SYNTHESIS OF 19-NORSTEROIDS III. (1) SYNTHESIS AND BIRCH REDUCTION OF d,l-13-PHENYL-18-NORESTRADIOL-3-METHYL ETHER (2)

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d,l-13-Phenyl-18-norestradiol 3-methyl ether (Va) was synthesized by use of 2-phenylcyclopentane-1,3-dione in place of 2-methylcyclopentane-1,3-dione in an established estrone synthesis proceeding from 1,2,3,4-tetrahydro-6-methoxy-1-vinyl-1-naphthol. Conversion of d,l-13-phenyl-18-norestradiol 3-methyl ether (Va) to d,l-13-phenyl-18,19-bisnortestosterone (XI) was possible by a selective Birch reduction providing the C-17 alcohol was masked as a tetrahydropyranyl ether. Alternatively d,l-13-phenyl-18,19-bisnortestosterone (XI) could be prepared from a C-13 dihydrophenyl analog by rearomatization.

We wish to report the first synthesis of steroid hormone analogs substituted at C-13 with a phenyl group (3).

The title compound (Va) was prepared by a sequence of reactions (Fig. 1) analogous to the sequence described by us and others in the synthesis of d,l-estrone methyl ether (4). 2-Phenylcyclopentane-1,3-dione (5) was condensed with 1,2,3,4-tetrahydro-6-methoxy-1-vinyl-1-naphthol to afford the expected 2-[2-(3,4-dihydro-6-methoxy-1(2H)-naphthylidene)ethyl]-2-phenylcyclopentane-1,3-done (I). Cyclization in acetic acid in the presence of p-toluenesulfonic acid afforded d,l-8(9),14-bisdehydro-13-phenyl-18-norestrone 3-methyl ether (II). Hydrogenation of this product (II) in the presence of palladium-on-charcoal catalyst, in benzene, stopped after uptake of one mole of hydrogen, and the major product was obtained crystalline, having ultraviolet λmax 285mμ, ε15.400. This compound is assigned

