A STUDY OF THE ALKALOIDS OF *Thermopsis Alterniflora*

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The epigeal part and seeds of Thermopsis alterniflora Tge. et. Schmalh. (family Leguminosae) have previously yielded cytisine and pachycarpine [1, 2] and also N-methylcytisine, thermopsine, and a base with mp 218-220° C [3].

We have studied the epigeal part of the plant collected on April 16, 1968 at the beginning of flowering (in the region of the village of Sidzhak, Tashkent oblast). Chloroform extraction gave 3.35% of combined alkaloids, which were separated into ethereal and chloroform fractions. The ethereal fraction yielded pachycarpine, N-methylcytisine, and the new alkaloid alteramine, $C_{15}H_{20}N_2O$, with mp 112° C, $[\alpha]_D$ –43° [4], and the chloroform fraction yielded N-methylcytisine, cytisine, and thermopsine.

Alteramine -- a monoacid base – forms a crystalline perchlorate, a hydrochloride, a hydriodide, a picrate, and a crystalline methiodide; the latter shows the tertiary nature of the basic nitrogen.

The IR spectrum of the alkaloid shows absorption bands at 1645 cm^{-1} (lactam carbonyl), 1565 and 1545 cm^{-1} (conjugated double bond) [5], and 3070, 910 cm^{-1} (isolated double bond in the form of a terminal methylene group) [6].

The UV spectrum has two maxima: λ_{max} 234, 312 nm (log ε 3.76, 3.79), which are characteristic for an α-pyridone chromophore [7].

The NMR spectrum of alteramine has signals corresponding to the α, β, and γ protons of the α-pyridone moiety (β_H quartet at δ 7.10 ppm, γ_H doublet at 6.14 ppm, and α_H doublet at 5.72 ppm), and also the signals of three olefinic protons showing the presence of a ring methylene group (4.91, 5.05, and 5.52 ppm) and a N-methyl group (δ = 2.15 ppm).

On hydrogenation in ethanolic solution in the presence of Raney nickel or of platinum black, alteramine very readily absorbed one mole of hydrogen forming a liquid compound – dihydroalteramine, with the composition $C_{15}H_{22}N_2O$ $[\alpha]_D$ – 100° (ethanol), giving a crystalline perchlorate with mp 272-273° C.

The IR spectrum of dihydroalteramine has absorption bands at 1660 cm^{-1} (lactam carbonyl) and 1575, 1555 cm^{-1} (conjugated double bond), and lacks bands at 3070, 910 cm^{-1} (isolated double bond).

In the NMR spectrum of the substance, the signals of olefinic groups have disappeared and the signals of a C-ethyl group have appeared at 0.9 ppm. The UV spectrum of dihydroalteramine is similar to that of the initial alkaloid.

These facts show that the double bond is isolated from the α-pyridone chromophore. The oxidation of alteramine with chromic anhydride in sulfuric acid by a modification of the Kuhn-Roth method [8] gave formic acid, and that of its dihydro derivative gave a mixture of acetic, propionic, and butyric acids. Consequently, the molecule of alteramine includes an allyl chain.

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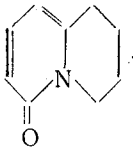
When alteramine was hydrogenated in conc. acetic acid over platinum black, three moles of hydrogen were absorbed, giving hexahydroalteramine $C_{15}H_{26}N_2O$, which formed a crystalline hydrochloride with mp 275-276° C. It was optically active and had a saturated nature.

Its IR spectrum lacked the characteristic bands for the α-pyridone moiety, and the absorption band of the carbonyl had shifted in the low-frequency direction (1625 cm^{-1}).

The catalytic reduction of alteramine over platinum black in 2 N hydrochloric acid and also the reduction of hexahydroalteramine with lithium aluminum hydride in absolute ether gave hexahydrodeoxyalteramine with the composition $C_{15}H_{28}N_2$, which formed a crystalline perchlorate with mp 128-130° C.

We have studied the mass spectra of alteramine and its dihydro, hexahydro, and hexahydrodeoxy derivatives together with some N-substituted homologs of cytisine.

