UDC 547.944/945

MASS AND NMR SPECTRA OF HAPLOPHYLLIDINE AND PERFORINE AND OF THEIR DERIVATIVES

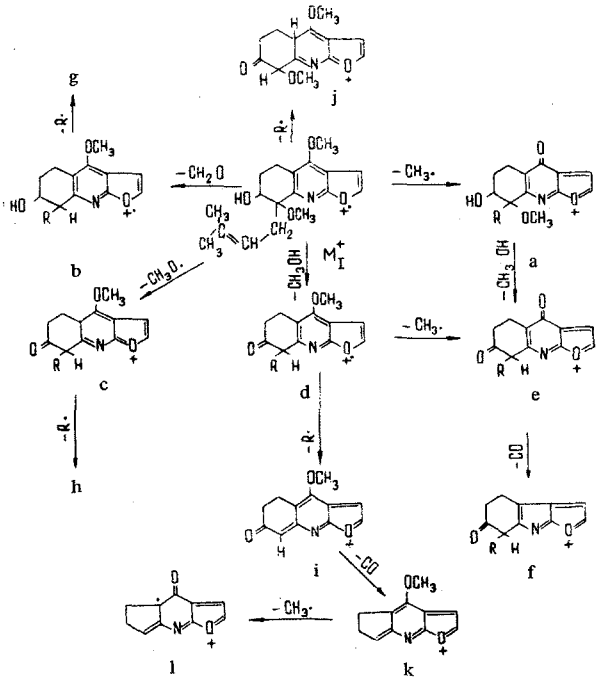
I. A. Bessonova, Z. Sh. Faizutdinova, Ya. V. Rashkes, M. R. Yagudaev, and S. Yu. Yunusov

Khimiya Prirodnykh Soedinenii, Vol. 5, No. 4, pp. 273–279, 1969

Structural formulas have been proposed previously [1] for haplophyllidine (I) and perforine (II) on the basis of an analysis of their chemical reactions and physical characteristics. In the present work we give the results of a discussion of the mass and NMR spectra of the alkaloids and the products of their conversion.

In the mass spectrum of haplophyllidine (I) the peak of the molecular ion with m/e 317 is of low intensity (Fig. 1). Still less marked are the peaks corresponding to the detachment of a $CH_3^{\cdot}$ radical from 4—OCH_3 and of a hydroxyl from C_7 and to the loss of water.

The main routes for the fragmentation of I, which are shown in Scheme 1 (in which R represents the side chain), are due to the presence of substituents at C_8. Because of the detachment of the substituents and subsequent rearrangements, stable oxonium ions are formed [2].



Scheme 1

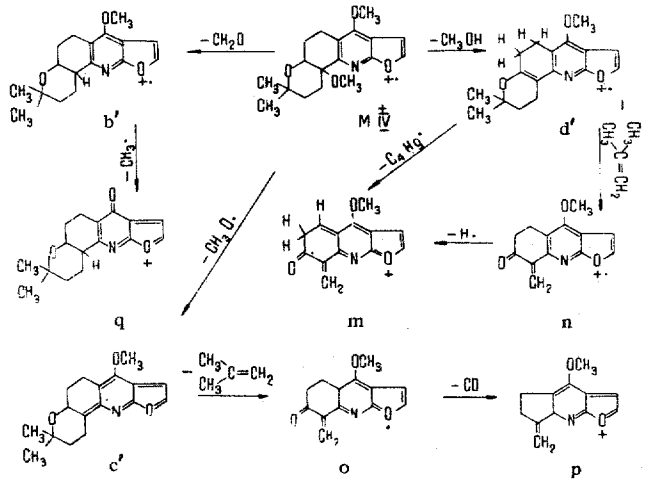
The ions b, c, and d are formed with the participation of the methoxyl group at C_8 by the splitting out of formaldehyde (M — 30), a methoxyl radical (M — 31), or a molecule of methanol (M — 32). The maximum peak in the spectrum of I is the ion e with m/e 270, which is obtained from the ion d by the splitting out of $CH_3^{\cdot}$ from the methoxyl group present in the aromatic ring. The splitting out of CO from the ion e forms the ion f with m/e 242.

