STEREOCHEMICAL ASPECTS OF THE FORMATION OF TOXISTEROLS A

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Mechanisms for the formation of toxisterol A are suggested. The connection between the conformation of the initial previtamin and the stereochemistry of the reaction products is discussed.

The photochemical isomerization of provitamins D and previtamins D is the key stage of the industrial production of calciferols – group D vitamins [1]. This process is complicated by the fact that toxisterols – products of the transformations of the hexa-1,3,5-triene chromophores of 9,10-secosterols – accumulate in the reaction mixture [2, 3]. The presence in the conjugated polyene system of voluminous cyclic substituents leads to a decrease in the conformational mobility of the 9,10-secosterols and has an influence on the stereochemistry of their reactions [4, 5]. A study of the mechanism of these processes is of interest for the photochemistry of polyenic natural compounds.

The aim of the present work was to study the cyclization of the conjugated triene chromophore of the 9,10-secosterols leading to the formation of toxisterols A.

After prolonged radiation of the initial ergosta-5,7,22-trien-3β-ol (ergosterol) (I), three diastereomers were isolated from the reaction mixture: toxisterol$_2$ A1 (V), toxisterol$_2$ A2 (IV), and toxisterol$_2$ A3 (III). The structures of the compounds investigated (III-V) were confirmed by the agreement of the results of physicochemical analysis (Table 1) with known characteristics [2, 3, 6].

Toxisterols$_2$ A (III-V) differ by the configurations of the substitutents at the C-4 and C-8 asymmetric atoms, as was established from their PMR spectra (see Table 1) [2, 6]. In the spectra of each of compounds (IV) and (V) the spin-spin splitting of the H-4 signal (δ = 2.46 and 2.70, respectively) corresponds to axial-axial interaction (J = 11 Hz) [7] with H-3α. Consequently, in toxisterols$_2$ A1 and A2 H-4 has the β-orientation (for the toxisterols the nomenclature and numbering of the atoms used for sterols are retained). This was confirmed by the high value $W_{1/2}$ = 35 Hz for the multiplet corresponding to H-3 [δ = 3.83 (V) and 3.77 (IV)] due to axial-axial interaction with two protons.

The small value of $W_{1/2}$ for the signals of the H-4 proton (δ = 2.62, $W_{1/2}$ = 9 Hz) and the H-3 proton (δ = 4.62 and $W_{1/2}$ = 19 Hz) in the spectrum of toxisterol$_2$ A3 is explained by the axial-equatorial interaction of these protons [2, 7]. Thus, in compound (III) H-4 has the α-orientation.

In the spectrum of toxisterol$_2$ A1 a very long-range spin-spin interaction of the vinyl proton at C-7 and the methyl group at C-13 is observed [2]. This indicates their spatial propinquity, which is possible only with the S-configuration of the substituents at C-8.

Thus, the toxisterols$_2$ A isolated from the reaction mixture have the following configurations of the chiral centers: 4S, 8S (A1, V); 4S, 8R (A2, IV); and 4R, 8R (A3, III). The formation of a fourth diastereomer, with the 4R, 8S configuration (VI), is possible, but this compound was not detected in the reaction mixture, which agrees with previous results [3].

Experiments on the irradiation of ergosterol in heptane and ethanol showed that toxisterols$_2$ A1 and A3 were formed in both solvents, while toxisterol$_2$ A2 was formed only in the alcoholic medium (see Table 1). Mass-spectrometric analysis showed the presence of a deuterium atom in the molecule of the toxisterol$_2$ A2 obtained as the result of the reaction in O-deuteromethanol. This was shown by an increase in the m/z values of the peaks

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TABLE 1. Relative Molar Yields, Physicochemical Characteristics, and Results of the Analysis of Toxisterols$_2$ A

