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X-RAY STRUCTURAL INVESTIGATION OF SESQUITERPENE ESTERS FROM PLANTS OF THE GENUS *Ferula*.

IV. STRUCTURE AND STEREOCHEMISTRY OF THE NEW CAROTANE ESTER PALLIDIN

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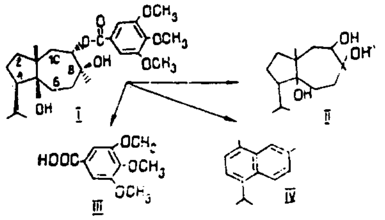
The structure and stereochemistry of a new carotane ester, pallidin, isolated from the roots of Ferula pallida *have been established by x-ray structural analysis. Its spectral characteristics and chemical properties have been studied.*

Continuing an investigation of esters of the giant fennel *Ferula pallida*, family Apiaceae [1-3], from a neutral fraction of an ethanolic extract of the roots we have isolated a new ester with the composition $C_{25}H_{38}O_7$, which has been called pallidin (I).

Taken together, the spectral characteristics (UV, IR, and PMR spectra) of pallidin show that it is an ester of a sesquiterpene alcohol with 3,4,5-trimethoxybenzoic acid. The dehydrogenation of pallidin showed that it was based on a carotane skeleton, while alkaline hydrolysis led to the formation of a new sesquiterpene alcohol $C_{15}H_{28}O_3$ — pallitriol (II) — and 3,4,5-trimethoxybenzoic acid $C_{10}H_{12}O_5$ (III).

Analysis of the PMR and mass spectra of pallidin in comparison with the carotane esters ferutin, ferutinol, pallinol, lapiferin, and others [3-8] permitted the probable positions of the two hydroxy groups at C5 and C8 of the carotane skeleton to be suggested.



The chemical behavior of pallitriol and the IR spectrum of the ketone (II) showed that the third hydroxy group could be present in one of three possible positions: C6, C7, or C9.

In order to establish the structure unambiguously and to determine the stereochemistry of pallidin, we have carried out an x-ray structural analysis (XSA). Its results enabled the structure of pallidin to be refined in the form of (I) and all the stereochemical aspects to be elucidated.

Figure 1 shows the spatial structure of the pallidin (I) molecule. The five-membered and seven-membered rings of (I) are cis-linked. At the present time, two series of carotane compounds have been isolated from plants of the genus *Ferula*, with cis and with the trans linkage of the carotane bicycle. As a rule, in substances having, like pallidin, a C5-OH group (daucol, linkiol, siol acetate, linkitriol p-methoxybenzoate, and vaginatin) [9-16], the carotene nucleus is cis-linked. It has been established that in (I) the methyl group at C1, the isopropyl group at C4, and the hydroxy groups at C5 and C8 have the β-orientation, while the methyl group at C8 and the ester radical at C9 are α-oriented. Table 1 gives the values of the torsion angles of the cyclopentane and cycloheptane rings of pallidin. Judging from these magnitudes (in comparison with the theoretical values for unsubstituted cyclopentane and cycloheptane [17]) the cyclopentane ring has a half-chair conformation, and the cycloheptane ring a twist-chair conformation. The plane passing through the atoms of the trimethoxybenzoic acid residue (C16-C22, O3-O7) is twisted by 70° relative to the mean-square plane of the seven-membered ring.

