ALKALOIDS OF Haplophyllum acutifolium

D. M. Razzakova, I. A. Bessonova, and S. Yu. Yunusov

UDC 547.944/945

In preceding papers [1, 2] we have described the results of an investigation of the alkaloids of the epigeal part of H. acutifolium, family Rutaceae, growing in the Kora-Kola region of the Turkmen SSR. From the combined alkaloids we have isolated a new base for which, on the basis of a spectroscopic study, the structure of 2-(hept-4-enyl)-1,4-dihydroquinolin-4-one has been proposed. We have called this base acutine (I). The catalytic hydrogenation of acutine formed a dihydro derivative (II), mol. wt. 243 (mass spectrometry) the IR spectrum of which retained the absorption bands characteristic for 1,4-dihydroquinolin-4-ones. The UV spectrum and melting point of dihydroacutine coincide with those for 2-heptyl-1,4-dihydroquinolin-4-one isolated from Pseudomonas microorganisms [3] (Fig. 1). For direct comparison, we obtained 2-heptyl-1,4-dihydroquinolin-4-one by condensing aniline with methyl 3-oxodecanoate and cyclizing the product in diphenyl ether [4]. Dihydroacutine proved to be identical with the resulting 2-heptyl-1,4-dihydroquinolin-4-one according to a mixed melting point, TLC, and UV and mass spectra.

The position of the double bond in the side chain of acutine was shown by a study of mass and NMR spectra.

The mass spectra of acutine (I) and its dihydro derivative (II) have the peaks of the molecular ions with m/e 241 and 243, respectively, and of a number of fragmentary ions formed by the successive splitting out of alkyl radicals from the side chain (Fig. 2). In all cases, the positive charge was localized in the aryl part of the molecule. The strongest peaks with m/e 159 and 172 in the spectra of (I) and (II) arise by the cleavage of the C–C bond present in the β,γ position to the ring, with the migration of the γ and α hydrogen radicals, respectively. One of the tautomeric forms of the ion with m/e 159, by eliminating a formyl radical, forms an ion with m/e 130 (chart). This fragmentation pathway is typical for the M^+ of 2-alkyl-1,4-dihydroquinolin-4-ones [5].

The spectrum of acutine differs somewhat from the spectrum of (II), on the basis of which it is possible to obtain useful information concerning the position of the double bond in the side chain. Thus, in the spectrum of (I) there is the peak of rearrangement ion with m/e 173, the intensity of which is slight in the spectrum of dihydroacutine. The considerable intensity of this peak shows that the bond that is cleaved is in the allyl position with respect to the double bond. Furthermore, the difference of two mass units existing in the values of the molecular ions of the compounds begins to be detected on the cleavage of the C_4–C_5 bond as in the alkaloid evocarpine [6]. Consequently, acutine has the structure (I).

The structure of acutine is also confirmed by the features of the NMR spectra of (I) and (II) (Fig. 3). In the spectrum of (I) there are two triplets at 7.32 ppm (2H, methylene group attached to a ring and connected with another methylene group; J = 7 Hz) and at 9.16 ppm (3H, CH_2–CH_3; J = 7 Hz). Thus, positions C_3–C_4 and C_4–C_5 remain for the double bond. The presence in the spectrum of (I) of a six-proton multiplet in the 7.85–8.40-ppm region from the protons of three methylene groups (its chemical shift is typical for allyl protons) and the absence of a two-proton signal in the 8.4–9.00 region shows the correctness of the structure (I) for acutine. The signal from the NH group appears in a very weak field – at δ 13.00.

The NMR spectrum of dihydroacutine lacks the signals of olefinic protons. In the region of aromatic protons signals are observed in the spectrum of (II) at 1.7 ppm (1H, doublet, H_5), 2.65 ppm (3H, multiplet,

Institute of the Chemistry of Plant Substances, Academy of Sciences of the Uzbek SSR. Translated from Khimiya Prirodnykh Soedinenii, No. 2, pp. 206-210, March-April, 1973. Original article submitted June 22, 1972.

