UDC 547.944/945

STRUCTURE OF FOLIFINE AND FOLIFIDINE

Z. Sh. Faizutdinova, I. A. Bessonova, and S. Yu. Yunusov

Khimiya Prirodnykh Soedinenii, Vol. 3, No. 4, pp. 257-260, 1967

We have previously reported the isolation from Haplophyllum foliosum Vved. of skimmianine, dubinidine, foliosine, and foliosidine [1], and of haplofoline [2]. On further separation of the total alkaloids, we obtained known bases, robustinine [3] and haplopine [4], and new bases, folifine and folifidine. We have also isolated folifine from the plant Haplophyllum bucharicum Litv.

Folifine, with the composition $C_{15}H_{17}O_3N$ is an optically active base; it is readily soluble in methanol, is less readily soluble in chloroform, ethanol and hot water, and is insoluble in alkalies and ether. It forms salts whose aqueous solutions readily hydrolyze.

A functional analysis of this substance has shown that it lacks methoxy groups and contains hydroxy and N-methyl groups. Its IR spectrum has bands at 3180 cm^{-1} (hydroxy group) and at 1510, 1555, 1605, and 1630 cm^{-1} with low integral intensities, which are typical for 2-alkoxy-4-quinolones [5, 6]. Consequently, the analytical formula of folifine will be

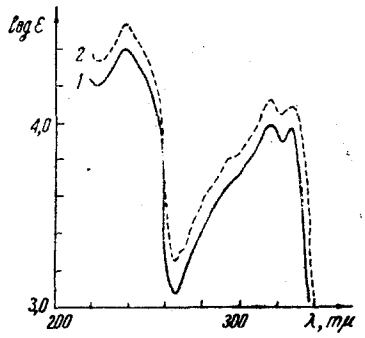
$$C_{13}H_{13}\ (N-CH_3)\ (CO)\ (OH)\ (-O-).$$

The presence in the substance of a hydroxy group with an alcoholic character is confirmed by the preparation of an O-acetyl derivative the IR spectrum of which lacks the absorption band of a hydroxy group, while bands characteristic for alcohol esters appear at 1735 and 1245 cm^{-1}.

The production of acetone when folifine is oxidized by the Kuhn-Roth method shows the presence of a gem-dimethyl group in it. Its UV spectrum is very similar to that of N-methylhaplofoline (III), from which its composition differs by one oxygen atom (figure). This permitted the assumption of a dihydropyranoquinolone structure for it.

The alcoholic nature of the hydroxy group and the optical activity of the base show that the hydroxy group in it is present in the pyran ring.

The NMR spectrum of folifine is similar to that of N-methylhaplofoline. In the latter there is a quartet at 1.73 (H-5 proton), a multiplet with a center at 2.70 (H-6, H-7, H-8 protons), a singlet at 6.45 ($N-CH_3$), a triplet at 7.46 (J = 7 Hz, protons at the γ-carbon atom of a dihydropyran ring), a triplet at 8.25 (J = 7 Hz, protons at a β-carbon atom of a dihydropyran ring), and a singlet of six protons at 8.59 (two $C-CH_3$). The intensities of the signals agree with their assignment in this way.

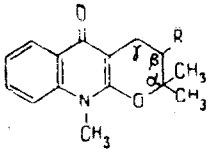


UV spectra. 1) Folifine; 2) N-methylhaplofoline.

In the region of aromatic protons, the NMR spectra of folifine (I), acetylfolifine (II), and N-methylhaplofoline (III) are almost identical. The spectrum of II has a one-proton quartet at 1.55 (H-5) and a three-proton multiplet with its center at 2.55 (H-6, 7, 8), Δ = 100 Hz. In III Δ = 97 Hz, which is characteristic for 2-alkoxy-2-quinolones but not for 4-alkoxy-2-quinolones [7, 8, 9].

The spectrum of folifine contains, in addition to the signals of the aromatic protons, five peaks with an intensity ratio of 1 : 3 : 2 : 3 : 3 at 6.14 (triplet), 6.56 (singlet), 7.12 (doublet), 8.52 (singlet), and 8.65 (singlet), due, respectively, to the fact that the alkaloid contains methine, N-methyl, methylene, and methyl protons. The absence from the spectrum of folifine of a signal from the β-methylene proton and the appearance of a one-proton triplet in the weak field shows the location of the hydroxy group on the β-carbon atom of the dihydropyran ring.

The C-methyl groups in folifine, unlike those in N-methylhaplofoline, are not equivalent, which is apparently also connected with the presence in I of a hydroxy group on the neighboring carbon atom.



R = OH I
R = OCOCH$_3$ II
R = H III

The NMR spectrum of acetylfolifine differs from the spectrum of folifine only by the signal of the protons of an acetyl group (8.00) and by the displacement of the signal of the methine proton to the weak-field region (4.85).

The phenolic base folifidine forms a hydrochloride and a picrate and gives an acetyl derivative. The properties of folifidine and its acetyl derivative agree with those for 1-methyl-4-methoxy-8-hydroxy-2-quinolone [10]. The results of a direct comparison of folifidine with the substance obtained by fusing foliosidine with alkali show that these substances are identical.

Experimental

The total alkaloids remaining after the separation of skimmianine, dubinidine, foliosine, foliosidine, and haplofoline [11] were separated into phenolic and nonphenolic fractions.

