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CHEMICAL MODIFICATION OF ESTAFIATIN

S. M. Adekenov, N. M. Gafurov,
and A. Zh. Turmukhambetov

UDC 547.314

The halogenation, epoxidation, acetylation, and oxidation of the sesquiterpene-γ-lactone estafiatin (I) has given eight derivatives. It has been shown that during the epoxidation of estafiatone (IV) the formation of a δ-lactone takes place as the result of the Bayer-Villiger oxidation of the cyclopentanone fragment. A stereoselective conversion of estafiatin into the known natural guaianolide isozaluzanin C is described. The structures of the derivatives synthesized were established on the basis of their IR, UV, PMR, and mass spectra.

In this paper we present the results of the chemical transformation of a sesquiterpene lactone of the guaiane type – estafiatin (I). Estafiatin is one of the guaianolides that are widely distributed in the natural flora [1-9]. The presence in the molecule of this compound of such structural fragments as an exomethylene group at C-10 and an α-epoxide ring at C-3, 4 has permitted the performance of such relations as halogenation, acetylation, and oxidation.

The reaction of estafiatin (I) with aluminum isopropanolate gave derivative (II). Its IR spectrum showed the presence of a hydroxy group (3500 cm^{-1}) in its molecule, while its PMR spectrum included the signal of a gem-hydroxylic proton – a triplet at 4.68 ppm (1H, J = 8 Hz) – and two broadened singlets with their centers at 5.35 and 5.48 ppm, which are characteristic for the protons of an exomethylene group at C4. These facts permit us to suggest for (II) the structure of 3α-hydroxyguaia-4(15),10(14),11(13)-trien-6,12-olide, identical with isozaluzanin C [10].

On the oxidation of (II) with chromium trioxide in pyridine, derivative (III) was obtained with 95% yield. The molecule of (III) included a keto group conjugated with a double bond, as was unambiguously characterized by its IR, UV, and PMR spectra, and this permitted us to put forward for (III) the structure of 3-oxoguaia-4(15),10(14),11(13)-trien-6,12-olide.

The interaction of estafiatin (I) with boron trifluoride etherate led to the formation of derivative (IV) with a yield of 90%; from its physicochemical constants and its IR and PMR spectra, (IV) proved to be identical with estafiatone [11].

When (IV) was epoxidized with m-chloroperbenzoic acid in chloroform, followed by the separation of the mixture of products by flash column chromatography, two derivatives, (V) and (VI), were obtained with yields of 68 and 16.3%, respectively. The IR spectrum of (V) showed an absorption band at 1170 cm^{-1} characteristic for an epoxy group and one at 1740 cm^{-1} characteristic for a keto group, while the PMR spectrum contained the signals of gem-epoxidic methylene protons: two doublets at 2.42 and 2.62 ppm (1H each, J = 3.5 Hz). On the basis of the spectral features found, for (V) we suggest the structure of 3-oxo-10(14)-epoxyguaia-11(13)-en-6,12-olide. The IR spectrum of the second derivative (VI) contained absorption bands characteristic for an epoxide group, at 1170 cm^{-1}, and for a carbonyl group,

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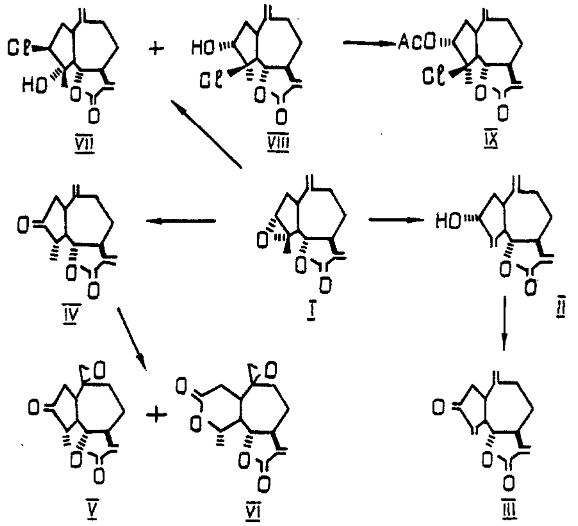

