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REDUCTION OF 17β-ACETOXY-17α-ETHYNYL-3-METHOXYESTRA-1,3,5(10)-TRIENE WITH METALS IN LIQUID AMMONIA

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One of the methods for obtaining 17-alkyl- or 17-alkenyl-substituted estranes, which are used as active hormonal compounds or intermediates in their synthesis, is the reduction of 17-ethynylestradiol and its derivatives. Particular interest is presented by the reduction of the latter by metals in liquid ammonia (the Birch reaction [1]), since in this process not only the ethynyl group but also ring A of the steroid is reduced [2-5].

We have reduced the 3-methyl ether of ethynylestradiol with sodium in liquid ammonia [6] and have found that in the case of the 17-acetate (Ib) the reaction takes place differently from the reduction of the 17-alcohol (Ia) [2, 3]. The main product of the reduction of the acetate (Ib) was 3-methoxy-19-norpregna-2,5(10),20-triene (III), isolated with a yield of 65% when tetrahydrofuran was used as the solvent for the steroid. When diethyl ether was used, a mixture of the triene (III) and the hydroxy vinyl compound (II) was obtained.

The IR spectrum of the enol ether (III) has the absorption bands of the C_{21}-methylene group at 3080 and 905 cm^{-1} and of double bonds at 1700 and 1670 cm^{-1}. The NMR spectrum of this compound has the signals of four ethylene protons: a weakly resolved, broadened, signal at 4.57 ppm (1 H at C_2), a group of signals in the 4.81-4.98-ppm region (2 H at C_{21}), and a multiplet with its center at 5.74 ppm (1 H at C_{20}), and also the isolated signals of the C_{19} methyl group at 0.54 ppm and of the methoxy group at 3.47 ppm, and a group of signals of the C_1 and C_4 methylene protons with an intensity of four proton units in the 2.5-2.64-ppm region.

The hydrolysis of the enol ether (III) in the presence of hydrochloric acid gave the α,β-unsaturated ketone (IV). The NMR spectrum of this compound did not show the signals of methoxy and methylene allyl protons of ring A, but it had a signal at 5.63 ppm (1 H at C_4) and the signals of the C_{17}-vinyl group remained unchanged. In the mass spectrum of the

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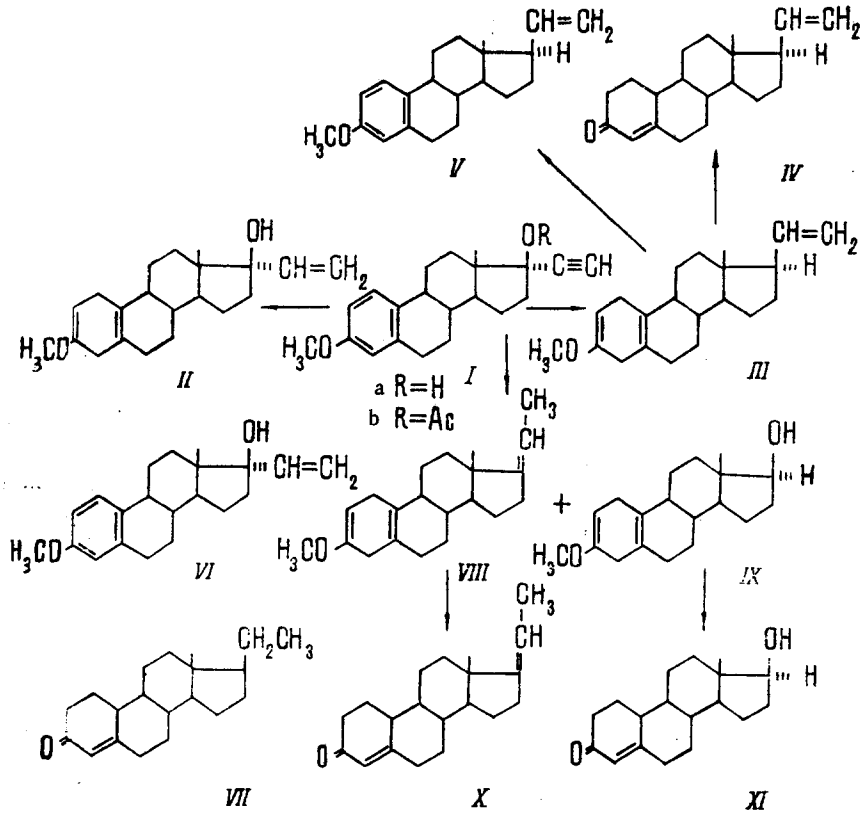
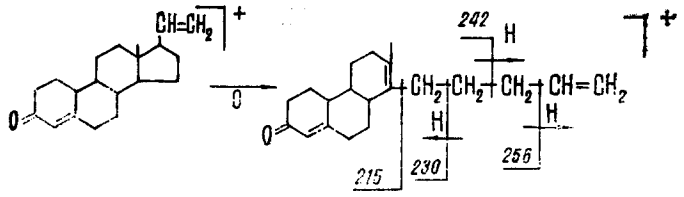


ketone (IV) in the region of high mass numbers, peaks were observed with m/e 284 (strongest), 256, 242, 230, 216, and 215, the appearance of which is apparently due to the decomposition of the side chain and of ring D according to the following scheme:



The mass spectrum of compound (IV) differs sharply from that of the ketone (X), in which the most suitable direction for the fragmentation of the molecular ion is the stepwise detachment of the side chain with the formation of the ions $[M - CH_3]^+$ and $[M - C_2H_5]^+$.

