OXIDATIVE TRANSFORMATIONS OF LABDANE DIOLS.

III. PREPARATION OF ACIDS WITH A STROBANE SKELETON FROM LARIXOL

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It has been shown that the oxidation of larixol with chromic acid mixture forms methyl 6-oxo-8α,13α-epoxystroban-14β-oate, methyl 6-oxo-8α,13α-epoxystroban-14α-oate, and 6,13-dioxo-14,15-bisnorlabd-7-en-17-oate.

In order to obtain perfume substances we have investigated the oxidation of the bicyclic diterpene diol larixol (I) with chromic acid mixture. The neutral components of this reaction were isolated and characterized previously [1].

In the present paper we give information on the composition of the acid products of the oxidation of larixol with chromic acid mixture containing different amounts of active oxygen.

Since the reaction takes place in an acid medium, in addition to oxidation it is impossible to exclude the cyclization of the larixol. There is a fairly large amount of information in the literature on such rearrangements of bicyclic diterpenoids [2-4].

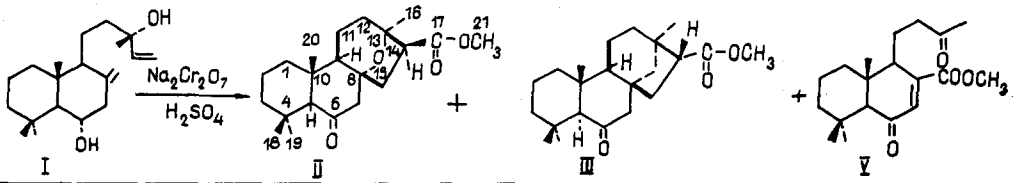
In the action on compound (I) of a chromic acid mixture containing 8 g-atoms of active oxygen about 60% of acidic substances was formed, but when the amount of active oxygen was increased to 10 g-atoms the amount of such substances fell to 41%.

The compositions of the acidic fractions of the reaction mixtures obtained with different amounts of oxidant were the same, consisting of three main components which were treated with diazomethane and analyzed in the form of the methyl esters.

By adsorption chromatography on silica gel we isolated a crystalline substance (II) with mp 183-183.5°C the IR spectrum of which contained absorption bands characteristic for keto (1720 cm^{-1}) and ester (1250, 1740 cm^{-1}) groups. The PMR spectrum of compound (II) showed the signals of four methyl groups — at (ppm) 0.80 (3 H), 0.90 (3 H), and 1.17 (6 H) and of a methoxy group at 3.62 (3 H, singlet). There were no signals of olefinic protons in the weak-field region of the spectrum. The ^{13}C NMR spectrum showed that the substance contained 21 carbon atoms including the fragments $>C_6=O$ and $-\overset{O}{\overset{\|}{C}}{}_{17}O-$ (208.25 and 174.4 ppm), $-HC_{14}-COOCH_3$ (66.2 ppm). In the mass spectrum of (II), the molecular ion with m/z 348 corresponded, according to the results of elementary analysis, to the empirical formula $C_{21}H_{32}O_4$. These facts permitted the assumption that in the process of oxidation a new carbon skeleton had been formed. To demonstrate the structure of the substance isolated we performed an x-ray structural analysis.

The structure and relative configuration of the molecule of (II) are shown in Fig. 1 (for a discussion, see below).

On the basis of IR, PMR, ^{13}C NMR spectra and XSA we established for the new compound the structure of methyl 6-oxo-8α,13α-epoxystroban-14β-oate (II).



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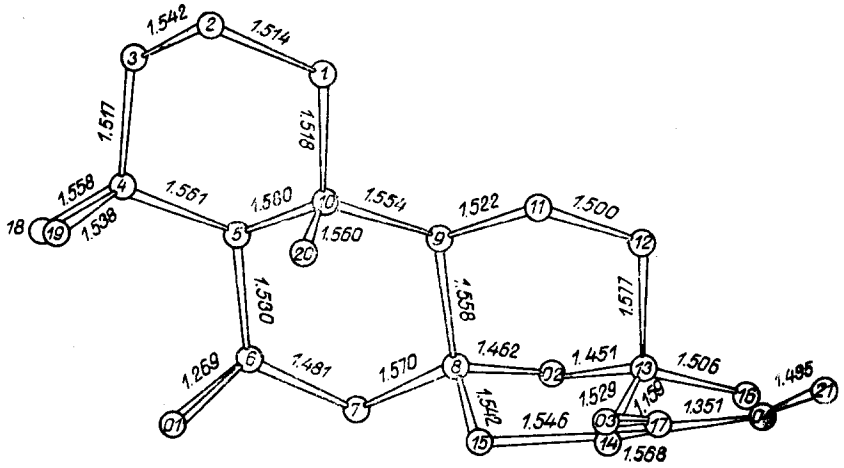


Fig. 1. Crystal structure of methyl 6-oxo-8α,13α-epoxystroban-14β-oate (II). The probable errors of the bond lengths are 0.020 Å.

