Cactaceae Alkaloids VII: Alkaloids of *Echinocereus merkeri*

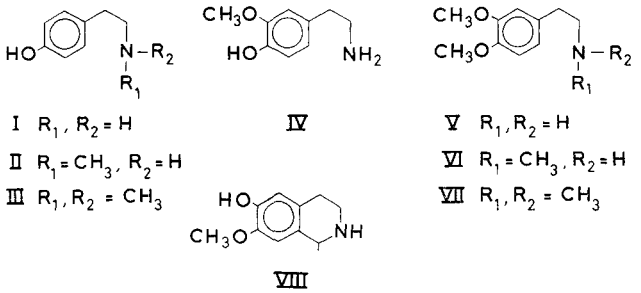
S. AGURELL, J. LUNDSTRÖM and A. MASOUD

Abstract □ *N,N*-Dimethyl-3,4-dimethoxyphenethylamine has been isolated for the first time as a natural product from *Echinocereus merkeri* Hildm. *N*-Methyl-3,4-dimethoxyphenethylamine, 3,4-dimethoxyphenethylamine, 3-methoxytyramine, and hordenine were also identified in this species together with the tetrahydroisoquinoline alkaloid salsoline.

Keyphrases □ Cactaceae alkaloids—*Echinocereus merkeri* □ *N,N*-Dimethyl-3,4-dimethoxyphenethylamine—isolation, identification □ β-Phenethylamines, salsoline—isolation, identification □ TLC—separation, identification □ GLC—identity □ Mass spectroscopy—identity

A recent screening of the family Cactaceae for the presence of alkaloids indicated that the genus *Echinocereus* is rich in alkaloids (1). Brown *et al.* (2) also reported the presence of several alkaloids in two *Echinocereus* species. However, up to date, there has been no structural work reported on the *Echinocereus* alkaloids.

Echinocereus merkeri Hildm., growing exclusively in Northern Mexico, is one of the 73 species of the genus *Echinocereus* which is indigenous to the U.S.A. and Mexico. Due to the considerable amount of alkaloids encountered in the authors' preliminary screening of this plant (1), it was decided to investigate the structure of these alkaloids



Alkaloid extraction followed by fractionation on an alumina column led to the isolation and identification of the compounds shown in Table I. These compounds were identified by comparison with synthetic reference materials using TLC, GLC, and mass spectra. The two major alkaloids, *N,N*-dimethyl-3,4-dimethoxyphenethylamine (VII) and *N*-methyl-3,4-dimethoxyphenethylamine (VI) representing some 60 and 20%, respectively, of the crude alkaloid extract, were isolated as hydrochlorides. It should be added that the proportions of these alkaloids are established for cacti extracted during the summer, however, the pattern appears to be somewhat different in plants extracted during the winter season.

The now identified compounds with the exception of salsoline (1-methyl-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline) are simple β-phenethylamines. So far all reported cactus alkaloids are either β-phenethylamines or simple ring closed derivatives thereof—*viz.*, tetrahydroisoquinolines.

Table I—Column Chromatographic Separation of the Crude Alkaloid Extract of *E. merkeri*

Solvent[a]	Alkaloid Identified	Structure
Chloroform–benzene		
1:2	—	—
1:1	*N,N*-Dimethyl-3,4-dimethoxyphenethylamine	VII
2:1	—	—
Chloroform	—	—
Chloroform–methanol		
4:1	*N*-Methyl-3,4-dimethoxyphenethylamine	VI
1:1	—	—
Methanol	3,4-Dimethoxyphenethylamine	V
Water–methanol		
1:1	3-Methoxytyramine	IV
	Hordenine	III
	Salsoline	VIII

[a] One hundred milliliters of each solvent was passed through the column. Fractions of 10 ml. each were collected and analyzed by GLC.

The occurrence of 3,4-dimethoxyphenethylamine (V) in nature was lately established for the first time in *Lophophora williamsii* (3). Since, it has been identified in several *Trichocereus sp.* (1). *N*-Methyl-3,4-dimethoxyphenethylamine (VI) has been encountered (1) in nature only once before, in *Lepidocorypantha runyonii*. *N,N*-Dimethyl-3,4-dimethoxyphenethylamine (VII) has never been reported before to occur in nature. Thus, a series of dimethoxy-β-phenethylamines, with none to two *N*-methyl groups has now been established in cacti.

Apart from the phenethylamines, the cactus extract also contained a phenolic alkaloid (M^+ 193) showing the fragmentation pattern of a 1-methyltetrahydroisoquinoline alkaloid with a base peak of *m/e* 178 ($M^+ - 15$). Comparison by GLC and mass spectrometry with authentic salsoline and its isomer (1-methyl-7-hydroxy-6-methoxytetrahydroisoquinoline) showed the isolated compound to be salsoline. Salsoline is previously only known from Chenopodiaceae although the closely related alkaloid carnegine (*O,N*-dimethylsalsoline) is known from Cactaceae.

EXPERIMENTAL

Experimental details and synthesis of reference materials have been described in previous publications (1, 4). Reference plants of *E. merkeri* are maintained in the author's greenhouse. Five cacti weighing 3.42 kg. were extracted to yield 538 mg. of crude alkaloids.

A small amount, about 10%, of the crude extract was fractionated on an ion-exchange column (IRA 400) into phenolic and nonphenolic alkaloids (1). These fractions were then chromatographed by GLC (Fig. 1) for preliminary qualitative and mass spectrometric information.

