Chemistry of Natural Compounds, Vol. 32, No. 5, 1996

ROBUSTAMINE *cis*-N-OXIDE AND MERENDERINE FROM *Merendera robusta*

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UDC 547.944.6

The structure and configuration of a new homoproaporphine, robustamine cis-N-oxide, isolated from Merendera robusta *(fam. Liliaceae) have been established by spectral characteristics and chemical transformations. It was found that the fraction of alkali-soluble bases from this plant consists mainly of the homoaporphine compound merenderine, the amount of which increases considerably towards the end of the vegetation period.*

We have previously [1] given some results of an investigation of the total alkaloids of *Merendera robusta* Bge. growing in Kyzyl-Kum (Bukharskaya oblast). We detected the presence in the plant of, together with known tropolone alkaloids and their photochemical isomers, a series of compounds not containing the tropolone ring, two of which were isolated in the crystalline form. The structure of one of them – robustamine – was established.

Continuing the study of the second compound, having the composition $C_{20}H_{27}O_5N$, mp 140-142°C, $[\alpha]_D$ −24°, we have established its structure. Its UV spectrum showed absorption maxima at 216 and 295 nm, and its IR spectrum absorption bands of a hydroxy group (3450 cm^{-1}) and of methylene and methoxy groups (2930, 2855, and 1467 cm^{-1}). In its PMR spectrum there were the signals of the protons of a benzene ring (6.48 ppm), of the protons of two O-methyl groups present in benzene and alicyclic rings (3.72 and 3.26 ppm), of an N-methyl group (3.20 ppm), of methylene and methine groups (3.70-1.28 ppm), and of an H-6a tertiary proton (4.09 ppm, 1H, t, J = 8 Hz; $\Delta\omega$ 16 Hz). The appearance of the signals of the protons of the N-methyl group and of the H-6a proton in a relatively weaker field than in the spectra of the tertiary bases corresponding to them is explained by the anisotropic influence of an electronegative substituent located on the nitrogen atom of the compound [2].

The mass spectrum of the compound, which included the peak of the molecular ion M^+ with *m/z* 361 and a triplet of peaks of ions with *m/z* 345 $(M-16)^+$, 344 $(M-17)^+$, and 343 $(M-18)^+$, confirmed this conclusion and showed that the base was an N-oxide. In view of the fact that this compound was detected in a fraction of bases together with robustamine and differed from it by 16 a.m.u., it was assumed that it was an N-oxide of the latter. To confirm this conclusion, we reduced the base with zinc dust in acid and obtained a product identical with robustamine (**2**).

On the basis of the CS of the protons of the N-methyl group (3.20 ppm) in the PMR spectrum and the intensity of the peak of the molecular ion in the mass spectrum, the compound was assigned to the *cis*-N-oxides [2-5]. This also agrees with the pronounced downfield shift of the signal of the H-6a proton in the PMR spectrum under the action of the N-oxide group of the base.

The high values of the SSCCs of the H-6a tertiary proton with the neighboring protons, H-7a and H-7e, appearing in the spectrum in the form of a triplet (doublet of doublets) because of their quantitatively identical constants, showed that it occupies the axial position in ring *C*. Consequently the base has the S-configuration at C-6a. In addition, the conversion of this N-oxide into (**2**) on reduction confirmed the C-6aS configuration proposed previously for the latter. The configurations at the C-8a, C-11, and C-12 asymmetric centers had been established previously for robustamine.

Thus, the base isolated is represented by the structure 11-hydroxy-2,12-dimethoxy-1,12-oxahexahydrohomoproaporphine *cis*-N-oxide with the 6aS,8aR,11S,12R configuration (**1**):

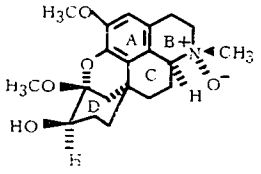
Tashkent State University, fax (3712) 46 24 72. Translated from Khimiya Prirodnykh Soedinenii, No. 5, pp. 734-738, September-October, 1996. Original article submitted February 26, 1996.

