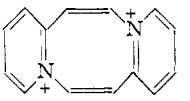
The diiodide of XI was prepared by adding potassium iodide to an aqueous solution of XI. After recrystallization from water it gave pale yellow crystals, m.p. 230–231°.[16]

*Anal.* Calcd. for $C_{19}H_{16}N_2I_2$: C, 36.07; H, 3.46. Found: C, 36.09; H, 3.76.

When an attempt was made to oxidize XI with dichromate in the hope of preparing the parent substance XV, the only reaction was the precipitation of the dichromate salt of XI. This, after recrystallization from water, yielded orange needles, m.p. 170–175° dec.

*Anal.* Calcd. for $C_{14}H_{16}N_2O_7Cr_2$: C, 39.26; H, 3.77. Found: C, 39.05; H, 3.89.

Similarly, attempts to oxidize XI using bromine water simply precipitated an unstable, yellow di-perbromide.



XV

**1,2,5,6-Bis-(tetramethylene)-octahydro-1,5-diazocine (XII).**—A solution of 1.60 g. of 3,4,7,8-tetrahydrodibenzo-[a,e]-1,5-diazocinium bromide (XI) in 25 ml. of water was subjected to hydrogenation at room temperature and atmospheric pressure using 100 mg. of Adams catalyst. When 6 moles of hydrogen had been absorbed, the hydrogenation was stopped and the catalyst removed. Neutralization of the filtrate followed by extraction with chloroform and concentration gave 600 mg. of a colorless oil; b.p. 105° at 0.2 mm., $n^{24}D$ 1.5800.

The infrared spectrum of the oil showed a strong band at 3.63 $\mu$ in addition to the usual absorption at 3.45 $\mu$. As has been pointed out by Wenkert and Roychaudhuri,[17] strong absorption in this region probably is due to an axial hydrogen at the bridgehead carbon.

*Anal.* Calcd. for $C_{14}H_{26}N_2$: C, 75.61; H, 11.79; mol. wt., 220. Found: C, 75.25; H, 11.58; mol. wt. (Rast), 208.

**The dimethiodide of XII** formed readily and, after recrystallization from a water–ethanol mixture, was obtained as white needles, m.p. 282–283° dec.

*Anal.* Calcd. for $C_{16}H_{28}N_2I_2$: C, 38.26; H, 5.62. Found: C, 37.87; H, 5.61.

**Reaction of XI with Piperidine.**—To a solution of 2.0 g. of XI in 4 ml. of water was added 1 ml. of piperidine. After the mixture had been boiled under reflux for 3 hours, it was concentrated under reduced pressure to give a tan solid. This, after recrystallization from a benzene–ethanol mixture, yielded 2.9 g. (89%) of N-(β-(2-pyridyl)-ethyl)-piperidine hydrobromide as white crystals, m.p. 173–175°.

*Anal.* Calcd. for $C_{12}H_{19}N_2Br$: C, 53.14; H, 7.06. Found: C, 53.99; H, 7.45.

Conversion of the above crystals to the corresponding dipicrate gave yellow crystals, m.p. 160–161.5°.[18] A mixture melting point determination with an authentic sample of the dipicrate of N-(β-(2-pyridyl)-ethyl)-piperidine showed no depression of melting point.

**N-(2-(2'-Piperidyl)-ethyl)-piperidine.**—A solution of 19.0 g. of N-(β-(2-pyridyl)-ethyl)-piperidine[18] in 200 ml. of a 10% hydrobromic acid solution containing 500 mg. of Adams catalyst was subjected to hydrogenation at room temperature and atmospheric pressure. After 3 moles of hydrogen had been absorbed, the catalyst was removed and the solution was made basic. Extraction with ether followed by concentration and distillation of the residue gave 18.0 g. (93%) of a colorless oil, b.p. 107° at 1 mm., $n^{29}D$ 1.4886. This was prepared for comparison with the reduction product from VI and was shown by comparison of spectra and other physical properties to be different.

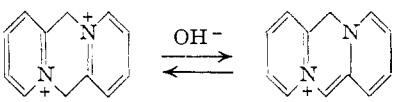
*Anal.* Calcd. for $C_{12}H_{24}N_2$: C, 73.41; H, 12.33. Found: C, 73 51; H, 11.90.

**Preparation of XI from 2-Vinylpyridine Hydrobromide.**—A sample of 4.0 g. of 2-vinylpyridine hydrobromide was heated in a sealed tube at 160° for 3 hours. The resulting solid was washed from the tube with absolute ethanol and collected by filtration. After recrystallization from an ethanol–water mixture, it yielded 2.7 g. (68%) of crystals, m.p. 238–240°. A comparison of these crystals with the sample of XI previously prepared showed them to have identical infrared spectra and a mixture of the two showed no depression of melting point.

**3,6-Dihydrodibenzo[a,d]-1,4-diazinium Dichloride (XV).**—In studying the behavior of XI toward alkali we were interested in repeating the observations of Šorm and Sedivy[12] on the analogous system XVI for comparison. When a solution of 2-chloromethylpyridine in dry acetonitrile was boiled under reflux for 5 days, a white solid separated. This, after recrystallization from an ethanol–water mixture, gave white needles, m.p. 253–255°.

*Anal.* Calcd. for $C_{12}H_{12}N_2Cl_2$: C, 56.48; H, 4.74. Found: C, 56.81; H, 5.02.

When an aqueous solution of these crystals was treated with dilute alkali, an intense red color developed and the colored substance could not be extracted from the aqueous solution with organic solvents. However, with stronger alkali, a highly unstable, dark red compound, soluble in organic solvents, did separate. It would appear that the intense red color formed in dilute alkali is due to XVII and only in strong alkali is the non-ionic, free base produced.



