PRODUCTS OF THE DECOMPOSITION OF 3β -ACETOXY- 17α -HYDROPEROXY- 16α -METHYLPREGN-5-EN-20-ONE

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In recent years, the steroidal hydroperoxides have attracted the attention of research workers in connection with their possible utilization as intermediate products in the synthesis of 17α -hydroxylated pregnanes [2, 6, 10]. It is known that 17α -hydroperoxypregnanes not containing a substituent at C(16) readily undergo thermal decomposition on heating in a solvent [3] or in the presence of alkali [7, 8] with the formation of 17α -hydroperoxy-16 β -methylpregnanes with perchloric acid in dioxane gives the 16β -methyl-17-keto compound besides the main product of the D-homooxa-rearrangement; the route of the decomposition is dependent on the nature of the substituent at C(16).

In connection with the fact that there are no literature data on investigations into the decomposition of 17α -hydroperoxypregnanes containing a methyl group in the α -configuration at C(16), it seemed expedient to us to study the properties of 3β -acetoxy- 17α -hydroperoxy- 16α -methylpregn-5-en-20-one (I), which was first obtained by us, as dependent on the different conditions of performing the reactions. We investigated the influence of solvents, acids and alkalis, and acetic anhydride, as well as metal ions of variable valency, on the stability of (I). It should be noted that the 17α -hydroperoxide (I) is stable in the crystalline form. The TLC data indicate that no appreciable decomposition occurs when a sample is stored for 3 yr at room temperature.



R=Ac(**Za**, **Z**a), H(IIb, IIIb)

In solutions of aprotic solvents (benzene, ether, acetonitrile, tetrahydrofuran), the decomposition of (I) is not observed, even after boiling the solutions for 25 h (TLC data). However, the addition of a catalytic amount of the salt of metals of variable valency leads to rapid decomposition. The decomposition proceeds in different ways. The main products are 3β -acetoxy-16-methylandrost-5-en-17-one (IIa) and 3β -acetoxy-17 α -hydroxy-16 α -methyl-pregn-5-en-20-one (IIIa); these were isolated and identified. The constants of compound (IIIa) correspond with those presented in the literature [5].

The structure of compound (IIa) is proved using the IR, mass spectrum, and PMR spectrum. The bands of the stretching vibrations in the region of $3500-3550 \text{ cm}^{-1}$, which are characteristic of the hydroperoxy and hydroxy groups, are absent from the IR spectrum. The PMR

S. Ordzhonikidze All-Union Chemico-Pharmaceutical Research Institute (VNIKhFI), Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 21, No. 12, pp. 1471-1475, December, 1987. Original article submitted November 13, 1986. spectrum of compound (I) is characterized by the presence of the signal of the proton of the hydroperoxy group at 8.26 ppm. The protons of the angular methyl groups are observed at 0.86 and 1.16 ppm (the $18-CH_3$ and $19-CH_3$ correspondingly). The signal of the protons of the methyl group at the position 16 is a doublet at 1.32 ppm (J = 7.73 Hz), and the protons of the 21-CH₃ group appear as a singlet at 2.44 ppm. The acetyl group is a singlet at 2.19 ppm. The proton at the position 3 is a multiplet at 4.7 ppm; the proton at the position 6 is a broad doublet at 5.5 ppm.

When the PMR spectra of the compounds (I) and (IIa) are compared, it is found that the signals of the proton of the OOH group and the protons of the methyl group at the position 21 are absent from the spectrum of compound (IIa). Significant shifts in the signals of the methyl groups at the positions 16, 13, and 10 are also observed; this conforms with the transition from a compound of the pregname series to a compound of the androstame series [1].

The decomposition of the hydroperoxide (I) in the presence of acidic or alkaline reagents proceeds more slowly by comparison with the action of metal ions, and is characterized by a more directed course for the process. The main products which are thereby formed in an acid medium at 3β -hydroxy-l6a-methylandrost-5-en-17-one (IIb) and 3β , 17a-dihydroxy-l6a-methylpregn-5-en-20-one (IIIb); the ratio of the products is $\sim 3:1$. The constants of compound (IIIb) correspond with those presented in the literature [5]. The structure of (IIb) is confirmed by the data of the mass spectrum and PMR spectrum.

