

TOTAL SYNTHESIS OF RACEMIC CHERYLLINE

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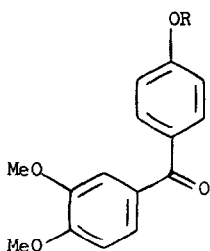
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The isolation, structure and absolute configuration of cherylline, an Amaryllidaceae alkaloid, has recently been reported (1). We now describe briefly the first synthesis of rac. cherylline (10). This was accomplished by reaction sequences which involved the preparation of the phenethylamine 6 by standard methods (2) and the diphenolic intermediate 2 by partial ether cleavage (3, 4).

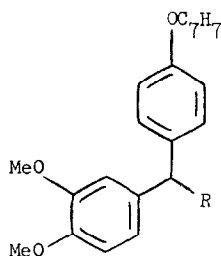
The benzophenone 1 (mp 166-167°), obtained by condensation of veratric acid with phenol, was converted to the benzyloxy derivative 2 (mp 166-167°, mmp with 1 146-150°) followed by reduction with sodium borohydride, treatment with thionyl chloride, fusion with cuprous cyanide and catalytic hydrogenation with Raney cobalt to give the phenethylamine 6·HBr (mp 160-161°) via the intermediates 3, 4 and 5 (5). Bischler-Napieralski cyclization of the N-formyl derivative 7 (bp 140°/0.02 mm, n_D^{25} 1.5699), prepared from 6 and methyl formate, followed by debenylation with conc. HCl at 25° yielded the monophenolic dihydroisoquinoline 8 [mp 194-196°; uv max (EtOH) 232 nm (33250), 279 (9850), 309 (5770); nmr (DMSO-d₆, Jeolco C-60 H) δ 3.63, 3.76 (s, 3 H each, OCH₃-6,7), 6.51, 7.04 (s, 2, CH-5,8), 6.60 and 6.88 (AA'BB'-pattern, 4, J = 8.5 Hz, CH-2', 3', 5', 6'), 8.20 (b, 1, CH-1), 9.13 (b, 1, OH)]. Treatment of 8 with 48% HBr under controlled reaction conditions provided the diphenol 9 [mp 216-218°; uv max (EtOH) 233 nm (30700), 280 (8400), 318 (5000); nmr (DMSO-d₆, Jeolco C-60 H) δ 3.65 (s, 3, OCH₃-6), 6.60, 6.82 (s, 2, CH-5,8), 6.70, 6.86 (AA'BB'-pattern, 4, J = 8.5 Hz, CH-2', 3', 5', 6'), 8.12 (b, 1, CH-1), 9.03 (b, 2, OH)]. Sodium borohydride reduction of the quaternary salt (mp 235-236°), obtained from 9 and methyl iodide, afforded rac. cherylline (10) [mp 215-216°; uv max (EtOH) 225 nm (16400) (infl), 282 (4800), 293 (3000) (infl); nmr (DMSO-d₆, Varian A-60 A) δ 2.27 (s, 3, N-CH₃), 2.4-3.0 (m, 2, CH₂-3), 3.42 (s, 2, CH₂-1), 3.54

(s, 3, OCH₃-6), 3.97 (t, 1, \underline{J} = 6 Hz, CH-4), 6.28 (s, 1, CH-5), 6.51 (s, 1, CH-8), 6.37, 6.47 (AA'BB'-pattern, 4, \underline{J} = 8.5 Hz, CH-2', 3', 5', 6'), 8.97 (b, 2, OH); mass spectrum m/e 285, 242, 241, 225, 211, 210, 197, 181, 169, 165, 152 and 77], identical in uv, nmr and thin layer chromatographic behavior (2 solvent systems) with natural cherylline (6).

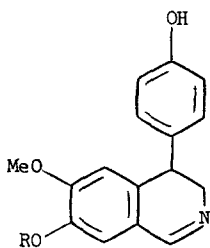
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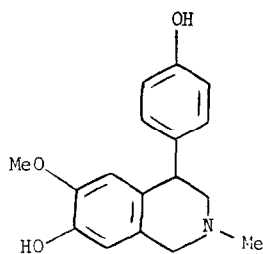
1, R=H
2, R=C₇H₇



3, R=OH
4, R=Cl
5, R=CN
6, R=-CH₂NH₂
7, R=-CH₂NHCHO



8, R=Me
9, R=H



10

REFERENCES

1. A. Brossi, G. Grethe, S. Teitel, W. C. Wildman, and D. T. Bailey, J. Org. Chem., 36, 0000 (1970).
2. Y. Inubushi, H. M. Fales, E. W. Warnhoff, and W. C. Wildman, J. Org. Chem., 25, 2153 (1960).
3. Based on the preferential O-demethylation of the 7-methoxyl in 6,7-dimethoxy-substituted 3,4-dihydroisoquinolines with mineral acid as reported by H. Bruderer and A. Brossi, Helv. Chim. Acta, 48, 1945 (1965).
4. The application of partial ether cleavage in the synthesis of certain phenolic isoquinoline alkaloids was presented by one of us (A.B.) at the 13th Symposium on the Chemistry of Natural Products, Sapporo, Japan, September 25-27, 1969, pp 177-186 of abstract. Details will be reported in Helv. Chim. Acta.
5. The intermediates 3, 4 and 5 were crystalline. All compounds including the methiodide of 2 gave satisfactory analyses and spectral data.
6. We are grateful to Professor W. C. Wildman, Iowa State University, for providing us with a sample of natural cherylline.