S. N. ANANCHENKO, V. N. LEONOV, A. V. PLATONOVA, and I. V. TORGOV

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Abstract

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S. N. ANANCHENKO, V. N. LEONOV, A. V. PLATONOVA, and I. V. TORGOV

A NEW ROUTE FOR THE SYNTHESIS OF STEROID COMPOUNDS

TOTAL SYNTHESIS OF *dl*-ESTRONE

(Presented by Academician M. M. Shemyakin, 9 VI 1960)

In one of our papers [1] we reported a three-step synthesis of 3-methoxy-$\Delta^{1,3,5,8,14}$-*D*-homo-estrapentaenone (I), starting from 6-methoxytetralone (II) through the corresponding vinylcarbinol (III) and the tricyclic diketone (IV).

$$\text{(II)} \xrightarrow{\mathrm{CH_2{=}CHMgBr}} \text{(III)} \xrightarrow[\mathrm{OH^-}]{\text{diketone component}} \text{(IV)} \xrightarrow{\mathrm{H^+}} \text{(I)}$$

By successive hydrogenation and dehydrogenation of methoxyketone (I), the methyl ethers of *D*-homoequilenin and *D*-homoisoequilenin were obtained, which previously [2] had been converted into equilenin and isoequilenin. Thus, their total synthesis was accomplished.

The present article describes the total synthesis of *dl*-estrone (V), starting from methoxyketone (I), according to the following scheme.

$$\text{(I)} \xrightarrow{\mathrm{H_2,\ Pd}} \text{(VI)} \xrightarrow[\mathrm{H^+}]{\mathrm{(CH_2OH)_2}} \text{(VII)}$$

$$\text{(VII)} \xrightarrow[\mathrm{C_2H_5OH}]{\mathrm{Li,\ NH_3}} \text{(VIII)} \xrightarrow{\mathrm{CrO_3,\ Py}} \text{(IX)} \xrightarrow{\mathrm{H^+,\ H_2O}} \text{(X)}$$

$$\text{(X)} \xrightarrow[\mathrm{OH^-}]{\text{furfural derivative, CHO}} \text{(XI)} \xrightarrow{\mathrm{H_2O_2,\ OH^-}} \text{(XII)} \xrightarrow[300^\circ]{\mathrm{PbCO_3}} \text{(XIII)}$$

$$\text{(XIII)} \xrightarrow{\mathrm{Py{\cdot}HCl}} \text{(V)}$$

Hydrogenation of methoxyketone (I) in tetrahydrofuran in the presence of palladium on calcium carbonate proceeds predominantly at the 14–15 position, with formation of the methyl ether of 8,9-dehydro-*D*-homoestrone (VI). The hydrogenation procedure in pyridine described earlier (^{1}) does not always give satisfactory results. Ketone (VI) was converted in the usual way into ethylene ketal (VII), which, on reduction with lithium and alcohol in liquid ammonia, gave the ethylene ketal of 3-methoxy-$\Delta^{2,5(10)}$-*D*-homoestradienone-17 (VIII).

Thus, the reduction affected not only the 8,9-double bond but also the aromatic ring. Dehydrogenation of ketal (VIII) by means of Sarett's complex (chromic anhydride-pyridine) led to the methyl ether of the ethylene ketal of *D*-homoestrone (IX), and its hydrolysis to the methyl ether of *D*-homoestrone (X). In another variant, ketal (VII) is reduced with potassium in liquid ammonia directly to ketal (IX). All stages proceed in good (65–85%) yields.

The conversion of the methyl ether of *D*-homoestrone (X) into the methyl ether of estrone (XIII) was carried out by Johnson' s method (^{3}). Condensation of ketone (X) with furfural gave the furfurylidene derivative (XI), which, under the action of hydrogen peroxide in alkaline medium, was oxidized to the known dicarboxylic acid (XII). The latter, when heated in vacuo with lead carbonate at 300°, gave the methyl ether of estrone (XIII), demethylation of which had previously afforded *dl*-estrone. The melting points of the benzylidene derivative of the methyl ether of *D*-homoestrone, of the dicarboxylic acid (XII), and of the methyl ether of *dl*-estrone (XIII) coincided with literature data. A mixed sample of the methyl ether of estrone (XIII) with an authentic specimen gave no depression of the melting point, and their IR spectra proved identical. The benzylidene derivative of the methyl ether of *D*-homoestrone was likewise identical in all respects with the corresponding specimen.

