SYNTHESIS AND TRANSFORMATIONS OF 3α-HYDROXY-5α-ANDROST-11-EN-17-ONE

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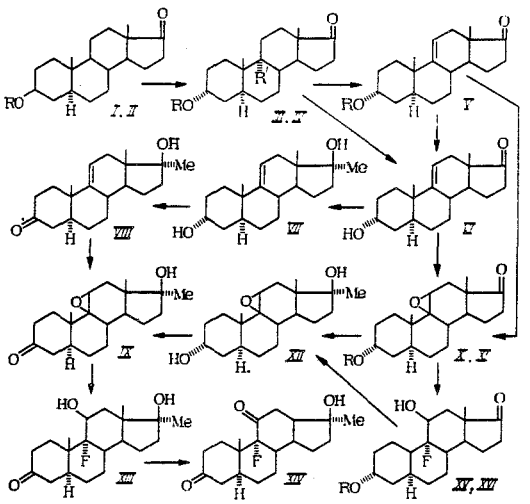
We described in our preceding communication the synthesis, based on tigogenin, of 9,11-unsaturated steroid compounds of the 5α-pregnane series by intramolecular radical 9-chlorination using the Breslow method [7, 11].

In the present work, we synthesized in a similar way 3α-hydroxy-5α-androst-9(11)-en-17-one (VI) from 3β-acetoxy-5α-androstan-17-one (I), which is also a transformation product of tigogenin [3], and studied the subsequent conversion of VI into 11β,17β-dihydroxy-17α-methyl-9α-fluoro-5α-androstan-3-one (XIII) and 17β-hydroxy-17α-methyl-9α-fluoro-5α-androstane-3,11-dione (XIV), which have androgenic and anabolic properties [4, 8]. Compound XIII is a saturated analog of the known anabolic fluoxymesterone [13].



R=H (I, III, V, XII, XIII); Ac (I); COC_6H_4I-м (III-V, XI, XIV)
R'=H (III), Cl (IV)

We have previously reported on the nonenzymatic synthesis of the unsaturated alcohol VI from acetal I [1]. The corresponding alcohol (II), obtained by hydrolysis of the acetate by the Mitsunobu method [16], was converted into m-iodobenzoate (III), the radical chlorination of which by means of $PhICl_2$ with irradiation led to chloride (IV). In an alkaline medium, this chloride undergoes dehydrochlorination and simultaneously hydrolysis to form the unsaturated alcohol VI. When chloride IV is deposited on silica gel, only its dehydrochlorination takes place with the formation of the unsaturated m-iodobenzoate (V), the benzoate group of which can subsequently be used as a protecting agent. The subsequent alkaline hydrolysis of V leads to the unsaturated alcohol VI.

Transformation of the unsaturated alcohol VI into the desired compounds XIII and XIV was carried out using 17α-methylation, followed by modification of rings A and C and also by preliminary introduction of fluorine into the 9α-position. The first of these paths was found to be preferable.

Thus, the unsaturated ketone (VIII) was synthesized by the reaction of VI with MeMgBr in ether, followed by oxidation according to Jones of the diol (VII) formed. Further treatment of ketone VIII with 1,3-dibromo-5,6-dimethylhydantoin (dibromantin) in the presence of

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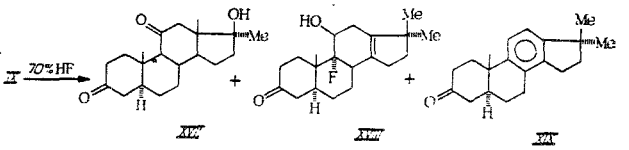
$HClO_4$ gave a bromohydrin, dehydrobromination of which without isolation led to epoxide (IX) in an overall yield of 55% (based on VI). By direct treatment of the unsaturated ketone VI with dibromantin in the presence of $HClO_4$, followed by dehydrobromination of the bromohydrin formed, epoxide (X) was obtained with an admixture of 9β,11-epoxy-5α-androstan-3,17-dione as a product of oxidation by dibromantin. Under the same conditions using m-iodobenzoate V, epoxide (XI) was obtained. The reaction of epoxide X with MeMgBr, followed by oxidation of the diol (XII) formed according to Jones led to epoxide IX, the overall yield of which was 35%, based on VI.

The opening of epoxide IX to give fluorohydrin was initially carried out using 70% HF. However, under these conditions a complex mixture is formed, from which, in addition to diketone (XVII) as a product of a known acidic rearrangement of epoxides into ketones [14], fluorohydrin (XVIII) and aromatic ketone (XIX) were isolated as products of the Wagner–Meerwein rearrangement and the subsequent aromatization.



