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SYNTHESIS OF PROAPORPHINE ALKALOIDS. (±)-HEXAHYDROPRONUCIFERINE

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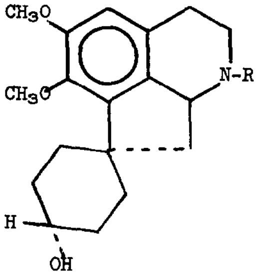
Several of the biosynthetically important proaporphine alkaloids[1] have been synthesized both by classical methods[2] and, although in very low yield, by oxidative cyclization procedures.[3] We wish to report a new synthetic approach to these alkaloids, exemplified by the synthesis of (±)-hexahydropronuciferine (1).

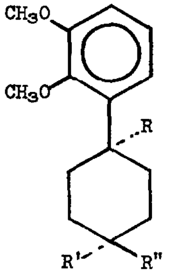
Following the general method of Hazama et. al.[4], 2,3-dimethoxyphenylacetonitrile[5] was converted to 4-cyano-4(2,3-dimethoxyphenyl)-cyclohexanone (2), mp 136-137°[6]. Reduction of 2 with lithium aluminum hydride, followed by acid hydrolysis gave 4-formyl-4(2,3-dimethoxyphenyl)-cyclohexanol (3),[6] mp 141-146°. The nmr spectrum of this material showed the carbinol proton as a broad multiplet at 3.70, leading to the indicated stereochemical assignment. The acetate of 3[6], mp 109-111°, on treatment with methoxy methylenetriphenylphosphorane, followed by acid hydrolysis afforded 1-(2,3-dimethoxyphenyl)-4-acetoxy cyclohexylethanal (4), characterized as the 2,4-DNP[6], mp 183-184°. Oxidation by chromic acid-acetone afforded 1-(2,3-dimethoxyphenyl)-4-acetoxy cyclohexaneacetic acid (5)[6]. mp 121-123°, which on treatment with polyphosphoric acid gave the substituted indanone (6)[6], mp 167-168°. Bobbit's modification of the Pomeranz-Fritsch reaction[7] led to the (±)-hexahydrostepharine (7), which was, without purification, converted to the N-methyl derivative by the method of Cava and Buck.[8] The sample of 1 obtained by this method was identical (tlc and infrared) to material prepared by Bernauer's procedure.[2,9] The base hydrochloride of 1, mp 209-219 (dec.) was also identical (mixed mp, infrared), to Bernauer's material.[2,9]

Various alternative approaches, and model syntheses will be discussed in the full paper.



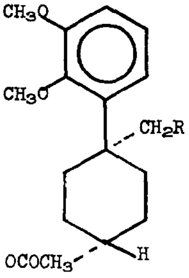
1 R = CH_3

7 R = H



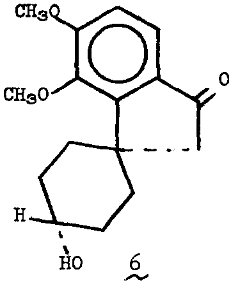
2 R = CN, R', R" = O

3 R = CHO, R' = OH, R" = H



4 R = CHO

5 R = CO_2H



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6. Satisfactory analytical data were obtained for all new compounds, and all compounds were characterized by infrared and nmr spectroscopy, and thin layer chromatography.

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9. The authors would like to thank Dr. Bernauer for a sample of (±)-hexahydropronuciferine, prepared as described in Ref. 1.