Chem. Pharm. Bull.
35(1) 182—187 (1987)

Corianin from *Coriaria japonica* A. GRAY, and Sesquiterpene Lactones from *Loranthus parasiticus* MERR. Used for Treatment of Schizophrenia

TAKUO OKUDA,*[,a] TAKASHI YOSHIDA,[a] XIN-MIN CHEN,[b] JING-XI XIE,[c] and MAKOTO FUKUSHIMA[d]

Faculty of Pharmaceutical Sciences, Okayama University,[a] Tsushima, Okayama 700, Japan, Chengdu Institute of Biology, The Chinese Academy of Sciences,[b] Chengdu, China, Institute of Materia Medica, Chinese Academy of Medical Sciences,[c] Beijing, China, and Laboratories, Pola Corporation,[d] Takashimadai, Kanagawa-ku, Yokohama 221, Japan

(Received July 21, 1986)

Pseudotutin previously isolated from *Coriaria japonica* A. GRAY was revealed to be a molecular compound consisting of equimolar tutin (**2**) and a new related sesquiterpene lactone, corianin (**3**). Corianin was also isolated together with coriamyrtin (**1**), tutin (**2**) and coriatin (**4**), from *Loranthus parasiticus* MERR., a parasitic plant that grows on the twigs of *Coriaria sinica* MAXIM. The structure of corianin was elucidated on the basis of nuclear magnetic resonance and chemical evidence. The previously proposed structure (**4**) for coriatin was also substantiated.

Keywords——*Coriaria japonica*; Coriariaceae; *Loranthus parasiticus*; Loranthaceae; pseudotutin; corianin; tutin; molecular compound; coriatin

Coriaria japonica A. GRAY (Coriariaceae) is known to produce several sesquiterpene lactones including coriamyrtin (**1**) and tutin (**2**), which are the main toxic principles.[1] Among them, pseudotutin, which was previously isolated from the fruit extract and analyzed as $C_{15}H_{18}O_6$,[2] was reexamined and shown to be a molecular compound composed of tutin (**2**) and a new related sesquiterpene lactone named corianin (**3**).[3]

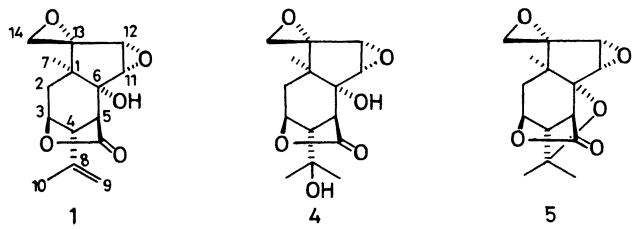
We have also isolated corianin, together with three sesquiterpene lactones, during an investigation of the active principles of *Loranthus parasiticus* MERR. (Chinese name: mā sāng jishēng, basō-kisei in Japanese pronunciation) (Loranthaceae), a parasitic plant that grows on the twigs of *Coriaria sinica* MAXIM. (Chinese name: mā sāng, basō in Japanese pronunciation) (Coriariaceae), which is distributed in the south and southwest parts of China and is a folk medicine used as a shock therapy for schizophrenia in the southwest area of China. In this paper we present a detailed account of the isolation and characterization of sesquiterpene lactones of *L. parasiticus*, and of the structure elucidation of corianin (**3**).

Although pseudotutin obtained by recrystallization from water has a constant, sharp melting point (184 °C)[2] and was regarded as a single compound, it has been found to give two spots on a thin-layer chromatogram (TLC), and two constituents have been separated by recrystallization from chloroform. The one which crystallized first was identified as tutin (**2**), and the other component, corianin (**3**), deposited from the mother liquor, showed mp 214—216 °C and analyzed as $C_{15}H_{18}O_6$ (M^+ 294.1160). Comparisons of the melting points of **2**, **3** and their mixtures indicated that pseudotutin is a molecular compound composed of equimolar **2** and **3** as found for picrotoxin.[4] Namely, the crystals obtained upon evaporation of the aqueous solution of 1 : 1 mixture of **2** and **3** displayed a melting point and infrared (IR) spectrum identical with those of pseudotutin, while the mixtures of different ratios near 1 : 1

showed lower melting points.