The presence of the $M^+-CH_2=CMe_2$ fragment in the mass spectra of XVIII and XIX confirms the existence of two geminal methyl groups at the 17-position. In the PMR spectrum, these methyl groups appear with the same (δ 0.97 ppm for (XVIII) or similar (δ 1.24 and 1.25 ppm for XIX) values of the chemical shifts. In the case of compound XIX, the signals are shifted to the weak field region due to the anisotropy of the aromatic C-ring. The proton signals of the aromatic ring are observed in the form of two doublets at δ 6.95 and 7.18 ppm (J 8 Hz). The presence in the ^{13}C NMR spectrum of ketone XIX (obtained in a regime suppressing the interaction with protons) of six signals of carbon atoms in the δ 119.4-149.9 ppm range confirms the existence of the aromatic ring. The presence in the ^{13}C NMR spectrum of ketone XVII of two signals at δ 210.5 and 211.3 ppm confirms the presence of two carbonyl groups.

The opening of epoxide IX by the complex of hydrogen fluoride with pyridine proceeded smoothly, and the desired fluorohydrin XIII was obtained in 72% yield. Its subsequent oxidation according to Jones led to diketone XIV. Fluorohydrins XV and XVI were obtained in a similar way from epoxides X and XI, respectively.

In the reaction of fluorohydrins XV and XVI with MeMgBr, a cyclization occurred unexpectedly with the formation of epoxide X. Fluoroorganic compounds are the least reactive halogen derivatives, since because of the high electronegativity of the fluorine atom, the C–F bond is fairly strong [9]. Nevertheless, fluorohydrins can be transformed into epoxides by the action of alkalies [2]. However, we do not know of a similar transformation by the action of a Grignard reagent, which was not taken into account even in the Breslow patent [7], where a similar reaction is proposed.

Thus, steroid fluorohydrins XIII and XIV, having anabolic and androgenic properties were obtained from tigogenin by a conventional chemical synthesis, without having recourse to microbiological oxidation.

EXPERIMENTAL

The course of the reactions was monitored by means of thin layer chromatography on Silufol plates. The melting points were determined on a "Boetius" heating stage (GDR). The optical rotation was measured in chloroform (c 1). The IR spectra were run on a "Perkin-Elmer 599" spectrophotometer (USA) in mineral oil, the NMR spectra on a XL-200 spectrometer ("Varian," Switzerland) in $CDCl_3$ with TMS as internal standard, and the mass spectra on a MAT-112 spectrometer ("Varian," GFR).

3β-Hydroxy-5α-androstan-17-one (II) is obtained by boiling acetate I with a 5% solution of KOH in methanol. Yield 95%, mp 173-176°C. According to the literature data [15], mp 172-174°C.

3α-m-Iodobenzoyloxy-5α-androstan-17-one (III). A solution of 18.3 g (105 mmoles) of $(NCOOEt)_2$ in 50 ml of tetrahydrofuran is added to a solution of 20.5 g (70 mmoles) of alcohol II, 17.5 g (70 mmoles) of m-iodobenzoic acid and 27.5 g (104 mmoles) of Ph_3P in 300 ml of

tetrahydrofuran distilled over $LiAlH_4$. The reaction mixture is stirred under N_2 for 4 h, and then the solvent is removed in vacuo, and the residue is treated with 50 ml of ether. The precipitate that separates is filtered, and 2.5 g of $(NHCOOEt)_2$, mp 137-138°C are obtained. The filtrate is held in a refrigerator overnight, and the precipitate is separated to yield 13 g of Ph_3PO. The mother liquor after separation of Ph_3PO is evaporated in vacuo, the oily precipitate is dissolved in benzene and the solution is held for 2 h at 0-5°C. The precipitate that separates is filtered and 26 g of m-iodobenzoate III are obtained. An additional amount of III is obtained from the mother liquor by chromatography on silica gel; overall yield 85.7%, mp 138-139°C (MeOH), $[\alpha]_D^{20}$ +58.29°. IR spectrum, ν_{max}, cm^{-1}: 1710, 1730 (C=O), the absorption of the OH group is absent. Mass spectrum, m/z: 520 (M^+), 272 ($M^+ - C_6H_4COOH$).

3α-m-Iodobenzoyloxy-9α-chloro-5α-androstan-17-one (IV). A solution of 5 g (9.26 mmoles) of m-iodobenzoate III and 3.5 g (12.7 mmoles) of $PhICl_2$ in 300 ml of CH_2Cl_2 is irradiated under N_2 at 10-15°C for 45 min with an incandescent lamp at 300 W, at a distance of 5 cm. The reaction mixture is washed with 5% solution of Na_2SO_3, the residue after the removal of the solvent is treated with 20 ml of ether, and the ether solution is held for 2 h at 0-5°C. The precipitate that separates is filtered to yield 4.45 g of chloride IV, yield 84%, mp 175-178°C, $[\alpha]_D^{20}$ +43°. Mass spectrum, m/z: 518 ($M^+ - HCl$), 270 ($M^+ - HCl - IC_6H_4COOH$).

