STEROIDS

XXXVII. The Stereospecificity of the Hydrogenation of 16α-Methyl-3-oxo-Δ^4-Unsaturated Compounds*

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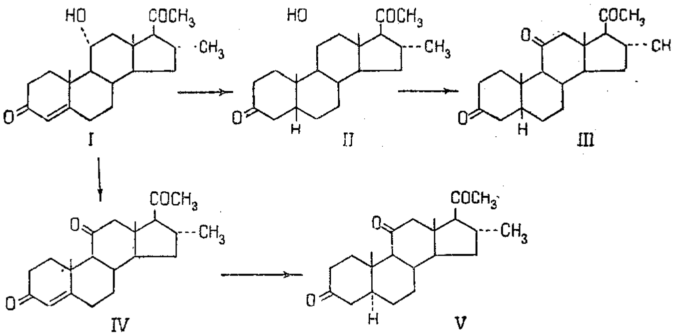
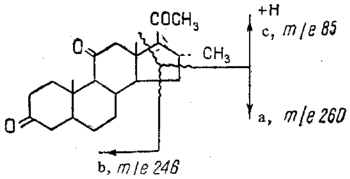
It has been found previously [1] that the hydrogenation of the double bond in Δ^4-3-ketones of the progesterone series in pyridine over a palladium catalyst takes place with a high degree of stereospecificity. The predominant formation of 5α- or 5β-pregnanes is determined mainly by the nature of the substituent at $C_{(11)}$.

Continuing these investigations, in order to study the influence of a 16α-methyl group, we have hydrogenated analogous 16α-methyl derivatives. It has been found that 11α-hydroxy-16α-methylpregn-4-ene-3,20-dione (I) forms 11α-hydroxy-16α-methyl-5β-pregnane-3,20-dione (II), which is oxidized by Kiliani's reagent to 16α-methyl-5β-pregnane-3,11,20-trione (III). Under the same conditions, 16α-methylpregn-4-ene-3,11,20-trione (IV) (obtained by the oxidation of I) gives 16α-methyl-5α-pregnane-3,11,20-trione (V).



The structures of products II, III, and V are in good harmony with their mass spectra. Thus, the presence in the spectra of these compounds of the molecular ions with m/e 346, 344, and 344, respectively, corresponds to their elementary compositions: $C_{22}H_{34}O_3$ for II and $C_{22}H_{32}O_3$ for III and V. The mass spectrum of the hydroxy derivative II, unlike those of the triketones III and V, shows the intensive formation of the M − H_2O ion (m/e 328), which determines the further course of the decomposition.

The main directions of the fragmentation of compounds III and V are connected with the substituents in ring D. The ions arising in this process, a, b, and c (m/e 260, 246, and 85) (figure) are typical for 16-methyl derivatives of progesterone [2].



At the same time the appearance of the ions d (m/e 207), e (m/e 220), f (m/e 233), g_1 (m/e 274), and g_2 (m/e 273) is characteristic for 11-oxo- and 3-oxosteroids [3].

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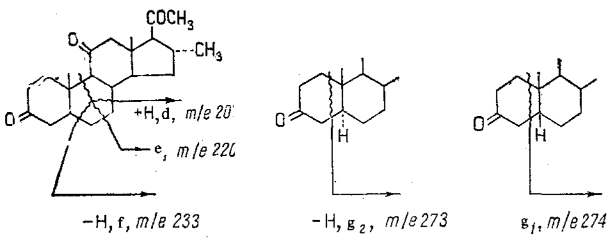
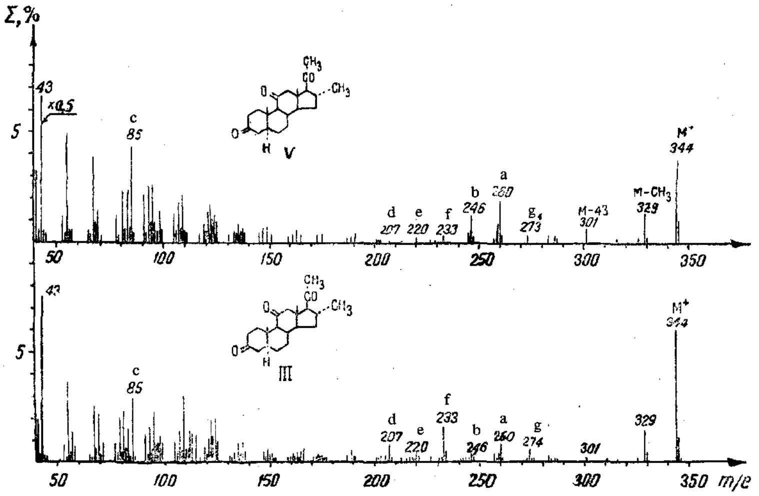
*For part XXXVI se KhPS [Chemistry of Natural Compounds], 6, 33, 1970 [in this issue].



V III

The mass spectra of compounds III and V (see figure) differ from one another only by the magnitude of the individual characteristic peaks, which is typical for the spectra of isomeric compounds. In actual fact, in the spectrum of III peaks d and f, which are formed by the cleavage of the $C_{(9)}-C_{(10)}$ bond at the position of the linkage of rings A and B, are considerably more intense than the corresponding peaks in compound V (Table 1). This permits a cis-linkage of rings A and B (5β- configuration) to be put forward for the triketone III and a trans-A/B linkage (5α-configuration) for compound V.



Mass spectra of the isomeric triketones III and V.

The more intensive formation of fragments arising by the cleavage of bonds at the position of linkage of rings A and B for compounds of the cis-A/B series as compared with their trans-A/B isomers has been observed previously [4] in the mass spectra of the 5α- and 5β- isomers of the 1-, 3-, 4-, 6-, and 11-oxosteroids.

