TRANSFORMED STEROIDS

COMMUNICATION 31. SYNTHESIS OF MODEL 20α , 21- AND 20β , 21-DIACETATES OF Δ^4 -ISOPREGNENE- 17β , 20ξ , 21-TRIOL-3-ONES IN ORDER TO ESTABLISH THE CONFIGURATION OF THE C-20 EPIMERIC Δ^4 -ISOPREGNENE- 17β , 20ξ -DIOL-3-ON-21-OIC ACIDS

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One of the very complex problems in the stereochemistry of steroids of the pregnane series is the determination of the configuration of the 20-carbon center. Previously we had described the synthesis of the C-20 epimeric Δ^4 -isopregnene-17 β ,20 ξ -diol-3-on-21-oic acids (Ia, b) and had established their stereo-chemistry via conversion by a series of reactions, not involving the asymmetric center, to the known 20α , 21-(IIa) and 20β ,21-diacetates (IIb) of the Δ^4 -isopregnene- 17β ,20 ξ ,21-triol-3-ones [1].



It should be mentioned that the stereochemistry of the 20-center in diacetates (IIa) and (IIb) was assigned arbitrarily by Reichstein [2, 3]. L. Fieser and M. Fieser [4], who made an analysis of methods for the preparation of 20-hydroxy compounds, proposed a method for assigning the configuration of the C-20 center. The configuration assigned by them to the indicated center coincided with the configuration adopted in [2, 3]. The authors of [4] attempted to corroborate the configuration of the C-20 hydroxy group on the basis of analyzing the increments of the angles of rotation for the C-20 acetates. However, in [5] it was shown that the increments of the angles of rotation of C-20 of the acetoxy compounds for the isopregnane series do not coincide with the standard values for the natural series, and consequently the assigned configuration at C-20 in the isopregnane series requires additional proof.



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Diacetates (IIa) and (IIb) can serve as convenient model compounds in solving the indicated stereochemical problems. The scheme for the synthesis of these compounds, proposed earlier in [2], gives low yields of the reaction products in the separate intermediate steps. The key moment in this synthesis is the chromatographic separation of the C-20 epimeric 3β , 20ξ , 21-triacetates of the Δ^5 -isopregnene- 3β , 17β , 20ξ , 21tetrols, which could not be effected on Al₂O₃ and other adsorbents (SiO₂ and florisil). This caused us to develop a new scheme for the synthesis of diacetates (IIa, b).

The first step in the synthesis of diacetates (IIa, b) is a partial hydrogenation of the triple bond in 17α -ethynyl- Δ^5 -androstene- 3β ,17 β -diol (III), and also in its 3-monoacetate (IV), in the presence of palladium catalyst deposited on calcium carbonate [6, 7]. Here we obtained $\Delta^{5,20}$ -isopregnadiene- 3β ,17 β -diol (VI) and its acetate (V). We found that better results are obtained if this reaction is run with acetate (IV) in ethanol. The use of an efficient method [8] for the hydroxylation of the side-chain double bond in (V) made it possible to greatly simplify the workup and obtain a mixture of the epimeric 3β -acetates of Δ^5 -isopregnene- 3β ,17 β ,20 ξ ,21-tetrols (VII) in high yield. The treatment of the mixed tetrols (VII) with acetone in the presence of perchloric acid as the catalyst gave a mixture of acetonides (VIIIa, b), which could be separated on aluminum oxide. It should be mentioned that hydrolysis of the 3β -acetoxy group is observed during the separation on Al₂O₃. The preparative method developed by us for the separation of the C-20 epimeric acetonides (VIIIa, b) made these model compounds readily available for the purpose of studying the stereochemistry of the C-20 center.

The oxidation of acetonides (VIIIa) and (VIIIb) with aluminum isopropylate by the Oppenauer method [2] gave the 3-ketones (IXa) and (IXb), in which the presence of the 3-keto- Δ^4 -grouping was corroborated by the UV spectra.

