THE STRUCTURE OF PERFAMINE

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We have found the alkaloid perfamine (I) in the seeds and epigeal part of *Haplophyllum perforatum* (family Rutaceae) collected in the "Gallyaaral" sovkhoz [collective farm], Samarkand oblast. The base is not extracted by acids from organic solvents and, like haplamine [1], remains in the neutral fraction of the extract. Preliminary results of a study of the structure of (I) have been published previously [2].

The UV spectrum of (I) (Fig. 1) differs from the corresponding spectra of furanoquinoline and 5,6,7,8-tetrahydrofuranoquinoline alkaloids [3]. The presence in the IR spectrum of the base of absorption bands at 3115 and 3145 cm^{-1} (furan ring) and 1670 cm^{-1} (conjugated carbonyl), the characteristics of the NMR spectrum of (I) (Fig. 2), and the optical activity of the base permitted the assumption that perfamine is based on a 4-methoxyfuranoquinoline nucleus in which the homocyclic ring A has been modified to form an ortho-dienone ring with methoxyl and isopentenyl substituents on one carbon atom.

Compounds containing a gem-substituted dyclohexadienone ring possess a high tendency to pass into substances with an aromatic structure in an acid medium [4]. Heating perfamine in dioxane in the presence of sulfuric acid led to a phenolic compound $C_{13}H_{11}NO_4$ (II), the UV spectrum of which was close to that of haplopine (III) (see Fig. 1) and those of other furanoquinoline alkaloids substituted in positions 7 and 8 [5]. The NMR spectrum of (II) has two pairs of doublets the chemical shifts and spin–spin coupling constants of which are typical for ortho-aromatic protons (2.21 and 2.99 ppm, J = 9 Hz), and for the α- and β-protons of a furan ring (2.61 and 2.95 ppm, J = 3 Hz) [6]. The chemical shifts of the signals of protons of the methoxy groups (5.69 and 6.24 ppm) show that they are both attached to an aromatic system, unlike the situation in the initial base. The characteristics given agree with those for haplopine. However, substance (II) obtained on the acid cleavage of perfamine, was not identical with haplopine in its melting point, IR spectrum, and TLC behavior. Their mass spectra were similar: (II) m/e (%) 245 (M^+, 100), 244 (20), 230 (28), 227 (77), 216 (30); (III) m/e (%) 245 (M^+, 100), 244 (22), 230 (28), 227 (78), 216 (14). The

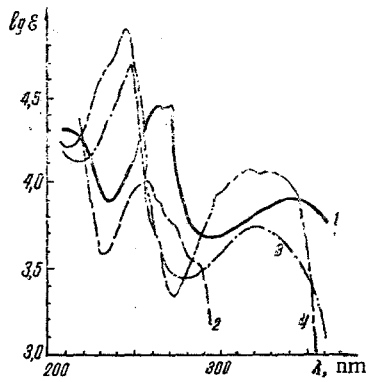

Fig. 1. UV spectra of perfamine (1), perforine (2) [3], 8-hydroxy-4,7-dimethoxyfuranoquinoline (3), and haplopine (4).