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

Experimental Part

3-Methoxy-$\Delta^{1,3,5,8,14}$-*D*-homoestrapentaenone (I) was obtained by the procedure described by us earlier (^{1}).

Hydrogenation of ketone (I). 6 g of ketone (I) was hydrogenated in 40 ml of abs. tetrahydrofuran in the presence of 10% palladium on calcium carbonate. In 2 hr 10 min, 509 ml of hydrogen (738 mm, 22°) was absorbed, as against 509 ml theoretical. The solution was filtered from the catalyst, the solvent was distilled off, and the product was crystallized from a mixture of alcohol and ethyl acetate (1:1). 4.63 g (77%) of the methyl ether of 8,9-dehydro-*D*-homoestrone (VI) was obtained, m.p. 120–123°. The pure ketone has m.p. 125–127°. In contrast to previous data (^{1}), the ketone is an individual product.

Preparation of the ethylene ketal of ketone (VI). A mixture of 11.5 g of ketone (VI), 85 ml of ethylene glycol, and 0.46 g of *p*-toluenesulfonic acid in 575 ml of toluene was boiled with slow distillation of toluene for 5 hr. After cooling, the mixture was washed with water and with soda solution; the toluene solution was dried over sodium sulfate, filtered, and the solvent was distilled off in vacuo. After crystallization of the solid residue from ethyl acetate, 10.2 g (77%) of the ethylene ketal of the methyl ether of 8,9-dehydro-*D*-homoestrone (VII) was obtained, m.p. 145–146°. λ_{max} (in alcohol) 274 mμ (lg ε4.24).

Found, %:	C 77.7; 77.7; H 8.5; 8.3
$C_{22}H_{28}O_3$. Calculated, %:	C 77.6; H 8.3

If ketalization is carried out longer (8–10 hr), the yield of ketal decreases to 50%.

Reduction of ketal (VII) with lithium and alcohol in liquid ammonia. To a solution of 1 g of ketal (VII) in a mixture of 140 ml of liquid ammonia and 100 ml of abs. tetrahydrofuran, 1.4 g (17-fold excess) of metallic lithium in small pieces was added; the mixture was stirred for 10 min and then, over the course of half an hour, 50 ml of abs. alcohol was added dropwise until the solution became decolorized. The ammonia was removed by gentle heating in a stream of nitrogen, and the resulting suspension was decomposed with water at 0–5°. The organic layer was separated, the aqueous layer was extracted with chloroform, and the combined extracts were neutralized with solid carbon dioxide, washed with water, and dried over sodium sulfate. After removal of the solvent and crystallization of the residue from ethyl acetate, 650 mg (64%) of ethylene ketal of 3-methoxy-$\Delta^{2,5(10)}$-*D*-homoestradienone-17 (VIII) was obtained, m.p. 152–154°. λ_{max} (in alcohol) 278 mμ (lg ε 2.42).

Found, %:	C 76.7; 76.6; H 9.3; 9.1
$C_{22}H_{32}O_3$. Calculated, %:	C 76.7; H 9.4

If the reduction is carried out with a 4-fold excess of lithium, part of the starting ketal is recovered.

Dehydration of ketal (VIII). To the Sarett complex, prepared in the usual manner (4) from 1.9 g of chromic anhydride and 20 ml of pyridine, a solution of 1.33 g of ketal (VIII) in 20 ml of pyridine was added at 0°; the mixture was heated to 70–80° and left for 12 hr. The reaction mixture was diluted with chloroform and filtered through a column of Al_2O_3. After removal of the solvent from the filtrate and crystallization of the residue from ethyl acetate, 1 g (75%) of the ketal of methyl ether of *D*-homoestrone (IX) was obtained, m.p. 141–142°.