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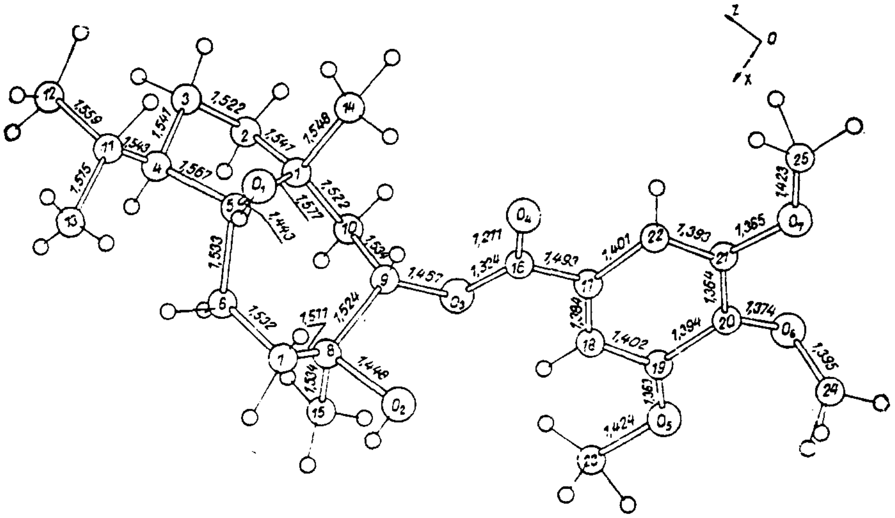

Fig. 1. Geometry of the pallidin molecule.

TABLE 1. Torsion Angles (ω, deg) of the Rings in the Pallidin Molecule

Fragment	ω_{exp}	ω_{theor} for half-chair	ω_{theor} for twist-chair	Cyclo-pentane	Cyclo-heptane
Cyclopentane			Cycloheptane		
C1C2C3C4	46,3	44.3	C1C5C6C7	−75 5	−97,0
C2C3C4C5	−35,9	−35,3	C5C6C7C8	80.9	75,8
C3C4C5C1	12,9	12,6	C6C7C8C9	−56,9	−52.9
C4C5C1C2	14,8	15,0	C7C8C9C10	68,1	75,8
C5C1C2C3	−37,9	−36,7	C8C9C10C1	−91,9	−97,0
			C9C10C1C5	53,9	41,2
			C10C1C5C6	16,9	41,2

TABLE 2. Valence Angles (φ) of the Pallidin Molecule

Angle	φ	Angle	φ	Angle	φ
C2C1C5	102,9	C6C7C8	117,8	O4C16C17	113,3
C2C1C10	110,5	C7C8C9	109,6	C16C17C18	122,5
C2C1C14	108.4	C7C8C15	111.7	C16C17C22	116,3
C5C1C10	116,3	C7C8O2	108,9	C18C17C22	121,2
C5C1C14	111,2	C9C8C15	113.5	C17C18C19	118,5
C1C2C3	104,4	C15C8O2	108,2	C18C19C20	120.7
C2C3C4	101,5	C8C9C10	115,4	C18C19O5	123,8
C3C4C5	105 5	C8C9O3	106,8	C20C19O5	115,5
C3C4C11	113,7	C10C9O3	107,7	C19C20C21	120,1
C5C4C11	117,0	C1C10C9	116,9	C19C20O6	120,3
C1C5C4	105,2	C4C11C12	109,3	C21C20O6	119,4
C1C5C6	113,3	C4C11C13	113,1	C20C21C22	120,9
C1C5O1	107,4	C12C11C13	108,1	C20C21O7	115,8
C4C5C6	108,8	C9O3C16	116,4	C22C21O7	123.3
C4C5O1	112,2	O3C16O4	123.7	C17C22C21	118,6
C6C5O1	110,0	O3C16C17	113 3	C19O5C23	119 0
C5C6C7	118,4	C9C8O2	104,7	C20O6C24	112,0
				C21O7C25	118,6

No anomalies are observed in the values of the valence angles (Table 2) and distances (Fig. 1). The mean-square deviations in the values of the valence bonds and angles are not more than 0.007 Å and 0.4°, respectively. An analysis of intermolecular contacts has shown that the hydroxy group (O1—H) and the carbonyl group form an intermolecular H-bond of the O—H · · · O type (the O1 · · · O4 distance is 2.78 Å), due to which the molecules transformed by 2_1 screw axes (x; 1/4; 0) form an infinite chain directed along the *a* axis.

