STRUCTURE OF FUMARIDINE AND FUMARAMINE

I. A. Israilov, M. S. Yunusov, and S. Yu. Yunusov

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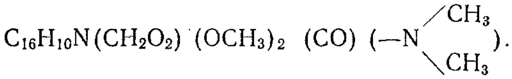
We have previously reported the isolation from Fumaria parviflora and F. vaillantii [1] of two bases, fumaridine $C_{22}H_{24}O_5N_2$ and fumaramine $C_{21}H_{20}O_5N_2$. Fumaridine (I) contains two methoxy groups and a methylenedioxy group. The UV spectrum of I has three maxima at 228, 297, and 368 nm (log ε 4.43, 4.02, and 4.35). The IR spectrum has the bands of a methylenedioxy group (935 and 1040 cm^{-1}), an aromatic ring (1500 cm^{-1}), and a carbonyl group (1705 cm^{-1}). The NMR spectrum (Fig. 1a) exhibits signals in the form of a six-proton singlet at 2.28 ppm due to a $-N(CH_3)_2$ group, two three-proton singlets at 3.93 and 4.10 ppm ($2\,OCH_3$), a two-proton singlet at 5.93 ppm (CH_2O_2), two one-proton singlets at 6.72 and 6.83 ppm (para aromatic protons), two one-proton doublets at 7.14 and 7.45 ppm (J = 8 Hz) (ortho aromatic protons), and a one-proton singlet at 6.40 ppm corresponding to an olefinic proton. On the basis of the given data and a functional analysis, fumaridine has the following expanded formula:



$C_{16}H_{10}N(CH_2O_2)(OCH_3)_2\ (CO)\ \left(-N\begin{matrix}CH_3\\ CH_3\end{matrix}\right)$.

The formation of trimethylamine in the first stage of the Hofmann degradation confirms the presence of $N(CH_3)_2$ group in fumaridine. In the UV spectrum of the 1-des-base (II) there are three maxima, at 230, 269, and 360 nm (log ε 4.56, 4.37, and 4.36). The NMR spectrum of II, taken in pyridine, lacks the signal due to the $N(CH_3)_2$ group. When II was hydrogenated according to Adams, tetrahydro-des-fumaridine (III) was obtained. The UV spectrum of III has one maximum, at 296 nm (log ε 3.91). The IR spectrum taken in chloroform has the absorption bands of an NH group at 3430 cm^{-1} and of a carbonyl group at 1685 cm^{-1}. In the mass spectrum there are strong peaks of two ions with m/e 192 and 163 and also a weak peak of an ion with m/e 164. There is practically no formation of other ions. The UV, IR, and mass spectra of III are characteristic for the protopine alkaloids [2, 3] and suggest structure III for tetrahydro-des-fumaridine on the basis of the NMR spectrum and biogenetic considerations. The scheme of the decomposition of III under the action of electron impact is given below.

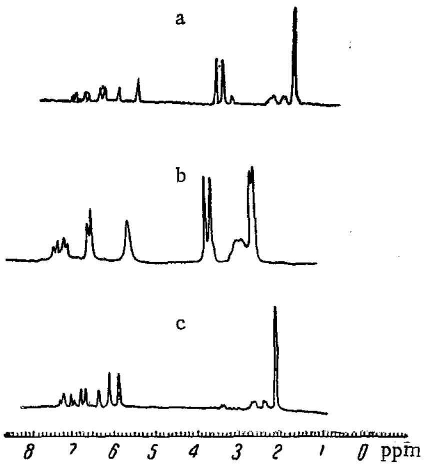
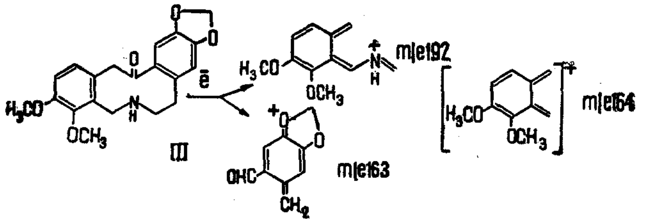


Fig. 1. NMR spectrum of: a) fumaridine (deuterochloroform); b) fumaridine (trifluoroacetic acid); c) fumaramine (deuterochloroform).



The absence of an NH group in I and II and its appearance in tetrahydro-des-fumaridine shows that

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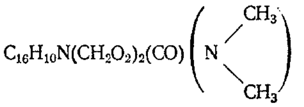
1-des-fumaridine has the structure II. The presence in fumaridine of a double bond between N and C_8 and the correctness of the location of the substituents are confirmed when the NMR spectrum of I is recorded in trifluoroacetic acid (Fig. 1b) and there is a downfield of the signals of the olefinic proton by 50 and 45.4 Hz and of the ortho aromatic protons by 25.4 and 30.4 Hz. The signals of the $N(CH_3)_2$ group (two three-proton singlets) are shifted by 77 and 82 Hz. The signals of the para aromatic protons and the protons of the methoxy and methylene dioxy groups undergo a small shift (3-12 Hz). According to the course of the Hofmann degradation, the $N(CH_3)_2$ group may be attached at C_5 or C_6. The strong downfield shift of the signals of all the methylene and methine protons when the NMR spectrum of I is taken in trifluoroacetic acid suggests that the $N(CH_3)_2$ group is located at C_5.

