VARIANTS OF THE COMPLETE SYNTHESIS OF d, *l*-19-NORTESTOSTERONE, d, *l*-19-NORANDROST-4-ENE-3, 17-DIONE, AND THEIR STEREOISOMERS

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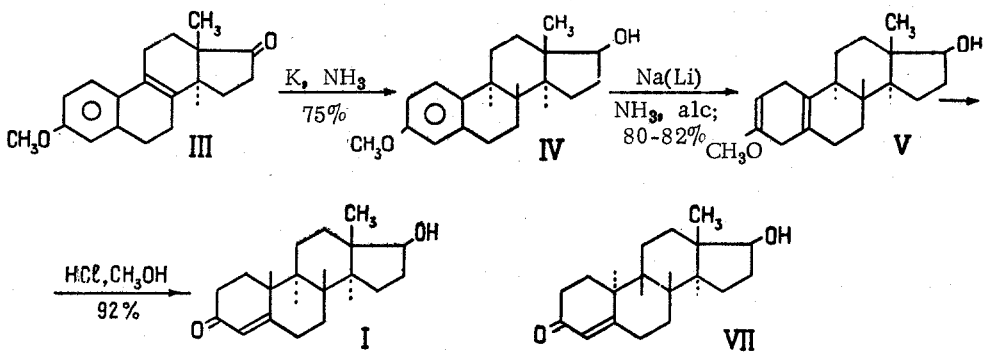
In a previous communication [1] we described the synthesis of d, *l*-19-nortestosterone (I) and d, *l*-19-norandrost-4-enedione (II) from the readily accessible 3-methoxyestra-1, 3, 5(10), 8-tetraen-17-one (III).

In the present paper we give a detailed account of some variants of the production of d, *l*-19-nortestosterone (I) and its epimers and derivatives, and also the results of tests for androgenic and anabolic activity.

In the first variant, the methyl ether of d, *l*-estradiol (IV), which is readily obtainable from the ketone (III) by a method described previously [3], is reduced by the Wilds-Nelson method [2]. The reaction goes in practically the same way with both lithium and sodium and, after hydrolysis of the intermediate methoxycarbinol (V), the expected ketol (I) is formed with yields of 56 and 55%, respectively.



Acylation of the ketol (I) gave the acetate (Ia) and the β-phenylpropionate (Ib); the latter is the racemate of the well-known anabolic durabolin. Oxidation of the ketol (I) gave d, *l*-19-norandrost-4-ene-3, 17-dione (VI) with a yield of 60%.

In the second pathway, the double bond and the aromatic ring of the ketone (III) were reduced in one stage with a large amount (20-fold excess) of alkali metal. Under these conditions, the stereospecificity of the reaction is not so strongly expressed and, after hydrolysis, in addition to d, *l*-19-nortestosterone (I), a considerable amount of its 9, 10-epimer (VII) was formed. In the reaction with sodium or lithium, the ratio of I: VII was 4: 1; with potassium, only traces of the ketol (VII) were formed. The total yield of epimers (already separated by crystallization) was about 60% with sodium and 50-55% with lithium and potassium. The results are almost independent of whether the reaction is carried out by Birch's method [4] or by Wilds and Nelson's method [2]. Oxidation of the ketol (VII) gave 9, 10-iso-19-norandrost-4-ene-dione (IX).

According to another variant, the ketone (III) was first reduced with lithium aluminum hydride to the corresponding carbinol (VIII) and the latter was subjected to Birch's reaction (under the conditions given by Wilds and Nelson) as a result of which there was again obtained (after hydrolysis) a mixture of the epimers (I) and (VII) in a ratio of 2: 1 in the case of potassium and 1: 2 with sodium and lithium. The total yield of epimers (already separated by crystallization) amounted to 50%, 30%, and 30%, respectively.

In the third variant, the ketone (III) in liquid ammonia was reduced successively with potassium and lithium, but, in contrast to the first variant, in one operation [5]. The total yield of 19-nortestosterone (I) amounted to 55%, and practically none of the epimer (VII) was formed. Consequently, this route is the best, since by the second route the yields of products are distinctly lower and by the first route, which gives the same yield (55-56%), two operations must be carried out instead of one.