The sesquiterpene lactones including corianin of *L. parasiticus* were isolated from the chloroform-soluble portion of the ethanol extract of the dried leaves. The mixture of sesquiterpene lactones was separated into four compounds by column chromatography over polyamide and then on silicic acid, followed by recrystallization. Among them, two components which showed strong convulsive action in mice, were identified as coriamyrtin (**1**) and tutin (**2**) and the other two were identified as corianin (**3**) and coriatin (**4**), by direct comparison with authentic specimens obtained from *Coriaria japonica*. The aqueous extractive of the plant, or a mixture of these crystalline sesquiterpenes including nontoxic corianin and coriatin, which gives effects comparable to insulin or electric shock, is currently used by muscle injection for the treatment of catatonia in hospitals in diverse areas of China.[5] The results described above show that coriamyrtin and tutin are the active ingredients of *L. parasiticus* for this therapy. The isolation of these sesquiterpenoids from *Coriaria sinica*,[6] suggests that these compounds have been transported from the host plant to the parasitic one, and accumulated in the latter without being metabolized.

Coriatin (**4**), $C_{15}H_{20}O_6$, a hydroxycoriamyrtin, was first isolated from the fruit juice of *Coriaria japonica* in 1961, and its structure (**4**) was proposed based mainly on the IR spectrum.[7] Further evidence of the structure has now been provided by the proton and carbon-13 nuclear magnetic resonance (^{1}H- and ^{13}C-NMR (Table I)) spectra which are very similar to those of coriamyrtin (**1**)[8] except that they show three tertiary methyl signals [δ_H 1.16, 1.30 and 1.43; δ_C 22.97, 30.17 and 28.39], and that the signals attributable to the



1 4 5

Chart 1

TABLE I. ^{13}C-NMR Data for Coriamyrtin (**1**), Tutin (**2**), Corianin (**3**) and Coriatin (**4**) in Pyridine-d_5

Carbon	1	4	2	3
1	39.71 (s)	39.98 (s)	45.94 (s)	55.58 (s)
2	30.93 (t)	31.80 (t)	72.16 (d)	81.86 (d)
3	78.61 (d)	78.82 (d)	84.40 (d)	85.38 (d)
4	48.59 (d)	49.57 (d)	49.95 (d)	48.81 (d)
5	50.06 (d)	52.60 (d)	50.76 (d)	50.17 (d)
6	76.38 (s)	75.41 (s)	77.90 (s)	75.30 (s)
7	23.35 (q)	22.97 (q)	22.97 (q)	22.86 (q)
8	142.58 (s)	68.37 (s)	142.69 (s)	140.69 (s)
9	110.46 (t)	30.17 (q)	110.46 (t)	112.36 (t)
10	23.02 (q)	28.39 (q)	21.29 (q)	22.21 (q)
11	61.54 (d)	61.22 (d)	61.00 (d)	63.92 (d)
12	58.89 (d)	58.45 (d)	60.19 (d)	60.78 (d)
13	66.36 (s)	67.07 (s)	65.98 (s)	90.20 (s)
14	52.17 (t)	52.17 (t)	52.06 (t)	77.74 (t)
15	175.20 (s)	175.36 (s)	175.63 (s)	175.68 (s)

isopropenyl group are missing. The mass spectrum (MS) exhibited a fragment ion peak $[(Me)_2C=OH]^+$ at m/z 59 as the base peak, whereas the base peak in coriamyrtin is at m/z 41 $[CH_3C=CH_2]^+$. Finally, the structure **4** was proved by the chemical conversion of coriatin into apocoriamyrtin (**5**)[9] by treatment with $POCl_3$. Therefore, the established structure of coriatin, including the absolute configuration, is represented by **4**.

The structure **3** is assigned to corianin on the basis of the following observations. The IR spectrum (KBr) shows absorption bands at 3450 (hydroxyl), 1760 and 1740 [1750 cm^{-1} in $CHCl_3$; γ-lactone], and 1640 cm^{-1} (double bond). The ^{13}C-NMR spectrum exhibits the lactone carbonyl carbon signal at δ 175.68 and resonances due to a terminal methylene at δ 140.69 (s) and 112.36 (t), and does not show any other signals in the sp^2 carbon region (Table I). The terminal methylene signal in the ^1H-NMR spectrum (pyridine-d_5) is a 2H broad singlet at δ 4.94, which is coupled with a methyl signal at δ 2.08. The double bond is thus in the isopropenyl group. An AB quartet at δ 3.84 and 4.27 (J = 3 Hz), which is analogous to the epoxide protons at C-11 and C-12 of tutin (**2**), is observed. The rest of the proton signals of **3** are also similar to those of **2**, with the exception that the AB quartet of the terminal epoxide

