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ALKALOIDS OF *Nitraria komarovii* SYNTHESIS OF NITRARINE AND ISONITRARINE

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The natural alkaloids nitrarine and isonitrarine with the new heterocyclic system 14,21-ethano-16-azayohimban have been synthesized.

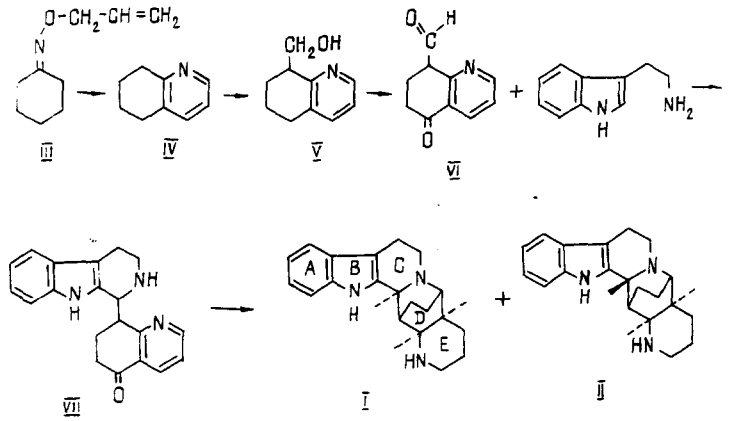
Nitrarine, which was first isolated from the plant *Nitraria schoberi* L. [1] and later from *N. komarovii* Iljin et Lava [2] possesses pronounced spasmolytic and coronary-dilating and moderate hypotensive amd tranquilizing properties [3, 4] and also an antiarrhythmic activity [5].

The alkaloid nitrarine, the molecule of which is based on the new heterocyclic system 14,21-ethano-16-azayohimban, has the structure (I) [1], which has been confirmed by the results of an x-ray structural investigation of nitrarine dihydrochloride [6]. Structure (I) differs from that of yohimban by the presence of a dimethylene bridge between the C-14 and C-21 atoms, and also by a nitrogen atom in position 16. The results of the x-ray structural study of nitrarine dihydrochloride have shown that the indole moiety A-B, together with the adjacent C-3 and C-6 atoms, is practically planar. The tetrahydropyridine ring C has a highly distorted conformation close to a half-chair. The substituted 2-azabicyclo[2.2.2]octane system comprises three "boats." The piperidine ring E also has a boat conformation. The cis linkage of rings C/D and the cis linkage of rings D/E correspond to a configuration with syn-orientated hydrogen atons at C-3, C-15, and C-20.

Isonitrarine is the epimer of nitrarine at C-3. Under the conditions of Adams hydrogenation, nitrarine isomerizes into isonitrarine, and after the reaction has proceded for 7 h an equilibrium arises between nitrarine and isonitrarine [7].

The aim of the present work was the synthesis of the alkaloid nitrarine (I) and also the submission of the intermediate compounds to pharmacological investigations in order to seek new biologically active substances.

Scheme



The alkaloid nitrarine was synthesized as shown in the scheme.

5,6,7,8-Tetrahydroquinoline and 8-hydroxymethyl-5,6,7,8-tetrahydroquinoline were synthesizd by a known procedure [8].

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The condensation of tryptamine with the aldehyde (VI) by the Pictet–Spengler method gave compound (VII) with mp 206-207°C (alcohol–acetone). Reduction of the base (VII) with zinc in hydrochloric acid and then with sodium tetrahydroborate in ethanol led to a mixture of bases, by the chromatographic separation of which on a column of silica gel it was possible to isolate 23 mg of product (I) with mp 255-256°C and 26 mg of product (II) with mp 208-209°C; in all their parameters, these compounds were identical with the natural alkaloids nitrarine and isonitrarine, respectively.

When compound (VII) was hydrogenated by the Adams method and then with sodium tetrahydroborate in alcohol, the reaction yield increased. On catalytic hydrogenation, apparently, the cis-decahydroquinoline form predominates, and its cyclization gives the desired product. The mixture formed was dissolved in alcohol, and an alcoholic solution of hydrogen chloride was added to bring the pH to 3-4. After the solution had been allowed to stand for 5-6 h, a crystalline precipitate with mp 238-239°C (alcohol) deposited, and after another 13-15 h crystals appeared with mp 265-266°C (alcohol) which were identified as the dihydrochlorides of isonitrarine and of nitrarine, respectively.

Thus, the synthesis of the natural alkaloids nitrarine and isonitrarine has been achieved.

EXPERIMENTAL

UV spectra were taken in alcohol on an EPS-3T spectrophotometer (Hitachi), mass spectra on a MKh-1310 spectrometer, and IR spectra on a UR-20 instrument (tablets with KBr). PMR spectra were recorded in $CDCl_3$ on a Tesla-567A (100 MHz) instrument with HMDS as internal standard.