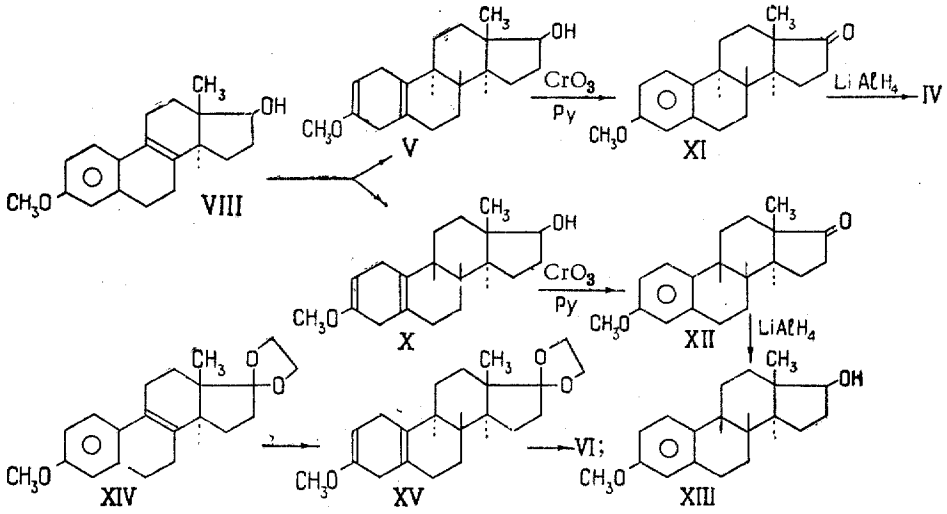
It was very difficult to demonstrate the structure of the epimeric ketol (VII), since it was not possible to convert it directly into a compound with a known configuration. Consequently, the following roundabout route was chosen. The mixture of intermediate carbinols (V) and (X) obtained by the reduction of the carbinol (VII), after separation of part of the carbinol (V) by crystallization, was dehydrogenated with chromic anhydride in pyridine to a mixture of the methyl ethers of estrone and 9β-estrone (XI) and (XII). A large part of the ketone (XI) was separated by crystallization, and the mother liquor was reduced by means of lithium aluminum hydride. From the resulting mixture of the 3-methyl ethers of

estradiol and 9β-estradiol (IV) and (XIII) it was possible to isolate the latter, as the less soluble, by fractional crystallization. Its melting point (141°) coincided with that given by Douglas et al. [6].

Thus, the configuration of the hydrogen atom in the 9-position in the ketol (VII) has been demonstrated. As regards the hydrogen at C_{10}, it is assumed to have the α-configuration as being the most thermodynamically stable; in the corresponding model of the ketol, all the six-membered rings have assumed the chair or semi-chair shape.

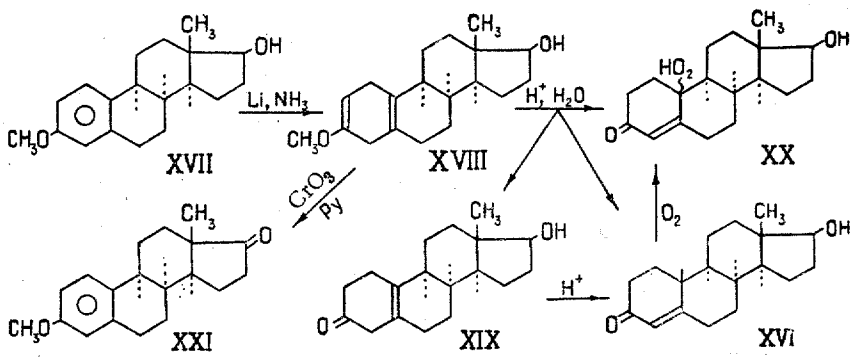
Examples of the non-stereodirected reduction (by Birch's method) of the styrene double bond are known in the literature [7].

It is interesting to note that the reduction of the ethylene ketal of 3-methoxyestra-1, 3, 5(10), 8-tetraen-17-one (XIV) with lithium and alcohol in liquid ammonia gave a high yield (73%) of the corresponding ketal (XV), hydrolysis of which gave d, *l*-19-norandrost-4-ene-dione (VI).



The isomeric ketal or (after hydrolysis) diketone could not be detected. Consequently, here, as in the D-homo series, the nature of the substituent at C_{17} affects the stereodirectivity of the reduction.