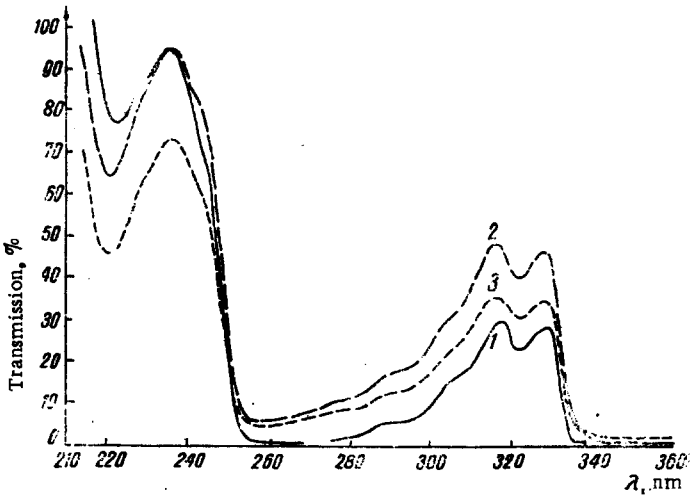


Fig. 1. UV spectra (ethanol) of acutine (c 0.007 mg/ml) (1), dihydroacutine (c 0.009 mg/ml) (2), and 2-heptyl-1,4-dihydroquinolin-4-one (c 0.0074 mg/ml) (3).

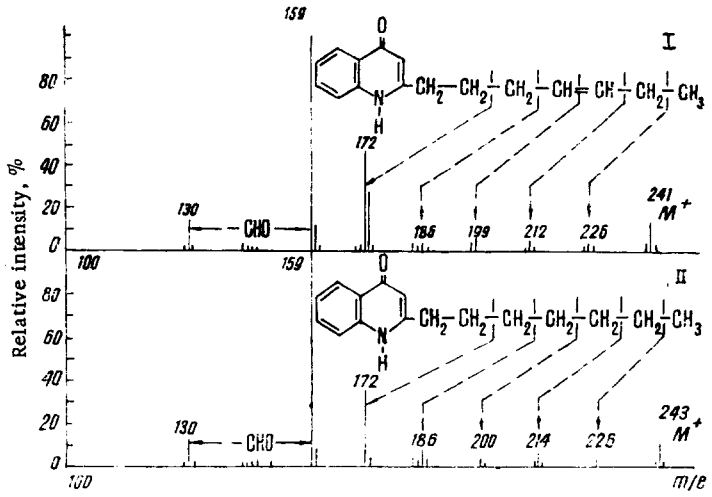


Fig. 2. Mass spectra of acutine (I) and dihydroacutine (II).

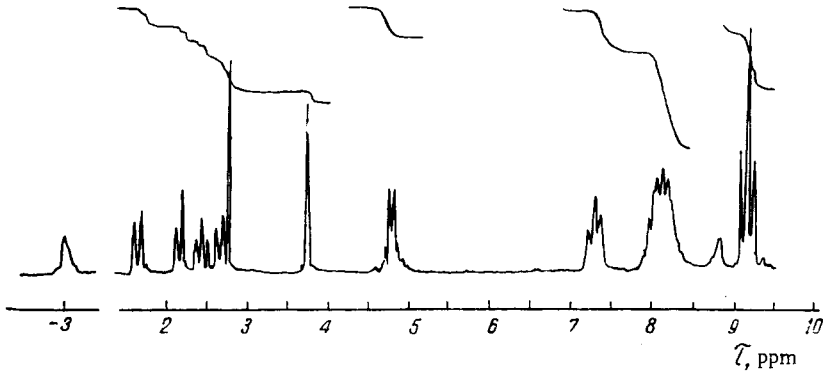
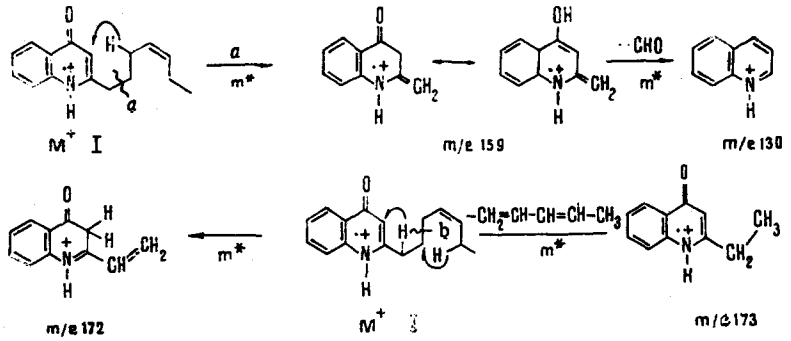


Fig. 3. NMR spectrum of acutine.

H_6, $_7$, $_8$), and 3.51 ppm (1H, singlet, H_3); signals of aliphatic protons – a two-proton triplet at 7.17 ppm and a two-proton signal at 8.3 ppm ($-CH_2-CH_2$ group attached to a ring); an eight-proton signal at 8.60-9.10 ppm (four CH_2 groups), and a three-proton triplet at 9.25 ppm (terminal methyl group).



Scheme of the fragmentation of acutine

We have also investigated the alkaloids from H. acutifolium collected in the Kizil-Arvat region of the Turkmen SSR. From the combined alkaloids we isolated skimmianine, acutine, and acetamide. We did not obtain eudesmine [2] from this raw material.