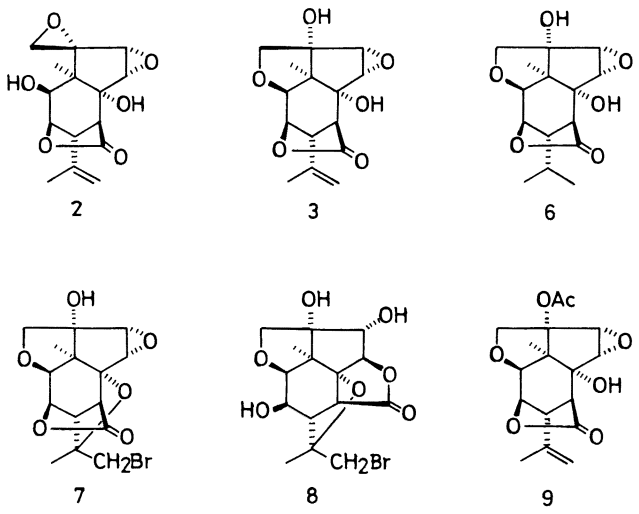


Chart 2

TABLE II. ^1H-NMR Data for Tutin (**2**) and Corianin (**3**) in Pyridine-d_5

Proton	Tutin (**2**)	Corianin (**3**)
H-2	4.75[a]	4.65 (d, J = 4 Hz)
H-3	5.23 (dt, J = 4, 1 Hz)	5.28 (dt, J = 4, 1 Hz)
H-4	3.43 (m)	3.40 (m)
H-5		3.48 (dd, J = 4, 1 Hz)
H-7 (CH_3)	1.93 (s)	1.60 (s)
H-9 (CH_2)	4.75[a]	4.94 (2H, br s)
	4.91 (br s)	
H-10 (CH_3)	2.13 (br s)	2.08 (br s)
H-11	3.53 (d, J = 3 Hz)	3.84 (d, J = 3 Hz)
H-12	4.11 (d, J = 3 Hz)	4.27 (d, J = 3 Hz)
H-14	3.10 (d, J = 6 Hz)	4.32 (d, J = 10 Hz)
	4.70 (d, J = 6 Hz)	4.46 (d, J = 10 Hz)

a) Overlapped.

[δ 4.70 and 3.10 (J=6 Hz)] in **2** is replaced in **3** by an AB quartet [δ 4.32 and 4.46] with a larger coupling constant J=10 Hz (Table II).

Hydrogenation of corianin (**3**) over Adams catalyst afforded dihydrocorianin (**6**), $C_{15}H_{20}O_6$ (M^+ 296), whose ^{1}H-NMR spectrum ($CDCl_3$) shows doublets at δ 0.98 (J=6 Hz) and 1.08 (J=6 Hz) due to an isopropyl group. Upon the treatment of corianin with bromine water, bromocorianin (**7**), $C_{15}H_{17}O_6Br$ (M^+ 372 and 374) was produced. Formation of an ether ring between the isopropenyl and a hydroxyl group upon the bromination is indicated by the ^{1}H-NMR spectrum of **7**, wherein the methyl and olefinic proton signals of the isopropenyl group observed in **3** are replaced by a methyl singlet at δ 1.56 and a singlet at δ 4.02 attributable to the bromomethyl group. These chemical and spectroscopic analogies between corianin and tutin lead to the assumption that corianin possesses a structure similar to tutin, on the same carbon skeleton. The difference between corianin and tutin is in the region of the terminal epoxide and C-2 oxygen function in tutin: in the ^{13}C-NMR spectrum of **3** (Table I), the signals due to C-13 and C-14 appear at δ 90.20 and 77.74, respectively, which are shifted downfield by 24.22 and 25.68 ppm from the corresponding signals of **2**, indicating the absence of the "spiro" epoxide ring in corianin. Significant downfield shifts of C-1 and C-2 in **3** compared with **2** are also observed. The other signals are virtually identical in chemical shifts as well as multiplicity with the signals of **2**.

In the ^{1}H-NMR spectrum measured in DMSO-d_6, the protons which are replaced by deuterium upon addition of D_2O appear as two singlets at δ 5.14 and 5.09 for corianin, while they appear as a singlet at δ 5.60 and a doublet at δ 5.16 for tutin. Corianin, therefore, should have two tertiary hydroxyl groups, the locations of which should be C-6 and C-13. Chemical evidence for this assumption was provided by the fairly high resistance to acetylation in a usual manner and to Jones oxidation. However, upon acetylation at an elevated temperature (80 °C), corianin gave a monoacetate (**9**), $C_{17}H_{20}O_7$ (M^+ 336.1180). The ^{1}H-NMR spectrum ($CDCl_3$) of **9** showed relatively large downfield shifts of one of the C-14 methylene proton signals and the H-12 signal, which can be explained by the deshielding effect of the acetyl group which is located spatially close to the hydrogens concerned.

