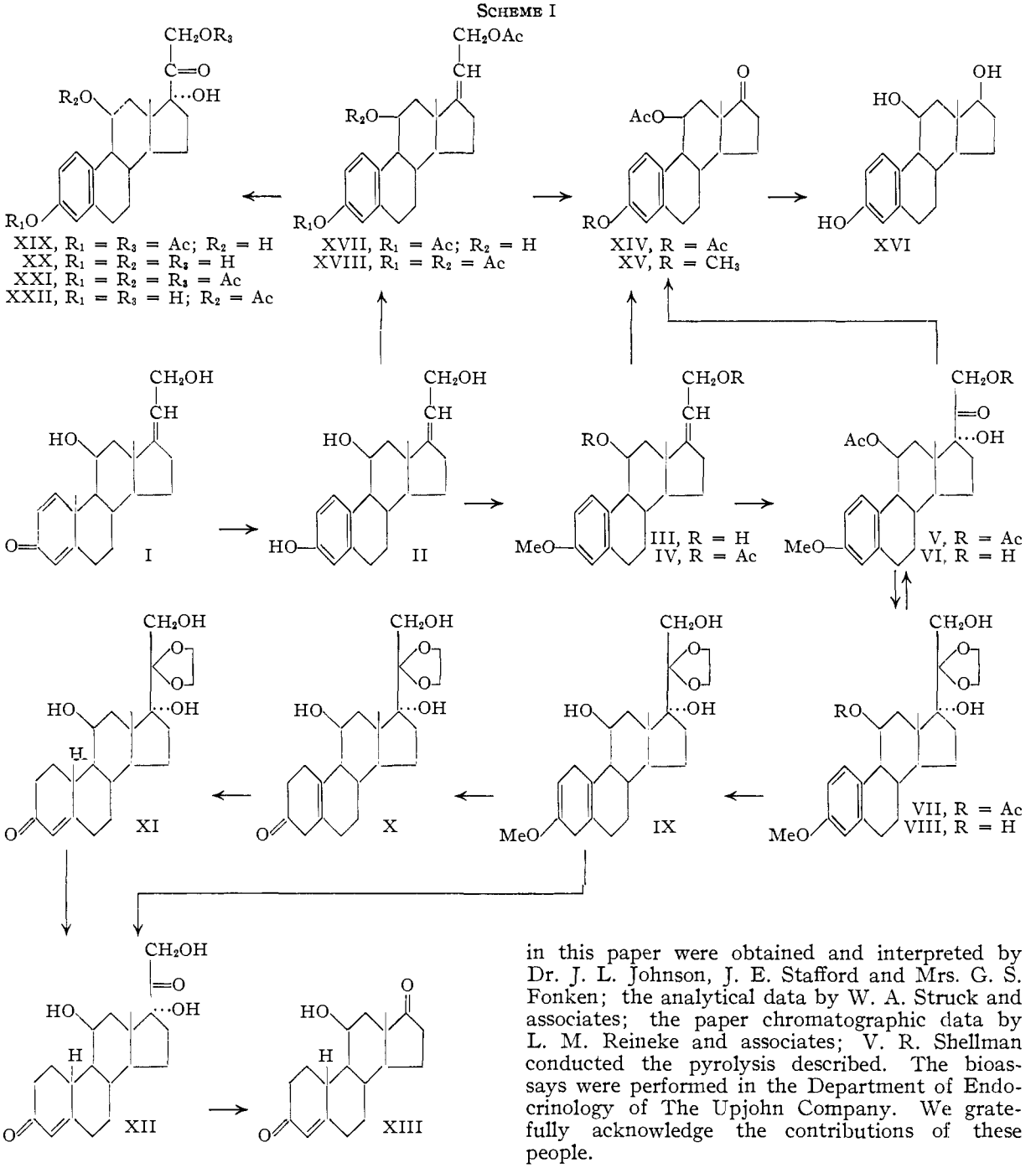


TABLE I

ENDOCRINE ACTIVITY

Compound	Glucocorticoid[a] X F	Anti-inflammatory[b] X F	Mineralocorticoid[a] X DCA
19-Norhydrocortisone XII	0.10	0.30	0.79
3,11β,17α,21-Tetrahydroxy-19-nor-1,3,5-(10)-pregnatrien-20-one (XX)	0.13	Slight[c]	0.02

[a] R. O. Stafford, L. E. Barnes, B. J. Bowman and M. M. Meizinger, *Proc. Soc. Exptl. Biol. Med.*, **89**, 371 (1955). [b] A. Robert and J. E. Nezamis, *Acta Endocrinol.*, **25**, 105 (1957). [c] This compound was reported to have anti-inflammatory activity equal to hydrocortisone.[1] Subsequent assays indicate only slight activity.

in this paper were obtained and interpreted by Dr. J. L. Johnson, J. E. Stafford and Mrs. G. S. Fonken; the analytical data by W. A. Struck and associates; the paper chromatographic data by L. M. Reineke and associates; V. R. Shellman conducted the pyrolysis described. The bioassays were performed in the Department of Endocrinology of The Upjohn Company. We gratefully acknowledge the contributions of these people.

