N-OXIDES OF THALICMIDINE AND PREOCOTEINE FROM THE ROOTS OF Thalictrum minus

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By chloroform extraction we have isolated 0.11% of combined ethereal and 0.50% of combined chloroform alkaloids from the roots of Th. minus collected in September, 1971 at Lyashkarakskai, Tashkent oblast, at the stage of the withering of the epigeal part.

From the chloroform fraction of the combined alkaloids, by separation on a column of alumina we have obtained thalicmine, thalicmidine, thalicminine, and a crystalline mixture of bases. The preparative separation of the latter gave a base (I) with mp 192-193° C (decomp.) and a base (II) with mp 199-200° C (decomp.).

Alkaloid (I) is readily soluble in water, methanol, and ethanol and less readily in acetone and chloroform. The UV spectrum of (I) [λmax 227, 282, 308 nm (log ε 4.42, 4.10, 4.07)] is characteristic for 1,2,9,-10-tetrasubstituted aporphine bases [1]. In the IR spectrum of (I) there are absorption bands at 3400 cm^{-1} (OH) and 2855 cm^{-1} (OCH_3). In the mass spectrum of the base there are fragments with m/e 357 (M^+) 6%; 341 (M−16) 100%; 340 (M−17) 97%; 326 (M−31) 11%; and 298 (M−59) 69%. The NMR spectrum of (I) has the signals of a N-methyl group (three-proton singlet at 6.92 ppm) and of three methoxy groups (nine-proton singlet at 6.45 ppm). In the weak-field region there are three one-proton singlets at 3.58, 3.46, and 2.23 ppm due to aromatic protons. The UV, IR, and NMR spectra of (I) and of thalicmidine are very similar, but the new base differs in its mass, solubility, and R_f values in various systems of solvents. Its solubility in water, the mass difference of 16 units, and the nature of its fragmentation – i.e., the low intensity of the molecular ion and the ejection of oxygen with the formation of a strong M−16 peak, which is frequently observed in the mass spectrometry of N-oxides of aliphatic amines [2] – permit the assumption that substance (I) is thalicmidine N-oxide.

The results of a comparison of the melting point, the R_f values, and the IR spectra of our base and of the thalicmidine N-oxide obtained by the oxidation of thalicmidine with H_2O_2 in ethanolic solution showed that they are completely identical. The reduction of (I) with Zn/HCl gave thalicmidine. The properties of base (II) are similar to those of base (I). The UV spectrum of (II) [λ_{max} 226, 282, 306 nm (log ε 4.52, 401, 411)] shows that base (II) also belongs to the 1,2,9,10-tetrasubstituted aporphine series. Its IR spectrum has absorption bands at 3400 cm^{-1} (OH) and 2855 cm^{-1} (OCH_3). Mass spectrum, m/e: 387 (M^+) 4%; 371 (M−16) 100%; 370 (M−17) 59%; 356 (M−31) 17%; 328 (M−59) 43%. NMR spectrum: 6.90 ppm (three-proton singlet of a N-methyl group); 6.45 ppm (three-proton singlet of a methoxy group); 6.37 ppm (nine-proton singlet of three methoxy groups); and 3.44 and 2.26 ppm (two one-proton singlets of aromatic protons). In a comparison of the NMR and mass spectra of bases (I) and (II) it was found that (II) differs from (I) by an additional methoxy group. The absence from the NMR spectrum of base (II) of a signal at 3.58 ppm due to the aromatic proton at C_3 shows that the additional methoxy group occupies the C_3 position. According to what has been said above, the base (II) must be 1-hydroxy-2,3,9,10-tetramethoxyaporphine N-oxide. An oily base – preocoteine – has previously been isolated from Th. fendleri, and for this the structure of 1-hydroxy-2,3,9,10-tetramethoxyaporphine has been established [3]. By the reduction of (II) we obtained an oily base (III). The NMR spectrum of (III) and of preocoteine were identical (Table 1).

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TABLE 1

Substance	N–CH_3	OCH$_3$					H_{arom}	
		C_4	C_8	C_3	C_9	C_{10}	C_6	C_{11}
Base (III)	7,44	—	6,09	6,09	6,14	6,14	3,29	2,01
Preocoteine	7,48	—	6,08	6,08	6,12	6,12	3,26	2,01

The methylation of (III) with an excess of diazomethane gave its monomethyl ether. The latter was shown to be identical with thalicmidine [4] by a comparison of R_f values and IR spectra. In this way we confirmed that the base that we had isolated is actually precoteine N-oxide.

