ALKALOIDS OF Nitraria komarovii.

XI. STRUCTURE OF KOMAVICINE AND THE PRODUCTS OF THE DEHYDROGENATION OF THE NITRARINE METHOD OF DEHYDROGENATION IN THE QUINOLINYL-β-CARBOLINE SERIES

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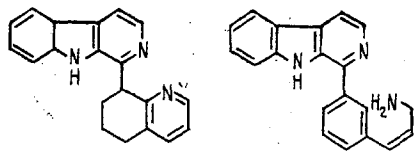
The new alkaloid komavicine has been isolated from the epigeal part of Nitraria komarovii, and its structure has been established on the basis of spectral characteristics and chemical transformations. The products of the dehydrogenation of nitrarine with selenium and sulfur have been studied. A method has been developed for the dehydrogenation of dihydro and tetrahydro derivatives in the quinolinyl-β-carboline series.

Continuing a study of the plant Nitraria komarovii Iljin et Lava [1], from combined ethereal extracts, and also from benzene and ethyl acetate mother solutions, we have isolated by column chromatography an optically inactive base with the composition $C_{20}H_{17}N_3$ which we have called komavicine. The molecular mass of the base is 299 (by mass spectrometry). The IR spectrum of the alkaloid had the absorption bands of an indole ring (1460, 1510, 1605), of an indole amino group (3140), and of an ortho-disubstituted benzene ring (760 cm^{-1}). In the UV spectrum there were the following absorption maxima: $\lambda_{max}^{C_2H_5OH}$ 215, 233, 272, 290, 355 nm (log ε 4.47, 4.45, 4.15, 4.18, 3.83), which changed on acidification: $\lambda_{max}^{C_2H_5OH+H^+}$ 254, 307, 375 nm.

This base, together with others, was first detected among the products of the dehydrogenation of nitrarine by selenium, and structure (I) was proposed for it [2]. A direct comparison showed the identity of the two bases. In view of the formation of komavicine from nitrarine in a dehydrogenation reaction, several variants of the structure may be suggested for it:



I

II

For a definitive answer to this question we dehydrogenated komavicine with sulfur. By preparative separation in a thin layer of silica gel we isolated two bases, with mp 228-229°C and 238-239°C. A direct comparison showed their identity with komarovine (III) [3] and komarovinine (IV) [4] (see Scheme 1).

The acetylation of komavicine with acetic anhydride in pyridine led to the formation of acetylkomavicine with mp 204-205°C. M^+ 341. ν_{max} 1660 cm^{-1} (amide carbonyl). The PMR spectrum included a signal at 2.19 ppm of $-NH-CO-\underline{CH_3}$ (s, 3 H).

The methylation of komavicine with methyl iodide in methanol led to the formation of N,N-dimethylkomavicine methiodide (V), with mp 275-276°C. $(M - HI)^+$ 341. The LSIMS secondary-ion mass spectrum also confirmed the formation of base (V). $(M - I)^+$ 342.

The PMR spectrum of (V) contained, in addition to a complex group of signals in the aromatic region of 7.25-9.0 ppm, the following signals (ppm): 3.76, $Ar-CH=CH-CH_2-N^+(CH_3)_3I^-$ (d, 2 H); 4.25 ppm, $-N^+(CH_3)_3I^-$ (s, 9 H); and the signal of an olefinic proton at 6.72 ppm, $Ar-\underline{CH}=CH-$ (d, 1 H). Emde degradation with Raney alloy did not take place.

