Biosynthesis of the Ipecac Alkaloids and of Ipecoside

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Summary Tracer experiments show that the Ipecac alkaloids are biosynthesised from secologanin (**3**) *via* desacetylipecoside (**4**) and provide information on the mechanisms involved.

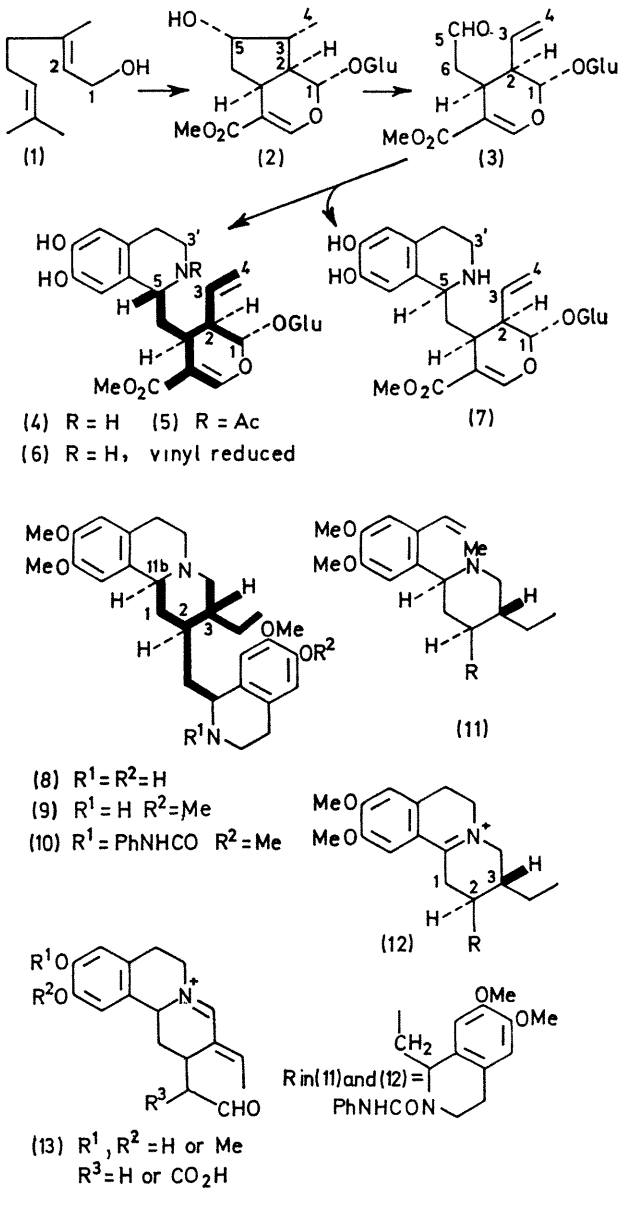
THE amoebicidal alkaloid emetine (**9**) occurs with cephaeline (**8**) and ipecoside[1,2] (**5**) in *Cephaelis ipecacuanha*. Earlier tracer experiments[3] proved that the C_{9-10}-unit of all three substances (thickened) is specifically derived from geraniol (**1**) and loganin (**2**). We now outline results which largely define the pathway beyond geraniol and provide mechanistic information about several stages.

The suggested pathway[4] involves loganin (**2**) → secologanin (**3**) → desacetylipecoside[2,5] (**4**) and its isomer (**7**) which could then be converted biologically into ipecoside (**5**), cephaeline (**8**), and emetine (**9**).

The role of secologanin was studied by feeding [O-*methyl*-^3H,6-$^3H_2$]secologanin[5,6] (**3**) to *C. ipecauanha* plants; the *O*-methyl label carried 58% of the total activity. Expt. 1 in the Table shows the incorporations. Zeisel degradation of ipecoside gave methyl iodide of activity corresponding to 64% of the total.