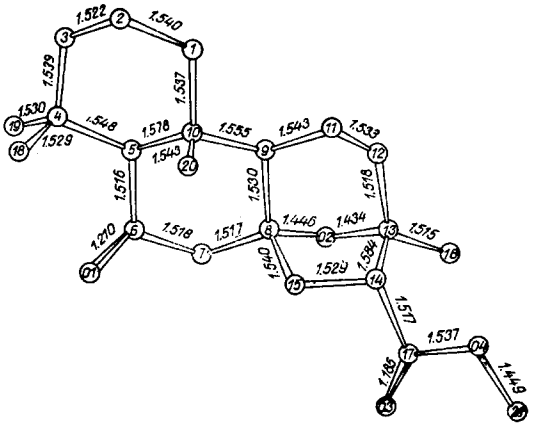


Fig. 2. Crystal structure of methyl 6-oxo-8α,13α-epoxystroban-14α-oate (III). The probable errors of the bond lengths are 0.008 Å.

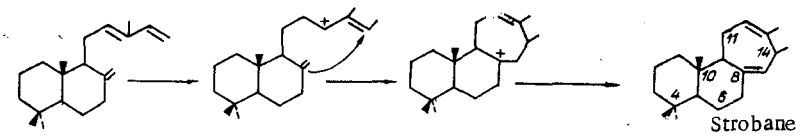
In addition to compound (II), we isolated a methyl ester with mp 148-149°C, which differed from (II) only by the chemical shifts of the methyl groups in its PMR spectrum [ppm: 0.86 (3 H); 0.90 (3 H); 1.18 (3 H); and 1.37 (3H)]. The downfield shift of the methyl group at C_{13} is due to the influence of the oxygen of the methoxycarbonyl group at C_{14}. Otherwise, the spectral characteristics of (II) and (III) are close, which permits them to be regarded as isomers.

For a definitive proof of the structure of (III) we carried out an x-ray structural analysis. The structure of the molecule established by this method is shown in Fig. 2. The geometries of the (II) and (III) molecules are of the usual type and are very close. All the 6-membered rings have the chair form and the 5-membered rings the envelope form. We may note a lengthened C_5—C_{10} bond of 1.580 (A) Å in (II) and 1.578 (7) Å in (III). In the molecule of (III), the $COOCH_3$ group is almost eclipsed by the C_{16} methyl group (the C_{16}—C_{13}—C_{14}—C_{17} torsional angle is 17°). Such a situation apparently leads to a lengthening of the C_{13}—C_{14} bond to 1.584 (8) Å and to a distortion of the envelope conformation of the 5-membered heterocycle. On the basis of the results of XSA, the compound has the structure of methyl 6-oxo-8α, 13α-epoxystroban-14α-oate (III) and differs from (II) only by the configuration of the methoxycarbonyl group at C_{14} (see Fig. 2 and Table 1).

Thus, the oxidation of larixol yielded two isomeric epoxy derivatives of strobane (II) and (III). The question of the formation of diterpenoids with the strobane skeleton has attracted scientists' attention [3, 5]. Hypotheses have been put forward according to which the precursors of strobane may be bicyclic diterpenoids the cyclization of which leads to the formation of the strobane skeleton.

