ALKALOIDS OF *Papaver arenarium*

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Continuing the separation of the total alkaloids of the plant *Papaver arenarium* M.B., collected in the region of Lake Sevan in the flowering period, we have isolated macrostomine, glycomarine, cheilanthifoline, sevanine, arenine, and two isomeric macrostomine N-oxides not previously described in the literature.

Continuing the separation of the combined alkaloids of *Papaver arenarium* M.B., [1, 2], collected in the flowering period in the region of Lake Sevan, from the nonphenolic fraction of the combined alkaloids we have isolated macrostomine, making up about 90% of the total amount of alkaloids, glycomarine [3], and bases (I) and (II), and from the phenolic fraction cheilanthifoline [4], arenine [5], and sevanine [6, 7]. All the alkaloids isolated were identified by comparison with authentic samples.

The amorphous base (I), $[\alpha]_D$ +35° (c 0.8; methanol) had an IR spectrum with absorption bands at 930 and 1040 cm^{-1} (methylenedioxy group), and 1520, 1570, and 1620 cm^{-1} (aromatic ring). Its PMR signal showed signals in the form of three-protons singlets at 2.79 ppm ($N-CH_3$), 3.86 and 4.06 ppm (2 OCH_3), two-proton singlets at 4.45 ppm (CH_2) and 5.82 ppm (CH_2O_2), and a one-proton triplet at 5.54 ppm. In the aromatic region of the spectrum there were signals from six protons at 6.65, 6.70, (2H), 7.33, 8.00, and 8.33 ppm. Signals from six protons were observed at 2.25-3.70 ppm. The mass spectrum of the base contained the peaks of ions with m/z 422 (M^+ 45%), 406, 405, 404, 363 (100%), 348, 84, 60, 43. UV spectrum, λ_{max}, nm: 248, 292, 320, 335 (log ε 4.49, 3.78, 3.57, 3.57).

The facts given show that the base belongs to the benzylisoquinoline alkaloids of the macrostomine type [6, 7]. The difference of 16 mass units in the molecular weight as compared with macrostomine permitted the assumption that the base was its N-oxide. Reduction of the base with zinc and sulfuric acid led to a product identical with macrostomine. Thus, base (I) is a macrostomine N-oxide.

Base (II) had mp 141-142°C (acetone), $[\alpha]_D$ +68° (c 0.8; methanol), and its UV spectrum had four absorption maxima at 243, 290, 320, and 333 nm (log ε 4.52, 3.43, 3.69, 3.48), which are characteristic for the benzylisoquinoline alkaloids [6, 7]. Its IR spectrum had absorption bands at 930 and 1045 cm^{-1} (methylenedioxy group) and 1525, 1570, and 1620 cm^{-1} (aromatic ring). The PMR spectrum of the base showed three-proton singlets of an N-methyl group at 3.02 ppm and of two methoxy groups at 3.85 and 3.97 ppm, two-proton singlets of a methylenedioxy group at 5.81 ppm and of a methylene group at 4.37 ppm, and a one-proton multiplet at 4.76 ppm. Methylene protons were revealed in the spectrum in the 2.10-3.90 ppm region. Aromatic protons appeared in the form of multiplets at 6.66-7.22 ppm and a broadened one-proton singlet at 8.63 ppm. When the spectrum was recorded in deuteromethane, the signals of the aromatic protons appeared in the form of one-proton singlets at 8.65, 7.47, and 7.37 ppm and a three-proton multiplet at 6.61 ppm. The mass spectrum of base (II) was identical with that of base (I). When base (II) was reduced with zinc and sulfuric acid, macrostomine was obtained. The oxidation of macrostomine with hydrogen peroxide gave two products that were identical with bases (I) and (II). Consequently, base (II) is a macrostomine N-oxide isomeric with (I). The presence of a strong peak of the molecular ion in the mass spectrum of each of the N-oxides, which is not characteristic for N-oxides shows the possibility of their isomerization during mass spectrometry. In order to investigate this in more detail, the macrostomine N-oxides (I) and (II) were subjected to vacuum pyrolysis at 200°C, and in both cases a good yield was obtained of one and the same product the PMR spectrum of which had the signals of methylene protons at 1.90-3.25 ppm, of an N-methyl group at 2.66 ppm, of two

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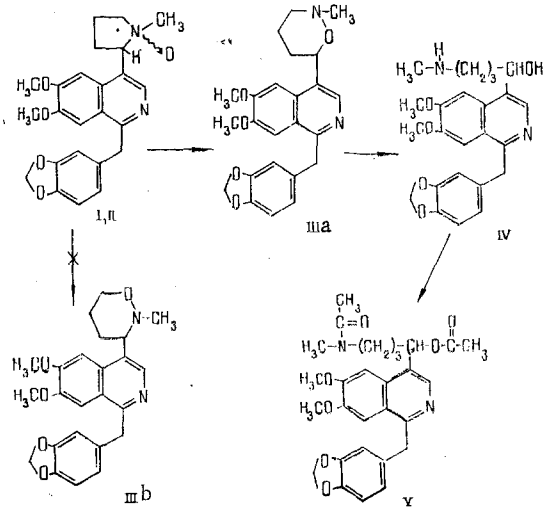
methoxy groups at 3.83 and 3.98 ppm, of a methylenedioxy group at 5.76 ppm, of a two-proton singlet from an isolated methylene group at 4.44 ppm, and a triplet at 5.25 ppm from the proton of a methine group. Six aromatic protons gave signals at 6.61 (3 H), 7.19, 7.39, and 8.24 ppm. The mass spectrum had the peaks of ions with m/z 422 (M^+, 100%), 404, 391, 389, 363, 360, 348. Under pyrolysis conditions it was possible for either a Cope rearrangement or an expansion of the heterocycle, which are characteristic for cyclic N-oxides [10], to take place. The facts mentioned give grounds for considering that in our case expansion of the heterocycle took place. This could form two products: (IIIa) and (IIIb). To investigate this question, the pyrolysis product was reduced with zinc and sulfuric acid, giving compound (IV). The PMR spectrum of (IV) contains signals in the form of three-proton singlets at 2.39 ppm from a N-methyl group and at 3.77 and 3.89 ppm from two methoxy groups, and two-proton singlets at 4.36 ppm from a methylene group and at 5.73 ppm from a methylenedioxy group. At 5.06 ppm there is a one-proton triplet. In the aromatic region of the spectrum are found the signals of six protons at 6.57 (3H), 7.17, 7.26, and 8.31 ppm. Methylene protons appear in the spectrum at 1.56-4.10 ppm. When (IV) was acetylated with acetic anhydride in pyridine, the O,N-diacetyl derivative (V) was obtained. In its PMR spectru, the signal of the methine proton at the acetoxy group appears at 6.27 ppm, which shows that the pyrolysis of the N-oxides gave compound (IIIa).



