Late Intermediates in the Biosynthesis of Narciclasine

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Summary Tracer experiments show the intermediacy of racemic noroxomaritidine (**5**), normaritidine (**7**), and crinine (**4**) in the biological conversion of *O*-methylnorbelladine (**1**) into narciclasine (**11**)

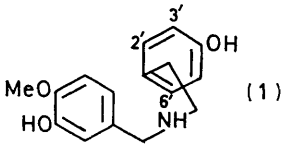
RECENT work[1] has shown that the conversion of *O*-methylnorbelladine (**1**) into narciclasine (**11**) involved loss of two carbon atoms from the C-15 skeleton of oxocrinine (**2**)

We report on feeding experiments designed to establish the nature of the intermediates immediately following the foregoing precursors on the biosynthetic route to narciclasine (**11**)

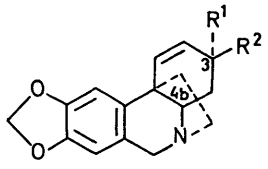
Racemic [1,4b-$^3H_2$]noroxomaritidine (**5**) was synthesised from [2′,6′-$^3H_2$]-*O*-methylnorbelladine (**1**)[2] by the reported procedure[3] Sodium borotritide reduction of the ketone (**5**) gave [1,3,4b-$^3H_3$]epinormaritidine (**6**) The latter, upon acid treatment,[4] was partially converted into [1,3,4b-$^3H_3$]-normaritidine (**7**), which was separated from the reaction mixture on thick plates The structure of the two epimeric alcohols is based on spectroscopic evidence and on their conversion by methylation into the known epimaritidine (**8**) and maritidine (**9**), whereas the labelling pattern was determined by oxidation of the latter two alkaloids to oxomaritidine (**10**), which retained *ca* 28% of the starting activity The relative activities for positions 1, 4b, and 3 for compounds (**6**) and (**7**) are thus 15 : 15 : 70

(±)-[3-^{3}H]Epicrinine (**3**) and (±)-[3-^{3}H]crinine (**4**) were obtained from synthetic oxocrinine (**2**) by the same procedure

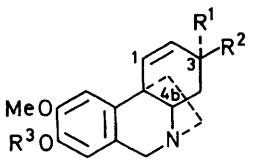
Daffodil plants ("Twink" and "Texas") incorporated (**4**), (**5**), and (**7**) into the alkaloid haemanthamine and into narciclasine (**11**) The labelling pattern of the radioactive narciclasine (**11**) from the three experiments was determined by degradation to narciprimine (**12**), which, after protection by methylation to (**13**), was brominated to (**14**),[5] and by oxidation of (**11**) to narciclasic aldehyde (**15**) The relative ^{3}H-molar activities of the degradation series (Table), in the



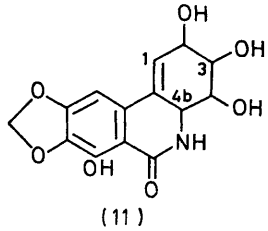
(1)



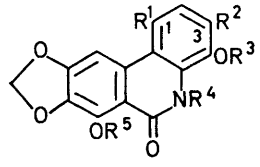
(2) R^1,R^2 = O
(3) R^1 = OH , R^2 = H
(4) R^1 = H ; R^2 = OH



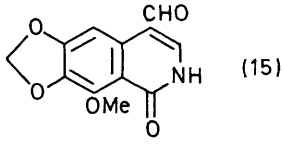
(5) R^1, R^2 = O , R^3 = H
(6) R^1 = OH R^2 = R^3 = H
(7) R^1 = R^3 = H, R^2 = OH
(8) R^1 = OH ; R^2 = H , R^3 = Me
(9) R^1 = H , R^2 = OH , R^3 = Me
(10) R^1, R^2 = O , R^3 = Me



(11)



(12) R^1 = R^2 = R^3 = R^4 = R^5 = H
(13) R^1 = R^2 = H ; R^3 = R^4 = R^5 = Me
(14) R^1 = R^2 = Br ; R^3 = R^4 = R^5 = Me



(15)

TABLE

^{3}H *Relative molar activities and incorporations*

	Expt 1 [1 4b $^3H_2$]Noroxomaritidine (**5**) (inc %)	Expt 2 [1,3,4b-$^3H_3$]Normaritidine (**7**) (inc %)	Expt 3 [3-^{3}H]Crinine (**4**) (inc %)[a]
Narciclasine (**11**)	100	100	100
	(1 8)	(0 8)	(2 1)
Permethylnarciprimine (**13**)	—	85	97
Narciprimine (**12**)	52	83	103
1,3-Dibromopermethyl-narciprimine (**14**)	—	*ca* 5	*ca* 4
Narciclasic aldehyde (**15**)	104	31	*ca* 6

[a] A low incorporation of [3-^{3}H]epicrinine was observed We do not consider it significant because the fed sample was of a purity not higher than 97%, and could contain some crinine Further, labelled epinormaritidine was not incorporated at all

light of previous results,[1] point to the following conclusions. (a) The conversion of *O*-methylnorbelladine (**1**) into narciclasine (**11**) proceeds through its phenol-coupling product (**5**), and through intermediates bearing a pseudoaxial hydroxy-group in position **3** of the crinane skeleton (expts. **1**—**3**). (b) Hydrogen removal from position **3** during the biosynthesis does not occur (expt. **2**). (c) Enzymes which are able to form the methylendioxy-group of the crinane skeleton irrespectively of the oxidation level at C-3 are involved [expts. **1**, **2**, and previous results[1] with oxocrinine (**2**)].

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