SYNTHESIS OF UZARIGENIN

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The synthesis of cardenolides with β-oriented substituents at C_{14} and C_{17} has not been effected in attempts which cover a long period of time [1], and only comparatively recently have methods been described for obtaining digitoxigenin [2-4], periplogenin [5], and 3α-epidigitoxigenin [4].

We have synthesized another cardenolide, uzarigenin. Studies on the preparation of this aglycone were begun by Ruzicka and his colleagues as early as 1947 [6], but they succeeded in synthesizing only the thermodynamically more stable but physiologically inactive 17α isomer of uzarigenin. Okada and Saito [7], on the basis of the well-known investigations by Swiss chemists concerning the synthesis of compounds of the dianhydrogitoxigenin type [18], synthesized uzarigenin acetate, but in this process they obtained mainly allouzarigenin, together with a small amount of the 17β isomer.

The starting material for our synthesis was 3β-hydroxy-5α-pregn-16-en-20-one acetate (I), which can easily be obtained from steroid sapogenins [9].

One of the key points of the synthesis of cardenolides is the introduction of the 14-hydroxy group into the β position with the retention of the β configuration of the chain at C_{17}. Among the small number of methods for introducing a 14β-hydroxy group into the steroid molecule [1] the route to 14β-hydroxysteroids from Δ^{14}-steroids is promising. In their turn, the Δ^{14}-steroids can be formed by the reduction of the corresponding $\Delta^{14,16}$-dienes.

To synthesize 5α-pregna-14,16-diene (II), the acetate I was subjected to allyl bromination with N-bromosuccinimide [10] and then dehydrobromination by boiling the bromide with sodium iodide in acetone solution. The crude reaction product proved to be a mixture of the initial acetate I and the diene II, which were separated chromatographically. Saponification of the acetate II with potassium hydroxide in tertiary butanol gave 3β-hydroxy-5α-pregna-14,16-dien-20-one (III) [11, 12].

While the hydrogenation of $\Delta^{14,16}$-dienes over platinum leads to 14β,17α-steroids, these compounds are reduced by sodium in propanol or by lithium in liquid ammonia to Δ^{14}-17β-steroids [13].

The reduction of II with sodium in boiling propanol formed substance IV. The IR spectrum of this compound lacked absorption in the region of ester and carbonyl groups. In IV the double bond at C_{14} and the β configuration of the side chain at C_{17} are shown by the conversion of IV on oxidation with chromic anhydride into the known 5α-pregn-14-ene-3,20-dione (VII) [13]. The acetylation of the diol IV led to the diacetate V.

The negative value of the increment of the molecular rotation of the diacetate V and of the diol IV ($[M]_D$ of the diacetate V + 61.2°, $[M]_D$ of the diol IV + 93.6°, $\Delta[M]_D$ −32.4°) shows the α configuration of the hydroxyl at C_{20} in IV [13, 14]. An additional proof of this is the conversion of IV on hydrogenation over platinum into 5α-pregnan-3β,20α-diol (VIII) [14]. Thus, the product of the reduction of II has the structure of 5α-pregn-14-ene-3β,20α-diol (IV).

The diacetate V was subjected to hypohalogenation with N-bromoacetamide [15]. After splitting off hydrogen bromide from the crude bromohydrin, substance VI was formed. The IR spectrum of VI has absorption bands at 885 and 3050 cm^{-1} corresponding to an epoxy group. In the NMR spectrum of this sub-

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stance at 3.29 ppm, i.e., in the region characteristic for the protons of epoxide groups [16], there is a one-proton singlet.

It is known [15] that by adding hypobromous acid C_{21} steroids with a Δ^{14} bond form 15α-bromo-14β-hydroxy derivatives which, on splitting out hydrogen bromide, give 14β,15β-epoxysteroids. Consequently, the epoxide VI is 14β,15β-epoxy-5α-pregnan-3β,20α-diol diacetate. This structure is also confirmed by the subsequent course of the synthesis.