The elimination of an isopentenyl radical from M_I^+ leads to a strong peak of the ion j (M — 69). The ions b, c, and d may also lose a C_5H_9 radical, giving the new series of ions g, h, and i.

The successive splitting out from the ion i of a molecule of CO and then a methyl radical from the 4—OCH_3 group gives rise to the ions k and l with m/e 188 and 173.

The fragments m and n with m/e 228 and 229 are formed from the isomeric cyclic form of molecular ion M_{IV}^+ via the intermediate stage d' (Scheme 2).

Mass spectrum of anhydroperforine (IV) (cf. Fig. 1). Anhydroperorine (IV) is a cyclic isomer of I, which is reflected appropriately in the mass spectrum of IV. For example, the absence of the peak of an ion l (M — 69) shows that the fragmentation of IV takes place mainly via the cyclic form of the molecular ion M_{IV}^+. This assumption is confirmed by the fact that the maximum peak in the spectrum of IV is that of the ion n, and the ion m also gives a fairly intense peak (see Scheme 2).



Scheme 2

The ions b', c', and d' in the mass spectrum of IV probably possess a cyclic structure. The appearance of the ions g, h, i, and k (see Scheme 1) apparently precedes the transition of M^+_{IV} into the open form M^+_I.

The formation of the new ions q, o, and p can be explained in the following way. The splitting out of the olefin C_4H_8 from the ion c' gives the ion o (M − 87) which then, by losing a molecule of CO, is converted into the ion P (M − − 115). On losing $CH_3^{\cdot}$, the ion b' gives the ion q.

Mass spectrum of the product V (see Fig. 1). The molecular ion of substance V has the structure of the ion d', and therefore the peaks of the ions n and o in the spectrum of V have a greater intensity. The formation of the ion r with m/e 201 can be explained by the detachment of a molecule of CO from the ion n.

The mass spectrum of acetylhaplophyllidine (III) (Fig. 1) has a very low intensity of the peak of the molecular ion.

The ion s with m/e 327 is obtained by the splitting off of a molecule of methanol from the molecular ion; subsequently with the detachment of a methyl radical from the 4—OCH_3 group the ion t with m/e 312 is formed. The loss by the molecular ion of the side chain in the form of the $C_5H_9^{\cdot}$ radical gives the ion u (M − 69) with m/e 290. The ion v is apparently formed by the elimination of CH_3COOH from the ion (M_{III} − 31), which leads to the aromatization of the system.

The decomposition of the ion formed by the elimination of ketene from M^+_{III} gives fragments of the initial alcohol (the ions e, j, k, and l).

The detachment from the ion l of the methyl radical from the 4—OCH_3 group gives rise to an ion with m/e 233.

The formation of a series of common ions in the decomposition of I, III, IV, and V shows that under the conditions of mass spectrometry the ions may pass from the cyclic state into the open state and conversely.

In the NMR spectra (τ scale) of I and II there are only two one-proton doublets from the α- and β-protons of the furan ring, which form an AB system, in the weak-field region. The doublet at 2.53 τ (J = Hz) corresponds to the α-proton and that at 3.13–3.15 τ (J = Hz) to the β-proton [3]. These signals are also observed in the spectra of anhydroperforine (IV) and of product V (Figs. 2 and 3).

The conversion of I, II, IV, and V into the iso compound VI causes a shift of the signal of the α-proton into the strong-field region because of the weakening of the aromaticity of ring B [3] and the descreening of the β-proton of the 4—CO group—a shift of the resonance signal of the β-proton into the weak-field region. Apparently, the influence of a CO group on the β-proton is greater than the effect of the diamagnetic anisotropy of ring B in the case of the 5,6,7,8-tetrahydroquinoline alkaloids as compared with the furoquinoline derivatives.