 Δ^4 -Isopregnene-17 β , 20 α , 21-triol-3-one (Xa) and Δ^4 -isopregnene-17 β , 20 β , 21-triol-3-one (Xb) were obtained by the hydrolysis of the acetonide protection in acetonides (IXa) and (IXb), by heating them under reflux in acetic acid solution. The acetylation of triolones (Xa) and (Xb) with acetic anhydride in pyridine gave the 20 α , 21-(IIa) and 20 β , 21-(IIb)-diacetates of the triolones, the constants of which coincided with the literature data [2].

The structure of all of the obtained products was corroborated by the IR and UV spectra, and also by the proton magnetic resonance (PMR) spectra.

EXPERIMENTAL

All of the melting points were determined on a Koffler block; the UV spectra were taken on an EPS-2 spectrometer; the IR spectra were taken on a UR-10 spectrometer, and the PMR spectra were taken on an INM-4H-100 spectrometer with an operating frequency of 100 MHz, using hexamethyldisiloxane as the internal standard. The adsorbents used for chromatographing were silica gel KSK, $6-24 \mu$ mesh, freed of

traces of iron, and Al_2O_3 , prepared as described in [9]. The detection of the compounds was done on plates containing SiO₂ by spraying with H_2SO_4 , and on Al_2O_3 using UV light.

<u>17α-Ethynyl-Δ⁵-androstene-3β</u>, 17β-diol 3-Acetate (IV). We acetylated 10 g of diol (III), with mp 246-248°, with 10 ml of Ac₂O in 100 ml of pyridine at room temperature. We obtained 8.5 g of crystals with mp 175-176°, R_f 0.72, on SiO₂, in the system cyclohexane – ethyl acetate (2:1); $[\alpha]_D^{24}$ -103.8 (C 1.196, dioxane).

 $\frac{3\beta-\text{Acetoxy}-\Delta^{5,20}-\text{isopregnadiene}-3\beta,17\beta-\text{diol}(V)$. A suspension of 70 mg of Pd/CaCO₃ (~7%) in 10 ml of absolute ethanol was saturated with hydrogen, after which a solution of 1 g of (IV) in 40 ml of absolute ethanol was added (hydrogen ~70 ml). The reaction mixture was filtered, the catalyst was washed with ethanol, the filtrate was evaporated, and the residue was dissolved in ether, washed with dilute HCl solution, water, NaHCO₃ solution, and again with water, dried over MgSO₄, and evaporated. We obtained 820 mg of crystalline residue with mp 130°. After two recrystallizations from methanol, mp 157–159°. When recrystallized from hexane, mp 159–161°; Rf 0.74, on SiO₂, in the system cyclohexane – ethyl acetate (2:1); $[\alpha]_D^{19} -50.2^\circ$ (C 1.01, acetone); ν , cm⁻¹: 1640, 1670, 1735, 3440, and 3475 (KBr).

 $\Delta^{5,20}$ -Isopregnadiene- 3β , 17β -diol (VI). A suspension of 50 mg of Pd/CaCO₃ (~7%) in 10 ml of pyridine was saturated with hydrogen, after which a solution of 1 g of (III), mp 246-248°, in 20 ml of pyridine and 1 ml of piperidine was added, and the mixture was hydrogenated at room temperature until the calculated amount of hydrogen had been absorbed. The catalyst was filtered and washed with methanol. The filtrate was evaporated, and the residue was dissolved in ether and the solution was washed in succession with dilute HCl solution, water, NaHCO₃ solution and water, after which it was dried over MgSO₄ and evaporated. We obtained 0.98 g of crystals (VI) with mp 174-175°. Recrystallization from methanol gave 720 mg of compound with mp 183-184.5°, $[\alpha]_{\rm D}^{24}$ -68.8° (C 0.95, dioxane).

 $\frac{3\beta-\text{Acetoxy}-\Delta^{5,20}-\text{isopregnadiene}-3\beta,17\beta-\text{diol}(V)}{2}$. To a solution of 9 g of (VI), mp 181-184°, in 90 ml of pyridine was added 45 ml of acetic anhydride and the mixture was allowed to stand overnight. The next day the reaction mixture was heated 2 h at 60°, after which it was evaporated, and the residue was dissolved in ether, washed in succession with dilute HCl solution, water, NaHCO₃ solution and water, dried over MgSO₄, and evaporated. We obtained 9.32 g of crystalline precipitate with mp 153-156°. Recrystallization from hexane gave 8.15 g of (V) with mp 161-163°; $[\alpha]_D^{19}$ -50.2° (C 1.009, acetone); Rf 0.74, on SiO₂, in the system cyclohexane – ethyl acetate (2:1). Found: C 77.15; H 9.40%. C₃₂H₃₄O₃. Calculated: C 77.10; H 9.50%.

