HAPLOPHYLLUM ALKALOIDS. IV. STRUCTURE OF FOLIOSIDINE

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An alkaloid foliosidine isolated from the plant Haplophyllum foliosum Vved. (Rutaceae family) has the formula $C_{16}H_{21}O_5N$. Its expanded formula is $C_{13}H_{13}$ (N-CH_3) (OH)$_2$ (OCH_3) (CO) (-O-), and it is 4-methoxy-8-(2', 3'-dihydroxy-3'-methyl-butoxy)-N-methylcarbostyryl (I).

We have previously reported the isolation of an optically active alkaloid, foliosidine [1], revised formula $C_{16}H_{21}O_5N$ [2], from the aerial part of Haplophyllum foliosum Vved. (Rutaceae family).

Analysis of functional groups shows that foliosidine contains two hydroxyls, a methoxyl group, and a methylimide one. The alkaloid does not give a specific reaction for the carbonyl group. However, its IR spectrum exhibits the absorption band of amide carbonyl (1645 cm^{-1}), as well as a band in the region 3270-3400 cm^{-1}, characteristic of the hydroxyl group. The fifth oxygen atom is inert and ethereal, the IR spectrum of the alkaloid containing an absorption band at 1150 cm^{-1} corresponding to it. Hence the formula of foliosidine can be expanded in the form $C_{13}H_{13}$ (N-CH_3) (OH)$_2$(OCH_3) (CO) (-O-).

The treatment of the alkaloid with acetyl chloride gives diacetylfoliosidine, $C_{13}H_{13}$(N-CH_3) ($OCOCH_3$)$_2$ (OCH_2) (CO) (-O-). The hydroxyl absorption band is absent from the IR spectrum of this derivative, its place being taken by the carbonyl group of a complex alcohol ester (1725 cm^{-1}), the intensity corresponding to two acetyl groups. Hence both hydroxyls in foliosidine are alcohol hydroxyls.

Saponification of diacetylfoliosidine yields the initial base. The alkaloid is not hydrogenated in the presence of platinum, and its IR spectrum lacks the 3110-3150 cm^{-1} absorption band corresponding to the valence vibrations of C-H in the furan ring [3].

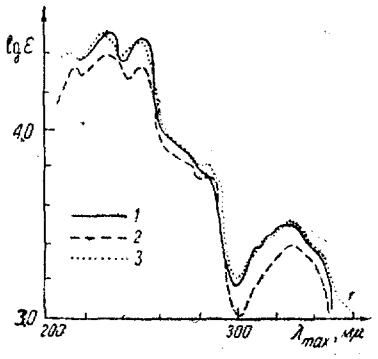


Fig. 1. UV spectra: 1) Foliosidine; 2) ether (IV); 3) 4, 8-dimethoxy-N-methylquinolone-2.

The UV absorption spectra of foliosidine and its derivatives (Fig. 1) closely resemble those of quinoline derivatives. Since the IR spectrum of the base (Fig. 2a) exhibits a band of high integral intensity in the region 1615-1650 cm^{-1}, foliosidine must be a derivative of N-methylquinolone-2 [4, 5].

Foliosidine (I) can readily be demethylated by heating with an alcoholic solution of hydrogen chloride, and this is characteristic of γ-methoxyquinolones. Norfoliosidine (II) results, with formula $C_{13}H_{13}$ (N-CH_3) (OH)$_3$ (CO) (-O-), and methylation of it with diazomethane gives back the original base. Alkali fusion of the alkaloid gives an optically inactive substance (III) of phenolic character C_8H_4 (N-CH_3)(OH)(OCH_3)(CO), differing from the initial foliosidine by the group of atoms $C_5H_8(OH)_2$. A phenolic hydroxyl can be formed by saponifying the simple ether linkage between the quinoline nucleus and the side chain $C_5H_9(OH)_2$. Thus the phenol (III) is a derivative of 4-methoxy-N-methylquinoline-2 in which the hydroxyl group can be present in one of five positions (3, 5, 6, 7, 8).

With acetic anhydride and pyridine [6] the phenol (III) forms an acetyl derivative (IIIa), C_8H_4(N-CH_3)($OCOCH_3$)(OCH_3)(CO), the IR spectrum of which lacks a hydroxyl band but exhibits a carbonyl absorption band of a complex phenol ester (1770 cm^{-1}).

