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CHEMICAL MODIFICATION OF THE trans,trans-GERMACRANOLIDE STIZOLICIN

SYNTHESIS, MOLECULAR, AND CRYSTAL STRUCTURE OF 6α-ACETOXY-13-METHOXY-1,10; 4,5-DIEPOXY-1,5,7α(H),8,11β(H)-E,E-GERMACR-8,12-OLIDE

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The results of the chemical modification of stizolicin, a sesquiterpene lactone of the trans,trans-germancrane type and, in particular, the epoxidation, saponification, and acetylation of its molecule are discussed. On the basis of the results of an x-ray structural experiment, for 6-acetoxy-13-methoxy-1,10-epoxystizolicin we propose the structure of 6α-acetoxy-13-methoxy-1,10: 4,5-diepoxy-1,5,7α(H),8,11β(H)-E,E-germacr-8,12-olide.

The chemical modification of the molecules of natural compounds is one of the methods for a purposeful change in their biological properties. In this respect, interest is presented by sesquiterpene γ-lactones, which are considered as polyfunctional compounds in chemical transformations [1].

Stizolicin (I), a sesquiterpene lactone of the germacrane type, is known as a compound with a cytotoxic action (LD_{50} = $9.4 \cdot 10^{-1}$ μg/ml and 4.7 μg/ml for cultures of P-388 and KB cells, respectively) and an antitumoral activity in vivo in relation to murine leukemia P-388 (T/C 123% at 16 mg/kg) [2].

In this paper we present the results of the epoxidation saponification, and acetylation reactions of stizolicin (I).

Stizolicin (I) is a trans-trans-germacranolide with the composition $C_{20}H_{26}O_7$, mp 152-153.5°C, $[\alpha]_D^{25}$ −32.4° (C 2.19; ethanol) isolated from Stizolophus balsamita (Lam.) Cass. ex Takht., S. coronopifolius (Lam.) Cass., Centaurea solstitialis L., and Saussurea elongata DC [3, 4].

In order to obtain a hydroxy derivative of stizolicin we performed the saponification of this lactone under various conditions.

As can be seen from the scheme of transformations, the reactions of stizolicin (I) with a 1 M solution of K_2CO_3 in methanol at pH 10-11 gave derivative (II). Its IR spectrum contained absorption bands in the 3450 cm^{-1} region that is characteristic for a hydroxy group, and at 1780 cm^{-1} characteristic for the carbonyl of a γ-lactone. The PMR spectrum lacked the signal of the protons of an ester group but a signal of the protons at C-6 and C-8 appeared in the form of a complex multiplet with its center at 4.15 ppm and so did the signals of the protons of a methoxy group, (singlet at 3.29 ppm (3H)) and of methylene protons at C-13 in the form of two doublets of doublets at 3.52 and 3.82 ppm with $J_{13a,11}$ = 9 Hz, $J_{13a,13b}$ = 2 Hz, $J_{13b,11}$ = 10 Hz for each. See scheme on following page.

To assign the complex multiplet at 4.15 ppm and to establish the structure of the molecule of derivative (II) we performed its acetylation. When (II) was treated with acetic

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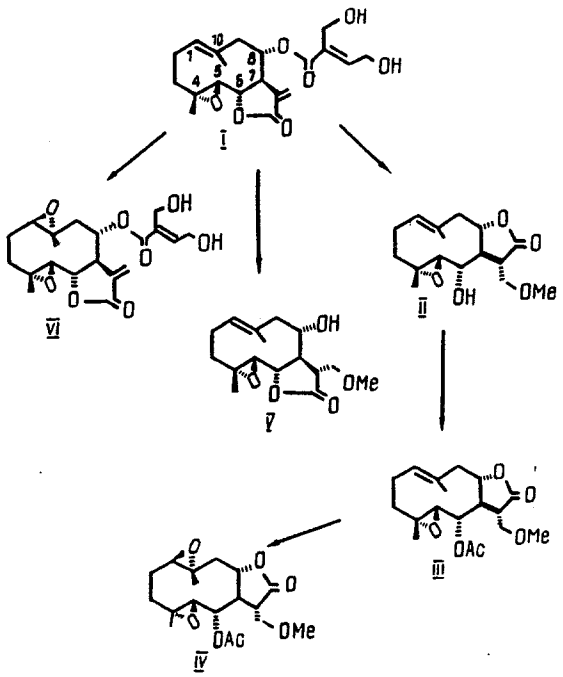