Reduction of ketal (VII) with potassium in liquid ammonia. To a solution of 1 g of ketal (VII) in a mixture of 250 ml of liquid ammonia, 20 ml of abs. dioxane, and 150 ml of abs. ether, over the course of 3 min, 2.1 g of metallic potassium was added, and the mixture was stirred for 40 min. At the end the blue color of the solution disappeared; the mixture was carefully decomposed by addition of 10 g of dry ammonium chloride and the ammonia was evaporated. To the resulting suspension, 250 ml of water was added and the mixture was extracted with ether. After the usual work-up and crystallization, 0.49 g of crystals with m.p. 129-135° was obtained. By repeated crystallization from alcohol-ethyl acetate, 300 mg of ketal (IX), m.p. 138-140°, was isolated; it gave no depression with the sample described above.

Preparation of the methyl ether of *D*-homoestrone (X). To a warm solution of 0.3 g of ketal (IX) in 10 ml of glacial acetic acid, 2 ml of 1 *N* HCl was added and the mixture was heated to boiling. The solution was cooled, diluted with water, and the precipitated crystals were filtered off. Obtained was 0.25 g (96%) of methyl ether of *D*-homoestrone (X), m.p. 162-163° (from ethyl acetate). $\lambda_{\max}$ (in alcohol) 278 mμ (lg ε 3.35).

Found, %:	C 80.45; 80.7;	H 8.8; 8.7
$C_{20}H_{26}O_2$. Calculated, %:	C 80.5;	H 8.8

The methyl ether of *D*-homoestrone can also be obtained without isolating the intermediate ketal (IX). In this case the yield over the two stages is 86%.

Condensation of the methyl ether of *D*-homoestrone (X) with aldehydes. To a solution of 2.54 g of ketone (X) and 1.9 g of freshly distilled furfural in 150 ml of methanol, a solution of 11.2 g of caustic soda in 100 ml of methanol was added. The mixture was stirred for 1 hr at 50-60°, cooled, and the precipitated crystals were filtered off and washed 4 times with water, 2 times with methanol, and once with ether. Obtained was 3.07 g (96%) of the furfurylidene derivative (XI), m.p. 161-162°. $\lambda_{\max}$ (in alcohol) 323.5 mμ (lg ε 4.35).

Found, %:	C 79.2; 79.35;	H 7.3; 7.4
$C_{25}H_{28}O_3$. Calculated, %:	C 79.75;	H 7.5

By an analogous route, the benzylidene derivative of methyl *D*-homoestronate was obtained, mp 146–147° (from ethyl acetate), $\lambda_{\max}$ (in alcohol) 222, 282 mμ (lg ε 4.14, 4.15).

Found, %:	C 83.6; 83.5;	H 7.8; 7.7
$C_{27}H_{30}O_2$. Calculated, %:	C 83.9;	H 7.8

Lit. (4) mp 147–148° (from alcohol), $\lambda_{\max}$ 218.5; 281 mμ (lg ε 4.24, 4.32).

Preparation of methyl ether of *dl*-estrone (V). Oxidation of the furfurylidene derivative (XI) with hydrogen peroxide in methanol according to Johnson (5) gave 3-methoxy-*D*-homomarianolic acid (XII), mp 223–224° (from aqueous acetone). Johnson (6) gives mp 225–227° (corr.).

Pyrolysis of acid (XII) in the presence of lead carbonate according to (3) gave methyl ether of *dl*-estrone (XIII), mp 143–144° (from ethyl acetate). $\lambda_{\max}$ 278.5, 287 mμ (lg ε 3.30, 3.30).

Found, %:	C 79.9; 79.8;	H 8.3; 8.3
Calculated, %:	C 80.2;	H 8.5

Lit. (6) mp 143–144° (corr.).

Institute of the Chemistry of Natural Compounds
Academy of Sciences of the USSR

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