ALKALOIDS OF Aconitum coreanum

VIII. STRUCTURE OF CORYPHIDINE

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A new C_{20}-diterpene alkaloid of the coryphine type has been isolated from the plant Aconitum coreanum (Levl.) Rapaics, and it has been called coryphidine. Its structure has been established on the basis of an analysis of IR and ^1H and ^{13}C NMR spectra. This is the second diterpene alkaloid having a hexahydro-N-methylindole fragment at C-17. Coryphidine contains an imide grouping, which is unusual for a diterpene skeleton.

Continuing an investigation of the alkaloid composition of the herb Aconitum coreanum (Levl.) Rapaics [1], we have isolated from the acorine mother liquors [2] a base (I) with mp 247-249°C, composition $C_{31}H_{44}N_2O_3$. The substance dissolved poorly in the majority of organic solvents and crystallized from methanol. According to its IR and NMR spectra, it contained no ester, α,β-unsaturated carbonyl, or exomethylene groups. The base was new and, after determining its structure, we have called it coryphidine.

The composition of coryphidine differs from that of coryphine (II) by a molecule of water. Under mass spectrometric conditions the molecular ion of coryphidine broke down in a similar way to that of (II) [1] into two fragments with m/z 341 and 151, corresponding to the compositions $C_{22}H_{31}NO_2$ (diterpene moiety) and $C_9H_{13}NO$ (hexahydro-N-methylinole substituent) (341.2349 and 151.0097, respectively, HRMS). This showed that the diterpene moiety of coryphidine differed from that of coryphine by one oxygen atom, and the nitrogen-containing substituent by two hydrogen atoms.

The IR spectrum of (I) had an absorption band at 3300 cm^{-1} of a hydroxy group. The presence of the latter was confirmed by a shift in the molecular peak by 1 m.u. in the deutero analogue (III) of coryphidine. The fact that in the mass spectrum of (III) the peak of the m/z 151 ion was also shifted by 1 m.u. showed that the hydroxy group was present in the $C_9H_{13}NO$ fragment. The above facts, and also a comparative analysis of the NMR spectra of (I) and (II) permitted the conclusion that this fragment had the structure of 2',3',3'a, 6',7',7'a-hexahydro-N-methylindol-6'-ol. In the PMR spectrum of coryphidine (CD_3OD) the signal of the N-methyl group appeared at 2.31 ppm (3H, s) and those of olefinic protons at C-4' and C-5' appeared in the 5.53-5.60 ppm region in the form of a complex signal because of the closeness of their chemical shifts. The signal of a gem-hydroxylic proton at C-6' was observed at 4.17 ppm (tdd, $J_{6',7'ax} = 10.8$ Hz, $J_{6',7'eq} = 5.5$ Hz, $J_{6',5'} = 1.8$ Hz, $J_{6',4'} = 1.8$ Hz), and the H-7'a signal at 2.95 ppm (ddd, $J_{7'a,7'ax} = 8.2$ Hz, $J_{7'a,7'eq} = 7.0$ Hz, $J_{7'a,4'} = 1.8$ Hz). A long-range SSCC observed in the PMR spectrum ($^4J = 1.8$ Hz) was obviously due to spin-spin interaction by the W pathway between the H-4' and H-7'a protons, which is possible only in the half-chair conformation of the cyclohexene ring, as agrees well with an analysis of models.

In the PMR spectrum of coryphidine (in deuteropyridine) the signals of the olefinic protons appeared in the form of three one-proton signals at (ppm) 5.51 (s, H-15), 5.58 (dd, $J_{5',4'} = 10.1$ Hz, $J_{5',6'} = 1.8$ Hz, H-5'), 5.90 (dd, $J_{4',5'} = 10.1$ Hz, $J_{4',7'a} = 1.8$ Hz, H-4').