TABLE 1. Coordinates of the Nonhydrogen Atoms ($\times 10^4$) in Fractions of the Cell of Compounds (II) and (III)

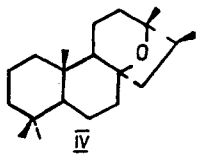
Atom	x	y	z	x	y	z
	Compound II			Compound III		
C_1	4039 (17)	0764 (14)	7207 (6)	1852 (6)	7092 (4)	11319 (5)
C_2	3766 (18)	0460 (16)	6585 (8)	2541 (5)	7999 (4)	11100 (6)
C_3	1742 (17)	0486 (15)	6427 (7)	2071 (6)	8525 (4)	10033 (5)
C_4	0598 (18)	−0402 (13)	6770 (7)	2089 (5)	7950 (4)	8878 (5)
C_5	0980 (15)	−0082 (14)	7405 (7)	1457 (5)	7014 (5)	9125 (4)
C_6	−0102 (20)	−0787 (14)	7853 (7)	1324 (4)	6343 (4)	8090 (4)
C_7	−0133 (15)	−0324 (14)	8444 (6)	0477 (5)	5550 (4)	8270 (5)
C_8	1824 (17)	−0068 (13)	8676 (6)	0634 (4)	5014 (3)	9421 (4)
C_9	3024 (15)	0557 (13)	8215 (6)	0864 (4)	5685 (4)	10454 (4)
C_{10}	3007 (14)	−0050 (13)	7618 (6)	1820 (4)	6424 (4)	10249 (4)
C_{11}	4879 (16)	0791 (15)	8473 (7)	0954 (6)	5116 (5)	11614 (5)
C_{12}	4706 (18)	1426 (14)	9036 (7)	−0025 (6)	4409 (4)	11712 (5)
C_{13}	3275 (20)	0810 (16)	9443 (7)	−0215 (5)	3870 (4)	10567 (4)
C_{14}	3592 (17)	−0571 (14)	9508 (7)	0948 (5)	3410 (4)	10166 (5)
C_{15}	2675 (21)	−1172 (14)	8987 (7)	1423 (5)	4152 (4)	9318 (5)
C_{16}	3041 (21)	1542 (15)	9980 (7)	−1233 (5)	3219 (5)	10645 (6)
C_{17}	5583 (21)	−1036 (17)	9588 (7)	0798 (5)	2457 (4)	9576 (5)
C_{18}	1000 (20)	−1763 (14)	6611 (8)	3306 (5)	7842 (5)	8428 (6)
C_{19}	−1415 (20)	−0138 (17)	6658 (7)	1410 (7)	8510 (4)	7961 (6)
C_{20}	3361 (18)	−1360 (12)	7629 (7)	2993 (5)	5956 (4)	10101 (5)
C_{21}	8257 (21)	−0578 (20)	10136 (8)	0454 (4)	0847 (4)	10002 (7)
O_1	−0970 (16)	−1756 (11)	7729 (6)	1840 (3)	6406 (3)	7167 (3)
O_2	1583 (11)	0832 (9)	9130 (4)	−0435 (3)	4546 (2)	9651 (3)
O_3	6253 (16)	−1839 (13)	9342 (7)	0758 (4)	2300 (3)	8546 (3)
O_4	6308 (12)	0342 (12)	10005 (6)	0702 (4)	1793 (3)	10409 (4)



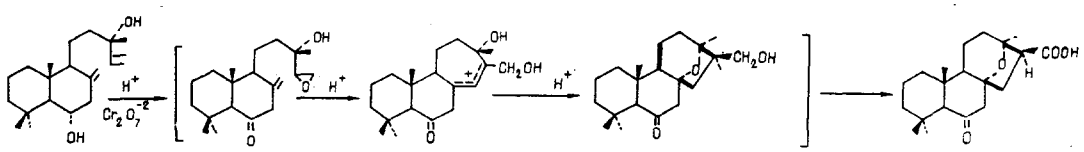
Strobane

Characteristic for the strobane skeleton is the presence of a secondary methyl group at C_{14}.

A biomimetic synthesis of the strobane skeleton has recently been effected by the oxymercuration-demercuration of epimanool, a precursor of larixol: 8,13-epoxystrobane (IV) was obtained. A cyclization of this type takes place only with epimanool, which determines the stereochemistry at C_{13} [6].


IV

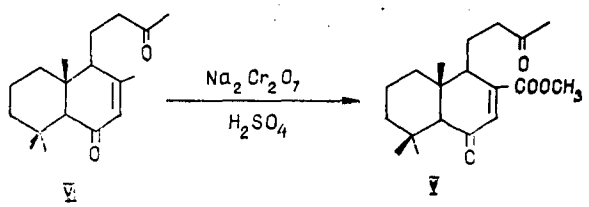
Consequently, the oxidation of larixol with chromic acid mixtures leads not only to oxidative transformations (formation of a keto group at C_6) but also to acid-catalyzed cyclization with the formation of compounds with a new skeleton. The formation of an epoxy analog of strobane under the reaction conditions is possible by the scheme



Earlier, on the oxidation of the dieterpene diol sclareol with chromic acid mixture, an oxa analog of the tetracyclic diterpenoid gibbane — 14-oxagibban-16-one — was isolated from the reaction products [2].

