REDUCTION OF SOME D-HOMOSTEROIDS WITH AN AROMATIC A RING BY ALKALI METALS UNDER THE CONDITIONS OF THE BIRCH REACTION. I.

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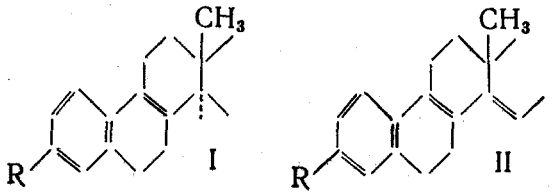
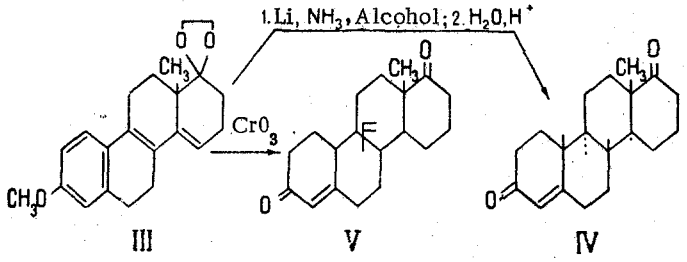
The most widespread use of the Birch reaction (or the modification proposed by Nelson and Wilds) in syntheses of steroid compounds is the reduction of an aromatic ring. Thanks to this reaction, various 19-norsteroids distinguished by high physiological activity have become available [1].



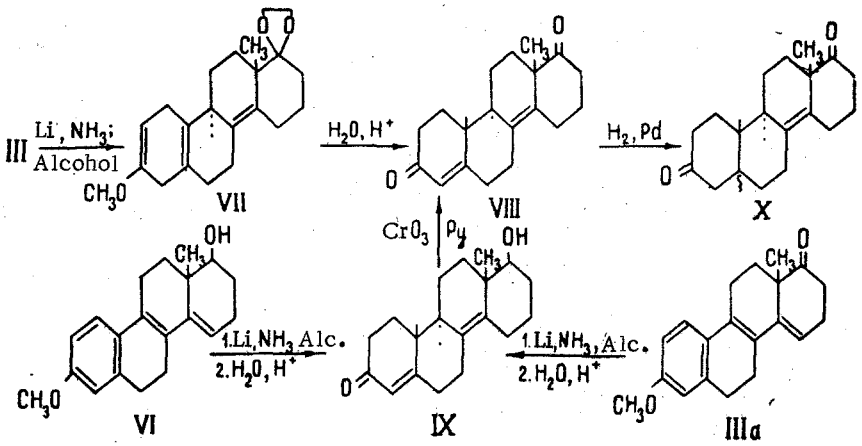
The Birch reduction of steroids of type (I) containing a styrene grouping is not often useful, although in some investigations on the complete synthesis of steroids it has given good results [2, 3]:

So far as concerns the reduction of phenylbutadiene steroid systems of type (II), it has scarcely been studied, although it is of interest since it would lead, in the final analysis, to compounds possessing anabolic activity. The experiments carried out previously in our laboratory on the reduction of the ethylene ketal of 3-methoxy-$\Delta^{1,3,5(10),8,14}$-D-homoestrapentaen--17-α-one (III) were of an exploratory nature [4]; the reaction product (after hydrolysis) was provisionally assigned the structure of $\Delta^{4,8}$-19-nor-D-homoandrostadienedione which, as it will be seen below, has proved to be incorrect.