The given values of the SSCCs of the gem-hydroxylic proton at C-6 with the protons at C-7' and C-5' unambiguously showed its pseudoaxial orientation. Consequently, the hydroxy group has the pseudoequatorial orientation. The vicinal coupling constants of H-6' with H-7'ax, H-7'eq, and H-5' (10.8, 5.5, and 1.8 Hz, respectively) found experimentally agreed with the values of the dihedral angles found with the aid of Dreiding models.

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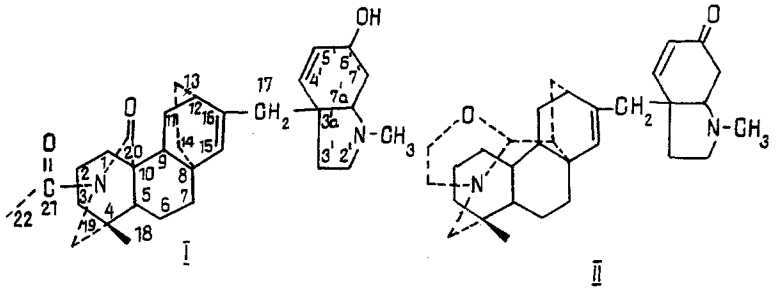
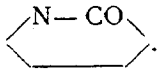
TABLE 1. Chemical Shifts of the Carbon Atoms of Coryphidine (I) in Py-d_5, 90°C, and Coryphine (II) in $CDCl_3$ (δ, ppm, 0 – TMS)

C atom	Multiplicity	δ, ppm		C atom	Multiplicity	δ, ppm	
		I	II [1]			I	II
1	t	46,31	44,44	16	s	147,82	146,48
2	t	22,41	23.08	17	t	36,50*	34,66*
3	t	40,46	41,46	18	q	27,58	28,45
4	s	38,90	34,95	19	t	55,35**	57,82
5	d	55,30	53,26**	20	s	171,41***	105,70
6	t	20,23	19,94	21		171,48*** (s)	51,69(t)
7	s	37,42*	34 33*	22		23,21 (q)	61,40(t)
8	d	40,5	43.82	2′	t	54,77**	54,60
9	s	52,78	48,25	3′	t	38,02*	36.00
10	t	55,27	47,13	3′a	t	43,14	47,13
11	t	28,74	27,93	4′	d	131,17	156,11
12	t	36,59	35,68	5′	d	130,68	125.86
13		32,91	31,37	6′		63,86 (d)	197,57 (s)
14		31,49 (t)	54,38** (d)	7′	t	35,05*	37,27
15	d	135,69	136,26	7′a	d	70,54	70,14
				$N-CH_3$	q	40,75	40,04

*, **, ***The assignments may be interchanged.



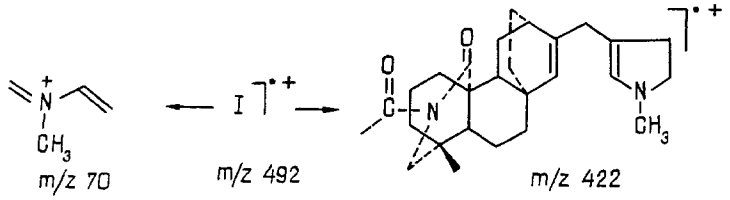
Thus, in both alkaloids the nitrogen-containing substituent has a hexahydro-N-methylindole structure, with, in coryphidine, a hydroxy group in place of a carbonyl group at C-6′.

The structure of the diterpene skeleton of coryphidine, containing 22 carbon atoms, was determined by a comparative analysis of the spectral characteristics of (I) and (II). In the PMR spectrum of coryphidine there were two three-proton singlets at 2.02 ppm ($N-COCH_3$) and 0.87 ppm (CH_3-18), and there were no signals of methylene protons of an oxazolidine ring. The region of carbonyl absorption in the ^{13}C NMR spectrum of (I) contained two singlets at 171.48 and 171.41 ppm the chemical shifts of which are typical for the carbon atoms of the carbonyl groups of imides [3]. This gave grounds for concluding that coryphidine contained a CH_3CO-  group. Absorption bands in the IR spectrum at 1710, 1650, and 1568 cm^{-1} corresponded to complex vibrations of this grouping [4]. The lactam carbonyl occupied the C-20 position, since if it had been located at C-19 the 18-methyl group would have resonated in a weaker field [5, 6].