As the presence of the oxygen function at C-2 and C-14 is evidenced by the ^{1}H- and ^{13}C-NMR spectra, these carbons should be in the five-membered ether ring, as in the structure **3**, which is compatible with the previously mentioned large coupling constant (J=10 Hz) of the C-14 proton signals.

The stereochemical relationship among the functional groups, *i.e.*, γ-lactone, C-4 isopropenyl group and C-6 hydroxyl group, on the cyclohexane ring has been established to be identical with that of tutin, as demonstrated by the formation of the ether bridge at C-6–O–C-8 on bromination, and also by the coupling constants of the H-2—H-5 signals which are analogous to those of tutin. The epoxide at C-11–C-12 in corianin (**3**) is hardly available for intermolecular nucleophilic attack, as found for tutin and coriamyrtin.[8] This stability can be rationalized in terms of protection of the epoxide moiety from backside attack by the γ-lactone group, and hence the epoxide at C-11–C-12 is *trans* to the γ-lactone. This assignment was chemically supported as follows: bromination of corianin afforded, in addition to **7**, a

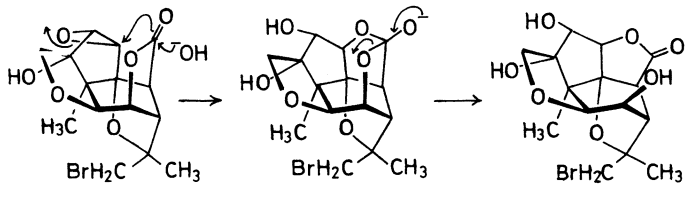


Chart 3

byproduct, isobromocorianin (**8**), $C_{15}H_{19}O_7Br$ (M^+ 390, 392), which retains the γ-lactone as indicated by an IR absorption band at 1750 cm^{-1}. The ^{1}H-NMR spectrum ($CDCl_3$) of **8** indicates the presence of the C-6–O–C-8 ether bridge [AB quartet at δ 3.46 and 3.56 (J= 14 Hz) (CH_2Br); 1.54 (3H, s)]. The H-3 signal is shifted upfield by 0.64 ppm from the corresponding signal of **7**, while a part of the AB quartet due to H-11 and H-12 showed a significant downfield shift. These spectral data, considered in conjunction with a molecular model, are consistent with the structure **8** for isobromocorianin. The transesterification during bromination is presumed to occur by intramolecular rearward attack on the epoxide by the lactone carbonyl oxygen, as illustrated in Chart 3.

The optical rotatory dispersion (ORD) curve of corianin is almost superposable on that of tutin. The absolute configuration of corianin is consequently represented by **3**.

Experimental

IR spectra were recorded on a Perkin-Elmer 683 spectrometer, optical rotations on a Perkin-Elmer 241 polarimeter, and MS on a ZAB-2F mass spectrometer or a Shimadzu LKB-9000 GC-MS spectrometer. NMR spectra were recorded on a Hitachi R-22FTS or a JEOL FX-90Q, with tetramethylsilane (TMS) as internal standard. Chemical shifts are given in δ (ppm) values. TLC was performed on Kieselgel PF_{254} plates (Merck), and spots were visuallized under ultraviolet (UV) light or by exposure to iodine vapor.

Separation of Tutin (2) and Corianin (3) from Pseudotutin——Pseudotutin, 184—185 °C, was recrystallized twice from $CHCl_3$ to give white crystals of mp 208—210 °C, which were identical with tutin (mixed melting point and IR comparison). Repeated recrystallization of the crystals obtained from the mother liquor afforded corianin (**3**), as colorless needles, mp 214—216 °C ($CHCl_3$). mp 224—225 °C (from EtOH), $[\alpha]_D$ +26.8° (c=1.1, EtOH–H_2O). IR (KBr) cm^{-1}: 3500, 3080, 1760, 1740, 1640, 1230, 1190, 1170, 1050, 917, 900, 860, 820. Accurate MS m/z: Calcd for $C_{15}H_{18}O_6$: 294.1103; Found: 294.1160. MS m/z (relative intensity, %): 279 (4), 248 (8), 250 (13), 217 (6), 205 (8), 165 (20), 125 (30), 124 (28), 95 (100), 41 (75). The ^{1}H- and ^{13}C-NMR spectra; see Tables I and II. ORD (c=0.08, MeOH); $[M]_{237}$ +4185°. *Anal.* Calcd for $C_{15}H_{18}O_6$: C, 61.21; H, 6.17. Found: C, 61.47; H, 6.16.

