PEGAMINE: A NEW ALKALOID FROM PEGANUM HARMALA

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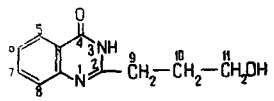
Continuing a study of the alkaloids of Peganum harmala [1], we have investigated the plant in the early stage of its vegetation (collected from March 30 to April 5, 1968, in the Samarkand region by I. Sharakhimov).

The total alkaloid content was 2.17%. When the alkaloids were separated with respect to their solubilities, via their salts, and with respect to their basicities, the following known bases were isolated (%, on the total): peganine 43.5, vasicinone 1.2, harmine 0.07, deoxypeganine 2.1, and deoxyvasicinone 5.4, together with 0.005% of a new base with mp 160–161° C which we have called "pegamine." Its UV spectrum [$\lambda_{max}^{ethanol}$ 226, 266, 306, and 318 mμ (log ε 4.27, 3.74, 3.35, and 3.21)] is similar to that of the quinazolinone alkaloids [2]. The quinazolinone structure of pegamine is also shown by its mass spectrum. In the region of low mass numbers it resembles the mass spectrum of vasicinone (119, 92, 90, 77, and 76 m/e), but the molecular ion in pegamine is shifted by two units in the high-mass direction compared with vasicinone. This made it possible for us to assume that the five-membered ring is open in the present compound. A 3H-quinazolin-4-one structure for the base is also shown by the absorption bands in the IR spectrum at 1618 and 1695 cm^{-1} [2–4].

The IR spectrum of pegamine has absorption bands for active hydrogen in the 2700–3700-cm^{-1} region. The presence of peaks of the ions M - 17, M - 18, and M - 19 shows the presence of an alcoholic hydroxyl in the side chain. This is confirmed by the formation of an acetyl derivative of pegamine under the action of acetic anhydride. The IR spectrum of acetylpegamine contains a series of absorption bands in the 2700–3200 cm^{-1} region; in the carbonyl-group region there is an additional absorption band at 1740 cm^{-1}, and in the NMR spectrum there is a three-proton singlet at 1.72 δ.

In the 7.5–8.3-δ region, the NMR spectrum of pegamine has the signals of four aromatic protons. Consequently, the benzene ring of the quinazoline part is unsubstituted. A one-proton doublet in the very weak field at 8.15 δ (J = = 7 Hz) relates to a proton in the peri position with respect to the carbonyl group, and the triplet with the center at 7.47 δ relates to the C_7 proton [2, 3].

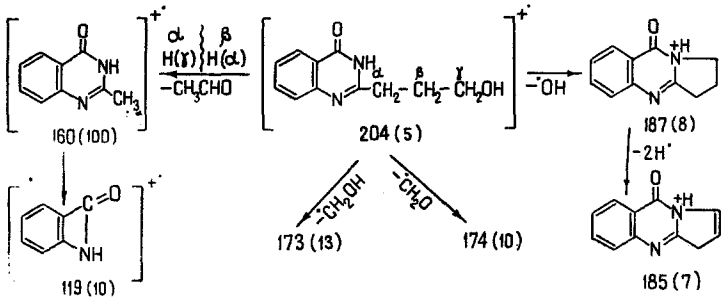
To determine the position of the substituent, we recorded the mass spectrum of the product of the deuteration of pegamine in CD_3OD. The M^+ peak was shifted by two mass units, which shows the absence of substituents in position 3. Thus, the only position for the addition of the side chain, which is a hydroxypropyl radical, is position 2. The structure of the hydroxypropyl substituent was established on the basis of the NMR and mass spectra. The absence of characteristic peaks for the protons of CH_3 and CH_3—CH_2 groups, and also of the peaks of M - 15 and M - 29 ions, enables all the possible variants to be excluded except one, i.e., a straight chain with a primary alcohol group. Hence, pegamine must have the structure I.



I

The NMR spectrum of I has the signals of the protons of three methylene groups (triplet at δ3, multiplet at 2.14, triplet at 4.2) which we have assigned to the 9-, 10-, and 11-methylene groups, respectively.

