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FATE OF C-1 HYDROGEN DURING THE INCORPORATION OF (S)- AND (R)-RETICULINE INTO THE OPIUM ALKALOID THEBAINE

S. Loeffler, R. Stadler and M.H. Zenk

Lehrstuhl für Pharmazeutische Biologie, Universität München,
Karlstrasse 29, D-8000 München 2, West Germany

Abstract: In contrast to reports in the literature the C-1 hydrogen atom of (S)-reticuline is completely lost while that of (R)-reticuline is fully retained during the incorporation of both precursors into thebaine in Papaver somniferum plants.

It has been reported in earlier work that radio-labelled (S)- and (R)-reticuline, administered to Papaver somniferum, were incorporated into the morphine alkaloids with about equal efficiency but with substantial loss of ^{3}H at the C-1 site.[1] In the case of the (S)-enantiomer between 82 - 87% of the tritium label was lost, whereas introduction of the (R)-counterpart resulted in retainment of only 32 - 58% of the label. A reversible facile oxidation-reduction system via 1,2-dehydroreticuline[2] - suspected to occur endogenously in poppy plants - could account for the loss of ^{3}H, thereby permitting inversion of configuration at C-1.[1,3] These results prompted us to repeat the earlier reported[1] feeding experiments employing doubly labelled (1-^{13}C, 1-^{2}H) chiral reticulines, synthesized according to standard procedures.[4,5] The optical purity of the bases was determined[5] as at least 98% ee. Labelled thebaine, obtained from plants that were exposed to either (R)-or (S)-reticuline, was subjected to rigorous MS and ^{13}C-NMR analysis. The ^{1}H-decoupled ^{13}C-NMR spectrum of thebaine isolated (0.12 mg) after application of the (R)-isomer (Fig. 1A), showed absolutely no NMR signal in the upfield region that could have corresponded to C-9. However, MS of the same sample revealed very high isotopic enrichment (38 atom-% excess) with an intense molecular ion peak at m/e 314 $(M+H+2)^{+}$ as compared with reference material m/e 312 $(M+H)^{+}$ (Figs. 2B+A). Both of the (R)-reticuline labels are therefore fully retained and non-randomly incorporated into thebaine. The lack of signal detection in the ^{13}C-NMR spectrum is not surprising as the expected C-9 triplet has only very low signal intensity (^{13}C-^{2}H coupling). Metabolic elimination of the ^{2}H label of the (R)-precursor is, according to MS and NMR data, if at all, less than 5%. In sharp contrast the ^{13}C-NMR spectrum of thebaine, isolated (0.16 mg) from seedlings to which (S)-reticuline had been administered, displayed an enriched resonance (singlet!) at 63.16 ppm corresponding to C-9 (Fig. 1B). Complete loss of the deuterium label was corroborated by MS revealing a prominent molecular ion peak (Fig. 2C) at m/e 313 $(M+H+1)^{+}$, with an isotopic enrichment of 32 atom-% excess. On the basis of these experiments we conclude that the (S)-isomer is subject to complete inversion of configuration via oxidative attack at the asymmetric site. Application of the (R)-isomer, not susceptible to oxidation, results in direct internal cyclization to afford the morphinan skeleton.

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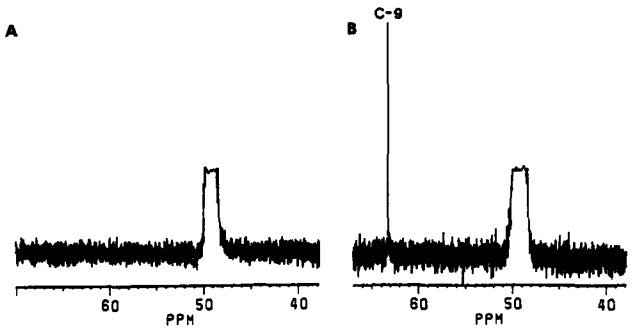


Fig. 1.
^{13}C-NMR partial spectra (90.16 MHz) of thebaine (CD_3OD). (A) Biosynthesized from (R)-(1-^{13}C,1-^{2}H)-reticuline and (B) biosynthesized from (S)-(1-^{13}C,1-^{2}H)-reticuline.

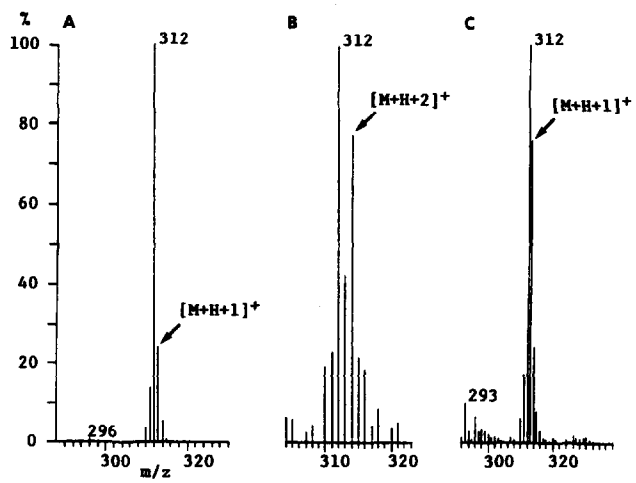
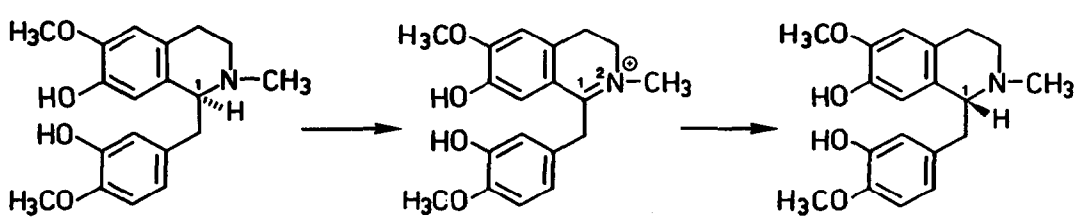


Fig. 2.
Expanded regions of the mass spectra (CI) of thebaine. (A) reference material; (B) obtained from a (R)-(1-^{13}C,1-^{2}H)-reticuline and (C) obtained from a (S)-(1-^{13}C,1-^{2}H)-reticuline feeding experiment.



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