XVI 2 $Cl^-$ XVII $Cl^-$

(16) Löffler[6] gives 211–213°.

(17) E. Wenkert and D. K. Roychaudhuri, THIS JOURNAL, **78**, 6417 (1956).

(18) W. E. Doering and R. A. N. Weil, *ibid.*, **69**, 2461 (1947), give 159-160° as the melting point of the dipicrate of N-(β-(2-pyridyl)-ethyl)piperidine.

ROCHESTER, NEW YORK

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES, THE UPJOHN CO.]

# Preparation and Reactions of 11-Substituted 1,3,5(10)-Estratrienes.[1] I. 11-Oxygenated Estrones and Estradiols

BY BARNEY J. MAGERLEIN AND JOHN A. HOGG

RECEIVED DECEMBER 26, 1957

The aromatization of steroidal 3-keto-1,4-dienes containing 11α-hydroxy, 11α-acetoxy and 11β-hydroxy substituents or 9,11-unsaturation is reported. The conversion of these products to the 11-oxygenated 19-nortestosterones is the first reported synthesis of this type of compound wherein the 11-hydroxyl group is present during the chemical modification of ring A. A novel compound obtained by a Birch-type reduction is described.

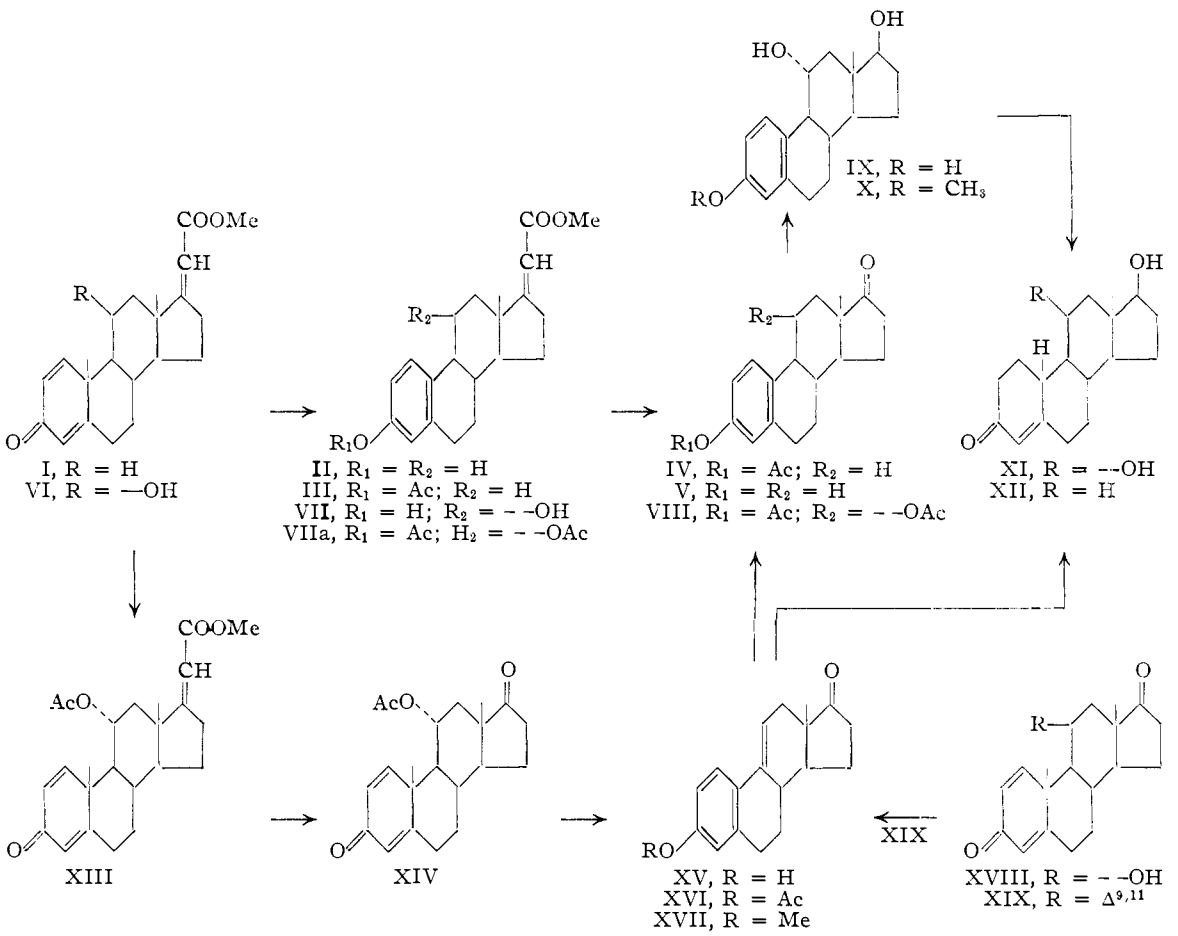
The pyrolytic method for the aromatization of 3-keto-1,4-dienes announced by Inhoffen in 1940,[2] has been used for the preparation of a variety of aromatic A ring steroids unsubstituted at C-11.[3] The pyrolysis of 11β-hydroxy, 11α-hydroxy, 11α-

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

(2) H. H. Inhoffen, *Angew. Chem.*, **53**, 471 (1940).

(3) See B. J. Magerlein and J. A. Hogg, *Tetrahedron* (in press), for a brief review of this reaction.

