DIMETHAMINE – A NEW BIMOLECULAR ALKALOID FROM Thermopsis alterniflora

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We have previously reported the isolation from the epigeal part of Thermopsis alterniflora of cytisine, N-methylcytisine, pachycarpine, thermopsine, and alteramine [1]. The mother liquors after the separation of the above-mentioned alkaloids were separated according to the strengths of the bases contained in them. The strongly alkaline fractions yielded an alkaloid with mp 203-204°C, identified by its IR and mass spectra and R_f values as argentamine, isolated previously from Ammodendron argenteum [2]. The feebly basic fractions, on trituration with acetone, gave a base with mp 258-259°C. The comparison of the IR and mass spectra, and also a mixed melting point, showed that this substance was argentine [3]. Chromatography of the combined fractions on a column of silica gel yielded a base with mp 216-217°C (decomp.). A mass-spectrometric determination of the molecular weight of this alkaloid and a comparison of osmotic pressures [4] agreed with the results of elementary analysis – $C_{24}H_{32}N_4O_2$. The alkaloid is optically active and gives a crystalline dihydrochloride, dipicrate, and dimethiodide. The composition and nature of the salt indicate that it has a bimolecular structure. Since the properties of this base differed from known ones, we have called it dimethamine (II).

The IR spectrum (Fig. 1) in the 1600-1700 cm^{-1} region and the UV spectrum of dimethamine coincide completely with the corresponding features of dithermamine [4]. The presence in the mass spectrum of dimethamine of the peaks of ions with m/e 160 and 146 shows that it contains a 1,3-disubstituted tetrahydroquinolizone system. The fragmentation pathways of dimethamine (Fig. 2) and of N-methylcytisine are similar.

The hydrogenation of the alkaloid (II) in glacial acetic acid over Adams' catalyst, which took place very slowly even on heating, gave a tetrahydro derivative the mass spectrum of which had the peaks of ions with m/e 58 (100%), 82, 148, 149, 160, 162, 204, 206, 412. In the IR spectrum of tetrahydrodimethamine a broad band appeared at 1630 cm^{-1} and a shoulder at 1680 cm^{-1} (amide carbonyl and double bond, respectively).

The catalytic hydrogenation of dimethamine in 2 N ethanolic hydrogen chloride gave a hexahydro base the mass spectrum of which had the peaks of ions with m/e 58, 81, 97, 137, 149, 151, 163, 206, 414. The results of a comparison of the IR and mass spectra of dimethamine and its hydrogenation products with those of dithermamine showed that these alkaloids have similar structures. In actual fact, the vacuum distillation of dimethamine gave an 85.4% yield of *l*-N-methylcytisine. The choice of the position of linkage of the residues of the two molecules was made on the basis of the NMR spectrum.

Primukhamedov [5] has stated that signals at δ 7.33, 6.47, and 6.05 ppm, respectively, relate to the β-, γ-, and α-protons of an α-pyridone, while Knöffel and Schutte [6] interpret these signals in the following sequence: β, α, γ. In order to make an unambiguous assignment of the signals of the protons of an α-pyridone system, we synthesized 5-(p-nitrophenyl)thermopsine (I) by the Meerwein reaction [7]. The spectrum of (I) (Fig. 3a) had the well-defined signals of two olefinic protons at δ 6.06 and 7.49 ppm in the form of doublets with $J_1 = J_2 = 7$ Hz, and there was no additional splitting of the doublets. Consequently, this reaction leads to the replacement of the γ-proton by an aryl residue.

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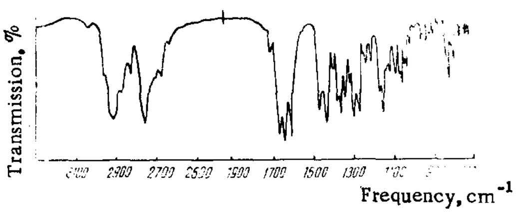

Fig. 1. IR spectrum of dimethamine in KBr.

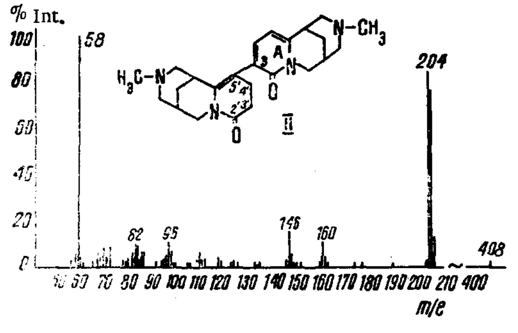

Fig. 2. Mass spectrum of dimethamine.

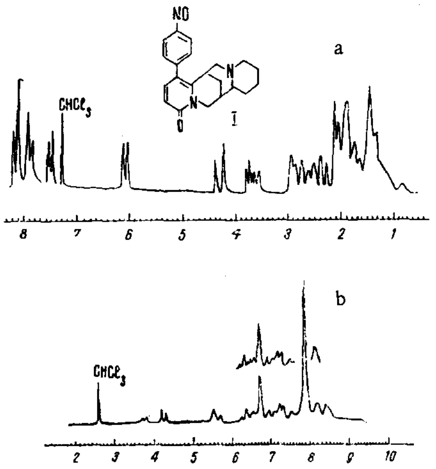

Fig. 3. NMR spectra of 5-(p-nitrophenyl)thermopsine (a) and of dimethamine (b).

The presence in the NMR spectrum of dimethamine (see Fig. 3b) of the signals of olefinic protons at δ 5.77 and 6.18 ppm in the form of doublets with a spin-spin coupling constant $J_1 = J_2 = 10$ Hz and additional splitting of the signal of the γ-proton (J=3 Hz) shows that the $C_{12}H_{17}N_2O$ residue is in position 3. Signals of protons at 1.97 and 2.12 ppm confirm the presence of two $>N-CH_3$ groups.