In the alkaline medium, compound (IV) is obtained together with (IIIb). Compound (IV) differs from (IIb) by the R_f value (according to the TLC data), but it has the same molecular mass (the data of mass spectroscopy). The comparison of the chemical shifts of the signals of the protons of the methyl groups at the position 16 in the PMR spectra of the compounds (IIb) and (IV) permits the conclusion that compound (IV) is an epimer of compound (IIb). In the spectrum of compound (IV), the signal of the protons of the methyl group at position 16 is displaced to lower field on account of its steric proximity to the methyl group at the position 13 in the transition to the β -configuration. On the basis of the PMR spectral data, the structure of compound (IV) is established as 3β -hydroxy-16 β -methylandrost-5-en-17-one.

Such a change in the configuration of the methyl group at C(16) in an alkaline medium is in accord with the literature data [9].

We also observed the decomposition of the hydroperoxide (I) under the conditions of acetylation. The main product is compound (IIa). Moreover, the compounds (IIIa) and (V) were isolated; the ratio of (IIa):(IIIa):(V) \approx 9:4:1. On the basis of the data of the elemental analysis and the ¹H and ¹³C NMR spectra, the structure of compound (V) was proposed to be $3\beta-17$, 17-triacetoxy- 16α -methylandrost-5-ene. In the PMR spectrum (in the CDCl₃ solution), the signals of the angular methyl groups are present in the form of singlets at δ 0.91 and 1.02 ppm. The doublet of the methyl group (J = 7 Hz) at C(16) is observed at 1.10 ppm. The signals of the three acetoxy groups at the positions 17 and 3 are observed in the form of two singlets at 2.04 and 2.08 ppm. This is evidently associated with the fact that the signals of the two groups at C(17) coincide. In fact, the signals of the three $OCOCH_3$ groups at 1.76, 1.82, and 1.86 ppm clearly differ in the spectrum of this compound in the solution of $C_6 D_5 Br$. The presence of the proposed structure is also confirmed by the ¹³C NMR spectra. In the low-field part of the spectrum, the signals of the carbon atoms of the carbonyl groups in the OCOCH₃ substituents are separated at 170.0, 168.5, and 167.9 ppm. Apart from the signals of the carbon atoms at the double bond (121.8 and 139.5 ppm), the spectrum contains a signal at 115.3 ppm which, from its position, can be assigned to the carbon atom, at position 17, connected to two oxygen atoms.

In the mass spectra, the peak of the molecular ion of the compound (V), corresponding to the structure established on the basis of the analysis of the ¹H and ¹³C NMR spectra, is not observed. The peak with the greatest mass number has the value of m/z = 386 (A). The decomposition of the ion (A) indicates the presence of two acetoxy groups. In the spectrum, the peaks of the following ions are observed: $[A - CH_3COOH]^+$ (326), $[A-2CH_3COOH)^+$. (266), $[A-CH_2CO]^+$ (344), $[A-CH_2CO-CH_3CO]^+$ (301), $[A-CH_3COOH-CH_2CO]^+$ (284) $[A-2CH_3COOH-CH_2CO]^+$ (269).

The absence of the peak of the molecular ion (molecular mass 446) is evidently associated with the presence of the two acetoxy groups at one atom, C(17). This renders the

molecule unstable under the conditions of the electron impact, and leads to the ready elimination of a molecule of acetic acid with the formation of the stable fragment (A).

The exhaustive rearrangement of the 17α -hydroperoxides in the series of 16β -methyl derivatives was noted under analogous conditions by J. Gardner and co-workers [3]. In connection with another configuration of the methyl group at C(16) in the initial compounds, 17aoxa-D-homopregnanes were obtained as the main products of the decomposition of the 17α -hydroperoxides. It can be concluded that the route of the decomposition of the hydroperoxides depends on the configuration of the 16-methyl group.