Methylation of phenol (III) with dimethyl sulfate gives a methyl ether (IV), C_8H_4 (N-CH_3) (OCH_3)$_2$ (CO), and the latter on heating with hydrochloric acid is demethylated to base (VII), C_8H_4(N-CH_3) (OH) (OCH_3) (CO), which is isomeric with phenol (III), and which on methylation gives ether (IV). With sodium nitrite in acid medium the phenol (VII) gives a nitroso derivative (VIII) C_8H_4O (N-CH_3) (NO) (OCH_3) (CO) which could arise only in the absence of a substituent at C_8 of the quinoline nucleus, so that the side chain does not occur at that position. Thus, four positions in the benzene nucleus of 4-methoxy-N-methylquinolone-2 are possible for the side chain.

The constants of the ether (IV) and related substances (VII, VIII) are close to those given in the literature [8, 9] for 4, 7-dimethoxy-N-methylquinolone-2 and corresponding derivatives. Furthermore, in known quinoline alkaloids the side chain joined to the quinoline benzene nucleus through a simple ester linkage is at position 7 [6, 7]. 4, 7-dimethoxy-N-methylquinolone-2 was therefore synthesized by a method described in the literature [8], but was found to differ from the substance obtained from the foliosidine ether (IV).

The hydroxyl group of phenol (III) appears as a continuous absorption from 2500-3300 cm^{-1} (Fig. 2b), which can be ascribed to strong intermolecular hydrogen bonding between the hydroxyl and the nitrogen or carbonyl of the pyridine ring. This kind of bonding can exist if the hydroxyl group of the phenol (III) is at C_3 or C_8. Since foliosidine and its derivatives are not substituted at C_3, the only remaining possibility is C_8, and this was shown to be correct by direct comparison of the ether (IV) with 4,8-dimethoxy-N-methylquinolone-2. For preparation of the latter the alkaloid γ-fagarine was submitted to oxidative degradation to the known 8-methoxy-4-hydroxyquinolone-2 [9], which was then treated with dimethyl sulfate to give 4,8-dimethoxy-N-methylquinolone-2. A mixed mp test, as well as comparison of UV and IR absorption spectra (Figs. 1 and 2), showed that the substance obtained was identical with the ether (IV).

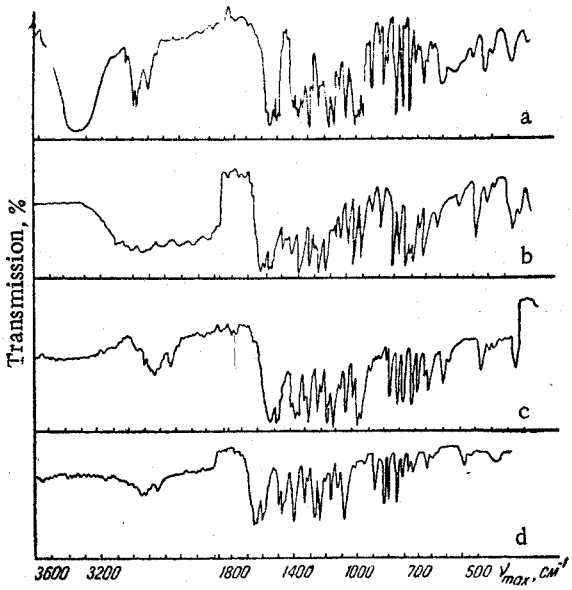


Fig. 2. IR spectra: a. foliosidine; b. phenol (III); c. ether (IV); d. 4,8-Dimethoxy-N-methylquinolone-2.

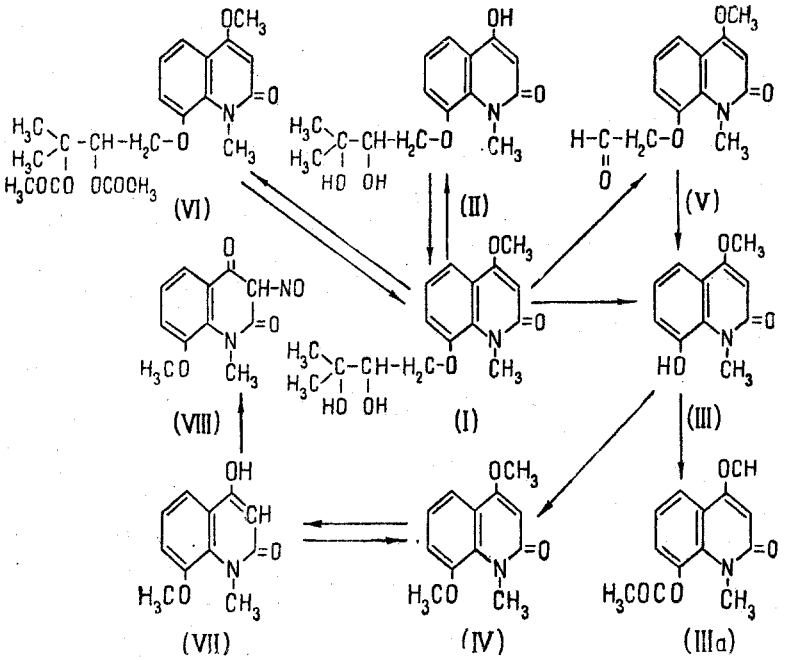
This established the basic nucleus and point of attachment of the side chain in foliosidine, which is 4-methoxy-N-methylcarbostyryl with an ethereal side chain $C_5H_9(OH)_2(-O-)$ at C_8.

