THE STRUCTURE OF FOLIMIDINE

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From the combined phenolic alkaloids of the epigeal part of Haplophyllum foliosum Vved. (family Rutaceae) we have isolated a new optically inactive base with mol. wt. 281 (mass spectrometry) and have called it folimidine. The base dissolves readily in alkalis, does not dissolve in acids, is sparingly soluble in the usual organic solvents, and crystallizes from methanol and ethanol. It gives a red-brown coloration with a solution of ferric chloride. It contains methoxy, methylimide, and hydroxy groups. The presence of the latter is shown by the fact that when the alkaloid is deuterated under the usual conditions the peak of the molecular ion shifts by one unit. The UV spectrum of folimidine has a double maximum at 327, 338.5 nm (log ε 4.08, 4.07) which, on acidification, undergoes the hypsochromic shift typical for quinolin-4-ones [1].

The IR spectrum of the base has absorption bands at (cm^{-1}) 1624, 1605, 1565, 1545, 1520, and 1510 (quinolin-4-one system) and 842, 870, and 770 (1,2,4- and 1,2-substituted aromatic rings [2, 4]) and a broad band at 3350 cm^{-1} (hydroxy group).

These facts and the close similarity of the UV absorption spectra of folimidine and foliosine isolated from the same plant [3] (Fig. 1) show that our alkaloid is based on a 2-phenylquinolin-4-one nucleus. The identity of foliosine and graveoline (III) has been established previously [4].

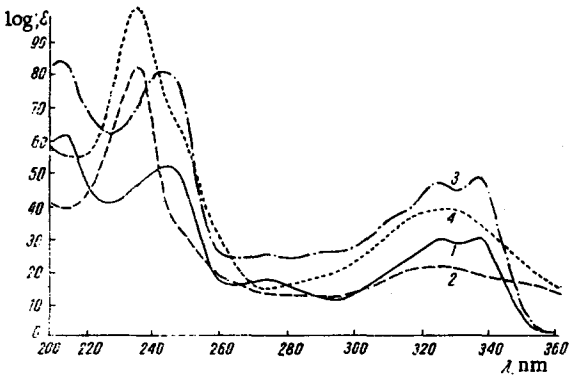

Fig. 1. UV spectra of folimidine in ethanol (1) and in acidified ethanol (2) and of graveoline (foliosine) in ethanol (3) and in acidified ethanol (4).

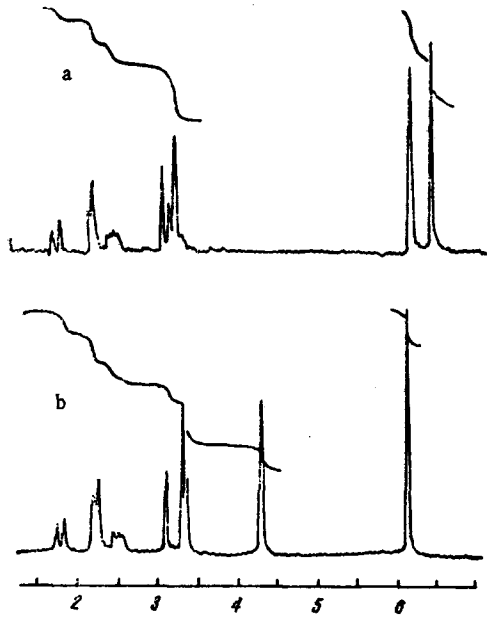

Fig. 2. NMR spectra of folimidine (a) and graveoline (b).

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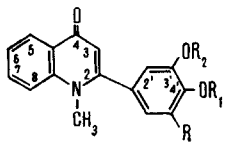
TABLE 1. Chemical Shifts (τ scale)