TABLE 3. Coordinates of the Basis Atoms (× 10^4) and the H Atoms (× 10^3) of the Pallidin Molecule

Atom	x	y	z	Atom	x	y	z
C1	472 (5)	5111 (4)	653 (1)	H2.1	155	673	994
C2	399 (7)	6085 (5)	1019 (2)	H2.2	−71	651	100
C3	621 (7)	5296 (5)	1424 (23)	H3.1	89	577	173
C4	2179 (6)	4439 (5)	1301 (1)	H3.2	−53	467	151
C5	1926 (5)	4143 (4)	812 (1)	H4	342	506	132
C6	3698 (5)	4302 (4)	585 (1)	H6.1	462	379	77
C7	3876 (6)	3812 (4)	127 (1)	H6.2	409	527	62
C8	3178 (5)	4638 (4)	−231 (1)	H7.1	535	341	7
C9	1230 (5)	4920 (4)	−155 (1)	H7.2	342	232	8
C10	832 (5)	5768 (4)	229 (1)	H9	70	404	−11
C11	2431 (7)	3300 (5)	1602 (2)	H10.1	−34	627	16
C12	2404 (9)	3768 (7)	2075 (2)	H10.2	177	650	24
C13	4149 (8)	2602 (5)	1528 (2)	H11	124	272	160
C14	−1360 (5)	4464 (5)	617 (2)	H12.1	274	283	225
C15	4299 (6)	5825 (4)	−292 (1)	H12.2	370	442	213
C16	− 885 (5)	5104 (3)	−712 (1)	H12.3	82	418	219
C17	−1420 (5)	5771 (3)	−1119 (1)	H13.1	422	218	131
C18	− 354 (5)	6559 (4)	−1312 (1)	H13.2	508	325	158
C19	− 941 (6)	7197 (4)	−1696 (1)	H13.3	414	162	176
C20	−2551 (5)	6858 (4)	−1871 (1)	H14.1	−223	512	59
C21	−3602 (5)	6001 (4)	−1666 (1)	H14.2	−138	382	34
C22	−3066 (5)	5440 (4)	−1284 (1)	H14.3	−176	404	86
C23	1682 (7)	8449 (6)	−1771 (2)	H15.1	542	575	−40
C24	− 2573 (9)	6822 (9)	−2604 (2)	H15.2	427	627	1
C25	−6300 (7)	4827 (6)	−1672 (2)	H15.3	379	629	−52
O1	1251 (3)	2891 (2)	741 (1)	H18	78	691	−117
O2	3214 (4)	3922 (3)	−626 (1)	H22	−385	473	−110
O3	577 (3)	5566 (2)	−540 (1)	H23.1	203	907	−206
O4	−1721 (4)	4240 (3)	−559 (1)	H23.2	252	760	−174
O5	7 (4)	8067 (3)	−1924 (1)	H23.3	165	858	−139
O6	−3151 (6)	7437 (3)	−2237 (1)	H24.1	−306	713	−289
O7	−5184 (4)	5753 (3)	−1857 (1)	H24.2	−127	758	−269
H24.3	−171	703	−272	H25.1	−758	485	−184
H25.2	−605	409	−142	H25.3	−700	489	−136
H(O1)	217	234	78	H(O2)	422	329	−63

EXPERIMENTAL

The spectra of the substances were obtained on the following instruments: Hitachi EPS-3T (ethanol); UR-20 (KBr); MKh-1310; VM-4H-100/100 MHz.

Isolation (separation) of Pallidin. After the rechromatography of fractions XXXII–LXXIII, 3 g of a substance with the composition $C_{25}H_{38}O_7$ was obtained having mp 109.5-110°C (from hexane–ethyl acetate). $[\alpha]_D^{20}$ 27.9° (c 0.1; $CHCl_3$). UV spectrum ($\lambda_{max}^{C_2H_5OH}$, nm): 215.265 (log ε 4.14). IR spectrum (ν_{max}^{KBr}, cm^{-1}): 3508, 3515, 2948, 1694, 1595, 1515. PMR spectrum (C_5D_5N, δ, ppm): 0.96; 0.99 (d, J = 7.5 Hz, each 3H); 1.46 (s, 3H); 1.65 (s, 3H); 3.60 (s, 6H); 3.76 (s, 3H); 4.64 (s, 1H); 4.66 (br.s, 1H), 5.74 (q, J = 12, J = 2 Hz, 1H); 7.37 (s, 2H). Mass spectrum (m/z): 450 (M^+), 238 $(M - C_{10}H_{12}O_5)^+$, 195 $(M - C_{10}H_{12}O_5C_3H_7)^+$.