Therefore, we showed that the decomposition of the hydroperoxide (I) proceeds in different ways for all cases. The cleavage of the unstable 0-0 peroxide bond leads to the formation of the 17α -hydroxy compounds (III). The breaking of the 0-0 bond and the adjoining C-C bond leads to the removal of the 17β -acetyl side chain; this results in the isolation of the an-drostane derivatives (II), (IV), and (V).

EXPERIMENTAL

The IR spectra of the compounds were taken on a Perkin-Elmer 599 instrument (Sweden). The PMR spectra were taken on an XL-200 instrument (Varian USA). The ¹³C NMR spectra were taken on a MAT-100 instrument (Varian USA). The mass spectra were taken on a MAT-112 instrument (Varian USA) using the ionizing voltage of 50 eV. The TLC analysis was carried out on Silufol UV-254 plates in the 3:2 system of hexane-acetone (A) and the 10:3 system of hexane-acetone (B); development was performed with a solution of vanillin in a 10% solution of perchloric acid.

Decomposition of (I) in the Presence of Acetic Anhydride. Compound (I) (5 g) (mp 169°C with decomposition, $[\alpha]_D^{20}$ -35.8°) is dissolved in 20 ml of pyridine prior to the addition of 5 ml of acetic anhyride. After 20 h, the reaction mass is added, dropwise, to 90 ml of a 10% aqueous solution of HCl at the temperature of 0-5°C with stirring. The oily residue is filtered off and washed with water to a neutral reaction. The mixture of (IIa), (IIIa), and (V) is obtained in the yield of 4 g; the mixture is dissolved in benzene and chromatographed on 40 g of silica gel. After the elution with benzene, 2.23 g of (IIa) (mp 112-113°C) are obtained; (IIa) is recrystallized twice from hexane. Compound (IIa) is obtained in the yield of 1.05 g. The mp is 106-107°C (hexane); the mp of (IIa) is 119.5-120.5°C according to the literature data [9]. The IR spectrum (ν_{max} , cm⁻¹) is as follows: 1740, 1730 (17 C=0, C=0, and OCOCH₃ groups), 1715 (C=C), and 1240 (OCOCH₃). The PMR spectrum (δ , ppm) in CDCl₃ is as follows: 0.94 s (3H, 18-CH₃), 1.04 s (3H, 19-CH₃), 1.10 d (3H, 16-CH₃, J = 7 Hz), 2.04 s (3-0COCH₃), 4.62 m (3-H), and 5.42 broad d (6-H). The mass spectrum (m/z) is characterized at 344 M⁺. Found, %: C 76.77 and H 9.49. C₂₂H₃₂O₃. Calculated, %: C 76.70 and H 9.36.

The 1:1 mixture of (IIa) and (V) is next eluted in the yield of 0.74 g; it is crystallized from ether. The resulting 0.2 g of (V) is recrystallized from hexane. The yield of 0.1 g of (V) with the mp 163-164°C is obtained. The IR spectrum (v_{max} , cm⁻¹) is as follows: 1725, 1750 (C=O and OAc groups), 1240 (3 OAc), and 1670 (C=C). The PMR spectrum (δ , ppm) in CDCl₃ is as follows: 0.91 s (3H, 18-CH₃), 1.02 s (3H, 19-CH₃), 1.10 d (3H, 16-CH₃, J = 7 Hz), 2.04, and 2.08 (3 and 17 OCOCH₃). The PMR spectrum (δ , ppm) in C₆D₅Br is as follows: 1.76, 1.82, and 1.86 (3, 17, 17-OCOCH₃). The ¹³C NMR spectrum (δ , ppm) is as follows: 170.0, 168.5, and 167.9 (3, 17, 17-OCOCH₃), 121.8, 139.5 (C=C), and 115.3 (17-C). The mass spectrum (m/z) is as follows: A [M⁺ - CH₃COOH] (386). Found, %: C 69.58 and H 8.59. C₂₆H₃₈O₆. Calculated, %: C 69.90 and H 8.58.

Compound (IIIa) is further eluted. It has the mp 193-195°C (according to the literature data [5], the mp is 203-205°C).

