Short Communication

ECSTASY ANALOGUES FOUND IN CACTI

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Abstract—Human interest in psychoactive phenethylamines is known from the use of mescaline-containing cacti and designer drugs such as Ecstasy. From the alkaloid composition of cacti we hypothesized that substances resembling Ecstasy might occur naturally. In this article we show that lophophine, homopiperonylamine and lobivine are new minor constituents of two cactus species, *Lophophora williamsii* (peyote) and *Trichocereus pachanoi* (San Pedro). This is the first report of putatively psychoactive phenethylamines besides mescaline in these cacti. A search for further biosynthetic analogues may provide new insights into the structure-activity relationships of mescaline. An intriguing question is whether the new natural compounds can be called "designer drugs."

Keywords— Ecstasy, homopiperonylamine, lophophine, lobivine, peyote, San Pedro

Mescaline is the major psychoactive alkaloid of two cactus species, *Lophophora williamsii* (Lem.) Coulter (peyote) and *Trichocereus pachanoi* Britton et Rose (San Pedro). Both species have been used for centuries in native cultures of North and South America, respectively, as ritual hallucinogens (Bruhn et al. 2002, 1978).

The alkaloid composition and the pharmacological properties of the two species are not identical. Whereas the alkaloids of *Trichocereus pachanoi* consist mainly of mescaline and related phenethylamines, *Lophophora williamsii* contains a mixture of mescaline and tetrahydroisoquinoline alkaloids, such as pellotine, anhalonidine, lophophorine and anhalonine (Bruhn et al. 1978).

Biosynthetically, the tetrahydroisoquinoline alkaloids are related to mescaline and can be considered as cyclized derivatives of mescaline and its precursors. An interesting feature of the tetrahydroisoquinoline alkaloids of peyote is the existence of a methylenedioxy substituent on the aromatic ring, in contrast to the three methoxy groups in mescaline.

The methylenedioxy substituent is derived biosynthetically from the cyclization of a precursor such as 3-methoxy-4,5-dihydroxyphenethylamine or 3,4-dimethoxy-5-hydroxyphenethylamine. However, from a biosynthetic reasoning, it could be hypothesized that these plants convert the same precursors also to phenethylamines with a methylenedioxy substituent. But this has so far not been demonstrated.

An analogy exists with nutmeg, from *Myristica fragrans* Houttuyn, which is used as a psychoactive drug and contains a number of aromatic ethers in the essential oil fraction, most notably myristicin (3-methoxy-4,5-methylenedioxysubstituted) and elemicin (3,4,5-trimethoxysubstituted). Of these, myristicin is considered a major contributor to the nutmeg intoxication syndrome (Shulgin 1966).

The synthetic mescaline analogue 3-methoxy-4,5-methylenedioxyphenethylamine has been known for a number of years (Shulgin 1973). This compound is also known as homomyristicylamine or lophophine, the latter name indicating its relation to the peyote plant (Shulgin 1979, 1976).

We now report our finding of lophophine, 3,4-methylenedioxyphenethylamine (MDPEA, homopiperonylamine), and N,N-dimethyl-3,4-methylenedioxyphenethylamine (lobivine) as new minor alkaloid constituents of both *Lophophora williamsii* and *Trichocereus pachanoi*. These three compounds have not previously been demonstrated as natural products.

EXPERIMENTAL

Living plants were obtained from a certified cactus nursery (CITES Nursery Reg No P-DE-1001) and extracted for alkaloids using established procedures (Bruhn et al. 1978). The three phenethylamines were synthesized according to published procedures (Shulgin & Shulgin 1991) and used as reference materials.

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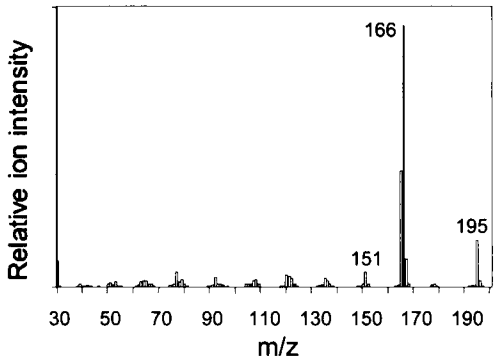
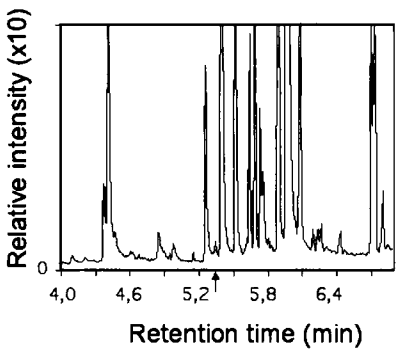
FIGURE 1
Identification of Lophophine by Gas Chromatography-Mass Spectrometry