3α-m-Iodobenzoyloxy-5α-androst-9(11)-en-17-one (V). A solution of 7.1 g of chloride IV in 100 ml of CH_2Cl_2 containing 0.5 ml of pyridine is stirred with 35 g of silica gel at 30-35°C for 3 h. The silica gel is then filtered and washed with 200 ml of CH_2Cl_2. The combined filtrate is evaporated in vacuo and the residue is treated with hexane. The precipitate that separates is filtered to give 5.9 g of the unsaturated m-iodobenzoate V, yield 90%, mp 141-142°C, $[\alpha]_D^{20}$ +112.7°. IR spectrum, ν_{max}, cm^{-1}: 1710, 1740 (C=O). PMR spectrum, δ, ppm: 0.84 s (3H, 18-CH_3), 0.99 s (3H, 19-CH_3), 5.27 m (3-H), 5.4 m (11-H).

3α-Hydroxy-5α-androst-9(11)-en-17-one (VI). A 50 ml portion of a 15% methanolic solution of KOH is added to a solution of 4.3 g of chloride IV in 20 ml of dioxane, the reaction mixture is boiled for 1.5 h under N_2, and then evaporated to half its volume and diluted with 30 ml of water. The precipitate that separates is filtered and washed with water. Yield 2.12 g (95% of the unsaturated alcohol VI), mp 186-189°C (acetone–hexane). According to the literature data [12], mp 187-189°C.

Compound VI is obtained in a similar way from 1 g of the unsaturated m-iodobenzoate V, yield 0.52 g (95%), mp 186-189°C.

17α-Methyl-5α-androst-9(11)-ene-3α,17β-diol (VII). A solution of 4 g (13.9 mmoles) of ketone VI in 100 ml of benzene is added at 0-5°C, under N_2 to a Grignard reagent prepared from 155 mmoles of MeMgBr in ether. The reaction mixture is stirred for 1 h at 20-25°C, poured into a NH_4Cl solution, and diol VII is isolated in 83% yield, mp 182-184°C (acetone). IR spectrum ν_{max}, cm^{-1}: 3320, 3370 (OH). PMR spectrum, δ, ppm: 0.797 s (3H, 18-CH_3), 1.22 s (3H, 19-CH_3), 1.52 s (3H, 17-CH_3), 4.05 m (3-H), 5.39 (11-H). Mass spectrum, m/z: 304 (M^+), 286 ($M^+ - H_2O$).

17β-Hydroxy-17α-methyl-5α-androst-9(11)-en-3-one (VIII). A solution of 3.5 g of alcohol VII in 110 ml of acetone is treated at 0-5°C with 6.5 ml of the Jones reagent. After 20 min, the reaction mixture is poured into water, and the precipitate that separates is filtered off. The yield of ketone VIII is 3 g (88%), mp 198-199°C (acetone). According to the literature data [5], mp 196-198°C (acetone).

17β-Hydroxy-17α-methyl-9β,11-epoxy-5α-androstan-3-one (IX). A. A 1.68 g portion of dibromantin is added at 0-6°C, in the course of 20 min, to a suspension of 2.5 g of unsaturated ketone VIII in a mixture of 170 ml of acetone, 2 ml of water, and 1.4 ml of a 10% solution of $HClO_4$. The reaction mixture is stirred for another 20 min and treated with a 10% solution of Na_2SO_3 to the disappearance of the yellow color. Then, 170 ml of MeOH and 22 ml of a methanolic 10% solution of NaOH are added. After stirring at 0-5°C under N_2 for 1.5 h, the reaction mixture is neutralized with AcOH, one half of the solvent is evaporated, and the residue is diluted with water. The precipitate that separates is filtered, and after recrystallization from acetone, 1.97 g (75%) of epoxide IX are obtained, mp 209-212°C. According to the literature data [5], mp 205-207°C (acetone).

B. A 0.1 ml portion of Jones reagent is added at 0-5°C to a solution of 50 mg of alcohol X in 5 ml of acetone. The reaction mixture is stirred for 20 min, treated with water, and extracted with CH_2Cl_2. From the extract, 35 mg of epoxide IX are isolated, yield 76%, mp 205-209°C (acetone).