On the basis of what has been said above and the obvious biogenetic closeness of the alkaloids coryphidine and coryphine (simultaneous presence in the plant, same numbers of carbon atoms in the diterpene moiety and in the nitrogen-containing substituent), structure (I) may be put forward for coryphidine. The proposed structure has been confirmed by an analysis of the ^{13}C NMR spectrum of coryphidine. The signals were identified by comparison with the spectrum of (I) taken in the regimes of complete decoupling from protons and of the gated decoupling procedure with the spectrum of coryphine [1] and of close model compounds [7]. The comparison of the spectra (Table 1) showed that the spectrum of coryphidine contained a quartet at 23.21 ppm, characteristic for an acetyl group, and the above-mentioned singlets at 171.41 and 171.48 ppm in place of the triplets at 51.69 and 61.40 ppm and a singlet at 105.70 ppm from the C-21, C-22, and C-20 atoms of the oxazolidine ring in the spectrum of (II). Moreover, the most substantial changes were observed for the signals of the

carbon atoms C-14 [triplet at 31.49 ppm in (I) in place of a doublet at 54.38 ppm in (II)], C-10 ($\Delta\delta$ = +7.64 ppm, the α-influence of the carbonyl of a lactam group), and C-6' [doublet at 63.86 in place of a singlet at 197.57 ppm in (II)].

The mass spectrum of coryphidine agreed well with structure (I). It contained, as well as the above-mentioned peaks of ions with m/z = 492 (M^+), 341, and 151, the informative peaks of ions with m/z 422 $(M - 70)^+$ and 70. Measurements of the elementary compositions of the ions showed that the $(M - 70)^+$ ion was formed by the ejection of a C_4H_6O fragment, and the ion with m/z 70 had the composition C_4H_8N. A possible route to the formation of these ions may be represented by the following scheme:



Such fragmentation is characteristic of mesembrine alkaloids containing a hexahydro-N-methylindole fragment [8].

Thus, the combination of spectral characteristics permits coryphidine to be assigned the structure (I) in which there is an imide grouping that is unusual for diterpene alkaloids. The alkaloid is therefore the second representative containing at C-17 the hexahydro-N-methylindole fragment that is characteristic for alkaloids of the genus Sceletium [9].

EXPERIMENTAL

IR spectra were obtained on a UR-20 instrument, and UV spectra on a Specord UV-VIS spectrometer. PMR spectra were recorded on a Bruker WM-400 NMR spectrometer with a working frequency of 400 MHz (CD_3OD; Py-d_5, 90°C, 0 – TMS), and ^{13}C NMR spectra on the same instrument at a working frequency of 100.61 MHz (Py-d_5, 90°C, 0 – TMS) in the regimes of complete decoupling from protons and of the gated decoupling procedure. Chromatographic monitoring was done by TLC (type LSL alumina, neutral) in the solvent systems chloroform–methanol (25:1) and (20:1).

For the isolation and separation of the alkaloids, see [10]. On the acetone treatment of the crystalline chloroform fractions containing acorine, 6.08 g of a crystalline mixture separated out, which was recrystallized from acetone. The acetone-soluble fraction yielded crystals of acorine (5.81 g), mp 212-214°C [2]. The acetone-insoluble residue was crystallized from methanol, which gave 70 mg of coryphidine.

Coryphidine (I), mp 247-249°C. Insoluble in ether, chloroform, and dimethyl sulfoxide. Sparingly soluble in ethanol, methanol, and pyridine. It crystallized from methanol in the form of thin needles. It formed no crystalline salts.