In addition to compounds (II) and (III), we isolated a methyl ester (V) with mp 46-47°C. The IR spectrum of this compuund had adsorption bands characteristic for an α,β-unsaturated ketone (1690, 1730 cm^{-1}). In the PMR spectrum there were the signals of three methyl groups, of the protons of a methoxy group at 3.74 ppm (3 H, singlet), of a methyl ketone group at 2.1 ppm (3 H), and of a trisubstituted double bond (6.3 ppm (1 H), doublet with J = 2 Hz). The ^{13}C NMR spectrum showed that compound (V) contained 19 carbon atoms, including the fragments >C₆=O, —C(=O)—CH₃ (207.9 and 199.7 ppm) —COOCH₃ (168.2 ppm) and two carbon atoms linked by a double bond (149.2 and 132.2 ppm) (>C=CH—). The UV spectrum showed an absorption maximum at 238 nm (log ε 2.91). In the mass spectrum, a peak with a mass of 320 corresponded to the molecular ion.

On the basis of its spectral characteristics, we ascribed to this compound the structure of methyl 6,13-dioxa-14,15-bisnorlabd-7-en-17-oate (V), which is the product of the oxidation of the diketone (VI) as was confirmed experimentally.



VI V

EXPERIMENTAL

Melting points were determined on a Kofler instrument. IR spectra were recorded on a UR-20 spectrophotometer using KBr tablets, and PMR and ^{13}C NMR spectra on a Bruker WP-200 SY instrument in $CDCl_3$ solutions. The chemical shifts, which are given on the δ scale, were measured relative to the solvent (7.24 ppm for $CHCl_3$ in PMR and 76.90 ppm for $CDCl_3$ in ^{13}C NMR). Mass spectra were recorded on a MS-902 instrument, and UV spectra in ethanol on a Specord UV-VIS instrument.

Oxidation of Larixol with a Chromic Acid Mixture Containing 10 g-Atoms of Active Oxygen per Mole of Diol. The procedure described in [7] was used. The chromic acid mixture prepared from 10.4 g of sodium dichromate, 10.4 ml of sulfuric acid (d 1.84), and 16 ml of water was used to oxidize 3.2 g of the diol (I) in 10 ml of acetic acid at room temperature, and this gave 1.36 g of neutral products and 1.65 g of acidic substances. The acidic products were treated with a solution of diazomethane, and the resulting methyl esters (1.5 g) were chromatographed on a column of silica gel.

The first fraction was eluted with petroleum ether—diethyl ether (20:1). This gave 0.03 g of a mixture of four products, which was not further investigated. The second fraction was eluted with petroleum ether—diethyl ether (1:1). This gave 0.77 g of a mixture of compounds (II) and (III). This fraction was additionally separated on a column of SiO_2, and petroleum ether—diethyl ether (1:1) yielded 0.48 g of the methyl ester (II) with mp 183-183.5°C (methanol—chloroform). By the same solvent, a mixture of compounds (II) and (III) (0.32 g) was isolated from the same fraction.

The third fraction was eluted with diethyl ether and yielded 0.6 g of a mixture of substances (III) and (V).

Additional purification of the mixture on a column of silica gel with diethyl ether—petroleum ether (70:30) led to the isolation of a white crystalline substance (III) (0.33 g) with mp 148-149.5°C (methanol—chloroform). In addition to compound (III), by means of diethyl ether this fraction yielded 0.24 g of compound (V) with mp 46-47°C (methanol—chloroform).

Methyl 8α,13α-epoxystroban-14β-oate (II). PMR spectrum, ppm: 0.8, 0.91, 1.17 (4 CH_3), 3.62 (—OCH_3). ^{13}C NMR spectrum, ppm: 16 (q, C_{20}—), 17.85 (t), 18.1 (t, C_2—), 21.65 (q, 38.38 (t), 38.65 (t), 39.83 (s, C_{10}—), 42.32 (t), 51.62 (q, C_{21}—), 52.35 (d), 54.95 (d, C_5—), 55.61 (t), 66.2 (d, C_{14}—), 81.69 (s, C_8—), 84.99 (s, C_{13}—), 174.4 (s, C_{17}—), 208.25 (s, C_6—).