Compound	Solvent	Aromatic protons at					OCH_3	NCH_3	O_2CH_2
		C_5	$C_{6,7}$	C_8	$C_{2',5',6'}$	C_3			
I	CF_3COOH	1,75 d	2,24 d	2,48 m	3,20–3,40 (3H)	3,14 s	6,43 s	6,17 s	—
II	CF_3COOH	1,75 d	2,24 d	2,48 m	3,34 (2H)	3,12 s	6,43 s	6,17 s	—
III	CF_3COOH	1,78 d	2,24 d	2,48 m	3,37(2H); 3,40(H)	3,15 s	—	6,17 s	4,33 s
IV	CF_3COOH	1,75 d	2,23 d	2,46 m	3,21(2H); 3,23(H)	3,14 s	—	6,16 s	—
VI	CCl_4	Aromatic protons 1,95-2,83 (8H)				3,26	—	—	4,11 s
VI	CF_3COOH	The same 2,00-3,01 (7 H)				3,34 d	—	—	4,29 s
		The same at C_4 1,45 d (J=8 Hz)				(J=8Hz)	—	—	—

Notes. s – singlet, d – doublet, m – multiplet; the spectra of (IV) and (VI) in CF_3COOH were taken on a JNM-C-60HL instrument



I. Folimidine — $R=R_1=H$; $R_2=CH_3$

II. Deuterofolimidine — $R_1=H$; $R_2=CH_3$; $R=D$

III. Graveoline (foliosine) — $R_1+R_2=CH_2$; $R=H$

IV. 2-(3',4'-Dihydroxyphenyl)-methylquinolin-4-one — $R=R_1=R_2=H$

V. O-Methylfolimidine — $R_1=R_2=CH_3$; $R=H$

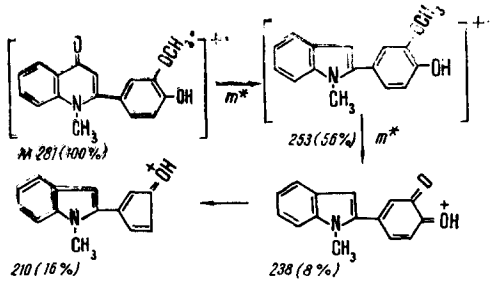
The molecular weights of folimid ine and of graveoline (mol. wt. 279, mass spectrometry), differ by two units, and their NMR spectra are similar (Fig. 2). In place of the signal from the proton of a methylenedioxy group in graveoline, the spectrum of folimidine has the signal from the protons of a methoxy group. The assignment of the signals is given in Table 1. The similarity of the complex shape of the signals from the four adjacent aromatic protons of folimidine and graveoline shows that the base isolated has no substituents in the benzene ring of the quinolinone nucleus and, therefore, it may be assumed that it is a structural analog of graveoline.

The methylation of folimidine with diazomethane formed O-methylfolimidine (V); the physical properties of this substances coincided completely with those of the product of the methylation of 2-(3',4'-dihydroxyphenyl)-1-methylquinolin-4-one (IV), obtained by the saponification of the methylenedioxy group of graveoline. Consequently, the mutual arrangement of the hydroxy and methoxy groups in the folimidine molecule is limited to positions 3' and 4'. In order to determine which of the possible structures corresponds to folimidine we used the capacity of the ortho and para protons of phenols for being replaced by deuterium, since the possibility of the formation of a mono- or a dideutero derivative depends on the position of the hydroxy group (4' or 3'). We deuterated the alkaloid under the conditions described for morphine [5]. This gave a substance which, after recrystallization from ethanol, had mp 247°C, mol. wt. 282 (mass spectrometry). The NMR spectrum of deuterated folimidine (II) differs from the initial spectrum only by the fact that in place of a three-proton signal in the 3.15-3.35 ppm region a narrow two-proton broadened singlet appears at 3.27 ppm. Hence, the structure of folimidine may be represented by formula (I).

A proton at C_3 usually resonates in the region around 4.00 ppm [6]. In the spectra of the compounds studied (see Table 1) it appears in a weaker field. The paramagnetic shift of the signal from H_3 is the result not of the influence of the solvent [for comparison the table gives the characteristics of the NMR spectra of dubamine (2-piperonylquinoline) (VI) taken in CCl_4 and CF_3COOH] but of hydroxy- and alkoxy-substitution in the phenyl nucleus. Signals from the methoxy group located in the phenyl ring are observed in a higher field than the signals from a N-methyl group.

It is known that D analogs have melting points close to those of the corresponding hydrogen compounds. By recrystallizing folimidine it was impossible to raise its melting point above 225°C. However, when the base was heated with dimethylformamide and subsequently crystallized from ethanol, folimidine with mp 247°C was obtained. The IR spectra of the alkaloids with mp 225 and 247°C were identical. A mixture of them gave no depression of the melting point.