The structures of compounds (III) and (IV) were confirmed by the conversion on silica gel of the enol ether (III) into the tetraene (V), which proved to be identical according to its IR and NMR spectra with 3-methoxy-19-norpregna-1,3,5(10),20-tetraene, obtained previously by Krubiner, Gottfried, and Oliveto [7].*

The use of lithium instead of sodium for the reduction of the acetate (Ib) led to a complex mixture of compounds with a predominance of the product of the complete reduction of the ethynyl group. After the acid hydrolysis of this mixture, we isolated 19-norpregn-4-en-3-one (VII). The IR spectrum of this compound confirmed the presence of an α,β-unsaturated oxo group (1670 and 1617 cm^{-1}), and the NMR spectrum contained the singlet signal of protons at 0.57 ppm (C_{18} protons), a triplet at 0.82 ppm (C_{21} protons), and a singlet at 5.62 ppm (C_4 proton). The mass spectrum of the ketone (VII) had, in addition to the strong peak of the molecular ion with a mass number of 286, ions with m/e 271, 258, 257, 244, 230, 216, and 215.

The predominant formation of compound (III) from (Ib) under the conditions of the Birch reaction can be explained by the influence of the acetoxy group on the direction of the reaction, which consists in some displacement of the electron density from C_{17} to the carbonyl group. As a result, the addition of an electron to C_{17} and the splitting out of the acetoxy group with the formation of a carbanion is facilitated. The subsequent α-protonation of the

*We thank Dr. Oliveto for providing us with the spectral characteristics of the tetraene.

C_{17} leads to the vinyl derivative (III). In the case of the 17-hydroxy compounds, the additional inductive effect of the hydroxy group prevents the addition of an electron to C_{17} and the subsequent protonation of this atom. The splitting out of a hydroxy group as the result of the protonation of the molecule is accompanied by a migration of the double bond to C_{17}, which leads to the 17-ethylidene derivative.

Thus, the reduction of mestranol acetate (Ib) under conditions capable of leading to the rapid hydrolysis of the acetate (in the presence of sodium isopropoxide) gave a mixture of the ethylidene derivative (VIII) and the alcohol (IX). By the hydrolysis of this mixture with hydrochloric acid followed by chromatographic separation, we obtained 19-norpregna-4,17(20)-diene-3-one (X) and 19-nortestosterone (XI). The alcohol (IX) was probably formed by the splitting out of the ethynyl group under the action of the sodium isopropoxide [8] followed by the reduction of the oxo group.

EXPERIMENTAL METHOD

The IR spectra were taken on a Perkin—Elmer 457 instrument in paraffin oil, the NMR spectra on a JNM-4H-100 instrument in solution in CCl_4 with HMDS as internal standard, the values of the chemical shifts being given in the δ scale, and the mass spectra on an MKh-1303 instrument with the direct introduction of the sample into the ion source. The energy of the ionizing electrons was 40 eV. The solutions of the substances obtained were dried over calcined sodium sulfate. The elementary analyses corresponded to the calculated figures.

3-Methoxy-19-norpregna-2,5(10),20-triene (III). Over 10 min, 1 g of metallic sodium was added to a suspension of 1 g of mestranol acetate (Ib) in 70 ml of redistilled liquid ammonia and 50 ml of anhydrous tetrahydrofuran, and the mixture was stirred for 45 min. Then 5 ml of absolute ethanol was added to decolorize the reaction solution. The ammonia was evaporated off, 100 ml of cold water was added, and the substance was extracted with chloroform. The chloroform solution was evaporated in vacuum. The residue was crystallized from methanol, giving 0.55 g of the triene (III) with mp 88-92°C. IR spectrum, ν, cm^{-1}: 3080, 1700, 1670, 1637; NMR spectrum (in $CDCl_3$), ppm: 5.74 (1 H at C_{20}), 4.81-4.98 (2 H at C_{21}), 4.57 (1 H at C_2), 3.47 (OCH_3), 0.54 (3 H at C_{18}); M^+ 298.

