OXIDATION OF THE SIDE CHAINS OF ERGOSTEROL DERIVATIVES

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In spite of the advances achieved in the field of the complete industrial synthesis of hormone preparations, natural sources of steroid raw material have not lost their importance and, as before, they remain fundamental. In connection with the development of the industrial microbiological method of obtaining protein substances from petroleum hydrocarbons, the prerequisite has been created for obtaining considerable amounts of ergosterol as a waste material from this production. Work on the conversion of ergosterol into key intermediates in the synthesis of hormone preparations began as early as the fifties, and the most interesting developments appeared in this period [1, 2]. Recently, work on the chemical transformation of ergosterol and its derivatives has amounted to attempts to improve individual stages of syntheses described previously [3].

The most widespread method of oxidizing the side chain of ergosterol derivatives is ozonolysis [1, 2, 4]. In the present paper we consider the possibility of using for oxidizing this side chain the permanganate–periodate method that is widely used in organic chemistry for oxidizing double bonds [5]. In steroid chemistry, it is used mainly for oxidizing ring double bonds [6].

We have studied the oxidation of the acetates of 5β-ergost-22-en-3α-ol (VI) and of ergosta-5,22-dien-3β-ol (XI). In the latter compound, the Δ^5 ring double bond was previously brominated.

The initial compounds (VI) and (XI) were obtained from ergosterol (I) by published methods [1, 7]: the oxidation of ergosterol by the Oppenauer method, the isomerization of the isoergosterone (II) obtained into the dienone (III), hydrogenation of the double bonds in the ring, and reduction of the keto group at C-3 to a hydroxy group.

At the stage of Oppenauer oxidation, instead of the traditional cyclohexanone we used 1,2,5-trimethylpiperidin-4-one as hydrogen acceptor [8]. This simplified the working up of the reaction mixture but lowered the yield of desired product (from 80–85 to 65–77%).

To obtain compound (IV) we exhaustively hydrogenated the double bonds of the dienone (III). In view of the fact that in order subsequently to create in the saturated ketone a Δ^4-3-keto grouping, it is desirable to have rings A and B in cis linkage [9] the hydrogenation of the dienone (III) was performed in an alkaline medium and, in agreement with literature information, the isomer of the 5β series was obtained.

The reduction of (IV) with lithium tetrahydroaluminate at room temperature in ether gave a 90% yield of 5β-ergost-22-en-3α-ol (V).

Hydrogenation of the dienone (III) led to the formation of ergosta-5,22-dien-3-one (IX). We performed the reduction of the 3-keto group in (IX) under conditions of thermodynamic control by sodium tetrahydroborate in methanol and isopropanol, with lithium tetrahydroaluminate, with lithium tetrahydroaluminate, with lithium tri(tert-butyl)hydroaluminate, and with a mixture of aluminum chloride and lithium tetrahydroaluminate. As a result it was found that the reduction of (IV), unlike that of (III) led to the formation of a mixture of ergosta-5,22-dien-3β-ol and the 3α isomer. The smallest amount of the 3α impurity (about 10%) was obtained by reduction with lithium tetrahydroaluminate in ether at 20°C. The reaction was monitored by thin-layer chromatography (TLC) [on "Silufol" in the benzene–methanol (19:1) system]. Chromatographing the mixture on silica gel yielded ergosta-5,22-dien-3β-ol (X) and its 3α isomer. It was also possible to isolate the 3β isomer by acetylating the mixture of isomers under the usual conditions. In the PMR spectrum of the alcohol (X), the proton at C_3 gives a signal in the form of a multiplet at 3.443 ppm, the line having a half-width of 25 Hz, which confirms its axial, 3α, position and, consequently, the equatorial, 3β, position of the hydroxy group.

The bromination of the Δ^5 double bond was performed by analogy with the case of stigmasterol [10], and the bromide was analyzed for its bromine content.