SCHEME I




acetoxy or 9,11-unsaturated-3-keto-1,4-dienes is now shown to give analogously substituted 1,3,5-(10)-estratrienes in contrast to the pyrolysis of 3,11-diketo-1,4-dienes which yields 9//(10)-seco-steroids.[3] These 11-oxygenated 1,3,5(10)-estra-trienes may be converted by the Birch reduction[4] to the 11-oxygenated-19-norsteroids hitherto avail-able only by the 11-hydroxylation of the corre-sponding 11-desoxy-19-norsteroids.[5]

The method described by Hogg and co-workers[6] for the preparation of 3-keto-1,4-dienes was used for the preparation of the unsaturated esters I, VI and XIII. The aromatization of these esters was accomplished by passing either a mineral oil solu-tion or suspension through a heated tube. The phenols II and VII resulting from the pyrolysis of I and VI, respectively, proved to be insoluble in dilute aqueous alkali, a property also reported for methyl 3-hydroxy-1,3,5(10)-estratriene-17-carbox-ylate.[7] The phenol II was acylated and ozonized to give estrone acetate (IV) in about 40% yield, thus establishing the skeletal structure of II. Although the precursor of II (I) is known to have the 17(20)-*cis*-configuration[8] it is not certain whether a change has occurred in the pyrolytic reaction.

In a similar series of reactions, 11α-acetoxy-estrone acetate VIII was formed from VII which when reduced with lithium aluminum hydride yielded 11α-hydroxyestradiol (IX). Methylation followed by a Birch reduction converted 11α-hydroxyestradiol (IX) to 11α-hydroxy-19-nortestos-terone (XI), a compound recently isolated from the microbiological oxidation of 19-nortestoster-one.[5]

When the aromatization reaction was extended to a 1,4-diene containing an 11α-acetoxy substitu-ent, concomitant loss of the elements of acetic acid occurred. Pyrolysis of 11α-acetoxy-1,4-androsta-diene-3,17-dione (XIV), obtained by the ozoniza-tion of XIII, furnished 3-hydroxy-1,3,5(10),9(11)-estratetraen-17-one (XV). Alternatively XV may be prepared by the aromatization of the triene XIX obtained by dehydration of 11β-hydroxy-1,4-andro-stadiene-3,17-dione (XVIII).[9]

In view of the described instability of the 11β-

(4) A. Birch, *Quart. Revs.*, **4**, 69 (1950).

(5) The 11α-hydroxyl group was introduced into a 19-norsteroid by a microbiological procedure; R. L. Pederson, J. A. Campbell, J. C. Babcock, S. H. Eppstein, H. C. Murray, A. Weintraub, R. C. Meeks, P. D. Meister, L. M. Reineke and D. H. Peterson, THIS JOURNAL, **78**, 1512 (1956). The 11β-hydroxyl group was introduced by an adrenal perfusion technique; F. B. Colton and J. W. Ralls, U. S. Patent 2,694,-080 (1954).

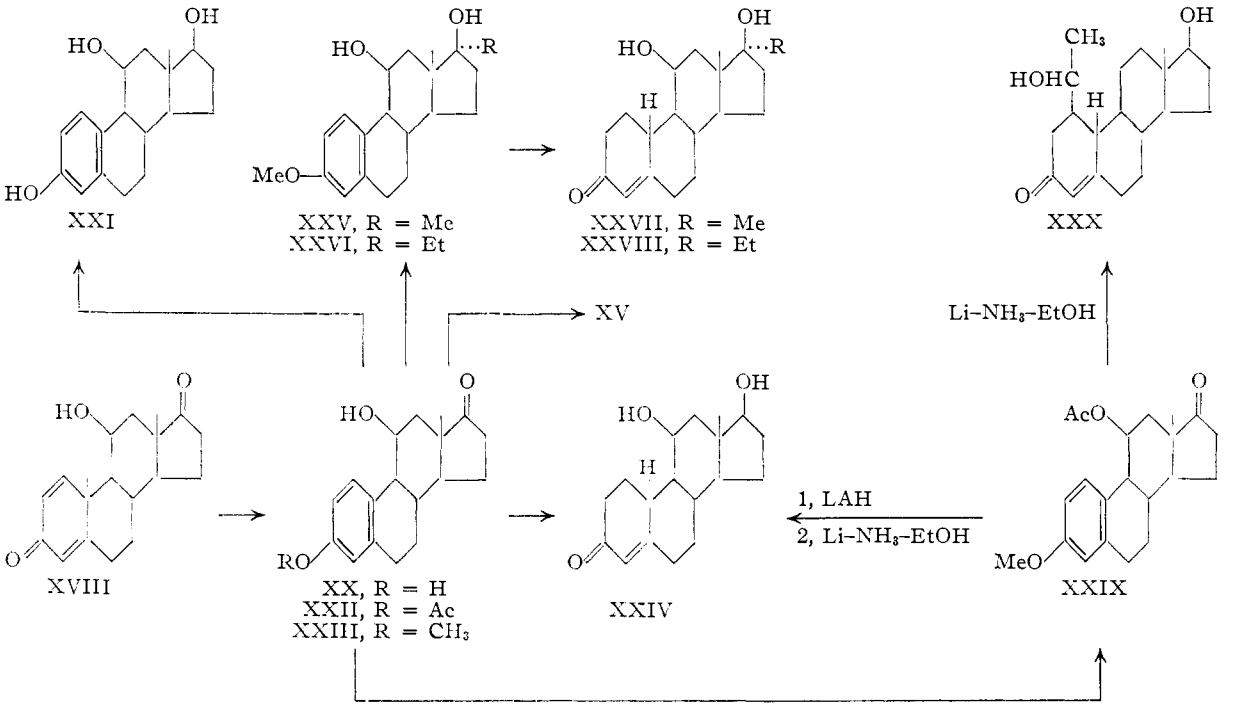
(6) J. A. Hogg, F. H. Lincoln, A. H. Nathan, A. R. Hanze, B. J. Magerlein, W. P. Schneider, P. F. Beal and J. Korman, *ibid.*, **77**, 4438 (1955).

(7) C. Djerassi and C. R. Scholz, *ibid.*, **71**, 3962 (1949).