Found, %: C 73.3; 72.2; H 9.3; 9.1. $C_{21}H_{32}O_4$.
Calculated, %: C 72.78; H 9.26. M 348.47.

Mass spectrum (m/z, intensity, %): 348(84), 332(16), 291(17), 287(10), 261(14), 262(4), 263(5), 243(10), 245(4), 224(8), 225(4), 219(8), 217(4), 182(16), 181(6), 164(3), 165(12), 151(32), 148(10), 149(8), 137(12), 131(10), 135(12), 123(32), 109(36), 95(24), 91(12), 83(24), 81(32), 79(18), 69(28), 55(40), 43(100).

Methyl 6-oxo-8α,13α-epoxystroban-14α-oate (III). PMR spectrum, ppm: 0.86 (3 H), 0.9 (3 H), 1.18 (3 H), 1.37 (3 H), 3.67 (—OCH_3). ^{13}C NMR spectrum, ppm: 15.96 (q, C_{20}—), 17.86 (t), 18.15 (t, C_2—), 21.69 (q, C_{19}—), 26.19 (q, C_{16}—), 32.08 (s, C_4—), 32.72 (q, C_{18}—), 33.90 (t), 36.50 (t), 38.52 (t), 39.97 (s, C_{10}—), 42.32 (t), 51.75 (q, C_{21}—), 54.13)d, C_5—), 55.60 (d, C_9—), 56.2 (t, C_{15}—), 66.39 (d, C_{14}—), 81.24 (s, C_8—), 84.29 (s, C_{13}—), 172.1 (s, C_{17}—), 208.3 (s, C_6—).

Found, %: C 72.36; 72.40; H 9.0; 9.1. $C_{21}H_{32}O_4$.

Calculated, %: C 72.78; H 9.26. M 348.48.

Mass spectrum (m/z, intensity, %): 348(100), 333(15), 330(18.5), 317(12.5), 316(11.7), 315(11.3), 286(11.7), 274(10.0), 263(3.8), 262(13.0), 263(26.3), 243(12.5), 231(6.3), 224(13.8), 219(8.8), 218(5.0), 217(2.5), 204(15.0), 197(5.0), 196(16.3), 192(7.5), 191(8.8), 181(10.5), 179(5.0), 178(8.0), 175(11.5), 166(7.5), 165(11.3), 164(13), 163(7.5), 151(41.5), 135(21.0), 123(31.0), 122(13.3), 119(8.8), 109(40.5), 107(22), 95(39.3), 94(24.5), 93(23.3), 83(30.3), 81(43.3), 79(23.5), 69(35.0), 67(33.0).

X-Ray Structural Analysis of Compounds (II) and (III). The x-ray structural investigations of (II) and (III) were performed on a Syntex $P2_1$ diffractometer using Mo radiation with a graphite monochromator.

Crystallographic characteristics of (II): a = 7.39(1), b = 10.89(2), c = 23.55(4) Å, z = 4; space group $P2_12_12_1$; d_{calc} = 1.22 g/cm³.

Crystallographic characteristics for (III): a = 11.780(3), b = 14.188(4), c = 11.295(3) Å, z = 4; space group $P2_12_12_1$; d_{calc} = 1.23 g/cm³.

The intensities of the reflections (±hk$l$ for (II) and hk$l$ for (III)) were measured by the 2θ/ω-scanning method in the range of 2θ < 40° for (II) (plate with a thickness of ~0.01 mm) and 2θ < 50° for (III). The structures were interpreted by the direct method and were refined by the method of least squares in the anisotropic full-matrix approximation to R = 0.084 and R = 0.058 for 788 and 1359 observed ($I > 2\sigma$) reflections for (II) and (III), respectively. The coordinates of the hydrogen atoms were given geometrically and were not refined. All the calculations were performed by the SHELX-76 program. The coordinates of the nonhydrogen atoms obtained are given in Table 1.

Methyl 6,13-dioxo-14,15-bisnorlabd-7-en-17-oate (V). IR spectrum: 1730, 1690 cm^{-1}.