The difference in the chemical shifts between the α- and β-protons in I–IV, $\Delta\tau$ = 60–63 Hz, and in IV, $\Delta\tau$ = = 26 Hz, almost coincides with the corresponding values for the furoquinoline alkaloids [3].

The absence of signals from the other aromatic protons in the spectra of these compounds shows that ring A is hydrogenated and ring B is completely substituted.

The spectrum of I has a one-proton signal in the 4.72 region (J = 7 Hz), corresponding to an olefinic proton. This signal is split into a triplet because of spin-spin coupling with the protons of the neighboring methylene group. The components of the triplet are broadened because of allyl interaction with the protons of the gem dimethyl group. The split-

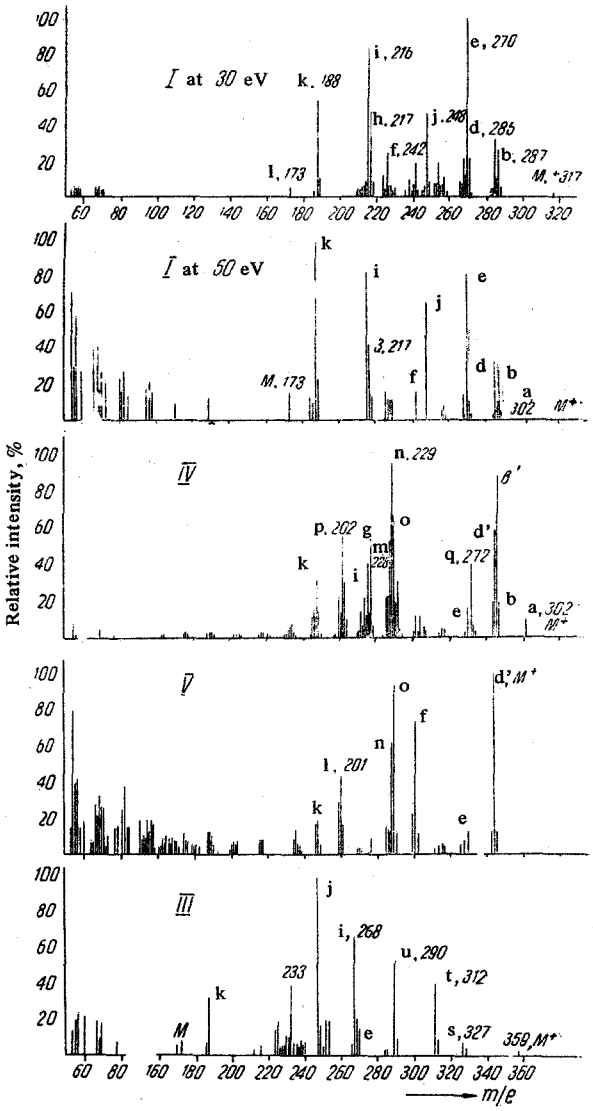


Fig. 1. Mass spectra of substances I, III, IV, and V.