Hydroxylation of $\Delta^{5,20}$ -Isopregnadiene- 3β ,17 β -diol 3-Acetate (V). To a solution of 5 g of (V), mp 161-163°, in 100 ml of pyridine was added 5 g of OsO₄ and the mixture was allowed to stand at room temperature for 48 h, after which were added a solution of 44 g of K₂S₂O₅ in 180 ml of water and 100 ml of pyridine, and the mixture was stirred for 30 min. Then the mixture was filtered and extracted with CHCl₃. The filtrate was washed well in succession with dilute HCl solution, water, NaHCO₃ solution and water, dried over MgSO₄, and evaporated. We obtained 5.14 g of crystalline (VII), which represented a C-20 epimeric mixture of the tetrols with mp 210-220°; R_f 0.26, on SiO₂, in the system cyclohexane – ethyl acetate (2:1).

 $\frac{20\alpha, 21-(\text{VIIIa})}{\text{of the mixed tetrols in 250 ml of acetone was added 15 drops of HClO₄ (~70%) and the mixture was allowed to stand at room temperature for 48 h. Then the reaction mixture was diluted with water, extracted with CHCl₃, washed with water, dried over MgSO₄, and evaporated. We obtained 3.45 g of oily product, 1 g of which was chromatographed on 60 g of Al₂O₃ (II activity). The fractions were taken as 25 ml aliquots, and the flow rate was approximately 100 ml/h. The gradient elution was done with a mixture (2 liters) ranging from hexane – ether (7:3) to hexane – ether (1:3). From fractions 69-90 we obtained 200 mg of (VIIIb). From fractions 91-116 we obtained 120 mg of mixed (VIIIa) and (VIIIb). From fractions 117-151 we obtained 510 mg of (VIIIa).$

 $\frac{20\beta,21-\text{Acetonide (VIIIb)}}{(1100)}$ Recrystallization from ether – hexane gave (VIIIb) with mp 162-164° (it melted initially at 130°, after which needles crystallized from the melt, which then melted at 162-164°); Rf 0.27, on Al₂O₃ (II activity), in the system hexane – wet ether (1:3); Rf 0.67, on SiO₂, in the system hexane – ether (1:4), detected with iodine vapors; $[\alpha]_D^{24}$ –53.5° (C 0.812, acetone); δ , ppm: 0.81 (CH₃ –18); 0.94 (CH₃ –19); 5.26 (H at E); 4.23 (H – C₂₀); 3.90 (2H – C₂₁). Found: C 73.52; H 10.01%. C₂₄H₃₈O₄. Calculated: C 73.84; H 9.74%. The mixed melting point with $20\alpha,21$ -acetonide (VIIIa) was 125-137°. From [2]: mp 157°, $[\alpha]_D^{13}$ –62.7°.

 $20\alpha, 21$ -Acetonide (VIIIa). Recrystallization from ether – hexane gave (VIIIa) with mp 162–164° (the crystals melted initially at 100°, after which needles crystallized from the melt, which then melted at 162–164°); R_f 0.20, on Al₂O₃ (II activity), in the system cyclohexane – ethyl acetate (2:1), R_f 0.18, on Al₂O₃ (II activity), in the system hexane – wet ether (1:3); R_f 0.62, on SiO₂, in the system hexane – ether (1:4), detected with iodine vapors; $[\alpha]_D^{19}$ –59.4° (C 1.054, acetone). δ , ppm: 0.80 (CH₃–18); 0.95 (CH₃–19); 5.27 (H at E); 4.11 (H – C₂₀); 3.88 (2H – C₂₁). Found: C 73.69; H 9.75%. C₂₄H₃₈O₄. Calculated: C 73.84; H 9.74%. The mixed melting point with $20\beta, 21$ -acetonide (VIIIb) was 125–137°. From [2]; mp 160°; $[\alpha]_D^{15}$ –59°.