Experimental[9]

19-Nor-1,3,5(10),17(20)-pregnatetraene-3,11β,21-triol (II).—The pyrolysis tube consisted of a vertically mounted Vycor glass tube (2.5 cm. diameter) packed with 5-mm. Vycor glass rings cut from 1-mm. tubing. This tube was heated over 30 cm. of its length by a combustion furnace. The influent solution was forced under nitrogen pressure from a reservoir through a flowmeter into the tube. The effluent gases and liquid were collected in an ice-cooled receiver vented to the exhaust system. The temperature was measured by a thermocouple inserted directly into the effluent and also by a thermocouple fastened between the pyrolysis tube and the furnace.

A suspension of 20 g. of 11β,21-dihydroxy-1,4,17(20)-[*cis*]-pregnatrien-3-one (I) in 2 l. of mineral oil (U. S. P. heavy)

(9) Melting points were taken in a capillary tube and are corrected.

was prepared by mixing in a Waring blender for 15 minutes. The suspension was passed through the pyrolysis tube at the rate of 10 ml./min. The temperature of the effluent was maintained at 400°. The upper thermocouple recorded 650°. The cooled effluent was extracted with 5% sodium hydroxide. Acidification, followed by extraction with methylene dichloride, gave, after distillation of the solvent, 8.0 g. of partially crystalline material. Chromatography over Florisil[10] furnished a fraction of 4.8 g. eluted with Skellysolve B[11]–acetone (4:1) (640 g. of Florisil was used, taking five 1280-ml. cuts per fraction). Recrystallization from ethyl acetate yielded 2.9 g. (15.2% yield), m.p. 197–199°. The analytical sample was recrystallized from methanol, m.p. 199.5–202°, $[\alpha]_D$ +110° (acetone), λ_{max}^{EtOH} 282 mμ, a_M 1916.

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.44. Found: C, 76.62; H, 8.66.

3-Methoxy-19-nor-1,3,5(10),17(20)-pregnatetraene-11β,21-diol (III).—To a solution of 7.7 g. of II and 33 g. of potassium hydroxide in 170 ml. of water there was added eleven 4-ml. portions of dimethyl sulfate at 15-minute intervals. The crude product, isolated by filtration, was chromatographed over Florisil. The fraction eluted with Skellysolve B–12% and 15% acetone weighed 4.5 g. It was recrystallized from ethyl acetate; yield 3.91 g. (48.6%), m.p. 141–144°. The analytical sample exhibited the following constants, m.p. 143–144°, $[\alpha]_D$ +122° (chloroform).

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.94; H, 8.74.

3-Methoxy-19-nor-1,3,5(10),17(20)-pregnatetraene-11β,21-diol, Diacetate (IV).—Acetylation of 2.82 g. of the methyl ether III with 20 ml. of acetic anhydride and 20 ml. of pyridine furnished, after chromatography over Florisil, an oily fraction of 3.17 g. (80% yield). It was eluted with Skellysolve B–3% and 6% acetone.

11β,21-Diacetoxy-3-methoxy-17α-hydroxy-19-nor-1,3,5(10)-pregnatrien-20-one (V).—A solution of 1.5 g. of 3-methoxy-19-nor-1,3,5(10),17(20)-pregnatetraene-11β,21-diol-11,21-diacetate (IV), 1.8 ml. of pyridine, 2.5 equivalents of N-methylmorpholine oxide peroxide[7] and 22 mg. of osmium tetroxide in 80 ml. of *t*-butyl alcohol was stirred at 26° for 1.5 hours. An excess of sodium hydrosulfite solution (1%) was added and the precipitated osmium removed by filtration. The solvent was distilled under reduced pressure. The residue was diluted with water and extracted with methylene dichloride. The extract was chromatographed over Florisil to yield a fraction of 1.1 g. eluted with Skellysolve B–9 to 12% acetone (110 g. Florisil, 220-ml. fractions of 4 each). Trituration with ether furnished 800 mg. (47.6% yield) of partially solvated crystals, m.p. 115–130°. After recrystallization from dilute acetone the crystals melted at 95–101°. Strong infrared bands at 3550, 3385 (hydroxyl) and 1658 cm.$^{-1}$ (H_2O) indicate a hydrate.