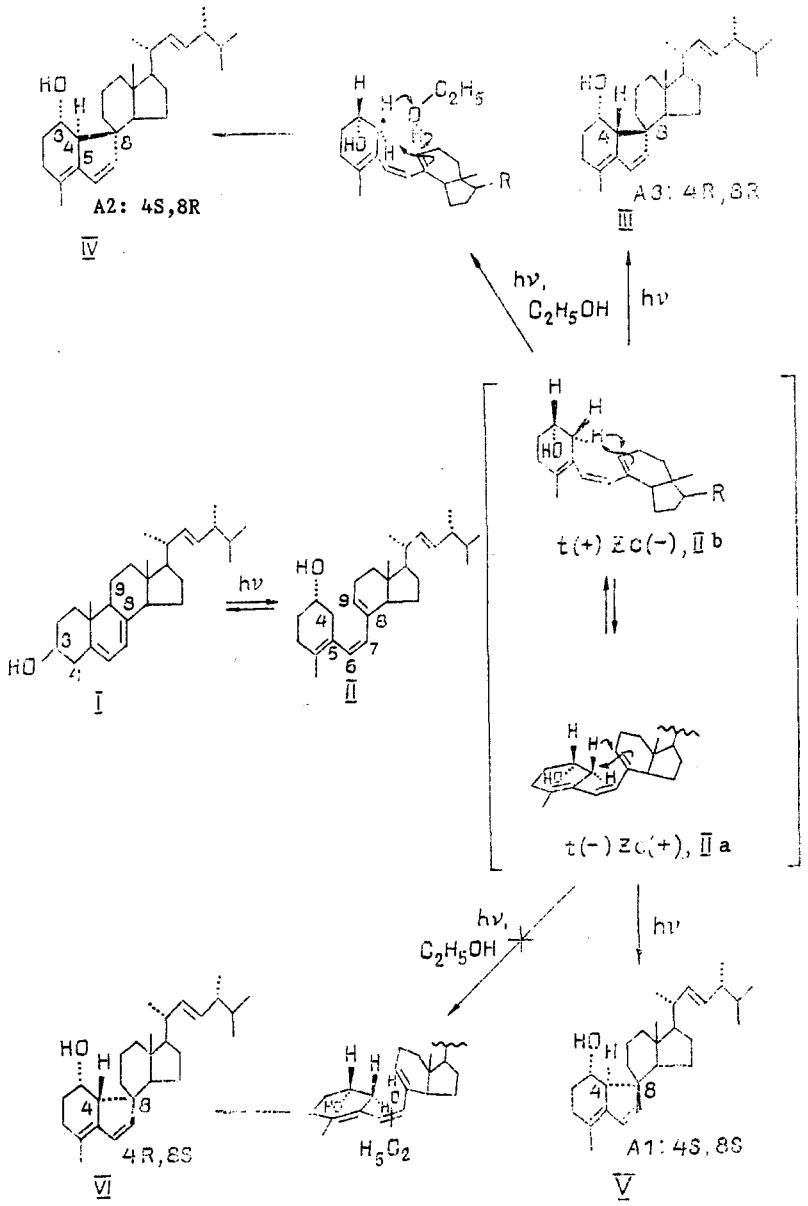
Index	Toxisterol$_2$ A1 $C_{28}H_{44}O$	Toxisterol$_2$ A1 $C_{28}H_{44}O$	Toxisterol$_2$ A1 $C_{28}H_{44}O$
Relative yield, %			
in heptane	5±1	0	2±1
in ethanol	3±1	6±2	1±0,5
Melting point, °C	93–95	Oil	Oil
R_f	0,57	0,31	0,35
Relative retention time in relation to ergosterol, R_t (GLC)	0,94	0,65	0,87
UV spectrum ($\lambda_{max}^{C_6H_{14}}$, nm (ε))	251 (15000)	251 (14200)	252 (13000)
PMR spectrum ($CDCl_3$; δ, ppm); J, Hz; 0 – TMS	0,84 (6H, d, J=7, CH_3-26 and CH_3-27), 0,91 (3H, s, CH_3-18), 0,94 and 1,01 (6H, 2 d, J=7, CH_3-21 and CH_3-28), 1,68 (3H, s, CH_3-19) 2,46 (1H, d, J=11, H-4β), 3,83 (1H, m, $W_{1/2}$=35, H-3α), 5,18 (2H, m, H-22 and H-23), 6,29 (2H, s, H-6 and H-7)	0,91 (3H, s, CH_3-18), 0,79 and 0,88 (6H, 2 d, J=7, CH_3-26 and CH_3-27), 0,99 and 1,09 (6H, 2 d, J=7, CH_3-21 and CH_3-28), 1,68 (3H, s, CH_3-19), 2,70 (1H, d, J=11, H-4β) 3,77 (1H, m, $W_{1/2}$=35, H-3α), 5,21 (2H, m. H-22 and H-23) 6,06 and 6,35 (2H, 2 d, J=7 H-6 and H-7	0,78 (3H, s, CH_3-18), 0,84 (6H, d, J=7, CH_3-26 and CH_3-27), 0,92 and 1,01 (6H, 2 d, J=7, CH_3-21 and CH_3-28), 1,76 3H, and CH_3-19), 2,62 (1H, m, $W_{1/2}$=9, H-4α), 4,62 (1H, m, $W_{1/2}$=19, H-3α). 5,18 (2H. m, H-22 and H-23), 5,40 and 6,20 (2H, 2 d, J=5, H-6 and H-7)
Mass spectrum (m/z, %)			
from ethanol	396 (31), 381 (3,8), 378 (83) 376 (100), 363 (18), 271 (13), 253 (16), 211 (19), 176 (52), 158 (74)	396 (41) 381 (5,1), 378 (80), 376 (100), 363 (15), 271 (15), 253 (31), 211 (25), 176 (61), 158 (81)	396 (42), 381 (2,7), 378 (87), 376 (100), 363 (11), 271 (21), 253 (28), 211 (17), 176 (58), 158 (89)
from O-deuteromethanol	396 (31), 378 (83), 376, (100), 363 (18), 271 (13), 176 (52), 158 (74)	397 (32), 379 (85), 377 (100), 364 (14) 272 (15), 177 (48), 159 (70)	396 (42), 378 (87), 376 (100), 363 (11). 271 (21), 176 (58), 158 (89)