Relation of the Composition and Melting Point of Tutin (2) and Corianin (3)——A mixture of **2** and **3** in several amount ratios was dissolved in hot H_2O, and then the solvent was evaporated off. The melting point of each crystalline mixture thus obtained was determined and compared with those of **2**, **3** and pseudotutin. The results are as follows: mp 209—212 °C (**2**:**3**, 10:0); mp 152—160 °C (**2**:**3**, 7:3); mp 184—186 °C (**2**:**3**, 1:1); mp 160—170 °C (**2**:**3**, 3:7); mp 215—216 °C (**2**:**3**, 0:10). The crystals consisting of equimolar **2** and **3** were identical with pseudotutin as judged by comparison of the IR spectra.

Isolation of the Sesquiterpene Lactones from *Loranthus parasiticus*——Dried leaves (32 kg) of *L. parasiticus*, collected at Ning nan Xian, Sichuan, China, were percolated in 95% EtOH (125 l) for 3 months. The solvent was concentrated under reduced pressure, and the precipitate was filtered off. The filtrate was extracted with $CHCl_3$. The $CHCl_3$ layer was evaporated to give a residue (50.5 g) which was chromatographed over polyamide (5.6 × 106 cm). The eluates with H_2O and H_2O–EtOH (9:1) were combined and concentrated. The deposited crystals (24.5 g) were recrystallized from EtOH to give coriatin (**4**) (6 g). The mother liquor of the crude crystals and also of the recrystallization gave tutin (**2**) (11.2 g) after concentration followed by crystallization from EtOH. The residue obtained from this mother liquor was finally purified by column chromatography on silicic acid to afford coriamyrtin (**1**) (2.7 g) and corianin (**3**) (0.45 g). The identities of these compounds were confirmed by direct comparisons of the physico-chemical data with those of authentic samples.

Preparation of Apocoriamyrtin (5) from Coriatin (4)——A mixture of **4** (145 mg) and $POCl_3$ (0.45 ml) in pyridine (10 ml) was left stading at room temperature for 24 h. The reaction mixture was poured into ice-water, and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with 10% HCl and 5% Na_2CO_3, and dried over Na_2SO_4. Removal of the solvent gave an orange oily residue (90 mg). Purification by prep. TLC using cyclohexane–EtOAc–MeOH (8:2:0.5) gave apocoriamyrtin (**5**) (20 mg), mp 207—210 °C, which was identical with an authentic sample.[9]

Dihydrocorianin (6)——A solution of corianin (**3**) (43 mg) in AcOH (10 ml) was hydrogenated over prehydrogenated PtO_2 (10 mg) at room temperature for 1 h. After removal of the catalyst by filtration, the solvent was removed to give a crystalline residue. Recrystallization from EtOH afforded dihydrocorianin (**4**) (36 mg) as colorless needles, mp 249—251 °C. IR (KBr) cm^{-1}: 3450, 1735, 916, 770. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, s, C_1-CH_3), 0.98, 1.08 [3H each, d, J=7 Hz, C_8-$(CH_3)_2$], 1.70—2.04 (1H, m, H-8), 2.10—2.30 (1H, m, H-5), 3.62, 4.16 (AB q, J=3 Hz, H-11 and H-12), 4.02 (2H, s, H-14), 3.88 (1H, d, J=4 Hz, H-2), 4.80 (1H, t, J=4 Hz, H-3), 3.00 (1H, d, J=4 Hz, H-5), 1.70—2.36 (OH). MS m/z (relative intensity, %): 296 (M^+, 15), 276 (15), 253 (78), 235 (18), 124 (42), 111 (36), 97 (78), 85 (38), 43 (80), 41 (100). *Anal.* Calcd for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80. Found: C, 61.03; H, 6.78.