To elucidate the nature of the $C_5H_9(OH)_2$ portion, foliosidine was oxidized with chromic acid in sulfuric acid and acetone was very readily formed, identified as the 2,4-dinitrophenylhydrazone showing the presence of the CH_3-C-CH_3 group in the residue $C_5H_9(OH)_2$.

Foliosidine is oxidized by iodic acid, so that the hydroxyl groups in the side chain are on adjacent carbon atoms. Acetone and the heterocyclic aldehyde foliosidinal (V) were isolated from the oxidation products. Such scission of foliosidine could occur only if the side chain contained the grouping $(CH_3)_2C(OH)$-CH(OH)-.

Foliosidinal is an optically inactive compound with the formula $C_{13}H_{13}O_4N$, or expanded, $C_{10}H_7(N\text{-}CH_3)(OCH_3)(CO)(-O-)$; it gives a silver mirror reaction, condenses with dimedone, and forms an oxime and 2,4-dinitrophenylhydrazone. Further, formaldehyde is among the products of oxidation with iodic acid. Alkaline 3% hydrogen peroxide converts foliosidine into the phenol (III). Hence foliosidinal contains the grouping OHC-CH_2-O- [6, 7]. These facts and the presence of an asymmetric carbon atom in the alkaloid indicate that the side chain of foliosidine has the structure $(CH_3)_2C(OH)$-CH(OH)-CH_2-O- [6, 7, 10].

Consequently foliosidine is 4-methoxy-8-(2',3'-dihydroxy-3'-methylbutoxy)-N-methylcarbostyryl (I), and its decomposition can be represented as follows:-



Experimental

Foliosidine was isolated from the total alkaloids of Haplophyllum foliosum Vved. by the method previously described and chromatographing on alumina. After recrystallizing from acetone and alcohol it has mp 141-142°, $[\alpha]_D^{25}$ + 41.6° (c 3.006; ethanol).

IR spectrum ν_{max}: 3350, 1645, 1150 cm^{-1}.

UV spectrum λ_{max}: 232, 252, 326 mμ (log ε 4.50, 4.46, 3.50 resp.)

Found %: C 62.70; 62.70; H 7.30; 7.05; N 4.60; 4.76; OCH_3 11.12; 11.46; N-CH_3 4.56; 4.41. $C_{16}H_{21}O_5N$. Calc. %: C 62.52; H 6.88; N 4.55; OCH_3 10.09; N-CH_3 4.89.

Diacetylfoliosidine. 0.5 g foliosidine and 7 ml acetyl chloride were heated together in a sealed tube; after 24 hr the tube was opened and excess acetyl chloride distilled off. The residue was suspended in water and 4% aqueous ammonia added till a faint alkaline reaction was obtained. The precipitate (0.7 g) was filtered off and crystallized from acetone and alcohol; mp 142-143°, $[\alpha]_D^{18}$ + 5.4° (c 4.41; ethanol).

IR spectrum ν_{max}: 1730, 1640 cm^{-1}.

Found %: C 61.4; 61.4; H 6.64; 6.64; N 3.54; 3.68; OCH_3 9.0; 9.7; N-CH_3 3.2. $C_{20}H_{25}O_7N$. Calc. %: C 61.36; H 6.43; N 3.57; OCH_3 8.0; N-CH_3 3.9.

Action of hydrochloric acid on foliosidine. Norfoliosidin. 0.5 g alkaloid were dissolved in 6.5 ml alcohol and 1.5 ml conc. HCl, and heated for 6 hr on a steam bath. When the reaction was complete the alcohol was distilled off and the residue taken up in 4% aqueous sodium hydroxide. The alkaline solution was washed with chloroform to remove unreacted alkaloid, and then acidified with acetic acid. The resultant precipitate of norfoliosidine (0.35 g) was crystallized from water; mp 235-236°, $[\alpha]_D^{18}$ + 50.4° (c 1.984; pyridine).