in the mass spectrum by 1 a.u. (see Table 1). At the same time, the mass spectra of samples of (V) and (III) obtained in heptane, in ethanol, and in O-deuteromethanol coincided. Thus, the mechanism of the formation of toxisterol$_2$ A2 differs from the mechanism of the formation of toxisterols$_2$ A1 and A3 and includes a stage of the interaction of the initial compound or an intermediate with an alcohol molecule, accompanied by the migration of a proton.

It is known that toxisterols$_2$ A are formed from the tZc-conformation of 9,10-secoergosta-5(10),6Z,8,22-tetraen-3β-ol (previtamin D_2) (II) – the primary product of the photoisomerization of ergosterol [4]. The conjugated trienic system of compound (II) is not completely planar, as is shown by the low value of the extinction coefficient (ε = 7900). The tZc-conformer of previtamin D_2, like ergocalciferol [8], probably consists of two conformers which undergo interconversion through rotation around the C-5–C-6 bond in the transoid and the C-7–C-8 bond in the cisoid part of the molecule: t(–)Zc(+) (IIa) ⇆ t(+)Zc(–) (IIb).

The closure of the 5-membered ring must be accompanied by the transfer of a proton from the C-4 to the C-9 atom [2]. Apparently, the cleavage of the C-4–H bond and the formation of the C-9–H and C-4–C-8 bonds take place synchronously, which lowers the activation energy of the process. It can be seen from the scheme that cyclization from the t(–)Zc(+)-conformer of the previtamin (IIa) leads to the 8S-configuration, and cyclization from the t(+)Zc(–)-conformer to the 8R-configuration. In the absence of a protonic solvent, in conformation (IIb) there is the transfer of the 4β-proton, which is spatially close to

the C-9 atom. Then a chiral center with the R-configuration arises at C-4 (scheme). Under the same conditions, in conformation (IIa) the transfer of the 4α-proton takes place and the S-configuration of the substituents on the asymmetric C-4 atom arises. In an aprotic solvent, the 4α proton in (IIb) and the 4β-proton in (IIa), which are spatially remote from C-9, do not undergo transformations. Thus, in heptane, toxisterol A1 (4S, 8S, V) is formed from the t(−)Zc(+)-conformer (IIa) and toxisterol A3 (4R, 8R, III) from the t(+)Zc(−)-conformer (IIb).