On Emde degradation with 3% sodium amalgam, substance (VI) with a molecular mass of 284, mp 132-133°C was formed. Its PMR spectrum had a signal at 2.01 ppm (d, 3 H) from a

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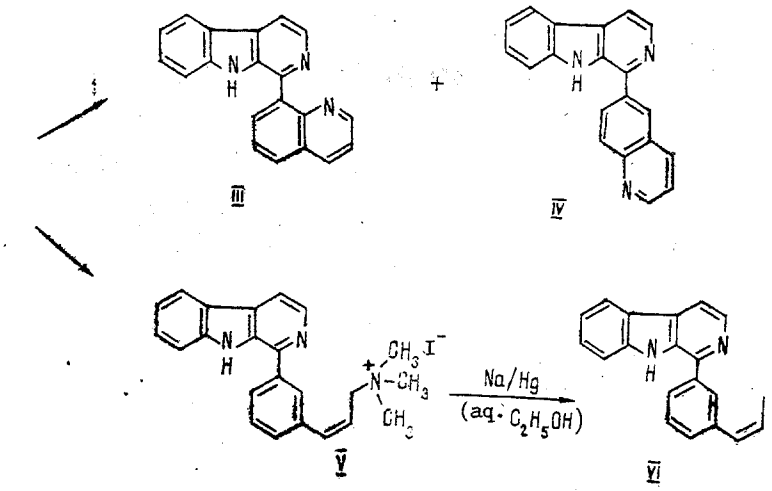
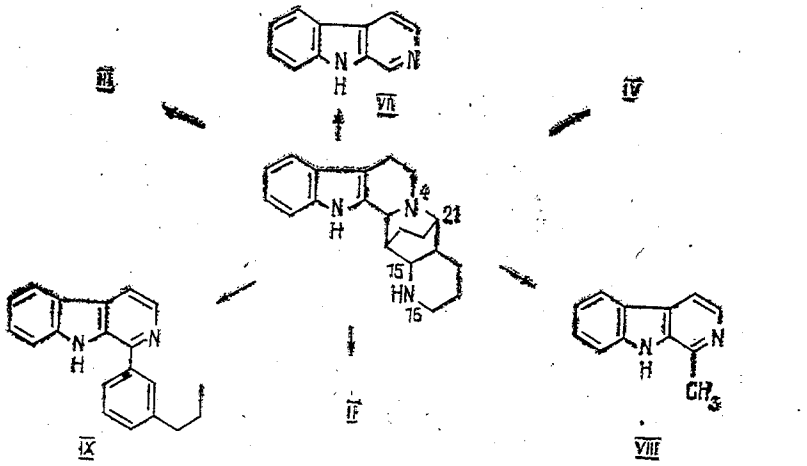


Scheme 1. Dehydrogenation of komavicine and Emde degradation.



Scheme 2. Products of the dehydrogenation of nitrarine.

methyl group, and the resonance signal of an olefinic proton appeared at 6.56 ppm (d, 1 H), Ar−C<u>H</u>=CH−; while other protons gave signals at 7.20-9.0 ppm.

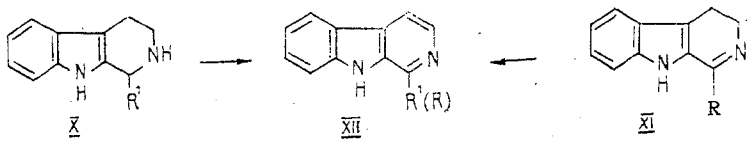
The experimental results showed that komavicine had the most probable structure (II). The spectral characteristics also confirmed structure (II). The formation of komavicine from nitrarine on dehydrogenation is discussed below.

We also investigated the products of the dehydrogenation of nitrarine by selenium and by sulfur. In addition to those described previously [2, 5], we isolated four compounds. Two of them – β-carboline and 1-methyl-β-carboline – were identified by comparison with authentic samples which we obtained by a generally known procedure starting from tryptamine and formic and acetic acids, respectively. Komavicine is apparently formed from nitrarine [2] after the successive cleavage of the N4−C21 and C15−N16 bonds.

All the bases isolated from the dehydrogenation products are shown in Scheme 2.

Proofs of the structures and the synthesis of 1-(quinolin-8-yl)-β-carboline and 1-(quinolin-6-yl)-β-carboline, and also a proof of the structure of 1-(3'-propylphenyl)-β-carboline are shown in the corresponding papers [3-5]. Komarovinine is apparently the product of the migration of a β-carboline residue from position 8 of the quinoline nucleus to position 6 during the dehydration of nitrarine, since the normal product komarovine, both in the pure form and in admixture with selenium, is stable on heating at 300°C or is formed from komavicine.