 0009-3130/96/3205-0716$15.00

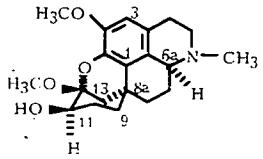
TABLE 1. Amounts of Total Alkaloids and of the Fractions of Bases in the Epigeal Parts of *Merendera robusta*, %*

Sample	Collection site and vegetation phase	Total alkaloids	Alkali-insoluble bases	Alkali-soluble bases	Literature
1	Tashkentskaya oblast, flowering	0.60	0.16	0.04	6
2	Ashgabatskaya obl., flowering	0.68	0.17	0.06	7
3	Surkhandar'inskaya obl., end of flowering	0.35	0.08	0.06	8
4	Ashgabatskaya obl., beginning of fruit-bearing (small fruits)	0.40	0.09	0.05	9
5	Maryiskaya obl., early fruit-bearing	0.83	0.24	0.15	Unpubl.
6	Tashkentskaya obl., fruit-bearing (large fruits)	0.40	0.05	0.05	9
7	Bukharskaya obl., incipient ripening of seeds	0.50	0.12	0.22	9
8	Ashgabatskaya obl., ripening of seeds	0.41	0.12	0.07	8
9	Tashkentskaya obl. ripening of seeds	0.26	0.07	0.02	9
10	Surkhandar'inskaya obl., ripening of seeds	0.28	0.07	0.08	8
11	Bukharskaya obl., ripening of seeds	0.38	0.09	0.16	1

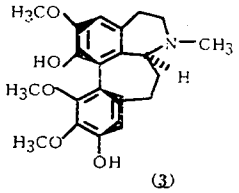
*Amounts of the fractions of alkaloids of neutral nature are not given here.



(1)



(2)



(3)

The fractions of alkali-insoluble and alkali-soluble bases of *Merendera robusta* form a small part of its total alkaloids (Table 1). However, they are interesting because of their qualitative composition, mainly their content of homoproaporphine and homoaporphine compounds.

The fraction of alkali-insoluble bases of *M. robusta* consisted mainly of the tropolone alkaloid colchamine, with a small amount of isoquinoline alkaloids which have not yet been investigated in detail. The presence of the latter somewhat complicates the preparative isolation of antitumoral alkaloid colchamine [1].

The fraction of alkali-soluble bases of the plant contains homoaporphine compounds and 2-demethylcolchamine as a small impurity [8]. On treatment with acetone the bulk of the fraction separated out in crystalline form, mp 220-221°C, $[\alpha]_D$ +14°. On the basis of these physical constants, the compound, differing from known homoaporphine alkaloids [8, 10] by the elementary composition $C_{21}H_{25}NO_5$ and by its chromatographic mobility, proved to be identical with merenderine (bechuanine) [11-13]. This was confirmed by the formation of derivatives described previously and by spectral results [11, 14].

The low values of the melting point and of the specific rotation of the merenderine from *Merendera robusta* are obviously due to its partial racemization during isolation. An analogous phenomenon has been observed previously in the case of another homoaporhine alkaloid – kreysigine [15, 16] – and also of the homomorphinan base kreysiginine [16].

Merendera robusta gathered in the period of seed ripening had alkaloids with a composition close to that of the alkaloids from *Merendera raddeana* Rgl., in which the main ones are colchicine and merenderine [17]. Both plants can be used for the isolation of these compounds.

EXPERIMENTAL

UV spectra were taken on a Specord UV-VIS spectrometer in methanol; IR spectra on a UR-10 double-beam spectrometer in KBr or as a film; PMR spectra on a Varian XL-100-15 instrument in $CDCl_3$; and mass spectra on a Varian MAT-311 mass spectrometer with a system for the direct injection of the sample into the ion source at an ionizing energy of 70 eV and a temperature of the ionization chamber of 120°C. Melting points were determined in an instrument with sulfuric acid, and specific rotations on a SM-3 circular polarimeter.

The conditions for chromatographing the substances are given in [8]. PC was used in the following systems: 1) *n*-BuOH–H_2O (1:1), and 2) *n*-BuOH–conc. HCl–H_2O (50:7.5:13.5).