It might be assumed that the action of lithium under Birch's conditions (i. e., in liquid ammonia in the presence of alcohol) would first lead to the reduction of the butadiene system and then that of the aromatic nucleus, which would give (after hydrolysis) Δ^4-19-nor-D-homoandrostenedione (IV). If, in the first stage, the reduction takes place partially, the final reaction product should be the dienedione (V). Under these conditions, the dione (IV) can be formed only if the unreduced double bond migrates to a position conjugated with the aromatic ring during the reaction:



We have investigated the Birch reduction of the ketal (III), the corresponding ketone (IIIa), and 3-methoxy-$\Delta^{1,3,5(10),8,14}$-D-homoestrapentaen-17aβ-ol (VI). When the ketal (III) was reduced with a 15 to 20-fold excess of lithium (calculated at the rate of two atoms of lithium per double bond), it was impossible to isolate the intermediate ether of the enol (VII) and the reaction product was subjected to hydrolysis by means of hydrochloric acid in chloroform. As a result, the dienedione (VIII) was obtained as the main reaction product. The structure of the dienedione (VIII) as $\Delta^{4,8(14)}$-19-nor-D-homoandrostadiene-3, 17a-dione was shown by its IR and NMR spectra and by the following reactions:

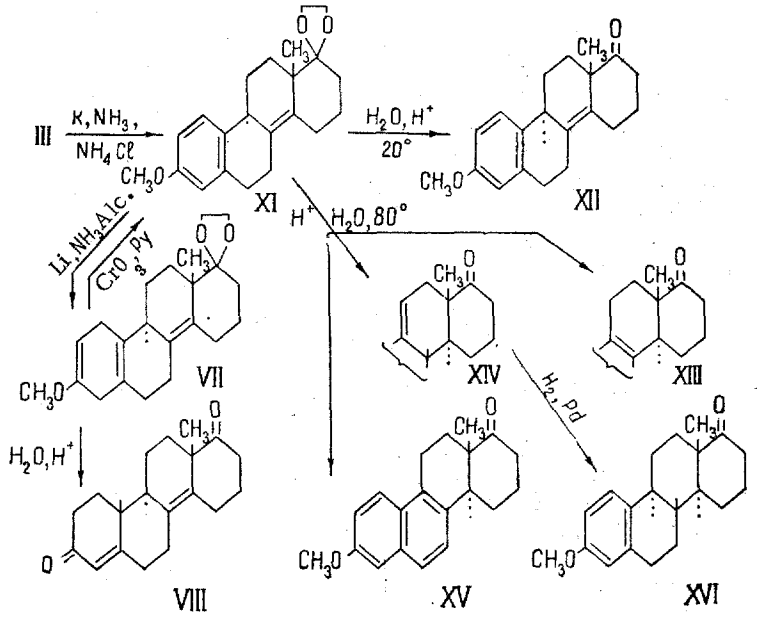


Reduction of the carbinol (VI) under the same conditions followed by hydrolysis gave the ketol (IX), differing from 19-nor-D-homotestosterone and its two isomers previously obtained by the same route from 3-methoxy-$\Delta^{1,3,5(10),8}$-D-homoestratetraen-17aβ-ol. The oxidation of the ketol (IX) with chromic anhydride in pyridine led to the dienedione (VIII), which shows that the course of the reduction is similar for the ketal (III) and the carbinol (VI). In the analogous reaction with the ketone (IIIa), no crystalline products could be isolated: the ketol (IX) was detected chromatographically. In addition, the reaction mixture contained compounds of a phenolic character.

The IR spectrum of the dienedione (VIII) exhibits frequencies at 1668 and 1695 cm^{-1} corresponding to a Δ^4-3-keto grouping and a 17α-keto group. It is interesting to note that the frequency of the 17α-keto group in the dienedione (VIII) is 10 cm^{-1} lower than the same frequency in the dione (IV) (1695 as compared with 1705 cm^{-1}). This can be ascribed to the influence by the β,γ double bond. A similar influence was noted in the NMR spectrum of the dione (VIII), where the chemical shift of the 18-CH_3-group is characterized by a signal with a δ of 1.25 ppm while the corresponding signal for the dione (IV) is at 1.15 ppm. This difference can be caused only by a closely adjacent double bond ($\Delta^{8(14)}$ or Δ^{14}); the $\Delta^{8(9)}$ bond, being more remote, cannot exert such a strong influence and is therefore excluded. Examples of a similar influence of a double bond and its position on the chemical shift of angular methyl groups have been reported previously [5].

