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STUDY OF STRUCTURE–ACTIVITY RELATIONSHIPS IN A SERIES OF ALKALOIDS OF *Aconitum zeravschanicum* AND THEIR ANALOGS

B. T. Salimov, Zh. Kh. Kuzibaeva, and F. N. Dzhakhangirov

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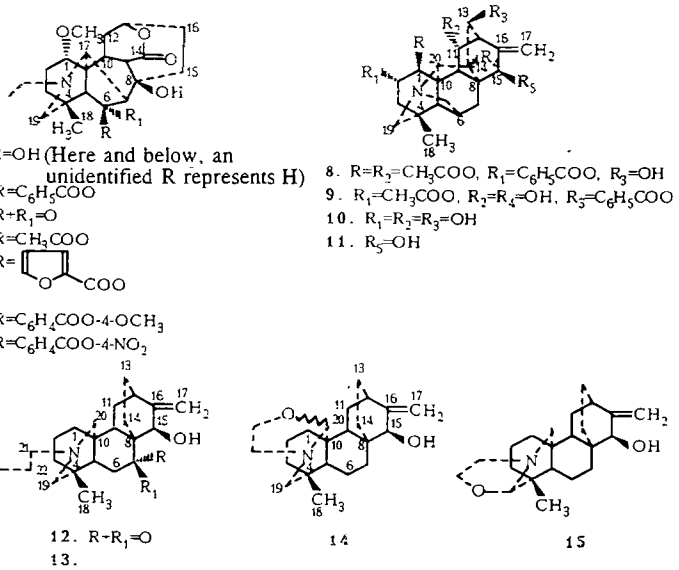
The toxic and antiarrhythmic activities of diterpene alkaloids from Aconitum zeravschanicum *and their synthetic analogs have been investigated. It has been established that, in the series of compounds studied, activity and toxicity depend on the type of skeleton, the nature and positions of substituents, and the basicity of the nitrogen atom.*

Aconitum zeravschanicum Steinb. is one of the few plants of the genus *Aconitum* L. (fam. Ranunculceae) in which the simultaneous presence of bases of the isoquinoline and diterpenoid series has been detected [1-5], and, in contrast to *A. leucostomum* Worosch. [2], this plant produces diterpene bases in fairly high yield up to the end of the vegetation period. The alkaloid heteratisine (**1**) [5], which is one of the main components of the mixture of bases in the early vegetation period of the plant, is detected with fairly high yield in the forms both of the free amino alcohol and of its ester with benzoic acid — 6-benzoylheteratisine (**2**) [6]. In the later stages of the vegetation period the yield of (**2**) falls sharply, and in the period of ripening of the seeds it can be detected only chromatographically.

Heteratisine (**1**) possess a pronounced antiarrhythmic activity (AA) [7]; nevertheless the AA activity of the total alkaloids of the epigeal part of *Aconitum zeravschanicum* considerably exceeds it [8]. In view of this, other diterpene alkaloids of *Aconitum zeravschanicum* belonging to the atisine, isoatisine, dihydroatisine, hetisine, and heteratisine types have been subjected to pharmacological investigation (Table 1).



1. R=OH (Here and below, an unidentified R represents H)
2. R=C_6H_5COO
3. R+R_1=O
4. R=CH_3COO
5. R=
6. R=C_6H_4COO-4-OCH_3
7. R=C_6H_4COO-4-NO_2
8. R=R_2=CH_3COO, R_1=C_6H_5COO, R_3=OH
9. R_1=CH_3COO, R_2=R_4=OH, R_5=C_6H_5COO
10. R_1=R_2=R_3=OH
11. R_5=OH
12. R+R_1=O
13.
14
15

Institute of the Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan, Tashkent, fax (3712) 89 14 75. Translated from Khimiya Prirodnykh Soedinenii, No. 3, pp. 384-387, May-June, 1996. Original article submitted February 26, 1996.

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TABLE 1. Toxicities and Antiarrhythmic Activities of Alkaloids from the Plant *A. zeravschanicum* and Their Analogs Using the Model of Aconitine Arrhythmia in Rats