Scheme of the chemical transformations of stizolicin (I).

anhydride in pyridine the acetyl derivative (III) was obtained. The IR spectrum of (III) showed the absorption band of the carbonyl of an acetyl group at 1760 cm^{-1} and an additional absorption band in the 1240 cm^{-1} region. The PMR spectrum contained the signals of the protons of an aceto group – a singlet at 2.1 ppm with an intensity of 3 H – and of a hemiacetyl proton – in the form of a triplet at 4.9 ppm with $J_{6,7}$ = 9 Hz. The change in the multiplicity of the lactone proton (q.d., 4.12 ppm, with $J_{8,7}$ = 10.5 Hz, $J_{8,9a}$ = 7Hz, $J_{8,9b}$ = 2 Hz) permitted the assumption of a possible relactonization of the lactone ring from the C_6–C_7 to the C_7–C_8 position.

On the basis of the spectral results obtained, for (III) we suggest the structure of 6-acetoxy-13-methoxy-4,5-epoxygermacr-1(10)-en-8,12-olide. Consequently, derivative (II) had the structure of 6-hydroxy-13-methoxy-4,5-epoxygermacr-1(10)-en-8,12-olide.

On the basis of the transformation described above, it was possible to conclude that on the hydrolysis of stizolicin at pH 10-11, in all probability, three successive reactions took place in situ: methoxylation at the exomethylene group of the γ-lactone, hydrolysis of the ester bond, and rearrangement of the lactone ring into the C-8 position which together led to derivative (II). The greatest interest is presented by the rearrangement of the lactone ring. It may be suggested that during the saponification of the ester group of stizolicin a fairly stable alcoholate ion was formed at C-8, which, being a good nucleophile, instantaneously attacked the carbonyl group of the γ-lactone with the formation of derivative (II). Such a rearrangement is also favored by the conformation of the basic skeleton of the (I) molecule and the spatial arrangement of the interacting active centers.

The epoxidation of (III) with m-chloroperbenzoic acid in chloroform in the presence of 0.5 M solution of sodium bicarbonate gave the crystalline derivative (IV). The structure of its molecule was determined by means of an x-ray structural experiment and is shown in Fig. 1. The bond lengths (see Fig. 1) and valence angles (Table 1) are the usual ones within the limits of error [5]. The lactone and germacrane rings are trans-linked (the torsional angle H7C7C7H7 is 136(2)°. The values of the torsional angles C2C1C10C9 (155(2)°) and C3C4C5C6 (155(2)°) relative to the C1–C10 and C4–C5 bonds, constricted by the epoxide bridges, permit the (IV) molecule to be assigned to the 1,10; 4,5-diepoxy-trans,trans-germacranolides. As can be seen From Fig. 1, the Me groups at the C4 and C-10 atoms have the syn orientation in the β-direction. The C10C1C4C5 pseudotorsional angle amounts to −79(2)°. On the basis of this and the values of the intracyclic torsional angles in the germacrane skeleton (Table 2), for the 10-membered ring we suggest a chair–chair conformation of the $_1D^{14}$, $^{15}D_5$ type.