The choice between $\Delta^{8(14)}$ and Δ^{14} double bonds was determined by the behavior of the dienedione (VII) on hydrogenation, when only one molecule of hydrogen was absorbed (with the formation of the diketone (X)). Consequently, the second double bond must be located in the 8-14 position, since, as is well known, hydrogenation in the 14-15 position takes place readily.

According to published data, the rate of reduction in the Birch reaction is considerably higher for a double bond than for a benzene ring conjugated with this bond [6]. This made it possible to assume that the action of lithium on the ketal (III) first led to 1, 4-addition to the butadiene system and then to the reduction of the aromatic nucleus. To confirm this assumption, we carried out the reduction of the ketal (III) by potassium in liquid ammonia with the addition of a mixture of alcohol and ammonium chloride, i.e., under milder conditions than described above. This gave us the ketal of 3-methoxy-$\Delta^{1,3,5(10),8(14)}$-D-homoestraen-17a-one (XI), the UV spectrum of which exhibited a maximum at 277 mμ (log ε 3.27) which signified that the presence of a double bond in the 8-9 position could be excluded, since if it were present the extinction would be considerably higher (log ε 4.1-4.3). The position of the double bond in ring D is also excluded, since the ketal (XI) did not hydrogenate with a palladium catalyst under the usual conditions. Thus, the structure given above remained to be adopted:



Further reduction of the ketal (XI) with lithium and alcohol in liquid ammonia led to the ketal (VII), the aromatization of which by means of chromic anhydride in pyridine gave the initial ketal (XI). Hydrolysis of the ketal (VII) with hydrochloric acid gave the above-described dienedione (VIII).

The action of hydrochloric acid on the ketal (XI) at room temperature led to the elimination of the ketal shield with the formation of the ketone (XII), the double bond not being affected. When the temperature was raised (by boiling with an alcoholic solution of hydrochloric acid), the double bond migrated into the 8-9 position and then into the 9-11 position, this being accompanied by the aromatization of ring B, and as a result a mixture of 3-methoxy-$-\Delta^{1,3,5(10),8(9)}$-D-homoestratetraen-17a-one-(XIII), its $\Delta^{9(11)}$ isomer (XIV), and the methyl ether of αl-D-homoequilenin (XV) was formed in a ratio of approximately 2:2:1. By using preparative thin-layer chromatography (or fractional crystallization) we succeeded in basically separating the ketones (XIII) and (XIV), but it proved impossible to purify either of these compounds from contamination with (XV). The ketone (XIII), which has a well-defined melting point, contained about 8% of the ketone (XV) (according to the results of UV spectroscopy). Some time ago, Johnson [7] noted the exceptional ease of aromatization for such structures.

The hydrogenation of the ketone (XIV) in the presence of a palladium catalyst produced the methyl ether of D-homoestrone (XVI), which, like the other compounds described above, could not be purified from contamination by the methyl ether of D-homoequilenin (XV).

Thus, it has been established that steroid systems containing a phenylbutadiene grouping are reduced in stages: 1, 4-addition to the butadiene system takes place first and is followed by reduction of the aromatic nucleus. In this process, the nature of the functional 17α-substituents has no influence.

In biological trials, $\Delta^{4,8(14)}$-19-nor-D-homoandrostadiene-3, 17a-dione (VIII) exhibited androgenic and anabolic activity, but to a smaller extent than 19-nor-D-homotestosterone.

EXPERIMENTAL

The melting points were determined on a Kofler block. Before analysis, the substances were dried at 60° in a vacuum of 1 mm over phosphorus pentoxide. The UV spectra were taken in alcohol on a SF-4 instrument, the IR spectra on a Hilger-800 (Zeiss) instrument in liquid paraffin, and the NMR spectra on a INMS-60 instrument. The course of the reaction was followed and the preparative separation carried out chromatographically on plates in a thin (1 mm) non-fixed layer of alumina (Brockman activity IV-V). 3-Methoxy-$\Delta^{1,3,5(10),8,14}$-D-homoestrapentaen-17a-one-(III), its ketal (III) and the carbinol (VI) were obtained by the recognized procedure [8].