The nonphenolic fraction (23.2 g) was chromatographed on alumina (500 g). Folifine and robustinine were isolated from the ether–chloroform eluates.

Folifine. The substance had mp 225–226° C (from ethanol), $[\alpha]_D$ +14.4° (c 2.772; methanol), UV spectrum: λ_{max} 238, 316, 382 mμ (log ε 4.40, 4.00, 3.98, respectively).

Found, %: C 69.7, 69.5; H 7.14, 6.96; N 5.51, 5.66; N–CH_3 4.06; 4.07. Calculated for $C_{15}H_{17}NO_3$, %: C 69.5; H 6.61; N 5.31; N–CH_3 5.78.

Folifine hydrochloride, mp 230–231° C (from methanol).

Found, %: Cl 12.0; 12.2. Calculated for $C_{15}H_{17}NO_3 \cdot HCl$, %: Cl 12.03.

Folifine picrate, mp 189–190° C (from methanol).

Folifine nitrate, mp 148–149° C (from acetone), precipitates when chloroform solutions of the base and of nitric acid are mixed.

O-Acetylfolifine was formed when folifine (0.1 g) was heated with acetic anhydride (2 ml) in the presence of pyridine (2–3 drops) for 1 hr. After the excess of acetic anhydride had been evaporated, a substance was left with mp 154–155° C (from petroleum ether). UV spectrum: λ_{max} 238, 316, 326 mμ (log ε 4.5, 4.0, 4.0, respectively).

Oxidation of folifine. One gram of chromic anhydride, 1 ml of concentrated sulfuric acid, and 4 ml of water were added to 0.1 g of folifine and the mixture was heated. The volatile products were trapped in a 0.1% solution of 2,4-dinitrophenylhydrazine hydrochloride. A precipitate of acetone 2,4-dinitrophenylhydrazone with mp 123–124° C (from ethanol) was formed.

N-Methylhaplofoline. The substance was obtained by methylating haplofoline [2]. It crystallizes with one molecule of water in the form of colorless prisms with mp 89–90° C (from ether or water). The drying of this product at 55° C for 1 hr gave anhydrous N-methylhaplofoline with mp 121–122° C. IR spectrum: 1630, 1605, 1590, 1550, 1510 cm^{-1}; there is no absorption band for a hydroxy group.

Robustinine. The base had mp 232–233° C (from acetone) and was shown to be identical with an authentic sample by a mixed melting point and by comparison of their UV and IR spectra.

The phenolic fraction (70 g) was chromatographed on alumina (1500 g). Folifidine and haplopine were isolated from the ether–chloroform eluates.

Folifidine. This compound, with mp 226–227° C (from ethanol), was identified as 1-methyl-4-methoxy-8-hydroxy-2-quinolone by a mixed melting point, comparison of UV and IR spectra, and the production of the acetyl derivative.

Folifidine picrate, mp 218° C (from alcohol).

Folifidine hydrochloride melted with foaming at 232° C (from alcohol).

Haplopine, mp 204° C, was identified by a direct comparison with our authentic sample.

The NMR spectra were taken by M. R. Yagudaev on a JNM-4H-100/100 MHz instrument in deuteriochloroform (folifine, acetylfolifine) and in CCl_4 (N-methylhaplofoline) with tetramethylsilane as internal standard. The values are given on the τ scale.

Summary

1. Robustinine, haplopine, and the new bases folifine and folifidine have been isolated from the mother liquors from Haplophyllum foliosum VVed.

2. Folifidine has the structure 1-methyl-α,α-dimethyl-β-hydroxy-α,β-dihydropyrano-4-quinolone.

3. Folifidine has been identified as 1-methyl-4-methoxy-8-hydroxy-2-quinolone.

REFERENCES

1. G. P. Sidyakin, M. Eskairov, and S. Yu. Yunusov, ZhOKh, 30, 338, 1960.
2. I. M. Fakhrutdinova, G. P. Sidyakin, and S. Yu. Yunusov, Uzb. khim. zh., 4, 41, 1963.
3. I. M. Saitbaeva (Fakhrutdinova), G. P. Sidyakin, and S. Yu. Yunusov, KhPS [Chemistry of Natural Compounds], 443, 1966.
4. G. P. Sidyakin and S. Yu. Yunusov, DAN UzSSR, 4, 39, 1962.
5. J. R. Price and J. B. Willis, Austr. J. Chem., 12, 589, 1959.
6. N. J. McCorkindale, Tetrah., 14, 223, 1961.
7. S. Goodwin, J. N. Shoolery, and L. F. Johnson, J. Am. Chem. Soc., 81, 3065, 1959.
8. J. A. Bosson, M. Rasmussen, E. Ritchie, A. V. Robertson, and W. C. Taylor, Austr. J. Chem., 16, 480, 1963.
9. A. V. Robertson, Austr. J. Chem., 16, 451, 1963.
10. V. I. Pastukhova, G. P. Sidyakin, and S. Yu. Yunusov, KhPS [Chemistry of Natural Compounds], 27, 1965.
11. L. T. Avazmukhamedov, T. T. Shakirov, and V. A. Tel'nov, KhPS [Chemistry of Natural Compounds], 143, 1966.

27 December 1966

Institute of the Chemistry of Plant Substances,
AS UzSSR