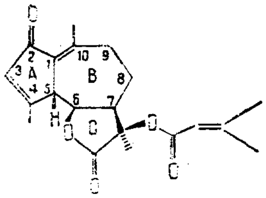
CRYSTAL AND MOLECULAR STRUCTURE OF THE SESQUITERPENE LACTONE FERULIDE

B. Tashkhodzhaev, M. K. Makhmudov, M. R. Nurmukhamedova,
and S. A. Talipov

UDC 547.324+548.737

The spatial structure of the sesquiterpene lactone ferulide has been determined by the x-ray structural method as 2-oxo-11α-senecioyl-5β,6α,7α(H)-guaia-3,10-dien-6,12-olide. This is the first time that the "sofa" conformation for the cyclopentene ring had been detected in natural guaianolides.

The sesquiterpene lactone ferulide $C_{20}H_{25}O_5$ (I), isolated from the seeds of Ferula penninervis Rgl. et Schmahl., has been studied previously by chemical and spectral methods; the following structure and relative configuration have been proposed for it [1-4]:



However, because of the ambiguity of the interpretation of the results of PMR spectroscopy, questions of the stereochemistry of esterified guaianolides like ferulide (montanolide, isomontanolide, and the slovanolides) have been disputed for more than a decade [5-11], and their reliable solution is possible only by bringing in the x-structural method.

The spatial structure of (I) found by x-ray structural methods is shown in Fig. 1 as a projection on the bc plane.

The conformation of the rings of the (I) molecule are well described by the intracyclic torsional angles given in Table 1. This also gives for comparison the torsional angles of

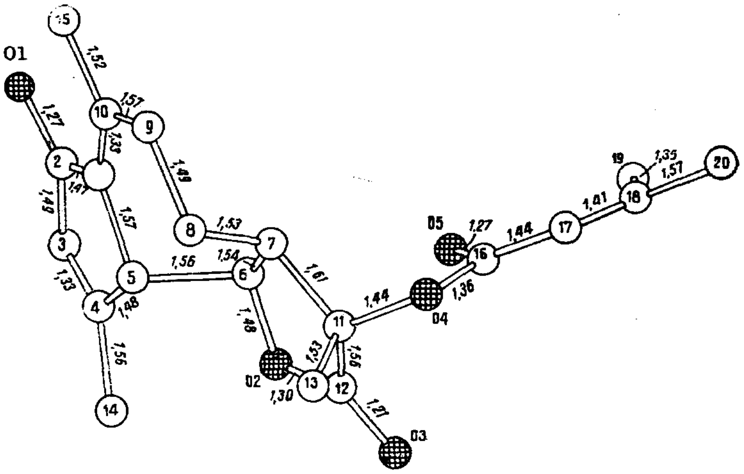


Fig. 1. Structure of the ferulide molecule.

Institute of the Chemistry of Plant Substances, Academy of Sciences of the Uzbek SSR, Tashkent. Translated from Khimiya Prirodnykh Soedinenii, No. 1, pp. 55-58, January-February, 1988. Original article submitted June 16, 1987.

0009-3130/88/2401-0046 $12.50

TABLE 1. Intracyclic Torsional Angles (°C) of the (I) Molecule in Comparison with the Theoretical Figures for Unsubstituted Cyclopentane and Cycloheptane [because of the absence of theoretical figures, the values are given for its chair (c) and boat (b) conformations]

Ring	Fragment	φ	φtheor	
			(c)	(b)
A	C1—C2—C3—C4	3	0	
	C2—C3—C4—C5	1	0	
	C3—C4—C5—C1	—4	0	
	C4—C5—C1—C2	5	0	
	C5—C1—C2—C3	—5	0	
B	C9—C10—C1—C5	0	—62	—62
	C10—C1—C5—C6	61	99	38
	C1—C5—C6—C7	—69	—82	—82
	C5—C6—C7—C8	—2	0	0
	C6—C7—C8—C9	81	82	82
	C7—C8—C9—C10	—61	—99	—38
	C8—C9—C10—C1	—2	62	62
C	O4—C12—C11—C7	14	46	
	C12—C11—C7—C6	—4	—29	
	C11—C7—C6—O4	—5	0	
	C7—C6—O4—C12	5	29	
	C6—O4—C12—C11	—12	—46	