In order to investigate the dependence of the anabolic activity of the 19-norsteroids on their structure, we synthesized d, *l*-19-nor-8α, 10β-testosterone (XVI). Reduction of the 3-methyl ether of d, *l*-8-isoestradiol (XVII) with lithium and alcohol in liquid ammonia gave an 87% yield of 3-methoxy-8-isoestra-2, 5-dien-17β-ol (XVIII), the hydrolysis of which gave a mixture of the expected ketol (XVI), its $\Delta^{5(10)}$ isomer (XIX), and the hydroperoxide of the ketol (XX).



The configuration of the hydrogen at C_{10} in the ketol (XVI) is given, as in the case of the ketol (VII), by a consideration of molecular models. The structure of the ketol (XIX) is confirmed by its IR and UV spectra (absence of a CH=CH–CO group), its capacity for isomerization under the action of hydrochloric acid into the ketol (XVI), and also by NMR (absence of a C_6 vinyl proton).

The proposed structure for the hydroperoxide (XX) corresponds to the features of the IR and UV spectra, and also to the fact that after its hydrogenation over palladium and oxidation by Sarett's reagent the final product retains a hydroxyl group (3420 cm^{-1}).

The unusual ease of oxidation of d, *l*-19-nor-8-isotestosterone (XVI) which takes place even in solution or on chromatography on alumina, must be mentioned.

The biological testing of d, *l*-19-nortestosterone (I), its ethers (Ia) and (Ib), and also d, *l*-norandrost-4-ene-3, 17-dione (VI) and the d, *l*-norandrosta-4, 8(14)-diene-3, 17-dione (VI) obtained previously [1] has shown that they all possess myotrophic activity, but less than that of d, *l*-19-nor-D-homotestosterone and its derivatives [8]. The tests were carried out by a recognized procedure [9]. The androgenic and myotrophic (anabolic) activity of testosterone propionate were taken as unity (see table).

Compound	Dose, mg	Activity		Index
		Anabolic	Androgenic	
d-19-Nortestosterone	0.1	0.89	0.22	4.0
d, *l*-19-Nortestosterone (I)	0.1	0.5	0.25	2.0
β-Phenylpropionate of (I) (Ib)	0.1	1.7	0.62	2.7
Acetate of (I) (Ia)	0.1	0.7	0.31	2.2
3-Methoxyestra-2, 5(10)-dien-17β-ol (V)	0.1	0.76	0.39	1.9
d, *l*-19-Norandrost-4-ene-3, 17-dione (VI)	0.1	0.58	0.32	1.8
d, *l*-9-Norandrosta-4, 8(14)-diene-3, 17-dione	0.7	0.24	0.1	2.4

Experimental

Before analysis, all substances were dried in vacuum (0.5-1 mm) over phosphorus pentoxide. The course of the reaction and the completeness of the conversion were followed by means of chromatography on a loose thin layer on plates [10]. The adsorbent was alumina (activity grades II, III), layer thickness 1-1.5 mm, solvents benzene and ether-benzene (1: 1 and 2: 1). Spots revealed in UV light or by means of iodine vapor.

The UV spectra were taken on an SF-4 spectrophotometer in 96% alcohol. The IR spectra were measured on IK-10 and IKS-14 double-beam spectrographs. As a rule, the measurements were carried out in a mull with liquid paraffin. The NMR spectra were taken on an INM-C-60 instrument.

3-Methoxyestra-1, 3, 5(10), 8-tetraen-17-one (III), its ketal (XIV), and 3-methoxyestra-1, 3, 5(10), 8-tetraen-17β-ol (VIII) were obtained by a method described previously [3].

Reduction of the 3-methyl ether of d, *l*-estradiol (IV). A solution of 3.5 g of the carbinol (IV) in 220 ml of anhydrous ether and 50 ml of anhydrous tetrahydrofuran was run into 350 ml of liquid ammonia at −70°, and then 3.56 g of lithium (21-fold excess) in small pieces was added over 20 min. The mixture was stirred for 30 min and then 150 ml of anhydrous alcohol was added in drops over 30 min. After the evaporation of the ammonia, the residue was decomposed with water at 0-5° and was extracted successively with ether and chloroform.

