DITHERMAMINE – A NEW BIMOLECULAR ALKALOID FROM Thermopsis lanceolata

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From the epigeal part of Thermopsis lanceolata, in addition to thermopsamine, thermopsine, cytisine, N-methylcytisine, pachycarpine, and rhombifoline, we have isolated a base with mp 235°C [1]. The results of a molecular weight determination by a comparison of osmotic pressures [2], by titration, and by mass-spectrometric methods has shown that this base possesses diacid properties and has mol. wt. 488, which corresponds to the results of elementary analysis, $C_{30}H_{40}N_4O_2$ (perchlorate, mp 221-222°C, ethanol; picrate, mp 203-204°C, ethanol). The IR spectrum of the alkaloid has absorption bands at 2600-2800 cm^{-1} showing the presence in it of a trans-quinolizidine grouping, and at 1670, 1645, and 1610 cm^{-1} (Fig. 1), having some similarity to the bands for an α-pyridone fragment but shifted in the high-frequency direction [3]. What has been said above shows that the alkaloid is the ancestor of a new bimolecular series of quinolizidine alkaloids. Consequently, we have called it dithermamine (I). The UV spectrum of dithermamine (λ_{max} 280 nm, log ε 3.61) has no absorption maxima characteristic for α-pyridone-containing alkaloids [4].

In the mass spectrum of (I), the peak of the molecular ion has a low intensity. The peaks of ions with m/e 146 and 160 confirm the presence in the alkaloid of a 1,3-disubstituted tetrahydroquinolizone (Fig. 2a) [5].

The noncorrespondence of the spectral characteristics can be explained by the conjugation of the α-pyridone fragment with other chromophoric elements. The ozonolysis of dithermamine formed a product identical with that obtained from thermopsine. This shows that (I) is based on thermopsine with a substituent having the composition $C_{15}H_{21}N_2O$ in ring A.

The hydrogenation of dithermamine in glacial acetic acid in the presence of platinum black led to the formation of a tetrahydro product (III) with mp 274-276°C the mass spectrum of which showed, in addition to the peaks of ions with m/e 160, 161, and 146, peaks of ions with m/e 162, 163, 148, and 149 (Fig. 2c). The IR spectrum of (III) showed an absorption band at 1630 cm^{-1} (lactam carbonyl) and a weak band at 1680 cm^{-1} (double bond).

When the alkaloid was subjected to catalytic hydrogenation in an ethanolic solution of hydrogen chloride, 3 moles of hydrogen were absorbed and hexahydrodithermamine (VI) with the composition $C_{30}H_{46}N_4O_2$, mp 298°C, was obtained. The mass spectrum of the latter (Fig. 2c) lacked the peaks of ions with m/e 146 and 160, and the peaks of ions with m/e 148, 151, 163, 177 which are characteristic of lupanine and aphylline [6], had appeared.

The reduction of (IV) with $LiAlH_4$ gave an oxygen-free base the mass spectrum of which had peaks with m/e 233, 208 (100%), 136, 134, 124, 122, 110, 96, 95, 81.

Interesting results were obtained in a comparison of the mass spectra of dithermamine and its hydrogenation products in the region of the molecular weight of thermopsine. In the spectrum of the initial alkaloid (I), the peak of the ion with m/e 244, corresponding to M^{++} of dithermamine and to M^+ of thermopsine, predominates. In the spectrum of the tetrahydro base, the strongest peak is that of the ion with

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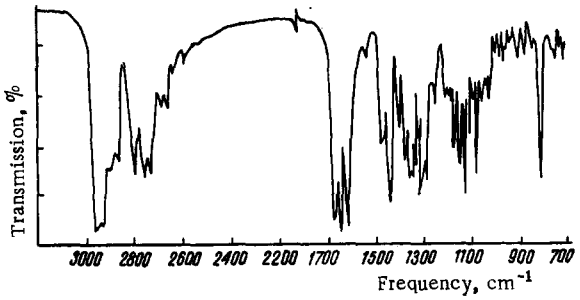


Fig. 1. IR spectrum of dithermamine (KBr).

