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Abstract

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A NEW ROUTE FOR THE SYNTHESIS OF STEROID COMPOUNDS

TOTAL SYNTHESIS OF *dl*-8-ISOESTRONE

(Presented by Academician M. M. Shemyakin, 22 XII 1960)

In one of our papers (1) we reported the total synthesis of *dl*-estrone, starting from 3-methoxy-$\Delta^{1,3,5,8,14}$-*D*-homoestrapentaenone (I) via the methyl ether of 8,9-dehydro-*D*-homoestrone (II).

$$\text{(I)} \xrightarrow[\text{Pd}]{\text{H}_2} \text{(II)} \xrightarrow[\text{8 stages}]{} \text{estrone derivative}$$

In the present article the synthesis of *dl*-8-isoestrone (III) on the basis of methoxyketone (II) is described, according to the following scheme:

$$\text{(II)} \xrightarrow[\text{Pd/SrCO}_3]{\text{H}_2} \text{(IV)} \xrightarrow[\text{OH}^-]{\text{furfural}} \text{(V)}$$

$$\text{(V)} \xrightarrow[\text{OH}^-]{\text{H}_2\text{O}_2} \text{(VI)} \xrightarrow[300^\circ]{\text{PbCO}_3} \text{(VII)} \xrightarrow{\text{Py}\cdot\text{HCl}} \text{(III)}$$

During catalytic hydrogenation of methoxyketone (II) in the presence of 30% palladium on strontium carbonate, as usual, *cis*-addition of hydrogen occurs and the methyl ether of *D*-homo-8-isoestrone (IV) is formed. Condensation of the latter with furfural gave derivative (V), which, under the action of hydrogen peroxide in alkaline medium, was oxidized to dicarboxylic acid (VI). Pyrolysis of acid (VI) in the presence of lead carbonate (2) led to the methyl ether of *dl*-8-isoestrone (VII), which, on heating with pyridine hydrochloride, gave *dl*-8-isoestrone (III). The melting points of acid (VI), ketone (VII), *dl*-8-isoestrone (III), and its

benzoate agreed with the literature data (3). A mixed melting-point test of the methyl ether of *dl*-8-isoestrone with an authentic sample gave no depression of the melting point, and their IR spectra proved to be practically identical.

The comparison of the samples and the recording of the IR spectra were kindly carried out by Prof. Johnson and Abraham at the University of Wisconsin, for which we express to them our deep gratitude.

Experimental Part

The methyl ether of 8,9-dehydro-*D*-homoestrone (II) was obtained by the method described by us earlier (^{1}), by hydrogenation of ketone (I) in tetrahydrofuran of high purity at a temperature not above 20°, in the presence of freshly prepared palladium on calcium carbonate.

Hydrogenation of ketone (II). 2.5 g of ketone (II) in 24 ml of benzene and 12 ml of absolute alcohol were hydrogenated in the presence of 0.6 g of 30% palladium on strontium carbonate. In 7 hr, 191 ml of hydrogen (21°, 755 mm) was absorbed, instead of the theoretical 205 ml, and hydrogenation practically ceased. The solution was filtered, the solvent was distilled off, and the residue was crystallized from ethyl acetate. This gave 1.43 g (57%) of the methyl ether of *D*-homo-8-isoestrone (IV), m.p. 122–125°. The pure ketone melts (after two recrystallizations from ethyl acetate) at 128–128.5° and gives a sharp depression (105–109°) in a mixed-melting-point test with the starting product. $\lambda_{\max}$ (in alcohol) 279 and 286 mμ ($\lg \varepsilon$ 3.32 and 3.29).

$C_{20}H_{26}O_2$.	Found, %:	C 80.7; 80.55;	H 8.75; 8.8
	Calculated, %:	C 80.5;	H 8.8

Condensation of the methyl ether of *D*-homo-8-isoestrone (IV) with furfural. 4.0 g of ketone (IV) were dissolved, with heating, in 400 ml of methanol; to the cooled solution were added 3 g of freshly distilled furfural and a solution of 18 g of NaOH in 150 ml of methanol. The mixture was stirred in a stream of nitrogen at 50–60° for 4 hr, left overnight, and the crystals that separated were washed with water and methanol. This gave 4.63 g (91%) of the furfurylidene derivative (V), m.p. 160–163°. The pure compound melts at 167–167.5° (from alcohol). $\lambda_{\max}$ 218 and 323 mμ ($\lg \varepsilon$ 4.10, 4.36).

$C_{25}H_{28}O_3$.	Found, %:	C 79.4; 79.4;	H 7.4; 7.6
	Calculated, %:	C 79.75;	H 7.5

Sometimes the compound is obtained in another modification with a double m.p. 140–141 and 167–167.5°. On standing for 6 months, the second modification changes into the first. Johnson (^{3}) gives for compound (V) m.p. 149–150.5° and $\lambda_{\max}$ 322 mμ ($\lg \varepsilon$ 4.35).

In an analogous manner (heating for 18 hr), the benzylidene derivative was obtained in 66% yield, m.p. 170–170.5°. $\lambda_{\max}$ 282 mμ ($\lg \varepsilon$ 4.33).

$C_{27}H_{30}O_2$.	Found, %:	C 83.8; 83.8;	H 7.7; 7.8
	Calculated, %:	C 83.9;	H 7.8

3-Methyl ether of homo-8-isomarrianolic acid (VI). To a solution of sodium methoxide (from 27.9 g of sodium and 400 ml of methanol) was added a solution of 1.5 g of the furfurylidene derivative (V) in 250 ml of methanol, and then immediately 280 ml of 30% hydrogen peroxide, the temperature rising to 50°. The mixture was stirred at 45-55° for 8 hr until the white precipitate disappeared, evaporated in vacuo to one-quarter of its volume, diluted with water, and extracted with ether. The aqueous layer was acidified with 10% H_2SO_4 and extracted five times with ether. The extract was washed with a small amount of water and with Mohr' s salt solution, dried over sodium sulfate, and evaporated. Crystallization of the residue from benzene gave 1.09 g

(77%) of acid (VI) with m.p. 208-211°. A pure sample has m.p. 212-214°. Johnson ([3]) reports m.p. 214-217°.

Methyl ether of *dl*-8-isoestrone (VII). A finely ground mixture of 0.45 g of acid (VI) and 0.58 g of lead carbonate was heated in a flask for microdistillation at 280-305° and 0.06-0.09 mm for 30 min. On cooling, the distillate crystallized. After crystallization from alcohol, 250 mg (68%) of methyl ether of *dl*-8-isoestrone (VII) was obtained, m.p. 150-151°. The analytical sample has m.p. 154-155°. $\lambda_{\max}$ 278.5 and 286 mμ (lg ε 3.31; 3.29). Johnson ([3]) reports m.p. 152.5-154.5°.

***dl*-8-Isoestrone (III).** A mixture of 200 mg of methyl ether of *dl*-8-isoestrone (VII) and 4 g of freshly prepared pyridine hydrochloride was heated under nitrogen at 200-210° for 2 h. The reaction product was stirred with 40 ml of 5% HCl and extracted with chloroform. The extract was washed with water, filtered, the solvent was removed, and the residue was crystallized from methanol. This gave 66 mg of 8-isoestrone (III), m.p. 251-252° (with decomposition). Johnson ([3]) reports m.p. 254-255°.

By benzoylation of 8-isoestrone (III) according to Schotten-Baumann, 8-isoestrone benzoate was obtained, m.p. 197-198° (from methanol). Johnson ([3]) gives m.p. 197-198°.

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CITED LITERATURE

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Note: Figure translations are in progress. See original paper for figures.