(8) Unpublished studies from these laboratories.

(9) H. L. Herzog, C. C. Payne, M. A. Jevik, D. Gould, E. L. Schapiro, E. P. Oliveto and E. B. Hershberg, THIS JOURNAL, **77**, 4781 (1955).

SCHEME II




hydroxy group[10] we were gratified to find that 11β-hydroxy-1,4-androstadiene-3,17-dione (XVIII) could be aromatized to 11β-hydroxyestrone (XX) (Scheme II) in yields comparable with those obtained using compounds possessing an 11α-hydroxyl. Dehydration of XX offered a third means of synthesis for $\Delta^{9,11}$-estrone (XV). The preparation of $\Delta^{9,11}$-estrone (XV) from both the 11α- and 11β-hydroxy steroids inter-related the two series of compounds. Catalytic reduction of XV completed the synthesis of estrone (V) from either 11α- or 11β-hydroxy sources.

3-Hydroxy-1,3,5(10),9(11)-estratetraen-17-one (XV) was methylated, readily forming XVII which when reduced with lithium in liquid ammonia and alcohol furnished the known 19-nortestosterone (XII).

11β-Hydroxyestrone (XX) was converted to the biologically active 11β-hydroxyestradiol (XXI) and also *via* XXIII to 11β-hydroxy-19-nortestosterone (XXIV).[11] The latter reaction sequence established the structure of 11β-hydroxyestrone (XX).

The estrogenic activities of the substituted estradiols as measured by the stimulation of uterine growth in castrate female rats are shown in Table I.

TABLE I

ESTROGENIC ACTIVITY

| | % Estradiol |
|---|---|
| 11β-Hydroxyestradiol (XXI) | 0.6 |
| 11α-Hydroxyestradiol (IX) | 0.05 |
| $\Delta^{9,11}$-Estrone (XV) | Slight |
| 11β-Hydroxyestrone (XX) | 5% of estrone |

(10) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," third edition, Reinhold Publishing Corp., New York, N. Y., 1949, p. 408.

(11) J. W. Ralls, U. S. 2,778,841 (1957). The authors are indebted to J. A. Campbell of these laboratories for an authentic sample of 11β-hydroxy-19-nortestosterone.

The 17α-alkyl-11β-hydroxy-19-nortestosterone derivatives XXVII and XXVIII were prepared from 11β-hydroxyestrone XX as indicated in Scheme II.

The oral anabolic and androgenic potencies of these 17-alkylated derivatives in terms of 17-methyltestosterone as a standard are recorded in Table II.

TABLE II

ORAL MYOTROPIC-ANDROGENIC ACTIVITY[12]

| | Myotropic | Androgenic |
|---|---|---|
| 17-Methyltestosterone | 1.0 | 1.0 |
| 17-Methyl-11β,17α-dihydroxy-19-nor-4-androsten-3-one (XXVII) | 8.0 | 2.6 |
| 17-Ethyl-11β,17α-dihydroxy-19-nor-4-androsten-3-one (XXVIII) | 1.1 | 0.8 |

Although the 11β-acetate derivative[13] XXIX was successfully converted to 11β-hydroxy-19-nortestosterone by reduction with lithium aluminum hydride and then by a lithium–ammonia–alcohol reduction, a novel reaction was encountered when the acetate XXIX was used directly in the Birch-type reduction. The product from this reaction, isolated in 10% yield, is assigned the structure XXX. The empirical formula for XXX was determined by elemental analysis. A C-methyl determination showed the presence of two C-methyl groups. Infrared absorption indicated a 3-keto-$\Delta^4$- and hydroxyl functions. A maximum is found in the ultraviolet absorption at 247 mμ.

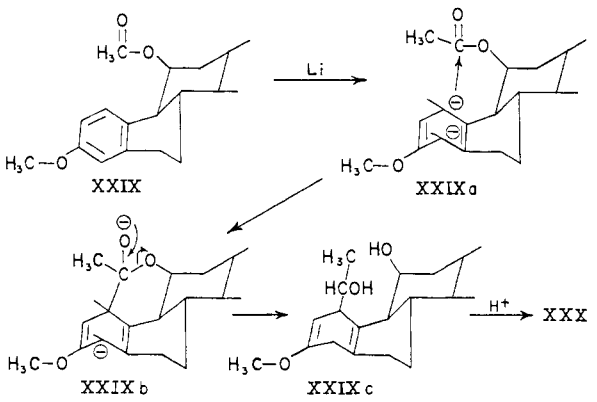
(12) Measured by weight increase in levator ani muscle and seminal vesicles in castrated immature rats.

(13) The 11β-hydroxy group is acylated with acetic anhydride–pyridine at room temperature in the 1,3,5(10)-estratriene series as well as in the 19-nor series. See also A. Zaffaroni, H. F. Ringold, G. Rosenkranz, F. Sondheimer, G. H. Thomas and C. Djerassi, THIS JOURNAL, **76**, 6210 (1954).

Chromic acid oxidation of XXX gives an oily product, showing a maximum in the ultraviolet at 240 mμ unchanged on addition of alkali. The latter data strongly suggest that the hydroxyethyl grouping is attached at C-1, for were it at either C-2 or C-4 a bathochromic shift of the ultraviolet absorption maximum would result.

Scheme III illustrates a probable mechanism whereby compound XXX may be formed, *i.e.*, by an internal Claisen-type transfer of the acetate group from oxygen at 11 to the carbon at position 1.

