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FURTHER INFORMATION ON THE ORIGIN OF THE AROMATIC, C-6-C-1 UNIT OF THE AMARYLLIDACEAE ALKALOIDS

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Feeding experiments support the biological derivation of the C-15 skeleton of the Amaryllidaceae alkaloids from phenylalanine and tyrosine, which provide, through indipendent ways, the C-6-C-1 and the C-6-C-2-N units, respectively, of the important intermediate norbelladine giving rise, once suitably methylated, to the different ring systems found amongst this family.[1,2] Cinnamic acid, hydroxylated cinnamic acids and 3,4-dihydroxybenzaldehyde have been recognized as certain intermediates following phenylalanine on the biosynthetic route to the C-6-C-1 aromatic unit.[3] Furthermore, recent investigations[4] established the fate of the hydrogen atoms in the position β of the phenylpropanoid precursors during the abovementioned degradative process.

In the light of these results, the early observation that 3-hydroxy-4-methoxy-N-methylbenzylamine was incorporated with loss of the N-methyl group into the C-6-C-1 unit of the alkaloids haemanthamine (4) and galanthamine (5) in 'King Alfred' daffodil remains reasonably explained through the operation of an amino-oxidase yielding 3-hydroxy-4-methoxybenzaldehyde, later converted into the abovementioned unit of O-methylnorbelladine, a well known precursor of these alkaloids.[1]

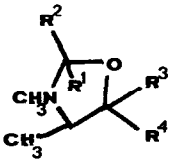
We refer on feeding experiments which support this view and, further, define the stereochemical course of the hydrogen removal occuring in the oxidation step and of the subsequent hydrogen addition required to form the benzylic methylene group.

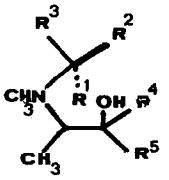
The required information had to be obtained by means of feeding experiments with the enantiomeric forms of the amine (3e) carrying asymmetric tritium labelling at benzylic position and ^{14}C label at the O-methyl group as reference. The present work deals *a)* with the synthesis of the stereospecifically labelled precursors, and *b)* with the manner of their incorporation

into the alkaloids haemanthamine (4), galanthamine (5) and oduline (6).

The obtainment of optically pure N-methyl-α-phenethylamines from (-)-ephedrine and aromatic aldehydes in a synthetic procedure taking advantage of the relevant stereochemical course of a) the condensation of (-)-ephedrine with aromatic aldehydes to form oxazolidines in a totally stereospecific manner, and b) the successive stereoselective ring opening by Grignard reagents to amino-alcohols with retention of configuration, suggested an exploration of the metal hydride opening of the oxazolidines prepared as under a), in the expectation of obtaining in this way stereospecifically labelled amino-alcohols, easily converted by $Pb(OAc)_4$ oxidation, into the required asymmetrically labelled N-methylbenzylamine, providing either reagent is used in an isotopically labelled form.[5]

The oxazolidine (1,e) was therefore prepared, and converted by AlD_3 treatment into the amino-alcohol (2,e). The latter, upon $Pb(OAc)_4$ oxidation, yielded the monodeuteriated amine (3,b). The stereochemistry at the chiral benzylic atom was determined measuring the relative intensities of the signals due to the diastereotopic benzylic protons in the n.m.r. spectrum of (+)-N(3,4-dimethoxybenzyl)-N-methyl-O-methylmandelamide, derived from (3,b) via standard procedures. The signals at 5.57 and 5.50 τ ($CHCl_3$, 100 MHz, Me_4Si, 60°) have been attributed to H_S and H_R, respectively, as shown from the spectrum of the amide prepared from optically active O-methylmandelic acid and monodeutero 3-benzyloxy-4-methoxybenzylamine, containing ca. 75% of the 1'R-isomer[6]; through a synthetic procedure involving amide formation, hydrogenolysis of the benzyl group and methylation to the abovementioned compound. Comparison of the two spectra indicated that the monodeuteriated amine (3,b), obtained via AlD_3 reduction contained ca. 70% of the 1'S-isomer, thereby indicating an inversion mechanism, at variance with the retention observed with the Grignard reagents[5]. Repetition of the sequence using $AlCl_2D$ as reducing agent led, however, to 75% of the 1'R-isomer, with the expected retention. Therefore, from [formyl-^{3}H; ^{14}C-O-methyl]3-benzyloxy-4-methoxybenzaldehyde and (-)-ephedrine, using AlH_3 and $AlCl_2H$, respectively, as reducing agent, the enantiomeric (1'R) and (1'S) amines (3,c) and (3,d) were prepared. Their optical purities (ca. 70%) rest on the results of the deuteriated series.





1a $R^1=R^3=H$; $R^2=R^4=C_6H_5$

1b $R^1=^2H$; $R^2=R^4=C_6H_5$; $R^3=H$

1c $R^1=R^3=C_6H_5$; $R^2=R^4=H$

1d $R^1=R^3=H$; $R^2=C_6H_3$-3,4-di-OMe

2a $R^1=R^4=H$; $R^2=^2H$; $R^3=R^5=C_6H_5$

2b $R^1=^2H$; $R^2=R^4=H$; $R^3=R^5=C_6H_5$

2c $R^1=^2H$; $R^2=R^5=H$; $R^3=R^4=C_6H_5$

2d $R^1=R^4=H$; $R^2=^2H$; $R^3=C_6H_3$-3,4-di-OMe $R^5=C_6H_5$

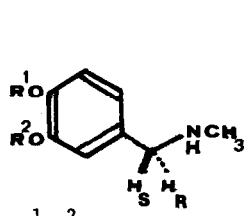
1e $R^1=R^3=H$; $R^2=C_6H_3$-3-$OCH_2C_6H_5$-4-OMe; $R^4=C_6H_5$ 2e $R^1=^2H$; $R^2=R^4=H$; $R^3=C_6H_3$-3-$OCH_2C_6H_5$-4-OMe; $R^5=C_6H_5$