Anal. Calcd. for $C_{25}H_{32}O_7 \cdot H_2O$: C, 64.91; H, 7.41. Found: C, 65.14; H, 7.19.

11β-Acetoxy-3-methoxy-17α,21-dihydroxy-19-nor-1,3,5(10)-pregnatrien-20-one (VI).—A solution of 1.12 g. of diacetate V and 1.0 g. of potassium bicarbonate in 10 ml. of water and 50 ml. of methanol was covered with nitrogen and stored at 26° for 17 hours. The solution was neutralized, concentrated under vacuum, diluted with water and filtered. The product, m.p. 184–187°, weighed 870 mg. (79.9% yield). The analytical sample, m.p. 210–215°, was obtained by successive recrystallizations from methanol and ethyl acetate.

Anal. Calcd. for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51. Found: C, 68.99; H, 7.57.

11β-Acetoxy-3-methoxy-17α,21-dihydroxy-19-nor-1,3,5(10)-pregnatrien-20-one Ethylene Ketal (VII).—One gram of diol VI, 50 mg. of *p*-toluenesulfonic acid, 6 ml. of ethylene glycol and 75 ml. of benzene was stirred and heated under reflux for 17 hours. The water formed was removed by codistillation with the benzene. The cooled solution was washed with dilute sodium bicarbonate solution and chromatographed over Florisil. The product fraction of 702 mg., eluted with Skellysolve B–acetone (4:1), gave a negative Tollens test. A yield of 590 mg. (50.9%) of VII, m.p. 214–218°, was obtained by crystallization from ethyl acetate. The analytical sample, recrystallized from ethyl acetate, melted at 220–223°. It was dried for 2 hours at 0.1 mm. pressure at 110°.

Anal. Calcd. for $C_{26}H_{34}O_7$: C, 67.28; H, 7.67. Found: C, 67.15; H, 7.50.

Acid Hydrolysis of VII.—Fourteen milligrams of ketal VII dissolved in 4 ml. of 25% acetic acid was heated under reflux for 2 hours. The crystals, which formed on dilution with water, were collected by filtration. The recovery was 10.1 mg. (79%), m.p. 198–202°. This material was identified as VI by infrared and paper chromatographic analysis.

3-Methoxy-11β,17α,21-trihydroxy-19-nor-1,3,5(10)-pregnatrien-20-one 20-Ethylene Ketal (VIII).—A solution of 200 mg. of ketal VII in 20 ml. of benzene was added to 400 mg. of lithium aluminum hydride in 75 ml. of ether. After stirring at room temperature for one hour, 10 ml. of water was added. The organic layer was decanted and evaporated yielding 184 mg. of crystals. Recrystallization from ethyl acetate gave 140 mg. of VIII, m.p. 178–180°, $[\alpha]_D$ +94° (acetone).

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.98. Found: C, 68.48; H, 7.92.

3-Methoxy-11β,17α,21-trihydroxy-19-nor-2,5(10)-pregnadien-20-one 20-Ethylene Ketal (IX).—One hundred and fifty milligrams of lithium was added to a solution of 185 mg. of ketal VIII in 5 ml. of dioxane, 1.5 ml. of ethanol and 30 ml. of ammonia. When the reaction was completed the ammonia was evaporated and water added. The product, m.p. 170–175°, recovered by filtration, weighed 190 mg. The analytical sample, m.p. 189–197°, was prepared from ethyl acetate. Repeated crystallization failed to sharpen the melting range of this compound.

Anal. Calcd. for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43. Found: C, 67.70; H, 8.60.

11β,17α,21-Trihydroxy-19-nor-5(10)-pregnene-3,20-dione 20-Ethylene Ketal (X).—After a solution of 30 mg. of ketal IX in 10 ml. of methanol and 1 ml. of 2.5% sulfuric acid stood at 26° for 0.5 hour it was neutralized with potassium bicarbonate, partially evaporated and diluted with water to give 22 mg. of crystals. The analytical sample, m.p. 250–252°, was obtained by two recrystallizations from acetone. This compound showed a strong Tollens test.

Anal. Calcd. for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22. Found: C, 67.22; H, 8.21.

19-Norhydrocortisone (XII). Method A.—A solution of 428 mg. of crude IX in 20 ml. of 50% acetic acid–water was heated under reflux for one hour. The acid was partially neutralized with potassium bicarbonate. The solution was extracted with methylene dichloride yielding 301 mg. of crude XII. Recrystallization from acetone gave 100 mg. of 19-norhydrocortisone (XII), m.p. 240–246°. Two recrystallizations gave a sample, m.p. 256–259°, $[\alpha]_D$ +119° (methanol); λ_{max} 242 mμ, log ε 4.21.[3]

Anal. Calcd. for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 69.21; H, 8.24.

