STEREOCHEMISTRY OF PROCESSES OF THE INTRODUCTION OF 16α-METHYL AND 17α-HYDROXYL GROUPS INTO THE STEROID MOLECULE

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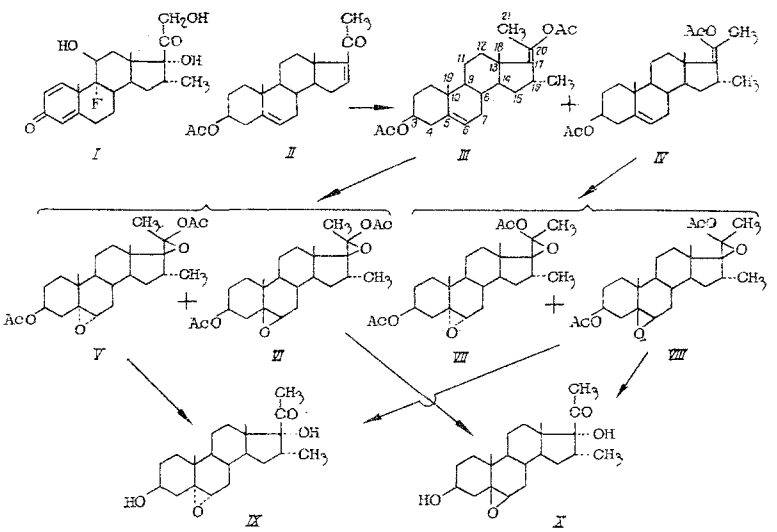
Of the antiinflammatory and antiallergic corticosteroids used in medicine, dexamethasone (I) [1, 2] is characterized by its high therapeutic activity with inappreciable side effects. In [3], a convenient method has been proposed for the simultaneous introduction of the 16α-methyl and 17α-hydroxyl groups into the molecule of Δ^{16}-20-ketopregnanes (II). In this synthesis, the authors [3] observed the formation of stereoisomers of intermediate compounds, i.e., enol acetates and epoxides, but did not study their steric structure.

The aim of the present work was to study the stereochemistry of the key stage processes in the synthesis of 16α-methylcorticosteroids by this method.

During a successive treatment of compound II with methylmagnesium bromide or iodide and acetyl chloride, a mixture of isomeric enol acetates (III, IV) is formed. We isolated the individual stereoisomers by column chromatography, followed by fractional crystallization; their properties correspond to those given in the literature [3].



The isomeric structure of diacetates III, IV was confirmed by PMR spectra, which are practically identical, except for the position of the proton signals of the methyl groups at C^{18} and C^{16}. The difference in the chemical shifts of these protons confirms the isomerism of compounds III and IV, particularly with respect to the $\Delta^{17(20)}$ double bond.

The configuration of isomers III, IV was established by PMR, using a paramagnetic shifting agent (PSA) tris-(dipivaloylmethanato)-europium [$Eu(DPM)_3$]. The PSA-induced shifts, which for each of compounds III, IV corresponds to an induced shift of methyl protons of the acetyl substituent at C^{20}, are listed in Table 1.

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TABLE 1. Relationship between $Eu(DPM)_3$-Induced Chemical Shifts of Protons in Isomers III, IV

Compound	Group							
	C^3H	C^3OCOCH_3	C^6H	$C^{16}CH_3$	$C^{18}H_3$	$C^{19}H_3$	$C^{20}OCOCH_3$	$C^{21}H_3$
III	3.95	2.89	0.06	0.45	0.30	0.41	1	0.79
IV	3,55	2.58	0.07	0.17	0.51	0.44	1	0.74

Note. For each of the compounds, an induced shift of methyl protons of the $C^{20}OCOCH_3$ group was taken as unity.