Oppenauer Oxidation of 20α , 21-Acetonide (VIIIa). A mixture of 600 mg of 20α , 21-acetonide (VIIIa) with mp 162-164°, 18 ml of anhydrous acetone, 50 ml of absolute benzene and 1.5 g of aluminum isopropylate was heated under reflux for 24 h. Then the mixture was evaporated in vacuo and the residue was dissolved in ether, washed with conc. potassium sodium tartrate solution, sodium carbonate solution and finally with water, dried over MgSO₄, and evaporated. We obtained 600 mg of an oily product, which was chromatographed on 25 g of Al₂O₃ (II activity). The fractions were taken as 25-ml aliquots, and the flow rate was approximately 40 ml/h. The gradient elution was done with 2 liters of hexane – ether mixture (ranging from 5 to 50% ether). From fractions 6-23 was obtained 300 mg of (IXa). From fractions 24-26 was obtained 60 mg of a mixture of (VIIIa) and (IXa). From fractions 27-33 was obtained 30 mg of (VIIIa). The recrystallization of 300 mg of (IXa), with Rf 0.33, on Al₂O₃ (II activity), in the system cyclohexane – ethyl acetate (2:1), from ether – hexane gave a product with mp 171-173°; $[\alpha]_D^{24} + 33.9°$ (C 0.916, acetone); λ_{max} 240 nm, ϵ 16,000 (ethanol). δ , ppm: 0.86 (CH₃ - 18); 1.12 (CH₃ - 19); 5.68 (H at \pm); 4.14 (H - C₂₀); 3.95 (2H - C₂₁). Found: C 74.22; H 9.28%. C₂₄H₃₆O₄. Calculated: C 74.19; H 9.34%. From [2]: mp 173-175°; $[\alpha]_1^{17} + 39.3°$.

Oppenauer Oxidation of 20β ,21-Acetonide (VIIIb). Using the procedure described above for (VIIIa), we oxidized 100 mg of 20β ,21-acetonide (VIIIb) with mp 162-164°. The obtained product was chromatographed on a plate (13 × 18) on Al₂O₃ (II activity), with a layer thickness of 1.5 mm, in the system cyclohexane – ethyl acetate (2:1). We obtained 51 mg of (IXb) with mp 215-220°. After recrystallization from ether – hexane: mp 220-221°; $[\alpha]_D^{24}$ +86.4° (C 1.005, acetone); λ_{max} 240 nm; ϵ 16,200; δ , ppm: 0.84 (CH₃-18); 1.12 (CH₃-19); 5.67 (H at E); 4.18 (H - C₂₀); 3.91 (2H - C₂₁). Found: C 74.02; H 9.20%. C₂₄H₃₆O₄. Calculated: C 74.19; H 9.34%. From [2]: mp 220-221.5°; $[\alpha]_D^{15}$ +66.7°.

 $\frac{\Delta^4 - \text{Isopregnene} - 17\beta, 20\alpha, 21 - \text{triol} - 3 - \text{one (Xa)}.$ To a solution of 500 mg of (IXa), with mp 171-173°, in 40 ml of CH₃COOH was added 10 ml of water and the mixture was heated at 70° for 1 h. Then 10 ml of water was added and the mixture was heated for another hour. The mixture was evaporated to dryness and the residue was recrystallized from methanol – ether. We obtained 372 mg of (Xa) with mp 230-233°; $[\alpha]_D^{24}$ +50° (C 0.394, dioxane); λ_{max} 242 nm, ε 11,200 (ethanol); δ , ppm: 0.89 (CH₃-18); 0.99 (CH₃-19); 5.65 (H at E); 4.30, (H - C₂₀).

