ALKALOIDS OF Nitraria komarovii.

XIII. NITRARAMINE N-OXIDE AND THE STRUCTURE OF DEHYDROSCHOBERINE

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Deoxyvasicinone, dℓ-vasicinone, ℓ-peganine, deoxypeganine, nitraramine, dihydronitraraine, nitraroxine, tryptamine, schoberine, and two new bases have been isolated for the first time from the epigeal part of the plant Nitraria komarovii. The structures of the new bases have been established on the basis of spectral characteristics and chemical transformations as nitraramine N-oxide and dehydroschoberine. Nitramidine, isoschoberine, nitraroxine, nitraraine, and tetramethylenetetrahydro-β-carboline N-oxide were isolated from the seeds with fruit.

Continuing a study of the alkaloids of Nitraria komarovii Iljin et Lava, 17 kg of the epigeal part of this plant collected in May, 1987, was extracted in the usual way [1]. This gave the following total alkaloids. Nonphenolic fraction: benzene – 28.67 g; ethereal – 2.13 g; chloroform – 33.09 g. Phenolic fraction: chloroform – 1.12 g; total yield 65.01 g, which amounts to 0.39% on the weight of the air-dry plant. The benzene fraction of the total bases (28.7 g) was boiled with petroleum either, and the solution was separated off. The residue, in an amount of 20.70 g, was chromatographed on a column of silica gel. The following alkaloids were isolated from individual fractions: deoxyvasicinone [2], dℓ-vasicinone [2], ℓ-peganine [2], deoxypeganine [2], nitraramine [3], dihydronitraraine [4], and nitraroxine [5], which have been described previously, and also the new base (I) (124 mg).

Base (I) with mp 251-252°C (alcohol), composition $C_{15}H_{24}N_2O_2$, $[\alpha]_D$ ±0. The mass spectrum contained the following ion peaks: m/z 264(1.5), 248.18747 ($C_{15}H_{24}N_2O$) (100), 247(20), 231(7), 219(24), 204(39), 190(16), 176(19), 162(29), 150(43), 136(14), 122(19), 109(18), 98(11), 96(26), 83(19), 70(17), 55(11). The UV spectrum of the alkaloid showed no absorption. The IR spectrum of (I) contained absorption bands at (cm^{-1}) 875, 910, 935, 955, 965, 1075, 1085, 1110, 1155, 1305, 1420, 1460, 2940, and 3350-3550 (w).

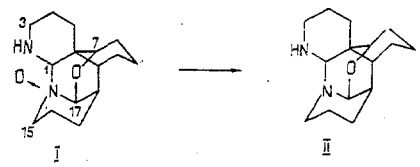
The molecular composition of the alkaloid showed 1 oxygen atom more than nitraramine but otherwise the mass spectral fragmentation was similar to that of nitraramine.

The presence in the IR spectrum of (I) of characteristic bands for N-oxides (935, 955, and 965 cm^{-1}) [6], the presence in the mass spectrum of intense peaks of the $(M - 16)^+$ and $(M - 17)^+$ ions, and its ready solubility in water showed its N-oxide nature.

The following signals (ppm) were observed in the PMR spectrum of (I): 4.58 (br.s, 1H) from C_{17}–H, 4.01 (br.s, 1H) from C_7–H, and 3.77 (s, 1H) from C_1–H. The equatorial protons at C(3) and C(15) resonated in the region of 3.57 ppm (m, 2H), while the axial protons at the same atoms resonated in the region of 2.75 ppm (m, 2H), while the other protons gave signals in the region of 2.25-0.90 ppm (m, 17H).

The hydrogenation of (I) with zinc in hydrochloric acid or sodium tetrahydroborate in methanol gave a substance with mp 85-86°C, which was identified from its IR spectrum and a mixed melting point as nitraramine (II) [3].

Thus, the alkaloid isolated was the N-oxide of nitraramine at N(16) and had the most probable structure (I).



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A "nitraramine N-oxide" which was actually a hydroxylamine derivative of nitraramine has previously been isolated from N. schoberi [7]: It was later renamed as nitraroxine [5]. Since in the present case the name nitraramine N-oxide completely reflects the actual structure of the alkaloid, we consider it desirable to retain this name.

Tryptamine was isolated from 2.13 g of the ethereal fraction of the total bases by column chromatography.

The petroleum ether fraction of the total bases (7.97 g) was chromatographed on a column of silica gel, and schoberine [8] and the new base (III), in the form of an oil, were isolated.