SCHEME III




The initial reaction with the lithium in ammonia is the formation of the dianion XXIXa. Due to the favorable steric relationship of the carbanion at 1 and the carbonyl of the 11 acetate it is postulated that nucleophilic addition to acetate carbonyl occurs resulting in XXIXb. Structure XXIXb represents the initial intermediate in this Claisen type transfer of acetyl from the 11-oxygen to the 1-position. The transition of XXIXb to the enol ether XXIXc involves: (1) the completion of the Claisen-type transfer of acetyl to position 1; (2) the acquisition of two protons, one at position 4 and one at position 11; and (3) reduction of the acetyl now located in position 1.

**Acknowledgment.**—The spectral data included 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 pyrolyses described. The bioassays were performed in the Department of Endocrinology of The Upjohn Company. We gratefully acknowledge the contribution of these people.

## Experimental[14]

**Methyl 11α-Hydroxy-3-keto-1,4,17(20)-[*cis*]-pregnatrien-21-oate (VI).**—To a solution of 50 g. of 11α-hydroxyprogesterone in 550 ml. of *t*-butyl alcohol at 55° there was added 82.5 ml. of diethyl oxalate and 82.5 g. of 25% sodium methoxide solution in methanol. The yellow glyoxalate precipitate was dissolved by the addition of a solution of 18.6 g. of sodium acetate, 21.9 ml. of acetic acid and 590 ml. of methanol. The reaction mixture was cooled to 0° and a solution of 76 g. of bromine in 400 ml. of methanol added over a period of 15 minutes. The cooling bath was removed, 155 g. of 25% sodium methoxide solution added and the mixture stirred at room temperature for 1.5 hours. The reaction mixture was poured into 4 volumes of ice-water with vigorous stirring. The amorphous bromide was collected by filtration and air-dried.

A solution of 20 g. of crude bromide in 60 ml. of collidine was heated under reflux for 50 minutes. The dark mixture was poured into cold, dilute hydrochloric acid. The product was collected by filtration and air-dried (14.5 g.).

Chromatography of 10 g. of crude diene-one VI over 200 g. of Florisil[15] gave 3.29 g. of partially crystalline product, eluted with 13% acetone–Skellysolve B[16] and 20% acetone–Skellysolve B. Crystallization from ethyl acetate yielded 1.6 g. of VI, m.p. 230–240°, which when recrystallized weighed 1.07 g., m.p. 245–252°, $[\alpha]_D$ +141° (acetone).

*Anal.* Calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 73.98; H, 8.07.

**Methyl 11α-Acetoxy-3-keto-1,3,17(20)-[*cis*]-pregnatrien-21-oate (XIII).**—Acylation of methyl 11α-hydroxy-3-keto-1,3,17(20)-[*cis*]-pregnatrien-21-oate (VI) with acetic anhydride and pyridine gave, after chromatography over Florisil (eluted with Skellysolve B–8% acetone), crystalline XIII. The analytical sample, m.p. 140–142°, $\lambda_{max}^{EtOH}$ 239 mμ, 23,925, was prepared by recrystallization from ethyl acetate–Skellysolve B.

*Anal.* Calcd. for $C_{24}H_{30}O_5$: C, 72.32; H, 7.59. Found: C, 72.15; H, 8.01.

**Methyl 3-Keto-1,4,17(20)-[*cis*]-pregnatrien-21-oate[17] (I).**—In a similar manner compound I was prepared from progesterone in 40% yield. The analytical sample melted at 173–177°.

*Anal.* Calcd. for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.14; H, 8.01.

**Methyl 3-Hydroxy-19-nor-1,3,5(10),17(20)-pregnatetraen-21-oate (II).**—A solution of 3.0 g. of methyl 3-keto-1,4,17(20)-[*cis*]-pregnatrien-21-oate (I) in 300 ml. of mineral oil (white mineral oil, visc. 85) was prepared by heating to 140°. This solution was passed through a Vycor glass tube (2 cm. × 50 cm.) at 550° at the rate of 10 ml./min. The pyrolysis tube was packed with triple turned Pyrex glass helices. The effluent was collected in a flask cooled in ice-water, gaseous by-products being passed through a condenser to the exhaust system. A stream of nitrogen was passed through the tube while it was heating to the desired temperature and also while cooling.

The effluent solution was refrigerated at 2° for 3–4 days, and the oil decanted from the precipitate. The crude steroid was dissolved in 160 ml. of methylene dichloride and chromatographed over 80 g. of Florisil. The crystalline fraction eluted with 6% acetone–Skellysolve B weighed 539 mg. The supernatant oil from above was diluted with 3 volumes of Skellysolve B and passed over 160 g. of Florisil. After eluting with several portions of Skellysolve B to remove the oil, the product was eluted with 6% acetone–Skellysolve B. The crystalline fraction weighed 413 mg.

The two crystalline fractions were combined and recrystallized from methanol to give 440 mg. of II, m.p. 131–136°. The yield was 15.3%. Two crystallizations from methanol raised the m.p. to 138.5–141°. There was evidence of a polymorphic form, m.p. *ca.* 165°.

*Anal.* Calcd. for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.44, 77.64; H, 8.32, 7.94.

**Methyl 3-Acetoxy-19-nor-1,3,5(10),17(20)-pregnatetraen-21-oate (III).**—A solution of 440 mg. of II in 1.5 ml. of acetic anhydride and 3.0 ml. of pyridine was permitted to stand at 26° for 18 hours. The solution was poured into ice-water and the crystals collected by filtration to yield 410 mg. of acetate, m.p. 159–163° (82.4% yield). Recrystallization from ethyl acetate furnished an analytical sample, m.p. 165–167°.

*Anal.* Calcd. for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 74.78; H, 7.85.

**Estrone Acetate (IV).**—A solution of 100 mg. (0.28 millimole) of III in 30 ml. of methylene dichloride was cooled in Dry Ice–acetone and treated with 0.31 millimole of ozone. The solvent was distilled at 20 mm. pressure. The ozonide was dissolved in 15 ml. of acetic acid, 150 mg. of powdered zinc added, and the mixture stirred 1.5 hours. The zinc

(14) Melting points were determined in a capillary tube and are corrected for stem exposure.

