ALKALOIDS OF *Aconitum karakolicum*. STRUCTURE OF ACETYLNAPELLINE

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UDC 547.944/945

From the epigeal part of *Aconitum karakolicum* collected in the upper reaches of the R. Tyup (Kirghiz SSR) in the budding period we have isolated aconitine, aconifine [1], songorine, napelline, and phenyl-β-naphthylamine [2], and a new base which we have called acetylnapelline (I) [3]. The alkaloid has the composition $C_{24}H_{35}NO_4$ and contains N-ethyl, tertiary C-methyl, acetoxy, and terminal methylene groups. The acetylation of (I) with acetic anhydride in the presence of pyridine yielded the diacetyl derivative (II), and alkaline hydrolysis gave an amino alcohol identified as napelline (III). Consequently, the base isolated is a monoacetate of napelline, and it remained to determine the position of acetoxy group.

It is known that in the mass spectra of alkaloids of this type an acetoxy group at C-1 is responsible for the peak of greatest intensity, while in the spectrum of our base it is second in intensity (Table 1). It is also known that an acetoxy group in position 17 is responsible for the intensive ejection of the acetyl radical [4]. In the mass spectrum of the diacetate (II) a marked increase in the size of the M − CH_3CO peak (36%) is observed, while in the spectrum of the alkaloid the peak of this ion amounts to 6%. These facts are in favor of the assumption that the acetoxy group in acetylnapelline is located at C-11. In order to exclude position 1 for the acetoxy group, we performed the selective saponification of the diacetate (II) by a published method [5] and obtained the C-1-monoacetate of napelline (IV), which was not identical with the alkaloid (I). In the mass spectrum of this compound, the peak of the M − 59 ion is the maximum peak, and its NMR spectrum has a characteristic quadruplet at 5.02 ppm (J_1 = 10 Hz, J_2 = 7 Hz) from the proton geminal to the C-1 acetoxy group [6]. When acetylnapelline (I) was oxidized with silver oxide, two products were obtained: an anhydrohydroxy derivative (V) with the composition $C_{24}H_{33}NO_4$ and a noracetyl derivative (VI) with the composition $C_{22}H_{31}NO_4$. The mass spectrum of (V) has the peak of an M − 56 ion which is characteristic for analogous compounds containing an internal α-carbinolamine ether group [4]. The formation of this product serves as an additional confirmation that the hydroxy group at C-1 is not esterified.

The Adams hydrogenation of the alkaloid led to the formation of dihydroacetylnapelline (VII), $C_{24}H_{37}NO_4$, and of isoacetylnapelline (VIII), $C_{24}H_{35}NO_4$.

TABLE 1

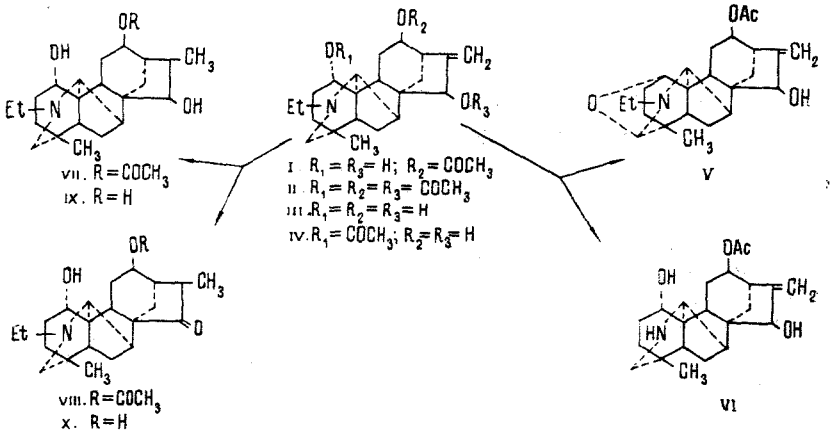
Compound	Intensities of the ion peaks, %							
	M	M-15	M-17	M-18	M-29	M-43	M-56	M-59
Acetylnapelline (I)	100	8	9	—	6	6	—	41
Monoacetylnapelline at C-1 (IV)	47	5	5	10	4	8	—	100
Triacetylnapelline (II)	37	—	—	—	—	36	—	100
Anhydrohydroxyacetylnapelline (V)	13	16	—	—	—	3	23	100
Isoacetylnapelline (VIII)	14	7	—	—	—	3	16	100
Dihydroacetylnapelline (VII)	100	10	9	—	7	7	—	57
Napelline (III)	100	6	11	10	4	—	—	7
Dihydronapelline (IX)	100	19	13	9	15	3	—	51
Isonapelline (X)	100	15	22	34	—	—	50	—

