# MICROLOBIN — A NEW COUMARIN FROM *Ferula microloba*

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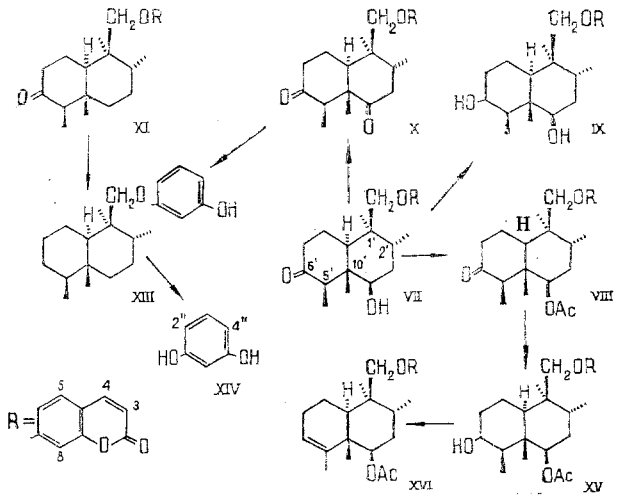
A new sesquiterpenoid 7-O-coumarin has been isolated from the roots of *Ferula microloba* Boiss. — microlobin, $C_{24}H_{30}O_5$, $M^+$ 398. mp 150-151°C, $[\alpha]_D^{20}$ +49° (c 0.5; $CHCl_3$), for which, on the basis of chemical transformations and spectral characteristics, the structure and configuration have been established as 7-(4'β-hydroxy-1'α,2'α,5'β, 10'β-tetramethyl-6'-oxo-trans-decalin-1'β-ylmethoxy) coumarin.

We have studied the roots of the plant of *Ferula microloba* Boiss. gathered in the environs of Babadurmez (TurkmSSR) and have isolated aurapten (I), methyl galbanate (II), galbanic acid (III), isosamarcandin angelate (IV), umbelliferone (V) [1-7], isosamarcandin (VI), and a new sesquiterpene 7-O-coumarin, microlobin (VII), with the composition $C_{24}H_{30}O_5$, $M^+$ 398, mp 150-151°C, $[\alpha]_D^{20}$ +46° (c 0.5; $CHCl_3$). The UV spectrum of (VII) is characteristic for umbelliferone derivatives. The IR spectrum contains characteristic absorption bands of a hydroxy group, of the carbonyl of an α-pyrone, and of a ketone (3540, 1730, 1720 $cm^{-1}$, respectively), and also shows the absorption bands of an aromatic nucleus (1620, 1570, 1515 $cm^{-1}$).

The reaction of (VII) with acetic anhydride in pyridine formed an acetyl derivative (VIII), $C_{26}H_{32}O_6$, $M^+$ 440. The reduction of (VII) with sodium tetrahydroborate methanol gave a diol (IX), $C_{24}H_{32}O_5$, $M^+$ 400. The oxidation of (VII) and (IX) with chromium trioxide in acetone led to a diketone (X), $C_{24}H_{28}O_5$, $M^+$ 396. The formation of the last-mentioned compound indicates that the terpenoid part of microlobin is a bicyclic sesquiterpene residue and contains one ketone and one secondary hydroxy group.

The PMR spectrum of microlobin (VII) is characteristic for compounds with a drimane skeleton [8], i.e., of the four methyl groups two are secondary and two are tertiary and, moreover, signal from the $-CH_2-OR$ group is observed in the form of a narrow singlet, as in the case of kamolone (XI), and kamolol (XII) [9, 10] (Table 1). This was confirmed in the following way. The Huang-Minlon reduction of (X) and of kamolone (XI) [11-13] led to the same compound (XIII) of noncoumarin nature, $C_{21}H_{32}O_2$, $M^+$ 316. The formation of resorcinol (XIV) on acid hydrolysis of the latter (XIII) indicates that, in addition to reduction, alkaline degradation of the coumarin nucleus has taken place [14].



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The production of (XIII) shows that (VII) has a drimane skeleton in which the conformation of the bicyclic system and the configurations of the methyl groups and the $-CH_2OR$ group are similar to those of kamolone [9, 10].