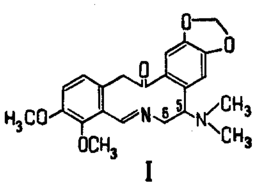
Fumaramine (IV) has two methylenedioxy groups and a $N(CH_3)_2$ group, and no methoxy or hydroxy groups. Its UV spectrum is similar to that of fumaridine and has three maxima, at 226, 292, and 365 nm (log ε 4.48, 4.08, and 4.38). IR spectrum, cm^{-1}: 935 and 1040 (CH_2O_2), 1500 (aromatic ring), and 1715 (CO). The NMR spectrum (Fig. 1c) has signals in the form of a six-proton singlet at 2.21 ppm due to a $N\begin{matrix}\diagup CH_3\\ \diagdown CH_4\end{matrix}$ group, two two-proton singlets at 5.89 and 6.11 ppm (2 OCH_2O_2), two one-proton singlets at 6.67 and 6.76 ppm (para aromatic protons), two one-proton doublets at 6.97 and 7.24 ppm (J = 8 Hz) (ortho aromatic protons), and a one-proton singlet at 6.36 ppm corresponding to an olefinic proton.

On the basis of these facts, the expanded formula of fumaridine is

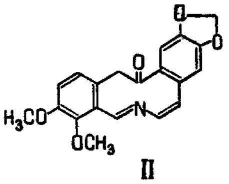


$$C_{16}H_{10}N(CH_2O_2)_2(CO)\left(N\begin{matrix}\diagup CH_3\\ \diagdown CH_3\end{matrix}\right)$$

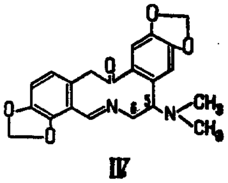
On comparing the expanded formulas of fumaridine and fumaramine and their spectra, it can be seen that the two alkaloids are based on the same heterocyclic skeleton. The difference consists in the fact that fumaramine has a methylenedioxy group in place of the two methoxy groups in fumaridine. A comparison of the NMR and mass spectra of these alkaloids shows that the position of the substituent groups in them is the same. Consequently, the structure of fumaramine is probably IV.



I



II



IV

EXPERIMENTAL

The NMR spectra were taken on a JNM-4H-100/100 MHz instrument in deuterochloroform with HMDS as internal standard (δ scale), and the mass spectra on an MKh-1303 instrument with a glass inlet device at an energy of the ionizing electrons of 40 eV and at 100-150°C.

Fumaridine (I). Yellow crystals with mp 189-190°C (chloroform–methanol). Found %: C 67.10, 67.00; H 6.22, 6.36; N 7.02, 6.98. $C_{22}H_{24}O_5N_2$. Calculated %: C 66.65; H 6.10; N 7.06. Mol. wt. 396 (by mass spectrometry).

Fumaridine Hydrochloride. The substance precipitates when ethanolic solutions of the base and HCl are mixed; mp 213-214°C (from ethanol).

Fumaridine Hydrobromide. Formed when HBr is added to an ethanolic solution of the base; mp 203-205°C (from methanol).

Fumaridine Methiodide. A mixture of 0.24 g of fumaridine and 2 ml of methyl iodide in 10 ml of methanol was heated in a boiling water bath for 3 h. The solvent was evaporated off to give 0.31 g of a product with mp 245-246°C (from methanol).

1-Des-fumaridine (II). A mixture of 0.25 g of the methiodide and 6 ml of 30% ethanolic KOH was boiled for 4 h. The solvent was evaporated off, the residue was treated with 15 ml of water, and the reaction product was extracted with chloroform. Distillation of the chloroform and treatment of the residue with methanol yielded 1-des-fumaridine with mp 224-225°C (from methanol). Found %: N 3.86, 3.78. Calculated %: N 3.98. Mol. wt. 351 (by mass spectrometry).

Tetrahydro-des-fumaridine (III). A solution of 0.2 g of II in 10 ml of conc. acetic acid was shaken in an atmosphere of hydrogen in the presence of freshly prepared platinum black for 10 h. The catalyst was separated off and washed with water. The solution was made alkaline with sodium carbonate and extracted with ether. On distillation of the ether, yellow crystals of tetrahydro-des-fumaridine deposited with mp 188-189°C (from ethanol). Mol. wt. 355 (by mass spectrometry).

Fumaramine (IV). Compound IV crystallizes from ethanol in the form of pale-yellow needles, mp 220-221°C, mol. wt. 380 (by mass spectrometry).

Fumaramine Hydrochloride. This compound is formed when alcoholic solutions of the base and HCl are mixed, mp 254-256°C (from ethanol).

Fumaramine Hydrobromide. This compound is obtained by the addition of HBr to an ethanolic solution of the base, mp 256-258°C (from ethanol).

CONCLUSIONS

The most probable structures have been proposed for fumaridine and fumaramine on the basis of their spectral characteristics and chemical transformations.

LITERATURE CITED

1. I. A. Israilov, M. S. Yunusov, and S. Yu. Yunusov, KhPS [Chemistry of Natural Compounds], 194 (1968).
2. W. Sangster and L. Stuart, Chem. Rev., 65, 102 (1965).
3. L. Dolejs, V. Hanus, and I. Slavik, Coll., 29, 2479 (1964).