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FURTHER INFORMATION ON THE BIOSYNTHESIS OF THE ALKALOID ISMINE

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Feeding experiments in several Amaryllidaceae plants support the biological derivation of the C-13 framework of the lactam narciclasine[1] and of the alkaloid ismine (8)[2] from O-methylnorbelladine (6) by para-para coupling, followed by late elimination of the 'ethano' bridge from the C-15 crinane skeleton.

Whereas a considerable set of information has been obtained up to now on the biosynthesis of narciclasine, mechanistic details are still lacking on the operations of the catabolic process leading to ismine (8). We refer now on feeding experiments designed to establish some stereochemical aspects of this biosynthesis.

[1',5"-$^{3}H_2$;1-^{14}C]O-methylnorbelladine (6) was synthesized from [formyl,5-$^{3}H_2$] 3-hydroxy-4-methoxybenzaldehyde (1) and [1-^{14}C]tyramine according to well known methods. The ratio of the labels between positions 1' and 5", determined by degradation, resulted 6:1, whereas the ^{3}H:^{14}C ratio was 14:1. This product was chemically converted[3] into noroxomaritidine (7) without significant tritium loss.

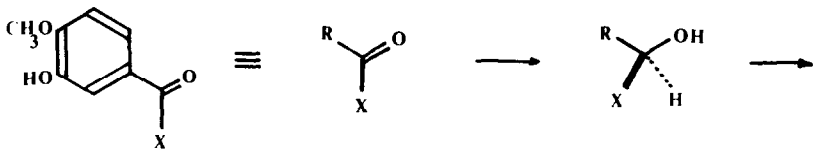
Sprekelia formosissima incorporated triply labelled (7) into the alkaloids ismine (8), haemanthamine (10), and haemanthidine (11) with 0.03%, 2%, and, respectively, 0.8% incorporations. Ismine (8) is devoid of ^{14}C activity, haemanthamine (10) holds an unchanged ^{3}H:^{14}C ratio, whereas haemanthidine retains nearly 55% of the starting tritium activity, thus confirming the previous findings with other precursors.[4]

The labelling pattern of the radioactive ismine (8) was determined by conversion[5] into the phenanthidone (9), which retains ca. 25% of the tritium activity. It follows that in the biological transformation of noroxomaritidine (7) into ismine (8) there is the loss of ca. 50% the tritium originally present at C-6 in noroxomaritidine (7), at benzylic position α to the tertiary nitrogen, thus suggesting a stereospecific hydrogen removal at some stage of the biosynthesis, followed by reduction. Further, the complete loss of ^{14}C activity indicates that the carbon atom at C-1 of (6) is not retained as N-methyl group into ismine (8).

It has been established that in the benzylic oxidation occuring in the conversion of haemanthamine (10) into haemanthidine (11), a pro-R hydrogen is lost.[6] In order to find a possible biosynthetic link between these alkaloids and ismine (8), feeding experiments with stereospecifically labelled precursors were devised.

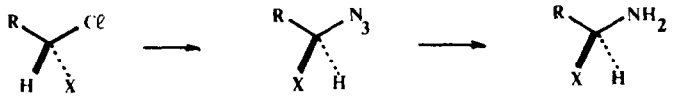
Therefore, [1'-^{3}H]O-methylnorbelladine, containing ca. 75% of the (1'R)-isomer (6a)[6] was mixed with [5"-^{3}H]O-methylnorbelladine (the ratio of the labels between positions 1' and 5" resulted 10:1), and the doubly labelled compound was converted into noroxomaritidine (7a). The latter stereospecifically labelled precursor was incorporated in Sprekelia formosissima into the abovementioned series of alkaloids with the usual efficiency. Degradation of the radioactive ismine (8) to the phenanthidone (9) caused 70% tritium loss. This result indicates ca. 70% tritium removal from C-6 of the precursor (7a).

Complementary evidence for the stereospecificity of the oxidation process arose from experiments with the (1'S)-isomer (6b). The latter compound was obtained in the following way. The alcohol (2), (X=^{3}H)[6], was converted upon treatment with triphenylphosphine in CCl_4[7] into the chloride (3). Azide displacement on (3) with NaN_3 in HMPA led to the azide (4), which was reduced with $LiAlH_4$ to the amine (5). The absolute configuration and the optical purity of the amine (5) was determined in the deuteriated series (in compounds (1) – (5), X=^{2}H) by degradation to [2-^{2}H]glycine.[6] As expected, o.r.d. measurements showed that the major enantiomer had (S) configuration, whereas the optical purity resulted ca. 70%.

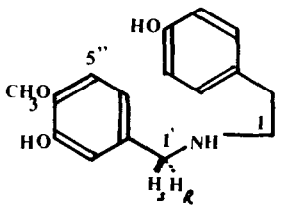


(1) X= ^{3}H or ^{2}H

(2) R= 3-benzyloxy-4-methoxyphenyl

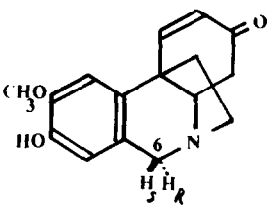


(3) (4) (5)



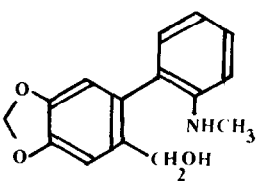
(6a) $H_S=^{1}H$; $H_R=^{3}H$

(6b) $H_S=^{3}H$; $H_R=^{1}H$

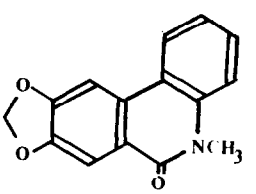


(7a) $H_S=^{1}H$; $H_R=^{3}H$

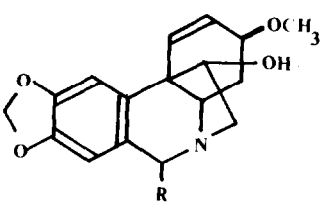
(7b) $H_S=^{3}H$; $H_R=^{1}H$



(8)



(9)



(10) R= H

(11) R= OH

Chemical conversion of the amine (5), (X=^{3}H), into doubly labelled noroxomaritidine (7b) (ratio of the labels between positions 1' and 5", ca. 12:1), was performed as usually. This radioactive compound (7b) was incorporated into ismine (8), which was degraded to the phenanthidone (9). The loss of nearly 90% of the tritium activity in this conversion indicates that 70% of the ^{3}H label originally at C-6 of (7b) is retained at benzylic position in ismine (8).

The evidence therefore establishes, within the accuracy of the radioactivity measurements, the stereospecificity of the benzylic oxidation in the biosynthesis of ismine (8), and that a pro-R hydrogen from C-6 of noroxomaritidine (7) is removed, as in the conversion of haemanthamine (10) into haemanthidine (11).

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