REDUCTION OF SOME D-HOMOSTEROIDS WITH AN AROMATIC A RING WITH ALKALI METALS UNDER THE CONDITIONS OF BIRCH'S REACTION. II.

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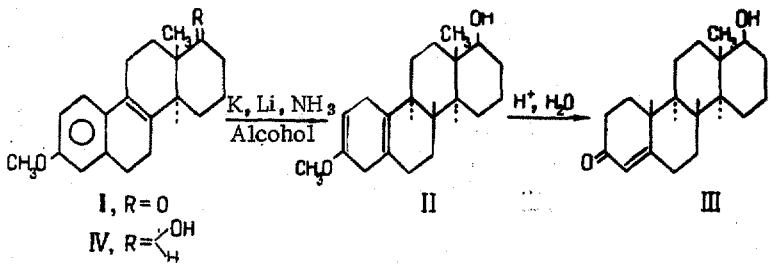
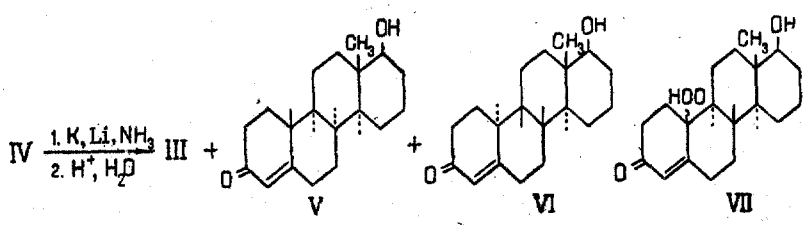
When D-homosteroids of type (I) are reduced by Birch's method (in the Nelson-Wilds modification), the carbinol (II) is formed in the main, and after hydrolysis this gives 19-nor-D-homotestosterone (III) [1].



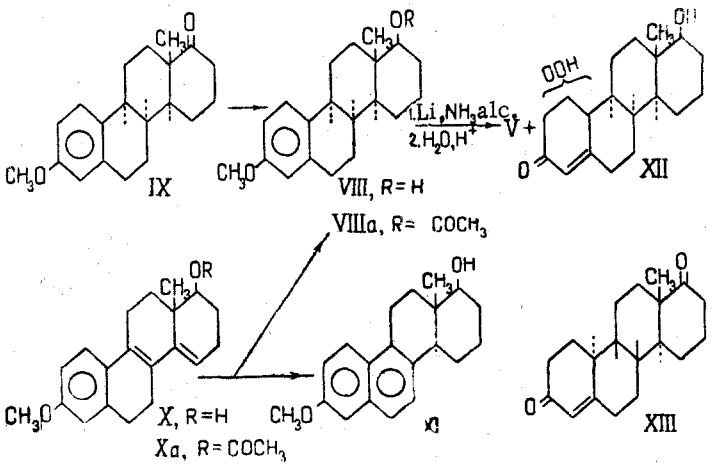
The high anabolic properties of 19-nor-D-homotestosterone (III) gave us an incentive to improve the method of obtaining this compound and its derivatives. A detailed study has been made of the key reaction – reduction with alkali metals in liquid ammonia in the presence of proton donors, particularly alcohol.

It is known [2] that the reduction of steroids with a styrene grouping generally leads to the products of the trans addition of hydrogen, and rarely [2] to a mixture of the trans- and cis-dihydro derivatives. Only in one case has the cis-dihydro product alone been formed [2]. Consequently, we have devoted particular attention to the stereodirectivity of the reduction and its dependence on the functional group in position 17*a*.

The reduction of 3-methoxy-D-homoestra-1, 3, 5(10), 8-tetraen-17*aβ*-ol (IV) with a large excess of potassium (15 g-atoms) and lithium (40 g-atoms) under Johnson's conditions with subsequent hydrolysis led to a mixture of products from which chromatography and fractional crystallization isolated, in addition to the main ketol (III), the isomers 8*α*-19-nor-D-homotestosterone (V) and 9*β*, 10*α*-19-nor-D-homotestosterone (VI) in amounts of approximately 5 and 12% (of the total reaction product). Considerable amounts (~ 7%) of the hydroperoxide of the ketol (VII) were isolated, this having been formed, as was shown by a special experiment, by the oxidation of the ketol (III) with atmospheric oxygen during the hydrolysis.



