Identification of New Peyote Alkaloids; Isomers of the Main Phenolic Tetrahydroisoquinolines

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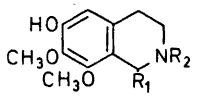
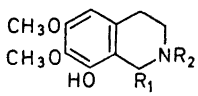
Peyote (*Lophophora williamsii*, Coult.) contains many alkaloid intermediates and trace alkaloids.[1,2] This report presents the isolation and identification of four new tetrahydroisoquinoline alkaloids, *1*–*4*, produced by this cactus. These alkaloids are isomers of the most abundant phenolic alkaloids, *5*–*8*, found in peyote [1,3] and thus provide further insight into alkaloid biosynthesis.





1. ISOANHALAMINE $R_1 = R_2 = H$

2. ISOANHALIDINE $R_1 = H$, $R_2 = CH_3$

3. ISOANHALONIDINE $R_1 = CH_3$, $R_2 = H$

4. ISOPELLOTINE $R_1 = R_2 = CH_3$

5. ANHALAMINE $R_1 = R_2 = H$

6. ANHALIDINE $R_1 = H$, $R_2 = CH_3$

7. ANHALONIDINE $R_1 = CH_3$, $R_2 = H$

8. PELLOTINE $R_1 = R_2 = CH_3$

Initial GLC-MS studies suggested the presence of alkaloids similar to *6* and *8*. Subsequently a mixture of compounds *1*–*4* was isolated by preparative GLC (SE-30, Fig. 1) which with further fractionation by TLC and GLC (XE-60) afforded small amounts essentially pure compounds *1*–*4*.* Identification was based upon direct comparison with authentic reference compounds by TLC and GLC-MS. The mass spectra of *1*–*4* exhibit fragmentation patterns similar to those obtained with the isomeric compounds *5*–*8*.[2,4]

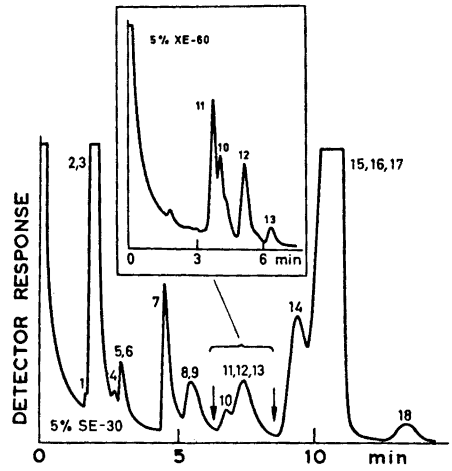


Fig. 1. Preparative GLC of phenolic peyote alkaloids (5 % SE-30),[7] and (inserted) analytical GLC (XE-60)[7] of the fraction 10–13, twice purified. The peak-numbers correspond to the following compounds: 1, tyramine; 2, *N*-methyltyramine; 3, hordenine; 4, 3-methoxytyramine; 5, *N*-methyl-3-methoxytyramine 6, *N*,*N*-dimethyl-3-methoxytyramine; 7, *11*; 8, *12*; 9, *N*,*N*-dimethyl-3-hydroxy-4,5-dimethoxyphenethylamine; 10, *2*; 11, *4*; 12, *3*; 13, *1*; 14, *6*; 15, *5*; 16, *7*; 17, *8*; 18, unknown.

The present evidence indicates that anhalamine (*5*) and anhalonidine (*7*) arise in peyote by condensation of 3-hydroxy-4,5-dimethoxyphenethylamine (*11*) with suitable ring closing units.[1,5] Recent results suggest that pellotine (*8*) arises in an analogous manner from the *N*-methyl derivative *12*, rather than by *N*-methylation of *7*.[1] It is suggested that the isomers *1*–*4* are formed *in vivo* from the same precursors *11* and *12*.

