

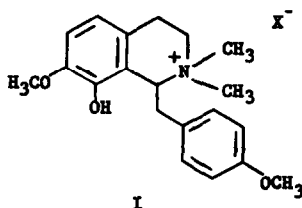
A TOTAL SYNTHESIS OF RACEMIC PETALINE\*

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According to McCorkindale et al. (1), the quaternary alkaloid petaline isolated from the roots of Leontice leontopetalum Linn. in the form of its reineckate (2) possesses structure I with the unusual substitution of the tetrahydroisoquinoline moiety with a methoxy and a hydroxy group at positions 7 and 8 respectively. The chloride of the natural product shows a rotation of  $[\alpha]_D^{25} + 11.3^\circ$  (2), and is, therefore, one of the two enantiomers of I with still unknown absolute configuration.



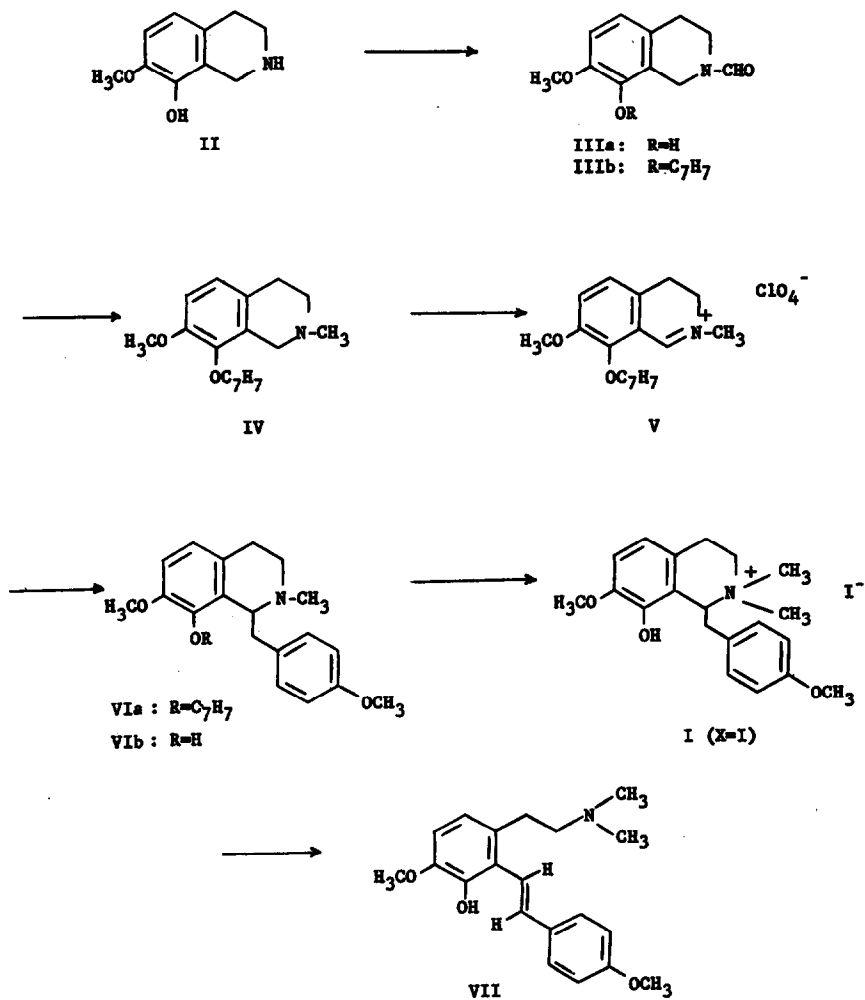
X=Cl, I,  $[\text{Cr}(\text{NH}_3)_2(\text{SCN})_4]$

We wish to report a straightforward synthesis of the iodide of the rac. alkaloid I (X=I) and the trans stilbene derivative, petaline methine VII,

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previously described as leonticine (1) (2), identical in all respects with an authentic specimen (3). The syntheses of I and VII have been achieved by the following sequence of reactions:



The readily available hydrochloride of 7-methoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline II (4) was converted to the free base by means of one equivalent of sodium ethoxide in very dilute methanolic solution. Formylation of II with a mixture of formic acid and triethylamine (5) gave the N-formyl derivative IIIa as a crystalline compound, m.p. 177-179°. Anal. Found: C, 63.93; H, 6.49; N, 6.61. Benzoylation of IIIa with benzyl chloride in dimethylformamide afforded the O-benzyl derivative IIIb as a brown oil which, without further purification, was reduced with lithium aluminum hydride in tetrahydrofuran to 8-benzoyloxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (IV), characterized as the crystalline hydrochloride, m.p. 191.5-192.5°. Anal. Found: C, 67.37; H, 7.23; N, 4.36.