Method B.—Fifty-five milligrams of X was dissolved in 50 ml. of methanol and 40 drops of sodium methoxide solution added (1 ml. of 25% NaOMe/10 ml. of MeOH). The reaction mixture was kept under nitrogen at 26° for 20 minutes. After neutralization with acetic acid and distillation of the solvent, the residue was extracted with methylene dichloride. The extract was chromatographed over Florisil yielding 35 mg. of crystalline 11β,17α,21-trihydroxy-19-nor-4-pregnene-3,20-dione 20-ethylene ketal (XI). This material, m.p. 225–230°, showed an acceptable infrared curve λ_{max}^{EtOH} 243 mμ, a_M 11,770. The entire 35 mg. was dissolved in 6 ml. of 50% acetic acid and heated under reflux for 1.5 hours. The solution was neutralized with potassium bicarbonate and extracted with methylene dichloride. There was obtained on evaporation of the solvent 26 mg. of crystalline residue. 19-Norhydrocortisone (XII) (17 mg.) m.p. 250–257°, was isolated on recrystallization from acetone.

11β-Hydroxy-4-estrene-3,17-dione (XIII).—A slurry of 10.0 mg. of 19-norhydrocortisone (XII), 0.4 ml. of acetic acid, 0.1 ml. of water and 70 mg. of sodium bismuthate was stirred at 25° for 45 minutes. A solution of 330 mg. of potassium hydroxide in 1 ml. of water was added with cooling. The solution was extracted with methylene di-.

(10) A synthetic magnesia–silica gel made by the Floridin Co., Warren, Pa.

(11) A saturated hydrocarbon fraction, b.p. 60–71 .

chloride which on evaporation deposited a residue of 8 mg. This residue was almost pure 11β-hydroxy-4-estrene-3,17-dione (XIII) when checked by papergram analysis.

19-Nor-1,3,5(10),17(20)-pregnatetraene-3,11β,21-triol Triacetate (XVIII).—Acylation of 610 mg. of triol II with pyridine–acetic anhydride in the usual manner gave an oily product (660 mg.) which resisted crystallization even after chromatography over Florisil. Its infrared curve showed the absence of the characteristic hydroxyl absorption.

3,11β-Diacetoxy-1,3,5(10)-estratrien-17-one (XIV).—The oily diacetate from above was dissolved in 40 ml. of methylene chloride, cooled to −78° and treated with 10% excess of ozone. The solution was concentrated under vacuum. The ozonide was decomposed by stirring for one hour with 5 ml. of acetic acid and 200 mg. of powdered zinc. Following the usual work up, chromatography over Florisil and recrystallization from methanol, there was obtained 230 mg. of XIV, m.p. 180–182°. The yield from II was 33.4%. The analytical sample was prepared from methanol, m.p. 184.5–186°, $[\alpha]_D$ +111° (chloroform).

Anal. Calcd. for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08; mol. wt., 370.43. Found: C, 71.51; H, 6.96; mol. wt., 371.5 ± 1%.

11-Hydroxyestradiol (1,3,5(10)-Estratriene-3,11β,17β-triol) (XVI).—A solution of 1.0 g. of diacetate XIV in 20 ml. of benzene was added to 1.5 g. of lithium aluminum hydride in 75 ml. of ether. After heating under reflux for one hour, the reaction mixture was hydrolyzed with 10 ml. of water. The ether–benzene solution was decanted. The residue was stirred with 50 ml. of dilute hydrochloric acid, filtered, washed and dried to give crude XVI. Recrystallization from acetone yielded 470 mg. of XVI, m.p. 280–290°. A second crop weighed 100 mg., m.p. 280–285°. The analytical sample melted at 285–288° dec., $[\alpha]_D$ +129° (dioxane).

Anal. Calcd. for $C_{18}H_{24}O_3$: C, 74.95; H, 8.39. Found: C, 75.18; H, 8.50.

3-Methoxy-11β-acetoxy-1,3,5(10)-estratrien-17-one (XV). Method A.—In the manner described above 500 mg. of IV was ozonized in methylene chloride. The product isolated by chromatography over Florisil (eluted with Skellysolve B–acetone, 9:1) after recrystallization from methanol weighed 120 mg., m.p. 220–230°. The analytical sample from methanol melted 236–238°, $[\alpha]_D$ +117° (chloroform).