 $\frac{\Delta^4 - \text{Isopregnene} - 17\beta, 20\beta, 21 - \text{triol} - 3 - \text{one (Xb)}}{(\text{IXb}), \text{ with mp } 220 - 221^\circ, \text{ was obtained } 80 \text{ mg of (Xb) with mp } 235 - 238^\circ \text{ (methanol); } [\alpha]_D^{24} + 51^\circ \text{ (C } 0.269, \text{ dioxane}); \nu, \text{ cm}^{-1}: 1620, 1662, 3435, \text{ and } 3560 \text{ (KBr)}; \lambda_{\text{max}} 242 \text{ nm}, 13,600 \text{ (ethanol)}; \delta, \text{ ppm: } 0.89 \text{ (CH}_3 - 18); 0.93 \text{ (CH}_3 - 19); 5.65 \text{ (H at L}); 3.99 \text{ (H - C}_{20}).$

 $\frac{\Delta^4 - \text{Isopregnene} - 17\beta, 20\alpha, 21 - \text{triol} - 3 - \text{one } 20\alpha, 21 - \text{Diacetate (IIa)}. \text{ To a solution of 300 mg of (Xa) in 4} \\ \text{ml of absolute pyridine was added 1 ml of Ac_2O. The solution was allowed to stand overnight at room temperature, after which it was heated at 60° for 1 h. Then the mixture was evaporated in vacuo to dryness, and the residue was dissolved in ether, washed in succession with dilute HCl solution, water, NaHCO₃ solution and water, dried over MgSO₄, and evaporated. The residue was chromatographed on Al_2O₃ (II activity) on a plate (20 × 25), with a layer thickness of 2 mm, in the system cyclohexane – ethyl acetate (1:2). We obtained 260 mg of diacetate (IIa) with mp 175-178°. After recrystallization from ether – hexane, mp 180-181°, Rf 0.78, in the system: wet ether, Rf 0.30, in the system: cyclohexane – ethyl acetate (1:1), on Al_2O_3 (III activity); <math display="inline">[\alpha]_D^{20}$ +45.3° (C 0.998, acetone); ν , cm⁻¹: 1620, 1680, 1740, and 3430 (KBr); λ_{max} 240 nm, ϵ 20,500 (ethanol); δ , ppm: 0.83 (CH₃ – 18); 1.12 (CH₃ – 19); 5.64 (H at E); 5.12 (H - C₂₀); 4.15, 4.54 (2H - C₂₁). Found: C 69.28; H 8.30%. C₂₅H₃₆O₅. Calculated: C 69.44; H 8.33%. Literature data: mp 180-181°; $[\alpha]_D^{15}$ +50.2° [2].

 Δ^4 -Isopregnene-17 β , 20 β , 21-triol-3-one 20 β , 21-Diacetate (IIb). The acetylation of 100 mg of (Xb), as described above for (IIa), gave 95 mg of crystalline (IIb) with mp 159-162°. After recrystallization from ether – hexane, mp 162-164°; R_f 0.52, in the system: wet ether; R_f 0.39, in the system cyclohexane – ethyl acetate (1:1), on Al₂O₃ (III activity); $[\alpha]_D^{20}$ +18.5° (C 1,899, acetone); ν , cm⁻¹: 1620, 1660, 1740, and 3380

(KBr); λ_{max} 240 nm, ϵ 20,500 (ethanol); δ , ppm: 0.86 (CH₃ - 18); 1.09 (CH₃ - 19); 5.66 (H at E); 5.08 (H - C₂₀); 4.05, 4.58 (2H - C₂₁). Found: C69.38; H 8.46%. C₂₅H₃₆O₅. Calculated: C69.44; H 8.33%. From [2]: mp 165-166°; $[\alpha]_{D}^{15}$ +21.6°.

CONCLUSIONS

1. A method was developed for the synthesis of the difficultly accessible, epimeric at the 20-carbon center, 20α , 21- and 20β , 21-diacetates of the Δ^4 -isopregnene- 17β , 20ξ , 21-triol-3-ones.

2. Conditions were selected for the preparative separation of the C-20 epimeric acetonides of Δ^5 isopregnene-3 β ,17 β ,20 ξ ,21-tetrol, and also of the acetonides of Δ^4 -isopregnene-17 β ,20 ξ ,21-triol-3-one.

3. The structure of all of the synthesized compounds was confirmed by chemical and physical methods.

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