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# GAIGRANIN AND GAIGRANDIN — NEW SESQUITERPENE LACTONES FROM *Gaillardia grandiflora*

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*Two new sesquiterpene lactones — gaigranin and gaigrandin — have been isolated from the epigeal part of* Gaillardia grandiflora, *and their structures have been established on the basis of spectral (IR, PMR, $^{13}C$ NMR, and mass) characteristics and x-ray structural analysis.*

*Gaillardia grandiflora* Hort is a perennial plant cultivated on the territory of the CIS. In Kazakhstan it is grown in botanical gardens and is used as a decorative plant.

By extraction with chloroform, followed by chromatography on a column of silica gel, the flowerheads and leaves of *Gaillardia grandiflora* yielded three sesquiterpene lactones, two of which proved to be new and have been called gaigranin (**1**) and gaigrandin (**2**), while the third was identified as the pseudoguaianolide spathulin (**3**) [1, 5].

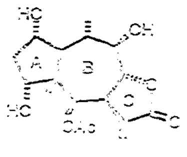
A quantitative yield of lactones from the raw epigeal part of this plant was ensured by extraction with chloroform followed by treatment of the total material isolated with ethanol—water (2:1) and chromatographic separation of the resin on a column of silica gel.

Gaigranin (**1**) — a colorless crystalline substance with the composition $C_{17}H_{24}O_7$, mp 186-189°C (from ethanol), $[\alpha]_D^{20}$ +17.3° (*c* 0.52; ethanol). The IR spectrum characterized the presence in its structure of a hydroxy group (3510 $cm^{-1}$) a $\gamma$-lactone carbonyl (1750 $cm^{-1}$) and an ester group (1710, 1250 $cm^{-1}$). In the UV spectrum, an absorption maximum at 215 nm (3894) showed the presence in the gaigranin molecule of a methylene group conjugated with the $\gamma$-lactone carbonyl, which was also confirmed by the PMR spectrum: one-proton doublets at 6.30 and 6.61 ppm, each with a SSCC of 3 Hz. A singlet at 1.96 ppm was assigned to the methyl of an acetyl group, and a doublet at 1.48 ppm (3H, SSCC 6 Hz) to a secondary methyl.

A singlet at 0.80 ppm (3H), characteristic for an angular methyl, permitted the assumption of a pseudoguaiane carbocycle for the gaigranin molecule.

The presence in the $^{13}C$ NMR spectrum of five doublets at 78.18, 78.34, 78.54, 79.08, and 82.30 ppm characterized the presence in its carbocycle of five methylene fragments linked with oxygen atoms. One of these carbon atoms was linked with the lactone ring, another with an acetoxy group, and the others with hydroxy functions. Consequently, the gaigranin structure includes three hydroxy groups.

The use of the procedure of two-dimensional $^1H$—$^1H$ (COSY) NMR spectroscopy permitted an assignment of the signals in the PMR spectrum taken in $C_5D_5N$. The signal of the gem-acyl proton — a doublet at 5.47 ppm — showed the location of the acetoxy group at C-6, while its SSCC of 2.5 Hz showed the *cis*-orientation of H-6 relative to the vicinal H-7 proton. A triplet at 4.86 ppm with a SSCC of 9.4 Hz was assigned to the lactone proton. The SSCCs of H-7, H-8, and H-9 permitted the assumption that the lactone ring was located at C7—C8 and characterized its *trans*-linkage to the carbocycle.



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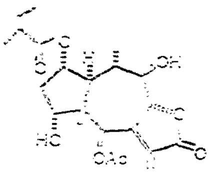

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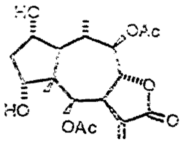

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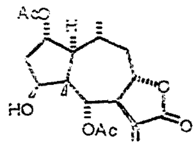