Decomposition of (I) in the Presence of Cu^+ or Fe^{2+} . Compound (I) (0.5 g) is dissolved in 50 ml of the 1:1 mixture of benzene and tetrahydrofuran prior to the addition of 0.1 g of CuCl; the mixture is held at 20°C for 1 h. The reaction mass is diluted with benzene and washed with water. The benzene solution is evaporated to dryness; 0.4 g of the oil containing (IIa) and (IIIa) is obtained. It is crystallized from the 1:1 mixture of ether and hexane; 0.02 g of (IIIa) having the mp 195-196°C is obtained. The mother liquor is evaporated to dryness; the residue is dissolved in benzene and chromatographed on 4 g of silica gel. Benzene is utilized to elute 0.12 g of an oil containing (IIa). It is crystallized from hexane to obtain 0.05 g of (IIa) with the mp 110-111°C The mixture of (IIa) and (IIIa) is obtained in the presence of FeSO4.

Decomposition of (I) in an Acidic Medium. Compound (I) (2.5 g) is dissolved in 110 ml of methanol prior to the addition of 5 ml of 35% HCl to the pH 1.0 with stirring at 20°C. After 24 h, the reaction mass is neutralized with a methanolic solution of NaOH; the mixture is concentrated to dryness. The oily residue is dissolved in chloroform, washed with water, and concentrated to a low volume. The precipitated residue is filtered off. Compound (IIIb) (0.5 g) is obtained; it has the mp 242-243°C (according to the literature data [5], the mp is 245-250°C). The mother liquor is evaporated to dryness. It is dissolved in benzene and chromatographed through the tenfold amount of silica gel. The 10:1 mixture of benzene and ether is utilized to elute1.26 g of (IIb) having the mp 139-140°C (according to the literature data [9], the mp is 138-140°C, and the $[\alpha]_D^{20}$ is -2.4°). The $[\alpha]_D^{20}$ is -16.5° (c 0.08, chloroform). The IR spectrum (v_{max} , cm⁻¹) is as follows: 3260 (3-OH), 1730 (17 C=O), and 1670 (C=C). The PMR spectrum (δ , ppm) in CDC1₃ is as follows: 0.92 s (3H, 18-CH₃), 1.04 s (3H, 19-CH₃), 1.10 d (3H, 16-CH₃, J = 7 Hz), 3.50 m (3-H), and 5.42 broad d (6-H). The mass spectrum (m/z) is characterized by 302 M⁺.

Compound (IIb) (0.1 g) is dissolved in 1 ml of pyridine prior to the addition of 1 ml of acetic anhydride. After 20 h, the reaction mixture is added dropwise at 0-5°C, with stirring, to 5 ml of a 10% aqueous solution of HCl. The residue is filtered off and washed with water until a neutral reaction is obtained. The yield of 0.12 g of (IIa) having the mp 103-104°C is obtained.

Decomposition of (I) in an Alkaline Medium. Compound (I) (3 g) is dissolved in 150 ml of methanol prior to the addition of 1 g of KOH with stirring at 20°C. After 72 h, the precipitated residue is filtered off and washed with water until a neutral reaction is obtained. The yield of 0.46 g of (IIIb), having the mp 244-245°C, is obtained. The mother liquor contains the 1:1 ratio of (IV) and (IIIb) according to the TLC data (system A); it is acidified with AcOH until a neutral reaction is obtained, and evaporated to a low volume. The precipitated residue is filtered off; 0.25 g more of (IIIb), with the mp 240-242°C, is obtained. The mother liquor is concentrated to dryness. The residue is dissolved in benzene and chromatographed on the tenfold amount of silica gel. The 10:1 mixture of benzene and ether is utilized to elute 1.15 g of (IV) with the mp 162-164°C (according to the literature data [9], the mp is 175-176°C). The IR spectrum (v_{max} , cm⁻¹) is as follows: 3485 (3-OH), 1740 (17 C=0), and 1700 (C=C). The PMR spectrum (δ , ppm) in CDCl₃ is as follows: 0.85 s (3H, 18-CH₃), 1.04 s (3H, 19-CH₃), 1.21 d (3H, 16-CH₃, J = 7 Hz), 3.54 m (3-H), and 5.42 broad d (6-H). The mass spectrum (m/z) is characterized by 302 M⁺.

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