Compound	LD_{50}, mg/kg	ED_{50}, mg/kg	LD_{50}/ED_{50}
Heteratisine type			
6-*p*-Nitrobenzoylheteratisine (7) [9]	27.5	0.2	137.5
6-*p*-Anisoylheteratisine (**6**)	6.0	0.05	120
6-Benzoylheteratisine (**2**) [6]	5.0	0.035	142.9
6-Furoylheteratisine (**5**)	16.2	0.07	231.4
6-Acetylheteratisine (**4**) [6]	182.0	5.0	36.5
Heteratisine (**1**) [5]	180.0	12.5	14.4
Dehydroheteratisine (**3**) [6]	165.0	20	8.2
Hetisine type			
Tadzhaconine (**8**) [10]	12.8	0.3	42.7
Zeravshanisine (**9**) [11]	34.1	0.5	68.0
Hetisine (**10**) [12]	26.2	1	26.0
Nominine (**11**) [13]	68.0	5	13.6
Dihydroatisine type			
Atidine (**12**) [14]	58.0	5	11.6
Dihydroatisine (**13**) [5]	38.0	1	38.0
Atisine type			
Atisine (**14**) [5]	9.0	–	–
Isoatisine type			
Isoatisine (**15**) [5]	8.0	–	–
Standard AA drugs			
Quinidine	66.9	20.0	3.3
Novocainamidum (Procainamide)	138.0	60.0	2.3
Ajmaline	33.0	5.0	6.6
Ritmilen	42.0	4.0	10.5

The results of the investigations show that the activities of alkaloids (**2**), (**8**), (**9**), (**10**), and (**13**) considerably exceed both that of (**1**) and that of the total bases of *A. zeravschanicum*, with (**2**) possessing the highest AA. In its AA and the breadth of its therapeutic action it not merely proved to be more active than compound (**1**) but it also considerably exceeded the antiarrhythmics of group I used in medical practice. Since the difference between (**1**) and (**2**) consists in the presence of a benzoyloxy group in place of a hydroxy group, we studied the influence on toxicity and AA of the nature of the substituent in a series of C-6 analogs of heteratisine. From (**1**) we obtained the known compounds dehydroheteratisine (**3**), 6-acetylheteratisine (**4**) [6], and 6-*p*-nitrobenzoylheteratisine (**7**) [9] and the previously undescribed 6-furoylheteratisine, $C_{27}H_{35}NO_7$ (**5**), amorph. hydrochloride with mp 206.5-207.5°C (from acetone, decomp.), 6-anisoylheteratisine, $C_{30}H_{39}NO_7$ (**6**), amorph., hydrochloride with mp 209.5-210.5°C (from acetone, decomp.), the structures of which were confirmed by their IR, PMR, and mass spectra.

A comparison of the toxicity and AA of (**3**) with those of (**1**) shows that the presence of a carbonyl group at C-6 instead of a hydroxy group, while causing no particular changes in toxicity, appreciably decreased the AA. The presence of an acetoxy group at C-6 in place of a hydroxy group scarcely affected toxicity but led to a more than twofold increase in AA. Aromatic acid residues, such as those of *p*-nitrobenzoic and *p*-methoxybenzoic acids, led to 6.5- and 30-fold rises in toxicity and to 62.5- and 250-fold increases in AA, respectively. With respect to its influence on toxicity and AA, a benzoic acid residue was considerably superior to the residues mentioned above and also to 6-furoylheteratisine, where aromaticity is expressed more feebly than in the case of the benzoyloxy group.

Carbonyl and carbonyl-containing groups lower the basicity of the diterpene alkaloids [15-18], this being expressed most strongly in compounds with the carbonyl group close to the nitrogen atom [17, 18]. It was found later that, being substances of lower basicity, ester compounds were — depending on the mutual positions of the substituents — considerably superior in toxicity and specific activity to the corresponding amino alcohols [19]. Taking this into account, on the basis of our study of the physiological activities of compounds (**1**—**7**) it may be concluded that the toxicities and AAs of alkaloids of the type of heteratisine and their analogs depend on the degree of oxidation of the C-6 atom and on the nature of any carbonyl-containing group present at C-6.

An increase in toxicity and a rise in AA in dependence on the nature of carbonyl-containing groups close to the nitrogen atom is also observed on passing from nominine to zeravshanisine and tadzhaconine. On passing from nominine to hetisine this is apparently due to the hydroxy groups at C-2, C-11, and C-13, the first two of which are similarly remote from the nitrogen atom, while the third is closer to it.

A considerable fall in AA with an insignificant change in toxicity, as in the case of compounds (**1**) and (**3**), is also observed in a comparison of the results of a study of the physiological activities of dihydroatisine and atidine.

On passing from alkaloids of the dihydroatisine type to alkaloids of the atisine and isoatisine types a considerable rise in toxicity and the appearance of a curare-like activity in place of the antiarrhythmic activity were observed. This is due to the possibility of the existence of atisine and isoatisine in the form of ammonium ions in aqueous solutions [20].

Thus, the results of the investigations performed show that physiological activity and toxicity among the alkaloids of *A. zeravschanicum* and their analogs depend on the type of skeleton, the nature and positions of any substituents, and the basicity of the nitrogen atom.

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