STRUCTURE AND SYNTHESIS OF LEONTIDINE

S. Iskandarov, R. A. Shaimardanov, and S. Yu. Yunusov

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The epigeal part of Leontice Albertii is rich in alkaloids the qualitative and quantitative composition of which depends on the growth site [1, 2]. These alkaloids belong to the pyridine, cytisine, biphenyl, matrine, and leontidine groups. On separating the combined alkaloids of the epigeal part collected in the flowering stage in the environs of the village of Sidzhak, Tashkent oblast, we isolated leontidine, which has been found previously in the epigeal part and tubers of Leontice Ewersmannii [3-5]. Some reactions of leontidine have been studied, but its structure has not been determined [6, 7].

The presence in the IR spectrum of leontidine of a trans band, especially absorption in the fingerprint region, shows that it is similar to the alkaloid thermopsine. The NMR spectrum shows the signals of three protons of α-pyridone (β_H quartet at 7.04 ppm, γ_H doublet at 6.12 ppm, α_H doublet at 5.75 ppm) and the multiplet of the proton of a methylene group attached to nitrogen, forming part of the α-pyridone system ($\delta = 4.03$ ppm).

The mass spectra of leontidine and its hydrogenation products (Fig. 1) have a number of features, and also peaks, characteristic for the quinolizidine alkaloids [8-10].

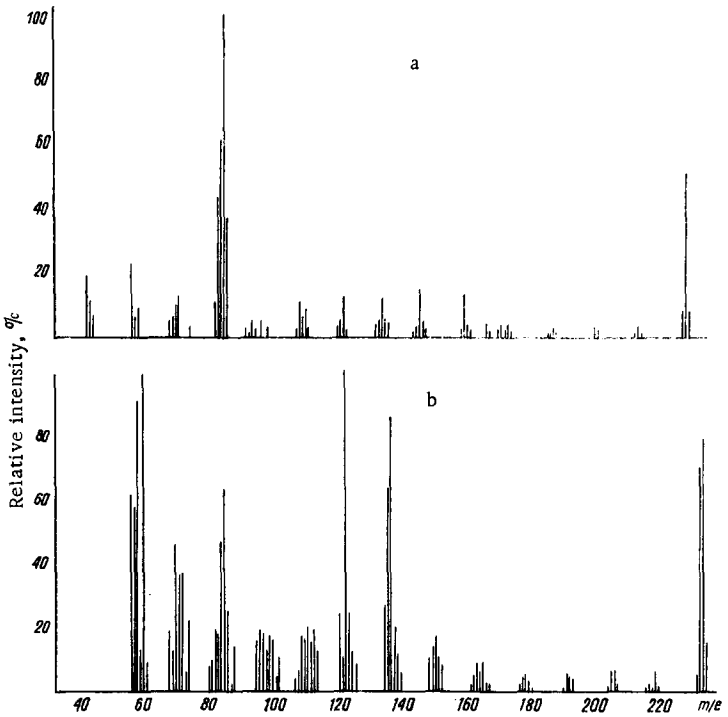

Fig. 1. Mass spectra of leontidine (a) and tetrahydroleontidine (b).

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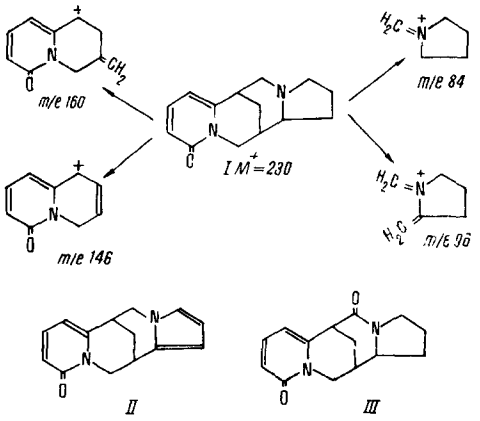
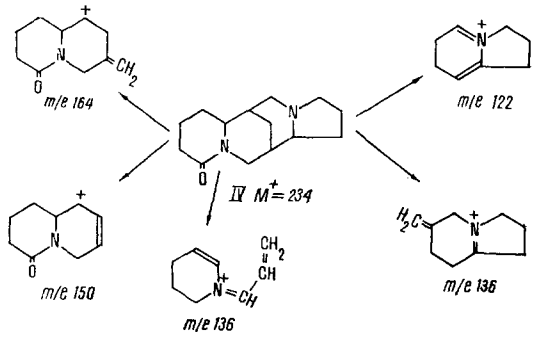
In addition to the peak of the molecular ion (M^+ 230), confirming the composition $C_{14}H_{18}N_2O$, the spectrum of leontidine has strong peaks of ions with m/e 160 and 146, which are characteristic of quinolizidine alkaloids containing a 1,3-condensed tetrahydroquinolizone fragment connected with at least one methylene group [11].