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

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

(17) This compound was first prepared by J. Korman of these laboratories.

was filtered and the filtrate concentrated under vacuum to 2–3 ml. This residue was diluted with methylene dichloride, washed with dilute hydrochloric acid, dried and concentrated to an oil. When chromatographed over Florisil, 19 mg. of a crystalline fraction (eluted with 6% acetone–Skellysolve B), m.p. 110–120°, was obtained. Recrystallization from methanol gave estrone acetate, m.p. 122–125°, whose m.p. was not depressed when admixed with an authentic sample of estrone acetate.

**Methyl 3,11α-Dihydroxy-19-nor-1,3,5(10),17(20)-pregnatetraen-21-oate (VII).**—In the manner described for the preparation of II, 5.5 g. of methyl 11α-hydroxy-3-keto-1,4,17(20)-[*cis*]-pregnatrien-21-oate (VI) was pyrolyzed at 600° in a solution of 500 ml. of freshly distilled tetralin and 50 ml. of mineral oil. The effluent was chromatographed over 200 g. of Florisil yielding a broad fraction of 2.65 g., eluted with 13% acetone–Skellysolve B and 16% acetone–Skellysolve B. Although this fraction could not be crystallized, papergram analysis and ultraviolet absorption data showed it to be essentially one compound, $\lambda_{max}^{EtOH}$ 224 mμ, ε 17,375; 279 mμ, ε 2,275; 287 mμ, ε 1.175.

**Methyl 3,11α-Diacetoxy-19-nor-1,3,5(10),17(20)-pregnatetraen-21-oate (VIIa).**—Acylation of 3.1 g. of crude VII in the usual fashion followed by chromatography over 200 g. of Florisil gave a broad fraction of 3.2 g. (83% yield) of oily VIIa (eluted with 3% acetone–Skellysolve B and 6% acetone–Skellysolve B).

**3,11α-Acetoxy-1,3,5(10)-estratrien-17-one (VIII).**—The oily acetate VIIa (3.2 g.) was dissolved in 200 ml. of methylene dichloride and ozonized as previously described. The crude product was chromatographed over 250 g. of Florisil. The fraction eluted with 9% acetate–Skellysolve B weighed 1.04 g. When crystallized from methanol there was isolated 0.5 g. of VIII, m.p. 168–171°. The yield was 19.7% based on VIIa. The analytical sample, prepared from methanol, melted at 172–173°.

*Anal.* Calcd. for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 71.36; H, 6.95.

**3,11α,17-Trihydroxy-1,3,5(10)-estratriene (11α-Hydroxyestradiol) (IX).**—A solution of 310 mg. of 3,11α-diacetoxy-1,3,5(10)-estratrien-17-one (VIII) in 5 ml. of benzene and 15 ml. of ether was added to 0.5 g. of lithium aluminum hydride in 50 ml. of ether. The reaction mixture was refluxed one hour and hydrolyzed by the addition of dilute hydrochloric acid. The yield of crude triol was 213 mg. (88.4% yield). The analytical sample, recrystallized from ethyl acetate, melted at 250–251°.

*Anal.* Calcd. for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 75.29; H, 8.23.

**3-Methoxy-11α,17-dihydroxy-1,3,5(10)-estratriene (X).**—A solution of 520 mg. of 3,11α,17-trihydroxy-1,3,5(10)-estratriene (IX) in 25 ml. of methanol and 5 ml. of water containing 3 g. of potassium hydroxide was cooled to 5° and four additions of 1.5 ml. of dimethyl sulfate were made at 30-minute intervals. After the fourth addition the methanol was removed by a stream of air and the reaction mixture worked up to give a partially crystalline product. Chromatography over 40 g. of Florisil furnished a crystalline fraction of 400 mg. (eluted with 20% acetone–Skellysolve B) which on two recrystallizations from ether melted at 144–145°.

*Anal.* Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.56; H, 8.70.

**11α-Hydroxy-19-nortestosterone (XI).**—To a solution of 400 mg. of X in 35 ml. of anhydrous ether and 25 ml. of liquid ammonia cooled in a Dry Ice–acetone-bath there was added 400 mg. of lithium. After the metal was dissolved, 4 ml. of absolute ethanol was added over a period of 30 minutes. The ammonia was evaporated, water added and the reaction worked up. The oily product was dissolved in 25 ml. of methanol containing 3 ml. of water and 1 ml. of concentrated hydrochloric acid. After refluxing for 30 minutes the product was extracted with methylene dichloride and chromatographed over 40 g. of Florisil. The yield was 178 mg. (46.5%), m.p. 168–172° (eluted with 50% acetone–Skellysolve B). Recrystallization from acetone raised the m.p. to 179–181°. This material showed no m.p. depression when mixed with a known sample of 11α-hydroxy-19-nortestosterone prepared by the bio-oxidation of 19-nortestosterone.[5]

**11α-Acetoxy-1,4-androstadiene-3,17-dione (XIV).**—A solution of 6 g. of crude acetate XIII was treated with 10% excess of ozone as described above. To this solution there was added 20 ml. of acetic acid and 1 g. of powdered zinc. The mixture was warmed to room temperature and stirred for 1 hour, during which time 4–5 further 1-g. additions of zinc were added. The zinc was removed by filtration and the methylene chloride solution washed with dilute hydrochloric acid and dried. There was obtained by chromatography over Florisil, when eluted with Skellysolve B–15% acetone, 1.91 g. of crude XIV. When recrystallized from ethyl acetate the yield of XIV, m.p. 235–242°, was 1.35 g. An analytical sample prepared by recrystallization from ethyl acetate melted at 246–248°.