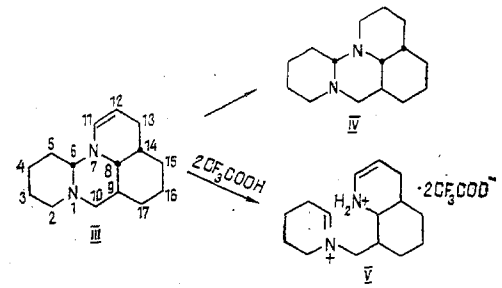
Base (III) had the composition $C_{15}H_{24}N_2$, $[\alpha]_D$ ±0. Its mass spectrum contained the peaks of ions with m/z 232(96), 231(45), 205(33), 203(52), 192(100), 190(51), 178(29), 176(37), 175(32), 148(22), 96(53), 61(60).

The IR spectrum of (III) contained the following absorption bands (cm^{-1}): 785, 815, 855, 895, 930, 950, 980, 1020, 1035, 1055, 1090, 1105, 1125, 1135, 1185, 1245, 1275, 1290, 1310, 1365, 1375, 1450, 1630-1680 (C=C), 2750, 2810, 2860, and 2940.

The following signals (ppm) were observed in the PMR spectrum of (III): 5.40 (br.s, 1H), 4.61 (br.s, 1H), and 3.18 ppm (m, 1H), the signals of the other protons being superposed upon one another and appearing in the form of two humps with centers at 2.65 and 1.5 ppm.

The molecular composition of the alkaloids was two hydrogen atoms less than in schoberine. The Adams hydrogenation of base (III) gave schoberine (IV).

On the basis of the spectral characteristics it was possible to assume that the double bond in (III) could be either at C(2)–C(3) or at C(11)–C(12). When the PMR spectrum was taken in a mixture of trifluoroacetic acid and deuterated methanol, the pattern changed sharply: A broadened one-proton signal arose at 8.72 ppm and a number of signals underwent downfield shifts: 5.88 ppm (br.s, 1H), 4.72 ppm (m, 1H), and 3.82, 3.48, 2.95, and 1.75 ppm. It is known that a characteristic feature of aminals is the cleavage in an acid medium of one of the C–N bonds with the formation of compounds of the type of (V) [8, 9]. A comparison of the PMR spectra of schoberine under analogous conditions showed that the broadened signal at 8.72 ppm had not changed, while a small paramagnetic shift of the olefinic protons in (V) showed that the double bonds were not conjugated and the double bond in base (III) was probably present at C(11)–C(12).



Thus, the new base was dehydroschoberine and had the most probable structure (III).

By chromatography on a column of silica gel, the mother solutions from the ethereal fracfraction of the seeds with fruit [10] yielded, in addition to the nitramidine [11], schoberine, and nitraroxime isolated previously [5], tetramethylenetetrahydro-β-carboline N-oxide [1] and nitraraine [11].

EXPERIMENTAL

The instruments and conditions for recording the spectra were identical with those given in [11].

For TLC we used silica gels of types L 5/40 and KSK, and alumina. The following solvent systems were employed: 1) benzene–methanol (4:1); 2) chloroform–methanol (1:1); 3) chloroform–methanol (4:1); 4) chloroform–methanol–ammonia (4:1:0.1); 5) chloroform–methanol (10:1); 6) chloroform–acetone–methanol (5:4:1); 7) chloroform–acetone–ethanol (5:4:1); 8) chloroform–acetone (4:1); 9) chloroform–acetone–methanol–ammonia (5:4:1:0.1); and 10)

chloroform–ethyl acetate–benzene–methanol (4:3:2:1). The revealing agents were the Dragendorff reagent and iodine vapor.

The finely comminuted epigeal part of the plant (17 kg) gathered in May, 1987, was moistened with an 8% solution of ammonia and was then left for 2 h and was extracted with chloroform 13 times. The bases were extracted from the concentrated chloroform extracts with 10% sulfuric acid. The acid extract was made alkaline with 10% caustic soda and was extracted with benzene and with ether, and then with chloroform. The phenolic fraction was extracted after the addition of NH_4Cl. The total yield was 65.01 g, which was 0.39% of the weight of the airy-dry plant.

The benzene fraction of the total bases (28.6 g) was boiled with petroleum ether, and the solution wsa evaporated off. The residue, amounting to 20.70 g, was chromatographed on a column of silica gel with elution by chloroform–acetone–methanol (5:4:1) and with chloroform–methanol (4:1), and then with system 4. Fractions with a volume of 80-100 ml were collected. In addition to those obtained previously, the following bases were isolated from individual fractions:

Deoxyvasicinone. Fractions 2-5 were combined and rechromatographed on silica gel with elution in system 5. Fractions with a volume of 10-15 ml were collected. By recrystallization from acetone, fractions 3-8 yielded 83 mg of a base with mp 110-111°C.

dl-Vasicinone. Fractions 8-12 were combined and rechromatographed on a column of silica gel with elution by system 6. Fractions with a volume of 15-20 ml were collected. By recrystallization from ethanol–acetone, fractions 11-19 yielded 117 mg of a base with mp 211-212°C $[\alpha]_D$ ±0.