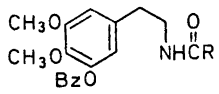
Schöpf and Bayerle [6] showed that condensation of dopamine or its *N*-methyl derivative with acetaldehyde under physiological conditions yielded almost quantitatively the respective 6,7-dioxygenated tetrahydroisoquinolines. Similar condensation of acetaldehyde with either *11* or *12* gave rise to the expected tetrahydroisoquinolines in excellent yield. Cyclization proceeded primarily *ortho* to the

* Due to rapid color formation, the determination of optical activity of *3* and *4* isolated from the plant was unsatisfactory. The *O*-methylated derivatitive of *7* occurs in an optically active form in peyote.[3] Compounds *7* and *8* rapidly racemize at neutral pH[9] and it is not known if these alkaloids occur optically active *in vivo*.

phenolic hydroxyl to yield anhalonidine *7* or pellotine (*8*), respectively, with only limited formation (2–3 %) of the isomeric products *3* and *4*.

Experimental. Isolation and identification of tetrahydroisoquinolines 1–4. The phenolic alkaloid fraction from peyote was subjected to preparative GLC (SE-30 column)[7] and the fraction containing compounds *1–4* was collected (Fig. 1). Approximately 7 mg were obtained from 500 mg of total phenolic alkaloids. This fraction was separated by TLC (Silica gel F, Woelm precoated; chloroform: ethanol : diethylamine 85 : 5 : 10); two bands containing *1*+*3* (R_F~0.3) and *2*+*4* (R_F~0.5), respectively. Fractionation of these mixtures from TLC by preparative GLC (XE-60 column)[7] yielded the isolated compounds *1–4* (Fig. 1). In practice, prior to the first GLC separation, enrichment by TLC (above) of *1–4* in two fractions was employed; the band (R_F 0.2–0.3) between anhalamine and anhalonidine contained *1* and *3*; the band (R_F 0.4–0.6) between anhalonidine and pellotine contained *2* and *4*. A sample of isoanhalonidine (2 mg) was obtained from the phenolic alkaloid fraction (500 mg) by repeated separation on TLC; twice on the silica gel system and once on aluminium oxide (Merck, chloroform : methanol 3 : 2).

Retention times on GLC (analytical columns of SE-30 and XE-60)[7], migrations in two TLC systems (above) and the mass spectra (LKB 9000) of the isolated compounds *1–4* were identical to those of synthesized reference compounds.



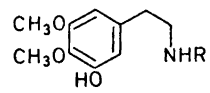
9. R = H
10. R = CH_3

Synthesis of isoanhalamine (1) *and isoanhalidine* (2). Bischler-Napieralsky condensation of *N*-formyl-3-benzyloxy-4,5-dimethoxyphenethylamine (*9*, 220 mg; cyclization proceeds in both possible directions[8]) followed by reduction ($NaBH_4$) and debenzylation (H_2/Pd) to yield a mixture of equal amounts of isoanhalamine (*1*) and anhalamine (*5*) was carried out as described by Brossi *et al.*[8] The compounds were separated by TLC (silica gel, above) and crystallized to yield 36 mg of isoanhalamine HBr, m.p. 213–215° (reported[8] 214.5–215.5°) and 45 mg anhalamine HCl, m.p. 257 (reported[3] 258°). Mass spectra of these compounds showed *m/e* 209 (M^+, 55 %) *m/e* 208 (base peaks) and *m/e* 180 (68 %).

To isoanhalamine HCl (15 mg) in methanol (2 ml) was added a formaldehyde solution (0.1 ml. 40 %) and after 15 min $NaBH_4$ (100 mg). The mixture was stirred for 2 h and the solvent evaporated. Alkaloid extraction and crystallization yielded 10 mg of isoanhalidine HCl, m.p. 215–218°. Mass spectrum *m/e* 223 (M^+, 50 %), *m/e* 222 (base peak) and *m/e* 180 (70 %).

Synthesis of d,l-isoanhalonidine (3) *and d,l-isopellotine* (4). 3-Benzyloxy-4,5-dimethoxyphenethylamine (200 mg) was dissolved in acetic anhydride (1 ml) and pyridine (1 ml) and the solution was left overnight. After thorough evaporation of the solvents the resulting amide *10* was treated analogously[8] to *9* to yield a mixture of isoanhalonidine (*3*) and anhalonidine (*7*). Separation on TLC (Al_2O_3, chloroform : methanol 3 : 2) and crystallization gave 32 mg of isoanhalonidine HBr, m.p. 209–211° (reported[8] 201.5–212°) and 35 mg of anhalonidine HCl. M.p. of the salicylate 223–225° (reported[8] 223.5–224.5°). Mass spectra of these compounds showed *m/e* 223 (M^+) and *m/e* 208 (base peaks).