*Anal.* Calcd. for $C_{20}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.42, 73.15; H, 7.95, 7.68.

**3-Hydroxy-1,3,5(10),9(11)-estratetraen-17-one (XV).**—A suspension of 1.5 g. of XIV in 150 ml. of heavy mineral oil was pyrolyzed at 600° in the manner previously described. The effluent was diluted with ether and extracted with 5% sodium hydroxide. Acidification of the alkaline extract followed by re-extraction gave 710 mg. of crude yellow crystalline XV which was recrystallized from ethyl acetate to yield 300 mg. of XV, m.p. 249–253° (yield 33.2%). The analytical sample melted at 257–259°; $\lambda_{max}^{EtOH}$ 263 mμ, ε 18,050; 298 mμ, ε 3,125.

*Anal.* Calcd. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.59; H, 7.82.

**Estrone (V) from 3-Hydroxy-1,3,5(10),9(11)-estratetraen-17-one (XV).**—A solution of 50 mg. of XV and 10 ml. of glacial acetic acid containing 25 mg. of platinum oxide was shaken under an atmosphere of hydrogen for 30 minutes. At the end of this time, there was no qualitative test for ultraviolet absorption at 264 mμ. The catalyst was filtered and the solvent evaporated. Estrone (20 mg.), m.p. 228–233°, was isolated by recrystallization from ethyl acetate. The infrared spectrum of this material was identical with that of a known sample of estrone.

**1,4,9(11)-Androstatriene-3,17-dione (XIX).**—11β-Hydroxy-1,4-pregnadiene-3,17-dione (XVIII)[9] (1.0 g.) was suspended in a mixture of 100 ml. of benzene, 40 ml. of ether, 20 ml. of water and 40 ml. of concentrated hydrochloric acid. The suspension was stirred vigorously and heated at reflux for 17 hours. The layers were separated and the product isolated by chromatography over Florisil (eluted with Skellysolve B–6% acetone). Several recrystallizations from ethyl acetate gave pure XIX, m.p. 164–166°, $[\alpha]D$ +102° (chf.).

*Anal.* Calcd. for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.66; H, 7.96.

**3-Hydroxy-1,3,5(10),9(11)-estratetraene-17-one (XV) from 1,3,9(11)-Androstatriene-3,17-dione (XIX).**—Pyrolysis of XIX by the above method gave 29% yield of XV, m.p. 255–257°. This material was proved to be identical with the pyrolysis product of XIV since both were converted to the methyl ether XVII.

**19-Nortestosterone (XII).**—To a solution of 50 mg. of XV in 1.5 ml. of methanol and 0.6 ml. of water containing 0.5 g. of potassium hydroxide was added a total of 0.6 ml. of dimethyl sulfate. When the reaction was completed, the methanol was removed by evaporation and water added. The product was removed by extraction with methylene chloride. Evaporation of the solvent followed by crystallization of the residue from ether–Skellysolve B gave 35 mg. of methyl ether XVII, m.p. 142–145°.

One hundred milligrams of lithium was added to a solution of 35 mg. of XVII in 15 ml. of ether, 1 ml. of ethanol and 25 ml. of ammonia. After the metal had reacted the ammonia was evaporated. The enol ether was extracted with methylene dichloride. The residue obtained after evaporation of the solvent was dissolved in 15 ml. of methanol, 0.5 ml. of hydrochloric acid and 2 ml. of water. The solution was heated under reflux for 0.5 hours. After working up as described above there was obtained 9 mg. of crystalline 19-nortestosterone (eluted from a Florisil column with Skellysolve β–acetone (7:1)). The identification was made on the basis of paper chromatography.

**3,11β-Dihydroxy-1,3,5(10)-androstatriene-17-one (XX).**—In a manner previously described 1.69 g. of XVIII in a suspension of 170 ml. of U.S.P. heavy mineral oil was pyrolyzed at the rate of 10 ml. per minute at a temperature of

approximately 600°. The effluent was diluted with ether and extracted with 5% sodium hydroxide. Acidification of the extract and recovery of the product by extraction with methylene chloride yielded after chromatography over Florisil (eluted with Skellysolve B–15% acetone), a crude fraction (0.24 g.) which when recrystallized from ethyl acetate melted 246–251°. Recrystallization from ethyl acetate raised the melting point to 255–258°. The analytical sample melted at 254–257°, $[\alpha]D$ +194° (dioxane).

*Anal.* Calcd. for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 75.39; H, 7.76.

A less polar compound also was isolated. This compound, though present in small amounts, was identified as 3-hydroxy-1,3,5(10),9(11)-androstatraen-17-one (XV) by infrared analysis.

Acylation of XX with acetic anhydride (1 mole) and pyridine yielded the **monoacetate XXII**, m.p. 186–187° $[\alpha]D$ +192° (chf.).

*Anal.* Calcd. for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 73.26; H, 7.54.

**3-Methoxy-11β-hydroxy-1,3,5(10)-estratriene-17-one (XXIII).**—To a solution of 150 mg. of XX and 160 mg. of potassium hydroxide in 1.6 ml. of water and 8 ml. of methanol there was added a total of 2.7 ml. of dimethyl sulfate. When the reaction was completed the solvent was evaporated under vacuum. Trituration of the residue with water gave 160 mg. of methyl ether XXIII, m.p. 150–155°. The analytical sample from methanol softened at 160°, resolidified, and remelted at 169–170°.

*Anal.* Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.06. Found: C, 76.09; H, 8.36.

