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Abstract

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Synthesis of trans-$\Delta^{4,9}$-Steradienone-3

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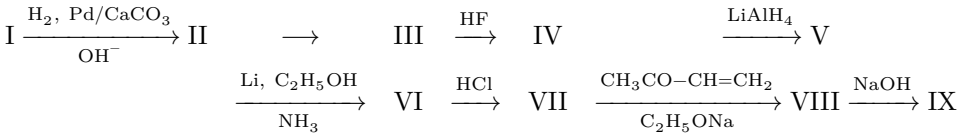
In the course of our work on the synthesis of polycyclic compounds with a strictly defined spatial configuration of the rings, we obtained trans-$\Delta^{4,9}$-steradienone-3 (IX; R = H) according to the following scheme:



The starting 3-(*p*-methoxyphenyl)-Δ^2-cyclopenten-1-one-2-acetic acid (I), obtained by us by the Robinson method (1), had m.p. 145.5–146°. (Found, %: C 68.12; H 5.76. $C_{14}H_{14}O_4$. Calculated, %: C 68.26; H 5.74.) Robinson and co-workers (1) and Terhen reported for it m.p. 133°. The methyl ester of this acid melted, in agreement with the literature data (2), at 88–89°.

On saponification of the methyl ester, the acid with m.p. 145.5–146° was obtained. The ultraviolet spectra of the acid ($\lambda_{max}^{C_2H_5OH} = 228$ mμ, 301 mμ; $\lg\varepsilon = 4.04; 4.33$) and of its methyl ester ($\lambda_{max}^{C_2H_5OH} = 228$ mμ, 301 mμ; $\lg\varepsilon = 4.03; 4.35$) are characteristic of α,β-unsaturated ketones conjugated with an aromatic ring (3).

Hydrogenation of the double bond in acid I in alkaline and neutral media in the presence of palladium on calcium carbonate at 3–5 atm and room temperature led to the formation of trans-3-(*p*-methoxyphenyl)-cyclopentan-1-one-2-acetic acid (II) with m.p. 106.5–107.5° (yield 77%. Found, %: C 67.73; H 6.55; $C_{14}H_{16}O_4$. Calculated, %: C 67.72; H 6.49), cis-2-(*p*-methoxyphenyl)-cyclopentan-1-acetic acid (X) with m.p. 73–74° (yield 8.5%. Found, %: C 71.72; H 7.68. $C_{14}H_{18}O_3$. Calculated, %: C 71.77; H 7.74), and the lactone of syn-cis-3-(*p*-methoxyphenyl)-cyclopentan-1-ol-2-acetic acid (XI) with m.p. 67–68° (yield 5.8%. Found, %: C 72.30; H 6.97. $C_{14}H_{16}O_3$. Calculated, %: C 72.39; H 6.94).

Upon hydrogenation of I in an acidic medium in the presence of palladium on carbon or barium sulfate at atmospheric pressure and room temperature, exclusively the cis acid X, m.p. 73–74°, was obtained.

Reaction scheme showing conversion of I by $H_2, Pd/CaCO_3, OH^-$ to II, X, and XI, and subsequent transformations of II with HF to XIV and with $NaBH_4$ to XII and XIII.

Figure 1: Reaction scheme showing conversion of I by $H_2, Pd/CaCO_3, OH^-$ to II, X, and XI, and subsequent transformations of II with HF to XIV and with $NaBH_4$ to XII and XIII.

Reaction scheme showing conversion of X to XV, XVI, XVII, and XVIII.

Figure 2: Reaction scheme showing conversion of X to XV, XVI, XVII, and XVIII.

Clemmensen reduction of the trans keto acid II leads to the formation of the trans acid (III; R=H), m.p. 55-56°—a diastereomer of the acid obtained after catalytic hydrogenation ($C_{14}H_{18}O_3$). Found, %: C 72.50; H 7.63).

Intramolecular acylation of the cis acid (X) and the trans acid (III; R=H) was carried out by three methods: under the action of polyphosphoric acid, hydrogen fluoride, and by the Friedel-Crafts method. In all cases, the cis acid gave, in quantitative yield, cis-4-keto-6-methoxy-1,2-cyclopentano-1,2,3,4-tetrahydronaphthalene (XV), m.p. 27-29° ($\lambda_{max}^{C_2H_5OH}$ = 250 mμ, lg ε = 3.8. Found, %: C 77.82; H 7.57. $C_{14}H_{16}O_2$. Calculated, %: C 77.75; H 7.44), whereas the trans acid gave the trans-tricyclic ketone (IV; R=H) in 70% yield, m.p. 95.5-96.5° ($\lambda_{max}^{C_2H_5OH}$ = 250 mμ, lg ε = 3.8. Found, %: C 77.47; H 7.51). The greater tendency toward cyclization of the cis isomer (X), compared with the trans isomer (III; R=H), is explained by the lower strain of cis-hydrindane ([4]).