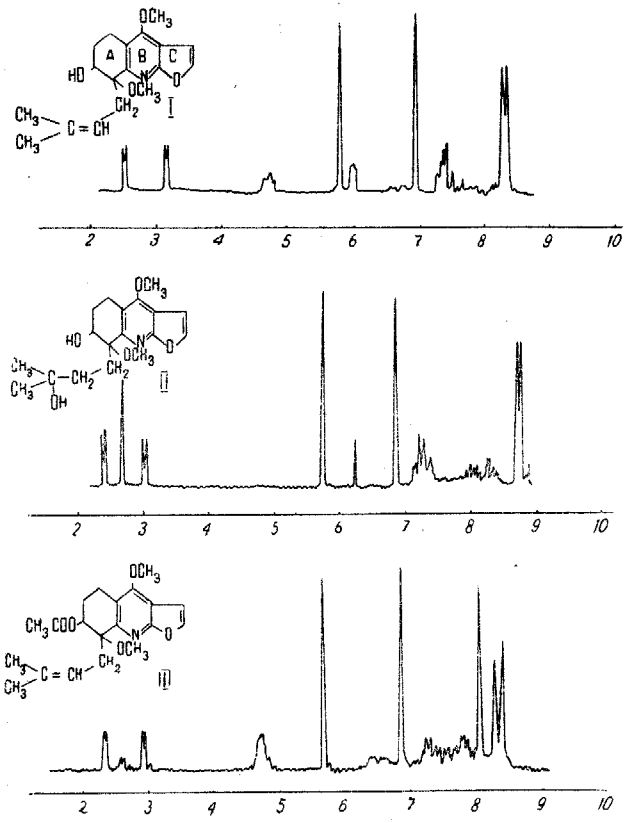


Fig. 2. NMR spectra of substances **I–III.**

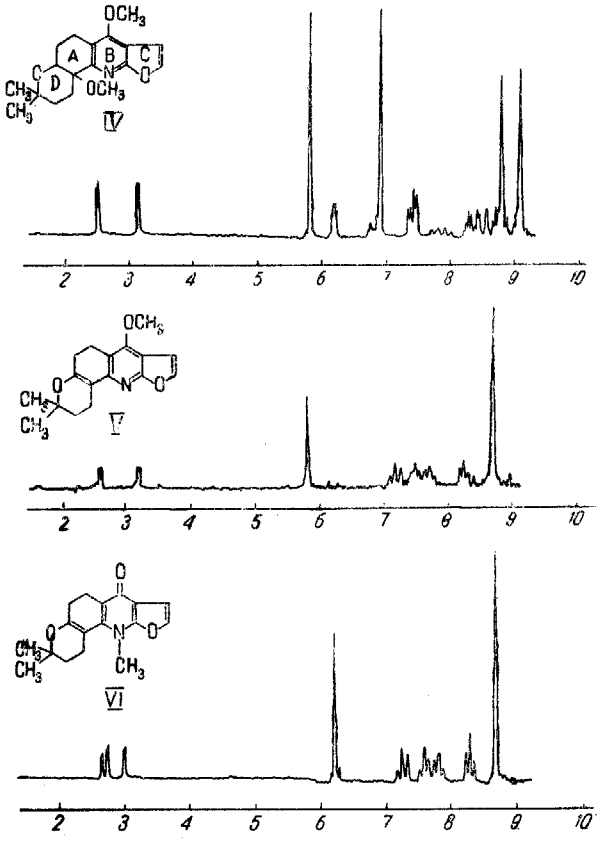


Fig. 3. NMR spectra of anhydroperforine (IV), product V, and the iso compound VI.

ting of the signal from the methyl groups of the side chain in I is not the result of spin-spin coupling (in acetylhaplophyllidine $\Delta\tau$ = 0.12 ppm and in the base itself it is 0.06 ppm), but of their nonequivalence. The broadening of each line is due to allyl interaction with the olefinic protons.

The spectra of I, II, and III each have a one-proton multiplet in the 5.85–6.24 region corresponding to the proton of the H—C—O group. In acetylhaplophyllidine (III) this signal is displaced in the weak-field direction by 1.25 ppm and is superposed on the signal of the olefinic proton. Consequently, the NMR spectrum of III lacks a signal at 6.00 but has a two-proton multiplet at 4.75 ppm.

In the spectrum of II the H—C—O— signal overlaps the singlet of the OCH_3 group, and in the spectrum of I there is a multiplet. However, a quartet is obtained in the spectrum of I taken at 50° C and also in the spectrum of IV, i.e., under conditions in which the interaction of the proton of the hydroxyl group with H—C—O is either weakened by heating or is completely absent. The low values of the spin-spin coupling constants (J = 2.5 and 3.5 Hz) of the quartet may be explained by two factors: in the first place, the equatorial nature of this proton and, in the second place, the presence of only two vicinal protons exerting axial-equatorial (J = 3.5 Hz) and diequatorial (J = 2.5 Hz) interaction [4].