Isoanhalonidine HCl (15 mg) was *N*-methylated as described for *1* to yield 11 mg of isopellotine HCl, m.p. 212–222°. Mass spectrum *m/e* 237 (M^+), *m/e* 222 (base peak).



11. R = H
12. R = CH_3

Condensations of 12 *and* 13 *with acetaldehyde.* 3-Hydroxy-4,5-dimethyoxyphenethylamine HCl (*12*, 120 mg) was dissolved in H_2O (5 ml) and added acetaldehyde (50 µl). The solution (pH 4.5) was left at room temperature for 32 h and then analyzed by GLC and GLC-MS. Anhalonidine (*7*) and isoanhalonidine (*3*) were present in the ratio 30 : 1. The starting compound *12* was not detected. Yield; anhalonidine salicylate, 130 mg, m.p. 223–225°.

N-Methyl-3-hydroxy-4,5-dimethoxyphenethylamine HCl[1] (*13*, 125 mg) was treated similarly to yield pellotine and isopellotine in the ratio 35 : 1. Yield of pellotine HCl was 95 mg. M.p. of the picrate 163–166° (reported[3] 167–169°).

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The Structure of 2,5-Diphenyl-3-methyl-6a-thiathiophthene

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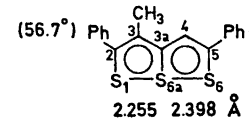
CNDO/2 calculations on mono-methyl and mono-phenyl substituted 6a-thiathiophthenes show that a 3-methyl group causes a shortening of the S(1) – S(6a) bond relative to that in 6a-thiathiophthene, while a twisted 2-phenyl group causes a lengthening of this bond.[1,2] The lengthening effect of the 2-phenyl group on S(1) – S(6a) varies with the twist angle, being negligible at twist angle 0° and most pronounced at 90°.[1]

A structure investigation of 2,5-diphenyl-3-methyl-6a-thiathiophthene (I) has been carried out in order to test the CNDO/2 predictions; the preliminary results are given.



(I)

The sulphur – sulphur bonds in I are S(1) – S(6a) = 2.255(1) Å and S(6a) – S(6) = 2.398(1) Å, and the 2- and 5-phenyl groups are twisted 56.7 and 23.7° about the respective connecting bonds. Thus, the effect of phenyl group 2 on the S-S bonding is opposed by the effect of phenyl group 5, and it seems likely that it is the 3-methyl group which has caused the shortening of S(1) – S(6a) in agreement with the results from the CNDO/2 calculations.

Other bond lengths in the 6a-thiathiophthene system of I are: S(1) – C(2) = 1.714(2) Å, S(6a) – C(3a) = 1.749(2) Å, S(6) – C(5) = 1.698(2) Å, C(2) – C(3) = 1.377(2) Å, C(3) – C(3a) = 1.429(3) Å C(3a) – C(4) = 1.406(2) Å, and C(4) – C(5) = 1.374(3) Å.

A sample of 2,5-diphenyl-3-methyl-6a-thiathiophthene was generously supplied by M. Stavaux.[3] The crystals are dark red and belong to the monoclinic space group $P2_1/c$. The cell dimensions are $a = 15.463(2)$ Å, $b = 8.015(1)$ Å, $c = 13.076(2)$ Å, and $\beta = 106.38(1)°$. There are four molecules per unit cell; density, calculated 1.393 g/cm³, found 1.388 g/cm³.

The structure analysis is based on X-ray data collected on a paper-tape controlled Siemens AED diffractometer using Cu$K\alpha$ radiation. 2865 reflections were observed within $\theta = 71°$.

The structure was solved by the heavy atom (S) method and refined by full matrix least squares. The final R factor is 0.033.

The authors are indebted to Dr. M. Stavaux, Faculté des Science de Caen, France, for providing a sample of 2,5-diphenyl-3-methyl-6a-thiathiophthene.

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