The major part, about 90%, of the crude extract was fractionated on a 2 × 20-cm. aluminum oxide column (Merck, activity II–III

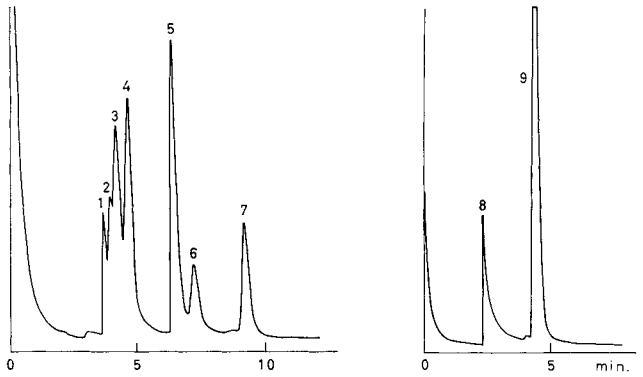


Figure 1—*Gas chromatogram of (left) phenolic; (right) nonphenolic alkaloid fraction of* Echinocereus merkeri. *Column: 1.83 m. (6 ft.) × 0.41 cm. (0.125 in.); 5% SE-30 on Gas Chrom P; initial temp. 130°, progr. 6°/min. Peak 1 = hordenine, peak 2 = 3-methoxytyramine, peak 3 = unknown, peak 4 = N,N-dimethyl-3,4-dimethoxyphenethylamine, peak 5 = salsoline, peaks 6–7 = unknowns, peak 8 = unknown (M^+ = m/e 140, base peak = 58), peak 9 = mixture of* N-*methyl- and* N,N-*dimethyl-3,4-dimethoxyphenethylamine.*

acc. to Brockmann) and eluted with the solvents shown in Table I. The eluates were investigated by TLC and GLC using SE-30 and XE-60 columns (1). *N,N*-Dimethyl-3,4-dimethoxyphenethylamine, and *N*-methyl-3,4-dimethoxyphenethylamine, were isolated using preparative column chromatography, and recrystallized as hydrochlorides from hot chloroform upon the dropwise addition of ether. Melting points of hydrochlorides, VII·HCl 193–196°, VI·HCl 134–136°. Reported (1) m.p.'s for these compounds are 194–197° and 196–197°, respectively.

Mass spectra were recorded with a gas chromatograph mass spectrometer (LKB9000), ion source 270°, electron energy 70 eV., and ionization current 60 μamp.

Mass spectrometric data; compounds IV-V, see *Reference* 4. *N*-Methyl-3,4-dimethoxyphenethylamine, major peaks, *m/e* 44 (100%), 151 (3%), 152 (40%), 195 (M^+ 1%). *N,N*-Dimethyl-3,4-dimethoxyphenethylamine, major peaks, *m/e* 58 (100%), 151 (3%), 152 (1%), 209 (M^+, 1%). Salsoline, major peaks, *m/e* 149 (3%), 153 (7%), 154 (4%), 178 (100%), 192 (6%), 193 (M^+, 3%).

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Ring Opening of Cyclic Salicylamides

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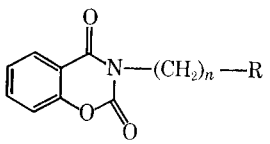
Abstract □ The ring opening of four cyclic salicylamides to their phenolic analogs is described. Compounds in which a basic group is separated from the amide nitrogen by a three-carbon chain were found to undergo this reaction considerably more slowly than compounds with a two-carbon chain. Ring opening was shown to be pH dependent and is base-catalyzed.

Keyphrases □ Salicylamides, cyclic—ring opening □ Phenolic salicylamides—synthesis □ pH effect—ring opening, salicylamides □ Radiometric determination—ring opening, salicylamides □ Colorimetric analysis—spectrophotometer

Because of the presence of the cyclic acyl urethan group and the consequent opportunity for nucleophilic attack on the carbonyl group, cyclic salicylamides of the type respresented by the generic structure



have been considered unstable in the presence of a base (1). The present report describes experiments undertaken in an effort to obtain a cyclic salicylamide which would be stable under physiological conditions and a study of the pH dependent nature of the conversion of a cyclic salicylamide to its phenolic analog.

METHODS AND MATERIALS

Chemical Synthesis—Four pairs of phenolic salicylamides and the corresponding cylic compounds (Table I) were prepared, the phenolic compounds by a single method, and the cyclic compounds by one of two methods [these methods represent modifications of the procedure described by Shapiro *et al.* (2)]; representative syntheses are described.

N-(2-Morpholinoethyl)salicylamide hydrochloride (III) was prepared by heating a mixture of 60.8 g. (0.40 mole) of methyl salicylate and 52.0 g. (0.40 mole) of *N*-(2-aminoethyl)morpholine under reflux for 18 hr. The resulting methanol was removed by distillation over a period of 4 hr. and the remaining material was then distilled under reduced pressure. A 63.5-g. fraction was collected between 180–190° at 0.1 mm.; the IR spectrum[1] showed an amide carbonyl absorption at 1650 $cm.^{-1}$. The hydrochloride was prepared by adding 50 ml. of a 2.2 *N* HCl solution in 2-propanol to 22.5 g. (0.09 mole) of the free base. Upon addition of ether, a white solid formed which was recrystallized from methanol–ether.

[1] IR spectra were obtained with a Perkin-Elmer model 237 grating spectrophotometer.