The structure of the ketol (V) was shown by independent synthesis starting from the 3-methyl ether of 8-iso-D-homoestradiol (VIII). The latter was obtained by the exhaustive hydrogenation of the previously described [3] 3-methoxy-D-homoestra-1, 3, 5(10), 8, 14-pentaen-17*aβ*-ol (X) in the presence of 30% palladium on calcium carbonate. In the hydrogenation, considerable amounts of the 3-methyl ether of D-homoequilenol (XI) are also formed and this is difficult to separate from the desired carbinol (VIII); consequently, it is more convenient to hydrogenate not the carbinol (X) but its acetate (X*a*) since the acetate of the carbinol VIII (VIII*a*) is easier to purify.

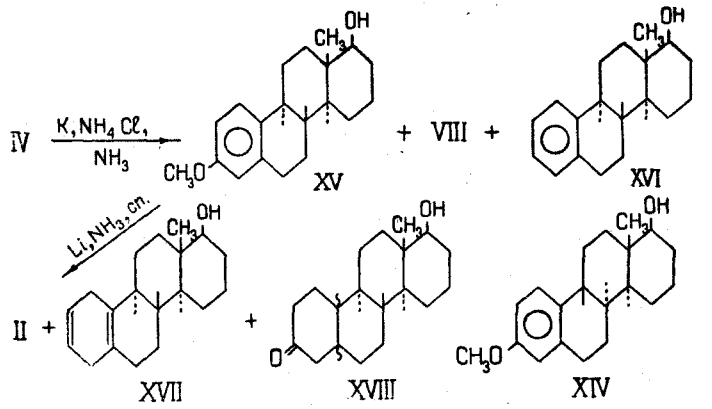


The reduction of the carbinol (VIII) or its acetate (VIII*a*) with lithium and alcohol in liquid ammonia with subsequent hydrolysis (the intermediate dienic carbinols could not be isolated) led to a ketol identical in all respects with the ketol (V) described above. The yield of the ketol (V) was low (10-15%); its isolation is made extremely difficult by the formation of the hydroperoxide (XII) both during hydrolysis and during chromatography. The anti configuration of the hydrogen atoms at C_9 and C_{10} is taken in accordance with the data of Nagata [4].

The structure of the ketol (VI) is confirmed by the following facts. It is not the 17*a* epimer of the ketol (III) (if it is assumed that such epimerization is possible), since on oxidation it gives the diketone (XIII) differing from 19-nor-D-homoandrost-4-enedione (XXIII). The ketol (VI) cannot be the 10-epimer of one of the ketols (III) or (V), either, since such thermodynamically unstable epimers are inevitably converted into the stable epimers (i.e., into III and V) under the conditions of acid treatment; the ketol (VI), as a special experiment showed, undergoes no change even under the action of dilute mineral acids. Since in the Birch reduction of a Δ^8 double bond the formation of a thermodynamically unstable product with a trans-syn-trans configuration (for example, XIV) is unlikely [5], the assumption is left of the cis addition of hydrogen atoms from the β-region, which must lead (after reduction of the aromatic ring and hydrolysis of the intermediate methoxydienol) to a compound with a trans-anti-cis-anti configuration which we also ascribe to the ketol (VI) and which, from a consideration of molecular models, proves to be completely stable. The proposed structure is also favored by a comparison of the NMR spectra of the pairs of isomeric ketols (III) and (VI) and 19-nortestosterone and its 9β, 10α isomer, in which the differences in the magnitude of the chemical shifts of the 18-CH_3 groups coincide (0.85 and 0.89 ppm, respectively, for the first pair, and 0.78 and 0.82 ppm for the second).

