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THE STRUCTURE OF FOLIFININE

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On further separation of the phenolic fraction of the total alkaloids of Haplophyllum foliosum Vved. [1], we have obtained a new optically inactive base—folifinine (I), $C_{17}H_{19}O_4N$.

The substance is readily soluble in alkalies and acids, less soluble in ethanol, methanol, and acetone, and sparingly soluble in chloroform, and forms a picrate and a hydrochloride. A functional analysis of the base shows the presence of a methoxy group and the absence of N-methyl groups. The IR spectrum of folifinine has a broad band at 3600-3100 cm^{-1} (hydroxy groups). The production of an O, O-diacetyl derivative (II), the spectrum of which lacks this band but exhibits absorption bands at 1735 and 1765 cm^{-1}, shows the presence in the base of one alcoholic and one phenolic hydroxy group. The saponification of diacetylfolifinine with alcoholic alkali gave the initial base.

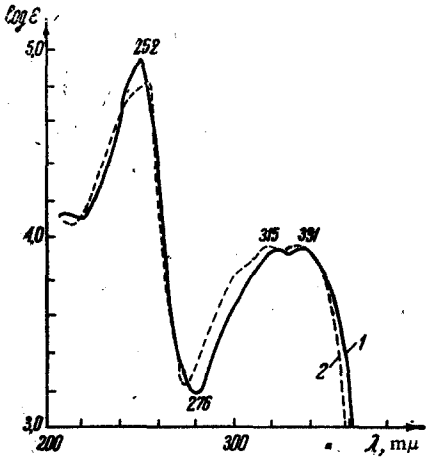


Fig. 1. UV spectrum of skimmianine (1) and folifinine (2).

In the IR spectrum of (II), absorption bands appear that are characteristic for the C—H vibrations of a furan ring (3135 and 3165 cm^{-1}) [2]. The fact that folifinine is a furoquinoline alkaloid is shown by its UV spectrum, which is typical for this group of alkaloids (Fig. 1) [3], and also by the hydrogenolysis reaction [4]. On hydrogenation over a platinum catalyst, the alkaloid absorbs four atoms of hydrogen, forming tetrahydrofolifinine (III). In the IR spectrum of (III), there are no absorption bands of the C—H vibrations of the furan ring, since the latter is opened with the formation of a 3-alkyl-2-quinolone. In the IR spectrum of (III) in the 1605-1640 cm^{-1} region there is a band with a high integral intensity (amide carbonyl group) [5] and there are no absorption bands in the 1555 cm^{-1} region characteristic for 2-alkoxy-4-quinolones [6, 9]. These results show that the furan and quinoline rings are linked linearly.

In the NMR spectrum of (II) (Fig. 2), there are a number of peaks with intensities in the ratio 1:1:1:1:3:2:3:2:3:6, corresponding to the 23 hydrogen atoms of diacetylfolifinine. The doublets b(τ = 2.50, J = 3 Hz) and d (τ = 3.08, J = 3 Hz) correspond to the α- and β- protons of a furan ring [7] and the doublets a (τ = 1.95; J = 9 Hz) and c (τ = 2.93, J = 9 Hz), from their chemical shifts and spin-spin coupling constants, to the ortho aromatic protons H_5 and H_6, respectively [8]. The three-proton singlet e (τ = 5.72) belongs to the protons of an O—CH_3 group present in position 4 of the quinoline nucleus [8, 9]. Consequently, folifinine is a 7,8-disubstituted 4-methoxyfuroquinoline derivative.

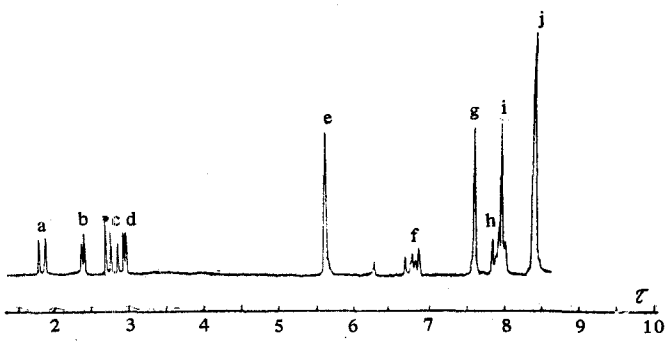
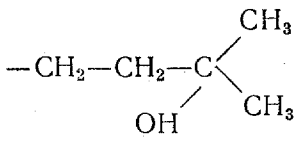
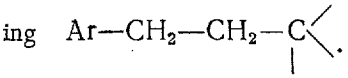


Fig. 2. NMR spectrum of the O,O-diacetyl derivative of folifinine.

In the region of the NMR spectrum due to aliphatic protons, there are two two-proton multiplets—f (τ = 6.86) and h (τ = 8.00)—which may be caused by an Ar—CH_2—CH_2—C group [10]. The considerable paramagnetic shift of the signal from the protons of the methylene group adjacent to the benzyl protons may be caused by the presence in the α-positions of such descreening groups as Ar— and —O—CO—CH_3 [7]. The two three-proton singlets—g (τ = 7.66) and i (τ = 8.04)— corresponding to the protons of the Ar—O—CO—CH_3 and R—O—CO—CH_3 groups [11] confirm the presence in folifinine of phenolic and alcoholic hydroxy groups.