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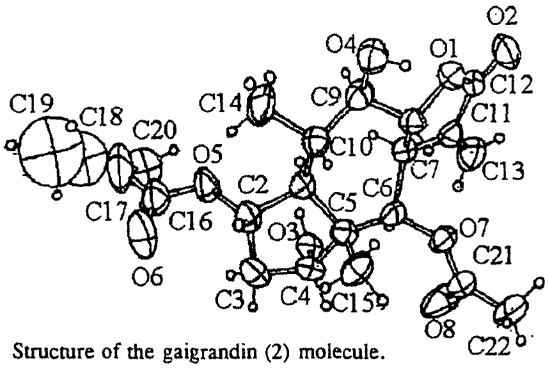
In the double-resonance PMR spectrum taken in $CDCl_3$, suppression of a signal at 2.54 ppm caused a change in the multiplicity of a signal in the 3.78 ppm region, which became a doublet. The signal at 2.54 ppm therefore corresponded to H-3 and that at 3.78 ppm to the gem-hydroxylic proton H-4. When a signal in the region of 4.96 ppm was suppressed, the multiplicities of signals at 2.29 and 2.54 ppm changed, which permitted the latter to be assigned to H-3a and H-3b and the triplet at 4.96 ppm, with a SSCC of 10 Hz, to the gem-hydroxylic proton H-2.



Structure of the gaigrandin (2) molecule.

To study the structure of gaigrandin (**2**) and the conformations of its rings we carried out an x-ray structural investigation. The lactone ring of gaigrandin has the conformation of a C-7 envelope that is characteristic for many sesquiterpene lactones of the guaiane, pseudoguaiane, and germacrane types [2]. According to the same source [2], other preferred conformations of the lactone ring are 6,7- and 7,8-half-chairs. Thus, the 7,8-half-chair conformation is found in the molecule of britanin (**4**) [3], a pseudoguaianolide with the same *trans,trans* linkage of the tricyclic skeleton. In the gaigrandin (**2**) molecule, the seven-membered ring has a form intermediate between a chair conformation (the plane of symmetry passes through C-9 and the center of the C5—C6 bond) and that of a *twist*-chair. The angle of pseudorotation $\Psi_3$ of the chair—*twist*-chair family is 9.7 and 9.2° [3], which is closer to the chair form ($\Psi_3 = 13°$). In the britanin (**4**) molecule the angle of pseudorotation for the seven-membered ring is $-3.2°$, which shows a closeness of the conformation to the *twist*-chair form ($\Psi_3 = 0°$). Judging from the torsional angles, the above-mentioned difference in the conformations of this ring in molecules (**2**) and (**4**) is caused by different configurations of the C-6 atom. A conformation of the seven-membered ring intermediate between chair and *twist*-chair is common for linear *trans,trans*-linked pseudoguaianolides and is weakly linked to the presence of substituents [2]. In the gaigrandin (**2**) molecule the five-membered ring is present in the form of C-5 envelope (the C-5 atom deviates by 0.69 Å in the direction of the C-15 methyl group in both molecules). However, in the britanin (**4**) molecule this ring has the form of a 4,5-half-chair. Apparently, in this case the effect of the substituents is shown.

In the crystal, the molecules are linked with one another into a three-dimensional network by hydrogen bonds O3-H...O8a distances O-H 0.85, H...O 2.01, O...O 2.824 Å, angle O-H...O 156°), O4-H...O6 (0.86, 2.04, 2.899 Å, 176°), O3-H...O8 (0.87, 2.04, 2.844 Å, 154°), O4a-H...O6a (0.85, 2.05, 2.902 Å, 176°).

On the basis of the physicochemical constants and spectral (IR, PMR) characteristics obtained, the substance (**3**) isolated was identified as the pseudoguaianolide spathulin [1, 5].

## EXPERIMENTAL

The individuality of the substances was checked by TLC on Silufol plates in the solvent systems hexane—diethyl ether (1:1) and diethyl ether. The revealing agent was a saturated solution of $KMnO_4$ in 5% $H_2SO_4$. We used type KSK silica gel for column chromatography, with the eluents benzene, diethyl ether, and acetone.

