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SYNTHESIS OF (22E,24R)-5α-ERGOSTA-2,7,22-TRIEN-6-ONE

N. V. Kovganko and S N. Sokolov

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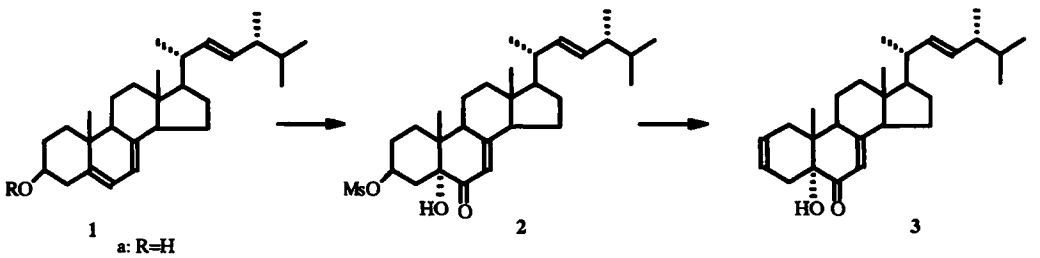
The synthesis of the 5α-hydroxy-2,7,22-trien-6-one (3) has been achieved by the mesylation of ergosterol (1a) and oxidation of the resulting mesylate (1b) with chromic acid to 3β,5α-dihydroxy-7,22-dien-6-one 3-mesylate, followed by elimination.

For the chemical synthesis of ecdysteroids and substances related to them great importance is attached to Δ^7-6-ketosteroids containing additional Δ^2- and Δ^{22}-double bonds [1, 2]. Starting from these compounds and using known methods, the fairly simple introduction of other structural fragments of ecdysteroid molecules is possible. In this connection, undoubted interest is presented by the 5α-hydroxy-2,7,22-trien-6-one (**3**), which can be obtained from ergosterol (**1**). It must be mentioned that the analogous derivative of the cholestane series, synthesized from 7-dehydrocholesterol, has been used previously to obtain structural analogs of the ecdysteroids [3]. However, the variant of the conversion of 7-dehydrocholesterol into the 5α-hydroxy-2,7-dien-6-one proposed in [3] is distinguished by a considerable number of stages and, because of this, a low overall yield.



1 a: R=H, b: R=Ms **2** **3**

To obtain the hydroxytrienone (**3**) from ergosterol (**1a**), we have developed a new scheme of synthesis simpler than the current one. First, by reaction with methanesulfonyl chloride in pyridine, ergosterol (**1a**) is converted into the mesylate (**1b**), and this, without purification, is subjected to oxidation with chromic acid in a mixture of ether and methylene chloride [4].

The structure of the 3β,5α-dihydroxy-7-en-6-one 3-mesylate (**2**) obtained in this way with a yield of more than 30% was shown by spectral methods. Thus, in the IR spectrum of compound (**2**) there were the bands of the stretching vibrations of a carbonyl group and of a double bond conjugated with it at 1665 and 1620 cm^{-1}, respectively, which is characteristic for an α,β-unsaturated ketone. In its turn, the UV spectrum had an intense absorption band at 249 nm the position of which is typical for Δ^7-6-ketosteroids. In the ^1H NMR spectrum, there were the signals of the methyl of a mesyl group (δ 3.04 ppm) and of the H-7 vinyl proton (δ 5.66 ppm), as well as others. A considerable downfield shift to 5.04 ppm of the multiplet of the H-3 methine proton was due, in the first place, to the esterification of the 3-hydroxy group and, in the second place, to the presence in the molecule of the compound under discussion of a 5α-hydroxy group in a diaxial position with respect to it. Furthermore in the spectrum there were the signals of the two vinyl protons, H-22 and H-23 (δ 5.14—5.28 ppm), the positions and forms of which coincided completely with the analogous characteristics in the spectrum of ergosterol.

For the introduction of another double bond, compound (**2**) was subjected to an elimination reaction. For this, we studied the interaction of the mesylate (**2**) both with lithium carbonate in dimethylformamide at the boil and with a mixture of lithium carbonate and bromide under the same conditions. In both cases the 5α-hydroxy-2,7,22-trien-6-one (**3**) was obtained

Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus, 220141, Minsk, ul. Akad. Kuprevicha.
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with yield of about 44—48%. The structure of (3) followed unambiguously from it spectral characteristics. In particular, from its UV, IR, and ^{1}H NMR spectra it was possible to conclude that in steroid (3) the 5α-hydroxy-7-en-6-one grouping and the 22-double bond had been retained. In the ^{1}H NMR spectrum the signal of the methyl protons of the mesyl group had disappeared and the signals of two additional vinyl groups had appeared in the 5.64—5.79 ppm interval. Although these signals partially overlapped with the H-7 signal, their position was typical for the H-2 and H-3 protons in the ^{1}H NMR spectra of 5α-hydroxy-2-ene-6-ketosteroids [5].

