

Biosynthesis of Narcissidine

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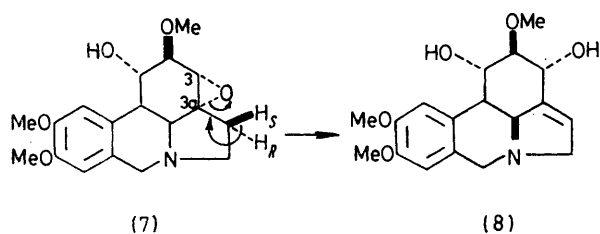
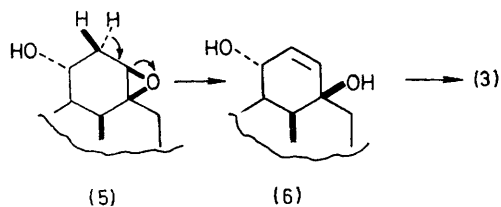
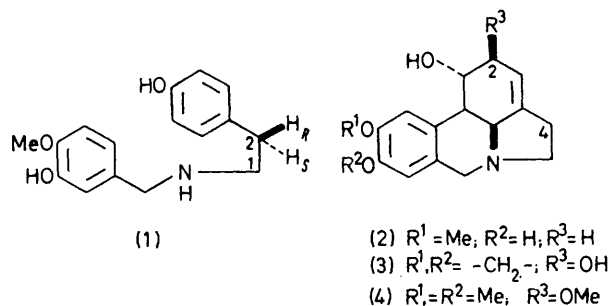
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Summary Feeding experiments show that the conversion of *O*-methylnorbelladine (**1**) into narcissidine (**8**) involves the loss of a *pro-S* hydrogen from C-4 of galanthine (**4**).

THE biological conversion¹ of norpluviine (**2**) into narcissidine (**8**) occurring in daffodil plants² involves the removal of a hydrogen atom from the allylic position β to the nitrogen atom of the lycorane skeleton. In these plants the allylic hydroxylation at C-2 of this type of alkaloid proceeds with

inversion, an abnormality which is tentatively explained³ through the participation of intermediates such as the β -3,3a-epoxide (**5**) [which by stereoselective opening of (**6**) followed by isomerisation would give lycorine (**3**)]. On the other hand in *Clivia miniata* hydroxylation with retention was observed.⁴ An analogous intermediate such as α -3,3a-galanthine epoxide (**7**) could conceivably afford narcissidine (**8**) by loss of the *pro-S* hydrogen from C-4, and consequently determination of the actual stereochemistry of the hydrogen loss at the centre was important.

Sempre Avanti daffodil incorporated [2-³H;1-¹⁴C]O-methylnorbelladine (**1**) into haemanthamine (48% tritium retention) (0.9% incorporation), galanthine (**4**) (98%



tritium retention) (0.08% incorporation), and narcissidine (**8**) (46% tritium retention) (0.09% incorporation). Clearly, there is no loss of tritium from C-4 of galanthine (**4**), whereas in the biosynthesis of narcissidine (**8**) and haemanthamine there is the loss of half the tritium from the corresponding positions β to the nitrogen, thus suggesting for the conversion of (**1**) into (**8**) a stereospecific process, as already observed for haemanthamine.⁵

The stereochemical course of the tritium loss was determined through feeding experiments with asymmetrically labelled precursors. Thus, (2*R*)[2-³H;1-¹⁴C]O-methylnorbelladine (**1**)⁶ was fed to the same plants, which incorporated it into haemanthamine (5% tritium retention), galanthine (**4**) (no tritium loss), and narcissidine (**8**) with 91% tritium retention, thereby indicating in the biosynthesis of (**8**) the loss of a *pro-S* hydrogen from C-4 of the intermediate with the lycorane skeleton. Indication of galanthine (**4**) as the latest intermediate arose from feeding experiments with ³H-galanthine (**4**), obtained from (**4**) by acid-catalysed exchange with tritiated water. There was 5.2% incorporation into narcissidine (**8**) and 11% recovery after two weeks.

Confirmatory evidence in favour of the above mentioned stereochemistry arose from feeding experiments with the (2*S*)-isomer of O-methylnorbelladine (**1**) in the *Ismene* hybrid 'Sulphur Queen'. Incorporation took place in haemanthamine (0.06%) with *ca.* 94% tritium retention and into narcissidine (**8**) (0.008%) with *ca.* 7% tritium retention.

The evidence therefore suggests that the hydrogen removal from the methylene β to the nitrogen atom occurring in the biosynthesis of haemanthamine and narcissidine (**8**) proceeds with opposite stereochemistry.⁵ Furthermore, the observed stereochemistry seems to indicate that narcissidine (**8**) is formed by a route not involving intermediates of the type (**7**).

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¹ Unpublished work by A. R. Battersby *et al.*, quoted by G. W. Kirby and Tiwari, *J. Chem. Soc. (C)*, 1966, 676.

² J. C. Clardy, W. C. Wildman, and F. M. Hauser, *J. Amer. Chem. Soc.*, 1970, **92**, 1781; A. Immirzi and C. Fuganti, *J. Chem. Soc. (B)*, 1971, 1218.

³ I. T. Bruce and G. W. Kirby, *Chem. Comm.*, 1968, 207.

⁴ C. Fuganti and M. Mazza, *J.C.S. Chem. Comm.*, 1972, 936.

⁵ A. R. Battersby, J. Kelsey, and J. Staunton, *Chem. Comm.*, 1971, 183; G. W. Kirby and J. Michael, *ibid.*, 1971, 187.

⁶ C. Fuganti, D. Ghiringhelli, and P. Grasselli, *J.C.S. Chem. Comm.*, 1973, 430.