ALKALOIDS OF Ziziphus jujuba

THE STRUCTURE OF JUZIPHINE AND JUZIRINE

R. Ziyaev, T. Irgashev,
I. A. Israilov, N. D. Abdullaev,
M. S. Yunusov, and S. Yu. Yunusov

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The alkaloids of the plant Ziziphus jujuba Mill. (family Rhamnaceae), which is widely cultivated in the south of the Soviet Union, including the central Asian region [1, 2], have not been studied previously. From the leaves of the plant Z. amphibia A. Cheval isolated the aporphine alkaloid nuciferine [3], from the bark of the roots of Z. jujuba the benzyltetrahydroisoquinoline alkaloid coclaurine [4], and from the leaves of Z. mucronata Willd. N-methylcoclaurine [5] and a number of peptide bases. In all the species of Ziziphus studied, the main alkaloids were peptide compounds [6-8].

We have investigated the leaves of Z. jujuba collected in the Tashkent oblast in the period of ripening of the fruit on October 3, 1975. Ordinary chloroform extraction yielded 0.031% of combined ether-soluble and 0.017% of combined chloroform-soluble alkaloids. Treatment of the combined ether-soluble alkaloids with acetone yielded coclaurine (I) [4, 9], which proved to be the main component of the mixture of bases. The mother liquor after the separation of the (I) was separated into phenolic and nonphenolic fractions. Chromatography of the phenolic fraction of the combined alkaloids on a column of silica gel yielded isoboldine [10], norisoboldine [11, 12], asimilobine [13], and new bases which we have called juziphine (II) and juzirine (III).

Juziphine, $C_{18}H_{21}NO_3$ (II), is an optically active phenolic base and forms a crystalline hydrochloride. Its UV spectrum [λ_{max} 227, 286 nm (log ε 4.33, 3.92)] is similar to that of coclaurine. The IR spectrum of (II) has strong absorption bands at 3210-3030 (−OH), 2845, 1245 (−OCH_3), 1610, 1590 cm^{-1} (aromatic ring). The mass spectrum of juziphine does not show the peak of the molecular ion but it has the peaks of ions with m/e 192 (100%), 177, 148, and 107, which are characteristic for benzyltetrahydroisoquinoline alkaloids with methoxy and hydroxy groups in the isoquinoline and hydroxy groups in the benzyl part of the molecule [14].

The PMR spectrum of (II) ($CDCl_3$) (Fig. 1a) has the signals from a N-methyl group (2.36 ppm, 3H, singlet), a methoxy group (3.82 ppm, 3H, singlet), and three methylene groups (2.30-3.45 ppm, 6H, multiplet), from C_1−H (4.19 ppm, 1H, quartet), and from two hydroxylic protons (5.96 ppm, 2H, broadened singlet).

Two-proton doublets at 6.35 and 6.99 ppm (J = 8 Hz) have been assigned to two equivalent pairs of ortho protons of a p-hydroxybenzyl substituent, and two other one-proton doublets at 6.56 and 6.70 ppm (J = 8 Hz) to the ortho-aromatic protons of the tetrahydroisoquinoline part of the juziphine molecule. Consequently, the methoxy group and the secondary hydroxy group may be present either at C_5 and C_6 or at C_7 and C_8. The results of measurements of the intramolecular nuclear Overhauser effect showed that irradiation with a strong radio-frequency field of the protons of the methoxy group (3.82 ppm) led to a 25% increase in the intensity of the doublet at 6.70 ppm. At the same time, the intensity of the second one-proton doublet at 6.56 ppm remained unchanged, but when the methylene protons at C_4 (~2.3 and ~2.7 ppm) were irradiated this likewise rose by 21%. These facts permit an umambiguous assignment of the doublet signals at 6.56 and 6.70 ppm to C_5−H and C_6−H, respectively, and establish the position of the methoxy group at C_7 and of the hydroxy group at C_6, as is shown in the structural formula of juziphine (II).