The combined extracts were neutralized with solid carbon dioxide, washed with water, and dried over sodium sulfate. Distillation of the solvent gave 3.2 g (80% of theoretical) of 3-methoxyestra-2, 5-dien-17β-ol (V) with mp 114-116°. An analytical sample had mp 118-119° (from alcohol) and 127-128° (from benzene-petroleum ether, 1: 2). UV spectrum, λ_{max}: 276 mμ (log ε 1.48). IR spectrum: 1667 (2—C=C), 1695 (5—C=C), 3527 (OH) cm^{-1}.

Found: C 78.94, 79.07; H 9.74, 9.83%. Calculated for $C_{19}H_{28}O_2$: C 79.12; H 9.79%.

The acetate (pyridine, $(CH_3CO)_2O$, 16 hr, 20°) had mp 148-149° (from alcohol). The similar reduction of 0.85 g of the carbinol (IV) in 40 ml of anhydrous ether, 40 ml of tetrahydrofuran, and 150 ml of liquid ammonia by means of 3.6 g of sodium and 50 ml of anhydrous alcohol gave 0.7 g (82% of theoretical) of the carbinol (V) with mp 117-120°. It is interesting to note that it gave no depression of the melting point in admixture with the initial carbinol.

Production of d, *l*-19-nortestosterone (I). A hot solution of 2 g of 3-methoxyestra-2, 5(10)-dien-17β-ol (V) in 100 ml of methanol was treated with 60 ml of 3 N hydrochloric acid, and the mixture was stirred for 15 min at 60°, cooled with water, and extracted with ether. This gave 1.76 g (92% of theoretical) of d, *l*-19-nortestosterone with mp 118-121° (from ether). An analytical sample had mp 124-125° (from ether). UV spectrum, λ_{max}: 240 mμ (log ε 4.32); IR spectrum: 1618 (C=C), 1665 (3—CO), 3420 (OH) cm^{-1}.

Found: C 78.79, 78.61; H 9.72, 9.69%. Calculated for $C_{18}H_{26}O_2$: C 78.79; H 9.55%.

The acetate (I) had mp 113-114° (cf. literature data [11]); β-phenylpropionate had mp 120-121° (from acetone-petroleum ether).

Found: C 80.01; H 8.43%. Calculated for $C_{27}H_{34}O_3$: C 79.76; H 8.3%.

Production of d, *l*-androst-4-ene-3, 17-dione (VI). The oxidation of 200 mg of the ketol (I) with chromic anhydride in acetic acid gave 120 mg of d, *l*-19-norandrost-4-ene-3, 17-dione (VI) with mp 156-157° (from cyclohexane).

UV spectrum, λ_{max}: 240 mμ (log ε 4.28); IR spectrum: 1622 (C=C), 1670 (3—CO), 1740 (17—CO) cm^{-1}.

Found: C 79.06, 79.17; H 8.96, 8.87%. Calculated for $C_{18}H_{24}O_2$: C 79.37; H 8.88%.

Reduction of the carbinol (VIII) with alkali metals and alcohol in liquid ammonia. a. With potassium (under Wilds and Nelson's conditions [2]). A solution of 300 mg of the carbinol (VIII) in 15 ml of anhydrous tetrahydrofuran and 15 ml of anhydrous ether was added to 100 ml of liquid ammonia at −70°. After 10 min, 4 g (20-fold excess) of metallic potassium was added in small pieces. Anhydrous alcohol was added in drops to the resulting dark blue solution until it was completely decolorized (18 ml over 20 min). After the usual working up, 300 ml of a non-crystallizing oil was obtained which gave only one spot on a chromatogram. The oil was dissolved in 3 ml of chloroform and was shaken for 30 min with 0.3 ml of concentrated hydrochloric acid [12].

After the usual working up and distillation of the solvent, the residue was subjected to preparative chromatography on plates. Examination in UV light revealed two layers. Ethereal elution of the layer with the higher R_f value gave 90 mg of d, *l*-19-nortestosterone (I) with mp 112-116°. Crystallization of the latter from acetone gave a pure sample of the ketol (I), identical in melting point, R_f, and spectral features with an authentic sample. Ethereal elution of the layer with the lower R_f gave 50 mg of d, *l*-19-nor-9, 10-isotestosterone (VII) with mp 173-185°. An analytical sample was obtained by crystallization from ethyl acetate, mp 191-192°. UV spectrum, λ_{max}: 240 mμ (log ε 4.25). IR spectrum: 1616 (C=C), 1662 (3—CO), 3430 (OH) cm^{-1}.

