Biosynthesis of the Apparently "Directly Coupled" Aporphine Alkaloids

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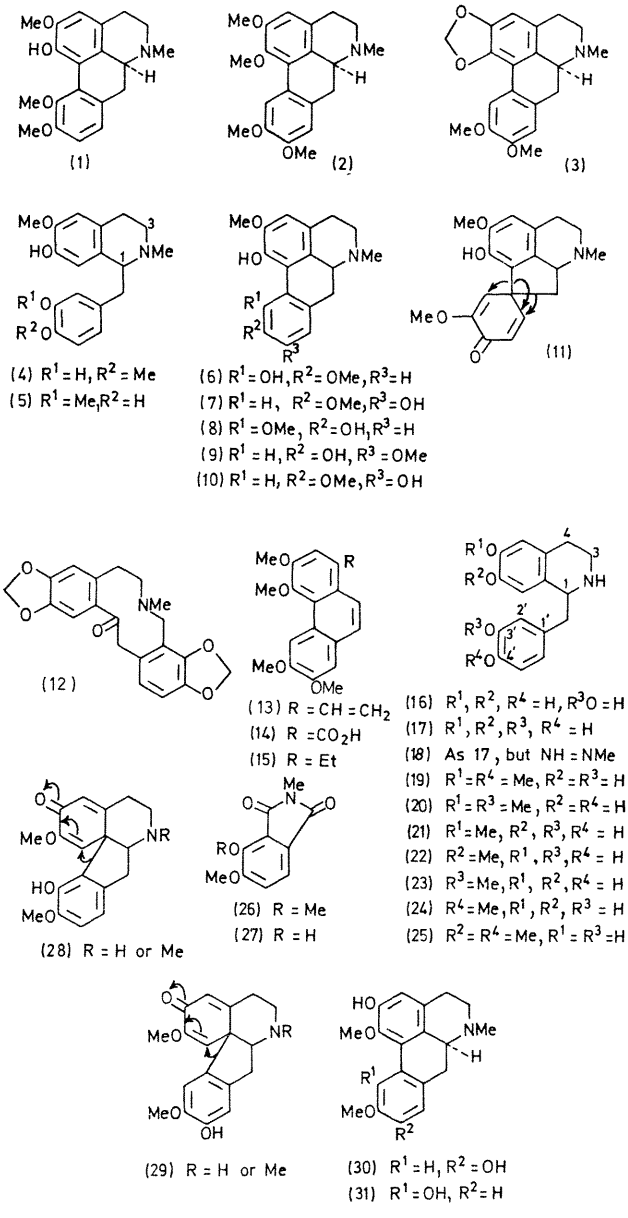
Summary Surprisingly, the aporphine alkaloids (1), (2), and (3) of *Dicentra eximia* have been shown by tracer experiments to be derived from norprotosinomenine (25), presumably *via* the dienones (28) and (29).

CORYDINE (1), glaucine (2), and dicentrine (3) occur in *Dicentra eximia*[1] and their structures can most readily be explained[2] as involving direct coupling of the radicals formed by oxidation of reticuline (4). *ortho–ortho*, and *ortho–para* coupling could yield (6) and (7), respectively, from which the three alkaloids are derivable in principle by unexceptional steps. This seemed the most likely biosynthetic route, particularly after the homoaporphines had been shown[3] to be formed *in vivo* by a direct coupling process. However, an alternative view[4] made use of the sequence orientaline (5) to orientalinone[5] (11) followed by dienone–phenol rearrangements as indicated to give (8), (9), or (10) which are also plausible precursors of the *Dicentra* alkaloids (1), (2), and (3). We outline below the surprising solution of the biosynthetic problem.

The two schemes above were tested by standard synthesis of labelled (±)-reticuline (4) and (±)-orientaline (5). Expts. 1 and 2 show that these phenols were ineffective as precursors of the alkaloids (1), (2), and (3); reticuline was converted well into protopine (12), as expected.[6,7] These results were not significantly changed by administering the labelled materials in different ways at various times over the growing season (seven expts.). Feeding labelled tyrosine (Expt. 3) in parallel with Expts. 1 and 2 confirmed that synthesis of the alkaloids was occurring. Degradation of the radioactive glaucine (2) from Expt. 3 by double Hofmann elimination gave (13) which was (*a*) oxidised to (14) [42% of original activity] and (*b*) reduced to (15) and this then oxidised (Kuhn–Roth) to acetic acid [59% of original activity]. 3,4-Dihydroxyphenylalanine (DOPA) was also incorporated well (Expt. 4) and similar degradation of the glaucine isolated gave (14) [<4% of original activity] and acetic acid [96% of original activity]. Thus, two building blocks derivable from tyrosine are used in the biosynthesis, as for other benzylisoquinoline alkaloids[8] but only one of these can be formed from DOPA, a result of general interest. However, norcoclaurine (16) is *not* a precursor of the alkaloids (Expt. 5).