Juzirine $C_{17}H_{15}NO_3$ (III) is an optically inactive crystalline base sparingly soluble in the usual organic solvents. Its UV spectrum [λ_{max} 239, 273, 280, 319, 331 nm (log ε 4.48, 3.63, 3.63, 3.31, 3.32)] is characteristic for the benzylisoquinoline alkaloids and is similar to that of papaverine [15, 16]. The IR spectrum of the alkaloid has a broad absorption band at 3380-3200 cm^{-1} showing the presence of hydroxy groups in the molecule. The

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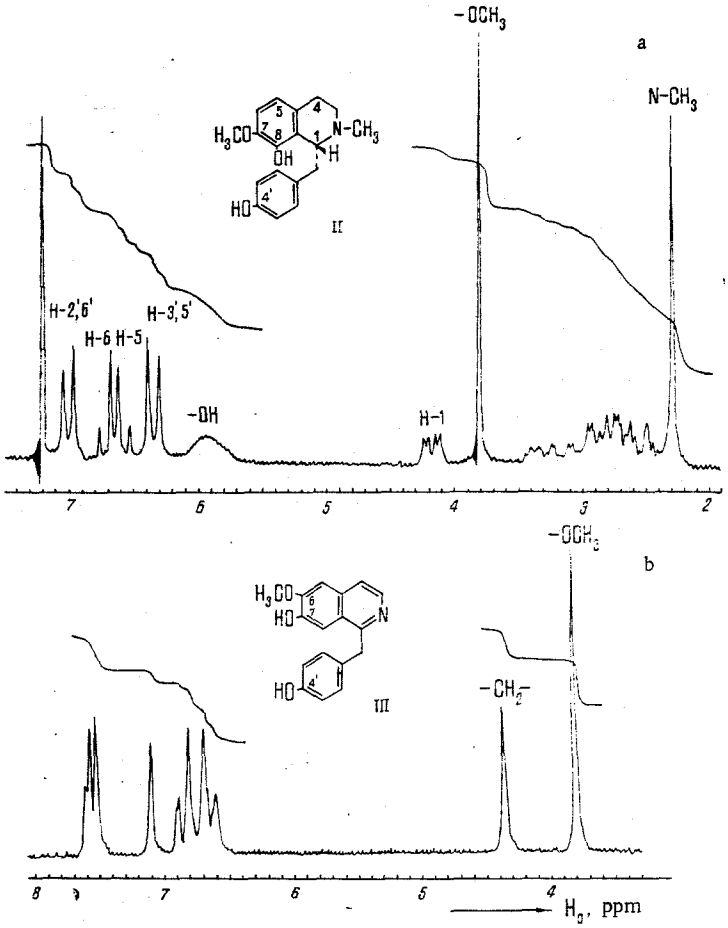

Fig. 1. PMR spectrum of juziphine in $CDCl_3$ (a) and of juzirine in CF_3COOH (b).

acetylation of (III) with acetic anhydride in pyridine gave O,O-diacetyljuzirine. The mass spectrum of juzirine (m/e 281 (M^+), 280 (100%), 265, 264, 249, 236, 220, M^{++} 140.5) is also characteristic for the benzylisoquinoline alkaloids [16]. The PMR spectrum of the alkaloid (CF_3COOH) (Fig. 1b) shows signals from the protons of a methoxy group (3.82 ppm, 2H, singlet), a methylene group (4.37 ppm, 2H, singlet), and eight aromatic protons (6.64-7.60 ppm). The facts given enable juzirine (III) to be assigned to the benzylisoquinoline alkaloids and the formula to be developed in the following way: $C_{16}H_{10}$ (>N−) (−OCH_3) (−$OH)_2$.