The positions of the functional groups were determined in the following way. In the skeleton of the drimane (VII) five positions are possible for the hydroxy group: $C_3'$, $C_4'$, $C_6'$, $C_7'$, and $C_8'$. In the PMR spectrum of (VII) the signal of the hemihydroxylic protons, interacting with two vicinal protons, appears in the form of a quartet with splittings of $J_1 = 11.5$ and $J_2 = 5$ Hz (see Table 1). This confirms the position of the OH group with equatorial orientation at $C_4'$ and excludes the remaining possible positions.

In the PMR spectrum of the reduction products (IX) of (VII), the signal from one secondary methyl undergoes a paramagnetic shift by 0.09 ppm, which gives grounds for assuming that one of the secondary methyls is in the α position with respect to the ketone group. To confirm this, (VIII) was reduced with sodium tetrahydroborate in methanol, which gave product (XV), $C_{26}H_{34}O_6$, $M^+$ 442. Subsequent dehydration of (XV) with phosphoryl chloride in pyridine [15] gave compound (XVI) $C_{26}H_{32}O_5$, $M^+$ 424.

The PMR spectrum of (XVI), as compared with the spectrum of the initial compound (XV), lacked one signal from two doublets of secondary methyl groups. In place of it, additional signals from a vinylmethyl group appeared at 1.52 ppm and from an olefinic proton at 5.14 ppm (see Table 1). Since the $C_3'$ position is excluded on the basis of the PMR spectrum of (VII), only position $C_6'$ remains for the oxo group.

Thus, microlobin has the structure and configuration of 7-(4'β-hydroxy-1'α,2'α,5'β,10'β-tetramethyl-6'-oxo-trans-decalin-1'β-ylmethoxy) coumarin (VII).

## EXPERIMENTAL

Type L 40/100 μ silica gel (Czechoslovakia) was used for column chromatography. TLC was performed on Silufol, type UV-254, plates in the chloroform–ethyl acetate (2:1) system.

UV spectra were taken on a Hitachi spectrophotometer (in ethanol), IR spectra on a UR-20 instrument (KBr tablets), mass spectra on a MKh-1303 instrument, and PMR spectra on a JNM-4H-100/100 MHz spectrometer in $CDCl_3$ solution, 0 — HMDS.

TABLE 1. Details of the PMR Spectra of Microlobin (VII) and Its Derivatives in $CDCl_3$, δ, ppm (multiplicity, J, Hz)

| Assignment | VII | VIII | IX | X | XI | XIII | XV | XVI |
|---|---|---|---|---|---|---|---|---|
| $C_1'$: $C_{10'}$ | 0,81 | 0,92 | 1,03 | 1,20 | 0,74 | 0,79 | 1,05 | 1,04 |
| 2C–$CH_3$C | 1,07 | 1,09 | 1,08 | 1,13 | 1,06 | 0,98 | 1,25 | 1,16 |
| $C_2'$; $C_5'$ | 1,03 | 0,85 | 0,93 | 1,00 | 0,85 | 0,85 | 1,04 | 0,99 |
| 2 H–C–$CH_3$ (d,7) | 1,10 | 1,11 | 1,19 | 1,10 | 0,96 | 0,95 | 1,07 | — |
| $C_1'$–$CH_2O$–(s) | 3,71 | 3,71 | 3,63 | 3,77 | 3,70 | 3,41 (d,10) 3,55 (d 10) | 3,62 | 3,66 |
| $C_4'$–O–C–H | 3,89 (q ,11,5;5) | 5,00 (q ,11,5; 5) | 3,63 (m) | | | | 4,75 (q 11,5;5) | 4,92 (t, 7,5) |
| $C_6'$– O –C–H (m) | | | 3,63 (m) | | | | | |
| $OCOCH_3$ (s) | | 1,97 | | | | | 1,94 | 1,97 |
| HC=C (m,10) | | | | | | | | 5,14 |
| $C_5'$=C–$CH_3$ (s) | | | | | | | | 1,52 |
| $C_4$–H (d,10) | 6,13 | 6,14 | 6,14 | 6,16 | 6,17 | | 6,11 | 6,13 |
| $C_8$–H (m) | 6,71 | 6,70 | 6,69 | 6,72 | 6,73 | | 6,66 | 6,69 |
| $C_6$–H (m) | 6,77 | 6,74 | 6,74 | 6,76 | 6,80 | | 6,74 | 6,74 |
| $C_5$–H (m) | 7,39 | 7,30 | 7,28 | 7,28 | 7,29 | | 7,23 | 7,26 |
| $C_3$–H (d, 10) | 7,53 | 7,54 | 7,54 | 7,55 | 7,58 | | 7,51 | 7,50 |
| $C_{2''; 4''; 6''}$–3H (m) | | | | | | 6,29 | | |
| $C_{3''}$ H(t,8) | | | | | | 6,95 | | |