Reduction of the ketal (III) with lithium and alcohol in liquid ammonia. With stirring, a solution of 2.75 g of the ketal (III) in 100 ml of absolute tetrahydrofuran, 50 ml of absolute ether, and 150 ml of absolute alcohol was added to 300 ml of ammonia at -70°. After 10 min, 6 g of lithium in small pieces was added to the solution over 30 min, whereupon the solution periodically became colored purple. After the addition of all the metal, a further 30 ml of absolute alcohol was added for decolorization. After 30 min, 100 ml of ether was added and the ammonia allowed to evaporate. The reaction mixture was dissolved in 400 ml of water at -5°. The aqueous layer was extracted with ether and then with benzene, the combined extracts were neutralized by the addition of dry ice, washed with a saturated salt solution and then with water, and were dried with anhydrous magnesium sulfate. After the elimination of the solvent, 2.9 g of a yellowish oily product was obtained, and this was subjected to hydrolysis without purification.

To a solution of 2.9 g of the reaction product in 29 ml of chloroform was added 2.9 ml of concentrated hydrochloric acid, and the mixture was stirred for an hour. The solution was poured into water and the aqueous layer was extracted with chloroform. The combined extract was washed with a saturated solution of sodium carbonate and water, dried with magnesium sulfate, and evaporated. This gave 2.95 g of oil, which was dissolved in 100 ml of benzene and filtered through a column containing 60 g of alumina. The adsorbent was washed with 100 ml of benzene and 100 ml of ether. After evaporation, 2.05 g of a yellowish oil was obtained which crystallized on trituration with ethyl acetate. This gave 1.3 g of $\Delta^{4,8(14)}$-19-nor-D-homoandrostadiene-3, 17a-dione (VIII) with mp 141-145°. Two crystallizations from acetone gave 0.92 g of the dione (VIII) with mp 153-155°. λ_{max} 238 mμ (log ε 4.21).

IR spectrum: 1668 (3-CO), 1695 (17a-CO), 1628 (4-C=C) cm^{-1}.

Found %: C 79.90, 80.95; H 8.66, 8.80. $C_{19}H_{24}O_2$. Calculated %: C 80.24; H 8.51.

Further washing of the column with ether gave 0.37 g of a reddish resin containing phenolic products.

IR spectrum: 1602 (aromatic ring), 3280-3410 cm^{-1} (OH group).

Reduction of the carbinol (VI) with lithium and alcohol in liquid ammonia. A solution of 2 g of the carbinol (VI) in 100 ml of absolute tetrahydrofuran and 160 ml of absolute alcohol was poured into 200 ml of ammonia, and 5 g of lithium was added at -70°. The further treatment and hydrolysis of the reaction product (2.12 g of yellow oil) were carried out in a similar manner to the preceding experiment. Filtration through alumina gave 1.62 g of unpurified ketol (IX), which crystallized after standing for a long time with a mixture of ethyl acetate and petroleum ether. Pure

$\Delta^{4,8(14)}$-19-nor-D-homoandrostadiene-17aβ-ol-3-one (IX) with mp 143-145° was obtained after chromatography on alumina (from the 10% benzene ether and ether fractions). λ_{max} 237 mμ (log ε 4.08).

IR spectrum: 1615 (4-C=C), 1673 (3-CO), 3410 (17aβ-OH) cm^{-1}.

The ketol (IX) gave depressions of the melting point with samples of 19-nor-D-homotestosterone (mp 146-147°) and its 8α- (mp 133-136° and 9β, 10α-epimers (mp 165-167°).

Acetylation of the ketol (IX). A mixture of 600 mg of the unpurified ketol (IX) and 3.6 ml of absolute pyridine was stirred with 2.5 ml of acetic anhydride and left overnight. After checking (on a chromatogram) the completeness of the acetylation, the red-brown mixture was poured into water and extracted with ether. The extract was filtered through 15 g of alumina and the solvent was eliminated. The residual oil was crystallized by tituration with a mixture of alcohol and petroleum ether. This gave 486 mg of the acetate of the ketol (IX) with mp 132-138°. The pure acetate had mp 150-152° (from alcohol) (the acetate of 19-nor-D-homotestosterone had mp 186.5-188°). λ_{max} 237 mμ (log ε 4.25).