Mercuric acetate dehydrogenation of IV in 10% aqueous acetic acid at 75° led to the 3,4-dihydroisoquinolinium salt V, which was isolated as the perchlorate, m.p. 181-183°;  $\nu_{\max}$  (isopropanol) 239  $\mu$  ( $\epsilon$  13200); 301  $\mu$  ( $\epsilon$  11760); 379  $\mu$  ( $\epsilon$  2700). Anal. Found: C, 56.87; H, 5.39; N, 3.44. Addition of the solid perchlorate to an excess of p-methoxybenzylmagnesium chloride (6) in ether afforded the benzyltetrahydroisoquinoline VIa in good yield. Crystalline hydrochloride, m.p. 191-193°. Anal. Found: C, 70.71; H, 6.82; N, 3.17.

Debenzylation with hydrogen over palladium-on-charcoal catalyst in acetic acid gave oily 8-hydroxy-7-methoxy-1-(4'-methoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline VIb which, without purification, was methylated with methyl iodide to rac. petaline iodide (I, X=I); crystallized from acetone as hemiacetonate, m.p. 134-138°;  $\nu_{\max}$  (isopropanol): 223  $\mu$  ( $\epsilon$  28200); 279/280  $\mu$  ( $\epsilon$  3980); 284/285  $\mu$  ( $\epsilon$  3980). Anal. Found: C, 53.47; H, 6.14; N, 2.93. The product showed infrared absorption ( $\text{CHCl}_3$ ) at 3530  $\text{cm}^{-1}$  (phenolic hydroxy group, intramolecularly hydrogen bonded to the methoxy group) and 1710  $\text{cm}^{-1}$  (acetone carbonyl). The nmr spectrum (7) indicated the presence of

0.5 mole of acetone (methyl group at 2.17 p.p.m.), two methyl groups at a quaternary nitrogen (3.35 and 3.50 p.p.m.), two methoxy groups (3.77 and 3.92 p.p.m.), tertiary hydrogen  $\alpha$  to the quaternary nitrogen (5.07 p.p.m.), and a phenolic hydroxy group (6.23 p.p.m.). In a low resolution mass spectrum (7) the first major peak appeared at  $m/e$  327, due to a fragment of structure VII formed by Hofmann degradation. Other major peaks at  $m/e$  206, 192, 177, 142, 121 and 58 could be assigned to reasonable fragments.

Racemic petaline iodide was transformed into rac. petaline reineckate, a pink amorphous compound, m.p. 178-181° (dec.), the infrared and ultraviolet spectra of which were superimposable with those of authentic optically active material (3).

Further proof for the structural assignment I to petaline iodide was provided by Hofmann degradation to petaline methine VII on a column of Amberlite anion exchange resin IRA-400 (OH) (1). The crystalline product obtained (m.p. 119-120°) was identical in all respects with authentic material (3). Anal. Found: C, 73.36; H, 7.43; N, 4.31. The infrared spectrum ( $\text{CHCl}_3$ ) of VII showed bands at  $3530\text{ cm}^{-1}$  (phenolic hydroxy group intramolecularly hydrogen bonded to the methoxy group),  $1610\text{ cm}^{-1}$  and  $973\text{ cm}^{-1}$  ( $-\text{C}=\text{C}-$  of trans-stilbene). The ultraviolet spectrum (isopropanol) exhibited maxima at 214/215  $\mu$  ( $\epsilon$  30400) and at 298-301  $\mu$  ( $\epsilon$  25000), due to steric inhibition of stilbene resonance by the 8-hydroxy group. The high intensities of the maxima further indicated a trans-configuration for VII.

The nmr-spectrum was also in complete agreement with structure VII for petaline methine. The dimethylaminoethyl side chain showed a singlet at 2.32 p.p.m. (6H) and an  $A_2B_2$ -pattern centered at 2.73 p.p.m. (4H). The methoxy groups were indicated by singlets at 3.83 and 3.88 p.p.m. (6H). The singlet

at 6.25 p.p.m. (1H) - disappearing on deuteration - was assigned to the phenolic hydroxy group. The aromatic protons appeared as a singlet at 6.72 p.p.m. (2H; C<sub>5</sub>-H, C<sub>6</sub>-H) and as an A<sub>2</sub>B<sub>2</sub>-pattern at 6.88 and 7.37 p.p.m. (4H; C<sub>2</sub>,-H, C<sub>3</sub>,-H, C<sub>5</sub>,-H, C<sub>6</sub>,-H), while the trans methylidene protons exhibited an AB pattern at 7.07 and 7.37 p.p.m. (J=16.5 cps, 2H).

In the low resolution mass spectrum the molecular ion peak appeared at m/e 327. The fragmentation pattern of petaline methine showed a striking similarity with that of petaline iodide with peaks at m/e 206, 177, 121 and 58, and additional weaker peaks at m/e 281, 268, 253 and 165.

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3. We are very grateful to Professor N.J. McCorkindale for providing us with authentic samples of petaline reineckate and petaline methine.
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7. The nmr-spectra were taken in CDCl<sub>3</sub> with tetramethylsilane as internal standard on a Varian A-60 spectrometer. The mass spectra were taken with a CEC 21-110 mass spectrometer at 70 e.V. using a direct insertion probe.