Scheme of the chemical transformations of estafiatin (I).

at 1750 cm^{-1}. In the PMR spectra we observed the signals of gem-epoxidic methylene protons (d, 2.76 ppm, and d, 2.82 ppm, with J = 4.5 Hz). In addition there were the signals of the protons of a secondary methyl – doublet at 1.50 ppm (3H, J = 4 Hz), shifted downfield by 0.3 ppm in comparison with that of the initial estafiatone (IV) – and also, in the weak field, a quintet with its center at 4.78 ppm (1H, J = 12.5 and 6.5 Hz) relating to a methine proton at C-4. The downfield displacement of the methine proton took place under the influence of the gem oxygen atom of a δ-lactone grouping formed on the Bayer-Villiger oxidation of the cyclopentanone part of the (IV) molecule. Thus, the derivative (VI) that had been obtained had the structure of 10(14)-epoxyguaia-11(13)-ene-4,3;6,12-diolide [sic].

When gaseous hydrogen chloride was passed through a methanolic solution of estafiatin (I) and the reaction products were separated by flash column chromatography, derivatives (VII) and (VIII) were obtained with yield of 80 and 15%, respectively. The IR spectrum of (VII) had an absorption band at 3530 cm^{-1}, which is characteristic for a hydroxy group. The following signals were observed in the PMR spectrum: a singlet at 1.34 ppm, which is characteristic for a gem-hydroxylic methyl, and a quartet at 4.26 ppm (1H, J = 12.5 and 7 Hz), assigned to a proton geminal to a chlorine atom, and a broadened doublet at 3.94 ppm (1H, J = 3 Hz), assigned to a gem-hydroxylic proton. Consequently, in the course of the reaction two isomeric chlorohydrins (VII) and (VIII) had been obtained: Their structures were confirmed by the performance of acetylation.

On the interaction of substance (VII) with acetic anhydride in pyridine it did not undergo acetylation, while substance (VIII) formed monoacetate (IX) with a yield of 60%.

The IR spectrum of (IX) lacked the absorption band characteristic for a hydroxy group. The PMR spectrum of this compound contained a singlet at 2.06 ppm (2H), characeristic for the methyl of an acetoxy group, and a doublet with its center 5.33 ppm (1H, J = 4.5 Hz), characteristic for a gem-acetyl proton at C-3.

Thus, according to the spectral results obtained and chemical transformations, derivative (VII) had the structure of 3-chloro-4-hydroxyguaia-10(14),11(13)-dien-6,12-olide, and (VIII) that of 4-chloro-3-hydroxyguaia-10(14),11(13)-dien-6,12-olide.

EXPERIMENTAL

The estafiatin used was a colorless crystalline substance with the composition $C_{15}H_{18}O_3$, mp 102-104°C (ether), $[\alpha]_D^{20}$ −10.3° ($CHCl_3$), that had been isolated from Achillea nobilis L. by the method described previously [1].

The courses of the reactions and the purities of the products synthesized were monitored by TLC on Silufol UV-254 plates with the hexane–ether (1:4) and ether systems, the revealing agent being a saturated solution of $KMnO_4$. The reaction products were separated by flash column chromatography on the sorbent Silicagel L (Chemapol) with a particle size of 100-160 μm.

Melting points were determined on a Boëtius stage. Specific rotations were measured on a SM-2 polarimeter in $CHCl_3$. IR spectra were taken on a UR-20 spectrometer (in KBr tablets or $CHCl_3$ solution), and UV spectra on a SF-26 instrument in C_2H_5OH. PMR spectra were obtained on a Bruker WP-200 SY instrument in $CDCl_3$, SCs being given in ppm (δ scale) relative to TMS, and SSCCs in Hz. Mass spectra were recorded on a Finnigan MAT-8200 instrument.