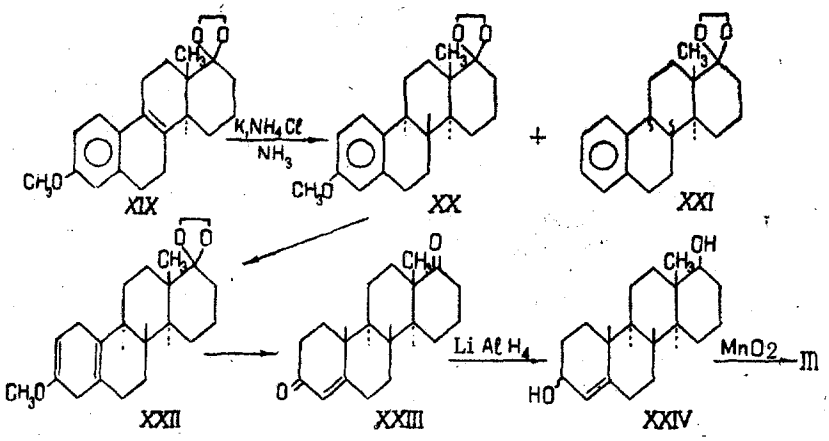
Two structures are possible for the hydroperoxide of the ketol (III) formed as a result of allyl oxidation: a 6- and a 10-hydroperoxide. Its structure as a 10-hydroperoxide (VII) is confirmed by the retention of the hydroxyl group after hydrogenation on 30% palladium on calcium carbonate and subsequent oxidation. This shows the tertiary nature of the hydroxyl group.

The absence of strict stereoselectivity was also observed in the reduction of the carbinol (IV) with potassium and ammonium chloride in liquid ammonia. Besides the product with the natural configuration (XV), the 8α-epimer (VIII) and the hydrogenolysis product (XVI) were also isolated:



Reduction of the aromatic ring of the carbinol (XV) (by means of lithium and alcohol in liquid ammonia) took place smoothly and led to the known methoxydienol (II) with a yield of more than 70%. From the mother liquor after hydrolysis we isolated the deoxy derivative (XVII) and a small amount of a ketol, apparently an isomer of 17*a*β-hydroxy-19-nor-D-homoandrostan-3-one (XVIII), since its IR spectrum contained a band of a non-conjugated CO group (1708 cm^{-1}) and there was no band for a quadruply-substituted ethylene bond. Moreover, the ketol did not isomerize on treatment with hydrochloric acid, which excludes a $\Delta^{5(10)}$-3-keto grouping.

A stricter stereodirectivity was found in the reduction of the ethylene ketal of 3-methoxy-D-homoestra-1, 3, 5(10), 8-tetraen-17α-one (XIX) by means of potassium and ammonium chloride in liquid ammonia. This yielded about 80% of the ketal of the methyl ether of D-homoestrone (XX) and, as a result of hydrogenolysis, a small amount of the ethylene ketal of D-homoestra-1, 3, 5(10)-trienone (XXI). Another, less polar, compound giving after hydrolysis a product free from the carbonyl group was detected chromatographically. Apparently, in addition to the splitting out of the methoxy group, a small amount of hydrogenolysis of the 17α-ketal grouping also takes place.



Reduction of the ketal (XX) with lithium and alcohol in liquid ammonia with subsequent hydrolysis of the methoxydiene (XXII) led only to 19-nor-D-homoandrostenedione (XXIII). This dione was converted into 19-nor-D-homotestosterone (III) by reduction with lithium aluminum hydride to a mixture of epimeric diols (XXIV) with subsequent oxidation by manganese dioxide and selective reduction with sodium borohydride. All this sequence of reactions is an additional proof of the configuration of 19-nor-D-homotestosterone (III). On reduction of 3-methoxy-D-homoestra-1, 3, 5(10), 8-tetraen-17α-one (I) with potassium and lithium in liquid ammonia in the presence of alcohol, the main product was the carbinol (II), which was isolated with a yield of about 55%. Hydrolysis of the mother liquor gave the ketol (III) and also the hydroperoxide (VII) and the hydrogenolysis product – the carbinol (XVII).

Thus, the stereodirectivity of the reduction of 3-methoxy -$\Delta^{1,3,5(10),8}$ - D-homosteroids depends on the nature of the functional group in the 17α position. The 17α ketal has the greatest stereodirectivity and the 17α carbinol the least. There is still no explanation of these facts; however, it must be noted that the carbinol and the ketone, in contrast to the ketal, react in the form of alkoxides.

EXPERIMENTAL

The melting points were determined on a Kofler block. The substances were dried before analysis 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 instrument in the form of a mull in vaseline oil, and the NMR spectra on a JNMC-60 instrument in deuterochloroform with tetramethylsilane as internal standard. The course of the reaction was followed by chromatography on plates with a thin (1 mm) non-fixed layer of alumina (Brockman activity IV-V).

3-Methoxy-D-homoestra-1, 3, 5(10), 8, 14-pentaen-17αβ-ol (X), 3-methoxy-D-homoestra, 1, 3, 5(10), 8-en-17αβ-ol (IV), and 3-methoxy-D-homoestra-1, 3, 5(10), 8-tetraen-17α-one (I) and its ethylene ketal (XIX) were obtained by recognized procedures [3].