Table 1. Intensities of the Ions d and f in the Mass Spectra of Compounds III and V

Compound	Intensities of the ions, % of M$^+$	
	d (m/e 207)	f (m/e 233)
III	17.3	34.6
V	5.2	6.6

While in compound III the ion g_1 (m/e 274) is formed by the simple cleavage of bonds in the molecular ion at the position of the linkage of rings A and B, the ion g_2 (m/e 273) in the spectrum of V arises as a result of the cleavage of the same bonds but with the migration of a H-atom from the charged fragment. The latter may be connected with the greater ease of migration of a H-atom in the 5α- compounds.

In addition, the considerable increase in the intensities of peaks a, b, and c in the spectrum of V as compared with the corresponding ions in the spectrum of III is apparently due to the fact that the processes of the formation of ions in the breakdown of ring B (the ions d–g) and D (the ions a–c) are competing and, therefore, a decrease in the probability of the formation of the ions d–g leads to a more intensive formation of the ions a–c.

It is an interesting fact that the results of a comparison of the NMR spectra of the triketones III and V does not permit their stereochemistry to be determined. In actual fact, the chemical shifts of the protons at C_{18} and C_{19} do not agree with the values calculated from the empirical additivity rule [5] (Table 2).

Table 2. Chemical Shifts of the Protons of the Angular Methyl Groups

Compound	Chemical shift, ppm			
	19—H		18—H	
	found	calculated	found	calculated
III	1.198	1.243	0.593	0.651
V	1.197	1.235	0.604	0.651

The formation of a compound of the 5α- series, V, in the hydrogenation of the 11-oxo derivative IV and of a compound of the 5β- series, III, in the hydrogenation of the 11α-hydroxy derivative I is in agreement with the results of a number of other workers [6,7]. Thus, the stereochemistry of the hydrogenation of the Δ^4-3-oxo system is determined, as in other cases, by the substituent at C_{11} and is practically independent of the presence of the 16α-methyl group.

EXPERIMENTAL

The mass spectra were recorded on a MKh-1303 industrial instrument fitted with a system for the direct introduction of the sample into the source at 160° C with an ionizing voltage of 60 V; the NMR spectra were recorded on a JNM-4H 100 instrument in $CDCl_3$; the IR spectra were recorded on a UR-10 instrument in paraffin oil; and the UV spectra were recorded in ethanol. The C and H contents found agreed with the calculated values.

11-Hydroxy-16α-methyl-5β-pregnane-3,20-dione (II). A solution of 0.66 g of 4-hydroxy-16α-methylpregn-4-ene-3,20-dione (I) in 20 ml of anhydrous pyridine was hydrogenated at room temperature and atmospheric pressure over 0.1 g of 10% $Pd/CaCO_3$ until the absorption of hydrogen ceased. The catalyst was filtered off and the pyridine solution was poured gradually with stirring into a mixture of dil HCl and ice. The precipitate was filtered off, washed with water to neutrality, and dried. This gave 0.57 g (yield 86.2%) of II with mp 125–127.1° C (from ethyl acetate–hexane or benzene–hexane); ν_{max} 1700 cm^{-1} (CO) and 3480 cm^{-1} (CH).

16α-Methyl-5α-pregnane-3,11,20-trione (V). A solution of 0.98 g of 16α-methylpregn-4-ene-3,11-20-trione (IV) in 30 ml of pyridine was hydrogenated over 0.18 g of 10% $Pd/CaCO_3$ as above. This gave 0.69 g (yield 70.2%) of V with mp 194.2–196.5° C (from a mixture of benzene and hexane); ν_{max} 1710 cm^{-1} (CO).

16α-Methylpregn-4-ene-3,11,20-trione (IV). A solution of 3 g of I in 100 ml of acetone was heated to 25° C, and then 6.5 ml of Kiliani's solution [8] was added (the temperature rising to 50° C) and the mixture was stirred for 0.5 hr. Then it was cooled to 10° C and was slowly added with stirring to 0.5 *l* of water containing ice, and the precipitate was filtered off, washed with water to neutrality, and dried. This material (2.58 g) was dissolved in benzene, transferred to a column of 40 g of Al_2O_3 (activity grade II, passivated by the addition of 2.5% glacial acetic acid) and eluted with benzene; the solvent was evaporated off from the eluate in vacuum, the residue was dissolved in 30 ml of benzene, and 90 ml of hexane was added to the hot solution, and, after cooling, 1.86 g (yield 62.4%) of IV with mp 179–180.5° C from a mixture of ethyl acetate and hexane was filtered off; ν_{max}, cm^{-1}: 1672 (CO unsat.) and 1706 (CO); λ_{max} 239 mμ.

Literature data: mp 183–185° C; λ_{max} 238 mμ [9].

16α-Methyl-5β-pregnane-3,11,20-trione (III). As above, a solution of 1.79 g of II in 100 ml of acetone was oxidized by the action of 3.88 ml of Kiliani's solution, the reaction mixture was poured into 300 ml of water and ice, and the precipitate was filtered off, washed with water to neutrality, and dried. This gave 1.48 g (yield 82.2%) of III with mp 174.5–176.5° C (from a mixture of benzene and hexane); ν_{max} 1703 cm^{-1} (CO).

CONCLUSIONS

1. It has been established that the hydrogenation of 11α-hydroxy-16α-methylpregn-4-ene-3,20-dione and of 16α-methylpregn-4-ene-3,11,20-trione over 10% palladium on calcium carbonate in pyridine takes place stereospecifically and is determined by the substituent at C_{11}.

2. It has been shown that a 16α-methyl group has practically no influence on the stereochemical directivity of the hydrogenation of the ethylenic bond of the Δ^4-3-oxo system.

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