Biosynthesis of the *Cinchona* Alkaloids: Middle Stages of the Pathway

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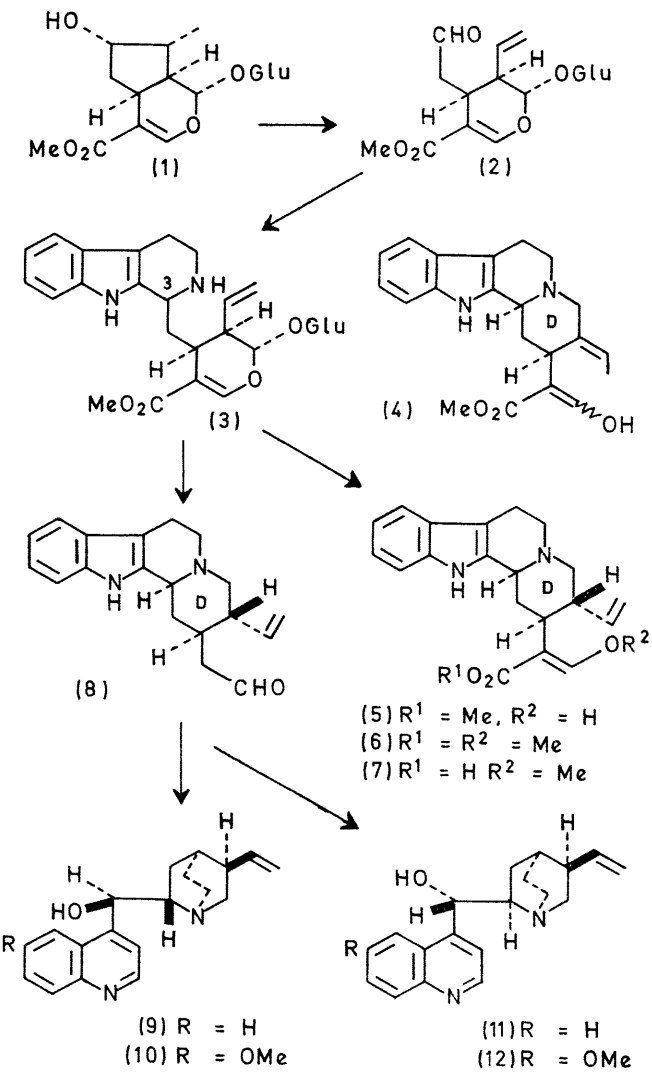
Summary Tracer experiments on *Cinchona ledgeriana* support the sequence (**1**) → (**2**) → (**3**) → (**8**) as the middle stages of the pathway to quinine and its relatives.

EARLIER work proved that quinine (**10**), a representative of the quinoline alkaloids of *Cinchona* (9—12), is biosynthesised by combination of indolic and monoterpenoid units. Tryptophan,[1] geraniol,[2,3] and loganin[4] (**1**) were proved to be precursors of quinine. Experiments bearing on the biosynthetic stages which lie beyond loganin are outlined here and in the following communication.[5]

The middle stages of the pathway were suggested[4] to be loganin (**1**) → secologanin (**2**) → vincoside (**3**) → corynantheine aldehyde (**5**), with later stages bringing about the transformation into the quinoline system. Evidence for involvement of the β-carboline system (**3**) was sought by administering [*Ar*-^{3}H]vincoside,[6] in admixture with its C-3 epimer, to *Cinchona ledgeriana* shoots. After 5 days, the shoots were extracted with cinchonidine (**9**), quinine (**10**) and cinchonine (**11**) being added as carriers. The isolated crystalline alkaloids were further purified by conversion into crystalline derivatives which were crystallised to constant specific activity. The dihydrochloride was used for quinine and the phenylcarbamate for cinchonidine and cinchonine (by reaction with phenyl isocyanate). The incorporations are shown in the Table (Expt. 1).

[*Ar*-^{3}H]Corynantheine aldehyde (**5**) was prepared by treatment of the inactive aldehyde[7] with [^{3}H]trifluoroacetic acid at 20°. Dilution of a portion of the rigorously purified product with geissoschizine (**4**) followed by separation of the two, showed < 0·1% of geissoschizine was present. When [*Ar*-^{3}H]corynantheine aldehyde was fed to *C. ledgeriana* shoots, there was no incorporation into any of the alkaloids (Expt. 2).

This result suggested that loss of the methoxycarbonyl group from (**3**) probably occurs at an early stage prior to, or concomitant with, formation of ring D of the *Corynanthe* skeleton. Accordingly, [*Ar*-^{3}H]corynantheal (**8**) was prepared as follows. Treatment of corynantheine (**6**) with [^{3}H]trifluoroacetic acid afforded *Ar*-^{3}H labelled material which was brought to radiochemical purity and hydrolysed[8] with base to give [*Ar*-^{3}H]corynantheic acid (**7**). This was recrystallised and treated with acid[8] to generate [*Ar*-^{3}H]-corynantheal, purified as its perchlorate. Good



incorporations of the aldehyde (**8**) were observed into the *Cinchona* bases (Expt. 3).

These results, when taken with earlier findings,[4] support

Tracer experiments on Cinchona ledgeriana

Expt. no.	Precursor	Incorporations (%) Cinchonine (**11**)	Cinchonidine(**9**)	Quinine(**10**)
1.	[*Ar*-^{3}H]Vincoside and C-3 epimer (**3**) ..	0·07	0·008	0·008
2.	[*Ar*-^{3}H]Corynantheine aldehyde (**5**)	0·0	0·0	0·0
3.	[*Ar*-^{3}H]Corynantheal (**8**)	0·13	0·04	0·007

the pathway (**1**) → (**2**) → (**3**) → (**8**) → *Cinchona* alkaloids. Further, they place tight restrictions on the number of indolic bases which can be considered as possible substrates for rearrangement to the quinoline system (see also following communication).

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