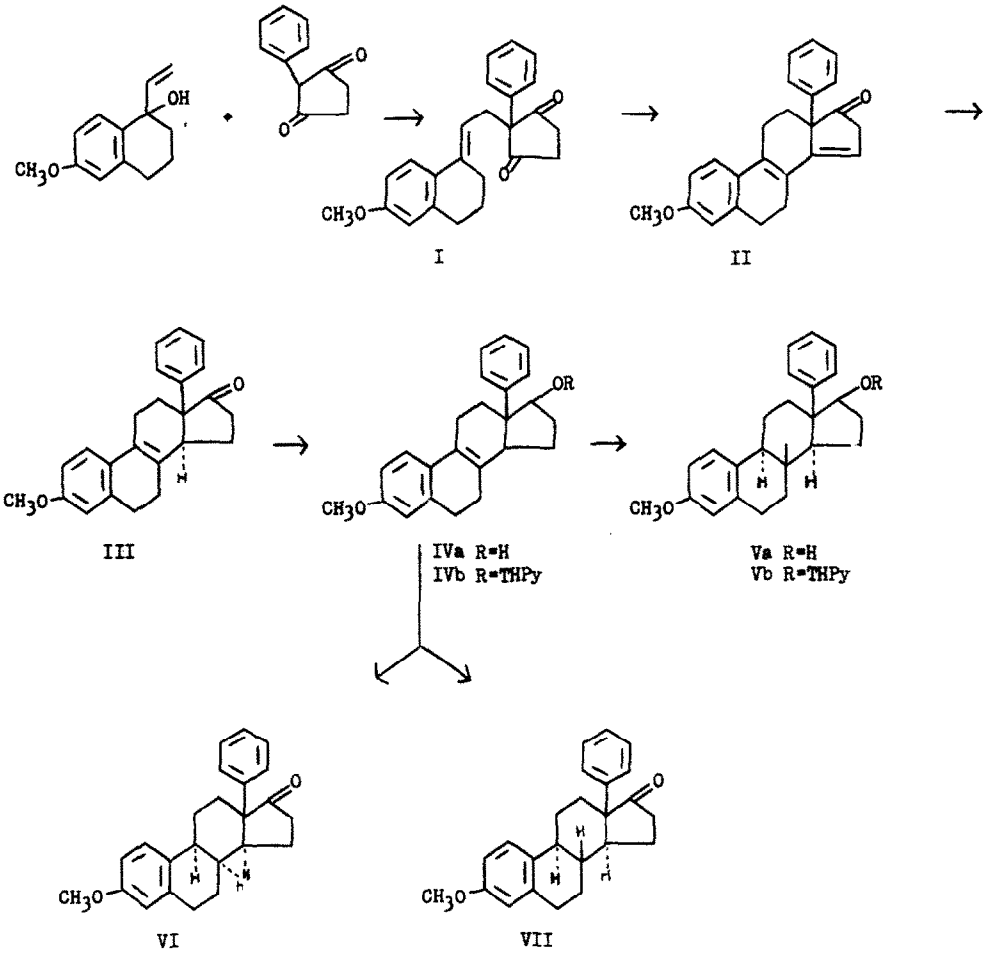


Fig. 1

structure III in which the stereochemistry at C-14 is considered to be α- as a result of hydrogenation from the less hindered side.

d,l-8(9)-Dehydro-13-phenyl-18-norestrone methyl ether (III) was reduced with sodium borohydride and then with excess potassium in liquid ammonia. The crude product was oxidized with CrO_3/pyridine to the C-17 ketone and chromatographed on alumina. Two isomers were isolated, the

estrone analog VII m.p. 196-198°, ultraviolet λmax 278, ε2138, and the ketone VI m.p. 172-174°, λmax 278, ε2780; obtained in an approximate ratio of 4:1. The stereochemistry of ketone VI was established by the finding that it is the major product formed in the hydrogenation of d,l-8(9)-dehydro-13-phenyl-18-norestrone methyl ether (III) using palladium-on-charcoal in acetic acid (cf. 4). Ketone VII is assigned 8β,9α-stereochemistry in analogy with results in the earlier mentioned estrone total syntheses.

In an alternate procedure, the alcohol IVa was converted to the 17-tetrahydropyranyl ether IVb before performing the potassium in liquid ammonia reduction. The crude product following this reduction was chromatographed on basic alumina to give in good yield the pure tetrahydropyranyl ether Vb. Hydrolysis of compound Vb afforded d,l-13-phenyl-18-norestradiol-3-methyl ether (Va). The stereochemical purity of this compound was confirmed by oxidation to the previously characterized d,l-13-phenyl-18-norestrone methyl ether VII.

In the preparation of 19-nortestosterone analogs and derivatives, a key step is Birch reduction of the aromatic A-ring. When this reaction was conducted on alcohol Va for a one-hour period with a large excess of sodium in liquid ammonia and t-butanol, it was found that in the major product IX both aromatic rings were reduced to the dihydro stage. The infrared spectrum of compound IX displayed absorption at 5.88, 5.98 and 10.4μ. N.M.R. showed one vinylic proton at 5.35τ (C_2) and three vinylic protons at 4.30τ (angular dihydroaromatic) (6). Further proof of structure was obtained by further conversion of compound IX to the nortestosterone derivative XI as reported below.

