VARIANTS OF THE COMPLETE SYNTHESIS OF d, *l*-ESTRONE FROM 1-VINYL-6-METHOXYTETRALOL AND 2-METHYLCYCLOPENTANE-1, 3-DIONE

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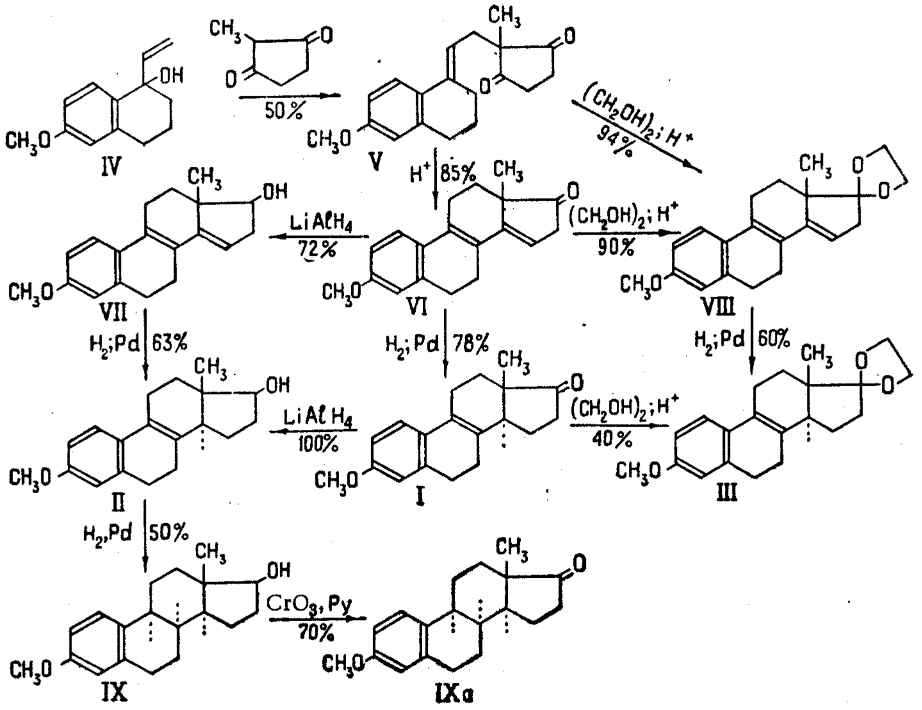
We have previously described the synthesis of d, *l*-estrone by the condensation of 1-vinyl-6-methoxytetralol with 2-methylcyclopentane-1, 3-dione [1]. The present paper gives the results of a detailed investigation of the reduction of derivatives of the methyl ether of 8-dehydroestrone in order to discover the optimum conditions for the synthesis of d, *l*-estrone. The reactions of 3-methoxyestra-1, 3, 5(10), 8-tetraen-17-one (I), 3-methoxyestra-1, 3, 5(10), 8-tetraen-17β-ol (II), and 17-ethylenedioxy-3-methoxyestra-1, 3, 5(10), 8-tetraene (III) with alkali metals (potassium, sodium, and lithium) in liquid ammonia in the presence of ammonium chloride were investigated.

The condensation of 1-vinyl-6-methoxytetralol (IV) with 2-methylcyclopenta-1, 3-dione was carried out in p-xylene in the presence of Triton B, with a yield of 50%, calculated from the vinylcarbinol (IV), or 60%, calculated from the 2-methylcyclopentane-1, 3-dione, of 3-methoxy-8, 14-secoestra-1, 3, 5(10), 9(11)-tetraene-14, 17-dione (V). Cyclization of the latter by means of p-toluenesulfonic acid in benzene gave an 85% yield of 3-methoxyestra-1, 3, 5(10), 8, 14-pentaen-17-one (VI).