TABLE 2. Valence Angles (ω, deg) of the (I) Molecule

Angle	ω	Angle	ω	Angle	ω	Angle	ω
C10C1C2	126	C4C5C6	118	C9C10C1	127	O3C12O2	125
C10C1C5	136	C1C5C6	104	C9C10C15	113	C6O2C12	112
C2C1C5	103	C5C6C7	115	C15C10C1	120	C11O4C16	122
C1C2C3	111	C5C6O2	106	C7C11C12	100	O4C16O5	118
C1C2O1	127	O2C6C7	107	C7C11C13	118	O4C16C17	107
O1C2C3	121	C6C7C8	118	C7C11O4	109	O5C16C17	135
C2C3C4	104	C6C7C11	101	C12C13C14	111	C16C17C18	114
C3C4C5	119	C11C7C8	113	C12C11O4	112	C17C18C19	129
C3C4C14	120	C7C8C9	112	C13C11O4	105	C17C18C20	114
C14C4C5	121	C8C9C10	113	C11C12O2	115	C19C18C20	117
C4C5C1	102			C11C12O3	120		

the most suitable conformation of unsubstituted cyclopentane and cycloheptane calculated theoretically [12]. It can be seen from Table 1 that the cyclopentane ring A has an almost planar structure. Judging from the torsional angles, the other five-membered ring — the lactone ring C — assumes the conformation of a highly flattened envelope with C_s symmetry.

It is known that unsubstituted cyclopentane usually assumes the chair, boat, twist-chair, and twist-boat forms with C_s and C_2 symmetries, respectively, and also two transitional forms, one of which has C_2 symmetry while the other is characterized by a planar position of the five atoms of the ring [13]. However, depending on the presence of substituents and of a double bond, the seven-membered ring is frequently found in an intermediate state between these symmetrical forms [14]. In the (I) molecule the cycloheptene ring B does not assume an intermediate state but unexpectedly acquires the rarely found sofa conformation (the five atoms, C1, C5 and C8, C9, and C10 of the ring are located in one plane, and the C6 and C7 atoms depart from it by 1.13 Å, with retention of C_s symmetry. This can be well seen in Fig. 1. This is the first time that the sofa conformation of a cyclopentene ring has been found in natural guaianolides. Its existence is apparently due to the cis-linkage of rings B/C and the C1=C10 position of the double bond. The cis-linkage of rings B and C is a case which in itself is fairly rare in natural guaianolides.

The senecioic acid residue in position 11 has a planar structure and is almost perpendicular (82°) to the mean-square plane of the lactone ring.

TABLE 3. Coordinates of the Atoms ($\times 10^4$) in the Structure of Ferulide

Atom	*x*	*y*	*z*
C1	7168(16)	1018(8)	9199(7)
C2	9005(26)	538(11)	9316(8)
C3	10090(22)	538(11)	8694(7)
C4	9041(19)	1006(11)	8244(7)
C5	7276(20)	1416(10)	8455(5)
C6	7020(23)	2672(9)	8509(6)
C7	5122(18)	3041(10)	8693(7)
C8	3809(17)	2129(8)	8847(6)
C9	3990(19)	1603(10)	9509(6)
C10	5975(18)	1098(9)	9647(6)
C11	4530(21)	3822(10)	8091(6)
C12	6273(22)	3855(9)	7668(7)
C13	2930(23)	3489(10)	7672(8)
C14	9635(16)	1171(10)	7508(6)
C15	6063(20)	630(10)	10344(6)
C16	5402(18)	55 6(8)	8584(5)
C17	4636(25)	6557(9)	8810(6)
C18	5832(46)	7361(12)	9027(9)
C19	76 9(48)	7396(18)	9113(12)
C20	48 5(40)	8405(11)	9249(7)
O1	9627(14)	161(9)	9857(5)
O2	7396(15)	3107(7)	7839(5)
O3	6404(17)	4462(8)	7196(5)
O4	4120(13)	4894(6)	8328(5)
O5	6982(16)	5197(8)	8621(5)

The lengths of the valence bonds and the sizes of the valence angles in the (I) molecules are given in Fig. 1 and in Table 2. On the whole, they agree within the limits of experimental error with the standard values [15] and those observed in related guaianolides [16, 17], with the exception of the shortened C18—C19 ordinary bond (1.35 Å), which can be explained by the greater thermal vibrations of the terminal atoms of the senecioic acid residue. The standard deviations of the valence bonds are not greater than 0.02 Å (apart from C18—C19 and C18—C20, where they reach 0.05 Å), and those of the valence angles are mostly no greater than 1.5° (but reach 2.2° for the corresponding atoms).

EXPERIMENTAL

Single crystals of (I) grown from a mixture of the solvents hexane and ethyl acetate were first studied by the photographic method. The space group and the parameters of the elementary cell were determined from precession photographs and were refined on a Syntex $P2_1$ diffractometer using Cu K_α radiation: $a = 7.510(4)$, $b = 12.283(6)$, $c = 20.126(8)$ Å; $d_{calc} = 1.241$ g/cm³; space group $P2_12_12_1$; $Z = 4$. A three-dimensional set of intensities was obtained on the diffractometer mentioned, and 681 structural factors exceeding 2σ were used in the calculation. (The unsatisfactory quality of the crystals did not permit the set of experimental results to be increased.) The structure was interpreted by the direct method by means of the Rentgen-75 program in the automatic regime using the Σ_1 relation [18]. The structure found was refined first by successive approximations of the electron density and the method of least squares (MLS) in the isotropic approximation, and then by a full-matrix MLS with allowance for the anisotropy of the thermal vibrations of the nonhydrogen atoms to $R = 0.098$. The coordinates of the nonhydrogen atoms of the (I) molecule are given in Table 3.

