STEROID ANALOGS WITHOUT THE BRING COMMUNICATION 1. SYNTHESIS OF 3-ETHYL-4-(p-METHOXYPHENYL)-2-METHYL-3-CYCLOHEXENE-1-CARBOXYLIC ACID

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For a number of years the attention of chemical research workers has been attracted by the synthesis of highly active analogs of estrogenic hormones which could find application in medicine and agriculture and could also serve as valuable intermediate products in the total synthesis of steroids. One of the ways of providing modifications of natural estrogens is the synthesis of their analogs with a decyclized B ring (5,6-seco steroids) or not containing a B ring at all (de-B steroids). Some of these compounds, while being simpler and more readily accessible than natural steroids, still retain a high level of physiological activity.

For example, in 1956 it was shown [1, 2] that analogs of dehydrodoisynolic acid (II) with a decyclized B ring (III) and (IV) have very high estrogenic activity (0.04–0.05 γ for mice), equal to the activity of the natural estrogenic hormone estradiol. At the present time only one method is known for the preparation of such compounds, and this is based on the conversion of Hagemann's ester (I) in five stages into (IV) in an overall yield of about 12% [1].



We here describe a method for the synthesis of (IV) – an analog of dehydrodoisynolic acid with a decyclized B ring – by a diene-condensation method. As diene we used the previously undescribed 3-ethyl-2-p-methoxyphenyl-1,3-pentadiene (IX), and as the dienophile – acrylic acid.

The diene (IX) was synthesized as follows. The acetylenic alcohol (V), prepared from 3-pentanone and acetylene under pressure by the Favorskii-Nazarov method [3], was subjected to Rupe isomerization with the aid of a cation-exchange resin (Amerlite IR-120) into 3-ethyl-3-penten-2-one (VI) [4, 5]. The desired ketone (VI) was then formed exclusively, whereas all the other methods for its preparation – the condensation of acetylene with 2-pentanone and subsequent dehydration of the secondary β - ketol [6] and the hydration of the acetylenic alcohol (V) with dehydration of the ketol formed [5, 7] – lead to mixtures of several products. The structure of the ketone (VI) was proved with the aid of its UV and IR spectra. The UV spectrum shows that (VI) is a conjugated ethylenic ketone of the disubstituted series. According to its IR spectrum [ν (C=O) 1672 cm⁻¹, ν (C=C) 1639 cm⁻¹], the ketone (VI) has a trans-s-trans configuration. It is known from the literature [8] that in ethylenic ketones of cis-s-cis configuration the bands of carbon-carbon and carbon-oxygen bonds are relatively remote from one another (Δ_{ν} =

N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 3, pp. 624-628, March, 1967. Original article submitted December 31, 1964.

 $\nu(C=O) - \nu(C=C) > 50 \text{ cm}^{-1}$, whereas in the trans-s-trans form, as in the case of the ketone (VI), these bands are close ($\Delta_{\nu} = \nu(C=O) - \nu(C=C) < 50 \text{ cm}^{-1}$).

The ketone (VI) reacts with (p-methoxyphenyl)lithium with formation of the alcohol (VII), the dehydration of which with potassium hydrogen sulfate leads to the diene (IX). On the basis of the mode of the synthesis of (IX) from the trans-s-trans ketone (VI), the methyl group in (IX) can be assigned the trans position relative to the p-methoxystyrene grouping, which should facilitate the reaction of (IX) in accordance with the diene-synthesis scheme. Apart from the method of preparation and the spectral data, the structure of the diene (IX) is proved by the formation of the adduct (VIII) with maleic anhydride. Theoretically, the condensation of the diene (IX) with acrylic acid can lead to the formation of two structural isomers (IV) and (X), each of which may exist in cis and trans forms.