The selective hydrogenation of the ketone (VI) in tetrahydrofuran in the presence of 10% $Pd/CaCO_3$ led to 3-methoxyestra-1, 3, 5(10), 8-tetraen-17-one (I) with a yield of 78%. Reduction of the ketone (VI) with $LiAlH_4$ in tetrahydrofuran formed the corresponding 17β-ol (VIII) with a yield of 72%, and this was converted by selective hydrogenation over 10% $Pd/CaCO_3$ in tetrahydrofuran with a 63% yield into 3-methoxyestra-1, 3, 5(10), 8-tetraen-17β-ol (II). The latter was also obtained in quantitative yield by the reduction of the ketone (I) with $LiAlH_4$ in tetrahydrofuran.

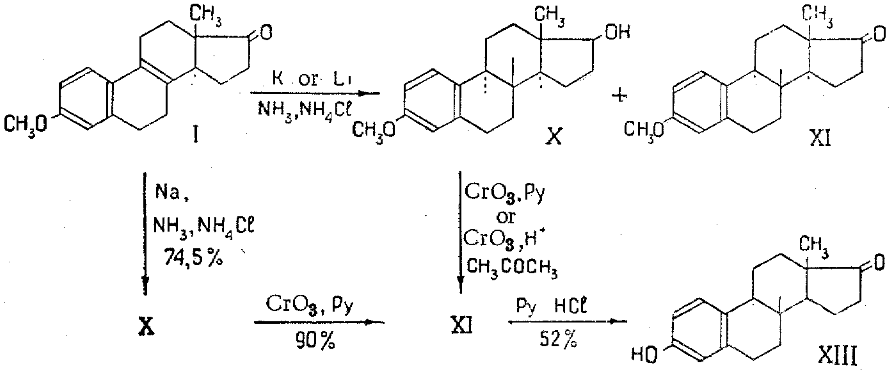
The ketal (III) was obtained by three routes: a) IV → V → VI → VII → III, b) IV → V → VI → I → III, and c) IV → → V → VIII → III, route (c) proving to be best as it was the shortest and gave the highest yield (28%).

The exhaustive hydrogenation of the carbinol (II) over 30% $Pd/SrCO_3$ in tetrahydrofuran gave a 50% yield of the methyl ether of d, *l*-8-isoestradiol (IX). The method of hydrogenation with platinum oxide in ethyl acetate recommended by Tsuda [2] for 3, 11β-dihydroxyestra-1, 3, 5(10), 8-tetraen-17-one was also tried. It was found that the ketone (I) did not hydrogenate at all under these conditions, while in the hydrogenation of ketone (VI) 2 moles of hydrogen were absorbed to give a mixture of ketones and carbinols (from the IR spectrum) not containing the equilenin system (from the UV spectrum).

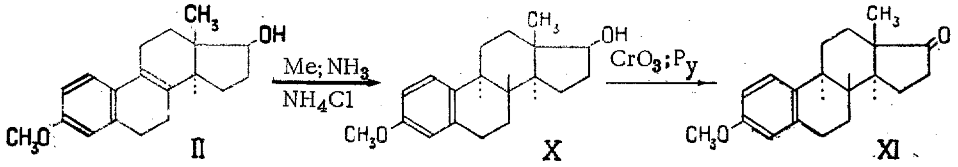
The reduction of the ketone (I) with potassium or lithium in liquid ammonia (dried by passage through a column containing alkali) in the presence of ammonium chloride formed a mixture of the methyl ethers of d, *l*-estrone (XI) and d, *l*-estradiol (X) in a 1: 2 ratio with yields of 82 and 60%, respectively. Oxidation of this mixture with chromic anhydride (by Jones's method) in acetone gave a yield of the methyl ether of d, *l*-estrone of only 62%.

When the ketone (I) was reduced with sodium and liquid ammonia in the presence of ammonium chloride, only the methyl ether of d, *l*-estradiol (X) was formed, with a yield of 74. 5%.

On reduction of the ketone (I) with lithium in ammonia that had been distilled over metallic sodium, a mixture of the ethers (X) and (XI) with the methyl ether of d, *l* -estradiol (II) predominating (ratio of XI to X, 1: 6) was obtained with a total yield of about 70%. Oxidation of the latter with Sarett's reagent gave a 90% yield of the methyl ether of d, *l*-estrone (XI). Demethylation of the latter by means of pyridine hydrochloride led to d, *l*-estrone (XIII) with a yield of 50%. Thus, the yield of the methyl ether of d, *l*-estrone (XI) from the vinylcarbinol (IV) by the best variant IV → V → VI → I → X → XI is 25%, calculated on the basis of the 6-methoxytetralol, and the yield of d, *l*-estrone by this route is 13%.