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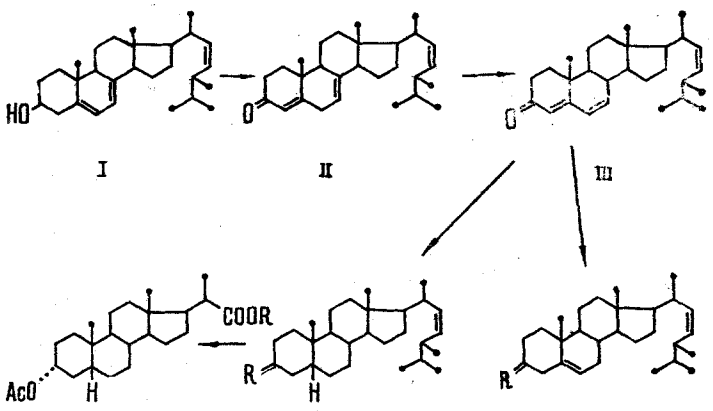

I II III

VII. R=H
VIII. R=Me

IV. R=O
V. R=αOH, βH
VI. R=αOAc, βH

IX. R=O
X. R=βOH, αH
XI. R=βOAc, αH

5β-Ergost-22-en-3α-ol acetate (VI) was oxidized with potassium periodate in tert-butanol in the presence of potassium permanganate at 60°C for 2 h. The reaction was followed by the TLC method and was continued until the initial compound had disappeared completely. As a result, the acetate of bisnorlithocholic acid (VII) was obtained with a yield of 65%. Treatment with diazomethane gave the methyl ester of the acid (VIII). The structure of the acid and its methyl ester agree well with their mass-spectrometric fragmentation. The mass spectrum of the acid (VII) contains the peak of the molecular ion with m/e 390. In the spectrum of the methyl ester (VIII), the molecular ion is represented by a peak with m/e 404. The fragmentation of the two compounds takes place by a common pathway and is determined both by the elimination of the substituents in rings A and D and by the stepwise degradation of ring D. The strongest peaks in the spectra of (VII) and (VIII) are due to the ion $[M - CH_3COOH]^+$, m/e 330 for (VII) [344 for (III)], and also to an ion with m/e 215 formed by the detachment of ring D from the $[M - CH_3COOH]^+$ fragment. In the region of high mass numbers, in addition, there are peaks corresponding to the elimination of the side chain attached to ring D: $[M - OR]^+$ [373 for (VII) and (VIII)], $[M - CH_3COOH - CH_3]^+$ [315 for (VII) and 329 for (VIII)], $[M - CH_3COOH - COOR]^+$ [285 for (VII) and (VIII)], and $[M - CH_3COOH - ROH]^+$ [312 for (VII) and (VIII)]. Ions with m/e 290, 257, and 230 are due to the stepwise degradation of ring D. The high intensity of the peak of the $[M - CH_3COOH - CH_3]^+$ ion observed in both spectra agrees well with the presence of a COOR group in position 20 of the molecule. The correctness of the assignments is shown by an increase of the mass numbers of the ions containing the COOR group by 14 a.u. in the spectrum of (VIII) as compared with that of (VII).

In the NMR spectrum of the acid (VII), the proton at C-3 gives a signal in the form of a multiplet at 4.637 ppm with a half-width of 20 Hz. This confirms its axial, 3β, position and, consequently, the equatorial, 3α, position of the acetoxy group.

We oxidized the acetate of ergosta-5,22-dien-3α-ol (X), having previously brominated the Δ^5 double gond of ring B, under conditions similar to those described above. However, in this case we observed no formation of products of the oxidation of the double bond of the side chain.

EXPERIMENTAL

The IR spectra of mulls of the compound in paraffin oil were taken on a UR-10 instrument, the NMR spectra on a JNM-4H-100 instrument in $CDCl_3$ (with hexamethyldisiloxane as internal standard, the signals being given in the δ scale), and the mass spectra on a MAT-112 instrument (with an ionizing voltage of 50 V). The specific rotations were determined on an ELPU-01 instrument in chloroform. The C and H contents corresponded to the calculated figures.

Ergosta-4,7,22-trien-3-one (II). A solution of 1 g of ergosterol and 5 ml of 1,2,5-trimethylpiperidinone in 100 ml of toluene was boiled with a Dean–Stark trap until the evolution of water ceased. Then 4 ml of a 25% toluene solution of aluminum isopropanolate was added and the mixture was boiled in a current of nitrogen for 15 min, cooled to 0°C, washed with 10% hydrochloric acid and with water, dried, and evaporated. This gave 0.62 g of (II) with mp 135-137°C, λ_{max} 242 nm, ε 20,000. Yield 67%. According to the literature [1]: mp 129-132°C, λ_{max} 242 nm, ε 14,800.

Ergosta-4,6,22-trien-3-one (III) was obtained by the method of Shepherd et al. [1], mp 102-103°C (MeOH), yield 80%. According to the literature: mp 105-108.5°C.