The elementary analyses of the compounds synthesized corresponded to the calculated figures.

3α-Hydroxyguaia-4(15),10(14),11(13)-trien-6,12-olide (II). At room temperature, 400 mg (2 mmoles) of aluminum isopropanolate was added to a solution of 100 mg (0.4 mmole) of estafiatin (I) in 20 ml of toluene, and the mixture was boiled in an atmosphere of argon for 18 h. Then the solvent was distilled off under pressure [sic], the residue was diluted with 10 ml of ethyl acetate, 10 ml of 2 M HCl was added, and, after stirring for 10 min, the ethyl acetate layer was separated from the aqueous layer, dried over anhydrous $MgSO_4$, and filtered, and the solvent was evaporated. The product was purified by flash column chromatography at a ratio of material to sorbent of 1:20. By elution with hexane—diethyl ether (2:3), 90 mg of (II) was isolated. Yield 90%. Colorless crystalline substance with the composition $C_{15}H_{18}O_3$, mp 142-144°C (ether). On TLC it gave a single spot with R_f 0.6.

IR spectrum (ν_{max}^{KBr}, cm^{-1}): 3500, 3000, 2950, 2870, 1780, 1680, 1655, 1460, 1430, 1400, 1270, 1160, 1000, 900. PMR spectrum (δ, ppm): 3.90 (1H, t, J = 9 Hz, H-6); 4.68 (1H, t, J = 8 Hz, CHOH); 4.78 and 4.90 (1H each, s, CH_2-10); 5.35 and 5.45 (1H each, br.s, CH_2-4); 5.45 and 6.21 (1H each, d, J = 3.5 Hz, CH_2-11).

3-Oxoguaia-4(15),10(14),11(13)-trien-6,12-olide (III). At room temperature, with stirring, 2 g (20 mmoles) of CrO_3 was added to a mixture of 13 ml of $CHCl_3$ and 2.5 ml (40 mmoles) of pyridine. Then a solution of 250 mg (1.02 mmoles) of derivative (II) in 1.5 ml of $CHCl_3$ was added, and the mixture was stirred for 10 min. After this, it was filtered, the filtrate was washed with $NaHCO_3$ solution, 2 M HCl, and water, and was dried over anhydrous $MgSO_4$ and filtered, the solvent was evaporated, and the residue (350 mg) was recrystallized from diethyl ether to give 220 mg of (III). Yield 90%. TLC showed a single spot with R_f 0.67. Colorless crystalline substance with the composition $C_{15}H_{16}O_3$, mp 134-135°C (ether).

UV spectrum ($\lambda_{max}^{C_2H_5OH}$, nm): 217 (14200). IR spectrum (ν_{max}^{KBr}, cm^{-1}): 3000, 2950, 2870, 1785, 1750, 1680, 1660, 1450, 1420, 1300, 1280, 1190, 1160, 1010, 980, 900. Mass spectrum, m/z (%): 244(41.6), 226(4.2), 215(27.7), 202(5), 186(10.4), 173(11), 159(9.7), 150(100), 145(11.8), 134(18.3), 117(11), 105(12.5), 94(9.7), 91 (30.5), 79(18), 67(11.1), 53(27), 44(8.3). PMR spectrum (δ, ppm): 3.99 (1H, t, J = 9 Hz, H-6), 4.67 and 4.91 (1H each, s, CH_2-10), 5.56 and 5.85 (1H each, d, J = 3 Hz, CH_2-11), 6.23 and 6.28 (1H each, d, J = 2 Hz, CH_2-4).