Found: C 78.77, 78.99; H 9.58, 9.75%. Calculated for $C_{18}H_{26}O_2$: C 78.79; H 9.55%.

b. With sodium. The reduction of 300 mg of the carbinol (VIII) in 15 ml of anhydrous tetrahydrofuran, 15 ml of anhydrous ether, and 100 ml of liquid ammonia using 2.4 g (20-fold excess) of metallic sodium and 60 ml of anhydrous alcohol was carried out under the conditions described above.

After working up, hydrolysis with concentrated hydrochloric acid in chloroform [12], and preparative chromatography on plates, 100 mg of a mixture with mp 110-118° was obtained, from which crystallization yielded 25 mg of the ketol (I) with mp 121-123° and 50 mg of the ketol (VII) with mp 188-190°. The analogous reduction of 0.3 g of the carbinol (IV) under Birch's conditions yielded 30 mg of the ketol (I) with mp 119-123° and 50 mg of the ketol (VII) with mp 185-190°.

c. With lithium. The reduction of 300 mg of the carbinol (VIII) in 15 ml of anhydrous tetrahydrofuran, 15 ml of anhydrous ether, and 100 ml of liquid ammonia with 0.74 g (20-fold excess) of lithium and 15 ml of anhydrous alcohol by the method described above yielded 27 mg of the ketol (I) with mp 119-123° and 45 mg of the ketol (VII) with mp 185-190°.

Reduction of the ketone (III) with alkali metals in liquid ammonia. a. With lithium. The reduction of 1 g of the ketone (III) in 40 ml of anhydrous tetrahydrofuran, 40 ml of anhydrous ether, and 250 ml of liquid ammonia using 3 g (25-fold excess) of lithium and 65 ml of alcohol under Wilds and Nelson's conditions yielded, after the working up described above, hydrolysis, and preparative chromatography, 0.4 g of the ketol (I) with mp 119-123° and 0.1 g of the ketol (VII) with mp 187-190°. The reduction of 1 g of the ketone (III) under Birch's conditions yielded 0.35 g of the ketol (I) with mp 118-121° and 80 mg of the ketol (VII) with mp 185-189°.

b. With sodium. The reduction of 1 g of the ketone (III) in 40 ml of anhydrous tetrahydrofuran, 40 ml of anhydrous ether, and 250 ml of liquid ammonia with 9.8 g (20-fold excess) of sodium and 90 ml of alcohol yielded, after the usual working up, hydrolysis, and chromatography, 0.43 g of the ketol (I) with mp 118-122° and 0.15 g of the ketol (VII) with mp 185-188°.

c. With potassium. The reduction of 0.5 g of the ketone (III) in 40 ml of anhydrous tetrahydrofuran, 40 ml of anhydrous ether, and 100 ml of liquid ammonia using 8.2 g (20-fold excess) of potassium and 60 ml of alcohol yielded, after the usual working up and hydrolysis, 0.25 g of the ketol (I) with mp 119-121° and 0.2 g of an oil which, from the results of plate chromatography, contained mainly the ketol (I) and the hydrogenolysis product, and only traces of the isomeric ketol (VII).

d. With potassium and lithium. A solution of 0.5 g of the ketone (III) in 30 ml of anhydrous tetrahydrofuran and 15 ml of ether was added to 100 ml of liquid ammonia at −65°. The solution was treated with 0.83 g of potassium and stirred for half an hour, and then 15 ml of alcohol was added over 15 min and (over 25 min) 2.1 g of lithium. The mixture was stirred until the color had disappeared and the ammonia was evaporated. After the working up described above, 0.37 g (72% of theoretical) of carbinol (V) with mp 118-120° was obtained. Hydrolysis of the mother liquor gave an oil consisting (according to a chromatogram) mainly of the ketol (I) and traces of the ketol (VII).

