Tetrahedron Letters No. 48, pp 4849 - 4852.

0040-4039/78/1122-4849$02.00/0

THE BASIC GLUCOSIDES RELATED TO THE BIOSYNTHESIS OF INDOLE AND IPECAC ALKALOIDS

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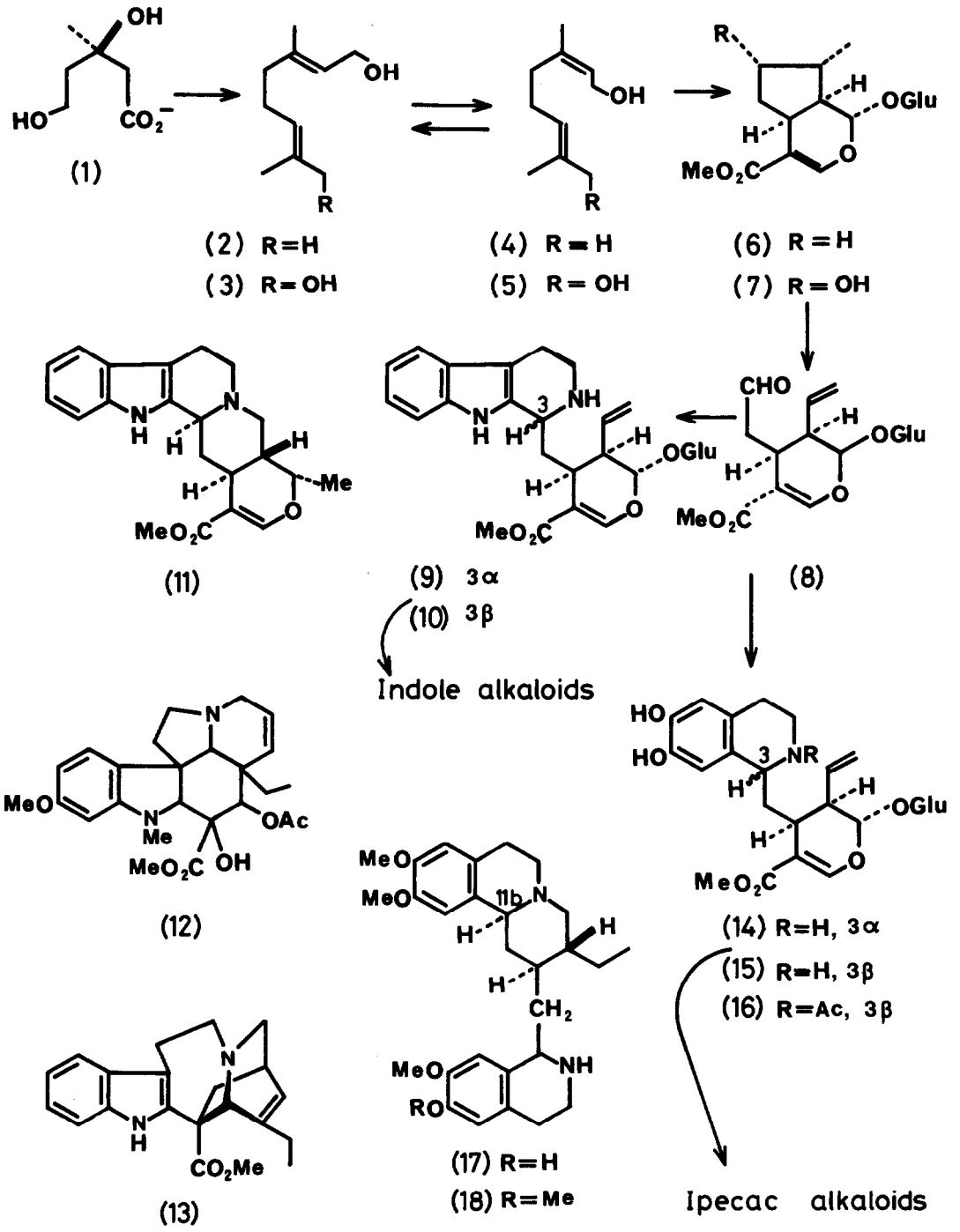
During the nineteen sixties, the biosynthetic pathways to the indole and Ipecac alkaloids were largely elucidated[1-3] by the efforts of several research groups. The non-tryptamine portion of the indole alkaloids was found to be derived from mevalonate (1) via geraniol (2) and nerol (4) which after hydroxylation to (3) and (5) yielded deoxyloganin (6) and subsequently loganin (7). A fascinating cleavage step then generated secologanin (8) which with tryptamine gave rise to strictosidine[4] (9) [≡ isovincoside[5]] together with vincoside[5] (10). The experimental approach for these studies involved tracer experiments in vivo combined with isolation work and structure determinations. As a result, many new substances were discovered among them being the biosynthetic intermediates deoxyloganin[6] (6), secologanin[7] (8) and the basic glucosides (9) and (10), these four having been predicted[1] to be involved with biosynthesis of indole alkaloids.