3-Oxoguaia-10(14),11(13)-dien-6,12-olide (IV). In an atmosphere of argon at 0°C, 0.25 ml of boron trifluoride etherate was added to a solution of 500 mg (2 mmoles) of estafiatin (I) in 4 ml of $CHCl_3$. After stirring for 5 min, 0.2 ml of pyridine ws added and then the mixture was diluted with 6 ml of $CHCl_3$, washed with water, dried over anhydrous $MgSO_4$, and filtered, and the solvent was distilled off. The product was recrystallized from ethyl acetate, giving 450 mg of (IV). Yield 90%. Colorless crystalline substance with the composition $C_{15}H_{18}O_3$, mp 140-142°C (ethyl acetate), $[\alpha]_D^{19}$ +126° (c 0.005; $CHCl_3$). On TLC it gave a single spot, with R_f 0.72.

IR spectrum ($\nu_{max}^{CHCl_3}$, cm^{-1}): 3000, 2950, 2910, 2890, 1780, 1750, 1680, 1650, 1460, 1420, 1340, 1310, 1280, 1260, 1160, 1120, 1100, 1010, 970, 920. PMR spectrum (δ, ppm): 1.20 (3H, d, J = 6 Hz, CH_3-4), 3.94 (1H, t, J = 8.5 Hz, H-6), 5.52 and 6.22 (1H each, d, J = 3.0 Hz, CH_2-11), 4.62 and 4.96 (1H each, br.s, CH_2-10).

3-Oxo-10,14-epoxy-11(13)-en-6,12-olide (V) and the Epoxydilactone (VI). At 0°C, 74 mg (0.4 mmole) of m-chloroperbenzoic acid was added to a solution of 53 mg (0.22 mmole) of estafiatone (IV) in 5 ml of $CHCl_3$. Then the temperature of the reaction mixture was raised to that of the room (18°C) and it was stirred for 24 h, the course of the reaction being monitored by TLC in the diethyl ether system. The resulting mixture was washed with 1 M $NaHCO_3$ solution (3 × 20 ml) and with water to neutrality, dried over anhydrous $MgSO_4$, and filtered, and the solvent was distilled off. The residue (100 mg), showing on TLC two spots with R_f 0.69 and 0.47, respectively, was chromatographed on a column containing 2 g of silica gel. When the column was eluted with hexane–diethyl ether (1:4), 30 mg of (V) was isolated. Yield 52%. Colorless crystalline substance with the composition $C_{15}H_{18}O_4$, mp 168-170°C (ethyl acetate), $[\alpha]_D^{17}$ +20° (c 0.004; $CHCl_3$), R_f 0.42.

IR spectrum (ν_{max}^{KBr}, cm^{-1}): 3000, 2950, 2920, 2890, 1770, 1740, 1675, 1460, 1420, 1400, 1350, 1310, 1270, 1170, 1140, 1010, 960. Mass spectrum, m/z (%): 262 (M^+, 7.2), 244(14.8), 216(9), 193(12), 149(51.2), 135(29.7), 105(25), 81(52.3), 69(55.4), 57(60.7), 44(100). PMR spectrum (δ, ppm): 1.24 (3H, d, J = 6.5 Hz, CH_3-4), 2.42 and 2.61 (1H each, d, J = 4 Hz, CH_2-10), 4.14 (1H, t, J = 9.5 Hz, H-6), 5.58 and 6.29 (1H each, d, J = 3.5 Hz, CH_2-11).

Elution of the column with diethyl ether provided 10 mg of (VI). Yield 16.3%. Colorless crystalline substance with the composition $C_{15}H_{18}O_5$, mp 149-152°C (ethyl acetate), $[\alpha]_D^{17}$ −18.5° (c 0.001; $CHCl_3$), R_f 0.3. IR spectrum (ν_{max}^{KBr}, cm^{-1}): 3010, 3000, 2950, 2870, 1780, 1750, 1680, 1550, 1450, 1390, 1300, 1270, 1240, 1140, 1030, 940. Mass spectrum, m/z (%): 278 (M^+, 2), 263(4.1), 234(36), 219(16), 206(36), 192(40), 175(49), 162(32), 146(17.5), 133(23), 105(16), 206(36), 192(40), 175(49), 162(32), 146(17.5), 133(23), 105(22.8), 91(35.1), 69(14), 53(100), 43(80). PMR spectrum (δ, ppm): 1.50 (3H, d, J = 6.5 Hz, CH_3-4), 2.76 and 2.82 (1H each, d, J = 4.5 Hz, CH_2-10), 4.78 (1H, br.quint., H-4, J = 12.5 and 6.5 Hz), 4.17 (1H, q, J = 11, 9.5 Hz, H-6), 5.76 and 6.31 (1H each, d, J = 3.5 Hz, CH_2-11).