Robustamine *cis*-N-oxide (1), mp 140-142°C (from acetone), $[\alpha]_D^{22}$ −24° (*c* 0.42; $CHCl_3$), readily soluble in water and alcohols, sparingly soluble in acetone, chloroform, and benzene.

IR spectrum (KBr, cm^{-1}): 3450, 2930, 2855, 1605, 1490, 1467, 1377, 1330, 1273, 1255, 1230, 1200, 1179, 1116, 1107, 1080, 1036, 990, 975, 960, 926, 895, 867.

Mass spectrum (*m/z*, %): 361(M^+, 21), 345(3), 344(10), 343(19), 342(19), 326(13), 302(100), 284(29), 283(19), 270(26), 269(25), 243(32), 237(35).

Reduction of (1) to Robustamine (2). Zinc dust* was added to 30 mg of (**1**) (R_f 0.52, syst. 1) in 7 ml of 15% AcOH, and the mixture was heated at 40-50°C until quantitative conversion into the tertiary base had been achieved. The reaction product was identified as robustamine (R_f 0.41).

Isolation of Merenderine (3). A 7.2-g solution of the fraction of alkali-soluble bases of *M. robusta* [1] in 150 ml of chloroform was extracted with 2% caustic soda solution (5 × 30 ml). The combined alkaline extract was washed with 50 ml of chloroform and was acidified with hydrochloric acid (1:1) to pH 1, after which it made alkaline (pH 8) with ammonia and was extracted with chloroform. The residue after the chloroform had been distilled off contained 5.19 g of a mixture of bases with R_f 0.87 (merenderine – the main substance) and 0.81 (Syst. 2) (2-demethylcolchamine). When this mixture of alkaloids was purified by passing a chloroform solution through a layer of alumina (activity grade II), 3.26 g of merenderine was isolated, with mp 220-221°C (from acetone) and $[\alpha]_D$ +14° (*c* 1.3; $CHCl_3$).

UV spectrum (CH_3OH, λ_{max}, nm) 260, 292 (log ε 410, 3.86).

IR spectrum (cm^{-1}): 3500-3300, 1595, 1568, 1452, 1428, 1392, 1347, 1248, 1228, 1182, 1104, 1082, 1014, 962, 926, 890, 870, 846, 813.

PMR spectrum ($CDCl_3$, ppm): 6.57 and 6.50 (1H × 2, s, H-3 and H-9), 6.00 (2 × OH), 3.85 (3H, s, OCH_3-2), 3.83 (3H, s, OCH_3-11), 3.50 (3H, s, OCH_3-12), 2.32 (3H, s, N-CH_3).

Mass spectrum (*m/z* %): 371 (M^+, 32), 356(50), 354(M-17)$^+$ (100), 342(22), 340(25), 338(20), 326(21), 204, 192.

O,O-Dimethylmerenderine was obtained by the action of a petroleum ether solution of diazomethane on a methanolic solution of (**3**).

PMR spectrum ($CDCl_3$, ppm): 6.58 and 6.45 (1H × 2, s, H-3 and H-9), 3.85 (6H, s, 2 × OCH_3), 3.83; 3.58; 3.50(3H × 3, s, 3 × OCH_3), 2.35 (3H, s, N-CH_3).

Mass spectrum (*m/z* %): 399(M^+, 24), 384(17), 368(M-31)$^+$(100), 351(12), 338(20).

O,O-Diacetylmerenderine. One drop of concentrated sulfuric acid was added to a solution of 50 mg of (**3**) in 2 ml of Ac_2O, and the mixture was left at room temperature for 2 h. The reaction product was isolated as in [1].

IR spectrum (cm^{-1}): 1770 (2 × $OCOCH_3$).

PMR spectrum ($CDCl_3$, ppm): 6.70 and 6.62 (1H × 2, s, H-3 and H-9), 3.80 (6H, s, 2 × OCH_3), 3.42 (3H, s, OCH_3), 2.40 (3H, s, N-CH_3), 2.27 and 2.00 (3H × 2, s, 2 × $OCOCH_3$).

Mass spectrum (*m/z*, %): 455(M^+, 10), 412(19), 396(M-59)$^+$ (100).

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*Amount not given – Translator.

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