On the basis of what has been said, structure (II), representing 3',4'-dihydro-3,5'-bi(N-methylcytisine), is proposed.

EXPERIMENTAL

The solvent systems described previously [1] were used for chromatography.

Argentine. The combined material (211 g) from the mother liquors after the separation of the bulk of the alteramine, N-methylcytisine, pachycarpine, cytisine, and thermopsine was dissolved in 2.5 liters of chloroform and the solution was treated with 5% sulfuric acid (12 × 180 ml). Each extract was made alkaline with 25% ammonia and extracted with chloroform. The alkaloids from fractions 9–12, after being made alkaline, were reextracted with benzene and then with chloroform. The residue from the distillation of the chloroform was triturated with acetone. This gave 0.37 g of a base with mp 258–259°C, R_f 0.61 (system 2). A mixture of this alkaloid with argentine gave no depression of the melting point, and their IR and mass spectra were identical.

Dimethamine. The material (60.2 g) from the mother liquors of fractions 1–5 after the separation of 33 g of cytisine were eluted from a silica gel column with chloroform–methanol, methanol, and 5% sulfuric acid. The chloroformic-methanolic fractions 7–16, on trituration with acetone, gave 1.56 g of dimethamine with mp 216–217°C (decomp., from methanol–acetone), $[\alpha]_D + 143°$ (c 0.58; methanol); R_f 0.13 (system 2), 0.3 (system 1).

Dimethamine is readily soluble in methanol, water, and chloroform, soluble in acetone, and sparingly soluble in benzene and ether. The dihydrochloride had mp 217–218°C (acetone–methanol), the dipicrate mp 218–219°C (decomp., ethanol), and the dimethiodide mp 253–254°C (decomp., ethanol).

Argentamine. The material (21 g) from the mother liquors after the separation of argentine and dimethamine was reseparated according to the strengths of the bases present into nine fractions. Fractions 1–3 were combined and were then separated into benzene and chloroform fractions. The benzene fraction yielded 0.5 g of dimethamine. The chloroform fraction yielded a perchlorate with mp 245–246°C (ethanol), the base from which had mp 203–204°C (decomp., benzene), R_f 0.38 (system 2). The alkaloid was identified by its R_f values and its mass spectrum as argentamine.

Dehydrogenation of Dimethamine. When 0.1045 g of the base was boiled with 0.1373 g of 44% Pd on asbestos and 0.15 g of maleic acid in 3 ml of water for 7 h, no changes were detected. When the water and the maleic acid were evaporated off and the mixture was then heated at 250°C for 30 min, 0.08 g of N-methylcytisine and a resinous residue with R_f at the origin (systems 1 and 2) were obtained.

Hydrogenation of Dimethamine in Acetic Acid. A solution of 0.3526 g of dimethamine in 10 ml of acetic acid was hydrogenated over 0.1720 g of PtO_2 with heating for 4 days. The thin-layer chromatography of the products obtained gave four spots. After elimination of the catalyst, the reaction products were separated in a thin layer of silica gel in system 1. The tetrahydrodimethamine (0.1 g) had R_f 0.45 (system 1) and consisted of a vitreous mass; it did not form crystalline salts; mol. wt. 412 (mass spectrometrically). IR spectrum, cm^{-1}: 1630, 1680. NMR spectrum: no signals between 5 and 6 ppm. UV spectrum: λ_{max} 270 nm.

Hydrogenation of Dimethamine in 2 N Ethanolic HCl. In 5 ml of a 2 N ethanolic solution of hydrogen chloride, 0.1280 g of dimethamine was hydrogenated over 0.1085 g of PtO_2 for two days. After the appropriate working up, the reaction mixture was repeatedly separated preparatively on silica gel. Hexahydrodimethamine (0.04 g) with R_f 0.4 (system 1) was isolated in the form of a vitreous mass giving no crystalline salts, mol. wt. 414 (mass spectrometrically). It showed no absorption in the UV region. IR spectrum: 1630 cm^{-1}.

Vacuum Distillation of Dimethamine. The alkaloid (II) (0.1137 g) was distilled in vacuum at 228°C (8 mm Hg). This gave 0.0971 g of a base (85.4%) with R_f 0.8 (system 1), $[\alpha]_D - 168°$ (c 0.5; ethanol), mp 130-132°C, showing no depression of the melting point with N-methylcytisine. Their IR spectra were also identical.

Preparation of 5-(p-Nitrophenyl)thermopsine. p-Nitroaniline (0.015 mole) was dissolved in 9 ml of dilute HCl (1 : 1) with heating. After cooling, the salt was diazotized at 2°C with a saturated solution of sodium nitrite (3.6 ml). The solution of the p-nitrobenzenediazonium chloride was added to a solution of 0.018 mole of thermopsine and 0.005 mole of $CuCl_2 \cdot 2H_2O$ in water. The reaction mixture was stirred at 20°C until the evolution of nitrogen ceased and was then made alkaline and extracted with chloroform. The mixture of products was separated on a column of Al_2O_3, with elution by ether. This gave 0.0005 mole of 5-(p-nitrophenyl)thermopsine with mp 227-229°C, R_f 0.95 (system 1).

SUMMARY

From the epigeal part of *Thermopsis alterniflora*, in addition to the alkaloids found previously, argentine, argentamine, and a new alkaloid, dimethamine, which is a representative of the bimolecular series, have been isolated. The structure of 3-(3',4'-dihydro-N-methylcytisin-5'-yl)-N-methylcytisine has been proposed for dimethamine on the basis of IR, UV, mass, and NMR spectra and also from its conversion products.

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