Hydrolysis of Pallidin. A solution of 70 mg of the substance in 15 ml of 5% KOH in ethanol was heated on the water bath for 1 h. After cooling, the reaction mixture was diluted with distilled water and extracted with ether. The ethereal extract was washed with water and dried, and the ether was evaporated off. This gave a compound $C_{15}H_{25}O_3$ (II) with mp 73.0-73.5°C (ether) and 3,4,5-trimethoxybenzoic acid, $C_{10}H_{12}O_5$ (III) with mp 210-212°C.

Dehydrogenation of (I). A mixture of 200 mg of the substance and 200 mg of 10% $Pd/CaCO_3$ was heated at 240-250°C for 3 h. After cooling, the reaction mixture was extracted with petroleum ether, and the extract was washed with phosphoric acid and with water and was dried over Na_2SO_4 and evaporated. The oil residue was chromatographed on alumina with elution by hexane. This gave 40 mg of daucalene (IV) with a characteristic naphthalene odor, mp 60-62°C (from ether).

Acetylation of (II). A solution of 97 mg of pallidol in 2 ml of dry pyridine was treated with 2 ml of acetic anhydride. The mixture was left at room temperature for a day. It was then diluted with water and extracted with ether, and the ethereal extract was washed with 5% sulfuric acid and then with water to neutrality, and was dried over Na_2SO_4 and evaporated. This gave 90 mg of a monoacetyl derivative of pallitriol, $C_{17}H_{30}O_4$, mp 121-122°C.

Oxidation of (II). A solution of 0.5 g of chromium trioxide in 10 ml of pyridine was added dropwise to a solution of 148 mg of the substance in 2 ml of pyridine, and the mixture was left for a day at room temperature.

It was then acidified with 5% sulfuric acid and extracted with ethyl acetate. The extract was washed with distilled water and was dried over anhydrous sodium sulfate, giving 0.03 g of a ketone derivative of pallitriol.

X-Ray Structural Analysis. Colorless single crystals of pallidin in the form of flat plates were grown from hexane–ethyl acetate solution and were first studied by the photo method. The space group and the parameters of the elementary cell were determined in a Weissenberg camera. These parameters were then refined in a Syntex-$P2_1$ diffractometer using CuK_α radiation: $a = 7.578$ (5), $b = 10.551$ (4), $c = 31.240$ (7) Å, $\rho_{\text{talc}} = 1.21$ g/cm^3, space group $P2_12_12_1$, $z = 4$.

A three-dimensional set of experimental reflections was obtained on the same diffractometer. In the primary treatment of the group, weak reflections with $I \leq 2\sigma$ were excluded. The final group of structural amplitudes amounted to 1777 independent reflections. The structure was determined by the direct method using the Rentgen-75 program [18]. Analysis of ansynthesis revealed 28 of the 32 nonhydrogen atoms. The missing atoms were found in the following electron-density (ED) synthesis plotted from the whole group of reflections. The structure was refined by successive ED approximations ($R = 0.151$) and then by the method of least squares (MLS) in the isotropic approximation ($R = 0.114$), and after this in the full-matrix MLS with allowance for the anisotropic thermal vibrations of the nonhydrogen atoms to $R = 0.083$. At this stage an ED difference synthesis was carried out and all the H atoms were localized. The final value of the divergence factor of four cycles of MLS taking the H atoms into account was 0.058. The coordinates of the atoms are given in Table 3.

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