However, from the crude product of the diene condensation $(160^{\circ}, 24 h)$, which was obtained in 62% yield, we could isolate only one isomer (IV), which was identical in all respects to the product obtained earlier [1] from Hagemann's ester (I). In this case, therefore, the diene synthesis goes with high structural and steric selectivity, which is in accord with known data [9-11] on the condensation of 1,2,3-trisubstituted dienes of type (IX). The adduct (IV) can also be prepared directly from the alcohol (VII) by boiling it with a mixture of acrylic acid and acetic anhydride, but in this case the yield of the adduct (IV) is very much lower than in the two-stage procedure via the diene (IX).

By the methylation of the acid (IV) with diazomethane we obtained the methyl ester (XI). In an attempt to isomerize this by prolonged boiling with a solution of sodium methoxide in methanol we obtained the original acid (IV) in high yield. It must therefore be supposed that the methyl and carboxy groups in (IV) are in the more stable trans position relative to one another.



When tested on mice, (IV) and (XI) showed high estrogenic activity. For a detailed description of these tests see [12].

EXPERIMENTAL

Thin-layer chromatography was conducted on glass plates in an unbound layer with use as adsorbents of silica gel (150 mesh) containing 17% of water and alumina of activity II [13].

<u>3-Ethyl-3-penten-2-one (VI)</u>. A mixture of 33.6 g of the acetylenic alcohol (V) (prepared from 2-pentanone and acetylene by the method described in [3]), 100 ml of acetic acid, 10 ml of water, and 20 g of the cation exchanger Amberlite IR-120 (in H form) was refluxed for 45 min. It was cooled, and the cation-exchange resin was filtered off and washed on the filter with ether. The filtrate was diluted with water and neutralized with sodium hydroxide. The organic layer was separated, and the aqueous layer was extracted several times with ether. The organic layer was combined with the ether extracts, washed with saturated sodium chloride solution, and dried over MgSO₄. Ether was driven off, and the residue was vacuum-fractionated. We obtained 22 g (66% on the acetylenic alcohol that had reacted) of the ketone (VI), b.p. 66-72° (36 mm); n_D^{25} 1.4432; Rf 0.72 (alumina, 60:40 benzene-ether). UV spectrum: λ_{max} 229 mµ (C₂H₅OH) (ϵ 14150). IR spectrum (CHCl₃): ν (C=O) 1672 cm⁻¹, ν (C=C) 1639 cm⁻¹. The 2,4-dinitrophenylhydrazone of the ketone had m.p. 156°. According to [5] the ketone (VI) has b.p. 73.4° (50 mm); n_D^{20} 1.4478. 2,4-Dinitrophenylhydrazone, m.p. 157°.

3-Ethyl-2-p-methoxyphenyl-3-penten-2-ol (VII). A 1-liter four-necked flask fitted with stirrer, reflux condenser, and tube for the passage of gas was charged with 200 ml of dry ether, and air was then displaced by means of carefully dried nitrogen. A strong stream of nitrogen was passed into the flask while 6 g of finely cut lithium was introduced through a glass funnel. The ordinary funnel was then replaced with a dropping funnel, and through this we added a few milliliters of a solution of 112 g of freshly distilled p-bromoanisole in 350 ml of dry ether. After a few minutes the reaction mixture went cloudy, after which with vigorous stirring and water cooling we added the remainder of the ethereal solution of p-bromoanisole in a thin stream. When the ether stopped boiling, the mixture was stirred further for 10 min, and the resulting ethereal solution of (p-methoxyphenyl)lithium was then forced over, with simultaneous filtration through glass wool, into a three-necked flask which had been filled with dry nitrogen. The solution of (p-methoxyphenyl)lithium was diluted with 150 ml of dry ether and cooled to -15° with a mixture of ice and salt. With vigorous stirring we added a cooled solution of 35 g of the ketone (VI) in 400 ml of dry ether dropwise. At the end of the addition the reaction mixture was stirred further for 2 h and then treated with 400 ml of ice water. The ethereal layer was separated, and the aqueous layer was extracted four times with ether. The combined ether extracts were washed with water until pH 8 was attained, and they were dried over MgSO4; ether was driven off, and the residue was vacuum-distilled in a stream of nitrogen. We obtained 34.5 g (53%) of the alcohol (VII) as a colorless viscous liquid, b.p. 130-135° (3 mm); nD²⁵ 1.5169; Rf 0.14 (alumina, 70:30 benzene-heptane). IR spectrum (CHCl₃): v 980, 1610, and 3595 cm⁻¹.