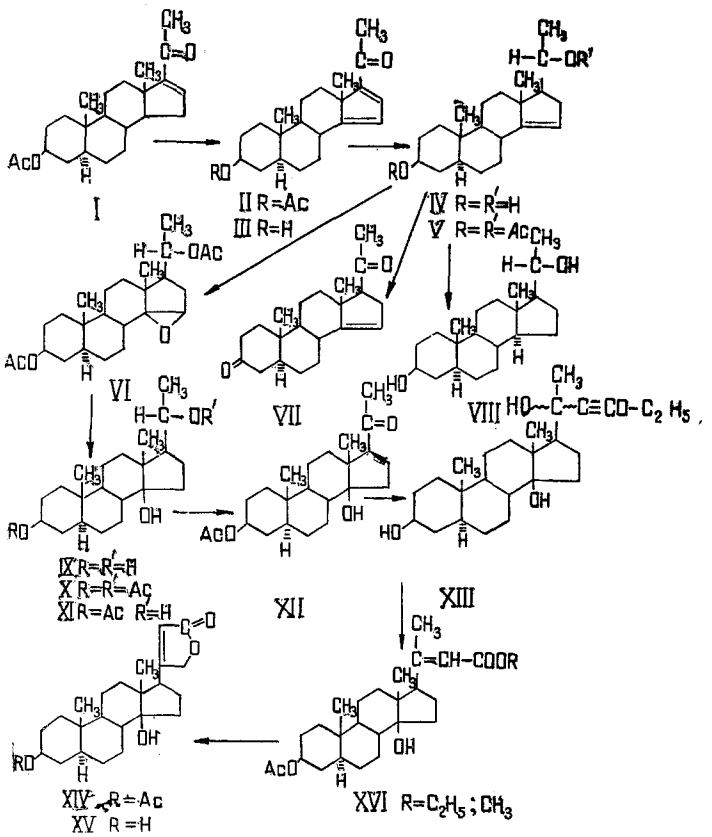
To open the oxide ring, the epoxide VI was reduced in absolute ether with lithium aluminum hydride. As expected, the IR spectrum of the reduction product had no absorption in the region of epoxide and ester groups. This type of reduction of 14β,15β-epoxysteroids leads to 14β-alcohols [17]. Consequently, compound (IX) is 5α-pregnan-3β,14β,20α-triol.

On acetylation with a large excess of acetic anhydride in pyridine, the triol IX gave the 3,20-diacetate (X). When the same triol was acetylated in pyridine with 2.5 moles of acetic anhydride, we obtained a mixture of the 3,20-diacetate (X) and a monoacetate (XI) which, according to the subsequent oxidation reaction, was the 3-monoacetate.

Oxidation of the monoacetate XI with chromic anhydride in glacial acetic acid led to 3β,14β-dihydroxy-5α-pregnan-20-one 3-acetate (XII) [10]. The fact that in compound XII the side chain has the 17β orientation is confirmed by the optical rotatory dispersion curve with a positive Cotton effect [18].

In order to effect the subsequent part of the synthesis, the construction of the lactone ring, it is necessary to extend the carbon side chain at C_{20}, for which purpose the hydroxy-5α-pregnanone acetate (XII) was converted into the ethoxyethynyl carbinol XIII.

Compound XIII could not be obtained by the reaction of the acetate XII with ethoxyethynylmagnesium bromide [1], but the ethoxyethynyllithium [19] that we used enabled this condensation to be carried out smoothly. The IR spectrum of XIII showed the absorption band at 2265 cm^{-1} characteristic for the $-C\equiv C-$ bond.



Rearrangement of the ethoxyethynyl carbinol (XIII), which takes place in the presence of sulfuric acid in aqueous methanol [2, 19], acetylation of the reaction product, and chromatographic purification led to the α,β-unsaturated ester (XVI). This compound crystallizes well, has a fairly sharp melting point, and on chromatography in various systems behaves as an individual substance. However, in the mass spectrum of XVI in addition to a peak with m/e 446, there is also a peak with m/e 432. This is apparently due to the fact that compound XVI is a mixture of the ethyl (mol. wt. 446) and methyl (mol. wt. 432) esters. The latter can obviously arise through trans esterification during the rearrangement of product XIII in methanol.

To close the lactone ring compound XVI was oxidized with selenium dioxide [2].

