ALKALOIDS OF Leontice darvasica

A. Zunnunzhanov, S. Iskandarov, and S. Yu. Yunusov

UDC 547.944/945

From the epigeal part of L. darvasica collected in the Uzbek SSR we have previously isolated thapsine, N-methylcytisine, and the new alkaloid darvasine, the alkaloid present in greatest amount being the N-methylcytisine [1]. An investigation of the alkaloids of the epigeal part collected in the Tadzhik SSR showed that the qualitative and quantitative composition of the combined alkaloids changes according to the growth site of the plant. To isolate the individual alkaloids a method of separation has been developed which is based on the different solubilities of the perchlorates and on chromatography on columns of silica gel. This has yielded 10 alkaloids belonging to the following groups: pyridine (anabasine), biphenyl (thapsine), cytisine (N-methylcytisine), sparteine (*l*-lupanine), matrine (leontine, d-sophoridine, darvasamine, darvasine, and leontalbinine), and leontidine. On the basis of the production of octadehydromatrine (III) by the dehydrogenation of darvasamine (I) and darvasine (II), and also the results of a study of their IR and NMR spectra, the structures of these two alkaloids have been established [1, 2].

In this communication we give the results of an investigation of the absolute configuration of these alkaloids. The reduction of darvasine with lithium tetrahydroaluminte forms deoxodarvasine (IV) with mp 140-141°C. The IR spectrum of this compound lacks the absorption band of the amide carbonyl and shows the absorption bands of a double bond at 1675 cm^{-1} and of a trans-quinolizidine system at 2700-2800 cm^{-1}, which excludes positions C_7-C_{11} and $C_{11}-C_{12}$ for the double bond, since when a double bond is present at a linkage node of a quinolizidine the trans band is absent [3].

The reduction of deoxodarvasine with sodium tetrahydroborate in an acid medium gave deoxodihydrodarvasine, identical with the product of the reduction of darvasamine – deoxodarvasamine (V). Consequently, darvasine is a dehydro derivative of darvasamine. To effect the transition between these alkaloids, we hydrogenated darvasine under various conditions. On hydrogenation in the presence of a platinum catalyst in glacial acetic acid and also in ethanol darvasine did not absorb hydrogen. The reaction took place only when an ethanolic solution was acidified with hydrogen chloride, but in these circumstances the carbonyl group was also reduced. A check of the information given by Bohlmann on the ease of hydrogenation of 5.17-dehydromatrine to matrine did not confirm this conclusion. None of the isomeric dehydromatrines containing a double bond at C_5-C_{17} changed on catalytic hydrogenation in ethanol and acetic acid over platinum black. Deoxodarvasine, on catalytic hydrogenation, readily absorbed one mole of hydrogen with the formation of a mixture of isomeric dihydro products. This shows the appearance of a new asymmetric center.

A study of the mass spectra of darvasamine, darvasine, and their transformation products showed that the direction of their fragmentation is similar to that of the matrine alkaloids and the differences that exist in the intensities of the main fragments can be explained by the spatial structures of the molecules [4, 5].

To establish the absolute configuration of darvasamine and darvasine we considered the ORD curves of these alkaloids. Darvasamine, just like matrine [6] gives a curve with a positive Cotton effect (Fig. 1). It has been shown that in darvasamine the conformation of ring C is the chair form and therefore on the basis of the shape and sign of the CE, the R configuration can be proposed for C_{11}. Thus, from the established relative configurations of the asymmetric centers the 11R, 7S, 6S, 5R configuration follows for darvasamine. The ORD curves of darvasine and leontalbine have a similar shape and sign, and the optically active band

---

Order of the Red Banner of Labor Institute of the Chemistry of Plant Substances of the Academy of Sciences of the Uzbek SSR. Translated from Khimiya Prirodnykh Soedinenii, No. 3, pp. 373-377, May-June, 1974. Original article submitted March 6, 1963.