19-Norpregna-4,20-dien-3-one (IV). A solution of 200 mg of the enol (III) in 7 ml of acetone was treated with 0.3 ml of dilute (1:1) HCl, and the mixture was stirred at room temperature for 3 h. Then 50 ml of cold water was added and the resulting mixture was extracted with benzene. The extract was washed with saturated sodium bicarbonate solution and evaporated, and after the residue had been recrystallized from petroleum ether it yielded 70 mg of 19-norpregna-4,20-dien-3-one (VI), mp 82-84°C; IR spectrum, ν, cm^{-1}: 3080, 1680, 1620-1635, 910; NMR spectrum (in $CDCl_3$), ppm: 0.62 (3 H at C_{18}), 4.83-5.00 (2 H at C_{21}), 5.72 (1 H at C_{20}), 5.77 (1 H at C_4); M^+ 284.

Reduction of Mestranol Acetate with Sodium in Ammonia and Ether. With vigorous stirring, at a temperature of the reaction mixture of −50 to −60°C, 1.59 g of metallic sodium was added in portions to a suspension of 1.59 g of mestranol acetate (Ib) in 80 ml of liquid ammonia and 100 ml of anhydrous diethyl ether. The mixture was stirred for another 45 min and then 6 ml of absolute ethanol was added in drops to decolorize the reaction mixture. The ammonia was evaporated off, and 200 ml of cold water was added. The ethereal layer was separated off and the aqueous layer was extracted with ether. After the usual workup, the ethereal solutions yielded 1.47 g of an oily product containing a mixture of the enols (II) and (III).

Aromatization of the Enols (II) and (III) on Silica Gel. The enols (II) and (III) obtained in the preceding experiment (1.36 g) were dissolved in a mixture of petroleum ether and benzene (1:9). This solution was used to impregnate 45 g of silica gel (type KSK) placed in a column, the column was left for a day, and then a mixture of petroleum ether and benzene eluted fraction I: 0.53 g of 3-methoxy-19-norpregna-1,3,5(10),20-tetraene (V), mp 108-110°C (from hexane and methanol); according to the literature [7], mp 112.5-113.5°C. Benzene eluted fraction II: 0.2 g of a mixture of the tetraenes (V) and (VI). A mixture of benzene and ether eluted fraction III: 0.39 g of 3-methoxy-19-norpregna-1,3,5(10),20-tetraen-17β-ol (VI), mp 112.5-113°C (from ether); according to the literature [9], mp 114-115°C.

19-Norpregn-4-en-3-one (VII). With stirring, 0.7 g of metallic lithium was added in pieces over 15 min to a suspension of 2 g of mestranol acetate (Ib) in 80 ml of anhydrous

ether and 80 ml of liquid ammonia. The mixture was stirred for another 1 h, and then 9.6 ml of absolute ethanol was added dropwise. The ammonia was evaporated off, water was added, and the substance was extracted with ether. The ethereal extract yielded 1.65 g of an oil. A mixture of 300 mg of this oil in 10 ml of acetone and 1 ml of dilute (1:1) HCl was left at room temperature for 2 h. After the usual workup, 260 mg of a product was obtained which crystallized on standing. Recrystallization from petroleum ether gave 40 mg of 19-norpregn-4-en-3-one (VII), mp 74.5-75°C. IR spectrum, ν, cm^{-1}: 1670, 1617; NMR spectrum, ppm: 0.57 (3 H at C_{18}), 0.82 (3 H at C_{21}), 5.62 (1 H at C_4); M^+ 286.

Reduction of Mestranol Acetate in Ammonia and Isopropanol. With vigorous stirring at −50 to −60°C, 4 g of metallic sodium was added in portions over 35 min to a suspension of 3.97 g of mestranol acetate (Ib) in 150 ml of redistilled ammonia, 60 ml of anhydrous tetrahydrofuran, and 40 ml of absolute isopropanol, the mixture was stirred for another 20 min, the ammonia was evaporated off, 200 ml of cold water was added, and the product was extracted with methylene chloride. After evaporation, 3.78 g of a mixture of the enols (VIII) and (IX) was obtained.

Isomerization of the Enols (VIII) and (IX). A solution of 3.78 g of the mixture of enols obtained in the preceding experiment in 28 ml of acetone and 8 ml of dilute (1:1) HCl was stirred at room temperature for 5 h, and then water was added and the product was extracted with methylene chloride. The extract was washed with saturated sodium bicarbonate solution and evaporated. The oil obtained (3.19 g) was chromatographed on 130 g of alumina (activity grade II). Benzene and a mixture of benzene and ether successively eluted: fraction I — 0.45 g of 19-norpregna-4,17(20)-dien-3-one (X), mp 121-122°C (from methanol), according to the literature [2], mp 124-125°C; fraction II — 0.22 g of a mixture of the ketones (X) and (XI); and fraction III — 1.35 g of 19-nortestosterone (XI), mp 118-120°C (from ether), according to the literature [6], mp 123.8-124.6°C.

SUMMARY

In the reduction of mestranol acetate with metals in liquid ammonia, as well as the reduction of ring A and the splitting out of the acetoxy group, the addition of hydrogen to C_{17} takes place and the main products are the 17-vinyl and 17-ethyl derivatives (III) and (VII), respectively. Under conditions favoring the saponification of the acetate, the reduction product is the 17-ethylidene derivative (VIII).

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