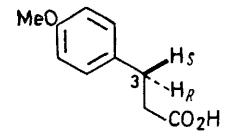
Stereochemistry of Hydrogen Removal β to Nitrogen in the Biological Conversion of *O*-Methylnorbelladine into the Montanine-type Alkaloids

By CLAUDIO FUGANTI,* DARIO GHIRINGHELLI, and PIERO GRASSELLI

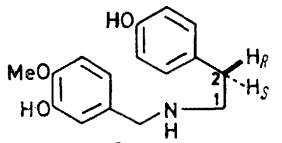
(*Istituto di Chimica del Politecnico, Centro del CNR per la Chimica delle Sostanze Organiche Naturali*, 20133 *Milano, Italy*)

Summary Feeding experiments with asymmetrically labelled precursors show that in the biological conversion of *O*-methylnorbelladine (**2**) into the 5,11-methanomorphanthridine alkaloid, montanine (**5**), a *pro-S* hydrogen from C-2 of the precursor is lost.

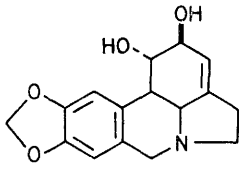
THE chemical conversion of 11-hydroxylated derivatives of the crinane nucleus [*e.g.* (**6a**)] into montanine-type derivatives supported the view[1] that the 5,11-methanomorphanthridine alkaloids produced by several *Haemanthus* spp. (*Amaryllidaceae*) biosynthetically derive from *O*-methylnorbelladine (**2**) by *para–para* coupling, followed by rearrangement of a haemanthamine-like intermediate.



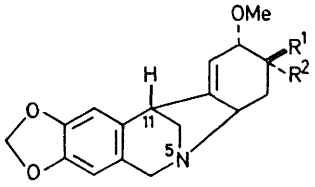
(1a) $H_S = {}^1H$, $H_R = {}^3H$
(1b) $H_S = {}^3H$, $H_R = {}^1H$



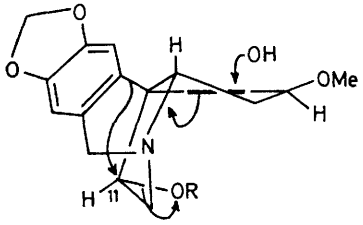
(2a) $H_S = {}^3H$, $H_R = {}^1H$
(2b) $H_S = {}^1H$, $H_R = {}^3H$



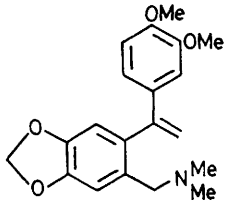
(3)



(4) $R^1 = H$, $R^2 = OH$
(5) $R^1 = OH$, $R^2 = H$



(6a) R = SO_2Me
(6b) R = H



(7)

We now report on feeding experiments in *Haemanthus coccineus* with asymmetrically labelled precursors which establish the intermediacy of *O*-methylnorbelladine (**2**) in the biosynthesis of manthine (**4**) and montanine (**5**) and, further, define that a *pro-S* hydrogen from C-2 of (**2**) is lost at some stage of the biosynthesis, thus suggesting, if a haemanthamine-like intermediate is involved in the skeletal rearrangement, a different stereochemical course of the hydroxylation at C-11 of the crinane skeleton from that already observed in daffodil plants.[2]

As shown in the deuteriated series,[3] palladium-catalysed ring-opening of optically active oxazines allows stereospecific labelling at benzylic carbon. According to this procedure, (3*R*)-3-(4-methoxyphenyl)[3-^{3}H]propionic acid (**1a**) and the (3*S*)-isomer (**1b**) were obtained from 4-methoxy-[*formyl*-^{3}H]benzaldehyde without tritium loss. The acids (**1a**) and (**1b**) were converted into (2*S*)-[2-^{3}H,1-^{14}C]-*O*-methylnorbelladine (**2a**) and, respectively, into the (2*R*)-isomer (**2b**) according to well-established methods.

Haemanthus coccineus incorporated the (2*R*)-isomer (**2b**) into lycorine (**3**), purified as diacetate, (0·8% incorporation) (98% ^{3}H retention), montanine (**5**), characterized as acetate, (0·09% incorporation) (104% ^{3}H retention), and into manthidine (**4**) (0·04% incorporation) (103% ^{3}H retention). The radioactive montanine (**5**) was converted into compound (**7**) with almost complete tritium loss, at the last step of the sequence, when the hydrogen at C-11 of the 5,11-methanomorphanthridine skeleton is removed.[4] Lack of radioactive material did not allow specific degradation for manthidine (**4**).

In a parallel feeding with the (2*S*)-isomer (**2a**) there was incorporation into lycorine (**3**) without tritium loss (0·6% incorporation), whereas montanine (**5**) (0·12% incorporation) retained less than 5% of the tritium activity.

Our evidence therefore establishes that a *pro-R* hydrogen at C-2 of (**2**) is retained at C-11 of the montanine skeleton, in agreement with *para–para* coupling of the precursor, followed by rearrangement. However, the observed stereochemistry of hydrogen removal from C-11 of the crinane skeleton is opposite to that determined in the biosynthesis of haemanthamine (**6b**) in daffodils.[2]

(*Received*, 15*th March* 1973; *Com.* 356.)

[1] W. C. Wildman, 'The Alkaloids,' ed. R. H. F. Manske, Academic Press, New York, London, 1968, ch. XI, p. 400.
[2] A. R. Battersby, J. Kelsey, and J. Staunton, *Chem. Comm.*, 1971, 183; G. W. Kirby and J. Michael, *ibid.*, p. 187.
[3] C. Fuganti, D. Ghiringhelli, and P. Grasselli, *J.C.S. Chem. Comm.*, 1972, 1152.
[4] Y. Inubushi, H. M. Fales, E. W. Warnhoff, and W. C. Wildman, *J. Org. Chem.*, 1960, **25**, 2153.