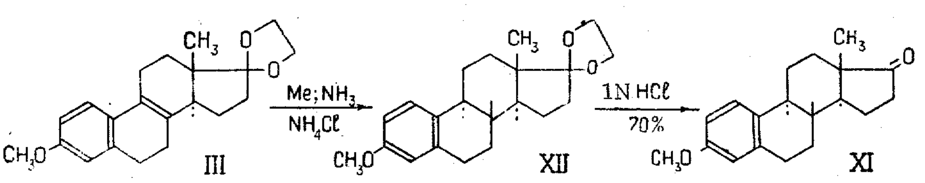


The analogous reduction of the carbinol (II) gave the methyl ether of d, *l*-estradiol (X) with a yield of 75% in the case of potassium, 80% in the case of sodium, and 60% in the case of lithium. Consequently, the yield of the methyl ether of d, *l*-estrone (XI) by the route IV → V → VI → I → II → X → XI is 22% for the use of potassium, 23. 8% for sodium, and 17% for lithium, and the yields of d, *l*-estrone (XIII) are 11. 3, 12. 1, and 8. 6%, respectively, calculated on the basis of the 6-methoxytetralone.



Reduction of the ketal (III) with sodium under the same conditions led to the 17-ketal of the methyl ether of d, *l*-estrone (XII) with a yield of 80%. Replacement of the sodium by lithium scarcely affected the yield (83%), while we have previously shown [1] that the analogous reduction of the ketal (III) with potassium gave a yield of ketal (XII) of only 66%. These results show that the yield of reduction products from derivatives of Δ^8-dehydroestrone depends to some extent on the reuduction potential of the metal [3]. The best yield with compounds with a substituted 17- function (ketals) is obtained with lithium, which possesses the greatest reduction potential (2. 99). In the case of the 17β- carbinols (II) and the ketones (I), the best results are given by sodium, with the lowest potential (2. 59).

The hydrolysis of the ketal (XII) by boiling with 1 N hydrochloric acid in tetrahydrofuran leads to the methyl ether of d, *l*-estrone (XI) with a yield of 70%. In working with the ketal (XII), it is most convenient to use the route IV → V → VIII → III → XII → XI. On reduction with potassium, the yield of the methyl ether of d, *l*-estrone (XI) amounts to 13%, with sodium 15. 8, and with lithium 15. 4%, calculated on the basis of the 6-methoxytetralol.



Thus, of all the variants of the synthesis of the methyl ether of d, *l*-estrone (XI) the best results are obtained by the route IV → V → VI → I → X → XI.

Experimental

The course of the reactions and the completeness of the conversions were followed by means of chromatography in a thin fixed layer on plates [4]. The absorbent was alumina (activity grade II-III), layer thickness 1-1.5 mm, ether-benzene (1:1 or 2:1) system; spots revealed in UV light or with iodine vapor. The IR spectra were taken in liquid paraffin (with some exceptions) on UR-10 and IKS-14 instruments; the UV spectra were taken in alcohol on a SF-4 instrument. The 1-vinyl-6-methoxytetralol (IV) [5] and the 2-methylcyclopentane-1,3-dione [6, 7] were obtained by previously described methods.

