

STRUCTURE OF ZANGEZURINE

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A new base with $[\alpha]_D +208^\circ$ (c 0.7; methanol) has been isolated from the combined nonphenolic alkaloids of *Papaver zangezuricum* A. D. Mikheev, and has been called zangezurine (I). The acetylation of (I) with acetic anhydride in pyridine yielded O-acetylzangezurine (II). The structure of zangezurine has been established on the basis of the UV, IR, mass, PMR, and ^{13}C NMR spectra of (I) and (II).

We have isolated a new amorphous base, which we have called zangezurine (I) from the combined nonphenolic fraction of the alkaloids of *Papaver zangezuricum* A. D. Mikheev (Miltantha section), family Papaveraceae [1, 2], collected in 1985 in the flowering stage in the Megri pass (Armenian SSR). Zangezurine had the composition $\text{C}_{22}\text{H}_{25}\text{NO}_7$, (M^+ 415.16504, HRMS). Its UV spectrum had two absorption maxima — at 234 and 293 nm ($\log \epsilon$ 4.15 and 3.76). The IR spectrum of (I) showed absorption bands at (cm^{-1}) 3400 (hydroxy group) 1610 (aromatic ring), and 1050 and 950 (methylenedioxy group). In the PMR spectrum of (I) (Table 1) there were the signals of a N-methyl group (2.43 ppm), of three methoxy groups (3.76 ppm, 3 H, and 3.88 ppm, 6 H), and of a methylenedioxy group (5.90 ppm). In the aromatic part of the spectrum there were four one-proton singlets at 7.03, 6.65, 6.50, and 6.34 ppm.

The facts given above and also the presence in the PMR spectrum of two one-proton doublets at 4.19 and 5.58 ppm with $J = 8.5$ Hz (H at C_2 and C_1 , respectively) indicated that this base belonged to the alkaloids of the rheadine type with the trans-linkage of rings B/D [3-15]. This conclusion was confirmed by the results of the mass-spectrometric fragmentation of zangezurine (scheme). Ions with m/z 252, 238, and 209 showed the presence of three methoxy groups in ring C. Consequently, the methylenedioxy group was present in ring A.

TABLE 1. Details of the PMR Spectra of Some Rheadine Alkaloids

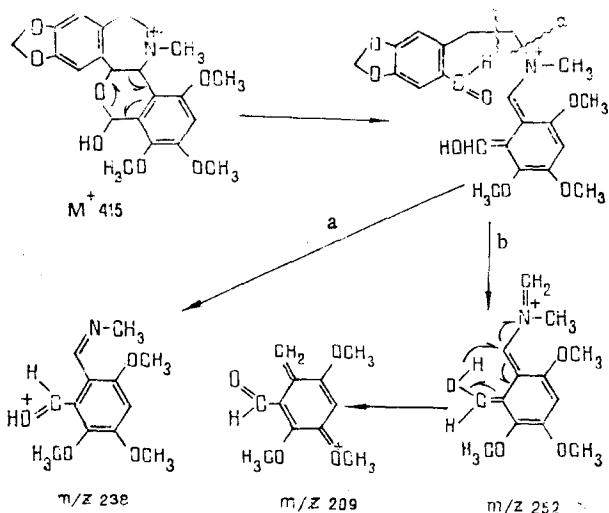
Atom	Zangezurine	O-Acetylzangezurine	Alpinigenine [4, 5, 13]	O-Acetyl-alpinigenine [5]	Epialpinine [4, 13]	Glaudine [3]	Epiglaudine [3]
H-1	5.88 d $J=8.5$ Hz	5.48 d $J=9$ Hz	5.80 d $J=9$ Hz	5.31 d $J=9$ Hz	5.57 d $J=8.5$ Hz	5.19 d $J=9$ Hz	5.57 d $J=9$ Hz
H-2	4.19 d $J=8.5$ Hz	4.09 d $J=9$ Hz	4.10 d $J=9$ Hz	3.95 d $J=9$ Hz	4.10 d $J=8.5$ Hz	4.08 d $J=9$ Hz	4.02 d $J=9$ Hz
H-6	6.65 s	6.53 s	6.67 s	6.43 s	6.68 s	6.67 s	6.68 s
H-9	7.03 s	7.18 s	7.27 s	7.03 s	7.33 s	7.37 s	7.32 s
H-10	—	—	7.28 d	7.15 d	7.16 d	7.06 d	7.05 d
H-11	6.50 s	6.39 s	6.75 d $J=8$ Hz	6.78 d $J=8$ Hz	6.90 d $J=8.5$ Hz	6.79 d $J=8$ Hz	6.79 d $J=8.5$ Hz
H-14	6.34 s	7.08 s	6.41 s	7.07 s	5.82 s	5.77 s	5.75 s
N—CH ₃	2.43 s	2.25 s	2.34 s	2.27 s	2.31 s	2.24 s	2.30 s
Ar—OCH ₃	3.76; 3.88 (6H)	3.67; 3.72; 3.82	3.86 (9H)	3.69; 3.73; 3.94	3.86; 3.87; 3.78;	3.88 (6H)	3.90 (6H)
OCH ₂ O	5.90 s	5.84 s	—	—	—	5.92 d $J=1.5$ Hz	5.98 d $J=1.7$ Hz
OCOCH ₃	—	2.02 s	—	2.02 s	—	6.04 d $J=1.5$ Hz	6.05 d $J=1.7$ Hz
OCH ₃ -14	—	—	—	—	3.57 s	3.69 s	3.56 s