A comparison of C2C1C10C9 and C3C4C5C6 torsional angles in trans,trans-germacranolides with C1=C10 and C4=C5 double bonds and with epoxide bridges at these bonds showed that the

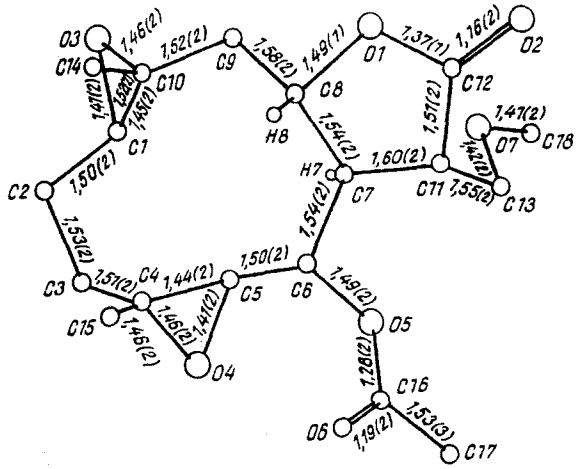

Fig. 1. Structure of the (IV) molecule.

TABLE 1. Valence Angles ω (degrees)

Angle	ω	Angle	ω
C8O1C12	113 (1)	C6C7C11	111 (1)
C1O3C10	59 (1)	C8C7C11	103 (1)
C4O4C5	60 (1)	O1C8C7	105 (1)
C5O5C16	113 (1)	O1C8C9	105 (1)
C13O7C18	114 (1)	C7C8C9	117 (1)
O3C1C2	117 (1)	C8C9C10	115 (1)
O3C1C10	60 (1)	O3C10C1	61 (1)
C2C1C10	123 (1)	O3C10C9	113 (1)
C1C2C3	111 (1)	O3C10C14	112 (1)
C2C3C4	113 (1)	C1C10C9	120 (1)
O4C4C3	112 (1)	C1C10C14	125 (1)
O4C4C5	58 (1)	C9C10C14	112 (1)
O4C4C15	113 (1)	C7C11C12	104 (1)
C3C4C5	119 (1)	C7C11C13	114 (1)
C3C4C15	118 (1)	C12C11C13	108 (1)
C5C4C15	121 (1)	O1C12O2	121 (1)
O4C5C4	62 (1)	O1C12C11	109 (1)
O4C5C6	118 (1)	O2C12C11	130 (1)
C4C5C6	128 (1)	O7C12C11	108 (1)
C5C6C5	106 (1)	O5C16O6	132 (1)
O5C6C7	105 (1)	O5C16C17	108 (1)
C5C6C7	113 (1)	O6C16C17	120 (1)
C6C7C8	114 (1)		

TABLE 2. Intracyclic Torsional Angles φ (degrees)

Angle	φ	Angle	φ
C10C1C2C3	−109 (2)	C8C9C10C1	−98 (2)
C1C2C3C4	52 (2)	C9C10C1C2	155 (2)
C2C3C4C5	−88 (2)		
C3C4C5C6	155 (2)	O1C8C7C11	24 (1)
C4C5C6C7	−118 (2)	C8C7C11C12	−24 (2)
C5C6C7C8	83 (2)	C7C11C12O1	14 (1)
C6C7C8C9	−101 (2)	C11C12O1C8	1 (1)
C7C8C9C10	90 (2)	C7C8O1C12	−17 (1)

epoxidation of the double bonds leads, as a rule, to a decrease in the corresponding angles from 179-163° to 156-148° (see, for example, [7-9]) in the chair–chair conformation of the 10-membered ring. When double bonds and epoxide bridges are absent, the corresponding angles may diminish to 100° [9].

Considerable changes are also undergone by other endocyclic torsional angles, but the chair–chair conformation is retained. It is interesting to note that a calculation by the method of molecular mechanics of the 10-membered 1,5-dienic ring in the chair–chair conformation by the program of Allinger and Bovill gives values of the endocyclic torsional angles at the double bonds of 172 and 168° , respectively [7]. At the same time, the molecule has an axis of twofold symmetry passing through the centers of the C2–C3 and C7–C8 bonds.

A comparison of the corresponding torsional angles (IV) and ivaxillin (VII) [10], which is 1,10:4,5,-diepoxy-1,5,7,11α(H),8β(H)-E,E-germacr-8,12-olide showed that their maximum difference was 5° and the mean difference 3°, which indicated only slight influence on the conformation of the 10-membered ring of an equatorially oriented acetoxy group at the C6 atom.