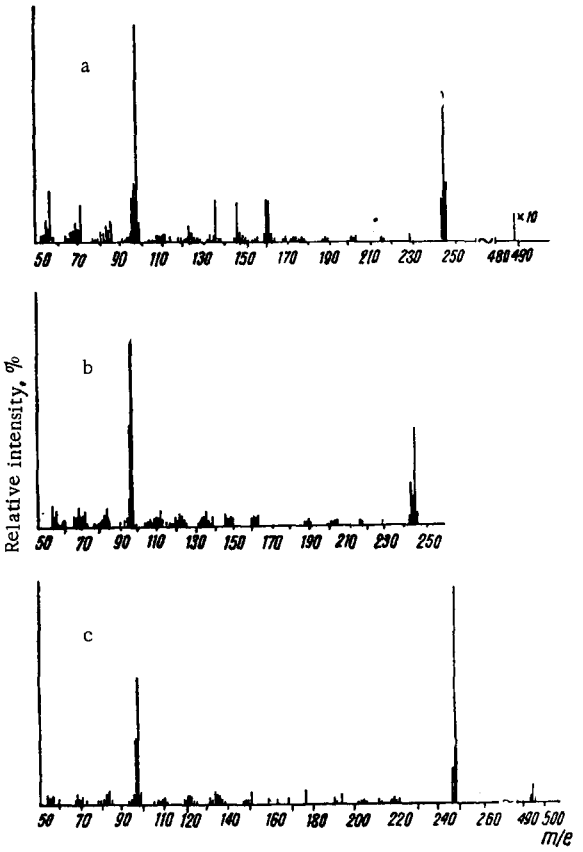


Fig. 2. Mass spectra of dithermamine (a), tetrahydrodithermamine (b), and hexahydrodithermamine (c).

m/e 246 (48%) rather than that with m/e 244 (22%). Consequently, the decomposition of dithermamine leads only to the ion of thermopsine, while (III) forms, in addition to this ion, a fragment with m/e 246 to a greater extent. In the decomposition of hexahydrodithermamine the pattern of the spectrum changes. The intensity of the peak of the ion with m/e 246 is 100%, but the peak of the ion with m/e 244 has disappeared. This course of the fragmentation confirms the conclusion that under the action of electron impact the dithermamine molecule splits with the formation of two molecules of thermopsine. In the decomposition of tetrahydro- and hexahydrodithermamines, however, no migration of hydrogen from one part of the molecule to the other takes place, since in neither of the spectra was a peak with m/e 248 observed. Taking this into account, it may be assumed that in the decomposition that part of the molecule at which the double bond arises acquires the positive charge.

The dithermamine molecule decomposes even on ordinary distillation in vacuum, giving a quantitative yield of *l*-thermopsine. The vacuum distillation of tetrahydrodithermamine gave a mixture of thermopsine and a base which remained at the start on chromatography.

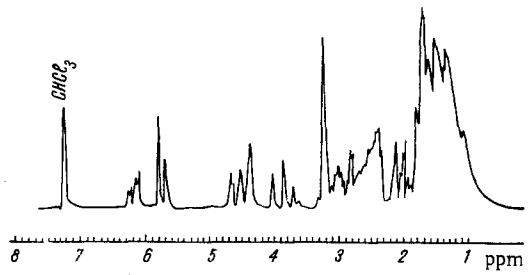
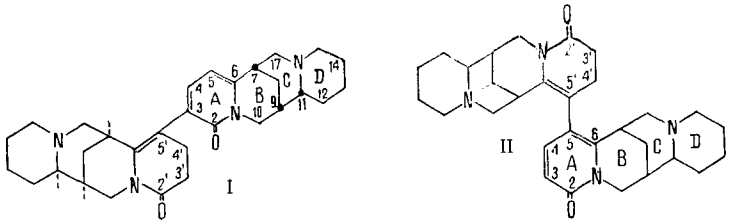


Fig. 3. NMR spectrum of dithermamine ($CDCl_3$).

What has been said above shows the bimolecular structure of the alkaloid. Several variants of the addition of the $C_{15}H_{21}N_2O$ moiety to ring A of thermopsine are possible. The choice was made on the basis of a study of the NMR spectrum of dithermamine (Fig. 3), which has the signals of two olefinic protons (doublet at δ 5.75 ppm and doublet at 6.12 ppm). These signals are in the weak-field part of the spectrum, which shows the presence of a conjugated system in (I). The hydrogens on the double bonds have the ortho arrangement, since $J_1 = J_2 = 10$ Hz. The results of an integral measurement of the signals of the protons are also in harmony with the results of elementary analysis.

