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NON-INVOLVEMENT OF 5 α-CARBOXYSTRICTOSIDINE AND -VINCOSIDE IN THE BIOSYNTHESIS OF SARPAGINE- AND AJMALINE-TYPE ALKALOIDS

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Ten years ago the tryptamine (1) and secologanin (3) derived gluco-alkaloids strictosidine (4)[1,2] and vincoside[2] were discovered in higher plants. Strictosidine (4) was proposed as key intermediate in the biosynthesis of monoterpen indole alkaloids[1] but in contrast vincoside was recognized as the biogenetic precursor[2]. Recent biosynthetic studies have established the exclusive role of (4) in alkaloid biosynthesis[3].

However, the possible significance of the corresponding tryptophan analogues 5 α-carboxystrictosidine (5) and 5 α-carboxyvincoside (6) for the biosynthesis of e.g. sarpagine- and ajmaline-type alkaloids was proposed[4,5] and the importance of such compounds in at least the biomimetic synthesis of ajmaline (11) was clearly demonstrated[5]. Indeed, the discovery of (5) in Rhazya orientalis[6] might suggest a precursor role similar to that of (4), especially in this series of alkaloids. In that case the biosynthetic pathway would involve the condensation of L-tryptophan (2) and the iridoid glucoside (3) to yield (5) and/or (6). Transformations similar to those known for heteroyohimbine-type alkaloids[7] would lead to the assumed key intermediate (8) by an additional oxidative decarboxylation step generating the reactive $\Delta^{4,5}$-iminium ion (8). (8) Would allow a simple aldol-type reaction between C-5 and C-16 forming the sarpagine structures, akuammidine (9) and sarpagine (10). (9) Ten could serve as a possible precursor of ajmaline alkaloids ajmaline (11), tetraphyllicine (12), and quebrachidine (13). The known occurrence of the 5-carboxyalkaloid adirubine (7)[8] would, in fact, support the idea of this pathway. However, an involvement of strictosidine (4) via the intermediates of the ajmalicine pathway[7] involving double bond isomerisation at N_b to (8) is an alternate possibility.

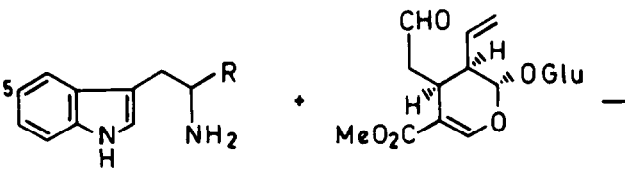
Since biosynthetic investigations regarding this question have not been published, the possible role of the 5 α-carboxy compounds (5) and (6) in the biosynthesis of sarpagine-ajmaline alkaloids and more sophisticated structures such as gelsemine (14) was investigated in the present communication.

For these studies, the putative precursors (5) and (6) were synthesized by simple condensation of (2) and (3) and both compounds were identified by spectroscopic methods after methylation (CH_2N_2), acetylation (Ac_2O/pyridine) or lactamisation (for (5) 12 hrs, 100°, in H_2O, sealed tube; for (6) 30 min, 100°, H_2O). Double labelled (5) and (6) were obtained using a mixture of L-tryptophan-[5-^{3}H] (250 µCi/ 11.5 µmol), L-tryptophan-[methylen-^{14}C] (114 µCi/ 11.6 µmol) and (3) (35 µmol) in yields of 27 % and 16 % resp., ^{3}H:^{14}C was 2.2:1. Both compounds were diluted with unlabelled material (final specific activity 10 µCi ^{3}H/mg) and fed to different plant species (Table). After dilution of plant extracts with carrier material alkaloids under examination were purified by chromatography and/or crystallisation to constant activity.

TABLE Feeding experiments with 5 α-carboxy-strictosidine (5) and -vincoside (6).

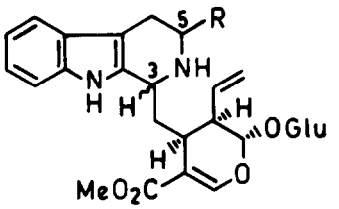
Plant Species and Isolated Alkaloids	Precursor and Incorporation Rates (%) (5)	(6)
Rauwolfia vomitoria		
Ajmaline (11)	0	0
Tetraphyllicine (12)	< 0.01	< 0.01
Quebrachidine (13)	< 0.01	< 0.01
Sarpagine (10)	< 0.01	< 0.01
Vallesia glabra		
Akuammidine (9)	< 0.01	< 0.002
Voacanga africana		
Akuammidine (9)	< 0.01	< 0.001
Gelsemium sempervirens		
Gelsemine (14)	< 0.001	< 0.001

The incorporation rates (Table) indicate that 5 α-carboxy-strictosidine (5) or its 3 ß-isomer (6) are not involved in the biosynthesis of sarpagine- and ajmaline-type alkaloids (9), (10), and (11), (12), (13) respectively, or in the biogenetic formation of gelsemine (14).* On the other hand, the natural occuring (5), isolated by G.N.Smith[6], might have a biosynthetic function in the formation of the acidic compounds with 3 α-stereochemistry, e.g. adirubine (7), or 5-carboxytetrahydroalstonine[9], or, more plausibly in the formation of the corresponding lactam found in Adina rubescens[10]? The results demonstrate that the compounds (5) or (6) are not biosynthetic precursors of ajmaline - sarpagine-type alkaloids.

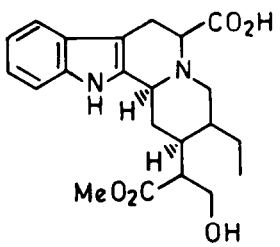


(1) R = H
(2) R = CO_2H

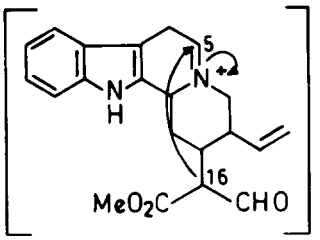
(3)



(4) 3α, R = H
(5) 3α, R = CO_2H
(6) 3β, R = CO_2H

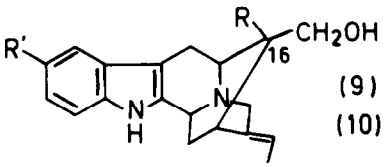


(7)

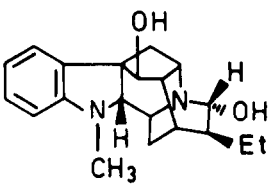


(8)

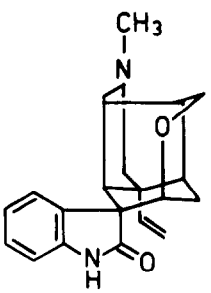
(5) or (6)



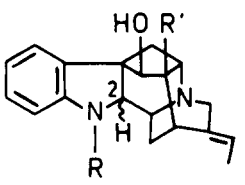
(9) R = CO_2Me, R' = H
(10) R = H, R' = OH



(11)



(14)



(12) 2β, R = CH_3, R' = H
(13) 2α, R = H, R' = CO_2Me

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* Feeding experiments with radioactive strictosidine (4) under identical conditions conclusively showed that (4) is the necessary intermediate in the biosynthesis of e.g. (11) and (14)[11]. The same result was obtained for the alkaloid (9) using Rhazya orientalis plants[12]. Therefore it seems that the presumed[5] key reaction - the oxidative decarboxylation of (5) or (6) - is not involved in the biosynthesis of these alkaloids.

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