The lactone ring in the (IV) molecule has the form of a 7α-envelope: the C8, C11, C12, and O1 atoms are present in one plane to an accuracy of ±0.008 Å, and the C7 atom departs from it by 0.41 Å (the C13 atom deviates from this plane by 1.02 Å in the α-direction, having a pseudoequatorial orientation). The O2 atom is present practically in the main plane of the ring. A comparison of the conformation of the lactone rings in (IV) and (VII) (7α-envelope) shows that the pseudoaxial orientation of the C13 atom in (VII) ($\Delta C_S^7 = 4.0°$) introduces a more considerable distortion into the envelope conformation of the lactone ring than the pseudoequatorial orientation in (IV) $\Delta C_S^7 = 2.1°$).

Thus, it has been established that the molecule of (IV) has the structure of 6α-acetoxy-13-methoxy-1,10:4,5-diepoxy-1,5,7α(H),8,11β(H)-E,E-germacr-8,12-olide.

The interaction of stizolicin with a 1 M solution of K_2CO_3 in methanol at pH 8-9 gave derivative (V). The IR spectrum of (V) contained absorption bands characteristic for a hydroxy group in the 3450 cm^{-1} region and for the carbonyl of a γ-lactone at 1780 cm^{-1}. The PMR spectrum lacked the signals of the protons of the ester group, but the signals of the protons of a methoxy group were observed – a singlet at 3.29 ppm of gem-hydroxylic proton – ddd 4.14 ppm with $J_{8,6} = 9$ Hz, $J_{8,7} = 4$ Hz, and $J_{8,9} = 8.5$ Hz – and of a lactone – triplet, 4.19 ppm, with $J_{6,7} = J_{6,5} = 8.5$ Hz.

On the basis of its spectral characteristics, for (V) we proposed the structure of 8-hydroxy-13-methoxy-4,5-epoxygermacr-1(10)-en-6,12-olide. This permitted the conclusion that a decrease in the basicity of the reaction medium to pH 8-9 in the hydrolysis of the ester group in the (I) molecule did not lead to a rearrangement of the lactone ring. However, under these conditions, as well, it was impossible to exclude methoxylation at the exomethylene group of the γ-lactone.

In order to obtain the 1,10-epoxy derivative of stizolicin, the initial lactone (I) was treated with m-chloroperbenzoic acid in chloroform in the presence of a 0.5 M solution of $NaHCO_3$. The IR spectrum of the derivative (VI) so obtained showed intense absorption bands of hydroxy groups in the 3450 cm^{-1} region and of carbonyls of a γ-lactone and of a ester group at 1750 and 1740 cm^{-1}, respectively. The PMR spectrum contained, in addition to the signals of the protons of the exomethylene group of the γ-lactone and those of an ester residue, the signals of the protons of methyl groups at epoxide rings: two singlets at 1.3 and 1.4 ppm of 3 H each and the signals of the epoxide protons – H-1 in the form of a broadened doublet of doublets at 3.32 ppm with $J_{1,2a} = 10$ Hz and $J_{1,2b} = 9$ Hz, and H-5 in the form of a doublet at 2.56 ppm with J = 9 Hz.

Since the stizolicin molecule has the conformation of a 1,4-trans,trans-germacradienolide, its epoxidation forms a 1β,10α-epoxy derivative. Consequently, for (VI), it is possible to suggest the structure of 8α-(4'5'-dihydroxytigloyloxy)-1β,10α:4α,5β-diepoxy-1,5,7α,6β(H)-E,E-germacr-6,12-olide.

EXPERIMENTAL

The course of the reactions and the purity of the products were monitored by TLC on Silufol UV-254 plates in the hexane–ethyl acetate S(1:4) and ethyl acetate systems; the revealing agents were saturated $KMnO_4$ solution and concentrated H_2SO_4. The reaction products were separated by flash column chromatography using type LL silica gel with a particle size of 100-160 μm (Chemapol) as sorbent.