Condensation of 1-vinyl-6-methoxytetral-1-ol (IV) with 2-methylcyclopentane-1,3-dione. An alcoholic solution of Triton B (prepared from 11.4 g of trimethylbenzylammonium chloride, 3.38 g of caustic potash, and 31 ml of alcohol) and 50 ml of p-xylene was placed in a four-necked flask fitted with a reflux condenser, dropping funnel, water-separator, and stirrer, and the alcohol was distilled off in a water bath. Then 100 ml of p-xylene and 41 g of 2-methylcyclopentane-1,3-dione were added to the catalyst. The mixture was heated to the boil, and a solution of 75 g of freshly-prepared 1-vinyl-6-methoxytetralol (IV) in 245 ml of p-xylene was added in drops at 140-160° (over 45-60 min), the water distilling off. Then the mixture was boiled for 30 min and cooled, and the unchanged diketone (7 g, mp 169-181°) was filtered off; the filtrate was washed with 5% caustic potash solution and with water and, after the solvent had been distilled off, crystallization gave 54.3 g of 3-methoxy-8,14-secoestra-1,3,5(10),9(11)-tetraene-14,17-dione (V) with mp 78-79° (from methanol). IR spectrum (in chloroform): 1610, 1728 cm^{-1}; UV spectrum, λ_{max}: 264 mμ, (log ε 4.27).

Found %: C 76.48; H 7.38.

Calculated for $C_{19}H_{22}O_3$: C 76.48; H 7.43%.

The yield of diketone (V) was 50%, calculated from the vinylcarbinol (IV) and 60% calculated from the 2-methylcyclopentane-1,3-dione that had reacted.

Cyclization of the diketone (V). A solution of 15.8 g of the diketone (V) and 0.9 g of p-toluenesulfonic acid in 300 ml of benzene was boiled in a flask fitted with a reflux condenser and a water separator for 5-10 min (until the evolution of water ceased). The benzene solution was washed with water, with saturated sodium carbonate solution, and with water again, and the solvent was distilled off to give 12.58 g (85% of theoretical) of 3-methoxyestra-1,3,5(10),8,14-pentaen-17-one (VI) with mp 109-110° (from ethyl acetate). UV spectrum, λ_{max}: 312 mμ (log ε 4.50); IR spectrum: 1140, 1252, 1570, 1599, 1610, 1740 cm^{-1}.

Found %: C 81.35; H 7.16.

Calculated for $C_{19}H_{20}O_2$: C 81.39; H 7.19%.

Hydrogenation of the ketone (VI). In the presence of 0.5 g of 10% Pd/$CaCO_3$, 13 g of ketone (VI) in 120 ml of anhydrous tetrahydrofuran was hydrogenated until 1 mole of hydrogen had been absorbed. The catalyst was filtered off and the solvent was distilled off in vacuum. The residue was crystallized from ethyl acetate to give 10.2 g (78% of theoretical) of 3-methoxyestra-1,3,5(10),8-tetraen-17-one (I) with mp 116-118°. An analytical sample had mp 120-121° (from ethyl acetate). UV spectrum, λ_{max}: 277 mμ (log ε 4.434); IR spectrum: 1140, 1252, 1570, 1610, 1740 cm^{-1}.

Found %: C 80.93; H 7.76.

Calculated for $C_{19}H_{22}O_2$: C 80.81; H 7.85%.

Reduction of the ketone (VI) to the carbinol (VII). A solution of 5 g of the ketone (VI) in 25 ml of anhydrous tetrahydrofuran was added over an hour to a stirred suspension of 0.5 g of lithium aluminum hydride in 5 ml of tetrahydrofuran at 20°. Then the mixture was stirred for a further 1 hr. It was then decomposed by the successive addition of 5 ml of ethyl acetate, 35 ml of water, and 2.5 ml of hydrochloric acid. The solution was extracted with ether, the extract was dried with magnesium sulfate, and the solvent was distilled off, after which crystallization from alcohol gave 3.6 g (72% of theoretical) of 3-methoxyestra-1,3,5(10),8,14-pentaen-17β-ol (VII) with mp 76-78°. UV spectrum: λ_{max}: 309 mμ (log ε 3.49); IR spectrum: 1615, 1621, 1638, 3508 cm^{-1}.

The acetate of the carbinol was obtained by acetylation with acetic anhydride in pyridine (20°, 16 hr), mp 110-111° (from alcohol).

Found %: C 77.81; H 7.40.

Calculated for $C_{21}H_{24}O_3$: C 77.75; H 7.46%.