TABLE 1. Coordinates ($\times 10^4$) and Equivalent Temperature Factors $U_{eq}$ ($Å^2 \times 10^3$) of the Nonhydrogen Atoms of Compound (1)

| Atom | $x/a$ | $y/b$ | $z/c$ | $U_{eq}$ |
|---|---|---|---|---|
| | | Molecule 1 | | |
| O1 | 1141(5) | 994 | 9448(3) | 52(2) |
| O2 | 1279(7) | −366(4) | 8851(4) | 69(2) |
| O3 | −2717(5) | 3357(4) | 7345(3) | 48(2) |
| O4 | 2183(6) | 2549(4) | 10156(3) | 62(2) |
| O5 | −91(6) | 5129(4) | 8143(4) | 68(2) |
| O6 | −888(9) | 6451(4) | 8572(4) | 79(3) |
| O7 | −2984(5) | 1634(4) | 9216(3) | 47(2) |
| O8 | −4914(6) | 1549(6) | 8370(4) | 85(3) |
| C1 | −671(7) | 3684(5) | 8765(4) | 42(2) |
| C2 | −1158(8) | 4676(5) | 8653(4) | 48(2) |
| C3 | −2710(9) | 4661(6) | 8265(5) | 60(3) |
| C4 | −3064(7) | 3675(5) | 8142(4) | 45(2) |
| C5 | −2208(7) | 3169(5) | 8814(4) | 42(2) |
| C6 | −2152(7) | 2136(5) | 8618(4) | 40(2) |
| C7 | −631(7) | 1727(5) | 8604(4) | 36(2) |
| C8 | 235(7) | 1811(5) | 9406(4) | 45(2) |
| C9 | 1238(7) | 2619(6) | 9459(4) | 45(2) |
| C10 | 419(8) | 3531(5) | 9488(4) | 48(2) |
| C11 | −561(7) | 749(5) | 8416(4) | 42(2) |
| C12 | 688(8) | 356(5) | 8891(5) | 48(2) |
| C13 | −1351(9) | 237(6) | 7938(6) | 65(3) |
| C14 | 1615(10) | 4270(7) | 9510(6) | 72(3) |
| C15 | −2957(8) | 3363(6) | 9624(4) | 54(3) |
| C16 | −107(11) | 6009(7) | 8143(6) | 72(4) |
| C17 | 942(25) | 6403(10) | 7503(18) | 194(14) |
| C18 | 1000(33) | 6951(26) | 7208(19) | 237(13) |
| C19 | 1974(38) | 7204(32) | 8161(24) | 312(17) |
| C20 | 439(18) | 5929(13) | 6554(11) | 134(5) |
| C21 | −4370(7) | 1364(6) | 9037(5) | 53(3) |
| C22 | −5108(9) | 909(7) | 9689(7) | 81(4) |
| | | Molecule 2 | | |
| O1a | 6144(5) | 3771(4) | 5538(3) | 53(2) |
| O2a | 6332(6) | 5126(4) | 6120(4) | 67(2) |
| O3a | 2235(5) | 1436(4) | 7645(3) | 49(2) |
| O4a | 7160(6) | 2200(4) | 4859(3) | 64(2) |
| O5a | 4790(6) | −333(4) | 6903(3) | 65(2) |
| O6a | 4077(9) | −1661(4) | 6412(4) | 81(3) |
| O7a | 2015(5) | 3179(4) | 5796(3) | 47(2) |
| O8a | 108(6) | 3276(6) | 6657(4) | 90(3) |
| C1a | 4293(7) | 1111(5) | 6235(4) | 39(2) |
| C2a | 3794(8) | 124(5) | 6346(4) | 47(2) |
| C3a | 2236(8) | 133(6) | 6710(5) | 58(3) |
| C4a | 1885(7) | 1137(6) | 6857(4) | 49(2) |
| C5a | 2787(7) | 1628(5) | 6179(4) | 43(2) |
| C6a | 2847(7) | 2654(5) | 6386(4) | 39(2) |
| C7a | 4396(7) | 3050(5) | 6396(4) | 37(2) |
| C8a | 5248(7) | 2964(5) | 5589(4) | 44(2) |
| C9a | 6230(7) | 2133(5) | 5547(4) | 44(2) |
| C10a | 5404(8) | 1231(5) | 5521(4) | 45(2) |
| C11a | 4481(7) | 4043(5) | 6581(4) | 42(2) |
| C12a | 5735(8) | 4407(5) | 6091(5) | 46(2) |
| C13a | 3706(9) | 4568(6) | 7049(6) | 69(3) |
| C14a | 6596(10) | 484(6) | 5526(6) | 69(3) |
| C15a | 2048(8) | 1447(6) | 5361(4) | 54(3) |
| C16a | 4804(10) | −1225(6) | 6889(6) | 67(3) |
| C17a | 5670(17) | −1575(9) | 7656(11) | 134(7) |
| C18a | 6180(26) | −2177(20) | 7705(15) | 193(9) |
| C19a | 6637(34) | −2727(27) | 6877(21) | 270(13) |
| C20a | 5418(14) | −1047(10) | 8469(8) | 107(4) |
| C21a | 630(8) | 3440(6) | 5981(5) | 55(3) |
| C22a | −110(9) | 3932(8) | 5351(7) | 85(4) |