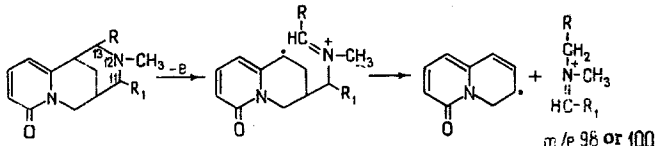
The results of a comparison of the spectra of alteramine (M^+ 244) and some derivatives of cytisine showed that the former also belong to the cytisine group, since the spectra exhibit peaks with mass numbers of 160 and 146 showing the presence of the fragment  – a 1,3-disubstituted tetrahydroquinolizinone [9].

On comparing the spectra of N-butylcytisine and dihydroalteramine it could be seen that there is a normal hydrocarbon chain in ring C, since in both spectra the peak with m/e 203 (M – 43) has the maximum intensity.

These conclusions are confirmed by the fact that the M – 43 peak and the peaks with m/e 146 and 160 in the spectrum of hexahydroalteramine are shifted by four atomic units (a.u.) by the substitution of two moles of hydrogen in the α-pyridone moiety of the molecule, leading to the appearance of peaks with m/e 207, 164, and 150.

The formation of peaks with mass numbers of 150 and 138 in the spectrum of hexahydrodeoxyalteramine instead of 164 and 150 also shows the presence of a 1, 3-substituted quinolizidine nucleus in the latter. Valuable information was obtained by a comparison of the low-molecular-weight fragments produced in the decomposition of alteramine and of its dihydro, hexahydro, and hexahydrodeoxy derivatives with cytisine and N-methyl- and N-butylcytisines and the products of their hydrogenation and reduction.

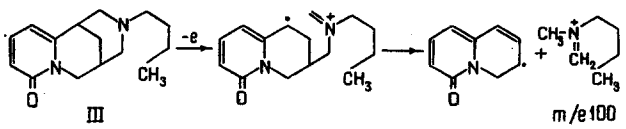
The spectrum of alteramine (I) has a peak with m/e 98 (9%) which is shifted in the spectrum of dihydroalteramine (II) by 2 a.u. and has an intensity two and a half times as great. Consequently, this fragment must arise from that part of the molecule in which the alkyl group is located.



I R or R_1-CH_2-CH=CH_2

II R or R_1-CH_2-CH_2-CH_3

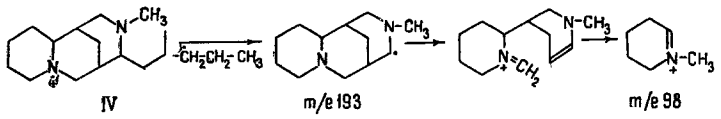
The peak mentioned above is also present in the spectrum of N-butylcytisine (III), while it is absent from the spectra of substances containing no substituents in ring C. Consequently it is formed only as a result as the detachment of N_{12} from the α-carbon atoms.



III

The peak of an ion with m/e 98 (38%) is also observed in the spectrum of hexahydrodeoxyalteramine (IV), but the existence of a metastable peak (49.7) shows that this ion is formed from a fragment with m/e 193 arising from the molecular ion by the elimination of the side chain.

The transition M → 193 is also confirmed by m = 158.



What has been said above shows that alteramine has the structure of 11-allyl- or 13-allyl-N-methylcytisine.

It is known that the hydrogenation and reduction of the alkaloid N-methylalbine gives tetrahydrodeoxy-N-methylalbine, which possesses the structure of 11-n-propyl-N-methyltetrahydrodeoxycytisine [10].

It was established by a comparison of the physical constants and IR spectra that hexahydrodeoxyalteramine is identical with tetrahydrodeoxy-N-methylalbine. Thus, alteramine has the structure 11-allyl-N-methylcytisine (I, R = H, $R_1 = CH_2 - CH = CH_2$).

EXPERIMENTAL

The mass spectra were taken on a MKh-1303 instrument and the NMR spectrum on a JNM-4H-100/100 MHz instrument.