Production of the carbinol (II). a. In the presence of 0.1 g of 10% Pd/$CaCO_3$, 2 g of the carbinol (VII) in 20 ml of tetrahydrofuran was hydrogenated until 1 mole of hydrogen had been adsorbed. After the usual working up and crystallization from alcohol, 1.25 g (63% of theoretical) of 3-methoxyestra-1,3,5(10),8-tetraen-17β-ol (II) with mp 131-132° was obtained. UV spectrum, λ_{max}: 274 mμ (log ε 4.30); IR spectrum: 1574, 1611, 3405 cm^{-1}.

Found %: C 80. 34; H 8. 52.

Calculated for $C_{19}H_{24}O_2$: C 80. 24; H 8. 51.

The acetate of the carbinol (II) was obtained in the usual way with mp 117-118° (from alcohol). UV spectrum, λ_{max}: 274 mμ (log ε 4. 3).

Found %: C 76. 83; H 8. 11.

Calculated for $C_{21}H_{26}O_3$: C 77. 27; H 8. 03%.

b. The ketone (I) was reduced with lithium aluminum hydride under conditions analogous to those for the reduction of the ketone (VI). The yield of carbinol (II) was quantitative.

Production of the methyl ether of d, *l*-8-isoestradiol (IX). a. In the presence of 30% $Pd/SrCO_3$, 1 g of the carbinol (VII) in 10 ml of anhydrous tetrahydrofuran was hydrogenated until 2 moles of hydrogen had been absorbed. The usual working up yielded 0. 53 g of a substance with mp 90-92°. Two crystallizations from alcohol gave 0. 36 g of the pure methyl ether of d, *l*-8-isoestradiol (36% of theoretical) with mp 100-100. 5° (after drying in vacuum); the substance readily gave a solvate with alcohol (mp 78-101°). UV spectrum, λ_{max}: 279 mμ (log ε 3. 56); IR spectrum: 1585, 1610, 3310 cm^{-1}.

Found %: C 79. 69; H 9. 13.

Calculated for $C_{19}H_{26}O_2$: C 79. 68; H 9. 15%.

b. In the presence of 0. 25 g of 30% $Pd/SrCO_3$, 5 g of the carbinol (II) was hydrogenated in 50 ml of anhydrous tetrahydrofuran. The hydrogenation took place very slowly and after 29 hr only 380 ml of hydrogen (as compared with 435 ml theoretically) had been absorbed. After the usual working up, 4. 62 g of a substance with mp 88-91° was obtained. Two crystallizations from alcohol and subsequent vacuum drying of the substance gave 2 g of the methyl ether of d, *l*-8-isoestradiol, mp 100-100. 5°. The mother liquors were again subjected to hydrogenation (after 28 hr 120 ml of hydrogen had been absorbed). After working up and crystallization, a further 0. 5 g of product with mp 99-100° was isolated. Total yield: 50% of theoretical.

Oxidation of the methyl ether of d, *l*-8-isoestradiol (IX). At 0°, a solution of 1 g of the methyl ether of d, *l*-8-estradiol (IX) in 10 ml of pyridine was added to a freshly prepared solution of the complex of chromic anhydride and pyridine (from 0. 4 g of CrO_3 and 10 ml of pyridine). The mixture was left for 24 hr at 20°C, and the usual working up and crystallization from alcohol yielded 0. 7 g (70% of theoretical) of the methyl ether of d, *l*-8-isoestrone (IXa) with mp 150-151°, the melting point and spectral characteristics of which were identical with those of sample obtained previously [8].

Preparation of the ketal (VIII). A mixture of 14 g of the dienone (VI), 100 ml of ethylene glycol, 1 g of p-toluenesulfonic acid, and 665 ml of toluene was boiled for 4 hr in a flask with a water separator; then it was cooled, the toluene layer was separated off, and the aqueous layer was extracted with ether. The combined ethereal and toluene extracts were washed with saturated sodium carbonate solution and with water, and distillation of the solvent and crystallization from a mixture of alcohol and ethyl acetate gave 14. 7 g (90% of theoretical) of the ketal (VIII) with mp 91-92°, identical in respect of melting point and spectral characteristics with a sample obtained by the ketalization of the diketone (V) [1].