After purification by chromatography on silica gel, the reaction mixture yielded uzarigenin acetate (XIV). The constants of the uzarigenin acetate that we had synthesized agree with those of the acetate of the natural compound [20, 21]. Saponification of the acetate XIV with potassium bicarbonate in aqueous methanol gave uzarigenin (XV), completely identical with respect to its constants and spectral features with an authentic sample of uzarigenin [21, 22].

The experimental part of our work had been completed when a report of another synthesis of uzarigenin appeared in the literature. The authors concerned [23] started from 15α-hydroxycortexone obtained by microbiological synthesis.

EXPERIMENTAL

The mass spectra were taken on an MKh-1303 instrument fitted with a system for the direct introduction of the substance into the ion source, the IR spectra on a UR-20 spectrometer in potassium bromide, and the NMR spectra on a JNM-4H-100 instrument with HMDS as internal standard (δ scale). The solvents were distilled off in vacuo after drying over anhydrous Na_2SO_4. The molecular weights were determined by mass spectrometry. The found values of C and H corresponded to the calculated ones.

3β-Hydroxy-5α-pregna-14,16-dien-20-one Acetate (II) from I. A solution of 5.6 g of the acetate I in 280 ml of absolute carbon tetrachloride was treated with 4.2 g of N-bromosuccinimide. The reaction mixture was boiled in a water bath with electric illumination (300 W) for 50 min. At the end of the reaction the succinimide that deposited was filtered off, and the filtrate was washed with sodium carbonate solution and then with water, and then evaporated to dryness. A solution of the resulting crude bromide in 300 ml of acetone was treated with a solution of 16 g of sodium iodide in 250 ml of acetone. The reaction mixture was boiled in a water bath in an atmosphere of nitrogen for 1.5 h. The solvent was distilled off in vacuo and the residue was treated with a mixture of water and chloroform. The chloroform layer was washed with sodium hyposulfite solution and then with water and evaporated to dryness. The residue, after recrystallization from cyclohexane, yielded 5.41 g of a crystalline product consisting, as shown by chromatography in a fixed thin layer of silica gel [heptane–ethyl acetate (5 : 1)], of a mixture of I and II. Chromatography of the reaction product on SiO_2 [elution with heptane–ethyl acetate (10 : 1)] gave the pure diene (II). The yield of II was 54.7%, taking the unchanged I into account. The diene II had mp 180-183°C (acetone–methanol), $[\alpha]_D^{20}$ + 416.0° ± 2.5° (c 1.70, chloroform); $\lambda_{max}^{C_2H_5OH}$ 310 nm (log ε 4.15). Literature data for II: mp 181-182.5°C, $[\alpha]_D^{25}$ + 370 ± 1° (c 0.52, chloroform); λ_{max} 310 nm (log ε 4.15) [12].

3β-Hydroxy-5α-pregna-14,16-dien-20-one (III) from II. A solution of 300 mg of the acetate II in 50 ml of tertiary butanol was treated with 5 ml of a 10% aqueous solution of KOH. The reaction mixture was left for 3 days at room temperature in an atmosphere of nitrogen. Then it was diluted with water, neutralized, and extracted with chloroform. The chloroform extract yielded 160 mg of the hydroxypregnadienone (III) with mp 159-160.5°C (ethyl acetate), $[\alpha]_D^{21.5}$ + 439.5° ± 2.5° (c 1.25, chloroform); $\lambda_{max}^{C_2H_5OH}$ 310 nm (log ε 4.20). Literature data for III, mp 160-161.5°C, $[\alpha]_D^{25}$ + 421 ± 1° (c 0.568, chloroform); λ_{max} 310 nm (log ε 4.12) [12].

5α-Pregn-14-en-3β,20α-diol, $C_{21}H_{34}O_2$ (IV) from II. In small portions over 2 h, 11 g of metallic sodium was added to a solution of 2 g of II in 330 ml of absolute propanol heated to the boil. Then the reaction mixture was boiled for another 2 h, by which time the sodium had dissolved completely, after which it was cooled, diluted with a small amount of water, and neutralized with HCl. The solvent was distilled off, and the residue was recrystallized from ethyl acetate to give 0.98 g of the pregnenediol IV. Yield 54.9%. The substance had mp 184-185.5°C; $[\alpha]_D^{18}$ + 29.4 ± 1.5° (c 0.76, chloroform); $\lambda_{max}^{C_2H_5OH}$ 201 nm (log ε 3.89). IR spectrum, cm^{-1}: 3340-3420 (OH), 3080 (H in H–C=C–), and 1650 (H–C=C–). NMR spectrum (in C_5D_5N) 5.14 ppm (H at C_{15}). Mol. wt. 318.

