STEROIDS

XLV.* THE STERIC HINDRANCE OF THE HYDROXY GROUPS IN 3α,11α-DIHYDROXY-16α-METHYL-5β-PREGNAN-20-ONE

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UDC 547.593.2:541.636

Continuing investigations on the synthesis of 16α-methyl-substituted pregnanes [1], we have studied the reduction of the 3-oxo group of 11α-hydroxy-16α-methyl-5β-pregnane-3,20-dione (I) under the action of $NaBH_4$.

It is known [2] that the stereochemical directivity of the reduction of unhindered 3-oxo steroids by complex metal hydrides is determined by the structure of the product formed; the reaction generally leads to a predominating amount of the stabler alcohol with the equatorial arrangement of the hydroxy group. This alcohol will belong to the 3α or the 3β series according to the linkage of rings A and B.

In accordance with this rule, in the reduction of ketone (I) by $NaBH_4$ we observed the formation of 3α, 11α-dihydroxy-16α-methyl-5β-pregnan-20-one (II) as the sole reaction product.

The presence of two equatorial hydroxy groups in the molecule of the diol (II) obtained enabled their relative steric hindrance to be studied. It can be seen from a consideration of a molecular model of the diol (II) (Fig. 1) that although both hydroxyls are equatorial, one of them (11α) is hindered to a somewhat greater extent because of the cis linkage of rings A and B. This hypothesis has not been put forward before, but previous experimental results [3] do not contradict it.

* For Communication XLIV, see Khim. Prirodn. Soedin., 7, 509 (1971).

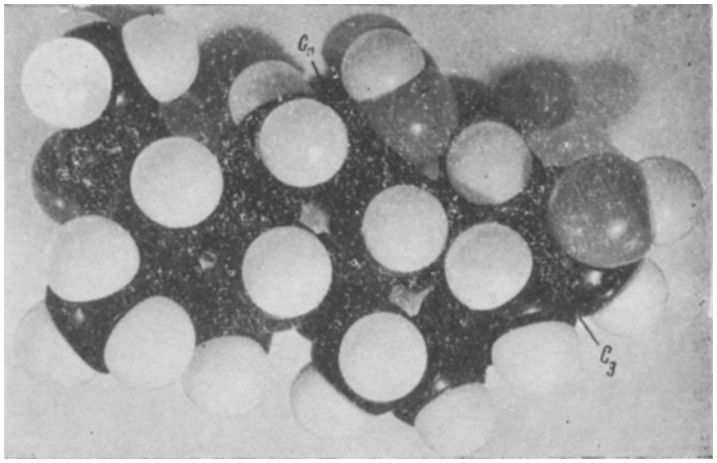

Fig. 1. Molecular model of 3α, 11α-dihydroxy-16α-methyl-5β-pregnan-20-one (II). View from the rear direction.

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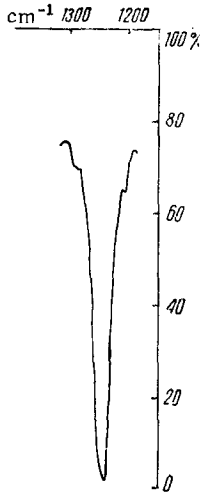


Fig. 2

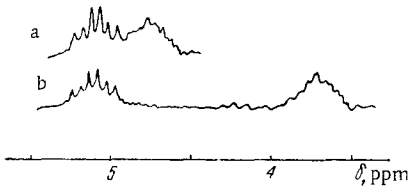


Fig. 3

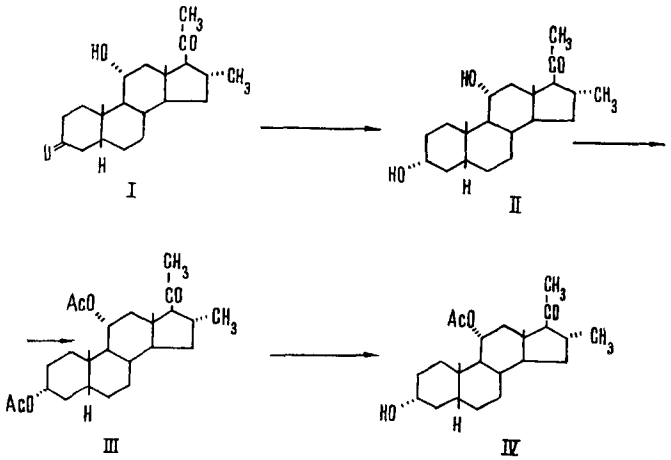
Fig. 2. IR spectrum 3α,11α-diacetoxy-16α-methyl-5β-pregnan-20-one (III).

Fig. 3. PMR spectra of: a) 3α,11α-diacetoxy-16α-methyl-5β-pregnan-20-one (III); b) 11α-acetoxy-3α-hydroxy-16α-methyl-5β-pregnan-20-one (IV).

When the diol (II) was treated with acetic anhydride in pyridine at room temperature, the acetylation of the two hydroxy groups apparently took place at similar rates, since the process led to the formation of the diacetate (III) (TLC).

Thus, we observed no difference in the spatial acessibility of the 3α and the 11α-hydroxy groups. However, such a difference was observed in the deacetylation of the acetate (III). It was found that when the latter was treated with a solution of KOH in aqueous ethanol at room temperature the 11-monoacetate of (II) was formed in admixture with a small amount of the diol (II).

On alkaline hydrolysis, less blocked acetoxy groups are saponified more easily [4]. The hindrance to the hydrolysis of the 11α-acetoxy group shows that it is spatially blocked to a greater extent than the 3α-acetoxy group.