Thus, of the six products of the dehydrogenation of nitrarine by selenium or sulfur, the structures of four bases have been established unambiguously by synthesis.



Scheme 3. Oxidation of dihydro and tetrahydro derivatives of quinolinyl-β-carbolines.

We have previously obtained isomeric quinolinyl-β-carbolines by the dehydrogenation of the corresponding dihydro or tetrahydro derivatives with sulfur, selenium, or Pd black. The yield ranged from 50 to 60% [3, 6].

In the case of 1-(quinolin-5-yl)-β-carboline, the dihydro and tetrahydro derivatives were oxidized in boiling nitrobenzene [1]. The yield amounted to about 50%, but the isolation and purification of the final product was difficult because of the use of nitrobenzene.

It is known from the literature that on the slow evaporation of an ethereal solution of 1-(o-methylbenzyl)-3,4-dihydro-β-carboline oxidation and dehydrogenation take place [7]. A reaction of this type is considerably accelerated if the dihydro derivative is boiled in a concentrated solution of caustic potash in methanol [8], but under these conditions cleavage of the bonds in the molecule may sometimes take place, as well [9] (see Scheme 3).

When tetrahydro derivatives of quinolinyl-β-carbolines are boiled in a concentrated solution of caustic potash in methanol no changes take place. However, on the slow evaporation of concentrated solutions of dihydro or tetrahydro derivatives of quinolinyl-β-carbolines in methanolic KOH dehydrogenation does occur (Scheme 3). The following compounds have been obtained in this way: nitramarine (XII, R^1 = quinolin-2-yl) [6], komarovine (III) (XII, R^1 = quinolin-8-yl) [3], komarovinine (IV) (XII, R^1 = quinolin-6-yl) [4], and isokomarovine (XII, R^1 = quinolin-5-yl) [1, 6]. In this case, probably, the "Claisen alkali" promotes oxidation with the formation of the corresponding quinolinyl-β-carbolines.

If chloroform is added to a concentrated solution of tetrahydro derivatives in methanolic KOH and the mixture is boiled, the Reimer–Tieman reaction, i.e., formylation, takes place. In this way N^2-formylkomarovicine, with mp 267-268°C (alcohol), M^+ 327.13768 has been obtained from komarovicine (X, R^1 = quinolin-8-yl) [2], and N^2-formylnitrarine, mp 303-305°C (alcohol, M^+ 335.19827) from nitrarine [2].

Thus, a method has been developed for the dehydrogenation of dehydro and tetrahydro derivatives of the isomeric quinolinyl-β-carbolines.

EXPERIMENTAL

The UV spectra of the alkaloids were taken on a EPS-3T instrument (Hitachi), IR spectra on a UR-20 instrument (tablets with KBr), mass spectra on MKh-1303 and MKh-1310 instruments, and PMR spectra (in a mixture of $CDCl_3$ and CD_3OD) on a JNM-4H-100/100 MHz instrument with HMDS as internal standard.

The homogeneity of the substances was confirmed by chromatography in thin layers of silica gel of types KSK and L 5/40 in the following systems: 1) benzene–methanol (4:1); 2) chloroform–methanol (4:1); 3) chloroform–methanol–ammonia (4:1:0.1); 4) chloroform–acetone (9:1); 5) chloroform–acetone–methanol (5:4:1); 6) chloroform–acetone–ethanol (5:4:1); 7) chloroform–acetone–methanol–ammonia (5:4:1:0.1); 8) chloroform–acetone–ethanol–ammonia (5:4:1:0.1); and 9) chloroform–ethanol–ammonia (5:1:0.1).

Revealing agents: the Dragendorff reagent: iodine vapor.

Komavicine. The mother solutions from the ethereal, benzene, and ethyl acetate extracts, after the isolation of isokomarovine, komarovidine and nitramarine, were chromatographed together on a column of silica gel with elution by chloroform (100 ml fractions) and then with chloroform–acetone (8:1). By the rechromatography of fractions 24-37 on a column of silica gel in the chloroform–acetone–methanol (10:2:1) system we obtained 65 mg of an amorphous base with a 299. Later, this base (27 mg) was also isolated by column chromatography from the benzene fraction of the total bases from the epigeal part of the plant gathered in 1987.