3-Chloro-4-hydroxyguaia-10(14),11(13)-dien-6,12-olide (VII) and 4-Hydroxy-3-chloroguaia-10(14),11(13)-dien-6,12-olide (VIII). Gaseous HCl was passed at room temperature through a solution of 500 mg (2 mmoles) of estafiatin (I) in 15 ml of methanol. After the methanol had been evaporated off, the reaction mixture was diluted with diethyl ether and was then washed successively with 3% $NaHCO_3$ solution and with water. The resulting product was dried with anhydrous $MgSO_4$ and was filtered, and the solvent was evaporated off under vacuum. The residue (840 mg), which gave two spots on TLC, with R_f 0.55 and 0.45, was chromatographed on a column containing 16.8 g of silica gel.

When the column was eluted with hexane–ether (3:7), 470 mg of (VII) was obtained. Yield 80%. Colorless crystalline substance with the composition $C_{15}H_{19}O_3Cl$, mp 205°C (diethyl ether), $[\alpha]_D^{25}$ −14° (c 0.013; $CHCl_3$), R_f 0.55. IR spectrum (ν_{max}^{KBr}, cm^{-1}): 3535, 3000, 2950, 2880, 1760, 1680, 1660, 1460, 1420, 1340, 1320, 1290, 1280, 1180, 1100, 1000, 980, 940, 910, 820, 740, 710, 680, 610, 510. Mass spectrum, m/z (%): 282 (M^+, 29), 264(25), 247(26), 229(39), 213(7), 190(19), 177(30), 150(26), 131(25), 111(20), 105(33), 91(44), 53(41), 43(100). PMR spectrum (δ, ppm): 1.34 (3H, s, CH_3-4), 4.17 (1H, q, J = 11 and 9 Hz, H-6), 4.26 (1H, q, J = 12.5 and 7 Hz, H-3), 5.01 and 5.08 (1H each, br.s, CH_2-10), 5.58 and 6.26 (1H each, d, J = 3 Hz, CH_2-11).

Elution with hexane–ether (1:4) led to the isolation of 84.6 mg of (VIII). Yield 15%. Colorless crystalline substance with the composition $C_{15}H_{19}O_3Cl$, mp 166-168°C (diethyl ether), $[\alpha]_D^{20}$ −18° (c 0.005; $CHCl_3$), R_f 0.45. IR spectrum (ν_{max}^{KBr}, cm^{-1}); 3536, 3000, 2950, 2880, 1760, 1680, 1659, 1460, 1420, 1340, 1320, 1290, 1280, 1180, 1100, 980, 940, 820, 720, 700, 650, 600, 515. Mass spectrum, m/z (%): 282 (M^+), 264 ($M^+ - H_2O$, 11.4), 246(31.4), 228(10), 221(15.7), 203(21.4), 185(5.7), 179(31.4), 161(20), 145(17.1), 131(24.2), 123(17.1), 117(14.2), 105(22.8), 91(34.2), 85(25.7), 74(10), 67(15.7), 53(32.8), 43(100). PMR spectrum (δ, ppm): 1.51 (3H, s, CH_3-4), 3.94 (1H, br.d, J = 3 Hz, H-3), 4.23 (1H, q, J = 10.5 and 9 Hz, H-6), 4.94 (2H, br.s, CH_2-10), 5.48 and 6.20 (1H each, d, J = 3 Hz, CH_2-11).

