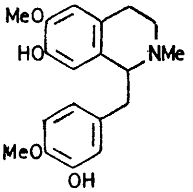
Biosynthesis of Magnoflorine from Reticuline by Direct Oxidative Coupling

By E. BROCHMANN-HANSSEN,* C.-H. CHEN, H.-C. CHIANG, and K. MCMURTREY

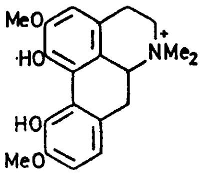
(*Department of Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco, California* 94122)

Summary Magnoflorine (**2**) has been shown by tracer experiments to be derived from reticuline (**1**) in *Aquilegia* plants, presumably *via* direct oxidative phenol coupling; labelled norprotosinomenine produced no incorporation of radioactivity, thus excluding a mechanism involving the dienone (**3a**).

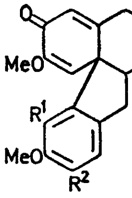
APORPHINES are biosynthesized[1] from phenolic tetrahydrobenzylisoquinolines either by direct oxidative coupling or by an indirect mechanism which utilizes an intermediate dienone. Rearrangement of the dienone with or without prior reduction may result in a large number of aporphines with different substitution patterns. Several investigators[2] have obtained evidence of the indirect pathway by tracer experiments and, in many instances, the results have been confirmed by isolation of the appropriate dienones (proaporphines). Direct coupling to aporphines has been observed in *Papaver somniferum* for isoboldine[3] and in *Corydalis cava* for bulbocapnine.[4] Reticuline would seem to lend itself readily to *ortho–para* coupling, whereas doubts have been expressed[3] regarding a direct *ortho–ortho* coupling because of steric factors. Battersby *et al.*[5] were unable to demonstrate either type of direct coupling for the biosynthesis of corydine, glaucine, and dicentrine in *Dicentra eximia.* On the other hand, they found evidence of an indirect mechanism involving norprotosinomenine and the dienones (**3**).



(1)



(2)



(3)

a; $R^1 = OH, R^2 = H$

b; $R^1 = H, R^2 = OH$

In a previous study[3] we failed to obtain incorporation of reticuline (**1**) into magnoflorine (**2**) in the opium poppy. Inactive magnoflorine was used as a carrier, and it was possible that our variety of *P. somniferum* (Indra) did not contain this alkaloid. The experiment was, therefore, repeated with *Aquilegia*, "McKana hybrid," which is a good source of magnoflorine. $(\pm)$-[N-^{14}CH$_3$]Reticuline was administered by a wick through the base of the flowering stem. Carrier dilution with authentic magnoflorine and isolation gave a product which after purification to constant activity had a specific activity of 38,990 d.p.m./mg, corresponding to an incorporation of 12·1% based on the amount of carrier added. Double Hoffmann elimination and isolation of the amine as ethyltrimethylammonium iodide showed that practically all radioactivity ($>$ 90%) resided in the N-substituents.

The possible existence of two pathways for biosynthesis of magnoflorine in *Aquilegia* was explored by the feeding of $(\pm)$-[3-^{14}C,7-O-methyl-^{3}H]norprotosinomenine. Magnoflorine isolated after carrier dilution was inactive (9 d.p.m./mg).

These experiments, which support Blaschke's work with bulbocapnine, indicate that magnoflorine in *Aquilegia* is biosynthesized by a direct *ortho–ortho* coupling of reticuline. An alternative pathway *via* norprotosinomenine and the dienone (**3a**) is not operative.

This work was supported by a grant from the National Institute of Mental Health.

(*Received, 8th September* 1972; *Com.* 1560.)

---

[1] A. R. Battersby in 'Oxidative Coupling of Phenols,' eds. A. R. Battersby and W. I. Taylor, Marcel Dekker, New York, 1967, p. 119.

[2] D. H. R. Barton, D. S. Bhakuni, G. M. Chapman, and G. W. Kirby, *J. Chem. Soc.* (*C*), 1967, 2134; L. J. Haynes, K. L. Stuart, D. H. R. Barton, D. S. Bhakuni, and G. W. Kirby, *Chem. Comm.*, 1965, 141; A. R. Battersby and T. H. Brown, *Chem. Comm.*, 1966, 170.

[3] E. Brochmann-Hanssen, C.-C. Fu, and L. Y. Misconi, *J. Pharm. Sci.*, 1971, **60**, 1880.

[4] G. Blaschke, *Arch. Pharm.*, 1968, **301**, 432; *ibid.*, 1970, **303**, 359.

[5] A. R. Battersby, J. L. McHugh, J. Staunton, and M. Todd, *Chem. Comm.*, 1971, 985.