The structures of the products corresponded to their spectral characteristics.

Thus, in the IR spectrum (solution in CS_2) of the diacetate (III) at 1240 cm^{-1} there is the strong singlet absorption band characteristic [5] of 3α-acetoxy-5β-steroids (Fig. 2).

In the PMR spectrum (Fig. 3) of the diacetate (III) there are two signals from protons at C_3 ($\delta = 4.74$ ppm) and C_{11} ($\delta = 5.0$ ppm) (geminal acetoxy groups).

TABLE 1. Chemical Shifts of the Protons of the Angular Methyl Groups

Compound	Chemical shift, ppm			
	19-H		18-H	
	found	calc.	found	calc.
III	1,01	1,03	0,66	0,68
IV	1,00	1,01	0,65	0,68

The assignment of the signals was made on the basis of their different multiplicities, determined by the number and orientation of the vicinal protons. The signal of the proton at C_{11} (sextet) is due to axial–axial coupling with the protons at C_9 and C_{12} (J_{aa} = 10.5 Hz) and to axial–equatorial coupling with the proton at C_{12} (J_{ae} = 5 Hz). The signal of the proton at C_3 is a multiplet which appeared because of coupling with the two axial and two equatorial protons at C_2 and C_4.

The monoacetate (IV) arising on partial hydrolysis gave the signal of a proton at C_{11} (δ = 5.06 ppm, geminal acetoxy group) and of one at C_3 (δ = 3.67 ppm, geminal hydroxy group) with retention of the nature of the splitting of the signals: the upfield shift of the signal in the spectrum (multiplet) is in harmony with the occurrence of hydrolysis at C_3 [6].

The constants found show the axial position of the protons at C_{11} and C_3, i.e. the equatorial position of the 3α- and 11α-hydroxy groups.

For compounds (III) and (IV) the values of the chemical shifts of the protons of the angular methyl groups determined from the PMR spectra do not agree satisfactorily with those calculated from the empirical rules of additivity [7] (see Table 1); similar discrepancies have been observed by Zuercher [7].

EXPERIMENTAL

The IR spectra were obtained in paraffin oil, and the PMR spectra on a JNM-4H-100 MHz instrument in $CDCl_3$ (with tetramethylsilane as internal standard). The C and H values found corresponded to the calculated figures. The reactions were monitored by thin-layer chromatography (TLC).

3α,11α-Dihydroxy-16α-methyl-5β-pregnan-20-one (II). With stirring at 20°C, a solution of 0.1565 g of $NaBH_4$ in 15 ml of anhydrous pyridine was added dropwise over 3 h to a solution of 1 g of the ketol (I) with mp 145-148°C and 0.355 ml of water in 10 ml of anhydrous pyridine. After ~12 h, the reaction mixture was poured into 31 ml of conc. HCl containing ice and stirred for 30 min, the precipitate was filtered off, and the filtrate was extracted with methylene chloride three times. The precipitate and the product from the extract were recrystallized from ethyl acetate. This gave 0.74 g (yield 74%) of the diol (II) with mp 198-201°C (from ethyl acetate); ν_{max} 1690 cm^{-1} (CO); 3370, 3430, and 3500 cm^{-1} (OH).

3α,11α-Diacetoxy-16α-methyl-5β-pregnan-20-one (III). At ~20°C, 1 ml of acetic anhydride was added dropwise to a solution of 1.18 g of the diol (II) in 35 ml of anhydrous pyridine. After ~12 h, the reaction mixture was poured into a mixture of 45 ml of conc. HCl and ice. It was extracted with chloroform, and the extract was washed with water and dried with Na_2SO_4. The solvent was evaporated off in vacuum, and the residue (1.4 g) was transferred to a column of SiO_2 and eluted with chloroform, the separation being monitored by the TLC method. The evaporation of the appropriate portions of the eluate gave 0.98 g (yield 69%) of the diacetate (III) with mp 182-185°C (from dilute ethanol); ν_{max} 1690 cm^{-1} (CO), 1715 and 1740 cm^{-1} (ester CO).

11α-Acetoxy-3α-hydroxy-16α-methyl-5β-pregnan-20-one (IV). To a solution of 0.2 g of the diacetate (III) in 57 ml of ethanol was added a solution of 0.26 g of KOH in 0.5 ml of water. After 1 h (~20°C), using the TLC method, the disappearance of the diacetate (III) from the reaction mixture was found. Then 0.28 ml of acetic acid was added, the solvent was evaporated off in vacuum, and the residue was treated with water. After ~12 h (in the refrigerator), the precipitate was filtered off (0.19 g) and transferred to a column containing 15 g of SiO_2. Elution was performed with a mixture of benzene and acetone (5 : 1), the separation being monitored by the TLC method. The product from the appropriate portions of eluate was recrystallized from dilute ethanol, giving 0.14 g (yield 77.4%) of the monoacetate (IV) with mp 166-167°C (from benzene–hexane); ν_{max} 1695 cm^{-1} (CO), 1730 cm^{-1} (ester CO), and 3360 and 3410 cm^{-1} (OH).

SUMMARY

1. The reduction of 11α-hydroxy-16α-methyl-5β-pregnane-3,20-dione with $NaBH_4$ forms 3α,11α-dihydroxy-16α-methyl-5β-pregnan-20-one.

2. In 3α,11α-dihydroxy-16α-methyl-5β-pregnan-20-one the 11α-hydroxy group suffers greater steric hindrance than the 3α-hydroxy group.

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