Because of the strong dependence of the PSA-induced shift on the distance between the Eu^{3+} ion and the proton under consideration [4], the influence of Eu^{3+} coordinated with the oxygen atoms of one of the acetyl groups of compounds III, IV on the chemical shifts of the methyl protons of the other acetyl group should be negligibly small, because of the large distance between these groups (this influence should be deliberately smaller than that of the PSA-induced shift for the H atom at C^6, located almost in the middle between the groups $OCOCH_3$ at C^3 and $OCOCH_3$ at C^{20}). Since the observed values of the induced shifts of the methyl protons of the $OCOCH_3$ groups at C^3 and C^{20} are comparable for each of the compounds III and IV, the Eu^{3+} ion can coordinate with the oxygen atoms of each of the acetyl groups to a comparable degree. Hence, the induced shifts of the methyl protons of the $C^{16}CH_3$, $C^{18}H_3$, and $C^{21}H_3$ groups (and certainly of $C^{20}OCOCH_3$) are determined mainly by the distance between these protons and the Eu^{3+} ion coordinated with the oxygen atoms of the nearest acetyl group, i.e., $C^{20}OCOCH_3$. We can thus relate the observed differences in the induced shifts of $C^{16}CH_3$ and $C^{18}H_3$ protons to the distance to the acetyl group at C^{20}, i.e., to the relative orientation of these groups with respect to the double bond. Thus, the higher value of the induced shift of $C^{18}H_3$ for the low-melting isomer (compared with the shift of $C^{16}CH_3$ in the same isomer, and of $C^{18}H_3$ in the higher-melting isomer) indicates an approximate cisoid orientation of the $C^{18}H_3$ and $C^{20}OCOCH_3$ groups, and a similar orientation of the $C^{16}CH_3$ and $C^{21}H_3$ groups (isomer (IV)). The high-melting isomer is correspondingly characterized by a transoid orientation of the $C^{16}CH_3$ and $C^{21}H_3$ groups (isomer (III)).

If the spectra are compared, we also note that in the case of isomer III, the doublet signal of $C^{16}CH_3$ protons is shifted to the strong field, and in isomer IV, the singlet signal of $C^{18}H_3$ protons is shifted. This shift takes place under the action of the magneto-anisotropic acetate grouping, which, depending on the structure, is situated closer to one or other methyl group. By using this relation, we estimated the ratio between isomers III and IV in the mixture of enol acetates formed in the reaction from the intensity of signals in the PMR spectra. We found that the main product is the trans-compound III, but the ratio between the products depends on the conditions of condensation of ketone II with the Grignard reagent. For example, in the reaction between II and CH_3MgBr at a temperature of about 0°C, or with CH_3MgI by the method given in [3] at 20°C, the III:IV ratio is about 2:1, and in the reaction with CH_3MgI at a temperature of about 0°C, it is nearly 4:1.

Compounds III and IV have identical mass spectra, which confirms their isomeric structure. The peaks of molecular ions are absent in the spectra. The main directions of fragmentation are due to the cleavage of the side chains: $[M - COCH_2]^{+\cdot}$ (m/e = 372), $[M - COCH_2 - CH_3]^+$ (357), $[M - CH_3 - COOH]^{+\cdot}$ (354), $[M - CH_3COOH - CH_2CO]^{+\cdot}$ (312), $[M - CH_3COOH - CH_2CO - CH_3]^+$ (297), $[M - CH_3COOH - COCH_2 - H_2O]^{+\cdot}$ (294), $[M - CH_3COOH - COCH_2 - COCH_3]^+$ (269).

We studied the epoxidation of the individual enol acetates III and IV. By the action of monoperphthalic acid, the two ethylenic bonds in the molecule become epoxidated, and each of the enol acetates forms a mixture of two stereoisomeric diepoxides (V, VI and VII, VIII). This reaction was studied in a greater detail using as an example the epoxidation of compound III; the isomeric diepoxides V, VI were separated by fractional crystallization.

The stereochemistry of compounds V, VI was determined by PMR. The spectra of the isomers differ mostly in proton signals at C^3 and C^6. Thus, the isomerism is due to the different stereochemistry at C^5 and C^6. In the spectrum of compound V, the proton signal at C^6 is observed in a stronger field than that of VI, which indicates, according to the literature data for similar isomeric oxides [5, 6], a 5α,6α-configuration of oxide V, and a 5β,6β-configuration for oxide VI. We also noted that 5α,6α-oxide V is characterized by a longer dis-

tance between the peaks of the doublet* of the C^6H proton (5 and 3 Hz, respectively), and by a broader multiplet signal of the C^3H proton (halfwidth 21 and 16 Hz, respectively).

The isomeric enol acetates VII, VIII are formed in the reaction between cis-enol acetate IV and monoperphthalic acid. Although only one single oxide VII was isolated, we observed the presence of the second isomer VIII in the mixture, similarly as that of the first, by PMR.