Partial reduction of alcohol Va with a slight excess of sodium in

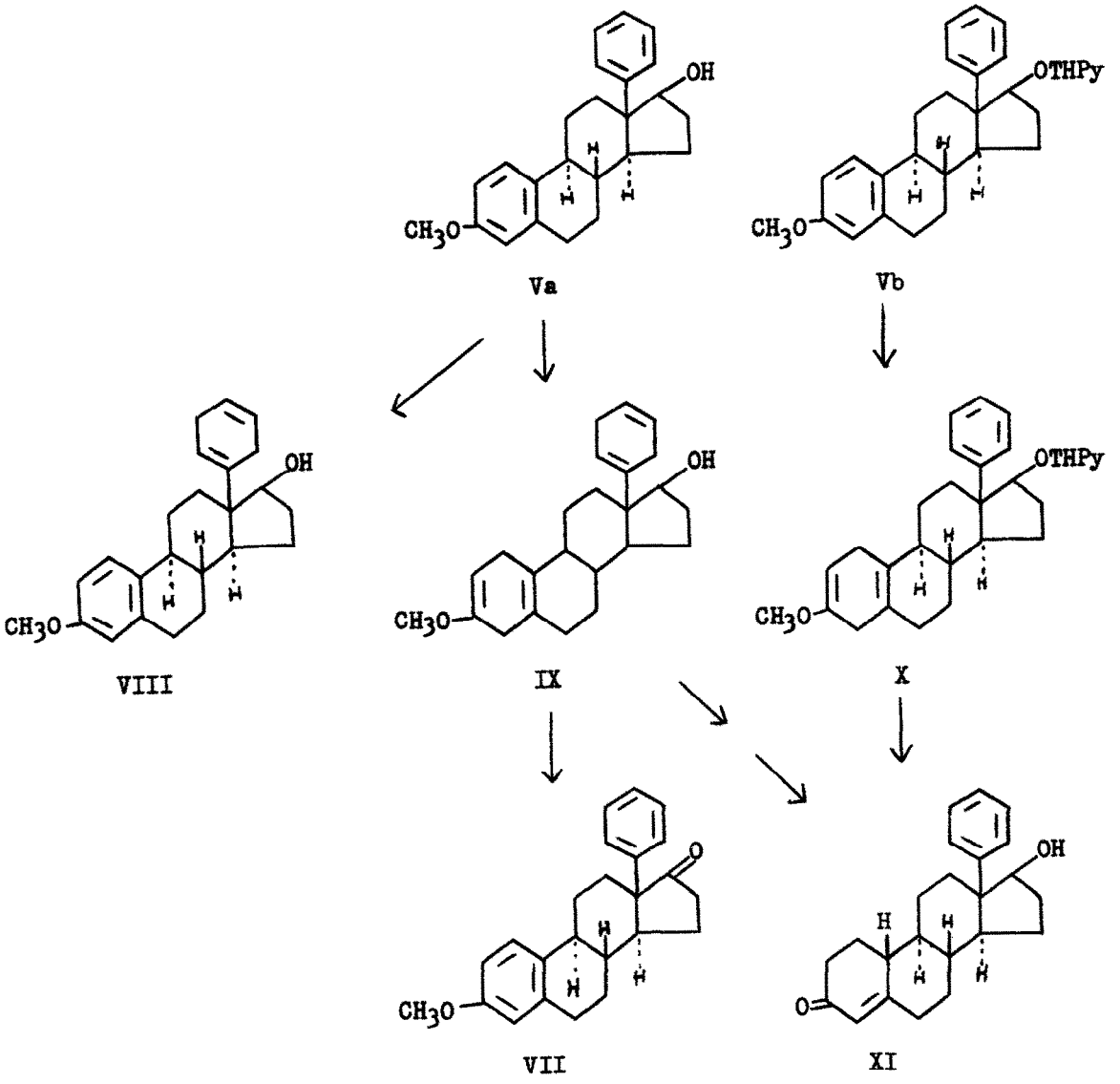


Fig. 2

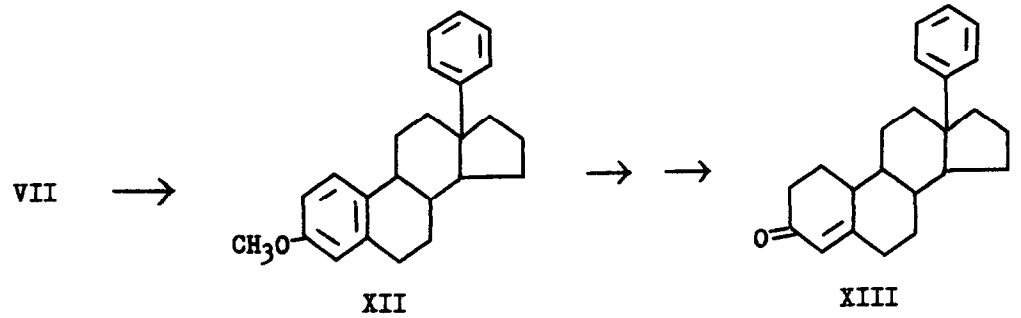
liquid ammonia and t-butanol for ten minutes resulted surprisingly in preferential reduction of the angular phenyl group, and compound VIII with an intact aromatic A-ring was isolated in good yield. Compound VIII displayed absorption in the infrared at 6.22, 6.70 and 10.4μ; its N.M.R. showed the vinylic protons at 4.30 τ.