Reduction of the carbinol (IV) with potassium, lithium, and alcohol in liquid ammonia. A solution of 2 g of the carbinol (IV) in 120 ml of absolute tetrahydrofuran and 70 ml of absolute ether was added to 300 ml of ammonia at –70°. After 10 min, 4 g of finely cut potassium (15 g-atom/mole) was added gradually. The purple solution formed was treated with 150 ml of absolute alcohol; the solution became colorless. Two grams of lithium (43 g-atom/mole) was added, whereupon the solution periodically became blue-purple. Stirring was carried out until the color had disappeared and then 100 ml of ether was added gradually and the ammonia was allowed to evaporate. The resulting suspension was decomposed at 0° with 300 ml of water. The aqueous layer was extracted with ether, the combined extracts were neutralized by the addition of dry ice, washed with saturated salt solution and then with water, and dried with anhydrous magnesium sulfate. After the solvent had been evaporated off, 2. 16 g of a yellow oily residue was obtained, and this was hydrolyzed without purification.

A mixture of a solution of 2. 16 g of the reduction product in 20 ml of chloroform and 2 ml of conc. HCl was stirred for 1 hour and was then poured into water. The aqueous layer was extracted with chloroform; the combined extract was washed with a solution of sodium carbonate and with water and was dried. The residue obtained after the evaporation of the solvent, which did not crystallize, was chromatographed on 80 g of alumina. Benzene eluted a mixture of 19-nor-D-homotestosterone (III) and its 8α epimer (V) in the form of an oil which crystallized on trituration with ethyl acetate-petroleum ether. Fractional crystallization from acetone gave 376 mg of the ketol (III) with mp 145-147°, and 94 mg

of the ketol (V) with mp 128-130° (identical with a known sample obtained below). The ethereal fraction yielded a mixture of the ketol (III) with its 9β, 10α epimer (VI), fractional crystallization of which from acetone-petroleum ether gave 120 mg of the ketol (III) with mp 141-143° and 256 mg of the ketol (VI) with mp 163-165°. The pure ketol (VI) had mp 172-173° (from ethyl acetate). λ_{max} 240 mμ (log ε 4.18).

IR spectrum: 1658 (3-CO), 1612 (4-C=C), 3415 (17*a*-OH) cm^{-1}.

Found %: C 79.20; 79.14; H 9.86; 9.65. $C_{19}H_{28}O_2$. Calculated %: C 79.12; H 9.79.

Chloroform eluted 140 mg of the hydroperoxide (VII) with mp 176-178°. A pure sample had mp 193-195° (from ethyl acetate-cyclohexane). λ_{max} 236 mμ (log ε 4.02).

IR spectrum: 1665 (3-CO), 3310, 3420 (17*a*-OH, 10-OOH) cm^{-1}.

Found %: C 71.70; 71.72; H 9.01; 9.04. $C_{19}H_{28}O_4$. Calculated %: C 71.22; H 8.81.

The ketol (VII) liberated iodine from a solution of sodium iodide. The same ketol was obtained when a solution of the ketol (III) in tetrahydrofuran was allowed to stand in the air for a long time.

Sixty milligrams of the ketol (VII) was hydrogenated in 15 ml of alcohol in the presence of 50 mg of reduced 30% palladium on calcium carbonate, about 2 moles of hydrogen being absorbed. The isolated product was dried in vacuum over phosphorus pentoxide (1 mm, 5 hr), after which it was dissolved in 0.6 ml of absolute pyridine and the solution was poured into a solution of 0.12 g of chromic anhydride in 1.2 ml of absolute pyridine. After the usual working up, 53 mg of an oil was obtained.

IR spectrum: 1705-7 (3, 17*a* C=O), 3340 (OH) cm^{-1}.

In another case of the analogous reduction of the carbinol (IV), the oily residue after the isolation of the isomeric ketols was acetylated with acetic anhydride in pyridine, and the reaction product was chromatographed on a column of alumina. Petroleum ether eluted a colorless mobile oil which crystallized on trituration with alcohol. The isolated acetate of the carbinol (XVII) (mp 165-166° from ethyl acetate-alcohol) exhibited no selective absorption in the UV in the 220-320 mμ region.