The mass spectra of compounds V-VII are similar, which confirms their isomeric structure. Molecular ions appear in the spectra (m/e 446) with a very low intensity. The most intense peaks correspond to fragments $[M - COCH_2]^{+\cdot}$ (404); $[M - COCH_3]^+$ (403); $[M - CH_3COOH]^{+\cdot}$ (386); $[M - COCH_3 - CH_3COOH]^+$ (343); $[M - COCH_3 - 2CH_2COOH]^+$ (283); $[M - COCH_3 - H_2O - 2CH_3COOH]^+$ (265).

Hydrolysis of diepoxides V, VII leads to the formation of a sterically pure compound IX. A peak of the molecular ion with m/e = 362 is observed in its mass spectrum, and also peaks corresponding to the splitting of the epoxide oxygen and substituents in ring D: $[M-O]^+$ (346); $[M - H_2O]^{+\cdot}$ (344); $[M - COCH_3]^+$ (319); $[M - COCH_3 - H_2O]^+$ (301); $[M - COCH_3 - 2H_2O]^+$ (283). The character of the proton signal at C^6 in the PMR spectrum of compound IX is similar to that described above for 5α,6α-epoxides V, VII, which confirms the configuration of the epoxide ring. During the hydrolysis of a mixture of diepoxides V-VIII, a mixture of isomers IX, X is also formed. From an analysis of the PMR spectra of this mixture, for compound X we can assume a 5β,6β-configuration of the epoxide group, and also an identical configuration at C^{17} in the two compounds (IX, X).

Thus, after the transformations according to the above scheme have been carried out, the formation of the mixture of isomers IX, X is due to the nonstereospecific course of the epoxidation stage of the enol acetates III, IV. By comparing the intensities of the proton signals at C^6, we determined the content of isomers in this mixture. We found that during the epoxidation of the mixture of enol acetates (III, IV) at 30°C, a mixture of compounds IX, X was obtained in a ratio of 4.5:1. At lower epoxidation temperature (10°C), the content of 5β,6β-oxide (X) increases, and the ratio of products is about 4:1.

EXPERIMENTAL CHEMICAL PART

The IR spectra were run on the "Perkin-Elmer 457" apparatus (Sweden) in mineral oil; the mass spectra — on the MAT-112 apparatus at an ionizing radiation of 70 eV; the PMR spectra — on the XL-100A, INM-4H-100 and C-60HL apparatus in $CDCl_3$. The values of the chemical shifts are listed on the δ scale, and the position of the tetramethylsilane signal was taken as 0.00 ppm. The course of the reactions and the purity of the compounds was controlled by TLC on Silufol plates.

trans-16α-Methylpregna-5,17(20)-diene-3β,20-diol Diacetate (III) and cis-16α-Methylpregna-5,17(20)-diene-3β,20-diol Diacetate (IV). A Grignard solution obtained from 2.25 g of magnesium, 6.05 ml of methyl bromide and 0.005 g of iodine in 105 ml of THF is added dropwise, at a temperature not higher than 3°C to a solution of 10 g of pregna-5,16-diene-3β-ol-20-one acetate (II) and 0.92 g of CuCl in 90 ml of anhydrous THF, cooled to −10°C. The mixture is stirred for 30 min at 20°C, cooled to 15°C, and a solution of 5.2 ml of acetyl chloride in 29 ml of THF is added dropwise in the course of 30 min. The mixture is stirred 30 min at 20°C, and a solution of 40 g of ammonium chloride in 160 ml of water is added dropwise at a temperature not higher than 25°C. The mixture is stirred for 15 min, and the aqueous layer is separated. The organic layer is washed again by the ammonium chloride solution, and dried, and the solvent is evaporated to dryness. The residue (10.19 g) is deposited on a column with 243 g of silica gel, and by elution with a mixture of chloroform and hexane (1:2), 6.25 g (54%) of a mixture of compounds III and IV are isolated in the form of a light yellow oil. The oil is dissolved in 11 ml of hexane, and held at −3°C, and compound III, and then compound IV are filtered. Enol acetate III, mp 141-144°C (from methanol). IR spectrum, cm^{-1}: 1740, 1745 (C=O). PMR spectrum, δ, ppm: 0.93 (s, $C^{18}H_3$), 1.01 (d, J = 7 Hz, $C^{16}CH_3$), 1.03 (s, $C^{19}H_3$), 1.90 (s, $C^{21}H_3$), 2.03 and 2.10 (s, 2× CH_3COO), 4.59 (m, C^3H), 5.41 (C^6H). Enol acetate IX, mp 107-111°C (from methanol). IR spectrum, cm^{-1}: 1740, 1745 (C=O). PMR spectrum, δ, ppm: 0.86 (s, $C^{19}H_3$), 1.02 (s, $C^{19}H_3$), 1.09 (d, J = 7 Hz, $C^{16}CH_3$), 1.87 (s, $C^{21}H_3$), 2.03 and 2.09 (s, 2× CH_3COO), 4.36 (m, C^3H), 5.40 (C^6H).