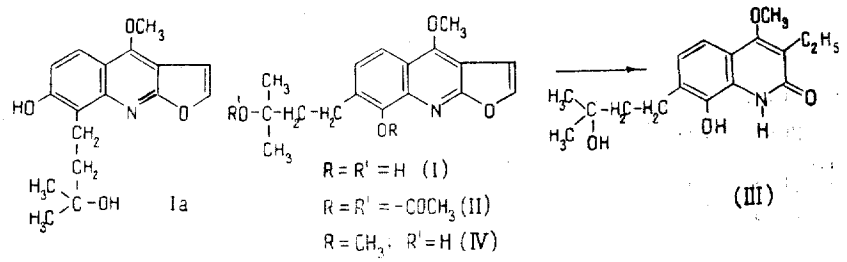
The six-proton singlet—j (τ = 8.48)—corresponds to the protons from two equivalent C—CH_3 groups present on carbon atom 4. The shift of the signal into the weak-field region is caused by the presence of an —O—CO—CH_3 group in the α-position. These features, and also the fact that the base has no optical activity, show the presence in folifinine of a side-chain with the structure



By methylating folifinine with diazomethane, we obtained an O-methyl derivative (IV) the spectrum of which, unlike that of (II), had two three-proton singlets at 5.76 and 6.13 ppm (two OCH_3 groups) and also two two-proton triplets at 6.85 ppm (J = 8 Hz) and 8.35 ppm (J = 8 Hz), confirming the presence in the side chain of folifinine of the grouping  .

In the NMR spectrum of (IV), the ortho protons of the aromatic ring appear at 2.10 ppm (J = 9 Hz) and 2.98 ppm (J = 9 Hz). The considerable paramagnetic shift of the signal from the H_5 proton ($\Delta\tau$ = 0.15 ppm) as compared with the signal from the H_6 proton ($\Delta\tau$ = 0.05 ppm) in (II) relative to the same signals of the O-methyl derivative (IV) permits the assumption [12] that the phenolic hydroxy group in the base occupies position 8.

Thus, of the two possible structures—(I) and (Ia)—(I) is the more likely.



Experimental

The combined alkaloids remaining after the separation of the skimmianine, dubinidine, and other alkaloids [1] was separated into a phenolic and a nonphenolic fraction.

The phenolic alkaloids (70 g) were chromatographed on alumina (1500 g). Folifinine was isolated from the ether-chloroform eluates.

Folifinine (I). The substance has mp 181–182° C (from acetone), $[\alpha]_D$ 0° (c 1.01; methanol); UV spectrum: λ_{max} 252, 315, 331 mμ (log ε 4.81; 3.95; 3.96).

Found, %: C 67.9, 68.00; H 6.36, 6.41; N 4.60, 4.52; OCH_3 10.23, 10.30. Calculated for $C_{17}H_{19}O_4N$, %: C 67.75; H 6.35; N 4.64; OCH_3 10.20.

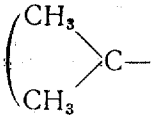
Folifinine hydrochloride precipitated when alcoholic solutions of the base and hydrochloric acid were mixed; mp 122–123° C (from ethanol).

Folifinine picrate, mp 162–163° C (decomp., from ethanol), precipitated when alcoholic solutions of the base and picric acid were mixed.

O,O-Diacetylfolifinine (II). The substance was formed by boiling folifinine (0.2 g) with acetic anhydride (0.3 ml) in the presence of pyridine (2–3 drops) for 2 hr. It forms colorless needles with mp 139–140° C (from acetone). The saponification of diacetylfolifinine with 20% methanolic caustic potash yielded folifinine.

Tetrahydrofolifinine (III). With the platinum catalyst prepared from 0.1 g of platinum oxide, 0.15 g of folifinine in 15 ml of ethanol was shaken in a current of hydrogen for 4 hr. The catalyst was filtered off with suction and washed with ethanol. When the ethanolic solution was concentrated, crystals of tetrahydrofolifinine with mp 199–201° C (from acetone) deposited.

O-Methylfolifinine. An ethereal solution of diazomethane was added to a suspension of 0.2 g of folifinine in 20 ml of dry ether. After 4–5 days, the solution was treated with a 4% solution of alkali, washed with water, and distilled. The residue formed an oil.

NMR spectrum of O-methylfolifinine: two three-proton singlets at 8.85 and 8.88 ppm  , a two-proton triplet at 8.35 ppm ($Ar-CH_2-\underline{CH_2}-C$), a two-proton triplet at 6.85 ppm ($Ar-\underline{CH_2}-CH_2-$), two three-proton singlets at 6.13 and 5.76 ppm (two OCH_3), two doublets at 3.22 and 2.66 ppm (α and β-protons of a furan ring), two doublets at 2.10 and 2.98 ppm (H_5 and H_6 aromatic protons).

The NMR spectra were recorded by M. R. Yagudaev on a JNM-4H-100/100 MHz instrument in deuteriochloroform (diacetylfolifinine) and in CCl_4 (the O-methyl derivative) with HMDS as internal standard (τ-scale).

Conclusions

1. A new base, folifinine, has been isolated from the epigeal part of Haplophyllum foliosum Vved. Its developed formula is $C_{16}H_{14}N(OH)_2(OCH_3)(-O-)$.

2. The structure 8-hydroxy-7-(3'-hydroxy-3'-methylbutyl)-4-methoxy-2,3-furoquinoline has been proposed for folifinine.

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