TABLE 2. Intracyclic Torsional Angles (degrees) in the Molecules of (**1**)

| Angle | | | | Molecule 1 | Molecule 2 |
|---|---|---|---|---|---|
| C5 | C1 | C2 | C3 | −25.1 | −24.0 |
| C1 | C2 | C3 | C4 | −1.5 | −3.4 |
| C2 | C3 | C4 | C5 | 28.8 | 29.7 |
| C2 | C1 | C5 | C4 | 41.2 | 41.4 |
| C10 | C1 | C5 | C6 | −76.0 | −77.8 |
| C3 | C4 | C5 | C1 | −43.6 | −44.3 |
| C1 | C5 | C6 | C7 | 13.8 | 15.2 |
| C5 | C6 | C7 | C8 | 59.4 | 59.1 |
| C12 | O1 | C8 | C7 | −13.8 | −13.0 |
| C6 | C7 | C8 | C9 | −94.0 | −94.1 |
| C11 | C7 | C8 | O1 | 19.8 | 19.6 |
| C7 | C8 | C9 | C1 | 67.4 | 67.4 |
| C5 | C1 | C10 | C9 | 77.6 | 77.2 |
| C8 | C9 | C10 | C1 | −55.3 | −54.1 |
| C8 | C7 | C11 | C12 | −19.2 | −19.3 |
| C8 | O1 | C12 | C11 | 1.8 | 0.6 |
| C7 | C11 | C12 | O1 | 11.6 | 12.4 |

The substances for analysis were dried in a vacuum pistol with $P_2O_5$ over alcohol for 6-8 h. The elementary analyses of the compounds agreed with the calculated figures. Specific optical rotations were measured on a Polamat polarimeter in a tube 0.5 dm long with a volume of 1 ml.

IR spectra were taken on a UR-20 spectrometer (in chloroform, KBr tablets); PMR spectra on a Bruker WP-200SY spectrometer (200 MHz, $CDCl_3$, 0 — TMS); and mass spectra on a Finnigan MS-9200 instrument (direct injection, 70, 90, and 120°C). The x-ray structural investigation was conducted on a SYNTEX-P2 diffractometer ($CuK_\alpha$ radiation, graphite monochromator).

**Isolation of the Lactones.** The epigeal part of *Gaillardia gandiflora* (1.5 kg) gathered in the flowering phase in the collection section of Karaganda botanical garden was exhaustively extracted with chloroform at 45-50°C. The chloroform was evaporated in vacuum, and the residue (200 g) was treated three times with ethanol—water (2:1) at 70°C. The ballast substances that precipitated were separated by decantation, and the filtrate (the aqueous alcoholic layer) was treated three times with chloroform. The chloroform extracts were evaporated, and the residue (75 g) was chromatographed on a column of KSK silica gel at a ratio of total substance to support of 1:20.

