Synthesis of the Alkaloid Cularine by Phenol Coupling

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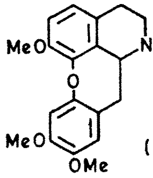
Summary (±)-Cularine (I) has been synthesised *via* oxidative coupling of the diphenolic benzylisoquinoline (III); preparation of the latter involved a new and mild variant of the Pomerantz–Fritsch isoquinoline synthesis followed by application of the Reissert procedure.

CULARINE (I) is the parent of a unique group of benzylisoquinoline alkaloids occurring only in the genera *Dicentra* and *Corydalis*.[1] They are characterised by the unusual oxygen bridge between the two aromatic nucleii in contrast to the bis-benzylisoquinoline alkaloids which possess ether bridges between the individual benzylisoquinoline units.

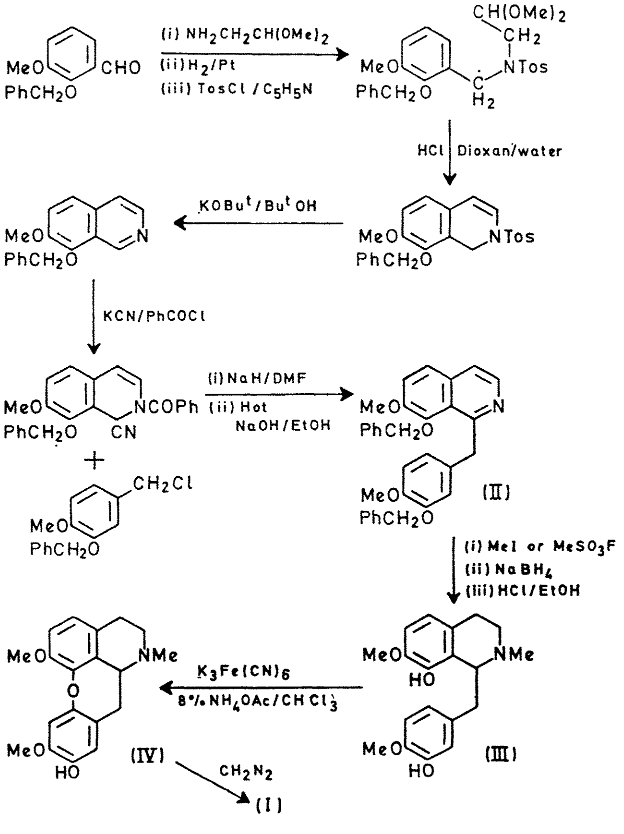


(I)

Cularine and its congeners are presumably[2] derived from two phenylalanine units like other benzylisoquinoline alkaloids, but Pictet–Spengler or Bischler–Napieralski type cyclisations with 3,4-di-oxygenated phenylethylamines almost invariably give rise to 6,7-di-oxygenated isoquinolines rather than to their 7,8-analogues.[3]

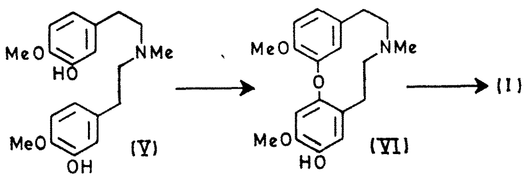
Previous syntheses of cularine and of its methiodide involved the formation of the nitrogen heterocyclic ring as the last stage.[4] We now describe a new synthesis of cularine (Scheme) involving phenol coupling of the benzylisoquinoline (III). The formation of the isoquinoline nucleus involves a new and mild variant of the Pomerantz–Fritsch synthesis[6] which is particularly suitable for the 7,8-oxygenated compounds. It also provides a direct route to fully aromatic isoquinolines[7] in contrast to the Bobbitt variation which leads more readily to tetrahydroisoquinolines.[8]

The 1-benzylisoquinoline (II), m.p. 119—120° was prepared by the Reissert procedure and converted into the diphenolic tetrahydroisoquinoline (III), m.p. 61—63°. Oxidation of the latter with potassium ferricyanide in a two-phase system (8% NH_4OAc-$CHCl_3$) gave the phenolic product, m.p. 126—127° (IV) in 7% yield. This was methylated with diazomethane, and after chromatography (column and t.l.c.) afforded (±)-cularine, m.p. 119° (lit.[4] m.p. 113—114°). The identity of the product was confirmed by elemental analysis, by its n.m.r. spectrum, and by chromatographic and mass spectral comparisons with natural material.



SCHEME

We are attempting by isotopic labelling experiments to determine whether or not the diphenol (III) is an intermediate in the natural pathway to cularine. An alternative



possibility is the phenol coupling of the open chain bis-(phenylethyl)amine (V) to the large ring diphenyl ether (VI); oxidative cyclisation of the latter followed by methylation would then afford cularine and account for the uncommon oxygenation pattern in the isoquinoline moiety.

We thank Dr. R. H. F. Manske for a sample of natural cularine.

(*Received, November* 20*th*, 1970; *Com.* 2011.)

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[1] *Cf.* R. H. F. Manske in "The Alkaloids—Chemistry and Physiology," ed. R. H. F. Manske and H. L. Holmes, Academic Press New York, 1954, vol 4, p. 1; T. Kametani, "The Chemistry of the Isoquinoline Alkaloids," Hirokawa, Tokyo, 1969, p. 74.

[2] *Cf.* N. S. Bhacca, J. Cymerman Craig, R. H. F. Manske, S. K. Roy, M. Shamma, and W. A. Slusarchyk, *Tetrahedron*, 1966, **22**, 1467.

[3] W. M. Whaley and T. R. Govindachari, *Org. Reactions*, 1951, **6**, 74, 151.

[4] T. Kametani and K. Fukumoto, *J. Chem. Soc.*, 1963, 4289; T. Kametani and K. Ogasawara, *ibid.*, 1964, 4142; T. Kametani, S. Shilruya, S. Seino, and K. Fukumoto, *ibid.*, p. 4146.

[5] Earlier attempts to synthesise the benzylisoquinoline (III), *e.g.* by addition of the appropriate benzyl Grignard or benzyl-lithium derivative to an isoquinoline or isoquinol-1-one, were all unsuccessful; G. A. Charnock, A. H. Jackson, J. A. Martin, and G. W. Stewart, unpublished work.

[6] *Cf.* W. J. Gensler, *Org. Reactions*, 1951, **6**, 191.

[7] *Cf.* also M. Sainsbury, D. W. Brown, S. F. Dyke, and G. Hardy, *Tetrahedron*, 1969, **25**, 1881.

[8] J. M. Bobbitt, K. L. Khanna, and J. M. Kiely, *Chem. and Ind.*, 1964, 1950; J. M. Bobbitt, J. M. Kiely, K. L. Khanna, and R. Ebermann, *J. Org. Chem.*, 1965, **30**, 2247.