Preparation of the desired 19-nortestosterone analog XI was achieved

by two methods. In the first one, the tetrahydropyranyl ether Vb was used as the starting material. When Birch reduction with several equivalents of sodium in liquid ammonia and t-butanol was performed on this compound for twenty minutes, reaction occurred almost exclusively in ring A, and intermediate X was obtained in good yield. It was characterized by its infrared absorption at 5.88, 5.98 and 14.3μ. In the N.M.R. the compound displayed a multiplet at 2.7 τ attributed to the C-13 angular phenyl group and one vinylic proton at 5.4 τ. On hydrolysis with methanolic-HCl, d,l-13-phenyl-18,19-bisnortestosterone XI was obtained after chromatography. Its N.M.R. showed a vinylic proton at 4.17 τ and the expected multiplet at 2.7 τ for the angular aromatic protons.

A second method for obtaining compounds with angular phenyl groups at C-13 is based on the observed ease of rearomatization of dihydro-aromatic compounds VIII and IX. Thus, when treated with CrO_3/pyridine at room temperature overnight, the alcohol IX was converted into the estrone analog VII. To obtain d,l-13-phenyl-18,19-bisnortestosterone (XI), the alcohol IX was treated first with methanolic-HCl to form the 3-keto-Δ^4-system. This intermediate was then treated in dilute, ice-cooled pyridine solution with CrO_3. Under these conditions preferential oxidation of the angular dihydrobenzene ring occurred within 30 minutes without appreciable oxidation at C-17. The product, isolated by chromatography, was the bisnortestosterone analog XI.

The change in selectivity in the partial Birch reduction brought about by formation of a 17-tetrahydropyranyl ether was considered of some interest. Accordingly, we also prepared d,l-13-phenyl-18-nor-17-desoxy-estradiol 3-methyl ether (XII) by Clemmensen reduction of ketone VII according to published conditions for the synthesis of 17-desoxyestradiol (7).



XII XIII

Fig. 3

Controlled Birch reduction of compound XII led after acid treatment to d,l-13-phenyl-18,19-bisnor-17-desoxytestosterone XIII, paralleling results obtained in the reduction of the 17-tetrahydropyranyloxy analog. Apparently an unprotected 17-hydroxyl group assists Birch reduction of the C-13 phenyl group.

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EXPERIMENTAL

Melting points are uncorrected, ultraviolet spectra were recorded in dioxane and infrared spectra were taken of chloroform films, if not specified otherwise. N.M.R. spectra were determined on an A-60 spectrometer in dilute $CDCl_3$ solution, using TMS as the internal reference standard.

2-[2-(3,4-Dihydro-6-methoxy-1(2H)-naphthylidene)ethyl]-2-phenylcyclopentane-1,3-dione (I) - A mixture of 13 g. of 6-methoxy-1,2,3,4-tetrahydro-1-vinyl-1-naphthol and 13 g. of 2-phenylcyclopentane-1,3-dione was refluxed in 104 ml. xylene and 52 ml. t-butanol in the presence of 5 ml. of a 40% methanolic solution of Triton B for 6 hours. After the solution was cool, approximately 150 ml. of ether were added, and some unchanged phenylcyclopentanedione was removed by filtration. The total filtrate was successively washed with 1N NaOH solution and water. The organic fraction was dried, concentrated in vacuo and the residue crystallized from ether, to yield 11.5 g. (50%) of I; m.p. 127-128°; ultraviolet, λmax 267.5mμ, ε21,000; infrared, 5.70 (weak) 5.80, 6.22, 6.70 and 14.36μ.

Anal. Calcd. for $C_{24}H_{24}O_3$: C, 79.97; H, 6.71. Found: C, 79.65; H, 6.65.

d,l-8(9),14-Bisdehydro-13-phenyl-18-norestrone methyl ether (II) - To a solution of 14.4 g. of the above tricycle I, in 1500 ml. of glacial acetic acid, there was added 15.2 g. of p-toluenesulfonic acid with stirring. The mixture was stirred at room temperature under nitrogen overnight and filtered from some impurities. The clear filtrate was slowly poured into 6 liters of ice water. The precipitate which formed was filtered, washed with water and ethanol and dried in vacuo. Material of this purity weighing 12 g. (88%) is suitable for the next step. Recrystallization from ethyl acetate afforded an analytical sample with m.p. 142-143°; ultraviolet, λmax 316mμ, ε29,700; infrared, 5.78, 6.22, 6.70 and 14.36μ.