Melting points were determined on a Boëtius stage. Specific rotations were measured on a SM-2 polarimeter in a 1 dm cell. IR spectra were recorded in tablets with KBr and in $CHCl_3$ solution on a UR-20 spectrophotometer, PMR spectra on a Bruker WP-200 SY instrument in $CDCl_3$ (CS, ppm; δ scale relative to TMS; SSCC, Hz), and mass spectra on a Finnigan MAT-8200 instrument. The elementary analyses of the compounds obtained corresponded to the calculated figures.

6α-Hydroxy-13-methoxy-4,5-epoxygermacr-1(10)-en-8,12-olide (II). At room temperature, 1.3 ml of a 1 M solution of K_2CO_3 (pH 10-11) was added to a solution of 500 mg (1.3 mmole) of stizolicin (I) in 14 ml of methanol and the mixture was stirred for 3 h. Then the solvent

was distilled off under vacuum, the residue was diluted with ethyl acetate and was washed with 0.5% HCl solution and with water and was filtered, and the solvent was eaporated off to give 0.45 g of crude product (residue). The residue, which gave two spots, with R_f 0.7 and 0.45, was chromatographed on a column containing 10 g of silica gel.

When the column was eluted with hexane–ethyl acetate (2:3), 270 mg (70% yield) of (II) was isolated. Colorless oily product with the composition $C_{16}H_{24}O_5$, $[\alpha]_D^{20}$ +47° (c 0.01; $CHCl_3$), R_f 0.7. IR spectrum ($\nu_{max}^{CHCl_3}$, cm^{-1}): 3450; 3030; 2945; 2870; 1780; 1540; 1460; 1400; 1210; 1190; 1020; 940. PMR spectrum (δ, ppm): 1.22 (3H, s, CH_3-4); 1.65 (3H, s, CH_3-10); 2.93 (1H, d, $J_{5,6}$ = 9 Hz, H-5); 3.29 (3H, s, CH_3–O-13), 3.52 and 3.82 (1H each, $J_{13a,11}$ = 10 Hz; $J_{13b,11}$ = 9, Hz, $J_{13a,13}$ = 2 Hz; CH_2-11); 4.15 (2H, m, H-6 and H-8); 5.15 (1H, br. d, J = 9 Hz, H-1).

Elution of the column with ethyl acetate yielded 123 mg (25%) of a colorless crystalline substance with the composition $C_{20}H_{26}O_7$, mp 152-153°c, R_f 0.45, which was identified as part of the initial stizolicin that has not reacted.

6-Acetoxy-13-methoxy-4,5-epoxygermacr-1(10)-en-8,12-olide (III). At room temperature, 0.15 ml of acetic anhydride was added to a solution of 210 mg (0.7 mmole) of derivative (II) in 0.12 ml of pyridine, and the mixture was stirred at 40-50°C for 50 h. Then, after cooling, the reaction mixture was diluted with chloroform and was washed with 3% HCl and with water to neutrality, dried over $MgSO_4$, and filtered, and the solvent was distilled off. The residue (250 mg) was recrystallized from ethyl acetate, giving 212 mg of (III). Yield 90%. On TLC it gave one spot with the composition $C_{18}H_{26}O_6$, mp 166-168°C, $[\alpha]_D^{22}$ +58° (c 0.003; $CHCl_3$). IR spectrum (ν_{max}^{KBr}, cm^{-1}): 3030, 2950; 2880; 1780; 1760; 1470; 1390; 1240; 1130; 1010.

PMR spectrum (δ, ppm): 1.28 (3H, s, CH_3-4); 1.78 (3H, s, CH_3-10); 2.1 (3H, s, CH_3CO–); 2.93 (1H, d, $J_{5,6}$ = 9 Hz, H-5); 3.39 (3H, s, H_3C–O-13); 3.52 and 3.82 (1H each, dd, $J_{13a,11}$ = 9Hz; $J_{13a,13b}$ = 2 Hz; $J_{13b,11}$ = 10 Hz, CH_2-11), 4.12 (1H, q.d., $J_{8,7}$ = 12.5 Hz; $J_{8,9a}$ = 7 Hz; $J_{8,9}$ = 2 Hz; H-8); 4.90(1H, tr., $J_{6,5}$ = $J_{6,7}$ = 9 Hz; H-6), 5.28 (1H; br. tr., $J_{12a,12b}$ = 8 Hz; H-1).