5β-Ergost-22-en-3-one (IV) was obtained from ergosta-4,6,22-trien-3-one by the method of Johnson et al. [7], mp 105-108°C (MeOH). According to the literature: mp 110°C.

5β-Ergost-22-en-3α-ol (V) was obtained by the reduction of 5β-ergost-22-en-3-one (IV) with lithium tetrahydroaluminate in ether, mp 142-144°C (MeOH), yield 88-90%. According to the literature [7]: mp 149-150°C.

The acetate of 5β-ergost-22-en-3α-ol (VI) was obtained by the action of acetic anhydride on the alcohol (V) in pyridine; mp 104-105°C (MeOH), yield 85%. According to the literature [7]: mp 114°C.

Ergosta-5,22-dien-3-one (IX) was obtained from ergosta-4,6,22-trien-3-one (III), mp 138-140°C (MeOH). The mp is not given in the literature.

Ergosta-5,22-dien-3β-ol (X) and the 3α Isomer. The ketone (IX) (0.5 g) was reduced with an excess of sodium tetrahydroborate in a mixture of methanol and methylene chloride at 20°C for 30 min. After the usual working up, 0.45 g of a mixture of the 3β and 3α isomers was obtained with mp 150-151°C. From this mixture by chromatography on silica gel we isolated ergosta-5,22-dien-3α-ol with the composition $C_{28}H_{46}O \cdot 0.5MeOH$, mp 166.5-167.5°C (MeOH). The subsequent fractions yielded the 3β isomer (X) with the composition $C_{28}H_{46}O \cdot 0.5MeOH$, mp 145-146°C (MeOH), $[\alpha]_D$ −65.6° (c 0.05). IR spectrum: 3320 cm^{-1}. NMR spectrum, ppm: 0.640, 0.737, 0.809, 0.89, 0.952, 0.982 (signals of the protons of the methyl groups), multiplet at 3.443 (3 H), quartet at 5.293 (6 H), and multiplet at 5.113 (22H and 23H). According to TLC on "Silufol," the smallest amount of the 3α isomer (about 10%) is found in the reduction of the ketone (III) with lithium tetrahydroaluminate in ether.

Acetate of Ergosta-5,22-dien-3β-ol (XI). A mixture of the 3β alcohol (X) and its 3α isomer obtained in the reduction of (III) with lithium tetrahydroaluminate (1.4 g) was stirred at 20°C with 6 ml of acetic anhydride in 25 ml of pyridine for 12 h. The reaction mixture was evaporated in vacuum to one third of its volume and 1 g of the acetate (IX) with the composition $C_{30}H_{48}O_2$, mp 150-151°C (MeOH) was filtered off. The acetate obtained from the mixture of alcohols was identical with that obtained from the 3β alcohol (X).

Acetate of Bisnorlithocholic Acid (VII). With stirring at 20°C, 0.42 g of potassium hydroxide was added to a solution of 0.7 g of the acetate of 5β-ergost-22-en-3α-ol in 70 ml of tert-butanol. The reaction mixture was heated to 60°C, and 2.8 g of sodium periodate in 70 ml of water and 21 ml of an aqueous solution of potassium permanganate (0.38 g of potassium permanganate in 25 ml of water) were added dropwise. The mixture was stirred at a bath temperature of 60°C for 2 h. After cooling, a saturated solution of $NaHSO_3$ was added until a yellow color appeared. Then ether extracted 0.4 g of the acid (VII), which, after recrystallization from a mixture of ether and hexane, had the composition $C_{24}H_{38}O_4$, mol. wt. 390 (mass spectrometry), mp 202-204°C, $[\alpha]_D$ +31.8° (c 0.05). IR spectrum, cm^{-1}: 2500-2750, 1740, 1720, 1640. NMR spectrum, ppm: 0.624 (18 Me), 0.887 (19 Me), triplet at 1.19 (21 Me), 1.982 (OAc), multiplet at 4.637 (3 H). On reaction with diazomethane, the acid (VII) gave the methyl ester (VIII) with the composition $C_{25}H_{40}O_4$, mol. wt. 404 (mass spectrometry), mp 96-97°C (MeOH), $[\alpha]_D$ +39.9° (c 0.04). IR spectrum: 1740 cm^{-1}.

SUMMARY

The acetate of bisnorlithocholic acid has been obtained with a yield of 65% from the acetate of 5β-ergost-22-en-3α-ol by permanganate-periodate oxidation.

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