The methoxyl group in position 4 of each of the compounds appears in the 5.72–5.85 ppm region and that at position 8 at 6.85–6.95 ppm in the form of sharp singlets.

The presence in the side chain of perforine (II) of a dimethyl carbinol group in place of the isopropylidene group in I agrees with the position of the two three-proton singlets in the spectrum of II at 8.75 and 8.80 ppm [5].

The large difference between the values of the chemical shifts of the methyl groups in anhydroperforine ($\Delta\tau$ = = 0.29 ppm) shows that in ring D one of them has the equatorial and the other the axial configuration relative to the H—C—O and the 8—OCH_3 groups.

The NMR spectra of V and VI lack the signals of the protons of the H—C—O and 8—OCH_3 groups. Correspondingly, the two methyl groups become equivalent and appear in the form of a six-proton singlet.

In contrast to compounds I–IV, in the spectra of which the signals from the methylene protons give complex multiplets, in the NMR spectra of V and VI there are four two-proton triplets in the 7.10–8.40 ppm region due to the interaction of the $-CH_2-CH_2$ groups in rings A and D. The triplet in the strong field region at 8.27 ppm in the spectrum of V corresponds to the protons of a β-methylene group (J = 6.5 Hz) and that at 7.52 ppm to a γ-methylene group (J = 6.5 Hz) of a dihydropyran ring. The protons of the methylene and gem dimethyl groups of the dihydropyran ring in the NMR spectrum of N-methylhaplofoline [6] have a similar pattern. Two other triplets (J = 8 Hz) correspond to the methylene protons of ring A, the triplet at 7.19 ppm to the benzyl protons at C-5, and the triplet at 7.5 ppm to the protons of the methylene group at C-6.

To determine the signals of the hydroxyl groups in I and II, their NMR spectra were taken with heating to 50° C. Under these conditions in the spectrum of II a signal appears in the 7.0 ppm region which was shifted from the methylene region at 7.30 ppm, and in the spectrum of I an OH signal is found in the strong field at 8.48 ppm.

Experimental

The mass spectra were taken on a MKh-1303 mass spectrometer under the following conditions: stabilized temperature of the inner tube of the inlet 150–180° C; ionizing voltage 30–50 V, cathode emission current between 1.0 and 1.5 mA.

The NMR spectra were taken on a JNM-4H-100/100 MHz instrument with HMDS as internal standard.

Solvents: CCl_4 (II–V) and $CDCl_3$ (I, VI).

Conclusions

The mass and NMR spectra of haplophyllidine, perforine, and their derivatives have been studied. The influence of the open and cyclic forms of the molecular ion on the nature of the fragmentation has been discussed. The main routes of fragmentation of the compounds considered are due to the presence of substituents at C_8 and C_4.

REFERENCES

1. Z. Sh. Faizutdinova, I. A. Bessonova, and S. Yu. Yunusov, KhPS [Chemistry of Natural Compounds], **3**, 356, 1967; vol. 4, 360, 1968.

2. G. Budzikiewicz, C. Djerassi, and D. Williams, Interpretation of Mass Spectra of Organic Compounds [Russian translation], Moscow, 1966; J. Beynon, Mass Spectrometry and Its Applications to Organic Chemistry [Russian translation], Moscow, 1964; Canad. J. Chem., **43**, 5216, 1965.

3. A. V. Robertson, Austr. J. Chem., 16, 451, 1963.

4. N. Bhacca and D. Williams, Applications of NMR Spectroscopy in Organic Chemistry [Russian translation], Moscow, p. 103, 1966.

5. O. E. Edwards and N. F. Elmore, Canad. J. Chem., 40, 256, 1962.

6. Z. Sh. Faizutdinova, I. A. Bessonova, and S. Yu. Yunusov, KhPS [Chemistry of Natural Compounds], **3**, 257, 1967.

22 March 1968

Institute of the Chemistry of Plant Substances AS UzSSR