Production of the 3-methyl ether of d, *l*-9-isoestra-3, 17-diol (XIII). Two grams of the carbinol (VIII) was reduced with sodium and alcohol in liquid ammonia as described above. The carbinol (V) was separated from the reaction product by crystallization, the mother liquor, containing the carbinols (V) and (X) was evaporated, and 0.8 g of the mixture of carbinols was oxidized with Sarett's reagent as in the following experiment. Working up gave 30 mg of the

methyl ether of d, *l*-estrone (XI) with mp 137-140° and 0.6 g of a mixture of the ketones (XI) and (XII) in the form of an oil. A solution of this mixture in 5 ml of anhydrous tetrahydrofuran was added dropwise over 1 hr to a stirred suspension of 60 mg of lithium aluminum hydride in 1 ml of anhydrous tetrahydrofuran. The mixture was stirred for 1 hr, and the usual working up gave 0.5 g of product in the form of an oil from which, on standing in the refrigerator with a small amount of methanol, 58 mg of a substance with mp 118-125° crystallized out. Four recrystallizations from methanol yielded 32 mg of the 3-methyl ether of d, *l*-9-isoestradiol (XIII) with mp 142-143°, giving a depression of the melting point in admixture with its 9-epimer. IR spectrum: 1260, 1575, 1613 (aromatic ring), 3330 (OH) cm^{-1}. According to literature data, mp 140-141° [6].

Production of d, *l*-19-nor-9, 10-isoandrost-4-ene-3, 17-dione (IX). With cooling, 80 mg of the ketol (VII) in 1.2 ml of anhydrous pyridine was added to Sarett's reagent prepared from 110 mg of chromic anhydride and 1.2 ml of anhydrous pyridine. The mixture was left for a day and after the usual working up and filtration through alumina 53 mg of d, *l*-19-nor-9, 10-isoandrostene-3, 17-dione (IX) with mp 139-145° was obtained. Crystallization from cyclohexane yielded 40 mg of the pure diketone (IX) with a double mp 150-151° and 156-157°. In admixture with the diketone (VI), this substance gave a depression of the melting point. UV spectrum, λ_{max}: 241, 299 mμ (log ε 4.34; 2.55). IR spectrum: 1668 (3—CO), 1740 (17—CO) cm^{-1}.

Found: C 79.40, 79.22; H 8.80, 8.83%. Calculated for $C_{18}H_{24}O_2$: C 79.37; H 8.88%.

Reduction of the ketal (XIV). A solution of 2 g of the ketal (XIV) in 200 ml of anhydrous tetrahydrofuran and 200 ml of anhydrous ether was added to 600 ml of liquid ammonia at −70°, 100 ml of anhydrous alcohol was added dropwise over 60 min until the solution was completely decolorized, the ammonia was evaporated off, and the usual working up and crystallization from alcohol gave 1.47 g (73% of theoretical) of the ethylene ketal of 3-methoxyestra-2, 5(10)-dien-17-one (XV) with mp 145-146°. The pure ketal had mp 148-150°. IR spectrum: 1668 (2 C=C), 1697 (5 C=C) cm^{-1}.

Found: C 76.57, 76.45; H 9.05, 9.13%. Calculated for $C_{21}H_{30}O_3$: C 76.32; H 9.15%.

Hydrolysis of the mother liquor gave an oil in which chromatography revealed the presence of the diketone (VI) and the 3-methyl ether of d, *l*-estrone (XI). Similar results were obtained on the reduction of the ketal (XIV) with lithium and alcohol in liquid ammonia under Birch's conditions.

The hydrolysis of 0.35 g of the ketal (XV) with hydrochloric acid in chloroform gave 0.21 g (75% of theoretical) of the diketone (VI) with mp 152-153°.

Reduction of the 3-methyl ether of 8-isoestradiol (XVII) and the 3-methyl ether of 8-isoestrone (XXI). A solution of 1.6 g of the methyl ether of 8-isoestradiol (XVII) [3] in 128 ml of anhydrous ether and 50 ml of anhydrous tetrahydrofuran was added to 200 ml of liquid ammonia at −70°, followed by 1.65 g (20-fold excess) of lithium over 20 min. The mixture was stirred for 30 min at −70° and then 105 ml of anhydrous alcohol was added in drops over 30 min until the solution was decolorized. After the evaporation of the ammonia and the usual working up, 1.4 g (87% of theoretical) of 3-methoxy-8-isoestra-2, 5(10)-dien-17β-ol (XVIII) with mp 118-125° was obtained. Two crystallizations from methanol gave the pure carbinol (XVIII) with mp 139-140°. UV spectrum, λ_{max}: 227, 287 mμ (log ε 2.18, 2.15); IR spectrum: 1675 (2 C=C), 1703 (5 C=C), 3490 (OH) cm^{-1}.