[1-^{14}C]Dopamine[7] condensed[5] with secologanin to afford [3′-^{14}C]desacetylipecoside (**4**) and [3′-^{14}C]desacetylisoipecoside (**7**). The former was incorporated significantly into ipecoside and the alkaloids (Expt. 2) whereas the latter was virtually ineffective (Expt. 3). These results parallel those obtained with the indolic analogues of (**4**) and (**7**) when they were tested as precursors of the indole alkaloids in *Vinca rosea*[2,8,9] Specific labelling of cephaeline (**8**) from Expt. 2 was established by *O*-methylation and conversion of the product into emetine *N*-phenylurea (**10**).[10] This by Hofmann degradation yielded the methine (**11**) which was cleaved with osmium tetroxide–periodate. The molar activity of the generated formaldehyde corresponded to 85% of that of the methine (**11**) after correction for dilution by formaldehyde derived from the *N*-methyl group of (**11**). The extent of this dilution was determined by repetition of the degradative sequence using [^{14}C]methyl iodide at the quaternisation step.

The specific incorporation of desacetylipecoside (**4**) rather than its isomer (**7**) into cephaeline (**8**) is surprising when one compares the configuration at the corresponding centres of (**4**), (**7**), and (**8**). Of several possible explanations some can be eliminated by showing whether the hydrogen atom at C-11b of (**8**) or (**9**) is, or is not, that originally at C-5 of loganin (**2**). Accordingly, the [^{3}H]emetine (**9**) obtained by incorporation of [5-^{3}H]loganin[11] (Expt. 6) was dehydrogenated as its *N*-phenylurea (**10**) with mercuric acetate to yield the dehydro-derivative (**12**). This was reduced with borohydride in anhydrous diglyme to regenerate (**10**) which carried 5% of the original activity in agreement with labelling of (**9**) at C-11b. However, it is conceivable that the label was at C-1 (by biochemical 1,2-transfer) and has been entirely lost by iminium–enamine equilibration of (**12**). This possibility was eliminated by carrying radio-inactive (**12**) through the conditions of dehydrogenation and the subsequent stages with deuteriated reagents and solvents. Reduction of recovered (**12**), as earlier, regenerated (**10**) which contained by mass spectrometry 28% D_0, 42%, D_1, and 30% D_2 species.



The biological conversion of the vinyl side chain of (**4**) into the ethyl group of (**8**) and (**9**) was studied by feeding dihydrodesacetylipecoside (**6**); Expt. 4 shows that no significant incorporation occurred. Further, Expt. 5

establishes that a ^{3}H-label at C-2 of geraniol (**1**) corresponding to C-2 of loganin (**2**), is retained throughout the cyclopentane ring cleavage and further steps to form ipecoside (**5**) but is lost before the ethyl group of emetine (**9**) or cephaeline (**8**) is formed.

The foregoing results lead to the following conclusions: (*a*) the pathway (**2**) → (**3**) → (**4**) → ipecoside (**5**), cephaeline (**8**), and emetine (**9**) is defined (Expts. 1—3), (*b*) the cleavage of loganin occurs by a mechanism which leaves the C-2 proton unaffected[12] (Expt. 5), (*c*) the ethyl group of the alkaloids is not generated by direct reduction of the vinyl group of (**4**) but presumably involves prior conversion into an ethylidene residue (Expts. 4 and 5); the intermediacy of (**13**) would account for our findings (*d*) the aldehydic proton of secologanin appears as expected at C-11b of emetine; the mechanism of the C-5 → C-11b inversion process (**4**) → (**8**) deserves investigation.

Tracer experiments on Cephaelis ipecacuanha

Expt. No.	Precursor	Incorporation (%) Ipecoside (**5**)	Cephaeline (**8**)	Emetine (**9**)
1	[O-*methyl*-^{3}H,6-$^3H_2$]Secologanin (**3**) ..	0·10	0·11	0·07
2	[3′-^{14}C]Desacetylipecoside (**4**)	0·59	0·34	0·07
3	[3′-^{14}C]Desacetylisoipecoside (**7**)	<0·02	<0·009	0 0
4	[3′-^{14}C]Dihydrodesacetylipecoside (**6**) ..	<0·05	<0·06	<0·002
5	[2-^{3}H,2-^{14}C]Geraniol (**1**) .. .. .. ^{3}H : ^{14}C ratio 4·8	0·03 (100% ^{3}H-retention)	0·01 (3% ^{3}H-retention)	0·01 (4·6% ^{3}H-retention)
6	[5-^{3}H]Loganin (**2**)	2·2	1·1	0·35

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