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Berberis ALKALOIDS.
XXXIV. TURCOMANINE — A NEW ALKALOID FROM *Berberis turcomanica*

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Berberine, isocorydine, glaucine, thalicmidine, aromoline, oxyacanthine, and the new 1-benzylisoquinoline alkaloid turcomanine have been isolated from Berberis turcomanica *Kar. The structure of the new alkaloid has been established on the basis of chemical transformations and spectral characteristics. This is the first time that isocorydine, thalicmidine, aromoline, and oxyacanthine have been isolated from this plant.*

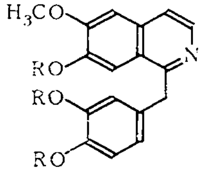
Continuing an investigation of *Berberis turcomanica* Kar. [1-3], we have studied the alkaloid composition of the leaves of this plant gathered in the incipient fruit-bearing stage in the region of Kara-Kala.

Chloroform extraction yielded 0.17% of bases, by the separation of which on a silica gel column seven alkaloids, including one new one (1), were isolated. Berberine and glaucine have been isolated previously but this is the first time that oxyacanthine, aromoline, isocorydine, and thalicmidine have been isolated from this plant. All the known bases were identified by their spectral characteristics and by direct comparison with authentic specimens.

Compound (1) was an optically inactive phenolic base forming a hydrobromide sparingly soluble in the majority of organic solvents.

The UV spectrum of (1) was close to that of papaverine [4]. Its IR spectrum contained absorption bands of active hydrogen in the 3380-2750 cm^{-1} region, corresponding to the stretching vibrations of free and associated OH groups. In the mass spectrum the strongest peaks were those of the M^+ and $[M - 1]^+$ ions which showed the aromatic nature of the alkaloid.

When (1) was acetylated with acetic anhydride in pyridine the triacetyl derivative (2) was obtained. The mass spectrum of (2) contained the peak of the molecular ion with *m/z* 423 and the peaks of ions with *m/z* 381, 339, 297, corresponding to the successive elimination of three acetyl groups. In the IR spectrum of (2) the band of active hydrogen had disappeared and the absorption band of an ester group had appeared at 1773 cm^{-1}.



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

In the PMR spectrum of (1) there were signals from methoxy and methylene groups. Seven one-proton signals appeared in the region of aromatic protons.

The combination of these facts permitted the assumption that compound (1) was a 1-benzylisoquinoline with one methoxy and three hydroxy groups.

To establish the mutual positions of the substituting groups in (1) we used measurements of the nuclear Overhauser effect (NOE). When the resonance transition of the nuclei of the methylene protons (4.95 ppm) was saturated with an additional

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radiofrequency field a response was observed immediately on three signals. These were a singlet at 8.14 ppm (12%), a doublet at 7.54 ppm (6%), and a doublet of doublets at 7.04 ppm (6%), which permitted their assignment to H-8, H-2′, and H-6′, respectively. When the protons of the methoxy group (3.92 ppm) were irradiated, a 24% response was observed on a singlet at 7.40 ppm, while the integral intensity of the H-8 signal remained unchanged. Consequently, the singlet at 7.40 ppm belonged to H-5 and the methoxy group was located at C-6.

Among the two doublet signals at 7.78 and 8.45 ppm interacting with a vicinal constant of 6.1 Hz and belonging to the H-4 and H-3 protons at a double bond, respectively, the former differed by a somewhat greater half-width and a lower intensity of the lines. On the irradiation of H-8 (8.14 ppm) with an additional field, the intensities of the lines of the doublet at 7.78 ppm increased by 16%, while the second doublet, at 8.45 ppm, did not change. When the resonance transitions of the H-5 nuclei were saturated, similarly, a 13% increase in the intensity of H-4 signal was observed. These changes between H-4 and H-5 were due to two factors: their spatial propinquity and the existence between them of a long-range spin-spin interaction, while the NOE factor was absent in the mutual relationships between H-4 and H-8. Consequently, in structure (**1**) there is long-range spin-spin coupling through five bonds between H-4 and H-8 the constant of which is far smaller than 1 Hz. Analysis of the multiplicities of the signals of the aromatic protons in combination with the NOE results permits us to place the hydroxy groups at C-3′, C-4′, and C-7.

Thus, compound (**1**) was a new alkaloid, found in nature for the first time and having the structure of 1-(3′,4′-dihydroxybenzyl)-7-hydroxy-6-methoxyisoquinoline; we have called it turcomanine. Turcomanine is a base of the papaverine (**3**) type.