Peaks of ions with m/e 96 and 84 show the presence of a saturated ortho-substituted six- or five-membered heterocycle, but the high intensity of the latter is in favor of the presence of a terminal pyrrolidine ring. Taking into account the tetracyclic structure of leontidine, we may ascribe to it structure (I), which agrees with the production of tetradehydroleontidine (II) on dehydrogenation over palladium and of oxoleontidine (III) on oxidation with potassium permanganate.

A comparison of the spectra of tetrahydroleontidine (IV) and of [3,3-D_2]tetrahydroleontidine (IV) confirmed the conclusion concerning the formation of the ions with m/e 160 and 146 from rings AB in the decomposition of (I), since in (IV) these peaks are displaced by 4, and in (V) by 6, atomic mass units.



The high intensities of the peaks of the ions with m/e 136 and 122 in (IV) are explained by the disappearance of the conjugated system of double bonds favoring the localization of the positive charge in rings AB. Consequently, in (IV) and (V) fragmentation accompanied by the cleavage of ring C becomes favored. In the mass spectrum of (V) there are also partial shifts of the peaks mentioned, which shows that they arise from rings AB.



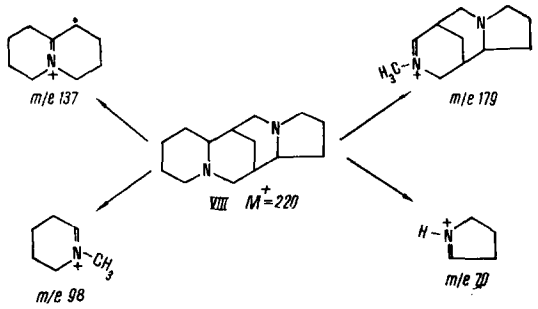
The spectrum of hexahydrodes-N-methylleontidine (VII),* obtained by the catalytic hydrogenation of des-N-methylleontidine (VI) is characterized by the presence of the maximum peak of an ion with m/e 58 and by the low intensities of the peaks of the ions formed from the indolizidine part of the molecule. This is due to the cleavage of the C_{11}–N_{15} bond in (I) (stage of Hofmann degradation).

In the spectrum of leontidane (VIII), the peaks of the molecular ion and of the fragment arising from the elimination of a hydrocarbon particle in the form of an allyl radical from ring A have the highest intensities. This is confirmed by a comparison with the spectrum of [2,2-D_2]leontidane (IX), where the peak of the ion with m/e 179 is also shifted and has the lowest intensity in the spectra of (I) and (IV). A comparison of the spectra of (VIII) and (IX) shows that the low-molecular-weight fragments are formed from rings AB and CD equally, which is explained by the closeness in space of the two linkages. In contrast to

* As in Russian original – Publisher.

the preceding compounds, the spectrum of the saturated product has the peaks of ions with m/e 137 and 136, the intensity of the first being greater than that of the second. This is due to the fact that the peak with m/e 137 arises mainly from the AB rings and the ion with m/e 136 from the CD rings.

Characteristic for the saturated product is the formation of a pair of peaks with ions having m/e 98 and 96, arising from different parts of the molecule – the first from ring A and the second from D. The ion with m/e 84 is formed from rings A and D, since it is shifted by two amu in the spectrum of (IX). The spectra of (VIII) and (IX) also show peaks of medium intensity with m/e 70 corresponding to the pyrrolidinium ion.



Thus, all the results obtained from an analysis of the mass spectra are in harmony with the proposed structure and permit a conclusion concerning the characteristic peaks of alkaloids of the leontidine group.

To confirm the structure given, the synthesis of leontidine has been performed. The starting material was cytisine, which was chlorinated with calcium hypochlorite; the resulting N-chlorocytisine was converted by treatment with ethanolic caustic potash into dehydrocytisine which, under the action of allylmagnesium bromide, gave 11-allylcytisine [12]. For the formation of ring D, the latter was heated with hydriodic acid in the presence of ammonium iodide in phenol. The product obtained and leontidine had the same sign of rotation, and they were shown to be identical by mixed melting points of the perchlorates and methiodides and by a comparison of their IR spectra.

Thus, leontidine is the parent of a new group of alkaloids including tetrahydroquinolizone and indolizidine fragments.