IR spectrum: 1658 (2-C=C), 1693 (5-C=C), 1735 (CO) cm^{-1}.

NMR spectrum: 0.87 (18-CH_3); 2.05 ($COCH_3$); 2.52 (1-CH_2; 4-CH_2); 5.65 (2-CH, 3-CH) ppm.

Found %: C 80.31; 80.54; H 9.81; 9.79. $C_{21}H_{30}O_2$. Calculated %: C 80.21; H 9.62.

Production of the 3-methyl ether of 8-iso-D-homoestra-3, 17*a*β-diol (VIII) and its acetate (VIIIa). 500 mg of the carbinol (X) in 15 ml of absolute tetrahydrofuran was hydrogenated in the presence of 100 mg of 30% palladium on calcium carbonate. After the absorption of about 90% of the theoretical amount of hydrogen (which took 16 hr), the solution was filtered, the filtrate was evaporated, and the residue was crystallized by trituration with alcohol. Fractional crystallization from alcohol gave 287 mg of the carbinol (VIII) with mp 148-150° (identical with the sample obtained below), and 60 mg of the 3-methyl ether of D-homoequilen-17*a*β-ol (XI) with mp 172-174°. λ_{max} 229, 267, 277, 320, 335 mμ (log ε 4.76, 3.70, 3.74, 3.33, 3.42).

IR spectrum: 1507, 1600, 1630 (aromatic ring), 3255, (17*a*-OH) cm^{-1}.

Found %: C 81.41; H 8.23. $C_{20}H_{24}O_2$. Calculated %: C 81.04; H 8.16.

The analogous hydrogenation of 1 g of the acetate (X*a*) gave 0.7 g of the acetate (VIII*a*) with mp 152-155°. The pure acetate had mp 164-165° (from methanol). λ_{max} 255, 277, 285 mμ (log ε 4.16, 3.52, 3.48).

Found %: C 77.30; 77.44; H 8.81; 8.80. $C_{22}H_{30}O_3$. Calculated %: C 77.15; H 8.83.

The methanolysis of 500 mg of the acetate (VIII*a*) in the presence of sodium methoxide (from 0.15 g of sodium) gave 420 mg of the carbinol (VIII) with mp 150-152°. The pure carbinol had mp 151-153° (from alcohol). λ_{max} 278, 286 mμ (log ε 3.28, 3.26).

IR spectrum: 1500, 1580, 1617 (aromatic ring), 3490 (17*a*-OH) cm^{-1}.

Found %: C 80.17; 80.34; H 9.39; 9.52. $C_{20}H_{28}O_2$. Calculated %: C 79.95; H 9.39.

Preparation of the ketol (V). To a solution of 1.2 g of lithium in 200 ml of liquid ammonia at −70° was added 1.25 g of the carbinol (VIII) in 150 ml of a mixture of absolute tetrahydrofuran and ether (1:1), and absolute alcohol was added in drops until decolorization was achieved (38 ml over 30 min). In the usual way, 1.3 g of reduction product was isolated in the form of an oil the chromatography of which on alumina led to partial hydrolysis to the ketol (V) and oxidation of the latter.

1.3 g of the oil was hydrolyzed by boiling its alcoholic solution (25 ml) with 15 ml of hydrochloric acid (1:2).

After the usual working up, 1.26 g of an oily residue was obtained, and this was chromatographed on a column of 60 g of alumina in an atmosphere of nitrogen. A mixture of petroleum ether and benzene (from 20 to 60%) eluted 130 mg of an oil with an R_f coinciding with the R_f of the carbinol (XVIII). The benzene fraction yielded 160 mg of a mixture of the ketol (V) with a less polar substance which was not identified. Crystallization of the mixture from ethyl acetate yielded 110 ml of the ketol (V) with mp 128-132°. The pure ketol with mp 133-136° (from ethyl acetate) gave a depression of the melting point with a sample of the ketol (III). λ_{max}240 mμ (log ε 4.18).

IR spectrum: 1604 (4-C=C), 1650 (3-CO), 3542 (17α-OH) cm^{-1}.

Found %: C 79.55; H 10.06. $C_{19}H_{28}O_2$. Calculated %: C 79.12; H 9.79.