**Gaigranin (1).** Acicular crystals deposited from the benzene (1:1) fraction. Three recrystallizations from ethanol yielded 3.82 g of a crystalline substance with the composition $C_{17}H_{24}O_7$, mp 186—189°C, $[\alpha]_D^{21}$ +17.3 (*c* 0.52, ethanol). In TLC it gave a single spot with $R_f$ 0.3 (ether). IR spectrum: 3510, 2985, 2920, 2880, 2850, 1750, 1710, 1670, 1460, 1430, 1410, 1375, 1360, 1325, 1310, 1280, 1250, 1240, 1205, 1190, 1150, 1135, 1085, 1050, 1030, 985, 965, 940, 925 $cm^{-1}$. PMR spectrum (ppm, intensity, multiplicity, SSCC): 0.80 (3H, s), 1.48 (3H, d, 6.0 Hz), 1.96 (3H, s), 2.54 (1H, m), 2.29 (1H, m), 2.29 (1H, m), 2.09 (1H, d, 5 Hz), 3.05 (1H, t), 3.78 (1H, t; 5 Hz), 3.68 (1H, t, 14 and 10 Hz), 4.50 (1H, t, 11.5 Hz), 4.96 (1H, t, 10 Hz), 5.96 (1H, d), 6.30 and 6.61 (each 1H, d, 3 Hz). UV spectrum, $\lambda_{max}$ 215 nm ($\varepsilon$ 3894). $^{13}C$ NMR spectrum (ppm, multiplicity, off resonance): 18.04 q, 20.31 q, 22.59 q, 27.30 d, 45.73 t, 49.41 d, 51.79 s, 78.18 d, 78.34 d, 78.54 d, 79.07 d, 82.30 d, 120.38 t, 137.77 s, 169.18 d, 171.04 s, 172.63 s.

**Gaigrandin (2).** When the column was eluted with ether, acicular crystals deposited. Three recrystallizations from ethanol yielded a colorless crystalline substance with the composition $C_{22}H_{30}O_8$, $R_f$ 0.3 (ethanol), mp 205-208°C.

**The X-Ray Structural Investigation of Gaigrandin (2).** Crystals monoclinic: $a = 9.057(1)$, $b = 14.766(2)$, $c = 16.436(2)$ Å, $\beta = 90.28(1)°$, space group, $P2_1$, $V = 2198.1(8)$ Å$^3$, $C_{22}H_{30}O_8$, $Z = 4$, $d_{calc} = 1.277$ (g/cm$^3$, $\mu = 0.77$ mm$^{-1}$, dimensions of the specimen 0.3 × 0.3 × 0.6 mm$^3$. The intensities of 3397 independent reflections with $2\theta < 120°$ were measured by the standard $\theta/2\theta$ method of scanning, and 3014 reflections with $I > 2\sigma$ (1) were used in the calculations. Corrections for absorption were made by the DIFABS program (coefficients 0.67-1.19) and for the systematic fall (to 94%) of the intensities of control reflections. The structure was interpreted by the direct method using the SHELX-86 program and was refined by the method of least squares in the anisotropic−isotropic approximation to $R = 0.071$, $R_w = 0.079$, $S = 2.60$ by the SHELX-76 program. The positions of the hydroxylic hydrogen atoms were found from a difference synthesis, and the coordinates of the other hydrogen atoms were given geometrically, the hydrogen parameters not being refined.

It must be mentioned that the localization of the C18, C19, and C20 atoms in both crystallographically independent molecules caused difficulties. Thus, refinement led to poor geometry and high values of the temperature factors of these atoms. Therefore, in the final refinement the C18—C2O and C18a—C20a atoms took part in the isotropic approximation. The reason for such a phenomenon is most probably a disorderedness of this fragment of the side-chain, although according to the results of the x-ray structural analysis, the possibility of the cocrystallization of the substance with isomers or a different structure of the fragment under consideration cannot be excluded. The coordinates obtained for the nonhydrogen atoms are given in Table 1, and the values of the endocyclic torsional angles in Table 2.

**Spathulin (3).** When the column was eluted with ether—acetone (1:1) acicular crystals deposited. After three recrystallizations from ethanol a colorless crystalline substance was obtained with the composition $C_{19}H_{26}O_8$, mp 261-262°C $[\alpha]_D^{25}$ +17.0° (*c* 1.0; ethanol). Yield 0.6 g (0.04% on the weight of the air-dry raw material). $R_f$ 0.57 (ether—acetone, 3:1). IR spectrum (cm$^{-1}$): 3505, 3320, 2990, 2975, 2940, 1780, 1740, 1705, 1670, 1470, 1430, 1410, 1380, 1340, 1330, 1310, 1260, 1245, 1175, 1165, 1135, 1125, 1095, 1085, 1040, 1010, 995, 985, 925. UV spectrum: 220 nm ($\varepsilon$ 2912). PMR spectrum (ppm, intensity, multiplicity): 0.87 (3H, s), 1.54 (3H, d), 2.05 (3H, s), 2.17 (3H, s), 6.28 (1H, d), 6.71 (1H, d), 4.89 (1H, t).

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