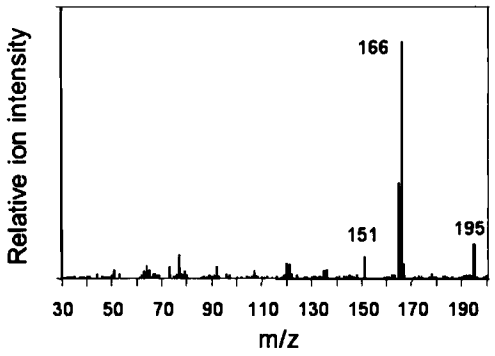
A. Electron impact mass spectrum of synthetic lophophine



B. Total ion chromatogram of the alkaloid extract of *Lophophora williamsii*.

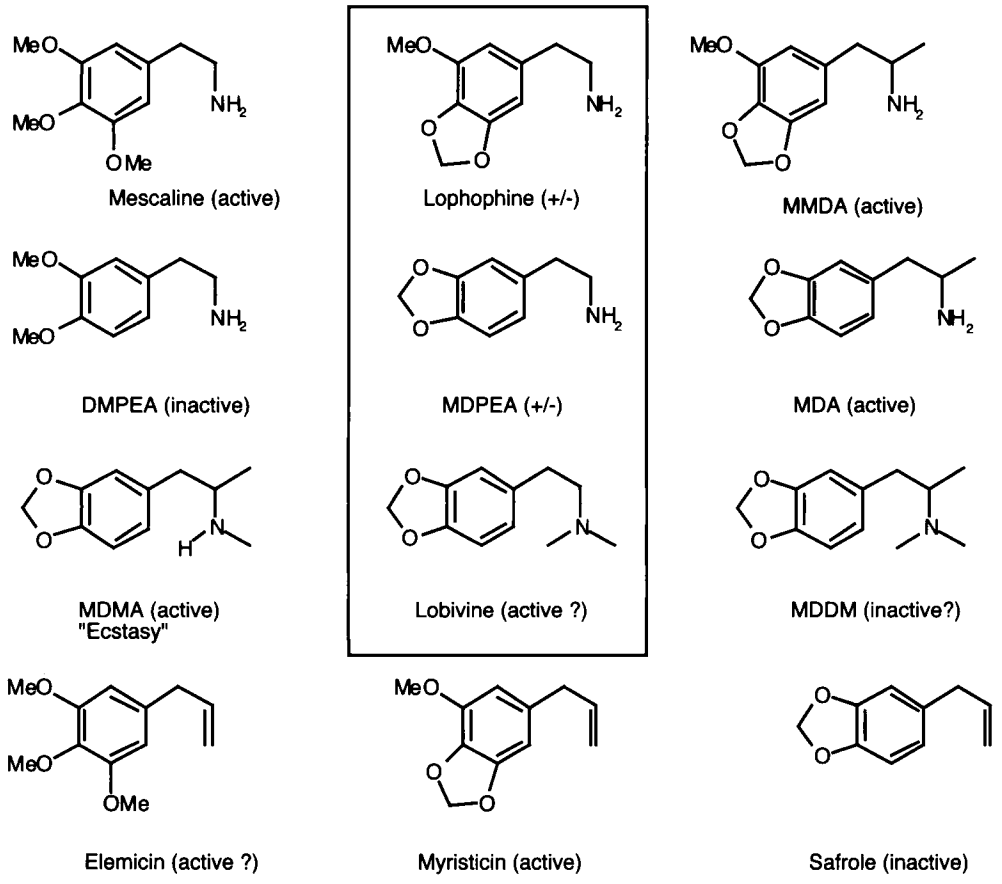


C. Mass spectrum of the lophophine peak in the extract of *Lophophora williamsii*.



A. Electron impact mass spectrum of synthetic lophophine. **B**. Total ion chromatogram of the alkaloid extract of *Lophophora williamsii* (lophophine peak is indicated by arrow). **C**. The background subtracted mass spectrum of the peak at the retention time of lophophine. The identification of lophophine in *Trichocereus pachanoi* was carried out in the same manner.