6α-Acetoxy-13-methoxy-1,10:4,5-diepoxygermacr-8,10-olide (IV). At room temperature, 75 mg (0.43 mmole) of m-chloroperbenzoic acid was added to a solution of 130 mg (0.38 mmole) of derivative (III) in 5 ml of chloroform and 5 ml of a 0.5 M solution of $NaHCO_3$, and the mixture was stirred for 12 h. Then it was washed with water, dried over $MgSO_4$, and filtered, and the solvent was distilled off. The residue (150 mg) which gave on TLC two spots, with R_f 0.8 and 0.40 was chromatographed on a column containing 7 g of silica gel. Elution of the column with hexane–ethyl acetate (4:1) led to the isolation of 29 mg (23%) of a colorless crystalline substance with the composition $C_{18}H_{26}O_6$, mp 166-168°C, R_f 0.8, identified as part of the initial acetyl derivative (III) that had not reacted.

Hexane–ethyl acetate (1:4) fractions yielded 102 mg (76%) of derivative (IV). Colorless crystalline substance with the composition $C_{18}H_{26}O_7$, mp 183-185°C (ethanol), $[\alpha]_D^{25}$ + 40° (c 0.001; chloroform, R_f 0.40. IR spectrum (ν_{max}^{KBr}, cm^{-1}: 3030, 2945, 2870, 1790, 1750, 1470, 1380, 1235, 1130, 1040, 920. PMR spectrum (δ, ppm): 1.3 (3H, s, CH_3-4); 1.4 (3H, s, CH_3-10), 2.1 (3H, s, OAc); 2.93 (1H, d, $J_{5,6}$ = 9 Hz, H-5; 3.05 (1H, dd, $J_{1,2a}$ = 3.5 Hz; $J_{1,2b}$ = 8.5 Hz, H-1), 3.39 (3H, s, MeO-13); 3.52 and 3.82 (1H each, dd, $J_{13a,11}$ = 8.5 Hz; $J_{13a,13b}$ = 2.5 Hz; $J_{13b,11}$ = 10 Hz; CH_2-11); 4.15 (1H, q.d., $J_{8,7}$ = 9 Hz; $J_{8,9a}$ = 6.5 Hz; $J_{8,9b}$ = 2 Hz, H-8), 4.96 (1H, q, $J_{6,5}$ = 11 Hz, $J_{6,7}$ = 9 Hz; H-6).

X-Ray Structural Experiment. The cell parameters and the densities of 1401 reflections from a crystal of (IV) were measured on a Hilger–Watts automatic four-circle diffractometer (λMoK_α, graphite monochromator, θ/2θ scanning, 2θ ≤ 60°). The crystals were tetragonal, a= 12.607(1), c = 11.576(2) Å, V = 1839.9(4) $Å^3$, M = 322.4, d_{calc} = 1.16 g/cm^3, Z = 4 ($C_{17}H_{22}O_6$), sp. gr. $P4_1$.

The structure was interpreted by the direct method and was refined by the block-diagonal MLS in the anisotropic approximation for the oxygen atoms and the isotropic approximation for the carbon atoms. The positions of the H atoms were revealed in a difference synthesis and were not refined. All the calculations were made on an Eclipse S/200 computer by the INEXTL programs [11]. The final divergence factors were R - 0.079 and R_w = 0.068. The coordinates of the nonhydrogen atoms are given in Table 3.