**11β-Hydroxy-19-nortestosterone (XXIV).**—To a solution of 40 mg. of XXIII in 1 ml. of ethanol, 10 ml. of ether and 25 ml. of ammonia there was added 100 mg. of lithium. After the lithium had reacted, the ammonia was evaporated. The product was isolated by extraction with methylene dichloride. The crude enol ether obtained by evaporation of the solvent was dissolved in 20 ml. of methanol, 2 ml. of water and 0.5 ml. of hydrochloric acid. After 15 minutes at 26° the mixture was neutralized. Chromatography over Florisil gave 18 mg. of 11β-hydroxy-19-nortestosterone (XXIV) (eluted with acetone–Skellysolve B, 1:1). This material was identical by infrared and paper chromatography analyses with a known sample of 11β-hydroxy-19-nortestosterone.[11]

**17-Methyl-3-methoxy-1,3,5(10)-androstatriene-11β,17β-diol (XXV).**—A solution of 160 mg. of methyl ether XXIII, 2 ml. of 4 *M* methylmagnesium bromide and 25 ml. of benzene was heated under reflux for 17 hours. The reaction mixture was poured onto hydrochloric acid–ice and extracted with methylene chloride. The crude product (160 mg.) was recrystallized from ethyl acetate–Skellysolve B to give 90 mg. of XXV, m.p. 155–158°. The analytical sample melted at 162–163°.

*Anal.* Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 76.26; H, 8.92.

**17-Methyl-11β,17β-dihydroxy-19-nor-4-pregnen-3-one (XXVII).**—Two hundred and fifty milligrams of lithium was added to a solution of 380 mg. of XXV in 10 ml. of dioxane, 80 ml. of ammonia and 2.5 ml. of ethanol. When the reaction was completed the solvent was evaporated, water added and the crude enol ether extracted with methylene chloride. The crystalline enol ether was not characterized but was dissolved in 20 ml. of methanol containing 2 ml. of water and 0.5 ml. of concentrated hydrochloric acid. The mixture was heated under reflux for 15 minutes. Excess sodium acetate was added, the methanol distilled under vacuum and the product extracted with methylene chloride. Crystallization of the residue obtained by the evaporation of the solvent furnished 140 mg. of XXVII, m.p. 216–222°. The analytical sample, m.p. 219–224°, $[\alpha]D$ +67° (chf.), was obtained from ethyl acetate.

*Anal.* Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.92; H, 9.36.

**17α-Ethyl-3-methoxy-1,3,5(10)-estratriene-11β,17β-diol (XXVI).**—To a solution of 3.1 g. of methyl ether XXIII in 160 ml. of benzene there was added a twenty-fold excess of ethyllithium in hexane. A white solid was rapidly precipitated. After 18 hours at 26° ice-water was added and the organic layer separated. This solution was percolated through a column of Florisil. Elution with successive portions of Skellysolve B–6% acetone and Skellysolve B–9% acetone led to the separation of 1.7 g. of starting ketone and 1.2 g. of 17α-ethyl-1,3,5(10)-estratrien-3,11β,17β-triol (XXVI). This triol was pure enough for use in the next step. The ketonic fraction was recycled. The analytical sample prepared from 2-propanol–Skellysolve B, melted at 148–149°.

*Anal.* Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.37; H, 9.41.

**17α-Ethyl-11β-hydroxy-19-nortestosterone (XXVIII).**—One and one-half grams of lithium was added to a solution of 1.8 g. of crude XXVI dissolved in 40 ml. of dioxane, 400 ml. of ammonia and 15 ml. of 95% ethanol. When the reaction was completed, the ammonia was evaporated and the residue chromatographed over Florisil. There was eluted with Skellysolve B–15% acetone 745 mg. of crystalline solid. Recrystallization from acetone gave 470 mg. of XXVIII, m.p. 165–167°.

*Anal.* Calcd. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.62; H, 9.41.

**11β-Hydroxyestradiol (XXI).**—Reduction of crude XX with lithium aluminum hydride yielded 45% of 11β-hydroxyestradiol,[18] m.p. 291–295°.

**17β-Hydroxy-1-(2′-hydroxyethyl)-4-estren-3-one (XXX).**—In the manner previously described 1.0 g. of 11β-hydroxyestrone (XX) was acetylated with 5 ml. of acetic anhydride and 7 ml. of pyridine. The resulting crude, crystalline 3-methoxy-11β-acetoxy-1,3,5(10)-estratrien-17-one (XXIX) was dissolved in a mixture of 30 ml. of dioxane,[19] 10 ml. of ethanol and 150 ml. of ammonia. One gram of lithium was added. When the reaction was completed, the ammonia was evaporated, water added and the product isolated by extraction with methylene dichloride. The solvent was evaporated. The residue was dissolved in a solution of 50 ml. of methanol, 5 ml. of water and 1 ml. of concentrated hydrochloric acid. After heating under reflux for 15 minutes, the methanol was distilled. The residue was extracted with methylene dichloride and percolated through a column of Florisil. The crystalline fraction eluted with Skellysolve B–acetone (1:1) was recrystallized from ethyl acetate. The yield of XXX, m.p. 210–215°, was 85 mg. The analytical sample, $\lambda_{max}^{EtOH}$ 247 mμ, $a_M$ 15,000, melted 221–222°.

*Anal.* Calcd. for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04; C-Me, 4.72. Found: C, 72.04; H, 8.90; C-Me, 7.67; C-Me (estradiol), 2.69.

**Oxidation of 17β-Hydroxy-1-(2′-hydroxyethyl)-4-estren-3-one (XXX).**—A mixture of 30 mg. of XXX and 47 mg. of chromic oxide in 2 ml. of acetic acid and 1 drop of water was maintained at 5° for one hour and at 25° for two hours. The product, isolated by dilution and extraction, weighed 24 mg. After chromatography over Florisil, the oily fractions showed $\lambda_{max}^{EtOH}$ 240–242 mμ, unchanged on addition of alkali. Infrared showed no hydroxyl absorption.

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