5α-Pregn-14-ene-3,20-dione (VII) from IV. At −10°C, 1.1 ml of the oxidizing reagent (the solution for oxidation was prepared from 26.6 g of CrO_3, 23 ml of H_2SO_4, and 100 ml of H_2O) was added to 50 mg of the 5α-pregn-14-enediol (IV) in 16 ml of acetone [24]. The reaction mixture was stirred at the same temperature for 15 min. Then 17 ml of a 10% solution of sodium acetate was added, and the reaction product was extracted with ether. Distillation of the ether yielded 20 mg of the pregnenedione (VII) with mp 188-190°C (from acetone), $[\alpha]_D^{29}$ + 75.8 ± 3.5°) (c 0.53, chloroform). Literature data for VII, mp 186-187°C, $[\alpha]_D^{20}$ + 77° (c 0.928, chloroform) [13].

5α-Pregnane-3β,20α-diol (VIII) from IV. In 10 ml of glacial acetic acid, 69 mg of the pregnenediol IV was hydrogenated over 35 mg of platinum black for 3 h. After separation of the catalyst and distillation of the solvent, 45 mg of pregnanediol with mp 215-216°C (from acetone) was isolated; $[\alpha]_D^{18}$ + 21.4 ± 4.3° (c 0.72, chloroform). Literature data for VIII, mp 218-219°C, $[\alpha]_D$ + 23° (c 0.9) [14].

5α-Pregn-14-ene-3β,20α-diol 3,20-Diacetate, $C_{25}H_{38}O_4$ (V) from IV. The acetylation of 150 mg of the pregnenediol IV in 6 ml of pyridine with 3 ml of acetic anhydride at room temperature for 24 h gave 140 mg of the diacetate V. Yield 74%. The product had mp 153-155°C (acetone), $[\alpha]_D^{20}$ 15.2 ± 3.0° (c 0.99, chloroform); $\lambda_{max}^{C_2H_5OH}$ 201 nm (log ε 3.81); IR spectrum, cm^{-1}: 3070 (H in H−C=C−), 1655 (−C=C−), and 1745 (CO of an acetate); NMR spectrum (in $CDCl_3$) 5.09 ppm (H at C_{15}). Mol. wt. 402.

14β,15β-Epoxy-5α-pregnan-3β,20α-dio 3,20-Diacetate, $C_{25}H_{38}O_5$ (VI) from V. To 0.61 g of the diacetate V in 23.5 ml of dioxane and 2.2 ml of water were added 0.4 g of N-bromoacetamide and 0.23 ml of 4 N perchloric acid. The reaction mixture was left at room temperature for 30 min and then diluted with water; and the oily product that separated was extracted with chloroform. The chloroform extract was washed with water and evaporated to dryness. The residue was dissolved in 30 ml of absolute ethanol and treated with 1.17 g of fused potassium acetate, and the resulting mixture was boiled for 10 h. After this, it was diluted with water and extracted with chloroform. Distillation of the chloroform yielded 0.57 g of an amorphous substance which was chromatographed on silica gel. Elution with heptane−ethyl acetate (10:1) gave 0.23 g (yield 69%) of the epoxide (VI) with mp 132-133°C (from ethanol−water); $[\alpha]_D^{23}$ + 22.2 ± 3.7° (c 1.22, chloroform); IR spectrum, cm^{-1}: 885 and 3050 (epoxy group) and 1740 (CO of an acetate); NMR spectrum: 3.29 ppm (H at C_{15}). Mol. wt. 418.