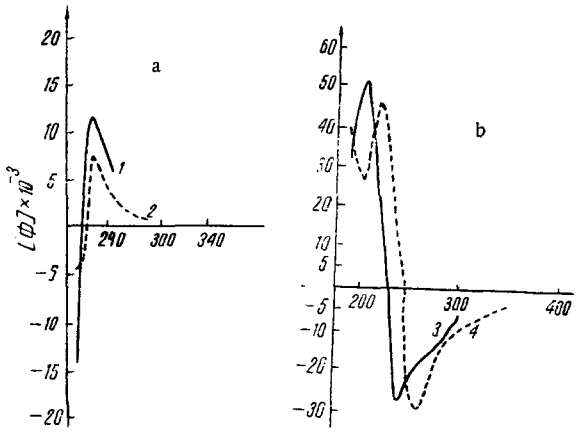
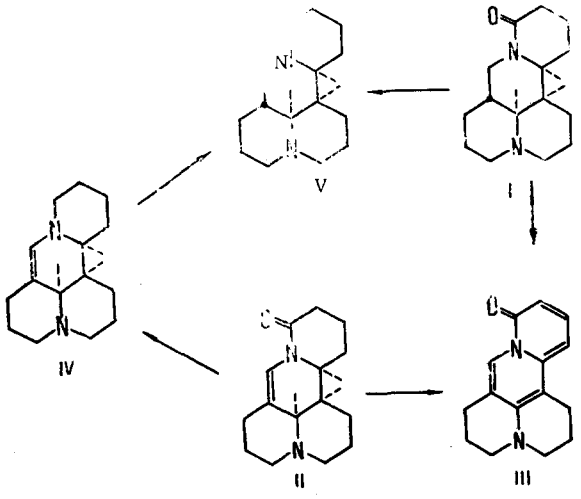


Fig. 1. ORD curves of matrine (1), darvasamine (2), leontalbine (3), and darvasine (4).

corresponds to the absorption maximum of the UV spectrum (Fig. 1b). This shows that the sign of the CE correlates with the C_{11} configuration in the unsaturated lactams of the matrine series as well.



EXPERIMENTAL

The epigeal part of L. darvasica (17.5 kg) was wetted with 8% ammonia solution and extracted with chloroform. When the concentrated extract was treated with 5% sulfuric acid, crystals of thapsine sulfate deposited. The acid mother liquor was made alkaline with 25% ammonia solution and the alkaline were extracted with chloroform. Yield 136 g.

The combined bases (136 g) in 300 ml of methanol were acidified with a 20% solution of perchloric acid. This gave crystalline N-methylcytisine perchlorate with mp 278-280°C. Yield 23.8 g.

Darvasine (II). When the methanolic solution of perchlorates was concentrated, prismatic crystals of a perchlorate with mp 249-250°C deposited. Yield 12.1 g. This perchlorate (12 g) was dissolved in 100 ml of water, the solution was made alkaline with 25% ammonia, and the base was extracted with ether. On concentration, acicular crystals of darvasine were formed with mp 145-146°C. Yield 8.0 g. The picrate had mp 231°C (decomp. ethanol) and the methiodide mp 262°C (acetone).

The perchlorate mother liquors were separated into ether-soluble (80 g) and chloroform-soluble (33g) fractions. The ether-soluble fraction (80 g) was dissolved in 100 ml of methanol, the solution was acidified with a 54% solution of perchloric acid, and, after the solvent had been driven off, the residue was dissolved in 150 ml of boiling water. On cooling, 5.1 g of leontine perchlorate was obtained with mp 255-256°C. The mother liquor from the leontine perchlorate was made alkaline with a 25% solution of ammonia and was extracted with ether. The ethereal extract was evaporated, the residue was dissolved in methanol, and the solution was acidified with a 54% solution of perchloric acid. The lupanine perchlorate that deposited was separated off, mp 208-210°C. Yield 2.0 g. The mother liquor was dissolved in water, perchloric acid was

added to pH 3, and the mixture was extracted with chloroform. This gave 40 g of perchlorates passing into the chloroform. On treatment with ethanol, anabasine perchlorate precipitated with mp 245-246°C. The combined mother liquors were dissolved in 5% sulfuric acid, and the solution was made alkaline with ammonia and was extracted with ether (17.6 g) and with chloroform (20.5 g).

The ethereal fraction (17.6 g) was dissolved in 100 ml of chloroform and the solution was extracted with 1% sulfuric acid (20×10 ml). Each fraction was made alkaline separately with 25% ammonia solution, and the bases were extracted with ether. The strongly alkaline fractions yielded a perchlorate with mp 270°C (acetone). Yield 1.0 g. Darvasamine – the base isolated from the perchlorate – melted at 102°C (ether), $[\alpha]_D$ +72° (ethanol). The hydriodide had mp 295-297°C (acetone).

d-Sophoridine. From the middle fractions obtained in separation according to basicity, d-sophoridine with mp 108-109°C was isolated by recrystallization from petroleum ether. Yield 4.0 g.