The incorporation of norlaudanosoline (17) into the *Dicentra* alkaloids (Expt. 6) established that these aporphines are modified 1-benzylisoquinolines whilst Expt. 7 with laudanosoline (18) showed the blocking effect of *N*-methylation at too early a stage. Accordingly, labelled nor-reticuline (19) and nororientaline (20) were tested; the results (Expts. 8 and 9) were interpreted as proof of their incorrect *O*-methylation pattern. A clue to the correct pattern was obtained (Expts. 10—13) by feeding the four mono-*O*-methyl ethers of norlaudanosoline (21, 22, 23, and 24); the last was incorporated well, a result confirmed by double-labelling (Expt. 14) which showed no loss (or at most, small loss) of the *O*-methyl group. Oxidation of the isolated corydine (1) gave metahemipinic acid which as (26) carried no ^{14}C and 98% of the original ^{3}H, and (26) was converted by boron trichloride[9] into (27) [93% of original ^{3}H]. This locates the site of ^{3}H-labelling in the original corydine (1).



The foregoing results lead logically to norprotosinomenine (25) as the di-*O*-methylated precursor of the *Dicentra* alkaloids and Expt. 15 showed good incorporation of (25) into the three aporphines. Oxidative coupling of norprotosinomenine (25) or of protosinomenine (corresponding *N*-methyl derivative) could yield the dienones (28) and (29). Dienone–phenol rearrangement as indicated could from (29) yield boldine (30) leading to glaucine (2) and dicentrine (3)

and from (28) to the aporphine (31) leading to corydine (1). Confirmation of the role of boldine was obtained from Expt. 16 which interlocks with the negative result given by isoboldine (10, Expt. 17).

These experiments support the following pathway to the aporphines of *Dicentra eximia*: (17) → (24) → (25) → (28) and (29) → (31) and (30) → (1), (2), and (3).

There is similar evidence to that summarised here supporting the intermediacy of dienone (29, R=H) for the biosynthesis of the Erythrina alkaloids;[10] the differing uses made of this skeleton in *Erythrina* (family Leguminosae) and *Dicentra* (family Papaveraceae) species is of biosynthetic and taxonomic interest.

Tracer experiments on Dicentra eximia

Expt.	(±)-Precursor	Incorporations (%) Corydine (1)	Glaucine (2)	Dicentrine (3)	Protopine (12)
1	[3-^{14}C, 4′-O-*methyl*-^{3}H]Reticuline (4)	0·0	0·0	<0·004	2·8
2	[3-^{14}C, 3′-O-*methyl*-^{3}H]Orientaline (5)	0·0	0·0	0·0	<0·02
3	[2-^{14}C]Tyrosine	1·7	2·7	1·2	0·12
4	[2-^{14}C]DOPA	0·36	0·40	0·34	a
5	[*aryl*-^{3}H]Norcoclaurine (16)	<0·001	<0·001	<0·001	<0·002
6	[*aryl*-^{3}H]Norlaudanosoline (17)	0·06	0·41	0·16	0·8
7	[*aryl*-^{3}H]Laudanosoline (*N*-methyl 17)	0·0	0·0	0·0	0·9
8	[*aryl*-^{3}H]Nor-reticuline (19)	0·0	0·0	0·0	0·5
9	[*aryl*-^{3}H]Nororientaline (20)	0·0	0·0	0·0	0·01
10	[*aryl*-^{3}H]Monomethyl ether (21)	<0·05	<0·08	0·1	<0·04
11	[*aryl*-^{3}H]Monomethyl ether (22)	<0·009	<0·003	<0·006	<0·002
12	[*aryl*-^{3}H]Monomethyl ether (23)	<0·07	<0·005	<0·005	a
13	[*aryl*-^{3}H]Monomethyl ether (24)	0·23	0·40	0·50	0·1
14	[3-^{14}C,4′-O-*methyl*-^{3}H]Mono-methyl ether (24); ^{3}H:^{14}C ratio 1·35	0·016[b] ^{3}H:^{14}C 1·21	0·01[b] ^{3}H:^{14}C 1·12	0·066[b] ^{3}H:^{14}C 1·35	a
15	[1-^{14}C]Norprotosinomenine (25)	0·24	0·12	0·03	<0·003
16	[*aryl*-^{3}H]Boldine[c] (30)	<0·007	0·36	0·17	a
17	[*aryl*-^{3}H]Isoboldine[c] (10)	a	<0·01	<0·01	a

[a] Not examined.
[b] Low incorporation in this case due to poor plants; the levels in Expt. 13 have been confirmed.
[c] Optically active, (+)-form.

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