Hydrolysis of the ketal (VIII) by boiling in alcohol with 1 N hydrochloric acid (5 min) yielded about 20% of the initial dienone (VI); the residue consisted of a dark purple non-crystallizing oil containing, according to the IR spectrum, a substance with the equilenin system (λ_{max}: 336 mμ).

Preparation of the ketal (III). a. A mixture of 1. 24 g of ketone (I), 50 ml of toluene, 7 ml of ethylene glycol, and 0. 1 g of p-toluenesulfonic acid was boiled in a flask with a water separator for 5 hr. After a working up similar to that described in the preceding experiment and three crystallizations from ethyl acetate, 0. 5 g (40% of theoretical) of the ketal (III) with mp 126-128° was obtained; UV spectrum, λ_{max}: 275 mμ (log ε 4. 20).

Found %: C 77. 25; H 7. 98.

Calculated for $C_{21}H_{26}O_3$: C 77. 27: H 8. 03%.

b. In the presence of 0. 25 g of 10% $Pd/CaCO_3$, 5 g of the ketal (VIII) in 50 ml of absolute tetrahydrofuran was hydrogenated until 1 mole of hydrogen had been absorbed. The usual working up and crystallization gave 3 g (60%) of the ketal (III) with mp 126-128°, identical in melting point and UV spectrum with an authentic sample.

Hydrolysis of the ketal (III). 2 ml of 1 N hydrochloric acid was added to a solution of 0. 4 of ketal (III) in 50 ml of acetic acid, which had been heated to 80°; the mixture was then stirred for 3 min and poured into 300 ml of water. It was extracted with ether. After distilling off the solvent and fractional crystallization from alcohol, we obtained 0. 15 g of ketone (I) with mp 115-118°, which gave no depression of the melting point with an authentic sample.

From the mother liquors we isolated 60 mg of the ethyl ether of d, *l*-trans-equilenin with mp 181-183°, identical in melting point and UV spectrum with an authentic sample [1].

Production of the 3-methyl ether of d, *l*-estra-3, 17β-diol (X). a. Reduction of the ketone (I) with potassium or lithium in liquid ammonia dried over caustic potash. A solution of 3. 3 g of the ketone (I) in 270 ml of tetrahydrofuran and 150 ml of ether was added at a temperature of –40 to –50° to 300 ml of liquid ammonia which had been dried by passage through a column containing caustic potash. At –50 to –60°, 5. 3 g of potassium (in small pieces) was added to the resulting solution, the mixture was left for 1. 5 hr at the same temperature, and then 15 g of dry ammonium chloride was carefully added. After the evaporation of the ammonia, the residue was treated with water (at –5 to 0°) and was extracted with ether. The ethereal extract was neutralized with solid carbon dioxide, washed with water, and dried over sodium sulfate. After the solvent had been distilled off, an oil was obtained which readily crystallized on the addition of alcohol to give 1. 4 g of the methyl ether of d, *l*-estra-3, 17β-diol (X) with mp 130-131°. When the mother liquors were chromatographed on alumina, a petroleum ether-benzene (2: 8) fraction yielded a further 0. 3 g of substance (X) with mp 129-130°. The fraction eluted by petroleum ether gave 0. 2 g of the initial ketone (I) with mp 116-119° giving no depression of the melting point with an authentic sample. The petroleum ether-benzene (8: 2) fraction gave 0. 63 g of the methyl ether of d, *l*-estrone (XI) with mp 139-141°, giving no depression of the melting point with an authentic sample, and the petroleum ether-benzene (1: 1) fraction gave 0. 4 g of a mixture with mp 116-124° containing, from the results of preparative chromatography on Al_2O_3 plates, a mixture of the methyl ethers of d, *l*-estrone (XI) and d, *l*-estra-3, 17β-diol (X) in a ratio of 1: 1. Thus, a total of 0. 83 g of the methyl ether of d, *l*-estrone (yield 25%) was obtained together with 1. 9 g (57% of theoretical) of the methyl ether of d, *l*-estra-3, 17β-diol (X) with mp 133-133. 5° (from a mixture of alcohol and ethyl acetate), UV spectrum, λ_{max}: 279 mμ (log ε 3. 56).