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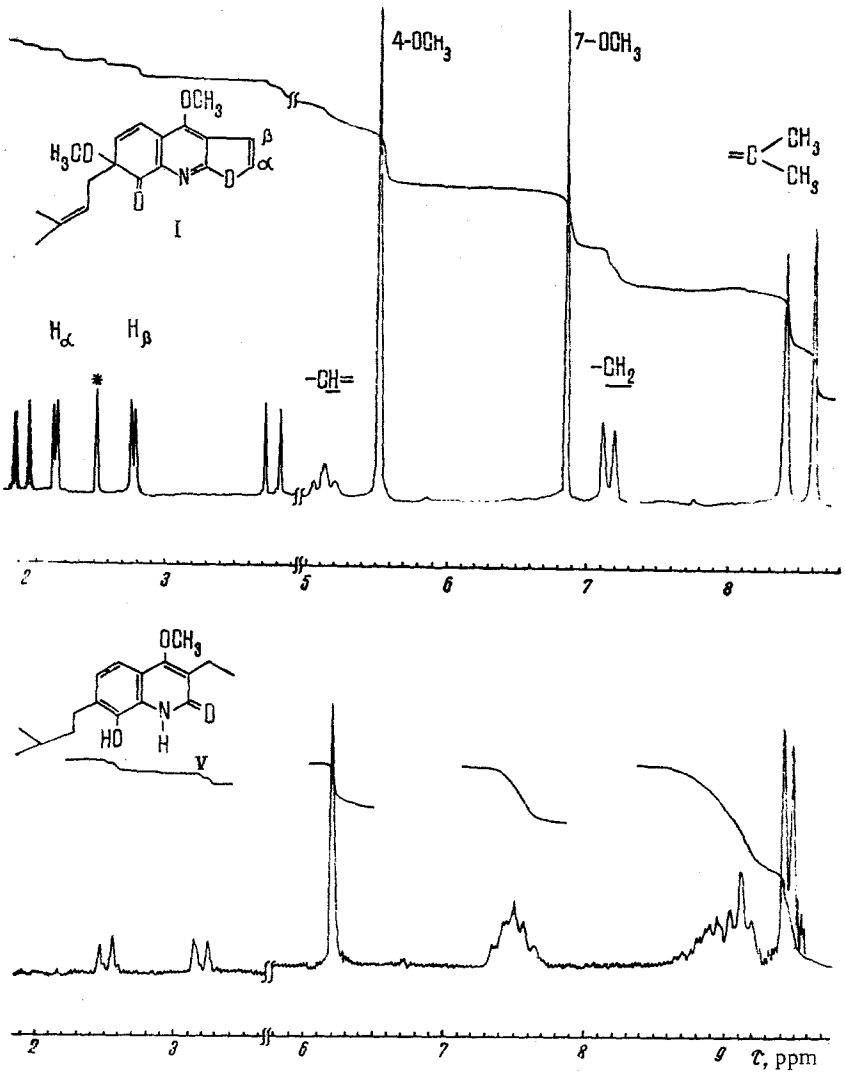
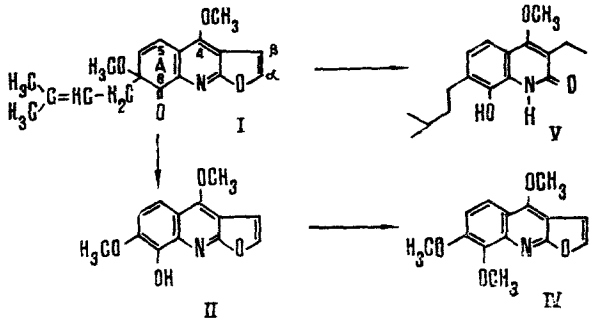
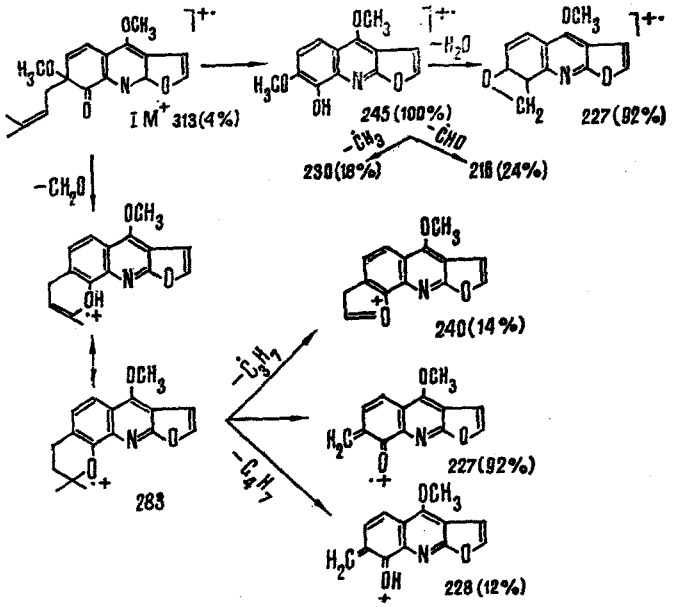


Fig. 2. NMR spectra of (I) ($CDCl_3$) and (V) (CF_3COOH).



Scheme 1. Transformations of perfamine.

main difference in the mass-spectrometric behaviors of these compounds is observed in the ejection of a formyl radical from the molecular ion. A higher intensity of the peak of the $(M - 29)^+$ ion is characteristic for compounds having a hydroxy group at C_8 [7, 8]. As in the case of haplopine, the methylation of (II) with diazomethane gave skimmianine (IV), which was shown to be identical with an authentic sample by TLC, melting point, and IR spectra. Consequently, substance (II) differs from haplopine only by the opposite position of the substituents in the homocyclic ring and has the structure of 8-hydroxy-4,7-dimethoxyfuranoquinoline. Correspondingly, structure (I) (Scheme 1) remains the only possible one for perfamine.