Anal. Calcd. for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.46; H, 7.60.

Method B.—A mixture of 100 mg. of VI, 700 mg. of sodium bismuthate, 4 ml. of acetic acid and 1 ml. of water was stirred at 26° for one hour. A solution of 3.3 g. of potassium hydroxide in 10 ml. of water was added. The mixture was diluted with methylene dichloride and filtered. Separation of the organic fraction followed by concentration yielded, after recrystallization from methanol, 20 mg. of XVIII, m.p. 226–232°, identical by infrared analysis with that prepared by method A.

3,21-Diacetoxy-19-nor-1,3,5(10),17(20)-pregnatetraen-11β-ol (XVII).—A solution of 200 mg. of 19-nor-1,3,5(10),17(20)-pregnatetraen 3,11β,21 triol (II) in 2 ml. of pyridine containing 0.13 ml. (about 5% excess) of acetic anhydride was worked up in the usual fashion after standing at 26° for 17 hours. The oily product was chromatographed over Florisil. Elution with Skellysolve B–9% acetone gave 176 mg. of product which crystallized when triturated with methanol. Infrared analysis showed the presence of the phenol acetate as well as another acetate which undoubtedly was at position 21. This material was not further purified but used directly in the next step.

3,21-Diacetoxy-11β,17α-dihydroxy-19-nor-1,3,5(10)-pregnatrien-20-one (XIX).—A mixture of 650 mg. of crude XVII, 28 ml. of *t*-butyl alcohol, 0.35 ml. of pyridine, 12.2 mg. of osmium tetroxide and 1.4 ml. of N-methylmorpholine oxide peroxide (38.8 ml. of 0.1 *N* $Na_2S_2O_5$/ml.) was stirred at room temperature for 2 hours. Excess 5% sodium hydrosulfite solution was added and then 0.5 g. of Magnesol. The mixture was filtered. The solvent was evaporated, the residue dissolved in methylene dichloride, washed with dilute acid, and dried. Chromatography over Florisil (elution with Skellysolve B–20% acetone) gave 385 mg. of crystalline product. Recrystallization from ethyl acetate–Skellysolve B yielded 320 mg., m.p. 166–168°. The analytical sample obtained by one recrystallization melted 167–168°, $[\alpha]_D$ 0° (dioxane).

Anal. Calcd. for $C_{24}H_{30}O_7$: C, 66.96; H, 7.02. Found: C, 67.24; H, 6.99.

3,11β,17α,21-Tetrahydroxy-19-nor-1,3,5(10)-pregnatrien-20-one (XX).—To a solution of 100 mg. of 21-acetate XIX in 10 ml. of methanol there was added a solution of 100 mg. of potassium bicarbonate in 1 ml. of water. The mixture was stirred at 26° under nitrogen for 18 hours. The solvent was evaporated after acidifying with a few drops of acetic acid. Trituration of the residue with water deposited 70 mg. of crystals, m.p. 240–245°. Several recrystallizations from acetone gave a sample, m.p. 256–258°, which was dried to constant weight under vacuum at 100°.

Anal. Calcd. for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57. Found: C, 69.20; H, 7.77.

17α-Hydroxy-3,11β,21-triacetoxy-19-nor-1,3,5(10)-pregnatrien-20-one (XXI).—Acylation of 1 g. of triol II formed the triacetate XVIII which was not purified but dissolved in 60 ml. of *t*-butyl alcohol, 1.2 ml. of pyridine and 3.2 ml. of N-methylmorpholine oxide peroxide. There was added 28 mg. of osmium tetroxide. The reaction was stirred at room temperature for 1.5 hours. An excess of sodium hydrosulfite solution was added, and then 3 g. of Magnesol. The mixture was filtered, concentrated under vacuum, diluted with water and extracted. Chromatography over Florisil yielded 1.02 g. of crude XXI. Recrystallization from ethyl acetate–Skellysolve B gave 800 mg. of XXI, m.p. 187–190° (yield 53.4%). The analytical sample melted 191–193°.

Anal. Calcd. for $C_{26}H_{32}O_8$: C, 66.08; H, 6.83. Found: C, 65.74; H, 7.19.

3,17α,21-Trihydroxy-11β-acetoxy-19-nor-1,3,5(10)-pregnatrien-20-one (XXII).—A solution of 40 mg. of XXI in 8 ml. of methanol containing 14 mg. of sodium methoxide was permitted to stand under nitrogen at 26° for 1 hour. The solution was neutralized by the addition of a few drops of acetic acid and the solvent evaporated under vacuum. Chromatography over Florisil gave a fraction (oil) whose infrared data indicated compound XXII. This material was not further investigated.

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