EXPERIMENTAL

The chloroform extraction of 5 kg of the epigeal part of the plant yielded 92 g of combined alkaloids. The mixture was dissolved in 5% sulfuric acid and, after being made alkaline with ammonia, it was separated into ethereal (73 g) and chloroformic (18 g) fractions. N-Methylcytisine (1.4 g) was isolated from the latter in the form of the hydrochloride. Then a perchlorate was obtained from the mother solution, and a mixture of acetone and ethyl acetate deposited a crystalline perchlorate giving on TLC [silica gel–gypsum (9 : 1)] in the chloroform–methanol (4 : 1) system two spots with R_f 0.32 and 0.61. When a hot aqueous solution of this mixture of perchlorates was cooled, acicular crystals with mp 278°C, R_f 0.3, deposited. The base from the perchlorate was crystallized from petroleum ether, and had mp 119°C, $[\alpha]_D$ −186.5° (c 1.22; methanol), and its IR spectrum was identical with that of leontidine.

Des-N-methylleontidine (VI). A solution of 2 g of the methiodide of (I) in 15 ml of ethanol was heated with 20 ml of 40% caustic potash solution for 2 h. The residue after evaporation was dissolved in water and extracted with ether. Yield 0.43 g, R_f 0.25; perchlorate with mp 265°C (ethanol).

Hexahydrodes-N-methylleontidine (VII). A solution of 0.4 g of (VI) in 20 ml of glacial acetic acid was shaken in an atmosphere of hydrogen in the presence of 0.35 g of PtO_2 for 3 h. The residue after the elimination of the catalyst and the solvent was dissolved in water, and the solution was made alkaline with ammonia and extracted with ether. After the solvent had been distilled off, the base was crystallized; mp 105°C, R_f 0.90.

Tetrahydroleontidine and leontidane were obtained as described in the literature [5, 6].

[3,3-D_2]Tetrahydroleontidine (V) was obtained by heating 0.01 g of (II) and 0.02 g of K_2CO_3 in 2 ml of D_2O in a sealed tube for 3 days.

[2,2-D_2]Leontidane (IX). A solution of 0.05 g of (II) in 50 ml of absolute ether was treated with 0.05 g of $LiAlD_4$, and the mixture was heated for 4 h, after which 10 ml of water was added and the (IX) was extracted with ether.

N-Chlorocytisine (X). By the method of Bohlmann et al. [12], 6 g of cytisine yielded 3.6 g of (X) in the form of a colorless oil with R_f 0.83.

Dehydrocytisine (XI). From 3.6 g of (X), 3.66 g of the dihydrochloride of (XI) was obtained with R_f 0.81.

Allylcytisine (XII). Four molar equivalents of an ethereal solution of allylmagnesium bromide were added to 3.6 g of the dihydrochloride of (XI) in absolute ether, and the mixture was stirred at room temperature for 3 h. Then it was decomposed with water and extracted with ether and methylene chloride.

Ethereal fraction: R_f 0.11, 0.36, 0.68, 0.81, 0.93. Methylene chloride fraction: R_f 0.11, 0.36, 0.68, 0.78, 0.81, 0.93.

The methylene chloride fraction (1.83 g) was separated preparatively on plates of silica gel, giving 0.32 g of (XII) with R_f 0.68 and traces of substances with R_f 0.80 and 0.90.

Leontidine (I). A mixture of 0.32 g of (XII) and 0.5 g of phenol was heated in the water bath until a homogeneous melt had been formed. Then 5 ml of freshly distilled hydriodic acid and 1.2 g of ammonium iodide were added. The mixture was heated to 150°C for 35 min. Then the temperature was raised to 225-230°C for 10 min. After cooling, the solid residue was dissolved in a small amount of 5% hydrochloric acid, and the solution was washed with ether until it had become decolorized. Then it was made alkaline with 20% caustic soda solution and extracted with ether and chloroform:

Ethereal fraction: R_f 0.09-0.10, 0.27, 0.41, 0.75, 0.87.

Chloroform fraction: R_f 0.09 (traces),0.32, 0.75 (traces).

The chloroform fraction (0.045 g) was separated preparatively on silica gel plates, and 0.03 g of (I) with R_f 0.32 was isolated.

SUMMARY

1. Leontidine has been isolated from the chloroformic fraction of the combined alkaloids of the epigeal part of Leontice Albertii.

2. The structure of leontidine has been established on the basis of chemical reactions and a study of mass spectra, and it has been confirmed by synthesis.

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