Scheme 2. Fragmentation of perfamine (I).

In contrast to haplopine, which is widely distributed in plants of the genus *Haplophyllum* and is found in other representatives of the family Rutaceae, compound (II) is new. Its O-acetyl derivative and hydrochloride have been obtained.

Elimination of the isopentenyl substituent in perfamine in the form of an isoprene molecule also takes place under the conditions of mass spectrometry. The ease of cleavage of the side chain is apparently due to the fact that the position of cleavage is in an allyl relationship to a keto group and to the double bonds of the chain and of ring A. The stability of the ion with m/e 245 formed in this process is due to its enolization to a phenolic compound which then fragments similarly to M^+ of haplopine and of compound (II) (Scheme 2).

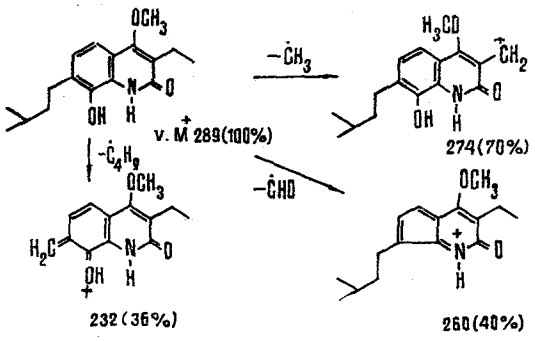
The spectrum of perfamine has the peaks of ions with m/e 283 (6%), 266 (14%), and 252 (8%), in the formation of which the methoxy group at C_7 participates. The ion with m/e 283 arises on the elimination of formaldehyde, the ion with m/e 266 on the elimination of a molecule of methanol and a methyl radical, and the ion with m/e 252 on the elimination of a molecule of methanol and a formyl radical. Decomposition of the cyclic form of the ion with m/e 283 by the elimination of isopropyl and isopropenyl radicals and an isobutylene molecule, which is characteristic of compounds containing a dimethyldihydropyran fragment [9], leads to ions with m/e 240, 228, and 227, respectively (see Scheme 2).

The catalytic hydrogenation of perfamine in glacial acetic acid formed an optically inactive phenolic compound (V), $C_{17}H_{23}NO_3$, the UV spectrum of which (Fig. 3) almost coincides with that of the tetrahydro derivative of foliminine [10].

The IR spectrum of (V) has absorption bands of a hydroxy group (broad maximum at 3200 cm^{-1}) and of an amide carbonyl group (high-intensity in the 1630-cm^{-1} region).

In the NMR spectrum of (V) (Fig. 2) there are two one-proton doublets in the region of aromatic protons at 2.40 ppm (H_5) and 3.11 ppm (H_6), J = 9 Hz. The signal of the methoxy group is a singlet at 6.14 ppm. The protons of the ethyl and isopentyl substituents appear in the regions of 7.43 ppm (4 H, multiplet, 2Ar–CH_2–); 8.70-9.10 ppm (3 H, multiplet, –CH_2–CH); 9.11 (3 H, triplet, J = 8.5 Hz, –CH_2–CH_3), and 9.43 ppm (6 H, doublet, J = 7 Hz, gem-dimethyl group). These facts, and also the disappearance from the spectrum of (V) of the signals of the protons of the furan ring, of the protons of the aliphatic methoxy group, and of the olefinic proton show that the reduction of perfamine in an acid medium involves the hydrogenolysis of the furan ring, the reduction of the double bond of the side chain, and the hydrogenolytic splitting off of the methoxy group accompanied by enolization into the phenolic compound (V).

In the mass spectrum of (V), the maximum peak is that of the molecular ion. The peak next in intensity is formed as the result of the splitting out of a methyl radical from the



Scheme 3. Fragmentation of (V).

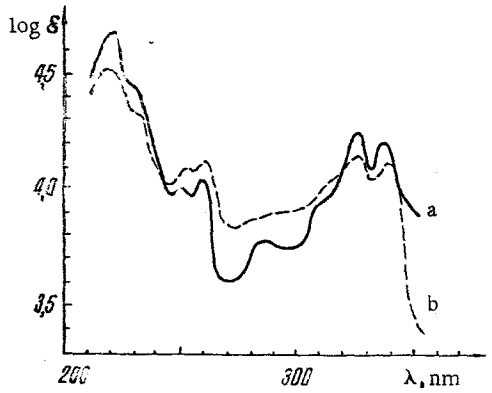


Fig. 3. UV spectra of (V) (a) and of tetrahydrofoliminine (b).

ethyl group (Scheme 3). In addition to this, the splitting off of a formyl radical with the participation of the hydroxy group in the β-cleavage of the side chain [the ions $(M - 29)^+$ and $(M - 57)^+$] is observed. Thus, the most stable fragments of the product of the hydrogenation of perfamine are in good agreement with structure (V).