FIGURE 2
Structure-Activity Relationship of Mescaline and Related Psychoactive Phenylethylamines and Amphetamines



The alkaloid fractions were analyzed by gas chromatography-mass spectrometry (GC-MS). The identities were confirmed by treating the extracts with propyl chloroformate, and analyzing the resulting carbamate derivatives. An Agilent GC-MS model 5890/5973N was used in the electron impact ionization mode (70 eV); column was a HP5MS (30m x 0.25 mm inner diameter x 0.25 μm film thickness); splitless injection with one minute delay was used; injector temperature was 200°C; oven temperature was held at 100°C for one minute and increased to 250°C at a rate of 30°C/minute and thereafter to 300°C at a rate of 10°C/minute.

RESULTS AND DISCUSSION

The results of the alkaloid analyses are shown in Figure 1. Quantitation was carried out for lophophine in comparison to the mescaline content of the two cactus extracts. In *Lophophora williamsii*, lophophine constitutes 3.3% to 5% of the mescaline concentration (peak area count). In *Trichocereus pachanoi*, lophophine reaches 0.23% to 0.31% of the mescaline peak.

Lophophine was first reported as psychoactive in man in 1973 (Shulgin 1973). The activity following its ingestion was described as "a peaceful elevation of mood, the generation of an euphoric state, and the enhancement of visual perception especially in the color sense." Preliminary human trials have shown that lophophine has some psychoactivity in the 150 to 250 milligram range, but the full active dosage has not yet been determined (Shulgin 1991, 1979, 1976).

Lophophine is also closely related to MMDA, 3-methoxy-4,5-methylenedioxyamphetamine, which is a potent psychotomimetic agent, first described in 1964 (Shulgin 1964).

Besides mescaline, both *Lophophora williamsii* and *Trichocereus pachanoi* contain the dimethoxy counterpart, 3,4-dimethoxyphenethylamine, DMPEA,which is not psychoactive (Shulgin & Shulgin 1991). The corresponding 3,4-methylenedioxyphenethylamine, MDPEA or homopiperonylamine is also a logical alkaloid intermediate in the two plants, and could conceivably be biosynthesized from the established precursors dopamine or 3-methoxy-4-hydroxyphenethylamine.

By comparison with synthetic MDPEA, we could establish that this compound is also present in both peyote and San Pedro cacti, but only in minute amounts.

Although close in structure to MDA (3,4-methylenedioxyamphetamine) and MDMA (Ecstasy), MDPEA is not known to be very active. Alles (Cutting 1967) is quoted as stating that it "produces tremor, mild visual and space illusions" without giving any dose. These effects were not reported from experiments with 200 mg (Alles 1959) or up to 300 mg (Shulgin 1991).

The third compound that we were able to identify as a trace component in both our extracts is N,N-dimethyl-3,4-methylenedioxyphenethylamine. This alkaloid was first found in *Trichocereus lobivioides* R Graser & F Ritter, synthesized and named lobivine (Shulgin Unpublished data). There are suggestions of activity at 20 to 50 mg, but lobivine is obviously less potent than its close congeners MDMA (Ecstasy) and MDA. Interestingly, N,N-dimethyl-3,4-methylenedioxy-amphetamine, MDDM, seems not to be psychoactive (Shulgin & Shulgin 1991).

The relationship of the three phenethylamines reported here to mescaline and the synthetic psychotomimetic amphetamines is presented in Figure 2. For comparison, the structures of three nutmeg compounds with similar substitution patterns are also given.

The contribution of the three new compounds to the overall pharmacological activity of the peyote and San Pedro cacti is most likely limited, due to the low concentrations found, as well as the relative low activity reported.

Our findings highlight the possibility that a directed search for further biosynthetic analogues to mescaline may provide new insights into the complex structure-activity relationships of this classical hallucinogen. Lophophine might also be a useful biomarker for naturally-derived mescaline or cactus extracts.

A final intriguing question is whether the naturally occurring compounds identified here can be regarded as "designer drugs."

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