When air was passed through a boiling ethanolic solution of macrostomine for 30 h it was impossible to detect (I) and (II) in the reaction mixture.

EXPERIMENTAL

Chromatography was performed on type KSK silica gel, and the following solvent systems were used for TLC: 1) benzene–ethanol (9:1); 2) chloroform–ethanol (9:1). UV spectra were taken on a Hitachi spectrophotometer in ethanol, IR spectra on a UR-20 spectrometer in KBr tablets, mass spectra on a MKh 1303 mass spectrometer, and NMR spectra on a JNM-4M-100/100 MHz instrument using $CDCl_3$ as the solvent with HMDS as internal standard; δ scale.

Isolation and Separation of the Total Alkaloids. The air-dry comminuted plant *P. arenarium* (7.8 kg) was extracted with methanol six times. Then the solvent was distilled off in vacuum. The residue was treated with 4% acetic acid. The acetic acid solution was washed with ether and was made weakly alkaline with Na_2CO_3, and the alkaloids were extracted with ether (fraction A, 6.61 g) and chloroform (fraction B, 2.78 g). After this, the alkaline solution was saturated with NH_4Cl, and alkaloids of phenolic nature were extracted with chloroform (fraction C, 0.93 g). Fraction A was dissolved in ethanol, and an ethanolic solution of hydrochloric acid was added. The resulting precipitate of macrostomine hydrochloride (4.1 g) was separated off. The mother liquor was dissolved in water and, after alkalinization with ammonia, the alkaloids were extracted with chloroform. The solvent was distilled off and the residue was chromatographed on a column of silica gel using as eluents benzene and mixtures of benzene and ethanol in various ratios. From the fraction eluted by benzene–ethanol (98:2) was isolated macrostomine (0.9 g), and from the (95:5) fraction 0.085 g of macrostomine N-oxide (I) and 0.12 g of macrostomine N-oxide (II) (mp 141-142°C). The fraction eluted by the (4:1) mixture yielded 0.12 g of glycomarine (mp 205-206°C; chloroform–

methanol). Fraction C was chromatographed on a column of silica gel. By eluting the alkaloids with mixtures of benzene and ethanol in various ratios as described above, 0.2 g of macrostomine, 0.08 g of cheilanthifoline (mp 179-180°C), 0.1 g of arenine, and 0.11 g of sevanine (mp 213-214°C) were isolated.

Reduction of the Macrostomine N-Oxide (I). Zinc dust was added to 30 mg of macrostomine N-oxide (I) in 10 ml of 5% sulfuric acid, and the reaction mixture was left at room temperature for two days. Then the acid solution was made alkaline with 25% ammonia and the base was extracted with ether. Elimination of the solvent gave a product identical with macrostomine (TLC, IR spectrum).

Pyrolysis of Macrostomine N-Oxide (I). Macrostomine N-oxide (I) (32 mg) was heated at 195-200°C in vacuum (1-2 mm) for 10 min. The pyrolysis product was purified on a column of silica gel with elution by chloroform. This gave 27 mg of an amorphous substance (IIIa).

Reduction of the Pyrolysis Product (IIIa). Zinc dust was added to a solution of 25 mg of (IIIa) in 5 ml of 10% sulfuric acid, and the reaction mixture was heated on the water bath for 10 h. The acid solution was made alkaline with 25% ammonia, and the reaction product was extracted with chloroform. After the solvent had been driven off, the residue was treated with methanol, which gave crystals of (IV) with mp 148-149°C.

Reduction of Macrostomine N-Oxide (II). Compound (II) (21 mg) was reduced in the same way as (I), giving macrostomine.

Pyrolysis of Macrostomine N-Oxide (II). The reaction was performed as described above for (I), and a product identical with (IIIa) was obtained.

Acetylation of (IV). A mixture of 21 mg of (IV), 1 ml of pyridine, and 3 ml of acetic anhydride was left at room temperature for 24 h. The solvent was evaporated off to dryness, the residue was dissolved in 5% acetic acid and, after alkalinization with 25% ammonia solution, the reaction product was extracted with ether. The solvent was distilled off, giving 20 mg of amorphous (V).

SUMMARY

Seven alkaloids have been isolated from *Papaver arenarium*, including two macrostomine N-oxides that have not been described previously. Their isomerization under thermal conditions has been studied.

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