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TABLE 2. Chemical Shifts (δ , ppm, CDCl_3 , 0 - TMS) of the ^{13}C Nuclei and Assignment of the Signals of the Carbon Atoms of Zangezurine

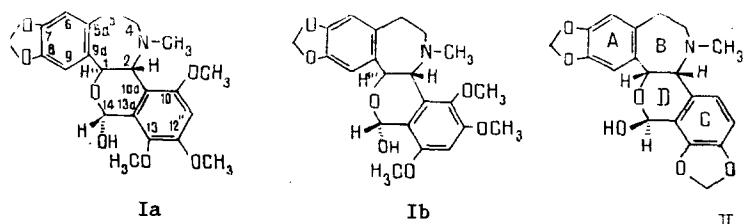
Atom	Zangezurine (Ia)	Rheadine (II)	Atom	Zangezurine (Ia)	Rheadine (II)
C-1	63.12 d	77.6	C-10	155.48 s	123.0
C-2	61.24 d	55.5	C-11	98.82 d	112.2
C-4	55.72 t	55.1	C-12	152.04 s	145.8
C-5	31.52 t	33.2	C-13	150.00 s	145.5
C-5a	132.17 s	136.5	C-13a		
C-6	109.95 d	110.5	C-14	88.22 d	96.2
C-7	146.03 s	147.5	—OCH ₂ O—	100.77 t	101.8
C-8	145.60 s	147.3	N—CH ₃	34.58 q	41.5
C-9	104.57 d	108.3	—OCH ₃	59.16 q	
C-9a	131.87 s*	130.9		57.14 q	
C-10a	132.17 s*	130.9		56.09 q	

*The assignment may be reversed.



Mass-spectrometric fragmentation of zangezurine.

To determine the positions of the methoxy groups in ring C of zangezurine we carried out an intramolecular NOE experiment. When the signal of the methoxy protons at 3.76 ppm was saturated, the intensity of the signal of one of the aromatic protons at 6.50 ppm increased by 25%. A considerable NOE (~25%) was also observed between the signals of the protons of the methoxy groups at 3.88 ppm and the same proton at 6.50 ppm. These NOE results unambiguously indicated that the aromatic proton at 6.50 ppm was located between two methoxyls in ring C of zangezurine. On the other hand, the experiment also showed an NOE of ~8% between the OCH₃ protons at 3.88 ppm and the signal at 6.34 ppm relating to the gem-hydroxylic proton at C₁₄ (the assignment is given on the basis of the fact that this signal shifted downfield by 0.7 ppm when (I) was acetylated).



Thus, the detection of a NOE between the protons of one of the methoxy groups and H-14, and also between the protons of two different OCH_3 groups and the aromatic proton at 6.50 ppm permitted the determination of the positions of these methoxyls in ring C of zangezurine as C_{10} , C_{12} , and C_{13} , or C_{10} , C_{11} , and C_{13} (Ia or Ib).

In view of the fact that all known rheadine alkaloids contain substituents in ring C at C_{12} and C_{13} [3], we suggest structure (Ia) for zangezurine.

A comparison of the PMR spectra (see Table 1) of a number of rheadine alkaloids, and also of their acetyl derivatives, showed the hydroxy group of zangezurine at C_{14} has the α -orientation [4, 5, 9, 10].

In the ^{13}C NMR spectrum of zangezurine obtained under the conditions of complete and incomplete decoupling of C-H interactions, signals appeared from 21 carbons (the signal from one quaternary sp^2 carbon atom was not clearly detected because of its low intensity). Table 2 gives the CSs and the assignments of the signals of the carbon atoms of zangezurine on the basis of the multiplicities of the signals and a comparison of their CSs with literature figures for the ^{13}C NMR spectrum of rheadine (II) [14, 15]. Apparently, the upfield shift by 6.9 ppm of the signal of the $\text{N}-\text{CH}_3$ carbon atom in zangezurine as compared with that of rheadine is due to the different linkages of rings B/D in these alkaloids. The presence of the signal of the C-11 aromatic carbon atom in a relatively strong field is obviously due to the ortho contributions of the two neighboring methoxy groups. The CS of the signal of the C-14 carbon atom in zangezurine is shifted upfield by 8 ppm in comparison with that of rheadine, which is apparently due to the difference in the contributions of OH and OCH_3 to the CS of the C-14 atom and also to the change in their orientation. The considerable upfield shift of the signal of the C-1 carbon ($\Delta\delta = 14.48$ ppm) and the downfield shift of the signal of the C-2 atom ($\Delta\delta = 5.76$ ppm) of zangezurine in comparison with the corresponding signals of rheadine can be explained by the different linkages of rings B/D in the two alkaloids.