Isolation of the Coumarins. The comminuted air-dry roots (1.9 kg) of the plant under investigation were extracted with ethanol. The extract was concentrated in vacuum, and the residue obtained was diluted with water (1:2) and extracted with ether (5 × 500 ml). The ethereal extract was treated with 5% sodium carbonate solution and was washed with water and dried, and the solvent was distilled off. This gave 46 g of the sum of the coumarins, which were chromatographed on a column of silica gel (1200 g). Elution was carried out with petroleum ether–ethyl acetate with increasing concentrations of the latter for successive groups of fractions: 1-8 (4:1), 8-12 (3:1), 13-16 (2.5:1), 17-19 (2:1), 20-32 (1.5:1). The volume of each fraction collected was 300 ml.

Aurapten (I). Fractions 1 and 2 yielded 3.8 g of crystals of (I) with $R_f$ 0.62 [3].

Methyl Galbanate (II). After the solvent had been distilled off from fraction 3-5, 4.5 g of (II) was isolated, $R_f$ 0.60 [2].

Galbanic Acid (III). The sodium carbonate solution after the treatment of the sum of the coumarins was acidified with 5% sulfuric acid and extracted with diethyl ether. The ethereal extract was washed with water and dried, and the solvent was evaporated off. This gave 7.2 g of (III) [1, 5].

Isosamarcandin Angelate (IV). After evaporation of the solvent from fractions 16-19, 0.6 g of (IV) was obtained [6].

Umbelliferone (V). The concentrated eluate of fractions 28-29 deposited 0.22 g of crystals of (V) [7].

Isosamarcandin (VI). The residue after the evaporation of fractions 30-32 was crystallized from a mixture of ethyl acetate and hexane, giving crystals of (VI) [4].

Microlobin (VI). Fractions 19-21 yielded 2.5 g of a crystalline compound, $C_{24}H_{30}O_5$, $M^+$ 398, mp 150-151°C (ethyl acetate–hexane), $[\alpha]_D^{20}$ + 49° (c 0.5; $CHCl_3$), $R_f$ 0.02.

UV spectrum: $\lambda_{max}$ 217, 244, 253, 295, 327 nm (log ε 4.16, 3.60, 4.42, 3.85, and 4.14, respectively).

Mass spectrum, m/z: 398 $(M)^+$, 380 $(M - H_2O)^+$, 237 $(M - R{\bullet}H_2O)^+$, 136 $(M - ROH)^+$, 218 $(M - ROH{\bullet}H_2O)^+$ 201 $(M - RO{\bullet}2H_2O)^+$, 162$(ROH)^+$, 163 $(R{\bullet}H_2O)^+$.

Acetylation of (VII). A solution of 0.185 g of (VII) in 2 ml of anhydrous pyridine was treated with 2 ml of acetic anhydride, and the reaction mixture was left for a day. After usual working up, 0.172 g of (VIII) was obtained: $C_{26}H_{32}O_6$, $M^+$ 440. $R_f$ 0.41, $[\alpha]_D^{20}$ −32° (c 0.5; $CHCl_3$).

IR spectrum: 1730, 1710 $cm^{-1}$ (C=O of an α-pyrone and of an ester group), 1620, 1565, 1515 $cm^{-1}$ (C=C of an aromatic ring).

Oxidation of (VII). A solution of 0.3 g of chromium trioxide in 3 ml of water was added dropwise to a solution of 0.3 g of (VII) in 20 ml of acetone. After 20 min, the mixture was diluted with water and was treated with ether. The ethereal solution was washed with water and dried with sodium sulfate. After the solvent had been distilled off, 0.26 g of the diketone (X) was isolated, $C_{24}H_{28}O_5$, $M^+$ 396, $[\alpha]_D^{20}$ +5° (c 0.2; $CHCl_3$), $R_f$ 0.39.

UV spectrum, $\lambda_{max}$: 222, 253, 296, 326 nm (log ε 4.38, 3.24, 3.68, 3.92).

IR spectrum: $\nu_{max}$ 1740, 1730, 1710 $cm^{-1}$ (C=O groups of an α-pyrone and of ketones), 1620, 1560, 1510 $cm^{-1}$ (C=C of an aromatic ring).