IR spectrum: 1617 (4-C=C), 1662 (3-CO), 1725 (CH_3COO) cm^{-1}.

Found %: C 76.77, 76.91; H 8.81, 8.78. $C_{21}H_{28}O_2$. Calculated %: C 76.79; H 8.59.

Reduction by the usual method with lithium and alcohol in ammonia of 1 g of the ketone (IIIa) using 1 g of lithium gave a non-crystalline product, the hydrolysis of which again gave an oil. Chromatography of the latter on alumina and acetylation of the fractions containing a substance with an R_f value close to the R_f for the ketol (IX) gave no individual crystalline acetate.

Oxidation of the ketol (IX) to the diketone (VIII). A solution of 1.02 g of the ketol (IX) in the form of an oil in 10 ml of absolute pyridine was added to a suspension of the complex from 1 g of chromic anhydride and 10 ml of absolute pyridine. The mixture was left overnight and then 50 ml of chloroform was added and it was passed through a column containing 20 g of alumina. The adsorbent was washed with chloroform, and elimination of the solvent gave a residue of 0.73 g of non-crystallizing oil, which was again chromatographed on alumina. Elution with benzene gave 0.69 g of the dione (VIII) in the form of an oil crystallizing on trituration with ethyl acetate. This yielded 210 mg of crystals with mp 140-145° and 410 mg with mp 130-142°. Two crystallizations of the first portion from acetone gave a substance with mp 154-156°, which was identical to the dione (VIII) described above.

Reduction of the ketal (III) with potassium and ammonium chloride in liquid ammonia. A solution of 2 g of the ketal (III) in 300 ml of absolute tetrahydrofuran was added to 250 ml of ammonia. Over 40 minutes, 9 g of potassium was added in small pieces to the mixture at -70°. The solution first became red and then, as more metal was added, blue-purple. After 20 minutes, 15 g of ammonium chloride was added to decolorize the solution. The ammonia was eliminated, 300 ml of water was added to the suspension, and the aqueous layer extracted with ether. After the usual treatment, 2.26 g of a yellowish oil was obtained, which crystallized on trituration with a mixture of alcohol and ethyl acetate. This yielded 1.35 g of the ketal (XI) with mp 85-90°. The pure ketal (XI) has mp 92.5-94° (from methanol-hexane). λ_{max} 277 mμ (log ε 3.27).

IR spectrum: 1500; 1587; 1612 (aromatic ring) cm^{-1}.

Found %: C 78.00, 77.91; H 8.30, 8.08. $C_{22}H_{28}O_3$. Calculated %: C 77.61; H 8.29.

A solution of 2.42 g of the non-crystalline substance from the mother liquors of three experiments in 30 ml of benzene was added to a column containing 120 g of alumina. The absorbent was washed with 500 ml of hexane and eluted successively with 3 × 100 ml of mixtures of hexane and benzene (9:1, 8:2, 7:3) (fraction I), 200 ml of a mixture of hexane and benzene (1:1), 200 ml of benzene (fraction II), and 300 ml of ether (fraction III). From the first fraction we isolated 0.79 g of an oil consisting of a mixture of the ketal (XI) and a less polar substance. The mixture was dissolved in benzene, transferred to a thin layer of alumina, and developed in the benzene-hexane (1:1) system. The fraction with the highest R_f gave, after elution with ether and evaporation of the solvent, 0.31 g of an oil which was apparently the product of the hydrogenolysis of the methoxy group into a ketal (XI) with λ_{max} 267 mμ (log ε 2.56). The following fractions gave 0.43 g of the ketal (XI) with mp 85-91°. The second fraction from the column yielded 0.16 g of the ketal (XI) with mp 88-90°, and the third gave 0.32 g of a yellow resin, the preparative separation of which in a thin layer of alumina gave 90 mg of an oil containing (judging from the IR spectrum) $\Delta^{8(9)}$-dehydro-D-homoestrone; λ_{max} 275 mμ.