Reduction of the aromatic ring in the cis ketone XV and the trans ketone (IV; R=H) by the Wilds method ([5]), with lithium in liquid ammonia and alcohol, did not proceed even when 50 equivalents of lithium were used. After reduction of the carbonyl group in the cis and trans ketones, there were obtained, in quantitative yield, respectively the cis alcohol (XVI), m.p. 72-73°. (Found, %: C 76.82; H 8.23. $C_{14}H_{18}O_2$. Calculated, %: C 77.02; H 8.30) and the trans alcohol (V; R=H), m.p. 92-93°. (Found, %: C 77.18; H 8.36). Reduction of the aromatic ring in these alcohols with 30 equivalents of lithium proceeded with the formation of 80% of dihydro derivatives (VI, R=H and XVII), the amount of which was established on the basis of ultraviolet spectra. Increasing the amount of lithium to 50 equivalents led to a quantitative yield of VI (R=H) and XVII. Reduction of the aromatic ring was accompanied by hydrogenolysis of the α-hydroxy group. Conversion of VI (R=H) and XVII into the α,β-unsaturated ketones VII (R=H) and XVIII by means of

saponification of the enol ether and isomerization was carried out by brief heating with a dilute solution of hydrochloric acid. trans-1,2-Cyclopentano-Δ^5-octalone-6 (VII; R = H) was obtained with m.p. 54-

55° ($\lambda_{max}^{C_2H_5OH} = 239$ mμ, $\lg \varepsilon = 4.37$. Found, %: C 81.86; H 9.34. $C_{13}H_{18}O$. Calculated, %: C 82.00; H 9.53), its 2,4-dinitrophenylhydrazone with m.p. 202–203.5°. The corresponding cis isomer (XVIII) had b.p. 107–111° at 0.55 mm ($\lambda_{max}^{C_2H_5OH} = 244$ mμ, $\lg \varepsilon = 4.38$. Found, %: C 82.05; H 9.45), 2,4-dinitrophenylhydrazone—m.p. 173–175°. α,β-Unsaturated ketones containing a secondary-tertiary double bond have λ_{max} 240 mμ (on the basis of Woodward' s rules ([6])).

The construction of ring A was carried out under the conditions described by Misher, Anner, and Wieland ([7]). Condensation of trans-1,2-cyclopentano-Δ^5-octalone-6 (VII; R = H) with methyl vinyl ketone proceeded in the presence of sodium ethylate in an alcohol-dioxane solution at a temperature of −5, −10°. The aldol obtained (VIII; R = H) was readily separated from the starting ketone (VII; R = H) and excess methyl vinyl ketone by chromatography on aluminum oxide. On heating the aldol (VIII; R = H) with a methanolic solution of caustic soda, dehydration occurred with formation of the tetracyclic ketone (IX; R = H), which was isolated as an oily substance with an absorption maximum $\lambda_{max}^{C_2H_5OH} = 309$ mμ, $\lg \varepsilon = 4.47$, characteristic of such a conjugated dienone. trans-$\Delta^{4,9}$-Steradienone-3 was characterized as the 2,4-dinitrophenylhydrazone with m.p. 253.5–254°. (Found, %: C 64.94; H 6.22; N 13.16. $C_{23}H_{26}N_4O_4$. Calculated, %: C 65.38; H 6.26; N 13.26.)

For the purpose of obtaining the tricyclic ketone IV, containing in position 1, corresponding to position 17 of the steroid molecule, the oxygen substituent R, we carried out the cyclization of the trans-keto acid (II) and of the ethylene ketal of this acid. We performed the intramolecular acylation of the trans-keto acid by two methods: according to Friedel–Crafts and with the aid of hydrogen fluoride. However, instead of the expected tricyclic ketone (IV; R = O), enol lactone XIV was obtained by the first method in 10–15% yield, and by the second in 35% yield, as an oily substance with b.p. 148–150° at 0.35 mm ($\lambda_{max}^{C_2H_5OH} = 275$ mμ, $\lg \varepsilon = 3.02$. Found, %: C 72.87; H 6.21. $C_{14}H_{14}O_3$. Calculated, %: C 73.02, H 6.13). This lactone is stable toward a solution of soda and alkali at room temperature, but on prolonged (14 h) boiling with an alcoholic solution of alkali the lactone ring opens with formation of the starting trans-keto acid II.