Bromination of Corianin (3)——Bromine water was added to a solution of corianin (**3**) (27 mg) in hot water (1 ml)

until the color of bromine was persistent, and the reaction mixture was heated at 100 °C for 30 min, then allowed to stand further at room temperature for 2 d. The products were extracted with EtOAc and purified by prep. TLC (cyclohexane–EtOAc–MeOH 5:5:0.8). Fractions of *Rf* 0.65 and 0.45 yielded bromocorianin (**7**) and isobromocorianin (**8**), respectively. Bromocorianin (**7**): white needles, mp 129—131 °C from MeOH. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, s, C_1-CH_3), 1.56 (3H, s, C_8-CH_3), 3.44, 3.56 (ABq, J=10 Hz, C_8-CH_2Br), 3.58, 3.84 (ABq, J=3 Hz, H-11 and H-12), 4.02 (2H, s, H-14), 4.06 (1H, d, J=4.5 Hz, H-2), 5.02 (1H, dt, J=4.5, 2 Hz, H-3), 3.22 (1H, t, J=4.5 Hz, H-4), 3.32 (1H, d, J=4.5 Hz, H-5). MS *m/z* (relative intensity, %): 372 (2), 374 (2) (M^+), 344 (17), 346 (17), 293 (8), 265 (70), 219 (17), 95 (80), 43 (100). *Anal.* Calcd for $C_{15}H_{17}BrO_6$: C, 48.27; H, 4.59. Found: C, 48.01; H, 4.87. Isobromocorianin (**8**): white long plates from MeOH, mp 180—183 °C (dec.). IR (KBr) cm^{-1}: 3520, 3380, 1740, 1720, 1360, 1155, 1045, 825. IR ($CHCl_3$) cm^{-1}: 1750. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, s, C_1-CH_3), 1.54 (3H, s, C_8-CH_3), 3.46, 3.56 (ABq, J=14 Hz, C_8-CH_2Br), 3.44, 4.34 (ABq, J=3 Hz, H-11 and H-12), 3.83, 4.26 (ABq, J=7 Hz, H-14), 4.43 (1H, s, H-2), 4.38 (1H, d, J=4 Hz, H-3), 2.84 (1H, t, J=4 Hz, H-4), 2.98 (1H, d, J=4 Hz, H-5). MS *m/z* (relative intensity, %): 390 (1.5), 392 (1.5) (M^+), 372 (11), 374 (11), 293 (13), 195 (20), 82 (93), 80 (100).

Acetylcorianin (9)——Corianin (**3**) (27 mg) was dissolved in pyridine (0.5 ml), and Ac_2O (1 ml) was added. After 2 d at room temperature, the reaction mixture was further allowed to stand at 80 °C for 5 h, and then poured into ice-water. The crystals deposited were collected and recrystallized from aq. EtOH to give colorless needles of acetylcorianin (**7**) (15 mg), mp 95—97 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.16 (3H, s, C_1-CH_3), 1.92 (3H, s, C_8-CH_3), 2.12 (3H, s, OAc), 3.97, 4.20 (ABq, J=3 Hz, H-11 and H-12), 4.06, 4.32 (ABq, J=11 Hz, H-14), 4.82, 5.00 (1H each, br s, H-9), 4.25 (1H, d, J=4 Hz, H-2), 3.18—3.22 (2H, m, H-4 and H-5), 5.02 (1H, t, J=4 Hz, H-3). Accurate MS *m/z*: Calcd for $C_{17}H_{20}O_7$: 336.1208; Found: 336.1180. MS *m/z* (relative intensity, %): 276 (58), 43 (100), 41 (46).

References

1) T. Okuda and T. Yoshida, *Chem. Pharm. Bull.*, **15**, 1955 (1967).
2) T. Okuda, *Chem. Pharm. Bull.*, **2**, 185 (1954).
3) The structure of corianin was outlined in a preliminary report, T. Okuda and T. Yoshida, *Tetrahedron Lett.*, **1971**, 4499.
4) E. J. Hansen and B. Jerslev, *Dansk Tidsskr. Farm.*, **28**, 25 (1954) [*Chem. Abstr.*, **49**, 2376*c* (1955)].
5) D.-J. Yuan, *Zhonghua Shenjingjingshenke Zazhi*, **12**, 196 (1979).
6) X.-M. Chen, *Chinese Medicinal Herbs Communications*, **11**, 34 (1977).
7) T. Okuda, *Chem. Pharm. Bull.*, **9**, 178 (1961).
8) T. Okuda and T. Yoshida, *Chem. Pharm. Bull.*, **15**, 1697 (1967).
9) T. Okuda and T. Yoshida, *Chem. Pharm. Bull.*, **15**, 1687 (1967).