5α-Pregnane-3β,14β,20α-triol, $C_{21}H_{36}O_3$ (IX) from VI. To a solution of 0.65 g of the epoxide (VI) in 230 ml of absolute ether was added 1.1 g of $LiAlH_4$ in 30 ml of ether and the reaction mixture was stirred at a gentle boil for 3 h. Then it was cooled with ice and the excess $LiAlH_4$ was decomposed with a solution of Rochelle salt. The precipitate that deposited was filtered off and washed with ether, and the filtrate was extracted with ether. The extract, after the evaporation of the solvent, yielded 0.47 g of triol (yield 90.0%) with mp 215-218°C (ethyl acetate), $[\alpha]_D^{19}$ + 3.6 ± 2.4° (c 1.00, chloroform); IR spectrum, cm^{-1}: 3200-3500 (OH). Mol. wt. 336.

5α-Pregnane-3β,14β,20α-triol 3,20-Diacetate, $C_{25}H_{40}O_5$ (X) from IX. Acetylation of 100 mg of the triol IX in 4 ml of pyridine with 4 ml of acetic anhydride for 24 h at 36-37°C yielded 100 mg (yield 77.5%) of the diacetate X with mp 130-132.5°C (from ethanol−water); $[\alpha]_D^{27}$ + 15.9 ± 1.8° (c 1.03, chloroform); IR spectrum, cm^{-1}: 3540 (OH), 1755 and 1730 (CO of an acetate). Mol. wt. 420.

5α-Pregnane-3β,14β,20α-triol 3-Monoacetate, $C_{23}H_{38}O_4$ (XI) and the Diacetate (X) from IX. A 400-mg quantity of the 5α-pregnanetriol (IX) was acetylated with 300 mg of acetic anhydride in 6.6 ml of pyridine at 36-37°C for 30 h. Then the reaction mixture was diluted with chloroform, and the chloroform solution was washed successively with dilute potassium bicarbonate solution, H_2SO_4, and water, and then evaporated to dryness. The residue consisted of 430 mg of a yellow, amorphous product. Chromatography of the reaction product in a thin layer of silica gel [benzene−methanol (20:1) system] showed the presence of two substances. The chromatographic separation of the reaction products on silica gel [elution with benzene−ethyl acetate (10:1)] allowed 110 mg of the diacetate X to be isolated from fractions 1-5, and from the subsequent fractions 280 mg (yield 60.0%) of the monoacetate XI with mp 191-193.5°C (acetone), $[\alpha]_D^{24}$ + 6.3 ± 3.0° (c 0.58, chloroform); spectrum, cm^{-1}: 3310-3430 (OH) and 1735 (CO of an acetate). Mol. wt. 378.

3β,14β-Dihydroxy-5α-pregnan-20-one 3-Acetate (XII) from XI. A solution of 200 mg of the monoacetate XI in 6 ml of glacial acetic acid was treated with 3.5 ml of a 2% solution of chromic anhydride in glacial acetic acid. The reaction mixture was left at room temperature for 24 h. The excess oxidizing agent was decomposed with an aqueous solution of sodium hyposulfite, and the solvent was distilled off to

dryness. The residue was treated with chloroform, and the chloroform solution was washed with dilute H_2SO_4 and then with water to neutrality, and the solvent was distilled off. The residue consisted of 180 mg (yield 90%) of compound XII with mp 174-176°C (from heptane); $[\alpha]_D^{28}$ 36.3 ± 1.3° (c 1.00, chloroform). Optical rotatory dispersion (dioxane, c 0.11); $[M]_{589}$ −380°, $[M]_{420}$ 0°, $[M]_{350}$ +440°, $[M]_{325}$ +2350°, $[M]_{312}$ +2450°, $[M]_{290}$ +400°, $[M]_{285}$ 0°, and $[M]_{275}$ −1700°. Literature data for XII, mp 172-174°C, $[\alpha]_D^{20}$ +36.5° (chloroform) [10].