The ethylene ketal of trans-3-(*p*-methoxyphenyl)cyclopentan-1-one-2-acetic acid (XIX) was obtained by alkaline saponification of the corresponding methyl ester formed by the interaction of the methyl ester of the trans-keto acid II with ethylene glycol in the presence of *p*-toluenesulfonic acid. It had m.p. 123–124°. (Found, %: C 65.89; H 6.93. $C_{16}H_{20}O_5$. Calculated, %: C 65.73; H 6.89.)

On its cyclization under the action of hydrogen fluoride, instead of the tricyclic ketone $\left(\text{IV; } R = \begin{matrix}O{-}CH_2\\O{-}CH_2\end{matrix}\right)$, a substance was formed in quantitative yield which is insoluble in soda solution but readily soluble in alkali and decomposes on distillation. On acidification of the alkaline solution of this substance, the starting

Reaction scheme: XIX → intermediate → XX

Figure 3: Reaction scheme: XIX → intermediate → XX

trans-keto acid (II) with m.p. 106.5–107° separated. Elemental analysis of the substance confirms preservation of the elemental composition $C_{16}H_{20}O_5$, as in the starting ethylene ketal of the keto acid (XIX. Found, %: C 66.09; H 6.86; OH 5.17. Calculated, %: C 65.73; H 6.89; OH 5.81). Its infrared spectrum indicates the presence of a lactone carbonyl group (1738 cm^{-1}) and a hydroxyl group (3440 cm^{-1}). The listed properties of the substance allow one to propose for it the structural

formula (XX). The formation of 5-(*p*-methoxyphenyl)-8-(*β*-hydroxy)-ethoxy-2-keto-1-hydroxybicyclo-(0,3,3)-octane (XX) may be represented as follows:

The acetate of substance (XX), obtained by the action of ketene on (XX) in the presence of sulfoacetic acid as catalyst, is a colorless, slightly mobile oil that decomposes on distillation. (Found, %: C 64.62; H 6.65. $C_{18}H_{22}O_6$. Calculated, %: C 64.65; H 6.63.)

Attempts to obtain compound IV with an oxygen-containing substituent R by intramolecular acylation of anti-trans-3-(*p*-methoxyphenyl)-cyclopentane-1-acetoxy-2-acetic acid likewise did not lead to positive results. Anti-trans-hydroxy acid XII was obtained by reduction of the carbonyl group in trans-keto acid II with sodium borohydride. As a result of the reduction, two epimeric alcohols were formed: 73.6% of anti-trans-hydroxy acid XII, m.p. 86–87°. (Found, %: C 67.22; H 7.26. $C_{14}H_{18}O_4$. Calculated, %: C 67.18; H 7.25) and 24% of anti-cis-hydroxy acid, isolated in the form of lactone XIII with m.p. 141–142°. ($C_{14}H_{16}O_3$. Found, %: C 72.63; H 7.03.)

The configuration of anti-trans-hydroxy acid XII, in which the position of the hydroxy group is analogous to the *β*-position of the hydroxyl at C_{17} of the steroid molecule, is especially favorable for the construction of analogs of steroid hormones.

The acetate of anti-trans-hydroxy acid, obtained by the action on hydroxy acid XII of a threefold excess of acetyl chloride, had m.p. 91.5–92.5°. (Found, %: C 65.99; H 6.91. $C_{16}H_{20}O_5$. Calculated, %: C 65.73; H 6.90.) Upon its cyclization by three methods—Friedel-Crafts, under the action of hydrogen fluoride, and with polyphosphoric acid—instead of the expected tricyclic ketone (IV; R—$OCOCH_3$), lactone XIII, m.p. 141–142°, was isolated as the sole reaction product in quantitative yield. The formation of lactone XIII from the acetate of anti-trans-hydroxy acid could have occurred as a result of Walden inversion at the carbon atom bonded to the hydroxyl.

The tendency toward formation of a lactone ring in the cyclization reactions of trans-keto acid II, its ethylene ketal, and the acetate of anti-trans-hydroxy acid indicates the energetic advantage of such a structure and is explained by the

absence of strain in two fused 5-membered rings in the cis position ([8]).

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