IR spectrum: 1607 (aromatic ring), 1730 (17a-CO), 3300-3400 (3-OH) cm^{-1}.

In addition, we obtained 32 mg of a non-crystalline product likewise consisting mainly of $\Delta^{8,(14)}$-dehydro-D-homoestrone; λ_{max} 276-278 mμ.

IR spectrum: 1607 (aromatic ring), 1724 (17a-CO), 3300-3400 (3-OH) cm^{-1}.

In an analogous experiment on the reduction of the ketal (III) in the form of a suspension (with a smaller amount of tetrahydrofuran), the ketal (XI) formed (with mp 82-84°) contained the initial compound as an impurity, judging from the λ_{max} at 305-206 mμ .

The reduction of the carbinol (VI) with potassium and ammonium chloride in liquid ammonia was carried out in a similar manner to that described above. Acetylation of the oily substance with an R_f value close to that of the 3-methyl ether of dehydro-D-homoestradiol isolated after chromatography on alumina led to a non-crystalline product with λ_{max} 278 mμ .

Reduction of the ketone (IIIa) with potassium and ammonium chloride was carried out in ammonia that had been distilled over sodium, and its evaporation was performed in a current of nitrogen. However, it was impossible to isolate any individual crystalline product.

Reduction of the ketal (XI) with lithium and alcohol in liquid ammonia. A solution of 0.7 g of the ketal (XI) in 100 ml of absolute tetrahydrofuran, 10 ml of absolute ether, and 10 ml of absolute alcohol was added to 130 ml of ammonia, and this was followed by 1 g of lithium; a bronze-colored deposit formed on the walls of the flask. The mixture was treated with 25 ml of absolute alcohol for decolorization. After elimination of the ammonia, the reaction mixture was treated by the usual method. This gave 0.72 g of the oily ketal (VII), which crystallized on trituration with a mixture of alcohol and hexane. Reprecipitation from ether gave 430 mg of the ketal (VII) with mp 105-107°. The pure ketal (VII) has mp 110-112° (from alcohol-hexane), λ_{max} 278 mμ (log ε 1.62).

In experiments on the hydrogenation of the ketal (VII) in the presence of 30% palladium in calcium carbonate, and also after its treatment with potassium and ammonium chloride in liquid ammonia, the ketal (VII) was recovered unchanged.

Hydrolysis of the ketal (VII). A solution of 0.2 g of the ketal (VII) in 15 ml of alcohol was boiled for 20 min with 10 ml of hydrochloric acid (1:2). The solution was cooled, poured into water, and extracted with chloroform. The extract was washed with a saturated solution of sodium carbonate and with water, and was dried with magnesium sulfate and evaporated. A little ether was added to the semicrystalline residue, and 156 mg of the dienedione (VIII) with mp 154-156° was isolated. After two recrystallizations from acetone, the dienedione (VIII) had mp 158-159.5° and gave no depression of the melting point with an authentic sample.

An attempt to isomerize the $\Delta^{8(14)}$ double bond in the dione (VIII) by boiling in methanolic solution with hydrochloric acid (1:1) in a current of nitrogen for 2 hours gave no results; the initial dienedione (VIII) was recovered.

Hydrogenation of the dienedione (VIII). 188 mg of the dienedione (VIII) in 10 ml of absolute tetrahydrofuran was hydrogenated with 40 mg of previously reduced 30% palladium in calcium carbonate. After the absorption of an equimolar amount of hydrogen, the hydrogenation practically ceased. After the usual treatment, 186 mg of $\Delta^{8(14)}$-19-nor-D-homoandrostene-3, 17a-dione (X) was isolated. The pure dione (X) has mp 108-110° (from ethyl acetate).

IR spectrum: 1707-1710 (3, 17-CO) cm^{-1}.

The product of the analogous hydrogenation of Δ^4-19-nor-D-homoandrostene-3, 17a-dione (IV) has mp 168-170°.

