

## A novel route for the synthesis of mescaline

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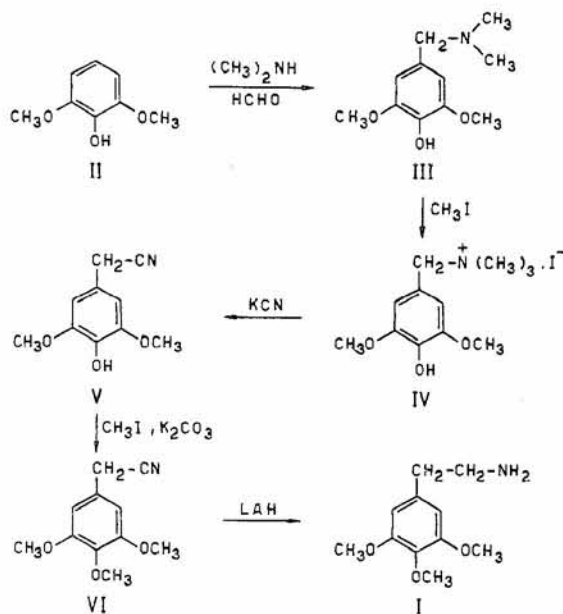
**ABSTRACT** A new plausible synthetic pathway for the synthesis of the peyote alkaloid mescaline in a satisfactory overall yield is reported.

The hallucinogen mescaline (I) is the main alkaloid isolated from the cactus plant *Anhalonium Lewinii* Hennings or *Lophophora Williamsii* Lemaire [1].

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Several methods have been reported describing the total synthesis of this alkaloid [2—7]. However, all these procedures were found to be tedious and costly as well as giving low overall yields of the alkaloid. In the present work, we would like to report a convenient new simple, facile and non-costly synthetic pathway of mescaline (I) leading to comparatively high overall yields. The scheme illustrates the route resorted to to achieve the base, starting from the inexpensive and easily available 2,6-dimethoxyphenol (II): II was allowed to undergo Mannich reaction to give the base III. Subsequent quaternization to IV, nucleophilic substitution to V and methylation resulted in 3,4,5-trimethoxybenzyl cyanide (VI) in high yields. Lithium aluminum hydride reduction of the latter afforded the alkaloid mescaline isolated as the hydrochloride in 42 % overall yield.



### Experimental

Melting points were determined on a Kofler melting point apparatus and are uncorrected.

Infrared spectra were recorded on a Perkin-Elmer Model 257 grating spectrophotometer and were consistent with the assigned structures.

Microanalyses were performed at the National Research Centre, Dokki, Cairo, Egypt. The analyses are indicated only by symbols for the elements; analytical results obtained were within  $\pm 0.4\%$  of the calculated value.

*4-Dimethylaminomethyl-2,6-dimethoxyphenol (III)*

To a solution of 23.1 g (0.15 mol) of 2,6-dimethoxyphenol (II) in 150 ml of methanol was added 17.1 g of 40 % aqueous solution of dimethylamine and 12.75 g of 35 % formaldehyde solution. The whole mixture was left well closed in the dark at room temperature for 10 days with occasional shaking. Thereafter, the methanol was driven off *in vacuo* and 45 ml of water was added to the residue. The separated product was filtered and recrystallized from petroleum-ether (60–80°C), m.p. 79–80°C, yield 25.3 g (80 %). IR (CHCl<sub>3</sub>) cm<sup>-1</sup>: 3580 (OH), 1620 (C=C), 1130 (C-O-C). Anal. (C<sub>11</sub>H<sub>13</sub>NO<sub>2</sub>): C, H, N.

*Quaternization of III to IV*

To a solution of 21 g (0.099 mol) of III in 90 ml of absolute ethanol, 28.2 g (0.198 mol) of methyl iodide was added under stirring and cooling, resulting in an exothermic reaction accompanied by the precipitation of the product IV. After complete addition, the reaction mixture was allowed to stand overnight. The separated solid was recrystallized from ethanol, m.p. 185–187°C, yield 35 g (99 %).

Anal. (C<sub>12</sub>H<sub>20</sub>INO<sub>2</sub>): C, H, N.

*3,5-Dimethoxy-4-hydroxybenzyl cyanide (V)*

A solution of 35.3 g (0.1 mol) of the methiodide IV and 26 g (0.4 mol) of KCN in 200 ml of water was refluxed for 2.5 h. After cooling, the solution was cautiously acidified with 2 M HCl and extracted with CHCl<sub>3</sub>. The CHCl<sub>3</sub> extract was dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent removed *in vacuo* to give 15.4 g of an oil (80 %), which is used as such without further purification in the next step.

*3,4,5-Trimethoxybenzyl cyanide (VI)*

To a solution of 30 g (0.156 mol) of V in 200 ml of dry acetone was added 27.6 g (0.2 mol) of K<sub>2</sub>CO<sub>3</sub> and 31.2 g (0.22 mol) of methyl iodide.

The mixture was refluxed for 20 h. After cooling and filtration, the filtrate was evaporated *in vacuo*. The residue was extracted with CHCl<sub>3</sub>. The CHCl<sub>3</sub> extract was washed with 2M NaOH, 10 % Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub>, and then with water. After drying over Na<sub>2</sub>SO<sub>4</sub> and removal of the solvent, the crystalline was recrystallized from petroleum-ether (60–80°C), m.p. 76–77°C, yield 27 g (83.8 %) (Lit. [4] 76–77°C). IR (CHCl<sub>3</sub>) cm<sup>-1</sup> = 2280 (C≡N).

VI was further identified by comparing mixed melting point and comparative IR spectrum with an authentic sample.

*Mescaline hydrochloride (I)*

To a suspension of 10 g LiAlH<sub>4</sub> in 300 ml of dry tetrahydrofuran was added a solution of 20.7 (0.1 mol) of VI in 60 ml of dry tetrahydrofuran over a period of 30 min.

After complete addition, the whole mixture was refluxed for 3 h and then cooled. The complex and excess hydride were decomposed with saturated Na<sub>2</sub>SO<sub>4</sub> solution and filtered. The combined filtrate and washings were evaporated *in vacuo*. The calculated amount of methanolic hydrogen chloride was added

to the residue and the mescaline hydrochloride was recrystallized from 2-propanol, m.p. 180—181°C, yield 19.5 g (79 %) (Lit. [8] 180—181°C). Mescaline hydrochloride was further identified by comparing mixed melting point and comparative IR spectrum with an authentic sample.

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Received April 17, 1979.