20ξ-Ethoxyethynyl-5α-pregnane-3β,14β,20ξ-triol (XIII) from XII). With stirring, 0.56 ml (6.4 mmole) of freshly distilled ethoxyacetylene dissolved in a mixture of 5 ml of absolute ether and 20 ml of absolute tetrahydrofuran was added dropwise to a solution of 0.14 g (6.4 mmole) of methyllithium in 8 ml of absolute ether. To the resulting solution of lithium ethoxyacetylide was added 120 mg of 5α-pregnanone (XII) dissolved in 25 ml of absolute tetrahydrofuran. The reaction mixture was stirred at room temperature in an atmosphere of nitrogen for 17 h. Then ice water was added, and the reaction products were extracted with ether. The ethereal extract was washed with water and, after distillation, it yielded 135 mg of the carbinol (XIII) in the form of a yellow oil. Compound XIII was not purified for further treatment. IR spectrum, cm^{-1}: 3200-3550 (OH) and 2265 (−C≡C−).

Methyl and Ethyl 3β-Acetoxy-14β-hydroxy-5α-pregn-20(22)-en-23-oates (XVI) from XIII. A solution of 135 mg of the ethoxy carbinol (XIII) in 8 ml of methanol was treated with 2 ml of 2 N Na_2SO_4. After standing 1 h at room temperature, the reaction mixture was diluted with water and the reaction products were extracted with ether. Distillation of the ether yielded 120 mg of an oily substance which was acylated with 1 mg of acetic anhydride in 4 ml of pyridine at room temperature for 23 h. The acetylation product was chromatographed on a column of silica gel and was eluted with a mixture of benzene and ether (49 :1). This gave 70 mg of the unsaturated ester XVI with mp 150-155°C (from acetone), UV spectrum: $\lambda_{max}^{C_2H_5OH}$ 232 nm (log ε 4.18) (in calculating the extinction coefficient, it was assumed that XVI was the pure ethyl ester); IR spectrum, cm^{-1}: 3535 (OH), 1710 (CO of an acetate), and 1625 (—C=C—). Vibrations characteristic for the −C≡C− bond were absent. According to the mass spectrum, the compound obtained is a mixture of the methyl and ethyl esters, $C_{26}H_{40}O_5$ (mol. wt. 432) and $C_{27}H_{42}O_5$ (mol. wt. 446). Yield 49.0% (calculated on XII).

Uzarigenin Acetate (XIV) from XVI. To 63 mg of the α,β-unsaturated ester XVI in 60 ml of dry benzene was added 80 mg of freshly distilled selenium dioxide. The reaction mixture was boiled on a water bath for 40 h. The metallic selenium that precipitated and the unchanged selenium dioxide were separated off by filtration, the filtrate was poured into water, and the reaction product was extracted with benzene. The benzene extract was washed with water and distilled to dryness. After chromatography on silica gel [with benzene−ether (4 :1) as the eluent], 25 mg of crystalline uzarigenin acetate was obtained with mp 256-263°C (acetone−heptane), $[\alpha]_D^{26}$ +6.6 ± 2.0° (c 0.48, chloroform); $\lambda_{max}^{C_2H_5OH}$ 218 nm (log ε 4.1). The IR spectrum of the synthesized uzarigenin acetate was identical with that of an authentic sample. Yield 43%. Literature data for uzarigenin acetate, mp 256-264°C, $[\alpha]_D$ +6.3° [20]; mp 266-272°C, $[\alpha]_D$ +5.6° [21].

Uzarigenin (XV) from XIV. A solution of 100 mg of potassium bicarbonate in 5.5 ml of water was added to a solution of 12 mg of uzarigenin acetate (XIV) in 12 ml of methanol. The reaction mixture was left at room temperature for 3 days, after which the methanolic solution was diluted with chloroform, washed with water, and evaporated to dryness. Recrystallization of the residue from acetone−heptane gave 8.4 mg of uzarigenin (XV) with mp 225-240°C, $[\alpha]_D^{20}$ +12.6 ± 2.3° (c 0.65, ethanol). The IR spectrum of XV and also its R_f values in a thin layer and on a paper chromatogram in several systems were identical with the corresponding indices for an authentic sample. Yield 79.2% calculated on the XIV. Literature data for uzarigenin, mp 230-246°C, $[\alpha]_D$ +14.0° [22]; mp 240-256°C, $[\alpha]_D$ +10.5° [21].

CONCLUSIONS

The aglycone uzarigenin has been synthesized from 3β-hydroxy-5α-pregn-16-en-20-one acetate.

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