Found %: C 79. 56; H 9. 16.

Calculated for $C_{19}H_{26}O_2$: C 79. 68; H 9. 15.

The acetate of the 3-methyl ether of d, *l*-estra-3, 17β-diol was obtained by acetylating the diol (X) in pyridine (20°, 16 hr), mp 148. 5-149° (from alcohol); UV spectrum, λ_{max}: 278 mμ (log ε 3. 36).

Found %: C 76. 56; H 8. 49.

Calculated for $C_{21}H_{28}O_3$: C 76. 79; H 8. 59%.

The similar reduction of 0. 5 g of the ketone (I) with 0. 25 g of lithium in 100 ml of ammonia, 40 ml of tetrahydrofuran, and 20 ml of ether, with subsequent decomposition by means of 2. 5 g of ammonium chloride, gave a mixture from which, by preparative chromatography on Al_2O_3 plates, we isolated 0. 2 g (40%) of the methyl ether of d, *l*-estra-3, 17β-diol (X) with mp 127-128°, 0. 11 g (20%) of the methyl ether of d, *l*-estrone (XI) with mp 140-143°, and 0. 15 g of a non-crystallizing oil containing, from the IR spectrum (1602, 3820 cm^{-1}), a phenolic hydroxyl group.

The similar reduction of 4 g of the ketone (I) with 5. 54 g of sodium in 400 ml of ammonia, 250 ml of tetrahydrofuran, and 150 ml of ether, with subsequent decomposition with 30 g of ammonium chloride, gave 2. 13 g of the methyl ether of d, *l*-estradiol (X) with mp 128-130°. Preparative chromatography of the mother liquors on Al_2O_3 plates gave a further 0. 87 g of the diol (X) and 0. 2 g of a non-crystallizing oil containing, from the IR spectrum (1605, 3280 cm^{-1}), a phenolic hydroxyl group. It was impossible to detect the presence of the methyl ether of d, *l*-estrone (XI) by chromatography. The yield of compound (X) was 74. 5%.

b. Reduction of the ketone (I) with lithium in liquid ammonia distilled over metallic sodium. Under similar conditions, 1 g of the ketone (I) in 75 ml of anhydrous tetrahydrofuran and 150 ml of ammonia (previously distilled over caustic potash and metallic sodium) was reduced at –50 to –60° with 0. 5 g of lithium. After the addition of 4 g of ammonium chloride and appropriate working up, 720 mg of an oil which partially crystallized was obtained and from this, crystallization yielded 550 mg of the methyl ether of d, *l*-estradiol with mp 127-130°. From the results of chromatography on plates, the mother liquors consisted of a mixture of the methyl ethers of d, *l*-estrone (XI) and d, *l*-estra-3, 17β-diol (X). On chromatography of this mixture on Al_2O_3, a petroleum ether-benzene 8: 2 fraction gave 70 mg of the methyl ether of d, *l*-estrone (XI) with mp 139-142°, a petroleum ether-benzene (1: 1) fraction gave 40 mg of a mixture of the methyl ethers of d, *l*-estrone (XI) and d, *l*-estradiol (X) with mp 115-125°, and a benzene fraction gave 43 mg of the methyl ether of d, *l*-estra-3, 17β-diol (X) with mp 129-131°. In total, 610 mg (61% of theoretical) of the methyl ether of d, *l*-estra-3, 17β-diol (X) and 90 mg of the methyl ether of d, *l*-estrone (XI) (yield 9%) were isolated. When 0. 8 g of the mixture of methyl ethers of d, *l*-estrone (XI) and d, *l*-estra-3, 17β-diol (X) in 20 ml of acetone was oxidized with 0. 75 g of chromic anhydride and 0. 65 ml of sulfuric acid in 3 ml of water (added over 10 min at –5 to 0°, the mixture being left for 6 hr at 20°), working up yielded 0. 5 g (62% of theoretical) of the methyl ether of d, *l*-estrone (XI) with mp 136-138°. Crystallization from ethyl acetate gave 0. 4 g of the pure methyl ether of d, *l*-estrone (XI) with mp 142-143°, identical in melting point and spectral characteristics with an authentic sample [9].

