

The Biosynthesis of Roemerine, Anonaine, and Mecambrine

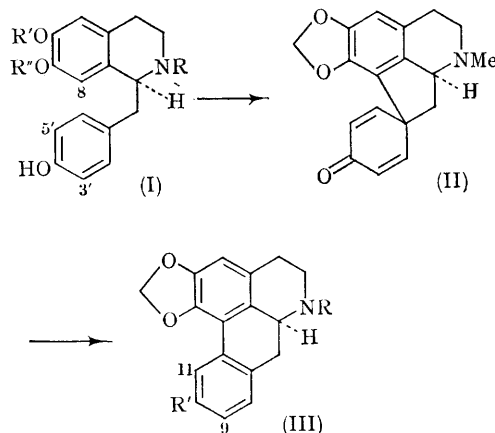
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ACCORDING to biogenetic theory¹ roemerine (III; R=Me, R'=H) and anonaine (III; R=R'=H) should be derived in Nature from a benzylisoquinoline [as (I)] via a dienone [as (II)] and a corresponding dienol. Evidence for the first step is available from studies on the biosynthesis of the dienone crotonosine.² We now report investigations which support the complete biosynthetic sequence.

(±)-Coclaurine (I; R=R''=H, R'=Me), (±)-isococlaurine (I; R=R'=H, R''=Me), (±)-norcoclaurine (I; R=R'=R''=H), and (±)-N-methylcoclaurine (I; R=R'=Me, R''=H), each labelled with tritium *ortho* to the phenolic hydroxyl groups,³ were fed to flowering *Papaver dubium* plants.⁴ Since (+)-roemerine (III; R=Me, R'=H), the major alkaloid of this poppy,⁵ was in short supply, the derived radioactive alkaloids were diluted with an excess of (±)-roemerine. In agreement with theory, coclaurine, norcoclaurine, and N-methylcoclaurine were all incorporated (see Table) into roemerine. Isococlaurine, which lacks the free phenolic hydroxyl group required for phenol coupling, was not incorporated.

(+)-roemerine, was incorporated. Since racemic roemerine was used for dilution, at least one step in biosynthetic sequence must be stereospecific. (±)-[N-methyl-¹⁴C]N-Methylnorcoclaurine (I; R=Me, R'=R''=H) was also a good precursor for roemerine. Herzig-Meyer demethylation of the



TABLE

Incorporation of coclaurine derivatives into roemerine in Papaver dubium*

1964 Season					
Precursor	(±)-Coclaurine	(±)-Isococlaurine	(±)-Norcoclaurine	(±)-N-Methylcoclaurine	
Incorporation (%)	0.062	0.00	0.34	0.48	
(±)-Roemerine was used throughout for dilution. A control feeding with (±)-[2- ¹⁴ C]tyrosine gave 0.17% incorporation. Precursors were labelled with tritium <i>ortho</i> to phenolic hydroxyl groups.					
1965 Season					
Precursor	(±)-Coclaurine	N-Methylcoclaurine			(±)-N-Methyl-norcoclaurine
		(±)	(+)	(-)	
Labelling pattern	[8,3',5'- ³ H ₃]	[NO-Me- ¹⁴ C]	[8,3',5'- ³ H ₃]	[8,3',5'- ³ H ₃]	[N-Me- ¹⁴ C]
Diluting alkaloid	(+)-Roemerine	(+)-Roemerine	(±)-Roemerine	(±)-Roemerine	(+)-Roemerine
Incorporation (%)	0.15	0.19	0.11	<0.000	0.10

* Incorporations have been corrected, where appropriate, for loss of tritium from C-8.

In the following season, parallel feedings of (+)-N-methylcoclaurine² (I; R=R'=Me, R''=H) and its antipode were carried out. Only the (+)-enantiomer, which has the same configuration as

radioactive alkaloid showed that all the activity was, as expected, in the N-methyl group. A feeding experiment with (±)-N-methylcoclaurine, labelled with ¹⁴C in the N-(81%) and O-methyl

(19%) groups, gave an unexpected result. The derived roemerine (relative molar activity 1.00) contained activity in the *N*-methyl (0.87) and methylenedioxy-(0.11) groups. A significant fraction of the methoxyl activity had therefore been lost during biosynthesis. The cyclisation of an *o*-methoxyphenol to give a methylenedioxy-group is well known⁶ but has not previously been observed accompanied by demethylation.

Experiments with other plants confirmed and extended these findings. (\pm)-[³H]Coclaurine and (\pm)-[³H]norcoclaurine were good precursors for (–)-anonaine [antipode of (III; R=R'=H)] in *Anona reticulata*. The incorporations observed, after dilution with (\pm)-anonaine, were, respectively,

0.44 and 0.49% (corrected for loss of tritium from C-8). (\pm)-[³H]-Coclaurine was also incorporated (0.066%, corrected for tritium loss), in *Mecanopsis cambrica*, into mecambrine (II).⁷ Treatment of the radioactive alkaloid with hot hydrochloric acid gave mecambroline (III; R=Me, R'=OH) of the same activity. This phenol, when heated in aqueous alkali, lost all its tritium which must therefore³ have been located, as expected, only at positions 9 and 11. Incorporation (0.03%) of the doubly labelled *N*-methylcoclaurine (see above) into mecambrine was also observed but insufficient material was available for degradation.

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¹ D. H. R. Barton and T. Cohen, "Festschrift A. Stoll", Birkhauser, Basel, 1957, p. 117.

² L. J. Haynes, K. L. Stuart, D. H. R. Barton, D. S. Bhakuni, and G. W. Kirby, *Chem. Comm.*, 1965, 141.

³ See: G. W. Kirby and L. Ogunkoya, *J. Chem. Soc.*, 1965, 6914.

⁴ We thank Dr. Stella Rogers (Queen Elizabeth College) for a generous supply of *Papaver dubium* seeds.

⁵ J. Slavík, *Coll. Czech. Chem. Comm.*, 1964, **29**, 1314.

⁶ D. H. R. Barton, R. H. Hesse, and G. W. Kirby, *J. Chem. Soc.*, 1965, 6379; and references there cited; A. R. Battersby, R. J. Francis, E. A. Ruveda, and J. Staunton, *Chem. Comm.*, 1965, 89.

⁷ J. Slavík and L. Slavíková, *Coll. Czech. Chem. Comm.*, 1963, **28**, 1720; we thank Dr. J. Slavík for a generous supply of mecambrine, and Dr. E. E. Kemp (Royal Botanic Gardens, Edinburgh) for *M. cambrica* roots.