Chromatography was carried out with type KSK silica gel and type "M" ["slow"] paper of the Volodarskii Leningrad Mill in the following solvent systems: 1) isobutanol–conc. HCl–water (100 : 13 : 27); 2) chloroform–methanol (4 : 1); and 3) chloroform–ethanol (5 : 1); the spots were revealed with Dragendorff's reagent.

Isolation of the Alkaloids. The epigeal part of Thermopsis alterniflora (100 kg) was wetted with 8% ammonia and extracted with chloroform. Then the extract was treated with 5% sulfuric acid. After the solution had been made alkaline, the alkaloids were exhaustively extracted with chloroform. This gave 3.35 kg of combined alkaloids (3.35%). Of the combined alkaloids, 702 g was dissolved in 5% sulfuric acid, the solution was washed with ether and chloroform and was made alkaline, and ethereal (78.2 g) and chloroformic (460 g) fractions were obtained.

The ethereal fraction had R_f 0.13, 0.44, 0.62, 0.76, and 0.88, and the chloroformic fraction had R_f 0.13, 0.44, 0.62, and 0.76 (TLC, system 2).

Of the ethereal fraction, 78.2 g was dissolved in 150 ml of methanol, and from this solution 37 g of pachycarpine perchlorate was obtained with mp 170-171° C (water).

Alteramine. The aqueous mother liquors from the perchlorate were separated into chloroform-soluble (A) and chloroform-insoluble (B) fractions. After being made alkaline, 28 g of A was separated into petroleum-ether, ethereal, and chloroform fractions. On concentration, the petroleum-ether fraction deposited alteramine with mp 112° C (3.52 g), $[\alpha]_D$ −43° (c 1; ethanol), R_f 0.87 (TLC, system 2), 0.43. (system 1); time of chromatography 32 h, migration of front 16 cm.

IR spectrum, cm^{-1}: 1645, 1565, 1545, 3070, 910 cm^{-1}. UV spectrum: $\lambda_{max}^{C_2H_5OH}$ 234, 312 nm (lg ε 3.76; 3.79).

Found %: C 73,60; 73,90; H 8,29; 8,46; N 11,48; 11,68. *M* 244 (mass spectrometric). $C_{15}H_{20}N_2O$. Calculated %: C 73,77; H 8, 19; N 11,47.

The melting point of the perchlorate was 234-235° C (ethanol), that of the hydriodide 212-213° C (acetone), that of the picrate 215-216° C (ethanol), that of the hydrochloride 185-186° C (methanol – acetone), and that of the methiodide 225-226° C (ethanol).

On treatment with hot petroleum ether, the ethereal fractions yielded another 1.4 g of alteramine, after which the mother liquor was separated on a column of silica gel. Elution was performed with a mixture of chloroform and methanol (99 : 1), and eluates 1-15 gave 6.2 g of alteramine.

N-Methylcytisine and Cytisine. The chloroformic fraction yielded N-methylcytisine in the form of the perchlorate with mp 281-282° C (4.2 g).

Then on treatment with acetone, 460 g of the chloroformic fraction yielded 172 g of cytisine with mp 153° C. The acetone mother liquor was separated into an ethereal (38.4 g) and a chloroformic (242 g) fraction. The ethereal fraction yielded N-methylcytisine perchlorate (30.1 g). The chloroformic fraction was dissolved in methanol and the solution was acidified with perchloric acid. A crystalline mixture of N-methylcytisine and cytisine perchlorates (127.7 g) deposited.

Thermopsine. The mother liquor from the perchlorates was converted into the bases (130 g) and separated on a column of silica gel. Elution with a mixture of chloroform and methanol (98 : 2) gave thermopsine with mp 206-207° C (26.9 g), N-methylcytisine, and cytisine.

Dihydroalteramine. Alteramine (0.52 g) was shaken in ethanol in an atmosphere of hydrogen in the presence of Raney nickel. The amount of hydrogen absorbed was 51 ml. The solution was separated from the catalyst, and a perchlorate with mp 272-273° C (ethanol) was obtained. The base formed an oil, $[\alpha]_D$ – 100° (c 1; ethanol), R_f 0.78 (TLC, system 3). IR spectrum, cm^{-1}: 1660, 1570, 1555. UV spectrum: $\lambda_{max}^{C_2H_5OH}$ 233, 310 nm (lg ε 3,64; 3,62). Mol. wt. 246 (mass spectrometry).