Aromatization of the ketal (VII). A solution of 45 mg of the ketal (VII) in 0.3 ml of absolute pyridine was poured into a suspension of a complex of 65 mg of chromic anhydride in 1.4 ml of absolute pyridine. The mixture was heated for 5 min at 60-70° and left overnight. After the usual treatment, 52 mg of an oily product was isolated. Preparative chromatography in a thin layer of alumina and development with benzene gave separation into five fractions. The fraction with the greatest R_f value gave 14 mg of the ketal (XI) with mp 87-90°. The next fraction gave 17 mg of a non-crystallizing oil apparently consisting of a mixture of the ketal (XI) with the ethylene ketal of the 3-methyl ether of D-homoequilenin (λ_{max} 227, 275, 305, 330-333 mμ). The other fractions consisted of dark brown non-crystallizing oils.

Production of the ketone (XII). To a solution of 48 mg of the ketal (VII) in 4.8 ml of chloroform was added 0.48 ml of conc. HCl, and the mixture was stirred for 30 min in a current of nitrogen and poured into water. The aqueous layer was extracted with chloroform, and the combined extracts washed with sodium carbonate solution and water and then evaporated. The oily residue was dissolved in benzene and filtered through a column containing 1 g of alumina. The filtrate yielded 45 mg of an oil crystallizing on triturating with hexane. The ketone (XII) had mp 125.5-127° (from methanol). λ_{max} 277 mμ (log ε 3.56).

IR spectrum: 1500 and 1612 (aromatic ring), 1705 (17a-CO) cm^{-1}.

Found %: C 81.86; H 8.22. $C_{20}H_{24}O_2$. Calculated %: C 81.04; H 8.16.

Hydrolysis of the ketal (VII) with isomerization of the $\Delta^{8,(14)}$ double bond. A solution of 100 mg of the ketal (VII) in 30 ml of alcohol was treated with 40 ml of hydrochloric acid (1:1) and was boiled for 2 hours in a current of nitrogen. The solution was cooled, poured into water, and the resulting aqueous layer extracted with chloroform. After the usual

treatment, 116 mg of a yellow oil which crystallized on trituration with hexane was obtained. This yielded 26 mg of the ketone (XIV) with mp 145-151°and λ_{max} 263, 335 mμ (log ε 4.22, 2.43). From the mother liquor we obtained 17 mg of the ketone (XIII) with mp 127-131°and λ_{max} 274-5, 335 mμ (log ε 4.16, 2.52). After crystallization from methanol, the ketone (XIV) had mp 152-157°. λ_{max} 261-3, 335 mμ (log ε 4.12, 2.93).

In other experiments, in which the ketone (XIV) could not be isolated by fractional crystallization, preparative separation in a thin layer of alumina was used.

Hydrogenation of the ketone (XIV) in the presence of 10% palladium in calcium carbonate until the absorption of hydrogen ceased produced the methyl ether of D-homoestrone (XVI) with mp 162-167° and λ_{max} 277-9, 335 mμ (log ε 3.12, 2.87). According to the UV spectrum, the product contained 28% of the methyl ether of D-homoequilenin.

SUMMARY

In the Birch reduction of steroid compounds with a phenylbutadiene grouping, i.e., the ketal of 3-methoxy-$\Delta^{1,3,5(10),8,14}$-D-homoestrapentaen-17a-one (III), the corresponding ketone (IIIa), and 3-methoxy-$\Delta^{1,3,5(10),8,14}$-D-homoestrapentaen-17aβ-ol (VI), 1,4 addition of the hydrogen takes place first, and is followed by reduction of the aromatic nucleus. In this way, 3-methoxy-$\Delta^{1,3,5(10),8(14)}$-D-homoestratetraenone (XII), $\Delta^{4,8(14)}$-19-nor-D-homoandrostadienedione (VIII), and $\Delta^{4,8(14)}$-19-nor-D-homoandrostadien-17aβ-ol-3-one (IX) have been obtained.

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