CONCLUSIONS

The spatial structure of the sesquiterpene lactone ferulide has been confirmed by the x-ray structural method as 2-oxo-11α-senecioyl-5β,6α,7α(H)-guaia-3,10-dien-6,12-olide. The sofa conformation of the cyclopentene ring has been found for the first time in natural guaianolides.

LITERATURE CITED

1. M. R. Nurmukhamedova, Sh. Z. Kasimov, and S. Melibaev, Khim. Prir. Soedin., 261 (1982).
2. M. R. Nurmukhamedova, Sh. Z. Kasimov, and G. P. Sidyakin, Khim. Prir. Soedin., 533 (1983).

3. M. R. Nurmukhamedova, Sh. Z. Kazimov, N. D. Abdullaev, and G. P. Sidyakin, Khim. Prir. Soedin., 261 (1982).
4. N. D. Abdullaev and M. R. Nurmukhamedova, Khim. Prir. Soedin., 240 (1987).
5. M. Holub, D. P. Popa, V. Herout, and F. Sorm, Coll. Czech. Chem. Commun., 35, 3296 (1970).
6. M. Holub and Z. Samek, Coll. Czech. Chem. Commun., 38, 731 (1973).
7. M. Holub, Z. Samek, S. Vasickova, and M. Masojidkova, Coll. Czech. Chem. Commun., 43, 2444 (1978).
8. M. Holub and Z. Samek, Coll. Czech. Chem. Commun., 38, 1428 (1973).
9. M. Holub, O. Mote, Z. Samek, and V. Herout, Coll. Czech. Chem. Commun., 37, 1186 (1972).
10. K. Vokas, V. Herout, and F. Sorm, Coll. Czech. Chem. Commun., 37, 1346 (1972).
11. Z. Smitalova, M. Budesinsky, D. Saman, S. B. Vasickova, and M. Holub, Coll. Czech. Chem. Commun., 49, 852 (1984).
12. J. V. Hendrikson, J. Am. Chem. Soc., 83, 4537 (1961).
13. V. G. Dashevskii, The Conformational Analysis of Organic Molecules [in Russian], Khimiya, Moscow (1982), p. 125.
14. A. T. McPhail and G. A. Sim, Tetrahedron, 1751 (1973).
15. International Tables for X-Ray Crystallography, Kynoch Press, Birmingham, Vol. III (1962).
16. G. Ruban, V. Zabel, K. N. Gensch, and H. Smalla, Acta Crystallogr., 34, 1163 (1978).
17. S. De Fortier, G. T. De Titta, and P. A. Grieco, Acta Crystallogr., 35, 1742 (1979).
18. V. I. Andrianov, Z. Sh. Safina, and B. L. Tarnopol'skii, Zh. Strukt. Khim., 15, 911 (1974).

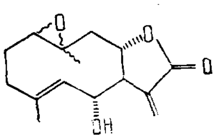
CRYSTAL AND MOLECULAR STRUCTURE OF THE SESQUITERPENE LACTONE MUCRIN

M. K. Makhmudov, B. Kh. Abduazimov, B. Tashkodzhaev,
B. T. Ibragimov, and M. R. Yagudaev

UDC 547.992:547.37+548.737

An x-ray structural investigation has been made of the sesquiterpene lactone mucrin, diffractometer: Cu K_α radiation, 942 reflections, direct method, R factor 0.083. The spatial structure of the molecule has been determined: the lactone ring is trans-linked with the germacrane ring, the epoxide group in the 1,10 position has the 1α,10β-orientation, and the hydroxy group in position 6 has the α-orientation.

We have previously reported the isolation from Tanacetopsis mucronata of the sesquiterpene lactone mucrin, for which structure (I) has been proposed [1]. Continuing a study of the structure of mucrin, we have investigated its PMR spectrum. It is worth noting that mucrin acetate has the same structure as pyrethrosin [2, 3]



I

A comparative analysis of the PMR spectra in $CDCl_3$ of pyrethosin and mucrin acetate showed that they differed mainly by the magnitudes of the chemical shifts (CSs) of the $10\text{-}CH_3$ and H-7 protons; the signal of the former was shifted downfield by 0.14 ppm and that of the latter upfield by 0.19 ppm. All these facts show that mucrin acetate differs from pyre-

---

Institute of the Chemistry of Plant Substances, Academy of Sciences of the Uzbek SSR, Tashkent. Institute of Bioorganic Chemistry, Academy of Sciences of the Uzbek SSR, Tashkent. Translated from Khimiya Prirodnykh Soedinenii, No. 1, pp. 59-63, January-February, 1988. Original article submitted June 16, 1987.