 $\frac{3-\operatorname{Ethyl-2-p-methoxyphenyl-1,3-pentadiene}{(IX)}$ A mixture of 13.5 g of the alcohol $\overline{(VII)}$, 0.1 g of potassium hydrogen sulfate, and 0.1 g of hydroquinone was introduced into a Claisen flask and kept in a vacuum in a stream of nitrogen for 15 min without heating. The mixture was then heated cautiously until the bath temperature reached 80-90° and kept at this temperature until foaming stopped. After distillation we obtained 9.5 g (78%) of the diene (IX) as a light-yellow liquid, b.p. 105-115° (2 mm); n_D²⁵ 1.5442; R_f 0.88 (alumina, 70:30 benzene-heptane). UV spectrum: λ_{max} 268 mµ (C₂H₅OH) (ϵ 11190).

A solution of 30 g of the ketone (VI) in 300 ml of dry ether was added dropwise to a cooled (-15°) ethereal solution of (p-methoxyphenyl)lithium prepared from 5.2 g of lithium and 94.5 g of p-bromoanisole in 450 ml of dry ether. After decomposition with water the reaction mixture was treated as described above in the synthesis of (VII). Ether and unchanged p-bromoanisole were driven off, 0.1 g of potassium hydrogen sulfate and 0.1 g of hydroquinone were added to the residue, and dehydration was conducted as described above. We obtained 17 g of the diene (IX), b.p. 110-118° (2 mm); nD²⁵ 1.5462. The yield was 29% based on the (VI) taken, as against 41% in the two-stage scheme with isolation of the alcohol (VII).

Diene Condensation of 3-Ethyl-2-p-methoxyphenyl-1,3-pentadiene (IX) with Maleic Anhydride. A mixture of 1.4 g of the diene (IX), 1.5 g of maleic anhydride, 0.1 g of hydro $quinone, and 5 ml of toluene was refluxed for 10 h. Toluene was driven off, and the oily residue was rubbed out with hexane. The powder obtained (1 g; yield 50%) was recrystallized from methanol, and we obtained colorless crystals of the adduct (VIII), m.p. 99-100°. UV spectrum: <math>\lambda_{max}$ 239 mµ (C₂H₅OH). (ϵ 10270). Found %: C 71.85; H 6.77. C₁₈H₂₀O₄. Calculated %: 71.98; H 6.71.

Dimethyl $4-Ethyl-5-p-methoxyphenyl-3-methyl-4-cyclohexene-1, 2-dicar-boxylate (XII). 1 g of the adduct (VIII) was heated in a water bath with 30 ml of 10% sodium hydroxide solution until the precipitate had dissolved and then further for 30 min. The solution was washed with ether, and the aqueous layer was acidified with 1:1 hydrochloric acid to pH 1-2. The oily diacid was methylated with excess of ethereal diazomethane. The residue (0.9 g of oil) obtained after the removal of ether was chromatographed on a column of 50 g of silica gel (150 mesh) containing 17% of water (elution was with an 85:15 mixture of petroleum ether and moist diethyl ether). We obtained 0.5 g of (XII) as an oil, which crystallized on standing; m.p. 68-69° (hexane-ether); <math>R_f 0.42$ (silica; 60:40 petroleum ether and moist diethyl ether). Found %: C 69.28; H 7.59. $C_{20}H_{26}O_5$. Calculated %: C 69.34; H 7.57.