*This signal is in the form of a doublet because of the low value of the constant of the spin-spin coupling with one of the vicinal protons at C^7 ($J < 1$ Hz).

Isomers of 16α-methyl-5,6,17,20-dioxidopregnane-3β,20-diol Diacetate (V-VIII). To a solution of 0.5 g of compound III in 15 ml of chloroform, 4.9 ml of a 16.8% ethereal solution of monoperphthalic acid are added dropwise in the course of 30 min at 25°C, and then after 15 h, a solution of 1.16 of $NaHCO_3$ in 35 ml of water is added dropwise at 30°C. The organic layer is separated, washed with water, and dried. The solvent is evaporated *in vacuo*, and 0.54 g (yield, almost quantitative) of a mixture of diepoxides V, VI is obtained. By fractional crystallization from methanol, compound V is isolated, and then compound VI. Diepoxide V, mp 192-194.5°C (from methanol). IR spectrum, cm^{-1}: 1720 (C=O). PMR spectrum, δ, ppm: 0.83 (d, J = 6 Hz, $C^{16}CH_3$), 0.90 (s, $C^{19}H_3$), 1.06 (s, $C^{19}H_3$), 1.70 (s, $C^{21}H_3$), 2.01 (s, 2 × CH_3COO), 2.86 (d, J = 5 Hz, C^6H), 4.93 (m, C^3H). Found, %: C 69.87; H 8.54; $C_{26}H_{38}O_6$. Calculated, %: C 69.98; H 8.51. Diepoxide VI, mp 181-183°C (from hexane). IR spectrum, cm^{-1}: 1720 (C=O). PMR spectrum, δ, ppm: 0.90 (d, J = 6 Hz, $C^{16}CH_3$), 0.95 (s, $C^{18}H_3$), 0.99 (s, $C^{19}H_3$), 1.72 (s, $C^{21}H_3$), 2.02 (s, 2 × CH_3COO), 3.10 (d, J = 3 Hz, C^6H), 4.75 (m, C^3H). Found, %: C 69.22; H 8.69. $C_{26}H_{38}O_6$. Calculated, %: C 69.68, H 8.51. Enol acetate IV is epoxidized as above, and from the mixture of compounds VII, VIII, diepoxide VII is isolated, mp 194-196°C (from methanol). IR spectrum, cm^{-1}: 1740 (C=O). PMR spectrum, δ, ppm: 0.80 (d, J = 6 Hz, $C^{16}CH_3$), 0.86 (s, $C^{18}H_3$), 1.07 (s, $C^{19}H_3$), 1.66 (s, $C^{21}H_3$), 2.02 (s, 2 × CH_3COO), 2.88 (d, J = 5 Hz, C^6H), 4.94 (m, C^3H, halfwidth 21 Hz). Found, %: C 70.25; H 8.64. $C_{26}H_{38}O_6$. Calculated, %: C 69.98; H 8.51.

16α-Methyl-5α,6α-hydroxypregnane-3β,17β-diol-20-one (IX). A solution of 0.5 g of compound V in 37 ml of methanol is boiled for 15 min in an argon atmosphere. The mixture is cooled to 20°C, and 0.25 g of KOH are added. After 2 h, the mixture is neutralized by 0.25 ml of acetic acid, the solvent is evaporated *in vacuo*, and 0.39 g (97.5%) of compound (IX), mp 246-250°C (from ethyl acetate) is filtered. According to literature data [7], mp 245°C. IR spectrum, cm^{-1}: 1699 (C=O), 3400 (OH). PMR spectrum, δ, ppm: 0.73 (s, $C^{18}H_3$), 0.90 (d, J = 6 Hz, $C^{16}CH_3$), 1.06 (s, $C^{19}H_3$), 2.22 (s, $C^{21}H_3$), 2.92 (d, J = 5 Hz, C^6H).

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