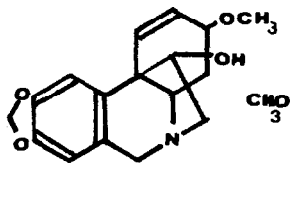
In an attempt to clear up the reasons of the dependence of the stereochemical course of the ring opening upon the nature of the reducing agent, the oxazolidines (1, a–d) were prepared, and converted under a variety of conditions (Table) into the amino-alcohols (2, a–d), whose stereochemistry at the isotopically labelled benzylic position was determined. This was achieved for the amino-alcohols (2, a–c) by conversion into the benzyl acid phtalates through a sequence involving as relevant step the acetate displacement of the quaternary metho-hydroxydes. This reaction has been reported to proceed with complete inversion of configuration; however, the optical purities at benzylic position of compounds (2, a–c), as deduced from the optical rotations of the derived acid phtalates[8] have to be regarded as minimum values. The amino-alcohol (2, d) was cleaved ($Pb(OAc)_4$) to the amine (3, a), carrying one deuterium atom at benzylic position. Its stereochemistry was determined through the abovementioned spectroscopic method.

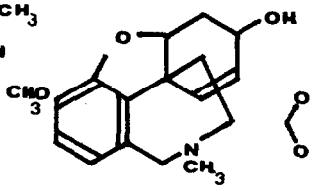
TABLE

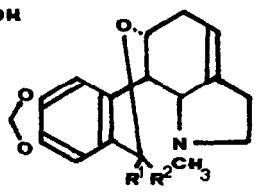
Expt	Oxazolid.	Reducing Agent	Stereochemical course of the ring opening	Major enant. amino-alcohol	% of the major enantiomer
1	1a	$AlCl_2D$	Retention	2a	66
2	1a	B_2D_6	"	"	65
3	1a	$LiAlD_4$	Inversion	2b	55
4	1a	AlD_3	"	"	76
5	1a HCl	$LiAlD_4$	Retention	2a	55
6	1b	$(i\text{-}C_4H_9)_2AlH$	Inversion	"	67
7	1b	di-isopinocamphenylborane	Retention	2b	65
8	1c	$AlCl_2D$	"	2c	70
9	1d	$AlCl_2D$	"	2d	70
10	1e	AlD_3	Inversion	2e	72

The results of Expts. 1–8 (Table) indicate that the stereochemical course of the ring opening depends upon the nature of the reducing agent, even though the optical yields are, however, lower than the ones obtained with Grignard reagents. Apparently, a change in the stereochemistry of the oxazolidines is not affecting the side of the attack (Expts; 1 and 8 with oxazolidines derived from ephedrine and pseudo-ephedrine), which seems rather dependent upon a preferential co-ordination either to the nitrogen or to the oxygen of the reducing agent, if a significance can be attributed to the results of expts. 3 and 5. Indeed, reduction with the same hydride of the oxazolidine (1, a) and of its hydrochloride gave opposite over-all stereochemical course. Furthermore, the optical yields seemed indipendent from the apparent bulkiness of the reagents (Expts. 2 and 7) and of the substituent at position 2 of the oxazolidine (Expts. 4 and 10).









3a $R^1=R^2=Me$

3b $R^1=Me$; $R^2=CH_2C_6H_5$

3c $R^1=^{14}C\text{-}Me$; $R^2=H$; $H_S=H$; $H_R=^3H$

3d $R^1=^{14}C\text{-}Me$; $R^2=H$; $H_S=^3H$; $H_R=H$

3e $R^1=^{14}C\text{-}Me$; $R^2=H$; $H_S,H_R=^3H,H$

4

5

6 $R^1=R^2=OH,H$

7 $R^1,R^2=O$

The two enantiomeric, doubly labelled amines (3,c) and (3,d), along with the randomly labelled compound (3,e) were incorporated in feeding experiments of 'King Alfred' daffodil into the alkaloids haemanthamine (4), galanthamine (5) and oduline (6) with nearly the same high (82-85%) tritium retention, thus suggesting an incorporation with hydrogen removal from benzylic position governed by a kinetic isotope effect. Furthermore, since the previous observations[6] on the stereochemical course of the conversion of norpluviine into lycorenine in daffodil plants, the tritium values observed so far for oduline (6) suggest that the hydrogen addition which follows the hydrogen removal from the benzylic position of the fed amines is stereospecific. A pro-R hydrogen is introduced, which is later removed in the oxidation of the intermediate leading to (6). Conversion of radioactive (6) into (7) caused complete tritium loss thereby confirming the incorporation pattern. The incorporations% were in the range of 0.03-0.09.

The evidence therefore suggests that N-methylisovanilamine (3,e) is incorporated into the aromatic unit of the Amaryllidaceae alkaloids through a process involving non stereospecific hydrogen removal from the benzylic methylene of the secondary amine, showing the subsequent biological operations the same stereochemical course observed for the incorporation into the same moiety of 3,4-dihydroxybenzaldehyde.[6]

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