IR spectrum ν_{max}: 3300, 1650 cm^{-1}.

UV spectrum λ_{max}: 234, 252, 278, 290, 326 mμ (log ε 4.16; 3.58; 3.56; 3.12 resp.).

Found %: C 61.1; 60.9; H 6.82; 7.02; N 4.90; 5.04; OCH_3 not detected. $C_{15}H_{19}O_5N$. Calc. %: C 61.4; H 6.52; N 4.77.

Methylation of norfoliosidine. 0.2 g norfoliosidine were suspended in 5 ml absolute alcohol, and an ethereal solution of diazomethane added. The oily residue was crystallized by triturating with acetone. Mp 141-142° (from acetone), mixed mp with authentic foliosidine undepressed.

Kuhn-Roth oxidation. 0.5 g foliosidine were mixed with an oxidizing mixture of 5 g chromic anhydride, 5 ml conc. H_2SO_4, and 20 ml water. A vigorous reaction took place with evolution of gaseous products, the latter being trapped in a 0.1% solution of 2,4-dinitrophenylhydrazine hydrochloride. The reaction was brought to a conclusion by heating for 6 hr on a steam bath and 2 hr on a sand bath. There was a precipitate of 2,4-dinitrophenylhydrazone acetone with mp 123-124°;

Alkali fusion of foliosidine. A mixture of 1 g foliosidine, 2 g KOH, and 0.5 ml water were heated for 3 min at 150°, cooled, and dissolved in water. The alkaline solution was washed with chloroform to remove unreacted alkaloid, then acidified with acetic acid. The phenol (III) (0.6 g) precipitated was crystallized from acetic acid and alcohol; mp 227-228°.

IR spectrum ν_{max}: 2500-3300, 1635 cm^{-1}.

UV spectrum λ_{max}: 212, 225, 254, 332 mμ (log ε 4.36; 4.38; 4.42; 3.34 resp.)

Found %: C 64.5; 64.5; H 5.87; 5.87; N 6.72; 6.63. $C_{11}H_{11}O_3N$. Calc. %: C 64.38; H 5.40; N 6.82.

Acetylation of the phenol (III). 0.5 g phenol (III) were mixed with 10 ml acetic anhydride and 2 drops of pyridine. The mixture was heated 2 hr on a steam bath, and the excess of acetic anhydride distilled off.

The resultant acetyl derivative (0.55 g) was crystallized from ethyl acetate and alcohol; mp 150-151°.

IR spectrum ν_{max}: 1760, 1660 cm^{-1}.

UV spectrum λ_{max}: 230, 272, 282, 320 mμ (log ε 4.63; 3.81; 3.82; 3.63 resp.)

Found %: C 63.6; 63.9; H 5.84; 6.06; N 5.77; 5.88; OCH_3 13.2; 13.32; N-CH_3 6.2; 6.4. $C_{13}H_{13}O_4N$. Calc. %: C 63.14; H 5.30; N 5.66; OCH_3 12.6; N-CH_3 6.07.

Methylation of the phenol (III). A solution of 0.5 g phenol (III) in 2.5 ml 10% sodium hydroxide solution was added to 2.5 ml dimethyl sulfate, a further 4 ml of 20 sodium hydroxide solution was added, and the mixture shaken. The precipitated crystals of the ether (IV) were taken up in chloroform and run through a column of alumina, then

crystallized from benzene-petroleum ether; mp 139-140°.

IR spectrum ν_{max}: 1640 cm^{-1}.

UV spectrum λ_{max}: 232, 252, 286, 328 mμ (log ε 4.38; 4.34; 3.74; 3.38 resp.)

Found %: C 65.6; 65.8; H 6.13; 6.27; N 6.48; 6.74; OCH_3 28.4; 28.7. $C_{12}H_{13}O_3N$. Calc. %: C 65.73; H 5.98; N 6.39; OCH_3 28.2.

Demethylation of ether (IV). 0.5 g of the methyl ether (IV) were mixed with 20 ml 5 N hydrochloric acid and boiled for 1 hr. The mixture was cooled and made alkaline with a 20% sodium hydroxide solution. The alkaline solution was extracted with chloroform and then acidified with acetic acid. The resultant precipitate was isolated (0.35 g) and crystallized from alcohol; mp 268-270°.