Our early tracer studies[5] with a mixture of the basic glucosides (9) and (10) established that one or both could be specifically incorporated by Catharanthus roseus (≡ vinca rosea) plants into representatives of the three major indole alkaloid families, viz. ajmalicine (11), vindoline (12) and catharanthine (13). The glucosides were doubly-labelled at well separated sites and the isolated alkaloids were suitably degraded to establish incorporation without randomisation. In addition, (9) & (10) were both isolated from C. roseus plants.[5] Feedings of the separated [O-methyl-^{3}H] bases (9) and (10) to the plants[5] led to the conclusion that 3β-isomer (10) was on the biosynthetic pathway to the alkaloids rather than the 3α-isomer (9) and other workers[8] also found no appreciable incorporation of labelled (9) into indole alkaloids when it was administered to C.roseus plants. However, the above double-labelling experiments established the main relationship of the indolic glucoside system with the alkaloids and the lack of match between the configuation at C-3 of (10) and the corresponding site of ajmalicine (11) remained as an incongruous spot on the large biosynthetic canvas.

Recent experiments[9] confirmed the foregoing double-labelling results and, satisfyingly, the 3α-isomer (9) was found to be incorporated into the alkaloids. However, (9) was again not incorporated under certain feeding conditions due to



Scheme. Biosynthesis of Indole and Ipecac Alkaloids

degradation of the precursor by non-specific glucosides and this is almost certainly one of the factors in the variable incorporation results observed in the basic glucoside area. We have therefore re-examined this stereochemical point using samples of (9) & (10) synthesised[7] from [aryl-^{3}H]tryptamine and secologanin (8), taking advantage of the advances in fractionation methods over the past 10 years. The results (Table) confirm that the 3α-isomer† (9) is incorporated, rather than the 3β (10) and additional confirmation[10] has been adduced.

In the Ipecac series (see Scheme), the earlier work had largely defined the pathway[3] and it followed the same track as for the indole alkaloids, outlined above, up to secologanin (8). This then condensed with dopamine, rather than with tryptamine, to form desacetylisoipecoside (14) and desacetylipecoside (15). Fresh syntheses of these two glucosides have been carried out using [1-^{14}C]dopamine and secologanin (8) and the separated products were fed

TABLE Tracer experiments on Vinca rosea and Cephaelis ipecacuanha

Plant and isolated aklaloids	Precursor and Incorporations (%)			
	3α-Isomer (9)	3β-Isomer (10)	3α-Isomer (14)	3β-Isomer (15)
V. rosea				
Ajmalicine (11)	1.1	<0.01	-	-
Vindoline (12)	0.96	<0.01	-	-
Catharanthine (13)	1.5	<0.01	-	-
C. ipecacuanha				
Cephaeline (17)	-	-	1.6; 1.1	<0.003;<0.01
Emetine (18)	-	-	0.32; 0.28	<0.001;<0.001
Ipecoside[11] (16)	-	-	<0.025;<0.011	0.32; 0.90

individually to Cephaelis ipecacuanha plants. The results in the Table clearly show that the 3α-isomer, desacetylisoipecoside (14) is the precursor of cephaeline (17) and emetine (18), not[3] the 3β-isomer. The 3α configuration of desacetylisoipecoside (14) matches[11] that of the corresponding centre (C-11b) of cephaeline (17) and emetine (18) and so here too the biosynthetic relationship is now stereochemically unexceptional.

† To simplify the literature, it is best that (9) should be known as strictosidine[4] and (10) as vincoside.

Acknowledgements

We thank Dr. I. Kompis (F. Hoffmann-La Roche, Basle) for a gift of secologanin, the N.R.C. (Canada) for a postdoctoral award (to N.G.L.) and the Nuffield Foundation and S.R.C. for financial support.

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(Received in UK 2 October 1978)