Oxidation of the ketol (VI). A solution of 20 mg of the ketol (VI) in 0.3 ml of absolute pyridine was poured into a solution of 40 mg of chromic anhydride in 0.8 ml of absolute pyridine and the mixture was left overnight. It was then poured into 40 ml of chloroform and filtered through a layer of 400 ml of alumina. The filtrate was evaporated; the resulting oil was crystallized by trituration with methanol. After crystallization from methanol, the dione (XIII) with mp 173-175° was obtained. A mixture with a sample of the dione (XXIII) (172-174°) melted at 148-153°.

IR spectrum: 1670 (3-CO), 1702 (17-CO) cm^{-1}.

Reduction of the carbinol (IV) with potassium and ammonium chloride in liquid ammonia. To 250 ml of liquid ammonia was added 3 g of potassium followed by a solution of 2 g of the carbinol (IV) in 125 ml of absolute tetrahydrofuran and 50 ml of absolute ether. After 10 min, 5 g of ammonium chloride was added gradually until decolorization was achieved. After working up analogous to that described above, the oily residue was crystallized by trituration with a mixture of petroleum ether and alcohol, giving 780 mg of the carbinol (XV) with mp 126-130° (identical with the sample which we obtained below). The semicrystalline mass from the mother liquor was acetylated in 6 ml of absolute pyridine with 5 ml of acetic anhydride. After the usual working up, 1.25 g of an oil was obtained which was dissolved in 120 ml of benzene and filtered through a column of 20 g of alumina. Two crystallizations (from alcohol) of the residue after the elimination of the solvent gave 220 mg of the acetate (VIIIα) with mp 155-157°, identical with an authentic sample. 1.03 g of the substance from the mother liquor was chromatographed on 80 g of alumina. The petroleum ether and petroleum ether-benzene (10-20%) fractions yielded 280 mg of an oil which crystallized on the addition of alcohol. This gave the acetate of D-homoestra-1, 3, 5(10)-trien-17αβ-ol (XVI) with mp 136-140° (from alcohol). λ_{max}266 mμ (log ε 2.78).

IR spectrum: 744 (aromatic ring), 1735 (C=O) cm^{-1}.

NMR spectrum: 0.90 (18-CH_3); 2.05 ($COCH_3$); 7.07, 7.20 (aromatic ring) ppm.

Found %: C 80.91; 81.14; H 9.11; 9.16. $C_{21}H_{28}O_2$. Calculated %: C 80.73; H 9.03.

Further elution with a mixture of petroleum ether and benzene and with benzene, and fractional crystallization of the product from alcohol, gave 60 mg of the acetate of the carbinol (XVI) and 110 mg of the acetate (VIIIα) with mp 157-159°.

Reduction of the carbinol (XV) with lithium and alcohol in liquid ammonia. To 200 ml of liquid ammonia was added a solution of 1 g of the carbinol (XV) in a mixture of 100 ml of absolute tetrahydrofuran and 25 ml of absolute ether, followed by 1 g of lithium at −70°. After 10 min, absolute alcohol was added until decolorization was achieved (26 ml over 30 min), the ammonia was removed, and the mixture was decomposed with water, and then, in a similar manner to that described, 730 mg of the diene (II) with mp 134-137° was isolated. The mother liquor was hydrolyzed without purification. After preparative chromatography on an alumina plate (210 × 150 × 4), the fraction with the greatest R_f gave 86 mg of the carbinol (XVII), identical with respect to melting point and IR spectrum with the authentic sample described below. The following fraction (with a lower R_f value) gave 25 mg of an oil – apparently 17αβ-hydroxy-19-nor-D-homoandrostan-3-one (XVIII).

IR spectrum: 1708 (3-CO), 3340 (17α-OH) cm^{-1}.

The third fraction contained 93 mg of the ketol (III).

Reduction of the ketal (XIX) with potassium and ammonium chloride in liquid ammonia. To 250 ml of liquid ammonia at −70° was added a solution of 2.95 g of the ketal (XIX) in a mixture of 150 ml of absolute tetrahydrofuran and 50 ml of absolute ether. To the solution was added 6.2 g of potassium (18 g-atoms/mole) and, after 30 minutes' stirring, 16.5 g of ammonium chloride; the purple solution lost its color. The further treatment was similar to that described above. Altogether, 3.05 g of a yellow oil was obtained, which crystallized on trituration with alcohol and gave 2.46 g of a substance with mp 126-130°. After recrystallization from alcohol, 2.12 g of the ketal (XX) with mp 138-5-139.5°, giving no depression of the melting point with an authentic sample, was obtained.