PMR spectrum, ppm: 0.87 (3 H), 1.06 (3 H), 1.33 (3 H), 2.1 (—$COCH_3$), 3.74 (—OCH_3), 6.3 (d with J = 2 Hz). ^{13}C NMR spectrum, ppm: 207.9 (s), 199.7 (s), 168.2 (s), 149.2 (s), 132.2 (d) 63.3 (d), 52.1 (q), 51.19 (d), 45.06 (t), 42.71 (t), 42.51 (s), 38.6 (t), 33.0 (q), 32.07 (s), 29.70 (q), 21.92 (t), 21.35 (q), 17.76 (t), 14.68 (q).

UV spectrum: $\lambda_{max}^{C_2H_5OH}$ 238 nm (log ε 2.91).

Oxidation of 6,13-Dioxo-14,15-bisnorlabd-7-ene (VI) with Chromic Acid Mixture. The chromic acid mixture prepared from 0.74 g of sodium dichromate, 0.74 ml of sulfuric acid (d 1.84) and 1.2 ml of water was used to oxidize 0.2 g of the diol (VI) in 0.7 ml of acetic acid at room temperature. This gave 0.02 g of neutral products and 0.13 g of acidic substances. The acidic fraction was treated with diazomethane and the resulting methyl esters were recrystallized from methanol and chloroform, giving 0.07 g of white crystals of substance (V) with mp 46-47°C. A mixture of the two samples of substance (V) gave no depression of the melting point.

SUMMARY

1. The acidic products of the oxidation of larixol by chromic acid mixture have been studied.

2. The structures of two isomeric diterpenoids having the carbon skeleton of strobane — methyl 6-oxo-8α,13α-epoxystroban-14β-oate and methyl 6-oxo-8α,13α-epoxystroban-14α-oate — have been established by spectral methods and x-ray structural analysis.

3. The structure of methyl 6,13-dioxo-14,15-bisnorlabd-7-en-17-oate is proposed for a new compound found in the reaction products.

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HYDROGEN BONDS OF 5α-CHOLESTANOLS AND THEIR ETHERS

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It has been shown by IR spectroscopy that the equatorial oxygen atoms of cholestanol and its methyl ether possess a greater capacity for forming H bonds as proton acceptors than the axial atoms of the corresponding epimeric compounds. The constants of the equilibrium phenol + ether $\rightleftarrows$ H-complex (1:1) in CCl_4 at room temperature are 13 and 7 liter/mole, respectively, for the methyl esters of cholestanol and of epicholestanol.

The determining role of the orientation of the 3-hydroxy group in the complex-formation by sterols is well known [1]. Sterols containing an equatorial 3-hydroxy group possess a greater tendency to form complexes than the epimeric compounds the hydroxy group of which is present in the axial position. This is shown in the formation of crystal hydrates and of complexes with acids, saponins, polyenic antibiotics, and phospholipids. An explanation of the observed differences in complex-formation is based on differences in the possibility of the formation of a hydrogen bond between the hydroxy group of the sterol and some acceptor of the proton of the second component of the complex, although the existence of a hydrogen bond has been shown experimentally only in sterol hydrates [2, 3].

In complexes with polyenic antibiotics and phospholipids there has been no proof of the formation of hydrogen bonds, but their existence is one of the working hypotheses in considering the structure of the complexes [4, 5]. The possibility of the formation of a hydrogen bond between the hydroxyl of a sterol and the ester group of a phospholipid has been confirmed by a consideration of molecular models [6-8]. Here, because of the hydrophobic interaction of the rigid cyclopentanoperhydrophenanthrene system and the fatty-acid chains of the phospholipid, the sterol molecule is fixed in relation to the phospholipid in such a way that only an equatorial, but not an axial, hydroxyl can form a hydrogen bond with the ester group of the phospholipid.

Thus, in a consideration of the possibility of the appearance of a hydrogen bond with the participation of an equatorial or an axial hydroxyl, it is assumed that the difference arises only because of the rigid fixation of the sterol molecules relative to the second component of the complex, and, consequently, because of the different positions of the hydroxyl in relation to the proton-acceptor. It is assumed that in general the proton-donating capacity of the 3-hydroxy group for the formation of a hydrogen bond does not depend on its orientation in the sterol molecule. The validity of this hypothesis has been confirmed by Kunst et al. [9] — in CCl_4 solution the thermodynamic parameters of the hydrogen bonds of the two epimeric 5α-cholestanols with tetrahydrofuran as proton acceptor are equal and the parameters of the hydrogen bond for dimerization are practically the same.

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