Chemistry of Natural Compounds, Vol. 32, No. 6, 1996

Berberis ALKALOIDS. XXXVI. TURCOMANIDINE — A NEW ALKALOID FROM *Berberis turcomanica*

I. I. Khamidov,[a] S. F. Aripova,[a] M. V. Telezhenetskaya,[a] M. F. Faskhutdinov,[a] A. K. Karimov,[b] and I. Dzhepberov[c]

UDC 547.944/945+543.51

The alkaloid composition of the leaves of Berberis turcomanica *has been studied. Together with known 1-benzylisoquinoline alkaloids, we isolated a new one — turcomanidine, the structure of which has been established by chemical transformations and a study of spectral characteristics. Of the known alkaloids, N-methylcorydaldine has been detected in plants of the* Berberis *genus for the first time.*

The isolation of a number of isoquinoline alkaloids from *Berberis turcomanica* has been reported previously [1-3]. Continuing a study of this plant, we have extracted leaves gathered in the phase of incipient fruit formation in the environs of the village of Khodzha-kala-2, Republic of Turkmenistan, in June, 1995. The total alkaloids were isolated by chloroform extraction in a yield of 0.11%. From this material, by column chromatography, we isolated the known alkaloids glaucine, thalicmidine, isocorydine, oxyacanthine, and berberine [3], and also armepavine, base (**1**) with mp 125-126°C, and base (**2**) in the form of an oil. The known alkaloids were identified from their physicochemical constants and spectral characteristics and by comparison with authentic specimens.

In the UV spectrum of (**1**) there were absorption maxima at 223, 261, and 297 nm, which are characteristic for isoquinolones [4]. The IR spectrum contained an absorption band showing the presence of an amide carbonyl group (1639 cm^{-1}). The mass-spectrometric fragmentation of (**1**) confirmed this fact and also showed that (**1**) was a simple isoquinolone alkaloid: the spectrum revealed intense peaks of ions with *m/z* 178 and 150 formed by the successive elimination of CH_2NCH_3 and CO groups. The PMR spectrum of (**1**) corresponded to that of the alkaloid N-methylcorydaldine [5]. The results obtained enabled (**1**) to be identified as N-methylcorydaldine [5, 6], this being the first time that it has been isolated from the Berberidaceae family.

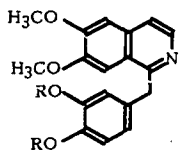
Compound (**2**) was an optically inactive base of phenolic nature. It formed a hydrobromide with mp 200-202°C. Its UV spectrum was similar to that of papaverine [7], which showed the closeness of these alkaloids. This was also confirmed by the mass spectrum, in which the strongest peaks were those of the molecular ions M^+ with *m/z* 311 and of the $(M - 1)^+$ and $(M - 15)^+$ ion, with *m/z* 310 and 296, respectively. The same fragmentation is observed in the mass spectra of papaverine [8] and turcomanine [3].

The fact that base (**2**) was a 1-benzylisoquinoline was also confirmed by its PMR spectrum taken in deuterochloroform. It contained two three-proton singlets from two methoxy groups and a two-proton singlet from the methylene group of the benzyl moiety of the molecule, and in the aromatic region there were two one-proton doublets in a weaker field with a spin–spin coupling constant (SSCC) J = 6.0 Hz, two one-proton singlets, and one three-proton broadened singlet at 6.65 ppm (see the Experimental part). Analysis of the spectral characteristics of (**2**) and of turcomanine [3] showed that the new alkaloid that we had isolated had a molecular weight differing from that of turcomanine (M^+ 297) by 14 units. A comparison of the PMR spectra of the two alkaloids showed that the (**2**) molecule contained two aromatic OCH_3 groups, unlike turcomanine. Consequently, in (**2**) one of the three hydroxy groups of turcomanine was methylated.

---

a) Institute of the Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan, Tashkent, fax (3712) 40 64 75. *b*) Andizhan State Medical Institute. *c*) Turkmen State Pedagogic Institute, Chardzhou. Translated from Khimiya Prirodnykh Soedinenii, No. 6, pp. 885-888, November-December, 1996. Original article submitted March 4, 1996.