Two grams of material from the mother liquors (after two experiments) was dissolved in 30 ml of benzene and transferred to a column containing 120 g of alumina. Hexane (100 ml) eluted 70 mg of an oil which crystallized on trituration

with alcohol. This gave 38 mg of a substance with mp 98-103°. The mother liquor was evaporated and the resulting oil was chromatographed in a thin layer of alumina (100 × 40 × 2) in the hexane-benzene (7:3) system. From the zones located at the front of the chromatogram we isolated 13.3 mg of an oil with λ_{max} 265-6 mμ (log ε 2.81) – apparently the product of the complete hydrogenolysis of the ketal (XXI). Treatment of the oil with hydrochloric acid caused no change in the product; there was no band of a carbonyl group in the IR spectrum. Further elution of the column with 100 ml of hexane gave 450 mg of an oil which crystallized on the addition of ether. After recrystallization from alcohol-ethyl acetate, a ketal (XXI) with mp 112-113.5° was isolated. λ_{max} 226 mμ (log ε 2.18).

IR spectrum: 745, 3050 (aromatic ring), 1190 (ketal) cm^{-1}.

NMR spectrum: 0.97 (18-CH_3); 3.90 (ketal); 7.03; 7.12 (aromatic ring) ppm.

Found %: C 80.93; 80.78; H 9.05; 9.15. $C_{21}H_{28}O_2$. Calculated %: C 80.73; H 9.03.

Subsequently, benzene (200 ml) eluted 760 mg of a mixture of ketals (XX) and (XXI). Elution with ether gave a brown resin containing phenolic products.

Acid treatment of an alcoholic solution of the ketal (XX) gave a quantitative yield of the 3-methyl ether of D-homoestrone.

Reduction of the ketal (XX) with lithium and alcohol in liquid ammonia. To a mixture of 300 ml of liquid ammonia and a solution of 1.3 g of the ketal (XX) in 150 ml of absolute tetrahydrofuran and 50 ml of absolute ether at −70°, 1.3 g of lithium was added, followed after 50 min by 64 ml of absolute ether to decolorize the mixture. The usual working up gave 1.28 g of a crystalline product. Recrystallization from alcohol-ethyl acetate gave 710 mg of the ketal of 3-methoxy-D-homoestra-2,5-dien-17α-one (XXII) with mp 146.5-147.5°. The mother liquor gave a further 270 mg of the ketal (XXII) with mp 140-143°.

A solution of 610 mg of the ketal (XXII) in 25 ml of alcohol and 10 ml of chloroform was mixed with 15 ml of hydrochloric acid (1:2) and the mixture was heated for 20 min at 70°. After cooling, it was decomposed with water and the aqueous layer was extracted with chloroform. After the usual working up, 460 mg of the dione (XXIII) with mp 164-166° was isolated. Two recrystallizations from ethyl acetate gave the pure dione (XXIII) with mp 173-174°, identical with respect to melting point and IR spectrum with an authentic sample [7].

Reduction of the dione (XXIII) with lithium aluminum hydride. A solution of 500 mg of the dione (XXIII) in 25 ml of absolute tetrahydrofuran was added in drops to a suspension of 400 mg of lithium aluminum hydride in 10 ml of absolute tetrahydrofuran. The mixture was stirred for 2.5 hr at 70°; in the usual way, 416 mg of a mixture of the epimeric carbinols (XXIV) with mp 126-130° was isolated. This was dissolved in 40 ml of chloroform and the solution was treated with 2 g of freshly prepared manganese dioxide [6] and stirred for 24 hr. When complete oxidation was shown by a chromatogram, the solution was filtered, and the residue on the filter was washed with hot chloroform. After the solvent had been eliminated, 306 mg of an oil was obtained. Extraction of the residue in a Soxhlet apparatus gave a further 76 mg of product. The oily residue was crystallized by trituration with ethyl acetate, giving 296 mg of the ketol (III) with mp 138-141°. From the mother liquor 56 mg of crystals with mp 172-177° was isolated and these, judging from the UV spectrum (λ_{max} 240, 282 mμ), consisted of a mixture of the ketol (III) with the product of its dehydrogenation 17αβ-hydroxy-19-nor-D-homoandrostan-4,6-dien-3-one.