The developed formulas of juzirine and coclaurine (I) have the same substituting groups but differ from one another by four hydrogen atoms. Consequently, it may be assumed that (III) is tetradehydrococlaurine. In actual fact, when coclaurine was dehydrogenated over palladium black a base identical with juzirine was obtained. Thus, juzirine (III) has the structure of 7-hydroxy-1-(4'-hydroxybenzyl)-6-methoxyisoquinoline.

From the phenolic fraction of the combined ether-soluble alkaloids of Corydalis gortschakovii collected in the upper reaches of the river Pskem [17, 18] a base was isolated with mp 158-159°C (methanol, $[\alpha]_D$ +18° (c 0.33; chloroform), giving a crystalline hydrochloride with mp 230-231°C (acetone). A direct comparison of this base with juziphine (TLC, NMR and mass spectra) showed their identity. A mixture of the hydrochlorides of the two bases showed no depression of the melting point. The ORD curve of juziphine, having two negative Cotton effects at 241 and 289 nm, practically coincides with that of gortschakoine [18, 19]. Consequently, the asymetric center of juziphine has the R configuration.

EXPERIMENTAL

For chromatography we used KSK silica gel. The UV spectra were taken on a Hitachi spectrophotometer (in ethanol), the IR spectra on a UR-10 spectrophotometer (molded tablets with KBr), the mass spectra on a MKh-1303 mass spectrometer, and the PMR spectra on a JNM-4H 100/100 MHz instrument with hexamethyldisilane as internal standard (δ scale).

Isolation of the Alkaloids. The air-dry comminuted leaves of Z. jujuba Mill. (25 kg) were wetted with 10% ammonia solution and the alkaloids were exhaustively extracted with chloroform. The chloroform extract was treated with 10% sulfuric acid. The acid solution was washed with ether and, with cooling, it was made alkaline with a 25% solution of ammonia. The alkaloids were extracted first with ether and then with chloroform. This gave 7.8 g of ether-soluble and 4.2 g of chloroform-soluble alkaloids (total yield 0.048% of the weight of the dried plant).

Coclaurine (I). When the combined ether-soluble alkaloids were treated with acetone, 3.2 g of a base was isolated. After crystallization from methanol, its mp was 218-220°C. A mixture with an authentic sample of coclaurine gave no depression of the melting point. Their IR spectra were identical.

From the coclaurine mother liquor by the addition of an ethanolic solution of hydrogen chloride we obtained 0.38 g of a mixture of hydrochlorides. Coclaurine hydrochloride with mp 261-263°C (methanol, decomp.) was isolated from them by fractional crystallization from methanol. The mother solution of hydrochlorides was evaporated, the residue was dissolved in water, the solution was made alkaline with ammonia, and the alkaloids were extracted first with ether and then with chloroform (0.41 g). The ethereal extract was treated with a 5% solution of caustic soda, after which it was washed with water and dried with anhydrous potassium carbonate. This gave 0.40 g of the nonphenolic fraction of the combined ether-soluble material. The alkaline solution containing the phenolic bases was acidified with hydrochloric acid, made alkaline with 25% ammonia solution, and the alkaloids were extracted with ether.

The phenolic fraction of the bases obtained (3.42 g) was chromatographed on a column of silica gel, using mixtures of benzene and methanol (98 : 2, 95 : 5, and 9 : 1). The benzene–methanol (98 : 2) eluate yielded isoboldine (0.25 g), asimilobine (0.16 g), and juziphine (0.05 g). Elution with the 95 : 5 mixture gave coclaurine (0.22 g) and a mixture of three bases (1.35 g). When this mixture was rechromatographed on a column of silica gel, juzirine (0.12 g) and norisoboldine (0.51 g) were isolated.

Isoboldine, mp 123-125°C (benzene–methanol); hydrochloride with mp 257-259°C (decomp.). A mixture with an authentic sample of isoboldine gave no depression of the melting point.

Asimilobine, mp 175-177°C (acetone), $[\alpha]_D^{22}-210°$ (c 0.17; chloroform); hydrochloride with mp 242-244°C (decomp.; acetone). A mixture with an authentic sample of asimilobine gave no depression of the melting point.