TABLE 3. Coordinates of the Nonhydrogen Atom (× 10^3)

Angle	x	y	z
O1	872 (1)	477 (1)	202 (1)
O2	898 (1)	493 (1)	15 (1)
O3	683 (1)	467 (1)	570 (1)
O4	701 (1)	66 (1)	388 (1)
O5	752 (1)	133 (1)	161 (1)
O6	878 (1)	14 (1)	207 (1)
O7	661 (1)	317 (1)	11 (1)
C1	670 (1)	356 (1)	531 (1)
C2	672 (1)	272 (1)	623 (1)
C3	661 (1)	162 (1)	569 (1)
C4	740 (1)	143 (1)	473 (1)
C5	712 (1)	174 (1)	357 (1)
C6	786 (1)	201 (1)	260 (1)
C7	773 (1)	316 (1)	216 (1)
C8	834 (1)	348 (1)	288 (1)
C9	760 (1)	465 (1)	379 (1)
C10	763 (1)	417 (1)	497 (1)
C11	824 (1)	329 (1)	90 (1)
C12	868 (1)	441 (1)	91 (1)
C13	742 (1)	320 (1)	−9 (1)
C14	871 (1)	413 (1)	556 (1)
C15	850 (1)	124 (1)	506 (1)
C16	808 (1)	50 (1)	150 (1)
C17	765 (1)	−12 (2)	46 (2)
C18	522 (1)	411 (1)	−84 (1)

8α-Hydroxy-13-methoxy-4,5-epoxygermacr-1(10)-en-6-olide (V). At room temperature, 0.7 ml of a 1 M solution of K_2CO_3 (pH 8-9) was added to a solution of 500 mg (1.3 mmole) of stizolicin in 10 ml of methanol, and the mixture was stirred for 4 h. Then the methanol was distilled off under reduced pressure, and the residue was diluted with ethyl acetate (9 ml), washed with water, dried over $MgSO_4$, and filtered, and the solvent was distilled off. The residue (480 mg), which gave two spots on TLC, with R_f 0.70 and 0.45, was chromatographed on a column containing 10 g of silica gel.

When the column was eluted with hexane–ethyl acetate (2:3), 232 mg (60% yield) of (V) was obtained. Colorless oily product with the composition $C_{16}H_{24}O_5$, $[\alpha]_D^{22}$ + 55° (c 0.015; $CHCl_3$), R_f 0.70. IR spectrum ($\nu_{max}^{CHCl_3}$, cm^{-1}): 3450; 3030; 2945; 2870; 1780; 1540; 1460; 1400; 1210; 1190; 1020; 940. PMR spectrum (δ, ppm): 1.22 (3H, s, CH_3-4); 1.65 (3H, s, CH_3-10); 2.93 (1H, d, $J_{5,6}$ = 9 Hz, H-5); 3.39 (3H, s, MeO-13); 3.52 and 3.82 (1H each, m, $J_{13a,11}$ = 8 Hz, $J_{13a,13b}$ = 2 Hz; $J_{13b,11}$ = 9 Hz, CH_2-11); 4.14 (1H, ddd, $J_{8,9a}$ = 9 Hz; $J_{8,9b}$ = 1.5 Hz; H-8), 4.20 (1H, tr, $J_{6,5,7}$ = 8.5 Hz, H-6); 5.15 (1H, br. d., $J_{1,2}$ = 9 Hz, H-1). Elution of the column with ethyl acetate led to the isolation of 167 mg (34%) of that part of the initial stizolicin that had not reacted, with R_f 0.45.

8α-(4',5'-Dihydroxytigloyloxy)-1,10;4,5-diepoxygermacr-6,12-olide (VI). At room temperature, 34 mg (0.2 mmole) of m-chloroperbenzoic acid was added to a solution of 100 mg (0.2 mmole) of stizolicin in 10 ml of MeOH and 10 ml of 0.5 M solution of $NaHCO_3$. The mixture was stirred for 13 h and was then washed with water, dried over $MgSO_4$, and filtered, and the solvent was distilled off. The residue (110 mg), which gave two spots on TLC, with R_f 0.45 and 0.30, was chromatographed on a column containing 2 g of silica gel.