Found: C 79.08, 79.13; H 9.77, 9.72%. Calculated for $C_{19}H_{28}O_2$: C 79.12; H 9.79%.

The analogous reduction of 1.5 g of the 3-methyl ether of 8-isoestrone (XXI) [13] in 80 g of anhydrous tetrahydrofuran, 100 ml of anhydrous ether, and 250 ml of liquid ammonia using 2.9 g of lithium (20-fold excess) and 150 ml of alcohol gave, after the usual working up and preparative chromatography on plates, 0.35 g of the initial ketone (XXI) and 1 g of the dienol (XVIII) with mp 119-125°.

Hydrolysis of the carbinol (XVIII). A solution of 1.5 g of the carbinol (XVIII) in 18 ml of chloroform was stirred for 30 min with 1.8 ml of concentrated hydrochloric acid, and after the usual working up 1.3 g of a mixture with mp 149-151° was obtained. Five crystallizations from acetone-petroleum ether (1:1) gave 120 mg of 17β-hydroxy-8-isoandrost-5(10)-en-3-one (XIX) with mp 166-168°. UV spectrum, λ_{max}: 283-285 mμ (log ε 1.66); IR spectrum: 1703 (3—CO), 3400 (OH) cm^{-1}.

Found: C 78.81, 78.90; H 9.62, 9.50%. Calculated for $C_{18}H_{26}O_2$: C 78.79; H 9.55%.

The mother liquor gave 68 mg of the hydroperoxide (XX) with mp 190-191°. Crystallization from acetone gave a pure sample with mp 199-200°. UV spectrum, λ_{max}: 240, 307, 315 mμ (log ε 4.30, 1.89, 1.88). IR spectrum: 1660 (3—CO), 3280 (10—OH), 3465 (17—OH) cm^{-1}.

Found: C 70.89, 70.78; H 8.37, 8.39%. Calculated for $C_{18}H_{26}O_4$: C 70.56; H 8.55%.

The mixture of substances was separated by preparative chromatography of the mother liquor on plates in the ether-ethyl acetate (4:1) system into four fractions. The first fraction (with the highest R_f value) gave 440 mg of the ketol (XIX) with mp 166-168°. The second fraction (290 mg) consisted of an oil. This fraction was not investigated further.

The third fraction yielded 150 mg of d, *l*-19-nor-8-isotestosterone (XVI) with mp 157-160°; crystallization from acetone gave a sample of the ketol (XVI) with mp 161-162° containing, from the IR spectrum, a small amount of hydroperoxide. UV spectrum, λ_{max}: 240 (log ε 4.30); IR spectrum: 1612 (C=C), 1660 (3—CO), 3260 (very weak), 3370 (OH) cm^{-1}. Further crystallization or attempts at the chromatographic purification of the ketol (XVI) on alumina or silica gel only increased the content of hydroperoxide. The fourth fraction gave another 150 mg of the hydroperoxide (XX) with mp 190-191°.

When hydrochloric acid was added to an alcoholic solution of the ketol (XIX), λ_{max} of the UV spectrum changed from 283 to 245 mμ, which indicates the shift of a double bond into a conjugated position.

The tests for myotrophic activity were carried out in the biological testing laboratory of the Institute for the Chemistry of Natural Compounds by I. B. Sorokina and T. I. Kornilova, under the direction of G. L. Zhdanov.

Summary

The complete synthesis of d, *l*-19-nortestosterone (I) and its 8-iso- and 9, 10-iso- stereoisomers, and also the synthesis of d, *l*-19-norandrosten-4-ene-3, 17-dione (VI) and its 9, 10-iso- stereoisomer (IX), has been carried out.

The stereodirectivity of the simultaneous reduction of the $\Delta^{8(9)}$ double bond and the aromatic ring conjugated with it by means of alkali metals and alcohol in liquid ammonia, both under Birch's conditions and Wilds and Nelson's conditions, depends on the nature of the substituent at C_{17}; in the case of the 17-ketone (III) and the carbinol (VIII), considerable amounts of the 9β- isomers are formed.

Compounds (I), (Ia), (Ib), (V), and (VI) possess anabolic activity, but to a smaller extent than the analogous compounds in the d, *l*-D-homo series.

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