Juziphine (II), mp 158-159°C (methanol), $[\alpha]_D+18°$ ($CHCl_3$), hydrochloride with mp 230-231°C (decomp.; acetone).

Norisoboldine, mp 192-194°C (acetone), $[\alpha]_D^{22}+42°$ (c 0.2; ethanol).

Methylation of Norisoboldine. Norisoboldine was methylated by Gress's method, and a crystalline substance was obtained with mp 122-124°C (benzene–methanol) which gave no depression of the melting point with an authetic sample of isoboldine.

Juzirine (III), mp 203-205°C (acetone); hydrochloride with mp 237-239°C (decomp.; acetone).

Dehydrogenation of Coclaurine. A carefully ground mixture of 0.1 g of coclaurine, 0.2 g of palladium black, and 1 g of naphthalene was heated in a current of nitrogen at 205°C for 5 h. Then the reaction mixture was treated with chloroform, the catalyst was filtered off, and the reaction product was extracted from the chloroform with 5% sulfuric acid. The acid solution was washed with ether and was made alkaline, and the bases were extracted with chloroform. The solvent was evaporated off, the residue was dissolved in 5 ml of acetone, and the solution was made weakly acid with an ethanolic solution of hydrochloric acid. The crystals of hydrochloride that deposited had mp 235-237°C (decomp.). A mixture with the hydrochloride of juzirine (III) gave no depression of the melting point. Their IR spectra were identical.

SUMMARY

Six bases have been isolated from the leaves of the plant Ziziphus jujuba Mill. family Rhamnaceae, cultivated in Tashkent: coclaurine, which has been isolated previously, and isoboldine, norisoboldine, asimilobine, which have been isolated for the first time, and the new juziphine and juzirine. It has been established that juziphine has the structure of 8-hydroxy-1R-(4'-hydroxybenzyl)-7-methoxytetrahydroisoquinoline, and juzirine that of 7-hydroxy-1-(4'-hydroxybenzyl)-6-methoxyisoquinoline.

Juziphine has also been isolated from the epigeal part of Corydalis gortschakovii.

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BIOSYNTHESIS OF ALKALOIDS IN *Sophora alopecuroides*

Yu. K. Kushmuradov, Kh. A. Aslanov, Kh. R. Sohütte, and S. Kuchkarov

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The alkaloid composition of Sophora alopecuroides L. has been studied by various workers [1-4]. This plant is characterized by a high content of quinolizidine alkaloids of the matrine, sparteine, cytisine, and aloperine groups.

We [5] have established that in S. alopecuroides sophoridine, matrine and sophocarpine, and sophocarpidine are formed from lysine or cadaverine. It was shown that when shoots were fed with [1,5-^{14}C]cadaverine the proportion of it included in the sophoridine was considerably higher than in the matrine. It is obvious that this plant species contains specific enzymes ensuring the formation of a A/B, A/C, C/D-trans, and B/C-cis conformations and of rings B/C in the boat form (sophoridine) that are considerably more effective than in the case of the synthesis of matrine (A/B-trans, A/B-cis, B/C-cis, C/D-trans linkage).

The schemes for the biosynthesis of alkaloids known in the literature [6], determined with the aid of labelled atoms, do not explain fine details of the alkaloid spectra connected with the stereochemical features of biosynthesis. In view of this we shall consider how the conformational state of the precursor of the quinolizidine alkaloids can affect the isomeric composition of the alkaloids formed. In the first place, we may note that, depending on the species of plant within a given family and its vegetation phase, a *l*-(amino acid) – lysine – leads to the formation of both the *l*- and d-forms of the quinolidizine bases (for example, pachycarpine,

V. I. Lenin Tashkent State University. Institute of Plant Biochemistry, Academy of Sciences of the GDR, Halle.

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