Reduction of the dione (XXIII) with sodium borohydride. A solution of 100 mg of the dione (XXIII) in 25 ml of methanol was treated with 20 mg of sodium borohydride and the mixture was stirred at 0°. Complete conversion of the dione, followed on a chromatogram, took 25 min. The excess of borohydride was decomposed with water and the product was extracted with benzene. This gave 86 mg of the ketol (III) with mp 136-142°; after recrystallization from acetone, mp 143-145°.

If after completion of the main reaction a few drops of acetic acid was added to the solution, after working up similar to that described above it was possible to isolate a mixture of the ketol (III) and 19-nor-D-homoandrosten-3, 17αβ-diol. Acetylation of 100 mg of this mixture in 1 ml of absolute pyridine and 1 ml of absolute acetic anhydride (20°, 18 hr) gave the acetate of 19-nor-D-homoandrosten-3,17αβ-diol with mp 138-140° (from alcohol).

IR spectrum: 1656 (4-C=C), 1728 (17α-$OCOCH_3$) cm^{-1}.

Found %: C 73.41; 73.46; H 8.95; 8.94. $C_{23}H_{34}O_4$. Calculated %: C 73.76; H 9.15.

Reduction of the ketal (XIX) with potassium, lithium, and alcohol in liquid ammonia. In a similar manner to the carbinol (IV), 3 g of the ketal (XIX) in 200 ml of absolute tetrahydrofuran and 100 ml of absolute ether was reduced in 400 ml of liquid ammonia by means of 6 g of potassium, 3 g of lithium, and 150 ml of absolute alcohol. This gave 1.4 g of the ketal (XXII) with mp 140-142°. Without purification, the mother liquor was subjected to hydrolysis, giving 230 mg of the dione (XXIII).

Reduction of the ketone (I) with potassium, lithium, and alcohol in liquid ammonia. To 700 ml of liquid ammonia at −70° was added a solution of 6.08 g of the ketone (I) in 200 ml of absolute tetrahydrofuran and 100 ml of absolute ether. After 15 min, 12 g (15 g-atoms/mole) of potassium was added. The purple solution was treated with 210 ml of absolute alcohol, and 12 g (85 g-atoms/mole) of lithium was added to the decolorized solution. After the usual working up, 3.38 g of the diene (II) with mp 134-137° was isolated.

The mother liquors from the experiment described and from the similar reduction of 5.16 g of the ketone were subjected without purification to hydrolysis with hydrochloric acid in methanol. The oily reaction product was dissolved in chloroform. Half the solution was transferred to an alumina plate (550 × 250 × 5) and was developed in ether. The fraction with the greatest R_f value gave 730 mg of the carbinol (XXVII) with mp 158-160°. The pure carbinol had mp 167-168° (from acetone) and exhibited no selective absorption in the 220-300 mμ region.

IR spectrum: 1667 (2-C=C), 1705 (5-C=C), 3357 (17α-OH) cm^{-1}.

NMR spectrum: 0.80 (18-CH_3); 2.53 (1-CH_2); 5.70 (2-CH, 3-CH) ppm.

Found %: C 83.82; 84.00; H 10.70; 10.38. $C_{19}H_{28}O$. Calculated %: C 83.77; H 10.36.

The following fraction gave 680 mg of the ketol (III) with mp 140-143°. The fraction at the start gave 700 mg of an oil, which was subjected to preparative chromatography on alumina in the ethyl acetate-ether (2:1) system. The more mobile fraction contained D-homoestradiol, identified by comparison with a known sample. The less mobile fraction yielded the hydroperoxide (VII) with mp 178-185°.

SUMMARY

1. The reduction of 3-methoxy-D-homoestra-1, 3, 5(10), 8-tetraen-17αβ-ol (IV) with alkali metals in the presence of ammonium chloride or alcohol gives, in addition to 8β, 9α-dihydro derivatives, the 8α, 9α and 8β, 9β-epimers, the structure of which has been shown partly by independent synthesis and partly on the basis of chemical reactions and NMR spectra.

2. Hydrolysis of the reduction products has given 19-nor-D-homotestosterone (III) and its 8α- and 9β, 10α-epimers (V) and (VI). The ketols (III) and (V) readily form hydroperoxides in air.

3. The reduction of the ethylene ketal of 3-methoxy-D-homoestra-1, 3, 5(10), 8-tetraen-17α-one (XIX) takes place stereodirectively and gives only 8β, 9α-dihydro derivatives.

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