Skimmianine was isolated from the roots of H. acutifolium collected in the fruit-bearing period in the Kora-Kola region near Palvan-Zau, Turkmen SSR.

EXPERIMENTAL

Thin-layer chromatography was performed with silica gel containing 5% of gypsum and the following solvent systems: 1) benzene–methanol (4:1), and 2) toluene–ethyl acetate–formic acid (5:4:1). The UV spectra were recorded on a Hitachi spectrophotometer, the IR spectra on a UR-10 instrument (tablets with KBr), the mass spectra on an MKh-1303 mass spectrometer, and the NMR spectra on a JNM-4H-100/100 MHz instrument in $CDCl_3$ (τ scale except where otherwise mentioned).

Isolation and Separation of the Combined Alkaloids. The extraction of 9 kg of the epigeal part of Haplophyllum acutifolium with chloroform yielded 6.31 g (0.07%) of combined alkaloids, which were chromatographed on a column of alumina. Elution with ether gave skimmianine and eudesmine with mp 107-108°C, and elution with chloroform gave acutine.

Acutine (I). Crystals deposited from acetone in the form of colorless prisms with mp 122-123°C which became pink on standing in the light and in solution. The substance is readily soluble in chloroform, ethanol, and methanol and insoluble in ether, petroleum ether, acids and water. IR spectrum, cm^{-1}: 1510, 1560, 1597, 1635.

Dihydroacutine (II). Acutine (35 mg) was hydrogenated in 15 ml of ethanol over a platinum catalyst at room temperature for 3 h. After the separation of the catalyst, the solution was evaporated, the residue was crystallized from acetone and ether to form white needles gathered into rosettes, with mp 142-143°C. IR spectrum, cm^{-1}: 1510, 1555, 1597, 1640.

Synthesis of 2-Heptyl-1,4-dihydroquinolin-4-one. A mixture of 6.82 g of methyl 3-oxodecanoate, 2.79 g of freshly distilled aniline, and two drops of 15% hydrochloric acid was left at room temperature for 20 h. The water that formed was separated off and the condensation product, after being dried over magnesium sulfate, was added by drops to boiling diphenyl ether (40 ml). The mixture was heated for 2 h, and on the following day it was diluted with ether and shaken with 15% hydrochloric acid. The acid solution deposited crystals of the hydrochloride of 2-heptyl-1,4-dihydroquinolin-4-one in the form of colorless needles with mp 80-83°C. The addition of ammonia to an aqueous suspension of the hydrochloride and extraction with ether gave crystals of 2-heptyl-1,4-dihydroquinolin-4-one with mp 142°C (from ether and acetone).

The combined alkaloids (5.96 g) from the chloroform extract of the epigeal part of H. acutifolium (10 kg) were boiled in petroleum ether–acetone (9:1). Acetamide was separated off with mp 79°C (from benzene–petroleum ether), and it was identified by a mixed melting point, by TLC, and by mass spectroscopy in comparison with an authentic sample. The remainder of the alkaloids were separated into benzene and chloroform fractions according to their solubilities. Chromatography of the benzene fraction on alumina yielded skimmianine and acetamide, and that of the chloroform fraction yielded skimmianine and acutine.

A chloroform extract of the roots of this plant (1 kg) gave 0.53 g of combined alkaloids from which skimmianine was isolated by chromatography on alumina.

SUMMARY

1. The plant Haplophyllum acutifolium has yielded eudesmine, acetamide, skimmianine, and a new base with the composition $C_{16}H_{19}NO$, mp 122-123°C, which has been called acutine.

2. It has been shown that acutine has the structure of 2-(hept-4-enyl)-1,4-dihydroquinolin-4-one.

LITERATURE CITED

1. D. M. Gulyamova, I. A. Bessonova, and S. Yu. Yunusov, Khim. Prirodn. Soedin., 850 (1971).
2. D. M. Razzakova, I. A. Bessonova, and S. Yu. Yunusov, Khim. Prirodn. Soedin., 665 (1972).
3. E. E. Hays, I. C. Wells, et al., J. Biol. Chem., 159, 725 (1945); I. C. Wells, J. Biol. Chem., 196, 331 (1952); J. W. Cornforth and A. F. James, Biochem. J., 63, 124 (1956).
4. N. J. Leonard, H. F. Herbrandson, and E. M. Van Heyningen, J. Amer. Chem. Soc., 68, 1279 (1946); Ch. R. Hauser and G. A. Reynolds, J. Amer. Chem. Soc., 70, 2402 (1948).
5. J. Reisch, R. Pagnucco, and N. Jantos, Phytochem., 7, 997 (1968).
6. R. Tschsche and W. Werner, Tetrahedron, 23, 1878 (1967).