For TLC we used silica gel of types KSK and L 5/40. The solvent systems for chromatography were as follows: 1) chloroform–acetone (4:1); 2) chloroform–acetone–methanol (5:4:1); 3) chloroform–acetone–ethanol (5:3:1); 4) chloroform–ethanol (4:1); 5) chloroform–methanol (4:1); 6) chloroform–methanol–ammonia (8:2:0.1); 7) chloroform–acetone–methanol–ammonia (5:4:1:0.1); 8) chloroform–acetone–ethanol–ammonia (5:4:1:0.1); 9) chloroform–ethanol–ammonia (8:2:0.1); 10) chloroform–acetone–diethylamine (5:4:1); 11) chloroform–ethanol (1:1); 12) chloroform–methanol (1:1); 13) benzene–methanol (4:1). Revealing agents: the Dragendorff reagent, and iodine vapor.

O-Allyl Ether of Cyclohexanone Oxime (III). A solution of 52.8 g of cyclohexanone oxime in 600 ml of methanol was treated with 82 ml of allyl bromide. The solution was cooled with a freezing mixture, and 25.3 g of caustic soda in 500 ml of methanol was added over 0.5 h. Then the mixture was boiled under reflux for 4 h. Two 80-ml portions of allyl bromide were added 1 and 2 h, respectively, after the start of boiling. After the end of the reaction, the solution was concentrated, the precipitate that deposited was filtered off, and the filtrate was extracted with hexane three times. The hexane was evaporated off, and the residue was distilled in vacuum. This gave 50.7 g (70.9%) of the ether (III) with bp 78-83°C/15 mm Hg. Mass spectrum, m/z: 153 (40), 138 (32), 136 (29), 125 (16), 111 (18), 96 (19), 82 (27), 81 (28), 79 (18), 69 (36), 67 (100), 55 (85).

IR spectrum, 840, 890, 930, 1010, 1050, 1110, 1235, 1260, 1350, 1460, 1650, 1710, 2865, 2940 cm^{-1}.

The PMR spectrum showed the following signals of protons: (δ, ppm): 1.56 (m, 6H), 2.08 and 2.37 (m, 2H each), 4.40 (m, 2H), 5.10 (m, 2H) 5.85 (q, 1H).

5,6,7,8-Tetrahydroquinoline (IV). The ether (III) (50.7 g) was heated in a sand bath under reflux at 170-180°C for 25 h. After the end of the reaction the product was distilled in vacuum. This gave 25.1 g (57.7 %) of the base (IV) with bp 102-106°C/15 mm Hg. The IR spectrum contained the following absorption bands: 840, 930, 1050, 1130, 1210, 1370, 1470, 2870, 2940, 3030 cm^{-1}.

UV spectrum: $\lambda_{max}^{C_2H_5OH}$ 215.270 nm (lg ε 3.55; 3.65).

Mass spectrum, m/z: 133 (96), 132 (100), 118 (23), 117 (25), 105 (27), 98 (33), 79 (11), 77 (13), 56 (17), 55 (100).

PMR spectrum: 1.85 (m, 4H), 2.72 (t, 2H), 2.83 (t, 2H), 6.90 (dd, 1H, J = 5.8 Hz), 7.24 (d, 1H, J = 8 Hz), 8.26 (d, 1H, J = 6 Hz).

8-Hydroxymethyl-5,6,7,8-tetrahydroquinoline (V). A mixture of 25.1 g of 5,6,7,8-tetrahydroquinoline and 15 g of paraformaldehyde was heated under reflux at 110-120°C for 3 h. After cooling, 100 ml of 20% hydrochloric acid solution was added. The insoluble part was filtered off. The filtrate was decomposed by the addition of alkali and was extracted with benzene, and the benzene was distilled off. The residue was distilled in vacuum. This gave 5.3 g (18.6%) of (V) with bp 153-157°C/15 mm Hg.

Mass spectrum, m/z: 163 (18), 161 (22), 147 (26), 133 (85), 132 (100), 118 (24), 117 (26), 105 (29), 98 (35), 79 (12), 77 (15), 56 (18), 55 (100). IR spectrum: 830, 855, 915, 1060, 1120, 1170, 1280, 1300, 1360, 1470, 2870, 2950, 3030, 3450 cm^{-1}.

PMR spectrum: 1.82 (m, 4H), 2.73 (t, 2H), 2.85 (m, 1H), 3.47 (s, 1H, OH), 6.82 (dd, 1H, J = 5.7 HZ), 7.20 (d, 1H, J = 7 Hz), 8.21 (d, 1H, J = 6 Hz).

5-Oxo-5,6,7,8-tetrahydroquinoline-8-carbaldehyde (VI). A round-bottomed flask was charged with 40 ml of tert-butyl alcohol, and 5.43 g of chromium trioxide was added in small portions. Then to the cooled mixture was added a mixture of 5.4 g of (V) and 10 ml of tert-butyl alcohol dropwise. The mixture was stirred for another 1 h and was left overnight. After the addition of 100 ml of water the mixture was made alkaline with conc. ammonia solution and was extracted with chloroform. The chloroform was evaporated off, and the residue was distilled in vacuum. This gave 2.73 g of compound (VI) with bp 145-148°C/15 mm Hg.