 $\frac{\text{Diene Condensation of } 3-\text{Ethyl-2-p-methoxyphenyl-1,} 3-\text{pentadiene (IX)}}{\text{Acrylic Acid.}}$ A mixture of 23 g of the diene (IX), 70 ml of freshly distilled acrylic acid, 0.01 g of hydroquinone, and 0.01 g of picric acid was refluxed for 24 h (temperature of mixture about 160°). The reaction product was extracted with hot benzene, solvents and unchanged acrylic acid were vacuumdistilled off, and the residue was fractionated in a high vacuum. We obtained 20 g (62%) of adduct, which distilled at a bath temperature of 185-200° (5-7 \cdot 10⁻³ mm), and this crystallized completely on standing. After recrystallization from a mixture of hexane and ether 3-ethyl-4-p-methoxyphenyl-2-methyl-3-cyclohexene-1-carboxylic acid (IV) was obtained in the form of colorless crystals, m.p. 156-157°; R_f 0.60 (silica; 90:10 propyl alcohol-ammonia). UV spectrum: $\lambda_{max} 230 \text{ m}\mu (C_2H_5OH)$ ($\epsilon 10000$). IR spectrum (CHCl₃): ν 1243 and 1697 cm⁻¹, diffuse band in the range 2800-3200 cm⁻¹. Found %: C 74.37; H 8.14. C₁₇H₂₂O₃. Calculated %: C 74.42; H 8.08. According to [1]: m.p. of (IV) 158.5-159°; $\lambda_{max} 230 \text{ m}\mu (C_2H_5OH)$ ($\epsilon 10740$).

A mixture of 9 g of the alcohol (VII), 25 ml of xylene, 8 ml of acrylic acid, 0.01 g of hydroquinone, and 15 ml of acetic anhydride was heated to the boil in an atmosphere of nitrogen. 0.1 g of potassium hydrogen sulfate was added to the mixture as it started to boil, and the mixture was then refluxed for 30 h. After the fractionation of the reaction products we obtained 3 g (27% on the alcohol) of the acid (IV), which after recrystallization from a mixture of hexane and ether had m.p. 156-157°, undepressed by admixture of the product obtained from the diene (IX) and acrylic acid.

<u>Methyl 3-Ethyl-4-p-methoxyphenyl-2-methyl-3-cyclohexene-1-carboxylate</u> (XI). Excess of ethereal diazomethane was added to a solution of 1.3 g of the acid (IV) in 50 ml of dry ether, and the mixture was left overnight. Ether was driven off, and we obtained 1.3 g of a yellow oil, which was chromatographed on a column of 100 g of silica gel (150 mesh) containing 17% of water with gradient elution with a mixture of 500 ml of hexane and 500 ml of an 80:20 mixture of hexane and moist ether. We obtained 1.1 g (81%) of the methyl ester (XI), m.p. 58.5-59.5° (petroleum ether); R_f 0.67 (silica 70:30 hexane-moist ether).

In an attempt to bring about its isomerization, 240 mg of the ester (XI) was boiled with sodium methoxide (0.5 g of sodium in 18 ml of absolute methanol) for 15 h. The reaction mixture was neutralized, methol was vacuum-evaporated, and the residue was diluted with water and acidified to pH 1-2. The crystals precipitated were filtered off, dried in air, and recrystallized from a mixture of hexane and ether. We obtained 200 mg (88%) of crystals of m.p. 151.5-153.5°, undepressed by admixture of a known sample of the acid (IV). Hence, the methyl ester (XI) is not isomerized under alkaline conditions.

CONCLUSIONS

A new scheme of synthesis was devised for 3-ethyl-4-p-methoxyphenyl-2-methyl-3-cyclohexene-1carboxylic acid – an analog of dehydrodoisynolic acid with a decyclized ring B – in which the key stageis the diene condensation of <math>3-ethyl-2-p-methoxyphenyl-1,3-pentadiene with acrylic acid.

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