The partial hydrogenation of alteramine over Pt in ethanol also gave dihydroalteramine.

Hexahydroalteramine. In 15 ml of glacial acetic acid in the presence of 0.253 g of PtO_2, 0.7 g of alteramine was hydrogenated for 7 h; 196 ml (3.05 moles) of hydrogen was absorbed.

After separation from the catalyst, the solution was concentrated, made alkaline with conc. ammonia, and extracted with ether. The residue after the distillation of the ether was dissolved in ethanol and acidified with an ethanolic solution of hydrogen chloride. Crystallization from a mixture of ethanol and acetone gave a hydrochloride with mp 275-276° C. From the hydrochloride the base hexahydroalteramine was obtained with mp 264-265° C (acetone), $[\alpha]_D$ – 52.5° (c 1.2; ethanol), R_f 0.65 (TLC, system 2). IR spectrum, cm^{-1}: 1625; mol. wt. 250 (mass spectrometry).

Oxidation of Alteramine. Alteramine (0.25 g) was dissolved in an oxidizing mixture consisting of 4 g of CrO_3 and 6 ml of conc. H_2SO_4 in 25 ml of water. The mixture was heated in the water bath under reflux for 4 h.

The reaction products were distilled off from the reaction mixture with steam. The aqueous distillate was made alkaline with diethylamine to pH 8 and concentrated to 2-3 drops.

The acid formed was identified as formic acid, R_f 0.42, on a thin layer of cellulose [tert-butanol–ammonia–water (20 : 1 : 4) system], plate dimensions 7 × 12 cm; revealing agent Bromophenol Blue.

Oxidation of Dihydroalteramine. Dihydroalteramine (0.1 g) was dissolved in chromic acid mixture (2 ml of conc. H_2SO_4 and 1 g of CrO_3) and 8 ml of water was added. The mixture was then heated in the water bath under reflux for 6 h.

The acids formed were distilled off from the reaction mixture with steam. The distillate was made alkaline with diethylamine and evaporated to 1-2 drops; this residue was then chromatographed with markers of acetic, propionic, butyric, and valeric acids treated with diethylamine. The mobile phase was butanol saturated with water. The vessel contained on the bottom a 0.025 M (aqueous) solution of diethylamine saturated with butanol. The time of chromatography was 16 h, the solvent front migrating 28 cm. The spots were revealed with a 0.04% solution of p-Bromocresol Purple in ethanol. Spots with R_f values of 0.35, 0.48, and 0.61, corresponding to acetic, propionic, and butyric acids, respectively, were formed.

Hexahydrodeoxyalteramine. A mixture of 0.1 g of alteramine and 0.1 g of PtO_2 in 10 ml of 2 N hydrochloric acid was shaken in an atmosphere of hydrogen. Over 4 h, 47 ml of hydrogen was absorbed. The solution was separated from the catalyst, made alkaline, and extracted with ether. The residue formed a perchlorate with mp 128-130° C (methanol–ether).

The Ir spectrum of the perchlorate coincided completely with that of the perchlorate of tetrahydrodeoxy-N-methylalbine, mol. wt. 236 (mass spectrometry).

Reduction of Hexahydroalteramine. To 0.2 g of hexahydroalteramine in 200 ml of absolute ether was added 0.4 g of $LiAlH_4$ in 50 ml of absolute ether, and the reaction mixture was heated for 5 h. Then 10 ml of water was added, the ethereal layer was separated off, and the aqueous layer was extracted with ether.

The perchlorate obtained from the ethereal residues was identical with the perchlorate of hexahydrodeoxyalteramine.

SUMMARY

1. The epigeal part of Thermopsis alterniflora at the beginning of flowering contains 3.35% of combined alkaloids. The separation of the combined bases yielded cytisine, N-methylcytisine, pachycarpine, thermopsine, and the new alkaloid alteramine.

2. The structure of 11-allyl-N-methylcytisine has been established for alteramine.

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