Elution of the column with hexane–ethyl acetate (1:9) led to the isolation of 227 mg (30%) of a substance with R_f 0.45, which was identified as the initial stizolicin (I).

Ethyl acetate fractions gave 70 mg (65% yield) of (VI). Colorless crystalline substance with the composition $C_{20}H_{26}O_8$, mp 208-210°C (methanol), $[\alpha]_D^{23}$ −196°C (c 0.003; acetone), R_f 0.16. IR spectrum (ν_{max}^{KBr}, cm^{-1}); 3450; 3030; 2945; 2870; 1750; 1740; 1675; 1655; 1470; 1300; 1200; 1130; 1080; 1040; 980. PMR spectrum (δ, ppm): 1.30 (3H, s, CH_3-4); 1.36 (3H, s, CH_3-10); 2.56 (1H, d, $J_{5,6}$ = 9 Hz; H-5); 3.22 (1H, dd, $J_{1,2a}$ = 10 Hz, $J_{1,2b}$ = 9 Hz, H-1); 3.7 (1H, m, H-7); 4.55 (1H, q, $J_{6,5}$ = 9 Hz, and $J_{6,7}$ = 6.5 Hz, H-6); 4.65 (2H, s, CH_2-2'), 4.72 (1H, d, $J_{8,7}$ = 4.2, $J_{8,9a}$ = 10.9, $J_{8,9b}$ = 1.5, H-8), 4.80 (2H, d, J = 5 Hz; CH_2-3'); 5.90 and 6.35 (1H each, d, J = 3 Hz; CH_2-11); 7.4 (1H, tr, $J_{3',4'}$ = 5.5 Hz; H-3').

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STRUCTURE OF A NEW PHENOL ALDEHYDE FROM THE LEAVES OF *Eucalyptus viminalis*

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A new terpenoid phenol aldehyde has been isolated from an alcoholic extract of the leaves of the ribbon eucalyptus by column chromatography on silica gel, and on the basis of the results of ^1H and ^{13}C NMR spectroscopy and mass spectrometry the structure of 4-[1-(3,5-diformyl-2,4,6-trihydroxyphenyl)-3-methylbutyl]-1edol is proposed for it. The relative configurations of the substituents in the terpenoid moiety of the molecule have been determined.

Continuing a chemical study of the leaves of the ribbon eucalyptus [1, 2], we have isolated a new compound, euvimal-1, with the composition $C_{28}H_{40}O_6$, mp 198-199°C, which, on the basis of its spectral characteristics, has been assigned to the euglobals – terpenoid phenol aldehydes of the phloroglucinol series. These compounds, which have the chromophoric fragment of diformylphloroglucinol, have been isolated previously from the Tasmanian blue eucalyptus [3]. The nature of the UV spectrum of euvimal-1 (λ_{max}^{EtOH,H^+} 278, 344 nm, ε 61562, 7646) is typical for the euglobals. The IR spectrum (ν 1630 cm^{-1}), the PMR spectrum (10.12, 10.20 ppm), and the ^{13}C NMR spectrum (191.61 and 192.82 ppm) confirmed the presence of two aldehyde groups in the molecule. Singlets at 13.4 and 13.7 ppm and a broad signal at 6.4 ppm (PMR, $CDCl_3$) were due to two chelated and one free phenolic hydroxyls.

The positions of the signals of the carbon atoms of the aromatic ring [107.80, 106.88, 106.93 (C-1, C-3, and C-5) and 171.51, 171.83, and 172.68 (C-2, C-4, and C-6)] also agreed with the type of substitution and the nature of the substituents characteristic of the euglobals [4, 5] and the robustadiols isolated from *Eucalyptus robusta* [6]. The peak of the molecular ion (M^+ 472) showed that the terpenoid moiety of the molecule consisted of four isoprene units.

A peak with m/z 251 (21.1%) is characteristic for the euglobals [4, 5]. It is due to ion A, which consists of the aromatic ring with one isopentyl residue. The further dissociative fragmentation of the ion took place with the elimination of an isobutyl fragment

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