We plan subsequently to use compound (3) in the synthesis of ecdysteroids.

EXPERIMENTAL

Melting points were determined on a Kofler block. IR spectra were recorded on a UR-20 instrument in the range of 700—3600 cm^{-1} in KBr tablets. UV spectra of solutions in ethanol were taken on a Specord M-400 instrument. ^{1}H NMR spectra of solutions in chloroform were obtained on a Bruker AC-200 spectrometer with a working frequency of 200 MHz. Chemical shifts are given relative to TMS as internal standard.

(22E,24R)-3β,5-Dihydroxy-5α-ergosta-7,22-dien-6-one 3-Mesylate (2). A solution of 4.0 g of ergosterol (1a) in 30 ml of pyridine was treated with 4 ml of methanesulfonyl chloride. The reaction mixture was kept at 8°C for 12 h, and then 35 ml of chloroform and 35 ml of water were added. The organic layer was separated off, washed with water, and evaporated in vacuum. The residue was treated with 15 ml of a mixture of benzene and toluene (1:1), and this was evaporated off in vacuum. Without further purification, the resulting ergosterol mesylate (1b) so obtained was dissolved in 50 ml of ether and 10 ml of methylene chloride, and then, with stirring, a solution of chromic acid (obtained by dissolving 6.3 g of chromium trioxide in 47 ml of water) was added. The reaction mixture was boiled with stirring for 2 h, and the organic layer was then separated off. The aqueous layer was extracted with a mixture of ether and methylene chloride (5:1), and the combined organic extracts were evaporated in vacuum. The residue was chromatographed on a column of silica gel,with elution by petroleum ether—tetrahydrofuran (2:1). This gave 1.68 g (32.8%) of the 5α-hydroxy-6-ketone (2), mp 128—129°C (decomp.) (hexane—acetone). IR spectrum (cm^{-1}): 3410 (OH), 1665 (C=O), 1620 (C=C). UV spectrum (nm): λ_{max} 249. ^{1}H NMR spectrum (δ, ppm); 0.62 (s, 18-Me), 0.82 (d, J=7 Hz, 26-Me), 0.84 (d, J=6.5 Hz, 21-Me), 3.04 (s, Ms), 5.04 (m, W/2=28 Hz, 3α-H), 5.14-5.28 (m, 22-H, 23-H), 5.66 (br.s, H-2).

(22E,24R)-5-Hydroxy-5α-ergosta-2,7,22-trien-6-one (3). A. A solution of 2.71 g of the mesylate (2) in 40 ml of dimethylformamide was treated with 3.95 g of lithium carbonate. The reaction mixture was boiled under reflux for 1.5 h and was then cooled to room temperature. The residual lithium carbonate was filtered off through a layer of alumina, and the filtrate was diluted with 30 ml of water and extracted with hexane—benzene (1:1). The organic extract was evaporated in vacuum, and the residue was chromatographed on a column of silica gel with elution by petroleum ether—tetrahydrofuran (3:1). This gave 0.97 g (44%) of the trienone (3), mp 231—232°C (hexane—acetone). IR spectrum (cm^{-1}) : 3445 (OH), 1685 (C=O), 1630 (C=C). UV spectrum (nm): λ_{max} 250. ^{1}H NMR spectrum (δ, ppm); 0.62 (s, 18-Me), 0.83 (d, J=6.5 Hz, 26-Me), 0.86 (d, J=6.5 Hz, 27-Me), 0.88 (s, 19-Me), 0.92 (d, J=6.5 Hz, 21-Me), 5.14-5.27 (m, 22-H, 23-H), 5.64-5.79 (m, 2-H, 3-H, 7-H).

B. A solution of 2.04 g of the mesylate (2) in 60 ml of dimethylformamide was treated with 2.97 g of lithium carbonate and 0.23 g of lithium bromide. The reaction mixture was boiled for 35 min and was then cooled to room temperature and the solid matter was filtered off through a layer of alumina. The filtrate was diluted with 35 ml of water and extracted with benzene—hexane (1:1). The organic extract was evaporated in vacuum and the residue was chromatographed on a column of silica gel, with elution by petroleum ether—tetrahydrofuran (3:1). This gave 0.80 g (48%) of the trienone (3).

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