Reduction of the carbinol (II). A solution of 1 g of the carbinol (II) in 80 ml of anhydrous tetrahydrofuran, 45 ml of anhydrous ether, and 150 ml of liquid ammonia was treated at −60° with 0.85 g of sodium. The mixture was stirred for 30 min and then 2.65 g of ammonium chloride was added. The ammonia was eliminated and the residue was treated with 150 ml of water; after the usual working up and crystallization from methanol, 0.81 g of the methyl ether of d, *l*-estra-3, 17β-diol (X) with mp 130-131°, identical in melting point and spectral characteristics with an authentic sample was obtained. Analogous reduction of the carbinol (II) with potassium yielded 75% of the methyl ether d, *l*-estra-3, 17β, diol (X).

Analogous reduction of the carbinol (II) with lithium gave the methyl ether of d, *l*-estra-3, 17β-diol (X) with a yield of 60%, together with 20% of a phenolic fraction (soluble in alkalis) in the form of a non-crystallizing oil.

Reduction of the ketal (III). At −50 to −60°, 0.85 g of sodium was added to a solution of 1 g of the ketal (III) in 80 ml of anhydrous tetrahydrofuran and 45 ml of anhydrous ether in 225 ml of ammonia. The dark blue solution was stirred for 30-40 min at the same temperature, and 7.65 g of ammonium chloride was added. The usual treatment with water, extraction, distillation of the solvent, and crystallization from a mixture of ethyl acetate and alcohol gave 0.8 g (80% of theoretical) of the 3-methyl ether of the ethylene ketal of d, *l*-estrone (XII) with mp 122-124°, identical in melting point with an authentic sample [1]. The analogous reduction of the ketal (III) with lithium gave 83% of the ketal (XII).

Production of the methyl ether of d, *l*-estrone (XI). a. A solution of 0.5 g of the ketal (XII) in 20 ml of tetrahydrofuran and 5 ml of 1 N hydrochloric acid was boiled for 15 min. The mixture was extracted with ether, and the extract was washed with sodium bicarbonate solution and water and was dried with sodium sulfate. After removal of the solvent by distillation, crystallization from ethyl acetate gave 0.3 g (70% of theoretical) of the methyl ether of d, *l*-estrone (XI) with mp 141-143°, identical in melting point with an authentic sample [8].

b. A solution of 0.5 g of the methyl ether of d, *l*-estra-3, 17β-diol (X) in 6 ml of anhydrous pyridine was added with cooling to Sarett's reagent prepared from 0.6 g of chromic anhydride in 7 ml of anyhydrous pyridine. The mixture was left for 16 hr at 20°C, and the usual working up and crystallization from ethyl acetate gave 0.45 g of the methyl ether of d, *l*-estrone (XI) with mp 141-143°.

Production of d, *l*-estrone (XIII). A mixture of 8 g of freshly-prepared pyridine hydrochloride and 0.4 g of the methyl ether of d, *l*-estrone (XI) was heated in a flask with a reflux condenser for 40-50 min at 210-230°. Then it was cooled, dissolved in 50 ml of 5% hydrochloric acid, and extracted with chloroform. The extract was washed with 5% caustic potash solution, and the alkaline solution was acidified with hydrochloric acid and extracted with chloroform. Distillation of the solvent and crystallization from a mixture of ethyl acetate and alcohol gave 0.2 g (52% of theoretical) of d, *l*-estrone (XIII) with mp 248-250°, identical with an authentic sample.

Summary

Various routes for the synthesis of the methyl ether of d, *l*-estrone (XI) and of d, *l*-estrone itself (XIII) have been investigated. The best results were obtained by synthesis according to the route IV → V → VI → I → X → XI → XIII, when the yield of the methyl ether of d, *l*-estrone (XI) was 25% and that of d, *l*-estrone 13%, calculated on the basis of 6-methoxytetralone.

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