0009-3130/96/3206-0873$15.00



1. R = H
2. R = Ac
3. R = CH_3

[sic]

When (2) was acetylated with acetic anhydride in pyridine the diacetyl derivative (3) was obtained. The mass spectrum of (3) showed the peak of the molecular ion with *m/z* 395 and the peaks of ions with *m/z* 352 and 308 formed by the successive elimination of two acetoxy groups. In the IR spectrum of (3) the band of active hydrogen had disappeared and the absorption band of an ester carbonyl group had appeared at 1780 cm^{-1}. The PMR spectrum of (3) revealed signals of the protons of acetyl groups in the form of a six-proton singlet at 2.21 ppm.

The facts given above permitted (2) to be assigned to the 1-benzylisoquinolines with two aromatic methoxy and two hydroxy groups.

To establish the relative positions of the substituent groups in compound (2) we used the NOE method. When the methylene protons (4.35 ppm) were suppressed, a response was observed on the signals at 7.37 ppm (8%) and 6.65 ppm (9%), which permitted them to be assigned to H-8 and the protons of the benzyl group. Consequently, the second one-proton singlet, at 7.01, ppm belonged to the H-5 proton. When the protons of the methoxy group giving a signal at 3.87 ppm were irradiated, a NOE was observed: the intensity of the 7.37 ppm singlet (H-8) increased by 16%; and when the second methoxyl (3.95 ppm) was suppressed the intensity of the singlet at 7.01 ppm (H-5) increased by 14%. Consequently, both methoxy groups were present in the isoquinoline part of the molecule, in positions 6 and 7.

As already shown, in the PMR spectrum of (2) taken in $CDCl_3$ the protons of the benzyl moiety resonated in the same region, forming a broadened singlet. An analogous pattern is observed in a series of benzylisoquinoline bases of the papaverine type [9, 10]. Such closeness of the chemical shifts of the signals of these protons made it difficult to determine the positions of the hydroxy groups. In the PMR spectrum of (2) taken in pyridine the benzyl protons gave three signals. The assignment of the signals at 7.12 ppm (d, J = 8.0 Hz), 6.93 ppm (dd, J = 8.0 and 2.5 Hz), and 7.28 ppm (J = 2.5 Hz) to the 5′, 6′, and 2′ protons, respectively, permitted the hydroxy groups to be placed unambiguously in the 3′ and 4′ positions of ring *C*.

Thus, base (2) is 1-(3′,4′-dihydroxybenzyl)-6,7-dimethoxyisoquinoline and has the structure shown. This compound has been synthesized previously, but this is the first time that it has been found in plants; we have called it turcomanidine.

We obtained (2) from papaverine (4) by its demethylation, using a procedure described in [8]. The product obtained proved to be identical with natural turcomanidine, which once again confirmed the structure of (2).

EXPERIMENTAL

For general observations and the isolation and separation of the total alkaloids, see [3]. The chloroform extraction of 1.3 kg of raw material gave 1.25 g of ether fraction and 0.2 g of chloroform fraction. By elution with chloroform—methanol (97:3) the chloroform fraction yielded 0.02 g of isocorydine, and chloroform—methanol (95:5) yielded 0.04 g of turcomanidine (2) and 0.01 g of berberine.

The ether fraction (1.25 g) was separated on a column of alumina in a similar way to the chloroform fraction. Elution with chloroform gave 0.02 g of N-methylcorydaldine (1); chloroform—methanol (99:1) gave 0.01 g of glaucine; chloroform—methanol (98:2) gave 0.02 g of isocorydine, 0.09 g of thalicmidine, and 0.05 g of oxyacanthine; and chloroform—methanol (97:3) 0.02 g of armepavine.

Turcomanidine·HBr — UV spectrum (EtOH, λ_{max}, nm): 238, 280, 310.

IR spectrum (KBr, ν, cm^{-1}) 3500-3200, 2941, 1238, 858, 838.

Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 311 (M^+, 70), 310 ($[M-1]^+$, 100), 296 ($[M-15]^+$, 50), 280, 265, 252, 236.

PMR spectrum (100 MHz, $CDCl_3$, ppm, δ, J, Hz, 0 − HMDS): 3.87, 3.95 (each 3H, s, $2OCH_3$), 4.35 (2H, s, CH_2), 6.65 (3H, br.s, H-2′, H-5′, H-6′), 7.01, 7.37 (each 1H, d, H-5, H-8), 7.43, 8.18 (each 1H, d, J = 6.0, H-4, H-3).

PMR spectrum (Py-d_5): 3.65, 3.69, (each 3H, s, $2OCH_3$), 4.62 (2H, s, CH_2), 7.12 (1H, d, J = 8.0, H-5′), 6.93 (1H, dd, J = 8.0 and 2.5, H-6′), 7.28 (1H, d, J = 2.5, H-2′), 7.07, 7.55 (each 1H, s, H-5, H-8), 7.42, 8.45 (each 1H, d, J = 6.0, H-4, H-3).

Acetylation of (2). To 30 mg of (2) were added 1 ml of acetic anhydride and 4 drops of pyridine. The reaction mixture was heated until the (2) had dissolved completely, and the solution was left at room temperature for 5 days. The resulting precipitate was separated off, dried, and recrystallized from alcohol, This gave diacetylturcomanidine (3), mp 224-226°C. IR spectrum: 1780 (ester group), 1512, 838, 805. Mass spectrum, *m/z* (%): 395 (100, M^+), 380 (30), 364 (60), 352 (70, $[M-Ac]^+$), 308 (10, $[M-2Ac]^+$). PMR spectrum ($CDCl_3$, δ, ppm): 2.21 (6H, s, 2Ac), 3.96, 4.07 (each 3H, s, $2OCH_3$), 5.02 (2H, s, CH_2), 7.07, 7.26 (each 1H, d, J = 8.0, H-6′, H-5′), 7.25-7.30 (2H, s, H-5, H-2′), 7.42 (1H, s, H-8), 7.88, 8.31 (each 1H, d, J = 6.0, H-4, H-3).

Demethylation of Papaverine. To 1.5 g of papaverine (4) was added 15 ml of a 47% solution of HBr. The reaction mixture was boiled for 10 min and, after cooling, the precipitate that had deposited was filtered off with suction. The residue was chromatographed on a column of silica gel, and elution with chloroform—methanol (95:5) led to a technical product. Recrystallization from MeOH gave 0.05 g of the hydrobromide of turcomanidine (2), with mp 200-202°C, R_f 0.5 (TLC, silica gel, chloroform—methanol (9:1) system).

REFERENCES

1. A. Karimov, M. G. Levkovich, N. D. Abdullaev, and R. Sh. Shakirov, Khim. Prir. Soedin., 77 (1993).
2. A. Karimov, M. G. Levkovich, N. D. Abdullaev, and R. Sh. Shakirov, Khim. Prir. Soedin., 866 (1993).
3. I. I. Khamidov, M. F. Faskhutdinov, M. V. Telezhenetskaya, A. Karimov, M. G. Levkovich, N. D. Abdullaev, and R. Sh. Shakirov, Khim. Prir. Soedin., 74 (1996).
4. R. W. Doskotch, P. Schiff, and J. L. Beall, Lloydia, **32**, 29 (1969).
5. M. Shamma and M. A. Podczasy, Tetrahedron, **27**, No. 4, 727 (1971).
6. R. H. F. Manske, The Alkaloids, Vol. XXI, Academic Press, New York (1983), p. 280.
7. A. W. Sangster and K. L. Stuart, Chem. Rev., **65**, 69 (1965).
8. R. H. F. Manske, The Alkaloids, Vol. X, Academic Press, New York (1968), p. 434.
9. I. I. Khamidov, A. K. Karimov, M. V. Telezhenetskaya, and B. Tashkhodzhaev, Khim. Prir. Soedin., 107 (1996).
10. A. Brossi and S. Teytel, J. Org. Chem., **35**, No. 5, 1684 (1970).