Institute of the Chemistry of Plant Substances, Academy of Sciences of the Uzbek SSR, Tashkent. Translated from Khimiya Prirodnykh Soedinenii, No. 4, pp. 479-482, July-August, 1978. Original article submitted May 16, 1978.

0009-3130/78/1404-0407$07.50

In the NMR spectrum of dihydroacetylnapelline, the signals of the terminal methylene group had disappeared and a signal had appeared from a secondary methyl group in the form of a doublet at 0.99 ppm. In the IR spectrum of isoacetylnapelline there was a strong broadened band at 1730 cm^{-1} due to a ketone group in a five-membered ring and to an ester carbonyl group.

In the IR spectrum of the saponification product — isonapelline (X) — the absorption band mentioned was retained. The formation of isoacetylnapelline shows that the hydroxy group at C-16 in the alkaloid is unsubstituted. On the basis of these facts, the structure of acetylnapelline is represented by formula (I).



The mass spectra of the alkaloids with a perhydrophenanthrene skeleton have been studied with songorine and its derivatives as examples [4]. The mass-spectrometric fragmentation of the derivatives of acetylnapelline and of napelline have some peculiarities (see Table 1). Thus, the spectrum of napelline is poorer than the spectrum of songorine which is apparently explained by the absence of a carbonyl function in napelline. A characteristic feature of the mass spectrum of napelline is the ejection of a molecule of water at the expense of the C-11 hydroxy group. Acetylnapelline is the only representative of this group of alkaloids containing an acetoxy group at C-11. Its mass spectrum is characterized by a 100% molecular ion, the ion with the second-greatest intensity being the M–59 ion which is formed at the expense of the acetoxy group. The splitting out of the acetoxy radical is the main direction of fragmentation of all the acetylnapelline derivatives, and their further decompositon takes place similarly to the schemes suggested previously [4]. At the same time, both the presence of an ether bridge (anhydrohydroxyacetylnapelline) and the introduction of a keto group into position 16 (isoacetylnapelline) increase the intensity of this peak.

EXPERIMENTAL

The melting points are uncorrected. The mass spectra were taken on an MKh-1303 instrument fitted with a system for direct introduction into the ion source, and the NMR spectra on a JNM-4H-100/100 MHz instrument in deuterochloroform with HMDS as internal standard (the results are given in the δ scale). Type KSK silica gel was used for chromatography.

Isolation and Separation of the Combined Alkaloids. The comminuted epigeal part of *Aconitum karakolicum* (27 g) was wetted with 5% sodium carbonate solution and extracted with chloroform. Extraction was repeated eight times. The combined chloroform extracts were treated with 5% sulfuric acid. The acid solution was washed with ether and, with cooling, was made alkaline with sodium carbonate. The alkaloids were extracted with chloroform and the chlorofrom was distilled off to give 146 g of combined alkaloids, and they were then extracted with ether, which gave 4.3 g of combined alkaloids.

The ether-extracted part of the combined alkaloids was chromatographed on a column of alumina, and elution by petroleum ether gave 160 mg of phenyl-β-naphthylamine [2].