Anal. Calcd. for $C_{24}H_{22}O_2$: C, 84.17; H, 6.47. Found: C, 84.31; H, 6.56.

d,l-8(9)-Dehydro-13-phenyl-18-norestrone methyl ether (III) - A solution of 7.6 g. of ketone II in 300 ml. benzene was hydrogenated in the presence of 760 mg. of 10% palladium-on-charcoal catalyst until one mole of hydrogen had been taken up. The catalyst was filtered and the solvent removed in vacuo at 40°C. The residue could be crystallized from ether, containing 10% ethanol. A first crop of 3.9 g. (51.5%) of ketone III, m.p. 161-162°C., was obtained. Occasionally, more material could be isolated on further crystallization of mother liquors. The analytical sample obtained from ether had m.p. 163°, ultraviolet, λmax 285mμ, ε15,400.

Anal. Calcd. for $C_{24}H_{24}O_2$: C, 83.69; H, 7.02. Found: C, 83.65; H, 7.08.

d,l-13-Phenyl-18-norestrone methyl ether (VII) - To a solution of 1.1 g. of ketone III in 40 ml. absolute ethanol there were added 700 mg. of $NaBH_4$, and the mixture was refluxed 1.5 hours. After cooling, the reaction mixture was poured into 400 ml. of ice water containing 20 g. of NaH_2PO_4. Repeated extraction with benzene, drying and concentration in vacuo yielded 1.05 g. of semicrystalline reduction product IVa devoid of carbonyl absorption. This material was dissolved in 70 ml. of dry tetrahydrofuran and added dropwise to a solution of 1 g. of potassium in 240 ml. of distilled, dry liquid ammonia. Discoloration usually occurred during this addition in which case another 1 g. of potassium was added. The solution was stirred and the ammonia kept refluxing for 6 hours. At the end of this period, ammonium chloride was carefully added and the ammonia was allowed to evaporate. The residue was distributed between ether and water and the ether phase was dried and concentrated. The total crude was reoxidized with CrO_3 and pyridine in the usual manner and chromatographed on a column of 26 g. acid-washed alumina. The fractions eluted with benzene-petroleum ether mixtures containing 30 to 40% benzene were combined and crystallized to yield 360 mg. of compound VII, m.p. 196-198°; ultraviolet, λmax 278mμ, ε2138.

Anal. Calcd. for $C_{24}H_{26}O_2$: C, 83.20; H, 7.56. Found: C, 82.98; H, 7.56.

Later fractions from the same column eluted with benzene yielded 85 mg. of compound VI, m.p. 172-174°; ultraviolet, λmax 278mμ, ε 2780.

Anal. Calcd. for $C_{24}H_{26}O_2$: C, 83.20; H, 7.56. Found: C, 83.02; H, 7.50.

d,l-13-Phenyl-18-nor-8-isoestrone methyl ether (VI) - Ketone III (300 mg.) was dissolved in 20 ml. of glacial acetic acid and hydrogenated in the presence of 300 mg. of 10% palladium-on-charcoal catalyst until one mole of hydrogen was consumed. After filtration of the catalyst, the solution was poured into excess ice water and extracted with chloroform. Removal of the dried solvent left behind a semicrystalline solid. Upon crystallization from ether, 185 mg. of product melting at 174°C., were obtained identical in all respects with compound VI described above.

Isolation and Birch reductions of d,l-13-phenyl-18-norestradiol 3-methyl ether (Va) - A sample of 500 mg. of the tetrahydropyranyl ether Vb, obtained as described below, was dissolved in 50 ml. methanol containing 2 ml. of conc. HCl. This mixture was stirred at room temperature under nitrogen for 6 hours, and the product isolated by pouring into ice-cold bicarbonate solution and extracting with benzene. The total crude residue was crystallized from ethanol and gave a first crop of d,l-13-phenyl-18-norestradiol 3-methyl ether (Va), m.p. 148-150°.

The analytical sample obtained after one more recrystallization from ethanol had m.p. 150-151°.

Anal. Calcd. for $C_{24}H_{28}O_2$: C, 82.72; H, 8.10. Found: C, 82.91; H, 8.03.