IR spectrum ν_{max}: 2800-3100, 1645 cm^{-1}.

UV spectrum λ_{max}: 234, 252, 288, 314 mμ (log ε 4.44; 4.40; 3.84; 3.38 resp.)

Methylation of phenol (VII). 0.3 g phenol were methylated with dimethyl sulfate as described above. The reaction product was isolated, and crystallized from benzene-petroleum ether; mp 139-140°, mixed mp with the ether (IV) was undepressed.

Nitroso derivative of phenol (VII). 0.3 g phenol (VII) in 10% sodium hydroxide solution and 0.12 g sodium nitrite were mixed and cooled to -10° to -15°, and acidified with 15% H_2SO_4. A red precipitate of the nitroso derivative was formed, mp 187-188° (from alcohol).

Found %: N 12.04; 12.03; OCH_3 13.5; 14.0. $C_{11}H_{10}O_4N_2$. Calc. %: N 11.95; OCH_3 13.2.

Preparation of 8-methoxy-4-hydroxyquinolone-2. 3 g γ-fagarin were dissolved in 50 ml acetone, and 5.52 g potassium permanganate in acetone added dropwise. The reaction mixture was stirred 2 hr, the manganese dioxide precipitate filtered off and treated alternately with 4% sodium hydroxide solution and hot water. The filtrate was acidified when cold, the precipitate of γ-fagarinic acid separated (2 g), mixed with 150 ml 30% HCl, boiled for 6 hr, and filtered hot. After 12 hr, there was a precipitate of 8-methoxy-4-hydroxyquinolone-2, with mp 243-245° (from acetic acid).

Methylation of 8-methoxy-4-hydroxyquinolone-2. A solution of 1 g of the compound in 5 ml 10% sodium hydroxide solution was mixed with four portions of 5 ml dimethylsulfate and 8.5 ml 20% sodium hydroxide. The resultant precipitate of 4,8-dimethoxy-N-methylquinolone-2 was separated off, and crystallized from benzene-petroleum ether; mp 139-140%.

IR spectrum ν_{max}: 1645 cm^{-1}.

UV spectrum λ_{max}: 232, 252, 286, 327 mμ (log ε 4.48; 4.44; 3.80; 3.48 resp.).

Iodic acid oxidation of foliosidine.

1. 0.5 g foliosidine was added to a solution of 0.5 g iodic acid in 12 ml water. After 24 hr, the precipitate of foliosidinal (0.4 g) was filtered off, and crystallized from methanol; mp 158-160°. The filtrate was distilled off on a sand bath into a 0.1% solution of 2,4-dinitrophenylhydrazine hydrochloride, to give a precipitate of 2,4-dinitrophenylhydrazone acetone with mp 123-124°.

2. 0.5 g foliosidine was oxidized with iodic acid in the way described above. The filtrate was distilled off on a sand bath into a hot 1% aqueous solution of dimedone. A precipitate of formaldehydedimidone formed immediately, insoluble on heating, with mp 187-188°.

Foliosidinaldimedone. A hot 1% dimedone solution was added to 0.1 g foliosidinal, the mixture was boiled for 10-15 min, and the precipitate filtered off and washed well with hot water. After drying and crystallizing from alcohol, the foliosidinaldimedone had mp 170-171°.

Foliosidinal oxime. A hot alcoholic solution of 0.2 g foliosidinal was mixed with 0.1 g hydroxylamine hydrochloride in water, and the mixture added to a warm solution of sodium carbonate (0.05 g). On standing, crystals of foliosidinal oxime with mp 207-208° (from alcohol) precipitated out.

Found %: C 59.2; 59.4; H 5.53; 5.63; N 10.59; 10.57; OCH_3 12.5; 12.98; $C_{13}H_{14}O_4N_2$. Calc. %: C 59.5; H 5.38; N 10.68; OCH_3 11.8.

Oxidation of foliosidinal with hydrogen peroxide. 0.2 g foliosidinal were added to 4 ml 10% sodium hydroxide solution and 5 ml 3% hydrogen peroxide. The mixture was heated on a steam bath, and after 10 min the clear solution was cooled and acidified with acetic acid. The resultant precipitate (0.1 g) was filtered off and crystallized from alcohol, mp 226-227°. The mixed mp with the phenol (III) was undepressed.

IR spectra were observed using a UR-10 instrument, the material being tableted with KBr; UV spectra were determined with a SF-4 instrument, the solvent being alcohol.

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