Biosynthesis of Chelidonine and Stylopine

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Two routes have been suggested for the biosynthesis of chelidonine (IV) and related benzophenanthridine alkaloids which occur in *Chelidonium majus*. One[1] involves the reaction of a one-carbon unit with two phenylacetaldehyde residues or their equivalents whereas the other[2] regards these alkaloids as being derived from the tetrahydroprotoberberine skeleton (*e.g.* II). Oxidative fission as illustrated at (*a*) and the joining of C-6 to C-13 could generate the skeleton (IV); plausibly, C-6 would be at the aldehyde oxidation level with C-13 being part of a 1,2-dihydroisoquinoline as in (III). Tracer experiments[3] with tyrosine and dopamine have given information about the simple precursors from which chelidonine is formed. Evidence is now reported which eliminates the first biogenetic suggestion and provides powerful support for the second.[4]

(+)-Reticuline (I) and (−)-reticuline were prepared[5] with multiple ^{14}C-labels as indicated and with tritium at the asymmetric centre, C-1; these were fed separately to *C. majus* plants to give the incorporations* reported in Table 1. The expected stereochemical specificity of the

* The incorporation of racemic reticuline into chelidonine has also been observed by Professor D. H. R. Barton, Dr. G. W. Kirby, and R. H. Hesse but, by friendly arrangement, their work was carried no further than this.

[1] R. H. F. Manske, *J.*, 1954, 2987.
[2] R. B. Turner and R. B. Woodward, "The Alkaloids," Ed. R. H. F. Manske and H. L. Holmes, Academic Press, New York, 1953, Vol. III, p. 54.
[3] E. Leete, *J. Amer. Chem. Soc.*, 1963, **85**, 473; E. Leete and J. B. Murrill, *Tetrahedron Letters*, 1964, 147.
[4] Part of this work was first reported at the I.U.P.A.C., Symposium on the Chemistry of Natural Products, Kyoto, Japan, April, 1964.
[5] A. R. Battersby, D. M. Foulkes, and R. Binks, *J.*, 1965,

enzymes involved in the biosynthesis was observed. (+)-Reticuline is clearly the true precursor of all three alkaloids; the specific incorporation of (±)-reticuline into protopine has been reported keeping with the suggested dihydroisoquinoline intermediate (III), but this is not the only explanation of tritium loss (see ref. 5). (−)-[^{3}H]Scoulerine (VII) and (±)-[^{3}H]stylopine (as II) were also

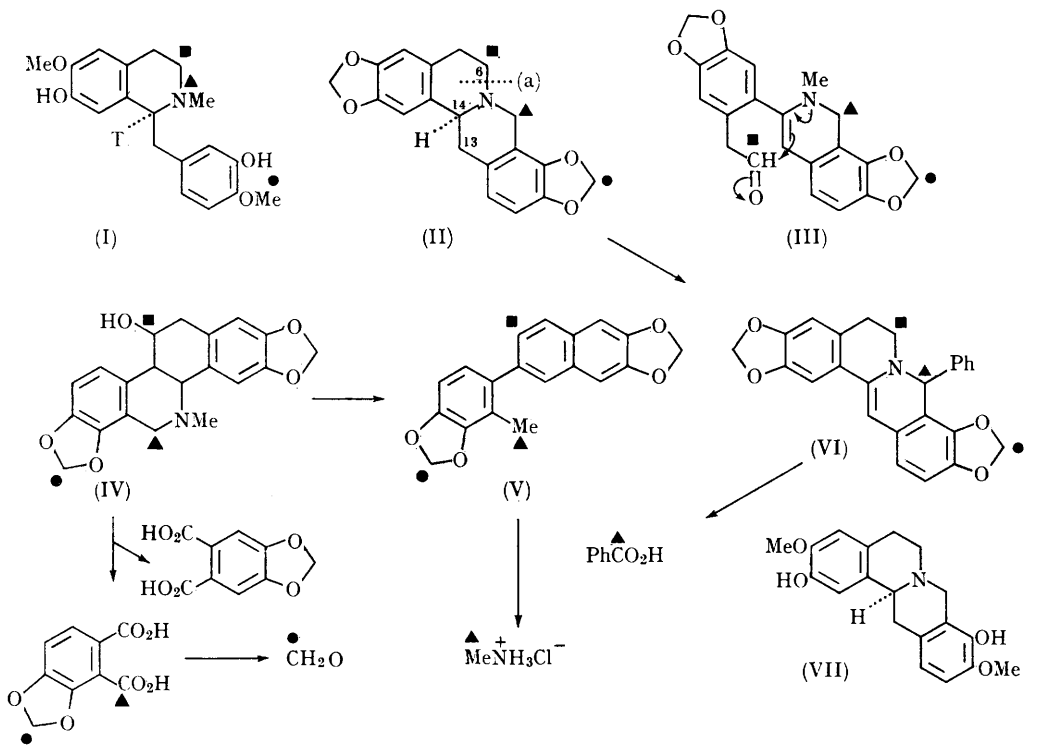

TABLE 1. % *Incorporations*

	(+)-Reticuline	(−)-Reticuline	(−)-Scoulerine	(±)-Stylopine
Chelidonine ..	0·5	0·01	1·5	0·8
Protopine	0·19	0·005	—	—
(−)-Stylopine ..	0·06	0·013	0·4	1·8

TABLE 2. *Relative Activities,* ^{14}C

	■	▲	●
(+)-Reticuline ..	0·76	0·11	0·13
Chelidonine ..	0·77	0·10	0·13
(−)-Stylopine ..	0·73	0·10	0·13

earlier.[6] Degradation of the active chelidonine (IV) derived from (+)-reticuline by the method outlined in the scheme showed that the labelling pattern (Table 2) corresponds exactly with that required by Woodward and Turner's suggestion. Further, the chelidonine contained no tritium, in incorporated into chelidonine (IV) (Table 1) in experiments with small plants which as control incorporated (+)-reticuline to the extent of 0·12% (cf. Table 1). Conversion of the tetrahydroprotoberberine skeleton into chelidonine is thus demonstrated. That the positions of tritium

[6] D. H. R. Barton, R. H. Hesse, and G. W. Kirby, *Proc. Chem. Soc.*, 1963, 267.

labelling corresponded in precursors and products was demonstrated by degradations which, with the synthetic methods, will be described in our full paper.

The radioactive stylopine (II) was converted *via* coptisine into phenyldihydrocoptisine (VI) which was oxidised to benzoic acid. Further degradation by a route analogous to that used for berberine[7] allowed the values reported in Table 2 to be derived. Clearly, (+)-reticuline (I) is converted without degradation into stylopine (II), and the probable intervention of (−)-scoulerine (VII) on the pathway is indicated by the incorporation of this substance (Table I) into stylopine.

The activities at the methylenedioxy-groups of chelidonine (IV) and stylopine (II) represent the fourth and fifth examples of derivation of this group from the *o*-methoxyphenol system in different alkaloids[6,8,9] and the generality of this step is in little doubt.

(*Received, February 9th,* 1965.)

[7] J. R. Gear and I. D. Spenser, *Canad. J. Chem.*, 1963, **41**, 783.
[8] D. H. R. Barton, G. W. Kirby, and J. B. Taylor, *Proc. Chem. Soc.*, 1962, 340.
[9] A. R. Battersby and M. Hirst, *Tetrahedron Letters*, 1965,