3-Acetoxy-4-chloroguaia-10(14),11(13)-dien-6,12-olide (IX). At room temperature (20°C), 0.13 ml of acetic anhydride was added to a solution of 200 mg (0.7 mmole) of derivative (VIII) in 0.1 ml of pyridine, and the mixture was stirred for 5 h. Then it was diluted with 15 ml of diethyl ether and was washed with 3% HCl and with water to neutrality, dried over anhydrous $MgSO_4$, and filtered, and the solvent was distilled off. The residue (280 mg), which gave two TLC spots, with R_f 0.64 and 0.45 [in the hexane–ether (1:4) system], was chromatographed on a column with 9.2 g of silica gel.

When the column was eluted with hexane–diethyl ether (1:1), 136 mg of (IX) was isolated. Yield 60%. Colorless crystalline substance with the composition $C_{17}H_{21}O_4Cl$, mp 147-149°C (ether), $[\alpha]_D^{16.5}$ −55.2° (c 0.003; $CHCl_3$), R_f 0.64. IR spectrum (ν_{max}^{KBr}, cm^{-1}): 3000, 2950, 2880, 1772, 1756, 1678, 1656, 1460, 1420, 1340, 1320, 1290, 1250, 1180, 1100, 980, 940, 820, 720, 690, 640, 600, 515. PMR spectrum (δ ppm): 1.74 (3H, s, CH_3-4), 2.06 (3H, s, CH_3CO), 4.39 (1H, q, J = 10 and 9 Hz, H-6), 5.33 (1H, d, J = 4.5 Hz, H-3), 5.08 (2H, br.s, CH_2-10), 5.51 and 6.22 (1H each, d, J = 3.5 Hz, CH_2-11).

Elution with hexane–ether (1:4) yielded 60 mg (30%) of a colorless crystalline substance $C_{15}H_{19}O_3Cl$, with mp 166-168°C (from diethyl ether), R_f 0.45, which was identified as 4-chloro-3-hydroxyguaia-10(14),11(13)-dien-6,12-olide (VIII), i.e., a part of the initial substance that had not reacted.

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MOLECULAR AND CRYSTAL STRUCTURE OF THE GERMACRANOLIDE ARGOLIDE FROM Artemisia glabella

S. M. Adekenov, K. A. Aituganov, K. M. Turdybekov,
S. V. Lindeman, and Yu. T. Struchkov

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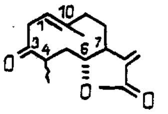
The new germacranolide argolide has been isolated from the epigeal part of Artemisia glabella, and its structure has been shown by its conversion into oxopelenolide B. From the results of an x-ray investigation it is suggested that argolide has the spatial structure of 3-oxo-4α,7α,6β(H)-germacra-1(10),-11(13)-dien-6,12-olide.

Sesquiterpene lactones of the guaiane type – arglabin, glabellin, and matricarin – and of the germacrane type – argolide and oxopelenolide B – have been isolated previously from the epigeal part of Artemisia glabella Kar. et Kir.

The molecule of argolide (I) is close in structure to germacranolides of the ketopelenolide group – ketopelenolides A (II) and B (III) [2] and tansanin [3].



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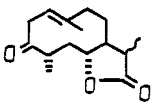

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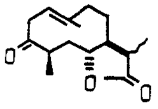

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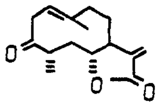

IV

Institute of Organic Synthesis and Coal Chemistry, Kazakh Academy of Sciences, Karaganda. A. N. Nesmeyanov Institute of Organometallic Chemistry, Russian Academy of Sciences, Moscow. Translated from Khimiya Prirodnykh Soedinenii, No. 5, pp. 653-657, September-October, 1991. Original article submitted December 15, 1990; revision submitted May 15, 1991.