IR spectrum: 760, 790, 860, 910, 1055, 1110, 1150, 1210, 1325, 1340, 1440, 1485, 1585, 1740, 2870, 2945, 3030 cm^{-1}. Mass spectrum: 175 (5), 146 (5), 144 (13), 113 (15), 101 (23), 98 (100), 83 (24), 79 (15), 77 (8), 69 (55), 55 (100). PMR spectrum: 1.94 (m, 2H), 2.68 (t, 2H), 3.05 (m, 1H), 7.04 (m, 1H), 7.38 (d, 1H, J = 5 Hz), 7.83 (br.s, 1H).

1-(5-Oxo-5,6,7,8-tetrahydroquinolin-8-yl)-1,2,3,4-tetrahydro-β-carboline (VII). A mixture of 2 g of tryptamine hydrochloride in 40 ml of water, 7 ml of 2 N sulfuric acid, and 2.73 g of the aldehyde (VI) was gradually heated in a sand bath to 110°C and was kept at that temperature for 1 h. After cooling, the acid solution was decomposed with a 10% solution of caustic soda and was extracted with chloroform. The chloroform was distilled off, to give 1.97 g of the base (VII) with mp 206-207°C. The mass spectrum contained the following ion peaks, m/z: 317 (11), 240 (50), 211 (17), 197 (100), 184 (15), 155 (18), 154 (14), 85 (48), 83 (48). IR spectrum: 750, 780, 835, 960, 1010, 1090, 1155, 1235, 1290, 1345, 1440, 1465, 1580, 1630, 1680, 1700, 2850, 2930, 3040, 3400 cm^{-1}. PMR spectrum: 1.80 (m, 4H), 2.70 (m, 3H), 3.12 (m, 3H, 7.0-7.65 (m, 6H), 7.96 (m, 1H).

Nitrarine (I) and Isonitrarine (II). a) Base (VII) (0.97 g) was reduced with zinc in hydrochloric acid. The acid solution was decomposed with 10% caustic soda solution and was extracted with chloroform, and the chloroform was evaporated off. The residue (0.53 g) was dissolved in 15 ml of ethanol. Sodium tetrahydroborate (1 g) was added in portions and then the mixture was boiled for 1 h. After the end of the reaction, the solvent was evaporated off. The residue was decomposed by the addition of water, and the product was extracted with chloroform. The chloroform was evaporated off, and the residue was chromatographed on a column of silica gel, with elution first by chloroform–methanol (4:1) and finally by chloroform–methanol–ammonia (8:2:0.1). Individual fractions yielded 23 mg of base (I) with mp 255-256°C (alcohol) and 26 mg of base (II) with mp 208-209°C (alcohol–acetone).

Base (I), composition $C_{20}H_{25}N_3$, mp 255-256°C (alcohol). M^+ 307. IR spectrum: 750, 885, 960, 1015, 1120, 1140, 1275, 1335, 1445, 1470, 1505, 1585, 1625, 2860, 2920, 2940, 3030, 3060, 3140, 3400 cm^{-1}. The PMR spectrum, taken in a mixture of $CDCl_3$ and CD_3OD showed a series of multiplets with their centers at 1.45, 1.64; 2.06; 2.80; 3.10; 4.35 (s, 1H), 6.90-7.36 (m, 4H).

UV spectrum: $\lambda_{max}^{C_2H_5OH}$ 226, 280-292 (lgε 4.52; 3.91).

Base (II), composition $C_{20}H_{25}N_3$, mp 208-209°C (chloroform). M^+ 307. IR spectrum: 755, 880, 965, 1140, 1280, 1335, 1460, 1580, 1630, 2860, 2940, 3140, 3400 cm^{-1}. The PMR spectrum, taken in CD_3OD, showed a series of multiplets with their centers at 1.20; 1.90; 2.22; 2.54; 3.12; 4.40 (d, 1H), 6.90-7.36 (m, 4H).

UV spectrum: $\lambda_{max}^{C_2H_5OH}$ 226, 280-292 nm (lgε 4.45; 3.82).

b) Base (VII) (1 g) was hydrogenated in 50 ml of alcohol over Pt for 7 h, and then the catalyst was filtered off, and the filtrate was reduced with sodium tetrahydroborate, with the addition of 2 g of sodium tetrahydroborate in portions, after which the mixture was stirred for another 2 h. The solvent was distilled off, and the residue was decomposed with water and extracted with chloroform. The chloroform was evaporated off and the residue was dissolved in 25 ml of alcohol the pH of which was then brought to 3-4 by the addition of an alcoholic solution of hydrochloric acid. On standing for 5-6 h the mixture deposited 0.16 g of a crystalline precipitate with mp 238-239°C (alcohol) and, after another 13-15 h, 0.19 g of crystals with mp 265-266°C (alcohol), which were identified as the dihydrochlorides of isonitrarine and of nitrarine, respectively. Decomposition of the salts yielded the corresponding bases.

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