The processes described above take place on irradiation in a protonic solvent (ethanol). In addition, in the excited state of the t(+)Zc(−)-conformer (IIb) a specific transfer of the 4α-proton to the oxygen atom of the alcohol takes place with the simultaneous transfer of the hydroxylic proton to the C-9 atom. As a result, a chiral center with the S-configuration at C-4 and, accordingly, toxisterol A2, (4S, 8R, IV) are formed. From the t(−)Zc(+)-conformer (IIa), the analogous process should lead to a diastereomer of toxisterols A with the R-configuration at C-4 and 8-S (VI), which has not been found in the reaction mixture. This is due to the steric hindrance for the nucleophilic attack by the alcohol molecule on the 4β-proton apparently created by the 3β-hydroxy group (see scheme). This mechanism explains the formation of toxisterol$_2$ A2 exclusively in an alcoholic solvent, and also the production of a deuterated compound when the reaction is performed in O-deuteromethanol. The absence of the deuteration of toxisterols$_2$ A1 and A3 under these

conditions is due to the impossibility of the participation of the voluminous hydroxy (deuteroxy) group of the alcohol in the process of proton transfer because of the small distance between H-4 and C-9 in this case.

EXPERIMENTAL

Mass spectra were taken on a MKh-1310 instrument with the direct introduction of the samples at an energy of the ionizing electrons of 7 eV. PMR spectra were obtained on a Tesla BS-497 spectrometer (100 MHz) with $CDCl_3$ as solvent, 0 – TMS. UV spectra were taken on a Shimadzu UV-3000 spectrophotometer in hexane. The preparative separation of compounds (I-V) was carried out on a 0.8 × 40 cm column of Silpearl silica gel with gradient elution [from hexane to hexane–ether (4:6)]. TLC was conducted on Silufol plates (Czechoslovakia) in the solvent system hexane–ether–methanol (20:30:1). The substances were revealed by spraying the plates with a mixture of 50 mg of $FeCl_3$ and 5 ml of acetic acid in 100 ml of 50% H_2SO_4. GLC was performed on Tsvet-105 chromatograph with a 2.5 mm × 4 m glass column containing 5% of the phase OV-17 on Chromaton N Super with a grain size of 150-200 μm, flame-ionization detector, carrier gas He at a rate of flow of 30 ml/min, temperature of the column thermostat 280°C.

Toxisterols, A (II-IV). A 100-ml quartz test tube was charged with 50 mg of ergosterol (I) in 50 ml of ethanol or heptane and was irradiated with the light of a DRL 250 mercury lamp under argon at 20°C for 5 h. The oxygen present in the solution had previously been eliminated by bubbling argon through it for 30 min. The quantitative analysis of the mixture was carried out by the GLC method. After the end of irradiation, the solvent was distilled off in vacuum and the reaction mixture was separated on a column of Silpearl silica gel.

The irradiation of 5 mg of ergosterol in 5 ml of O-deuteromethanol was carried out by the same procedure in a 20-ml quartz test tube. To retard deuterium exchange, the process was conducted at a temperature of 0°C. The mixture was separated by TLC.

SUMMARY

1. The formation of toxisterol A2 includes a stage of the transfer of a proton from the hydroxy group of the solvent – an alcohol – to a molecule of a previtamin D.

2. Mechanisms of the formation of toxisterols A have been suggested which take into account the link between conformation of the initial previtamin and the configuration of the chiral centers in the reaction products.

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