Dehydrogenation of Komavicine. A mixture of 30 mg of komavicine and 20 mg of sulfur was heated at 180-200°C for 40 min. The products were then worked up in the usual way. Chromatography in a thin layer of silica gel in system 5 showed the formation of four compounds. The

mixture was separated by the preparative method in a thin layer of silica gel in system 5. Two substances were isolated, with mp 228-229°C and 238-239°C (CH_2Cl_2). A direct comparison of these bases with authentic samples showed their identity with komarovine and komarovinine, respectively.

N,N-Dimethylkomavicine Methiodide (V). A solution of 30 mg of komarvicine in 5 ml of methanol was treated with 0.5 g of CH_3I, and the mixture was boiled under reflux for 3 h. After cooling, the solvent was evaporated off. The residue was chromatographed on a column of silica gel in system 5. This gave 16 mg of (V) with mp 275-276°C. The mass spectrum of (V) contained the peaks of ions with m/z 341 $(M - HI)^+$ (1.5), 327(3), 326(4), 313(100), 312(57), 311(4), 298(10), 296(21), 284(7), 282(5), 269(6), 256(5), 255(5), 242(4), and others.

N-Acetylkomavicine. A solution of 21 g of base (II) in 1.5 ml of pyridine was treated with 1.2 ml of acetic anhydride. The mixture was left for 3 days, and then the solvents were distilled off in vacuum. The residue was chromatographed on a column of silica gel with elution by chloroform–acetone–ethanol (5:4:1). Fractions with a volume of 3-5 ml were collected. From fractions 4-11 were isolated 13 mg of a base with mp 204-205°C. The mass spectrum contained the following peaks of ions, m/z: 341 M^+ (64), 327(8), 326(6), 323(12), 311(14), 300(22), 299(80), 298(43), 297(20), 296(30), 295(38), 294(26), 282(12), 270(12), 259(13), 255(14), 224(44), 223(22), 210(18), 209(44), 208(24), 196(33), 195(94), 183(93), 182(100), 181(74), 168(63), 43(100).

Emde Degradation of N,N-Dimethylkomavicine Methiodide. A solution of 37 mg of base (V) in 5 ml of aqueous ethanol was treated with 2 g of 3% of sodium amalgam in portions. After the end of the reaction, the solution was separated off and the solvent was distilled off in vacuum. The residue was dissolved in 5% hydrochloric acid. The acid solution was decomposed with 10% caustic soda and extracted with chloroform. The chloroform was distilled off, and the residue was chromatographed on a column of silica gel with elution by system 6. Fractions with a volume of 3-5 ml were collected. Fractions 3-9 yielded 16 mg of a base with mp 132-133°C. M^+ 284. IR spectrum, cm^{-1}: 750, 820, 1240, 1335, 1460, 1500, 1620, 2860, 2940, and 3060.

Dehydrogenation of Nitrarine. a) A mixture of 3 g of nitrarine and 3 g of selenium in a round-bottomed flask was placed in a sand bath previously heated to 290°C. The temperature was raised over 10 min to 300°C and was maintained for another 2 min. After cooling, the products were extracted with 10% sulfuric acid. The salts were decomposed with 15% caustic soda, and the products were extracted with either and then with chloroform. This gave 1.6 g of ethereal and 0.1 g of chloroform extracts. The ethereal extract (1.6 g) was separated on a column of silica gel with elution by chloroform and by chloroform–acetone–methanol (18:6:1) and then by system 2.

The chloroform extract, after reseparation on a column of silica gel, yielded 0.04 g of a base with 143-144°C, M^+ 286. A direct comparison of its physicochemical and spectral characteristics showed its identity with the natural alkaloid komaroine.

From the chloroform–acetone–methanol eluates, by reseparation on a column in solvent mixture 5 we isolated 0.05 g of an amorphous base with a molecular mass of 299. A direct comparison with physicochemical and spectral characteristics showed its identity with the natural alkaloid komavicine.

