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LYTHRACEA ALKALOIDS. TOTAL SYNTHESIS OF (±) METHYL DECININE

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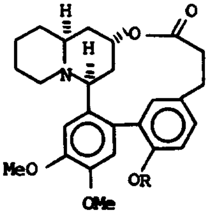
The Lythraceae family of plants has been a prolific source of alkaloids (1), over 20 having been isolated since the first crystalline alkaloids were isolated in the early 1960's (2). Those that are found in the Heimia and Decodon genera are characterized by the presence of large lactone rings and the quinolizidine moiety. There has been a recent upsurge of interest in the synthesis of these alkaloids. Hanaoka et al. (3) and Wrobel and Golebiewski (4) recently reported the synthesis of decaline, one of the related diphenyl ether containing alkaloids by a route that utilizes the facile formation of diphenyl ethers. We wish to report the first total synthesis of a biphenyl containing alkaloid, decinine (I, R=H), as its methyl ether (I, R=Me). Previous attempts at the total synthesis of the biphenyl alkaloids have been unsuccessful (5).

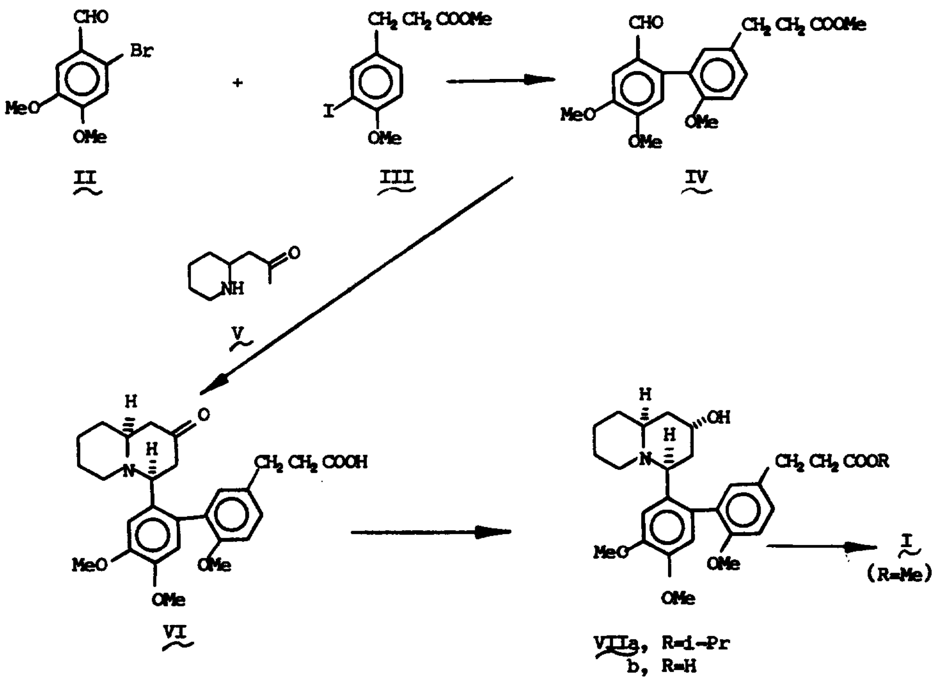


I

Our synthetic sequence is illustrated in Scheme I.

The crucial unsymmetrical biphenyl aldehyde IV was obtained by the Ullmann coupling of 6-bromoveratraldehyde (II) and III using copper powder in the absence of solvent (30% yield; bp.195-8/0.005mm, m/e 358) (6). This coupling does not occur if the methyl ether in III is replaced by the corresponding benzyl ether, by the acetate or by the carbonate, nor if the bromo analog of III is used.

Scheme I



6-Bromoveratraldehyde was most readily obtained by mercuration of veratraldehyde followed by bromination (7); compound III was prepared from 3-(4'-hydroxyphenyl)-propionic acid by iodination with iodine monochloride (8)(60% yield), esterification of the iodo compound in methanol with AG50W-X8 ion-exchange resin as catalyst (95% yield), and finally methylation in DMSO and NaH with methyl iodide (80% yield). Condensation of IV with isopelletierine (V) (9), in aqueous alcoholic sodium hydroxide gave the keto-quinolizidine VI (60% yield, m/e 539 mono tms deriv). Although Matsunaga *et al.* (10) claimed that condensation of benzaldehyde with isopelletierine, under similar conditions, gave a mixture of *cis* and *trans* quinolizidines, Wrobel and Golebiewski (11) reported that isovanillin gave only condensation product in which the ring juncture is *trans* and the phenyl substituent is equatorial. The stereochemistry of VI is in agreement with the latter finding as supported by Bohlmann bands (12) at $2830 cm^{-1}$ (as isopropyl ester). Reduction of VI with the Henbest iridium tetrachloride catalyst (13) resulted in the axial alcohol as the major product (90%, single spot tlc as the isopropyl ester, m/e 511, VIIa), which was hydrolyzed to the hydroxy acid VIIb, which, on heating in benzene with catalytic amounts of methanesulfonic acid, cyclized to (±) methyldecinine. The overall yield of crystalline **I** (R=Me) after "dry-column" chromatography (14) on alumina is 35% from keto-acid **VI**. The spectral properties of the synthetic material (ir in chloroform solution, nmr, mass spec.) are identical to the compound obtained by methylation (Me_2SO_4/NaOH/dioxane) of natural decinine (15).

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References

(1) J. P. Ferris, C. B. Boyce, R. C. Briner, U. Weiss, I. H. Qureshi, and N. E. Sharpless, *J. Am. Chem. Soc.*, **93**, 2963(1971); E. Fujita and Y. Saeki, *J. Chem. Soc. Perkin I.*, 306 (1973) and references therein.

(2) J. P. Ferris, *J. Org. Chem.*, **27**, 2985(1962).

(3) M. Hanaoka, N. Ogawa, and Y. Arata, *Tetrahedron Letters*, 2355(1973).

(4) J. T. Wrobel and W. M. Golebiewski, *Tetrahedron Letters*, 4293(1973).

(5) J. P. Rosazza, J. M. Bobbitt and A. E. Schwarting, *J. Org. Chem.*, **35**, 2564(1970).

(6) Combustion analyses were obtained on most of the intermediates and were consistent with assigned structures.

(7) Although mercuration of phenolic ethers preferentially takes place at the *ortho* position, 6-bromo and 6-iodo-veratraldehyde were the exclusive products obtained by the mercuration - halogenation sequence.

(8) J. Runeberg, *Acta. Chim. Scand.*, **12**, 188(1958).

(9) J. Van Noordwijk, J. J. Mellink, B. J. Visser and J. H. Wisse, *Rec. trav. chim.*, **82**, 763 (1963).

(10) T. Matsunaga, I. Kawasaki, and T. Kaneko, *Tetrahedron Letters*, 2471(1967).

(11) J. T. Wrobel and M. W. Golebiewski, *Rocz. Chem.*, **45**, 705(1971).

(12) F. Bohlmann, *Angew. Chem.*, **69**, 541(1957); T. A. Crabb, R. F. Newton and D. Jackson, *Chem. Rev.*, **71**, 109(1971).

(13) H. B. Henbest and T. R. B. Mitchell, *J. Chem. Soc.* (c), 785(1970).

(14) B. Loev and M. M. Goodman, *Chemistry and Industry*, 2026(1967).

(15) J. P. Ferris, C. B. Boyce, and R. C. Briner, *J. Am. Chem. Soc.*, **93**, 2942(1971).