In the mass spectrum of pegamine the maximum peak is that of the ion with m/e 160, the formation of which from M^+ is confirmed by a metastable transition; the peaks of ions with m/e 187, 185, 173, 174, and 119 are probably formed by the following fragmentation scheme:



EXPERIMENTAL

The NMR spectrum was taken on a JNM-4H-100/100 MHz instrument in CF_3COOH, and the mass spectra on a MKh-1303 instrument fitted with a system for the direct introduction of the substance into the ion source at 100° C with an ionizing voltage of 40 V.

Isolation of the alkaloids. The comminuted air-dried epigeal part (85 kg) was moistened with 8% ammonia solution and exhaustively extracted with chloroform. The chloroform extracts were treated with 10% H_2SO_4, and the acid extracts were made alkaline with gaseous ammonia. This gave 1100 g of precipitate (fraction A). The aqueous alkaline mother liquor was shaken with ether and then with chloroform. This gave 420 g and 324 g mixtures of bases (fractions B and C, respectively).

Fraction A (400 g) was triturated with acetone, which gave 280 g of peganine. The residue, after the elimination of the acetone, was dissolved in chloroform, and the chloroform solution was treated successively with 5% acetic acid, 0.2 M citric acid, and 10% H_2SO_4. The acid solutions were made alkaline with ammonia and exhaustively extracted with ether and chloroform (fractions 1–3). Fraction 2, on treatment with an ethanol acetone mixture, yielded 1.45 g of vasicinone.

Fraction B was recrystallized from 1.5 *l* of acetone. This gave 245 g of an insoluble fraction (fraction D) and 175 g of an acetone-soluble fraction (fraction E). On separation according to the solubilities of the hydrochlorides in ethanol and methanol, fraction D yielded 91 g of peganine and 14 g of vasicinone, and fraction E yielded 111 g of hydrochloride from which 30 g of deoxyvasicinone, 8 g of deoxypeganine, and 14.7 g of peganine were obtained. The mother liquors from fractions D and E were combined, dissolved in 500 ml of 0.6 N H_2SO_4, and made alkaline with 500 ml of 0.6 N NaOH in 50-ml portions. The bases were extracted with chloroform. Fraction 1 yielded 44 g of deoxyvasicinone, and fractions 2 and 3, after treatment with ethanol, gave 2.36 g of vasicinone. Fraction 5, on recrystallization from ethanol, gave 0.38 g of peganine, and the alcoholic mother liquor, when treated with nitric acid, yielded 5.13 g of deoxypeganine nitrate. The mother liquor after the production of the nitrate was converted into a base, and 0.21 g of harmine, sparingly soluble in ether, deposited. From fractions 6–10, using differential solubilities in ethanol and conversion into nitrates, 7 g of deoxypeganine and 4.3 g of peganine were obtained.

The mother liquor from the hydrochlorides of fraction E yielded a mixture of bases which were separated according to their basicities into nine fractions as described above. The yield from the fractions was as follows: 1 and 2) 22.75 g of deoxyvasicinone, 3) 0.65 g of vasicinone, 4) 1 g of vasicinone, 6–8) 9 g of deoxypeganine, and 5) 1.11 g of harmine. The fraction 9 was dissolved in ethanol and the solution was treated with perchloric acid. After a day, 0.22 g of a perchlorate with mp 192–193° C was separated off. The base obtained from the perchlorate, with mp 160–161° C, proved to be pegamine.

Acetylpegamine. A mixture of 50 mg of the base, 1.5 ml of acetic anhydride, and 0.5 ml of pyridine was shaken and left for a day. The precipitate was filtered off with suction and washed with ethanol. Yield 50 mg, mp 173–174° C.

Saponification of acetylpegamine. A mixture of 50 mg of the substance and 10 ml of 15% methanolic alkali was heated for 3 hr. After cooling, the reaction mixture was treated with ether. The solvent was evaporated off and the residue was recrystallized from ethanol–acetone. The substance obtained gave no depression of the melting point (160–161° C) with pegamine.

CONCLUSIONS

The structure of pegamine has been established from its UV, IR, NMR, and mass spectra.

2. A fragmentation scheme for pegamine on mass spectrometry has been proposed.

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