The presence in the molecule of the alkaloid of three double bonds while there are signals from only two olefinic protons permits us to put forward for dithermamine the alternative structures (I) and (II).



On comparing the NMR spectra of the α-pyridone-containing alkaloids, the following values of the spin–spin coupling constants were found: $J_{\beta,\gamma} = 9$–10 Hz, and $J_{\alpha,\beta} = 7.5$ Hz [7].

In the dithermamine spectrum, J = 10 Hz, and furthermore, it shows long-range interaction (3 Hz), which is possible only when a γ proton is present. Consequently, dithermamine corresponds to structure (I): 3',4'-dihydro-3,5'-bithermopsine.

EXPERIMENTAL

Ozonolysis of Dithermamine. The base (0.3 g) was ozonized in chloroform for 20 h. The products were extracted from the chloroform with 5% H_2SO_4, and the extract was washed with ether, made alkaline, and extracted with chloroform. The mixture of products (0.180 g) was separated preparatively on silica gel in system 1 [1]. This gave 30 mg of crystals with mp 227°C having the same R_f values as the product of the ozonolysis of thermopsine performed similarly. IR spectrum, cm^{-1}: 1640 $\left(\diagup\!\!\diagdown N-\overset{|}{C}=O\right)$, 2700-2800. Mass spectrum: M^+ 194.

Hydrogenation of (I) in Acetic Acid. The hydrogenation of 0.506 g of dithermamine was performed with heating in 17 ml of acetic acid in the presence of 0.3127 g of PtO_2 for 80 h. After the separation of the catalyst, the solution was concentrated, made alkaline, and extracted with ether and chloroform. The resulting mixture of four substances was repeatedly separated by means of their different basicities, and then on a column of Al_2O_3 (elution with ether, ether–chloroform, and chloroform), and they were finally purified preparatively on silica gel. In this way, 80 mg of the base (III), 30 mg of the base (IV), and 40 mg of the initial alkaloid were isolated.

Tetrahydrodithermamine (III). Melting point of the base 274-276°C (decomp.), $[\alpha]_D$ +3° (c 1.1; chloroform), R_f 0.47 (1), no absorption in the UV region. The NMR spectrum lacked signals of olefinic protons. The distillation of (III) in vacuum at 280°C (8 mm Hg) gave thermopsine, this being identified by its R_f values in three systems and by its UV spectrum in comparison with an authentic sample, and also a carbonizing residue which remained at the start on chromatography and amounted to $\approx 50\%$ of the weight of tetrahydro base taken.

Hydrogenation of (I) in an Ethanolic Solution of Hydrogen Chloride. Dithermamine (0.1 g dissolved in 7 ml of 2 N ethanolic HCl) was hydrogenated over 0.250 g of PtO_2. After the appropriate working up and purification, the initial base and 70 mg of hexahydrodithermamine (IV) with mp 298°C (decomp.), R_f 0.4 (1), were obtained. The NMR spectrum of (IV) lacked signals in the 5-7 ppm region (on the δ scale). The IR spectrum showed strong bands at 1680 and 2680-2800 cm^{-1}. On vacuum distillation, substance (IV) decomposed into two bases with R_f 0.15 and 0 (system 3) [1].

Reduction of (IV) with $LiAlH_4$. A solution of 0.1 g of hexahydrodithermamine in 12 ml of tetrahydrofuran was treated with 0.2 g of $LiAlH_4$. The mixture was heated in the water bath for 4 h. Then it was decomposed, and the product was worked up and purified. The hexahydrodeoxydithermamine isolated consisted of an oil remaining at the starting line on chromatography (1). In its IR spectrum the band at 1630 cm^{-1} had disappeared.

Vacuum Distillation of (I). The vacuum distillation of 0.109 g of dithermamine at 240-250°C (9 mm Hg) gave 0.1065 g of a base with mp 205-206°C, $[\alpha]_D$ −150° (c 1; ethanol), R_f 0.7 (1), and 0.0012 g of residue. The base obtained was identified as thermopsine by means of its IR spectrum.

SUMMARY

The epigeal part of Thermopsis lanceolata has yielded a new alkaloid – dithermamine – which is the first representative of a bimolecular series of quinolizidine alkaloids. As the result of a study of the NMR and mass spectra of dithermamine and its reaction products, and also by its conversion into thermopsine, its structure has been established as 3-($\Delta^{5'}$-dehydro-α-isolupan-5'-yl)thermopsine.

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