3α-Hydroxy-9β,11-epoxy-5α-androstan-17-one (X). Epoxide X is obtained from the unsaturated ketone VI under the conditions of the conversion of VIII into epoxide IX. The compound is purified by crystallization from acetone, mp 223-226°C. IR spectrum, ν_{max}, cm^{-1}: 3480 (OH), 1720 (C=O), 860 (-O-). PMR spectrum, δ, ppm: 0.975 s (18=CH_3), 1.05 s (19=CH_3), 3.52 m (11=H), 4.06 m (3=H). Mass spectrum, m/z: 304 (M^+), 289 ($M^+ - CH_3$), 286 ($M^+ - H_2O$). From the mother liquor, an additional amount of X was isolated by chromatography on silica gel (overall yield 65%), as well as 5.5% of 9β,11-epoxy-5α-androstane-3,17-dione, mp 175-176°C. IR spectrum, ν_{max}, cm^{-1}: 1710 (C=O), 1740 (C=O), 860 (-O-). PMR spectrum, δ, ppm: 1.07 s (18=CH_3), 1.22 s (19=CH_3), 3.52 (11-H). Mass spectrum, m/z: 302 (M^+), 287 ($M^+ - CH_3$).

3-α-m-Iodobenzoyloxy-9β,11-epoxy-5α-androstan-17-one (XI). Epoxide XI is obtained from the unsaturated m-iodobenzoate V, under the conditions of the conversion of VIII into epoxide IX, in a yield of 62%, mp 152-155°C, $[\alpha]_D^{20}$ +71.09°. IR spectrum, ν_{max}, cm^{-1}: 1740, 1720, (C=O), 860 (-O-). PMR spectrum, δ, ppm: 103 s (18=CH_3), 1.06 s (19-CH_3), 3.55 m (11-H), 5.24 m (3-H). Mass spectrum, m/z: 534 (M^+), 286 ($M^+ - IC_6H_4COOH$).

17α-Methyl-9β,11-epoxy-5α-androstan-3α,17α-diol (XII). Diol XII is obtained from ketone X under the conditions of the synthesis of diol VII, yield 71%, mp 159-162°C (ether). IR spectrum, ν_{max}, cm^{-1}: 3410 (OH), 860 (-O-). PMR spectrum, δ, ppm: 0.96, 1.07 s (19-CH_3), 1.19 s (17=CH_3), 3.52 m (3-H), 4.05 m (11-H). Mass spectrum, m/z: 304 (M^+). Diol XII is obtained under the same conditions from ketones XV and XVI, yield 86 and 69%, respectively, mp 159-162°C.

11β,17β-Dihydroxy-17α-methyl-9α-fluoro-5α-androstan-3-one (XIII). A 1 g portion of epoxide IX is added to 5 ml of a complex of hydrogen fluoride with pyridine [10] cooled to -78°C. The reaction mixture is stirred at the same temperature for 1 h, and poured into a mixture of ammonia and ice. The precipitate that separates is filtered off, and after crystallization from acetone, 0.68 g of fluorohydrin XIII is obtained, mp 268°C. According to the literature data [8], mp 268°C.

17β-Hydroxy-17α-methyl-9α-fluoro-5α-androstan-3,11-dione (XIV). Diketone XIV is obtained from fluorohydrin XIII under the conditions of the synthesis of ketone VI, yield 72%, mp 210-215°C (acetone). According to the literature data [4], mp 210-215°C.

3α,11β-Dihydroxy-9α-fluoro-5α-androstan-17-one (XV). A. Fluorohydrin XV is obtained from epoxide X under the conditions of the synthesis of fluorohydrin XIII, yield 71%, mp 244-245°C (acetone). IR spectrum, ν_{max} cm^{-1}: 3510, 3370 (OH), 1740 (C=O), PMR spectrum, δ, ppm: 1.08 s (18-CH_3), 1.13 s (19-CH_3), 3.99 m (3-H), 4.25 m (11-H). Mass spectrum, m/z: 324 (M^+).

B. Fluorohydrin XV is obtained from XVI under the conditions of the conversion of V into VI, in 92% yield.

17β-Hydroxy-17α-methyl-5α-androstane-3,11-dione (XVII), 11β-Hydroxy-17,17-dimethyl-9α-fluoro-18-nor-5α-androst-13-en-3-one (XVIII), and 17,17-Dimethyl-18-nor-5α-androstane-8,11,13-trien-3-one (XIX). A 900 mg portion of epoxide IX is added to cooled (-40°C) 70% HF, the reaction mixture is stirred at the same temperature for 1 h and then poured into a mixture of ammonia and ice. The precipitate that separates is filtered off, crystallized from MeOH, and 50 mg of ketone XIX is obtained, mp 144-145°C. Mass spectrum, m/z: 282 (M^+), 267 ($M^+ - CH_3$), 225 ($M^+ - CH_2$=CMe_2). From the mother liquor, 170 mg of XIX and 170 mg of diketone XVII, mp 203-207°C (according to the literature data [6] mp 210°C) and 150 mg of fluorohydrin XVIII, mp 223-225°C are isolated by chromatography on silica gel. Mass spectrum, m/z: 320 (M^+), 305 (M^+ - Me), 287 (M^+ - Me - H_2O), 267 (M^+ - Me - H_2O - HF).

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