A sample of 110 mg. of alcohol Va having m.p. 148-150° was dissolved in 1.2 ml. pyridine and added to a suspension of 110 mg. of chromium trioxide in 1.2 ml. pyridine. After 18 hours at room temperature the product was isolated as usual and percolated through a column of 1.5 g. acid-washed alumina in benzene solution. The obtained crystalline product (96 mg.) was identical by m.p., I.R. spectrum and T.L.C. behavior with the pure estrone analog VII.

A solution of 600 mg. of alcohol Va in 25 ml. of tetrahydrofuran was added to 40 ml. of dry, distilled ammonia. To this mixture was added 12 ml. of t-butanol and then 1.1 g. of sodium was added in portions and the mixture was allowed to stir under reflux for one hour. Excess metal was carefully destroyed by the addition of methanol, the ammonia evaporated and the residue extracted with ether and water. The resultant product after removal of dried solvent could not be obtained crystalline but was assigned structure IX, based on its spectral characteristics; N.M.R., one vinylic proton at 5.35τ and three vinylic protons at 4.30τ; infrared, 5.88, 5.98 and 10.4μ. Its structure was confirmed by reoxidation of 100 mg. of compound IX which were dissolved in 1 ml. pyridine and 100 mg. chromium trioxide in 1 ml. pyridine. After 18 hours at room temperature, the product was isolated as usual and percolated in benzene solution through a column of 1 g. of acid-washed alumina. The crystalline product (70 mg.) was identical by I.R. spectrum, m.p. and T.L.C. behavior with the estrone analog VII.

One gram of alcohol Va was dissolved in 45 ml. of dry tetrahydrofuran and added to a solution of 75 ml. of dry, distilled liquid ammonia. Then 16.5 ml. of t-butanol and 186 mg. of sodium metal were added and the reduction was allowed to proceed for 10 minutes. Excess metal was destroyed by careful addition of methanol, the ammonia was evaporated and the residue worked up in the usual way. The major product (VIII) weighing 750 mg. (74%) was obtained crystalline from isopropanol. The best obtainable sample had m.p. 173-176°; N.M.R., vinylic protons at 4.30τ; infrared, 6.22, 6.70 and 10.4μ.

Anal. Calcd. for $C_{24}H_{30}O_2$: C, 82.24; H, 8.63. Found: C, 81.78; H, 8.58.

Compound VIII was further characterized as the 17-acetate, m.p. 149°; infrared, 5.75, 6.22, 6.70 and 10.4μ.

Anal. Calcd. for $C_{26}H_{32}O_3$: C, 79.55; H, 8.22. Found: C, 79.76; H, 8.21.

Preparation and Birch reduction of d,l-13-phenyl-18-norestradiol 3-methyl ether-17-tetrahydropyranyl ether (Vb) - A 1.5 g. sample of the sodium borohydride reduction product IVa obtained as above was suspended with stirring in 6.5 ml. of a freshly distilled solution of dry dihydropyran. p-Toluenesulfonylchloride (65 mg.) was added and the mixture was stirred overnight under nitrogen. A little pyridine was added and the reaction mixture was then poured into ice water and extracted repeatedly with ether. After drying, the organic phase was concentrated under reduced pressure to constant weight. This product (IVb) was then reduced by dissolving it in 78 ml. of tetrahydrofuran and slowly adding the solution to 320 ml. of liquid ammonia containing 1.3 g. of potassium. After the addition, another 1.3 g. of potassium were added, and the reduction was allowed to proceed at the reflux temperature of ammonia for 6 hours. The work up was done as before and 2.1 g. of crude product were obtained. It proved advantageous at this point to purify it by chromatography on basic alumina. The fractions eluted with benzene-petroleum ether mixtures containing 30 to 80% benzene were combined and concentrated. The obtained crystalline residue (compound Vb) was about one gram.

A sample of 500 mg. of ether Vb dissolved in 28 ml. of tetrahydrofuran and 8.5 ml. of t-butanol was added to a solution of 45 ml. of liquid ammonia. Sodium (135 mg.) was added and the reduction was allowed to proceed for 20 minutes. The product (420 mg.), isolated as in the previous experiments, was identified as structure X by spectroscopic data. N.M.R. showed a multiplet at 2.7τ and one vinylic proton at 5.4τ. Infrared absorption bands were at 5.88, 5.98 and 14.3μ. It was further characterized by its hydrolysis to compound XI.