The combined chloroform-extracted alkaloids were separated according to their basicities into 10 fractions. From the second fraction, with the aid of acetone, 3.1 g of aconifine was obtained. The third and fourth fractions were treated with acetone, the crystals that deposited were separated off, and after two recrystallizations from acetone, 4 g of acetylnapelline was obtained. The fifth and sixth fractions were also treated with acetone, the crys-

talline product was separated off, and the mother liquors of fractions 4-6, by the action of an ethanolic solution of hydrogen chloride, yielded 7.2 g of songorine hydrochloride. When fractions 7-10 were treated with acetone followed by two recrystallizations, 10.6 g of napelline was obtained. The first fraction (1.8 g) was reseparated according to basicity into seven subfractions, and from the first two of them 170 mg of aconitine was isolated.

Acetylnapelline (I): M^+ 401. NMR spectrum, ppm: 0.70 (3 H, singlet), 1.05 (3 H, triplet), 1.91 (3 H, singlet), 4.93 and 5.10 (one-proton doublets, J = 1.5 Hz).

Saponification of Acetylnapelline. A solution of 0.2 g of acetylnapelline in 5 ml of 5% KOH solution in methanol was boiled under reflux for 2 h. The methanol was evaporated off and the reaction product was dissolved in water and extracted with ether. The ethereal extract, after drying over sodium sulfate and distillation, yielded 90 mg of napelline.

C-1-Monoacetate of Napelline (IV). A solution of 0.3 g of napelline triacetate (II) in 12 ml of 5% methanolic KOH was boiled under reflux for 45 min. The methanol was evaporated off, the residue was dissolved in water, and the reaction product was extracted with ether. The ethereal extract was dried over sodium sulfate. The oily product obtained after the evaporation of the solvent was treated with acetone, with gave 68 mg of the monoacetate (IX) with mp 167-169°C, M^+ 401. NMR spectrum, ppm: 0.69 (3 H, singlet), 0.99 (3 H, triplet), 2.00 (3 H, singlet), 5.07 and 5.27 (one-proton doublets, J = 1.5 Hz), and 5.01 (1 H, quartet, J_2 = 7 Hz, J_1 = 10 Hz).

Oxidation of Acetylnapelline with Silver Oxide. A mixture of 0.3 g of the base and 0.46 g of silver oxide in 30 ml of 50% ethanol was stirred for 30 h. The solid matter was separated off and washed with methanol, and the filtrate was evaporated to 15 ml and was left in the refrigerator for 12 h. The acicular crystals that had deposited were separated off and recrystallized from acetone to give 90 mg of anhydrohydroxyacetylnapelline with mp 191-193°C, M^+ 399.

The aqueous mother liquor was acidified with 2% sulfuric acid, washed with ether, made alkaline with sodium carbonate, and extracted with ether. The extract after being dried over sodium sulfate was evaporated, and with the aid of acetone the residue yielded 0.04 g of noracetylnapelline with mp 249-251°C, M^+ 373.

Adams Hydrogenation of Acetylnapelline. A solution of 0.3 g of the base in 20 ml of methanol was hydrogenated over a platinum catalyst for 16 h. The catalyst was separated off, the methanol was evaporated off, and the reaction product was chromatographed on a column of silica gel. On elution with petroleum ether, fractions 1-3 yielded, with the aid of acetone, 9 mg of isoacetylnapelline with mp 224-226°C, M^+ 401. IR spectrum: 3440, 1730 cm^{-1}.

On elution with petroleum ether-methanol (25:1), 50 mg of amorphous dihydroacetylnapelline was isolated, M^+ 403. NMR spectrum, ppm: 0.68 (3 H, singlet), 0.99 (3 H, doublet, J = 7 Hz), 1.01 (3 H, triplet), 1.98 (3 H, singlet).

SUMMARY

From the epigeal part of *Aconitum karakolicum* growing in the upper reaches of the R. Tyup (KirghizSSR) have been isolated phenyl-β-naphthylamine, aconitine, aconifine, songorine, napelline, and the new base acetylnapelline. On the basis of a study of spectral characteristics and chemical transformations it has been shown that the alkaloid is the C-11-monoacetate of napelline.

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