We have synthesized compound (**1**) by the procedure of [5] and have also obtained its triacetyl derivative and have shown them to be identical with turcomanine and its corresponding derivative by direct TLC comparison and also by the absence of any depression of mixed melting points. This yet again confirmed the proposed structure of turcomanine (**1**).

EXPERIMENTAL

General Observations. Melting points were determined on a Boëtius stage. UV spectra were taken on a Perkin-Elmer Lambda 16 spectrometer, IR spectra on a Perkin-Elmer model 2000 Fourier spectrometer, mass spectra on a Kratos MS 25 RF spectrometer, and PMR spectra on a Tesla BS 567 A/100 MHz instrument. The purity of the alkaloids was monitored by TLC on Chemapol plates with KSK LS 5/40 silica gel and alumina (Brockmann activity grade II) in the chloroform—methanol (9:1), chloroform—methanol (95:5), and benzene—methanol (9:1) systems. Revealing agents: the Dragendorff reagent and iodine vapor. Column chromatography was conducted on the sorbents silica gel and alumina with particle dimensions of 125-160 μm.

Isolation and Separation of the Total Alkaloids. The chloroform extraction of 0.4 kg of raw material yielded 0.41 g of ethereal and 0.18 g of chloroform fractions.

The ethereal fraction of alkaloids (0.41 g) was chromatographed on a column containing 12 g of silica gel. The alkaloids were eluted with chloroform and with mixtures of chloroform and methanol. The chloroform eluates yielded 0.02 g of isocorydine, 0.01 g of glaucine, and 0.02 g of thalicmidine. Chloroform—methanol (98:2) eluates gave 0.01 g of aromoline, (97:3) eluates 0.16 g of oxyacanthine, and (9:1) eluates 0.11 g of turcomanine.

The chloroform fraction of the total alkaloids (0.18 g) was separated as described above, with the isolation of 0.02 g of isocorydine, 0.02 g of thalicmidine, and 0.01 g of berberine.

Turcomanine — $C_{17}H_{15}NO_4 \cdot HBr$, mp 247-248°C.

UV spectrum (EtOH, λ_{max}, nm): 236, 282, 312. λ_{min}: 210, 270, 297.

IR spectrum (KBr, ν, cm^{-1}): 3380-2750, 1451, 1300.

Mass spectrum (EI, 70 eV), m/z (I_{rel}, %): 297 (M$^+$, 45), 296 (M-1$^+$, 100), 280, 264, 252, 236, 159, 125 (55).

PMR (100 MHz, Py-d_5, δ, ppm, J, Hz, 0-HMDS): 3.92 (3H, s, OCH_3), 4.95 (2H, s, CH_2), 8.45, 7.78 (each 1H, d, J = 6.1, H-3, H-4), 7.54 (1H, d, H-2′, J = 1.9), 7.14 (1H, d, J = 8.4, H-5′), 7.04 (1H, dd, J = 8.4 and 1.9, H-6′), 8.14, 7.40 (each 1H, s, H-8, H-5).

Acetylturcomanine. To 50 mg of (**1**) were added 1 ml of acetic anhydride and four drops of pyridine. The mixture was heated until the solid had dissolved completely and was then left at room temperature for six days. The crystals that had deposited were recrystallized from alcohol, giving 35 mg of (**2**), with mp 203-205°C,

IR spectrum (KBr, ν, cm^{-1}): 1773, 1371.

Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 423 (M^+, 10), 381 (20), 339 (22), 297 (45), 296 (100), 280, 264, 252.

PMR ($CDCl_3$, δ, ppm): 2.17 (6H, s, 2Ac), 2.35 (3H, s, 1Ac), 4.03 (3H, s, OCH_3), 4.87 (2H, s, CH_2), 8.33 and 7.95 (each 1H, d, J = 6 Hz, H-3, H-4), 8.06, 7.47 (each 1H, s, H-8, H-5), 6.94-7.40 (3H, m, H-5, H-6′, H-2′).

Demethylation of Papaverine. Papaverine (0.5 g) was treated with 5 ml of a 47% solution of HBr. A precipitate deposited 20 min after the beginning of boiling. Heating the reaction mixture was continued for another hour. After cooling the hydrobromide, with mp 247-248°C, was filtered off with suction, and from this the acetyl derivative was obtained in the form of the base in the same way as for acetylturcomanine (**2**), mp 203-205°C. A mixture with acetylturcomanine gave no depression of the melting point, and the TLC behaviors of the acetyl derivative obtained and of (**2**) were identical.

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