d,l-13-Phenyl-18,19-bisnortestosterone (XI) - The total crude product X, obtained above, was hydrolyzed overnight in 70 ml. of methanol containing 1.75 ml. of conc. HCl. After the usual work up the product was chromatographed on 13 g. of acid-washed alumina. From the fractions eluted with 30-50% ether in benzene, 230 mg. (60% yield) of crystalline compound XI was obtained displaying these characteristics; ultraviolet, λmax 240mμ, ε15,200; infrared, 2.84, 6.00, 6.18 and 14.3μ; N.M.R., one vinylic proton at 4.17τ and a multiplet at 2.7τ. The analytical sample was obtained as a solvate with 0.5 mole of ether, m.p. 91-92°.

Anal. Calcd. for $C_{23}H_{28}O_2 \cdot 1/2\ C_4H_{10}O$: C, 80.38; H, 8.91. Found: C, 80.25; H, 8.84.

A sample of 300 mg. of intermediate VI was hydrolyzed as above with 30 ml. of methanol containing 0.9 ml. conc. HCl. The crude product (250 mg.) was dissolved in 5.5 ml. pyridine, ice cooled and added to a chilled solution of 47.5 mg. of CrO_3 in 5.5 ml. pyridine. After being stirred for one hour in the ice bath, the mixture was diluted with excess ethyl acetate, the insoluble salt filtered, washed, and the filtrate dried and concentrated. The residue was chromatographed on 6 g. of acid-washed alumina. From the fractions eluted with 20-40% ether in benzene, there were isolated 85 mg. of the bisnor XI, identical in all respects to the material described above.

d,l-13-Phenyl-18-nor-17-desoxyestradiol methyl ether (XII) - Zinc amalgam was prepared from 5 g. of zinc powder which was suspended in 30 ml. water and treated with 3 drops of conc. HCl and then with a solution of 5 g. of $HgCl_2$ in 30 ml. of water. After the amalgam had been stirred for 30 minutes, the water was decanted and a solution of 560 mg. of compound VII in 30 ml. of dioxane was added followed by 25 ml. of conc. HCl.

The mixture was refluxed with stirring for 16 hours. As infrared and T.L.C. data showed incomplete reduction, the isolated total crude steroid was resubjected to this same treatment.

Final work up was done by benzene extraction, repeated water washings, drying and concentration in vacuo. This product was chromatographed on a column of 10 g. of acid-washed alumina and the material which eluted with petroleum ether was collected. The total weight of product after one crystallization from ethyl acetate was 320 mg., m.p. 125-129°. The analytical sample was characterized by m.p. 128-129°; ultraviolet, λmax 277mμ, ε 3100.

Anal. Calcd. for $C_{24}H_{28}O$: C, 86.70; H, 8.49. Found: C, 86.40; H, 8.47.

Birch reduction of d,l-13-phenyl-18-nor-17-desoxyestradiol methyl ether (XII) - Crystalline compound XII (200 mg.) was dissolved in 15 ml. tetrahydrofuran and added to a solution of 60 ml. of distilled, dry liquid ammonia. After the addition of 4.8 ml. of t-butanol, 350 mg. of sodium were added and the mixture was allowed to reflux with good stirring for 45 minutes. The excess metal was destroyed with methanol, the ammonia evaporated and the residue worked up in the usual way. The infrared spectrum showed the presence of some unreacted aromatic A-ring but as another experiment showed that further reduction will eventually lead to some attack on the angular phenyl group, the total crude obtained in this experiment was hydrolyzed by stirring it overnight under nitrogen in a mixture of 25 ml. of methanol, 25 ml. of ethanol and 2.5 ml. of conc. HCl. The usual work up yielded 180 mg. of noncrystalline material whose infrared spectrum indicated predominantly a 3-keto-Δ^4-structure. By preparative thin-layer chromatography there were obtained 90 mg. of crystalline d,l-13-phenyl-18,19-bisnor-17-desoxytestosterone (XIII), m.p. 137-139°. The analytical sample, recrystallized from ether displayed m.p. 141°; ultra-

violet, λmax 241mμ, ε16,800; infrared, 6.00, 6.20 and 14.3μ; N.M.R., one vinylic proton at 4.15τ and a multiplet at 2.7τ.

Anal. Calcd. for $C_{23}H_{28}O$: C, 86.20; H, 8.81. Found: C, 86.22; H, 8.69.

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