In the mass spectra of (I) and its derivatives, the maximum peak is that of the molecular ion; the second-strongest peak is formed as the result of the ejection of CO from M^+. The fragmentation of the molecular ion of folimidine is shown by the following scheme.



Folimidine is the third alkaloid of the 2-phenylquinolin-4-one series to have been isolated from H. foliosum [8].

EXPERIMENTAL

TLC was performed on silica gel containing 5% of gypsum with the following solvent systems: 1) benzene–methanol (4 : 1) and 2) toluene–ethyl acetate–formic acid (5 : 4 : 1). The UV spectra were taken on a Hitachi spectrophotometer, the UV 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.

Isolation of Folimidine (I). The combined chloroform-extracted alkaloids (950 g) were separated into phenolic and nonphenolic fractions. By the acetone treatment of the ether-soluble phenolic fractions, 170 mg of (I) was isolated with mp 225°C (from ethanol). When the chloroform-extracted phenolic fraction (1.4 g) was chromatographed, chloroform eluates yielded 130 mg of folimidine with mp 225°C. By heating the base with dimethylformamide and subsequent crystallization from ethanol, the melting point of the folimidine was raised to 247°C. On TLC in systems 1 and 2, the substance gave a single spot fluorescing with a dull greenish light on UV irradiation and revealed by means of Dragendorff's reagent.

O-Methylfolimidine (V). A few drops of absolute methanol was added to a suspension of 67 mg of folimidine in 20 ml of an ethereal solution of diazomethane to dissolve the solid matter, and additional diazomethane solution was added periodically for a week. The ethereal solution was washed with a solution of alkali and with water, and dried over sodium sulfate, and the solvent was distilled off. The residue formed a crystallizing oil with mp 186-187°C (from ether), mol. wt. 295 (mass spectrometry). IR spectrum, cm^{-1}: 1628, 1601, 1522, 1500, 850, 835, 770.

Saponification of the Methylenedioxy Group of Graveoline. A mixture of 1 g of carefully ground foliosine (graveoline), 2 g of phloroglucinol, and 15 ml of concentrated hydrochloric acid was heated in a sealed tube at 150-160°C for 5 h. The acid solution was removed from the precipitate (A), diluted with water (10 ml), and made alkaline with gaseous ammonia in the presence of ether. The precipitate of ammonium chloride mixed with (IV) that deposited was combined with precipitate A and boiled in chloroform (1 : 1000). Then the solvent was distilled off to give a substance with mp 275°C (from chloroform–methanol). The yield of (IV) was 0.3 g (technical), mol. wt. 267 (mass spectrometry). IR spectrum, cm^{-1}: 3515, 1620, 1595, 1555, 1530, 1502, 865, 838, 765.

Methylation of (IV). A solution of 0.15 g of (IV) in 1.5 ml of 4% NaOH and 0.7 ml of dimethyl sulfate was heated in the water bath for 1.5 h. The cooled reaction mixture was made alkaline and extracted with chloroform. The solvent was distilled off and the residue was crystallized from ether; mp 186-187°C. A mixture with O-methylfolimidine melted at the same temperature. On TLC in systems 1 and 2, the two substances gave identical spots; mol. wt. 295. Their IR spectra were also identical.

Deuteration of Folimidine. A solution of folimidine (58 mg) in dimethylformamide (0.5 ml) and D_2O (0.13 ml) was heated in a sealed tube filled with nitrogen at 118-120°C for 72 h. Then the solvent was evaporated off, and the residue was recrystallized from ethanol to give 47 mg of deuterated product with mp 246-247°C. Mass spectrum: 282 (M^+, 100%), 254 (30%), 239 (6%), 211 (7%).

SUMMARY

A new alkaloid, folimidine, with the composition $C_{17}H_{15}O_3N$, has been isolated from the plant Haplophyllum foliosum Vved. On the basis of chemical and spectral facts the structure 2-(4'-hydroxy-3'-methoxyphenyl)-1-methylquinolin-4-one has been proposed for it.

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