EXPERIMENTAL

Chromatography was performed on type KSK silica gel and Woelm type M alumina. The following solvent systems were used for TLC: 1) benzene-ethanol (9:1) for silica gel, and 2) benzene-ethanol (95:5) for alumina. UV spectra were taken on a Hitachi spectrometer (ethanol), IR spectra on a UR-20 spectrophotometer (KBr tablets), mass spectra on a MKh-1310 mass spectrometer, and ^1H and ^{13}C NMR spectra on a BS-567 A NMR spectrometer (Czechoslovakia) in CDCl_3 with TMS as internal standard at frequencies of 100 MHz for ^1H and 25.142 MHz for ^{13}C .

Isolation of Zangezurine. The combined nonphenolic alkaloids (4.22 g) were chromatographed on a column of silica gel (1:30). Elution with chloroform-methanol (95:5) gave 0.25 g of zangezurine with $[\alpha]_D = 208^\circ$ (*c* 0.7; methanol). The R_f values of zangezurine for systems 1 and 2 were, respectively, 0.36 and 0.88. Some time after being revealed with iodine vapor, the zangezurine spot on the silica gel plate became crimson red, and the color did not disappear for a long time.

Acetylation of Zangezurine. A mixture of 30 mg of zangezurine in 0.5 ml of pyridine to which 2 ml of acetic anhydride had been added was left at room temperature for 24 h. After the solvent had been evaporated off and the usual working-up procedure, 27 mg of O-acetylzangezurine were obtained ($M^+ 457$). The R_f values of O-acetylzangezurine in systems 1 and 2 were respectively, 0.4 and 0.96.

SUMMARY

The new alkaloid zangezurine has been isolated from Papaver zangezurium A. D. Mikheev. Its structure has been established on the basis of UV, IR, mass, PMR, and ^{13}C NMR spectra.

Zangezurine is the first alkaloid of the rheadine type with five substituents in the aromatic rings.

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ELECTROCHEMICAL EXTRACTION OF ALKALOIDS FROM EPHEDRA HERBAGE

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The process of extracting ephedra herbage in a constant electric field has been studied. It has been shown that the application of an electric field considerably accelerates the isolation of the alkaloid molecules from the cellulose of the plant raw material. The main kinetic characteristics of the electroextraction of the total alkaloids as functions of various factors have been obtained.

The existing method of obtaining the alkaloid ephedrine, which is widely used in medical practice, presupposes the extraction of the alkaloids with hot water in a diffusion battery on the countercurrent principle. The disadvantages of this method include its lengthiness, its high temperature, the incomplete extraction of the desired substances, and others.

Our aim was to develop a more effective electrochemical method of extracting medicinal substances from ephedra herbage. Methods of extracting certain natural compounds are known that are based on the principle of the electromigration of polarized molecules. Veratrine is isolated by the electrolysis of an aqueous alcoholic extract of sabadilla seeds [1], "electropium" is isolated from poppy heads, and narcotine and morphine are isolated from opium by electrophoresis [2]. The electrochemical method has permitted a 20% increase in the yield of scopolamine from Datura stramonium and a considerable shortening of the time of extraction [3].

We have investigated the herbage of Mongolian ephedra (Ephedra equisetina Bunge) with a moisture content of 10.6% (alkaloid content 1.72%). For the extraction of the alkaloid, the ephedra was ground to 0.5 and 1-2 mm [4, 5]. As can be seen from the curves of the dependence of the yield of extractable alkaloids on various factors, two periods were observed in the extraction process - fast and slow extraction (Fig. 1). The relative amount of substances obtained in the period of fast extraction (elution coefficient) was 48-49% for particles of raw material with a size of 0.5 mm, and 10-15% for the 1-2 mm fraction. While the rate of the process in the period of rapid extraction depends on the hydrodynamic conditions, in the period of slow extraction it depends on the rate of diffusion of the alkaloids from the cell tissue of the plant raw material. There are a number of factors that increase the rate of diffusion of the substances from the raw material: a rise in the temperature, the use of ultrasound, the addition of surface-active agents, etc. [5].

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