Reduction of (VII) with Sodium Tetrahydroborate. A solution of 0.08 g of (VII) in 25 ml of 90% aqueous methanol was treated with 0.08 g of sodium tetrahydroborate. After 60 min, the mixture was acidified with 5% sulfuric acid solution and extracted with ether. The ethereal solution was washed with water and dried, and the solvent was distilled off. This gave 0.065 g of the diol (IX), $C_{24}H_{32}O_5$, $M^+$ 400, $R_f$ 0.1.

UV spectrum, $\lambda_{max}$: 223, 253, 237 nm (log ε 4.58, 4.06, 4.19).

IR spectrum, $\nu_{max}$: 3480 $cm^{-1}$ (–OH group), 1730 $cm^{-1}$ (C=O of an α-pyrone), 1615, 1560, 1510 $cm^{-1}$ (C=C of an aromatic ring).

Huang-Minlon Reduction of (X). A mixture of 0.1 g of compound (X), 1.5 ml of hydrazine hydrate, 0.2 g of caustic potash, and 25 ml of diethyleneglycol was heated at 95-102°C. After an hour, when the low-boiling products had been distilled off, the temperature of the reaction

mixture was raised to 190-210°C, and it was kept there for 5 h. Then the reaction mixture was acidified with 5% aqueous sulfuric acid and treated with ether. After the solvent had been distilled off, 0.03 g was obtained of the dark-colored oily compound (XIII), $C_{21}H_{32}O_2$, $M^+$316, $[\alpha]_D^{20}$ −48.2° (c 1.24; $CHCl_3$). $R_f$ 0.89.

UV spectrum, $\lambda_{max}$: 223, 378, 284 nm (log ε 3.58, 3.31, 3.23).

Huang-Minlon Reduction of Kamolone (XI). Taking 0.6 g of (XI), the reaction was carried out in a similar manner to that described above. This gave 0.22 g of a compound identical with (XIII).

Acid Hydrolysis of (XIII). A solution of 0.19 g of (XIII) in 0.5 ml of acetic acid and 0.05 ml of concentrated sulfuric acid was heated at 80°C for 20 min. Then it was diluted with water and treated with ether. After washing and evaporation of the ethereal solution, 0.025 g of resorcinol with mp 110°C was obtained.

Reduction of (VIII) with Sodium Tetrahydroborate. The reduction of 0.15 g of (VIII) with sodium tetrahydroborate was carried out as described above. This gave 0.134 g of compound (XV), $C_{24}H_{34}O_6$, $M^+$442, $[\alpha]_D^{20}$ ± 3° (c 0.15; $CHCl_3$). $R_f$ 0.02.

UV spectrum, $\lambda_{max}$: 212, 220, 253, 294, 327 nm (log ε 4.08, 4.03, 3.35, 3.67, 3.95).

Dehydration of (XV) with Phosphoryl Chloride. A solution of 0.085 g of (XV) in 1 ml of pyridine was treated with 0.4 ml of phosphoryl chloride ($POCl_3$). The reaction mixture was left at room temperature for 22 h without the access of moisture. Then it was diluted with water and treated with ether. The ethereal solution was washed successively with hydrochloric acid solution, sodium carbonate, and water and was dried and evaporated. It gave 0.07 g of (XVI), $C_{26}H_{32}O_5$, $M^+$424, $[\alpha]_D^{20}$ −10° (c 0.5; $CHCl_3$). $R_f$ 0.7.

IR spectrum, $\lambda_{max}$: 1730 $cm^{-1}$ (C=O of an α-pyrone), 1610, 1560, 1510 (C=C of an aromatic ring).

## SUMMARY

The roots of *Ferula microloba* Boiss. have yielded aurapten (I), methyl galbanate (II), galbanic acid (III), isosamarcandin angelate (IV), umbelliferone (V), isosamarcandin (VI), and a new sesquiterpene 7-O-coumarin — microlobin (VII) with the composition $C_{24}H_{30}O_5$, $M^+$398, mp 150-151°C, $[\alpha]_D^{20}$ + 49° (c 0.5; $CHCl_3$). On the basis of chemical transformations and spectral characteristics it has been established that compound (VII) is 7-(4'β-hydroxy-1'α,2'α,5'β,10'β-tetramethyl-6'-oxo-trans-decalin-1'β-ylmethoxy)coumarin.

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