Among the quinoline alkaloids perfamine is the first representative in which the homocyclic ring is modified into a gem-disubstituted cyclohexadienone ring.

EXPERIMENTAL

For TLC we used silica gel containing 5% of gypsum and the following solvent systems: 1) toluene–ethyl acetate–formic acid (5:4:1) and 2) benzene–methanol (4:1). The UV spectra were taken on a Hitachi spectrometer, 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 spectrometer using the τ scale.

Isolation of Perfamine. An ethanolic extract of the dry comminuted seeds (20 kg) of *H. perforatum* was separated into basic and neutral fractions. The mother solution of the neutral fraction remaining after the separation of haplamine and eudesmine was chromatographed on a column of Al_2O_3. Ethereal eluates yielded perfamine (0.2 g). Perfamine (0.005% of the weight of the dry raw material) was isolated similarly from the neutral fraction of an extract of the epigeal part (150 kg).

Perfamine (I) formed yellowish crystals with mp 164-165°C (ether–acetone), $[\alpha]_D$ +53.4° (c 0.28; chloroform). Perfamine is readily soluble in chloroform, less readily in ethanol, methanol, acetone, and ether, and is insoluble in water and in dilute acids and alkalis, and it gives a single spot with R_f 0.60 (system 1). It fluoresces dull green in UV light.

8-Hydroxy-4,7-dimethoxyfuranoquinoline (II). Concentrated H_2SO_4 (five drops) was added to a hot solution of 0.03 g of (I) in 5 ml of dioxane. The solution immediately became turbid. After heating for a minute, crystals of (II) deposited with mp 224-225°C, these being sparingly soluble in all organic solvents apart from methanol and readily soluble in alkali. Substance (II) fluoresced in UV light and was revealed by Dragendorff's reagent (spot col-

ored blue, like that of haplopine); R_f 0.33 (system 1). UV spectrum (C_2H_5OH); λ_{max} 250, 325 nm (log ε 4.67, 3.73). It gave no depression of the melting point in admixture with a sample of haplopine. The hydrochloride of (II) precipitated when ethanolic solutions of the base (II) and hydrochloric acid were mixed; mp 172-173°C.

8-O-Acetyl-4,7-dimethoxyfuranoquinoline. Substance (II) (0.02 g) was heated with 0.2 ml of acetic anhydride in the presence of two drops of pyridine on the water bath for 2 h. When the solution was evaporated, crystals of the acetyl derivative precipitated; mp 183-184°C. IR spectrum: λ_{max} 1765 cm^{-1}.

8-O-Methyl-4,7-dimethoxyfuranoquinoline. An ethereal solution of diazomethane was added to a solution of 0.03 g of (II) in 10 ml of absolute methanol. The solution was left for four days and it was then shaken with a 4% solution of caustic soda, washed with water, and passed through a column of Al_2O_3. Ethereal eluates yielded crystals of (IV) with mp 174-175°C which gave no depression of the melting point with an authentic sample of skimmianine. Their IR spectra and R_f values on TLC (0.28; system 1) were identical.

Hydrogenation of Perfamine (Product V). A solution of 0.05 g of (I) in 20 ml of glacial acetic acid was hydrogenated for four days. Product (V) was isolated in the usual way, mp 225°C (from ethanol); readily soluble in alkali, sparingly soluble in organic solvents, and insoluble in water. It did not fluoresce in UV light and gave a weak coloration with Dragendorff's reagent; R_f 0.75 (system 2).

UV spectrum (C_2H_5OH), λ_{max}, nm: 220, 235 inflection, 253, 261, 282 inflection, 295 inflection, 325, 339 (log ε 4.50, 4.29, 4.07, 4.11, 3.86, 3.90, 4.15, 4.12).

SUMMARY

1. The leaves and epigeal part of *Haplophyllum perforatum* have yielded a new alkaloid perfamine — the first representative of the quinoline series in which the benzene ring is modified into a gem-disubstituted cyclohexadienone ring.

2. On the basis of spectral data, chemical transformations, and conversion into skimmianine, structure (I) has been established for perfamine.

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