The chloroform fraction (20.5 g) was dissolved in 100 ml of methanol and the solution was acidified with 10% aqueous perchloric acid. On cooling, a perchlorate with mp 305-306°C deposited. Yield 9.0 g. A mixed melting point with a sample of leontidine perchlorate gave no depression of the melting point. The acid mother solution from the leontidine perchlorate was made alkaline with 20% aqueous caustic soda and extracted with chloroform. The resulting mixture of bases (13 g) was chromatographed on a column of silica gel and was eluted with chloroform and with chloroform–methanol. The first chloroform–methanol fractions yielded 2.0 g of leontalbinine with mp 107-108°C.

Octadehydromatrine (III). A mixture of 0.3 g of (I) and 0.15 g of 45% palladium black on asbestos was heated at 300-320°C for 30 min. After the mixture had cooled, it was dissolved in hot acetone and the solution was separated from the catalyst and the acetone was distilled off. The residue was washed with water and extracted with a mixture of acetone and ether (3:1). After concentration, the solution deposited in crystals of (III) with mp 175-176°C $[\alpha]_D$ +0°. Yield 0.015 g. A mixture with a sample of octadehydromatrine gave no depression of the melting point.

By the method described above, 0.5 g of (II) and 0.3 g of palladized asbestos gave 0.02 g of (III).

Deoxodarvasamine (V). A solution of 0.2 g of (I) in 50 ml of absolute ether was treated with 0.2 g of lithium tetrahydroaluminate in 10 ml of absolute ehter, and the mixture was heated for 6 h. After cooling, 10 ml of water was added to it. The ethereal layer was separated, the aqueous layer was extracted with ether. The combined ethereal extracts yielded 0.15 g of (V) with mp 106°C, $[\alpha]_D$ –12° (0.5; ethanol). Perchlorate, mp 243-245°C (acetone); hydriodide, mp 310-312°C (decomp., acetone).

Deoxodarvasine (IV). The reduction of 4.1 g of (II) with 6 g of $LiAlH_4$ by the method described yielded 3.8 g of (IV) with mp 140-141°C, (ether), $[\alpha]_D$ –17° (ethanol). Picrate, mp 113-115°C (methanol); methiodide, mp 186-187°C (acetone).

Deoxodihydrodarvasine (V). A solution of 0.25 g of (IV) in 20 ml of methanol was acifidied with 54% perchloric acid and 0.5 g of sodium tetrahydroborate was added. The mixture was heated on the water bath under reflux for 20 min. After cooling, it was acidified with an ethanolic solution of hydrogen chloride, and the solvent was distilled off. The dry residue was dissolved in 10 ml of water and the solution was made alkaline with 25% ammonia and exhaustively extracted with ether. Distillation of the solvent yielded 0.24 g of (V) with mp 106°C. A mixture with a sample of deoxodarvasamine gave no depression of the melting point.

CONCLUSIONS

The qualitative and quantitative composition of the combined alkaloids of Leontice darvasica depends on the growth site of the plant. From the combined alkaloids, ten belonging to six groups have been isolated. The structures and absolute configurations of darvasamine and darvasine have been established.

LITERATURE CITED

1. S. Iskandarov and S. Yu. Yunusov, Khim. Prirodn. Soedin., 132 (1969).
2. A. Zunnunzhanov, S. Iskandarov, and S. Yu. Yunusov, Khim. Prirodn. Soedin., 851 (1971).
3. F. Bohlmann, Ber., 91, 2151 (1958).
4. S. Iskandarov and S. Yu. Yunusov, Khim. Prirodn. Soedin., 106 (1968).
5. S. Iskandarov, Ya. V. Rashkes, D. Dzh. Kamalitdinov, and S. Yu. Yunusov, Khim. Prirodn. Soedin., 331 (1969).
6. S. Iskandarov, D. Dzh. Kamalitdinov, and S. Yu. Yunusov, Khim. Prirodn. Soedin., 628 (1972).