The last fractions, by separation on a column in system 7, yielded two bases: 0.02 g with mp 228-229°C, and 0.03 g with mp 238-239°C (CH_2Cl_2). A direct comparison of their properties showed the identity of these bases with the natural alkaloids komarovine and komarovinine, respectively.

The initial fractions of the chloroform–methanol eluates were reseparated on a column of silica gel with elution by chloroform, and then with chloroform–methanol (4:1) (15-20 ml fractions). On recrystallization from benzene, fractions 24-31 yielded 0.03 g of a base with mp 234-235°C. Direct comparison with an authentic sample showed its identity with harman. Eluates 35-44 yielded 0.02 g of a base with mp 199-200°C which was identified as norharman.

b) A mixture of 2 g of nitrarine and 1 g of sulfur was placed in a sand bath heated to 180°C. A temperature of 180-200°C was maintained for 45 min. Then the products were worked up as in the preceding experiment. This gave 1.2 g of ethereal and 0.1 g of chloroform extracts.

The ethereal extract (1.2 g) was separated on a column of silica gel with elution by benzene, ether, chloroform, and chloroform–methanol (4:1). The benzene eluates, after recrystallization from petroleum ether $-CH_2Cl_2$, yielded 0.02 g of a base with mp 143-144°C. A mixed melting point with komaroine gave no depression. The chloroform eluates, after reseparation on a column of silica gel in the chloroform–acetone–methanol (8:2:1) system yielded 0.03 g of an amorphous base with molecular mass of 299. A direct comparison showed its identity with komavicine. Fractions 2-13 from the chloroform–methanol eluates were reseparated on a column of silica gel in solvent mixture 7, and two bases were isolated: 0.02 g with mp 228-229°C and 0.03 g with mp 238-239°C. Mixed melting points with komarovine and komarovinine, respectively, gave no depression.

The last fractions were separated on a column of silica gel with elution by chloroform–methanol (4:1). Two bases were isolated: 0.015 g with mp 234-235°C, and 0.01 g with mp 199-200°C. They were identified by direct comparison with authentic samples of harman and norharman, respectively.

Komarovine. A solution of 150 mg of komarvicine in 5 ml of methanol was treated with 1.5 g of caustic potash in portions. The solution was left for 2 days to evaporate. Water was added to the dry residue, and the insoluble part and the solution were extracted with chloroform. This gave 127 mg of a base with mp 229-230°C (CH_2Cl_2).

Isokomarovine. A solution of 100 mg of 1-(quinolin-5-yl)-1,2,3,4-tetrahydro-β-carboline in 5 of methanol was treated with 1.6 g of caustic soda in portions. The solution was slowly evaporated under a hood. After 1.5 days, the dry residue was dissolved in 5% hydrochloric acid. The solution was decomposed with 10% caustic soda solution, the products were extracted with chloroform, and the chloroform was distilled off. This gave 89 mg of a base with mp 321-323°C (CH_2Cl_2).

N^2-Formylkomarovicine. A solution of 170 mg of komarovicine in 6 ml of methanol was treated with 2.0 g of caustic potash. The mixture was boiled for 13-15 h, whereupon no changes took place. After the addition of 2 ml of chloroform, boiling was continued for another 15 h. After cooling, the solvent was dissolved off in vacuum, and after the addition of water to residue it was extracted with chloroform. Chromatography on a column of silica gel with elution by system 9 led to the isolation of 106 mg of a base with mp 267-269°C. M^+ 327.

N^{16}-Formylnitrarine. A solution of 250 ml of nitrarine in 10 ml of methanol was treated with 2.5-3.0 g of caustic potash and the mixture was boiled for 12-13 h. No changes took place. On the addition of 5 ml of chloroform, an exothermic reaction began. The mixture was boiled for another 15 h and, after cooling, the solvent was distilled off in vacuum. The residue was treated with water and extracted with chloroform. The products were separated by chromatography on a column of silica gel with elution by system 3. This gave 227 mg of a base with mp 303-305°C. M^+ 335.

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