EXPERIMENTAL

The UV spectra were taken on a Hitachi instrument in ethanolic solution, the mass spectra on an MKh-1303 instrument with a glass inlet system at 40 eV and 0.5 mA, and the NMR spectra on a JNM-4H-100/100 MHz instrument with HMDS as internal standard, using the τ scale. The spectra of (I) and (II) were obtained in CF_3COOH and that of III in $CDCL_3$. The IR spectra were recorded on a UR-10 instrument.

Isolation of the Alkaloids. The base was extracted with chloroform from 3 kg of air-dry finely comminuted plant material moistened with 8% aqueous ammonia. The chloroform extract was treated with 10% sulfuric acid, and the acid extracts were washed with ether and were then made alkaline with 25% aqueous ammonia. The bases were extracted with ether and then with chloroform. This gave 3.5 g of combined ethereal alkaloids and 15.0 g of combined chloroform alkaloids.

The chloroform fraction (15.0 g) was chromatographed on a column of alumina (300 g). The bases were eluted successively with ether, ethyl acetate, chloroform, acetone, and methanol (fraction A). The ethereal fraction was treated with acetone. Thalicmine was isolated. On evaporation, the ethyl acetate fraction gave thalicmidine, and the chloroform and acetone fractions thalicminine.

Thalicmidine and Preocoteine N-Oxides. When fraction A was treated with acetone, a crystalline mixture of bases deposited and this was separated preparatively on a fixed layer of silica gel–gypsum (10:1) in the chloroform–methanol (5:1) system. The bases were eluted with chloroform, giving thalicmidine N-oxide with mp 192-193°C (decomp.), R_f 0.36, and preocoteine N-oxide with mp 199-200°C (decomp.), R_f 0.18.

Oxidation of Thalicmidine; Thalicmidine N-Oxide. A solution of 70 mg of thalicmidine in 13 ml of ethanol was treated with 4 ml of 30% hydrogen peroxide. After 5 days, 13 ml of water was added to the reaction mixture, and the ethanol was distilled off under vacuum. The residue was made alkaline with 25% aqueous ammonia and the base was extracted with chloroform. Yield 34.5 mg, mp 192-193°C (decomp.).

Preocoteine. A solution of 200 mg of preocoteine N-oxide in 12 ml of conc. hydrochloric acid was treated with zinc, and the mixture was left for two days. Then it was filtered, and the filtrate was made alkaline with 25% aqueous ammonia, the bases were extracted with ether and with chloroform. Distillation of the solvents yielded 120 mg of an ethereal and 70 mg of a chloroform fraction.

The ethereal fraction (120 mg) was chromatographed on a column of alumina. The ethyl acetate eluate gave 41 mg of preocoteine in the form of an oil.

Monomethyl Ether of Preocoteine (Thalicmidine). An ethereal solution of diazomethane was added to a solution of 34 mg of preocoteine in 2.5 ml of methanol. After six days (check for complete methylation by TLC), the solvent was evaporated off. The residue was chromatographed on a column of alumina. Preparative separation (silica gel–gypsum) in the chloroform–methanol (10:1) system gave thalicmidine in the form of an oil.

SUMMARY

The roots of Th. minus have yielded thalicmine, thalicmidine, and thalicminine, and two new bases: (I) with mp 192-193°C (decomp.) and (II) with mp 199-200°C (decomp.). It has been established that (I) is thalicmidine N-oxide and (II) preocoteine N-oxide.

LITERATURE CITED

1. M. Shamma and W. A. Slusarchyk, Chem. Rev., No. 1, 59 (1964).
2. N. Bild and M. Hesse, Helv. Chim. Acta, 50, 1885 (1967).

3. M. Shamma, R. J. Shine, and B. S. Ducock, Tetrahedron, 23, No. 7, 2887 (1967); M. Shamma and R. S Ducock, J. Pharmac. Sci., 57, No. 2, 262 (1968).
4. Z. F. Ismailov, M. V. Telezhenetskaya, and S. Yu. Yunusov, Khim. Prirodn. Soedin., 136 (1968).