UV spectrum: $\lambda_{max}^{C_2H_5OH}$, nm: 205 (log ε 3.95). IR spectrum, ν_{max}^{KBr}, cm^{-1}: 3300, 1710, 1650, 1568. PMR spectrum (CD_3OD, δ, ppm): 5.60-5.53 (3H, m, H-4', H-5', H-15), 4.17 (1H, tdd, J = 10.8; 5.5; 1.8 Hz, H-6'), 3.45 and 3.14 (1H, d, 1H each, J = 13.2 Hz, H-19α and H-19β), 2.95 (1H, ddd, J = 8.2; 7.0; 1.8 Hz, H-7'a), 2.31 (3H, s, N–CH_3), 1.92 (3H, s, N–$COCH_3$), 0.87 (3H, s, CH_3-18); (in deuteropyridine at 90°C): 5.90 (1H, dd, J = 1.01; 1.8 Hz, H-4'), 5.58 (1H, dd, J = 10.1; 1.8 Hz, H-5'), 5.51 (1H, s, H-15), 3.70 and 3.41 (d, 1H each, J = 13.6 Hz, H-19α and H-19β), 2.95 (1H, t with poorly resolved components, J = 8.0 Hz, H-7'a), 2.28 (3H, s, N–CH_3), 2.02 (3H, s, N–$COCH_3$), 0.98 (3H, s, CH_3-18). Mass spectrum, m/z (%): 492(M^+, 10), 485(12), 464(5), 449(4), 422(18), 341(5), 152(47), 151(100), 150(22), 134(24), 121(19), 70(12), 44(10).

HRMS*: Calculated for $C_{31}H_{44}N_2O_2$ (M^+) 492,3352. Found 492,3341; for $C_{27}H_{38}N_2O_2$ $(M—C_4H_6O)^+$ 422,2933. Found 422,2937; for $C_{22}H_{31}NO_2$ $(M—C_9H_{13}NO)^+$ 341,2355. Found 341,2349; for $C_9H_{13}NO$ 151,0997. Found 151,0997; for C_4H_8N 70,0657. Found 70,0659.

*The high-resolution mass spectra were taken by Yu. M. Mil'grom.

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ALKALOIDS OF Aconitum sajanense

I. STRUCTURE OF ACOSANINE

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From the epigeal part of the previously unstudied plant Aconitum sajanense we have isolated the new alkaloid acosanine, the structure of which has been established on the basis of spectral characteristics and has been confirmed by a direct comparison with a sample of demethyldelcorine.

Alkaloids of plants of the genus Aconitum L. (family Ranunculaceae) have been described in a large number of publications [1], but many representatives of this genus have not hitherto been investigated. These plants include Aconitum sajanense Kumin. There is no information in the literature available to us on the chemical composition and use of this plant in folk medicine [2].

A. sajanense is a tall plant (90-100 cm) found in Eastern Siberia [3]. It is the main component of the subalpine meadows of the Central Sayan mountains located at heights of 1500-2000 m above sea level [4].

We have studied the alkaloids of the epigeal part of the plant gathered by a VILR [All-Union Institute of Medicinal Plants] expedition on August 9, 1990, in Krasnoyarsk Territory (Ermakovskii region, Western Sayan mountains, Kedranskii range, environs of Lake Oiskoe on the route from Abakan to Kyzyl at a height of 1600 m above sea level). The total alkaloids were obtained by the usual method, and these amounted to 0.63% of the weight of the dry raw material. By column chromatography, a crystalline alkaloid with mp 78-80°C, composition $C_{25}H_{41}NO_7$ (HRMS) was isolated. The base was new, and we have called it acosanine.

The IR spectrum of acosanine (I) contained absorption bands at 3600-3300 cm^{-1} (OH) and 1100 cm^{-1} (C–O). There were no absorption bands of carbonyl groups.

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