L-Peganine. The following fractions, 13-17, were rechromatographed on a column of silica gel with elution by chloroform–methanol (9:1). Fractions 14-23 yielded 47 mg of a base with mp 210-211°C (alcohol–acetone), $[\alpha]_D$ −57° (c 1.2; alcohol).

Deoxypeganine. The following fractions, 19-23, and the mother liquor of fractions 10-17 were combined and were chromatographed on a column of silica gel with elution by system 7. Fractions with a volume of 10-15 ml were collected. Fractions 11-21 yielded 85 mg of a base with 86-87°C (petroleum ether) giving a hydrochloride with mp 255-256°C (alcohol).

Dihydronitraraine. The mother fractions after the isolation of dl-vasicinone were combined and rechromatographed on a column of silica gel with elution by system 7. Fractions with a volume of 10-13 ml were collected. By recrystallization from alcohol, fractions 11-17 yielded 37 mg of a base with mp 285-286°C.

Nitraroxine. The mother solutions from the fractions after the isolation of deoxyvasicinone, dihydronitrarine, and dl-vasicinone were rechromatographed on a column of silica gel with elution by system 5. Fractions with a volume of 15-20 ml were collected. Fractions 4-10 yielded 41 mg of a base with mp 220-221°C (alcohol).

Nitraramine N-Oxide (I). Fractions 25-31 were rechromatographed on a column of silica gel with elution by system 7. Fractions with a volume of 10-15 ml were collected. Fractions 17-25 yielded 124 mg of a base with mp 251-252°C (alcohol).

Nitraramine. The following fractions (27-31), were combined and crystallized from petroleum ether, giving 34 mg of a base with mp 85-86°C.

Reduction of Nitraramine N-Oxide. Nitraramine. a) A zinc granule was dropped into a solution of 26 mg of base (I) in 5 ml of 10% hydrochloric acid, and the mixture was left overnight. Then it was decomposed with 10% caustic soda solution and extracted with chloroform. The solvent was distilled off and the residue was crystallized from petroleum ether, giving 16 mg of a base with mp 85-86°C.

b) In portions, 50 mg of sodium tetrahydroborate was added to a solution of 29 mg of the base in 5 ml of methanol, and the mixture was left overnight. The solvent was eliminated in vacuum and the residue was decomposed with water. Then it was extracted with chloroform, the solvent was distilled off, and the residue was crystallized from petroleum ether, giving 21 mg of a base with mp 85-86°C.

Tryptamine. By chromatography on a column of silica gel with elution by chloroform–methanol (4:1), with the collection of 25- to 30-ml fractions, 2.13 g of the ethereal fraction of the total bases was separated. By crystallization from acetone, fractions 17-23 yielded 97 mg of a base with mp 116-117°C giving a hydrochloride with mp 247-248°C (alcohol–ethyl acetate).

The petroleum ether fraction of the total bases (7.97 g) was chromatographed on a column of silica gel with elution by chloroform–methanol in various ratios (20:1, 10:1, and 4:1). Fractions with a volume of 15-20 ml were collected. The following bases were isolated from individual fractions:

Dehydroschoberine (III). Fractions 2-4 were combined and rechromatographed in a column of silica gel with elution by chloroform–methanol (10:1). Fractions 2-7 were combined and were boiled with petroleum ether. The solvent was distilled off, giving 317 mg of a base in the form of a transparent oil.

Schoberine. The residue after the isolation of dehydroschoberine and fractions 5-7 were combined and was separated by column chromatography on silica gel with elution by chloroform–ethanol (10:1). After evaporation of the solvents and long standing, fractions 4-7 crystallized in the form of rosettes. In this way we obtained 56 mg of a base with mp 61-62°C. $[\alpha]_D$ ±0. M^+ 234.

Hydrogenation of Base (III). Schoberine. Base (III) (0.047 g) in 5 ml of alcohol was hydrogenated over Pt for 4 h, and then the catalyst was separated off and the alcohol was eliminated in vacuum. The residue was chromatographed on a column of silica gel with elution by chloroform–acetone–alcohol (5:4:1). After the removal of the solvent, fractions 2-7 crystallized in the form of rosettes. mp 61-62°C. $[\alpha]_D$ ±0. Molecular mass 234 (mass-spectrometrically).

Individual fractions yielded, in addition, deoxypeganine, nitraramine, and nitraramine N-oxide.

Separation of the Total Alkaloids from the Seeds with Fruit. The mother solutions of the fractions after the isolation of nitrarine, isonitrarine, and schoberine [10] were rechromatographed on a column of silica gel with elution by chloroform–alcohol (4:1) and then by chloroform–methanol–ammonia (4:1:0.1). Individual fractions yielded nitramidine, isoschoberine, nitraroxine, tetramethylenetetrahydro-β-carboline N-oxide, and nitraraine. The direct comparison of these bases with authentic samples showed their identity with respect to all their parameters.

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