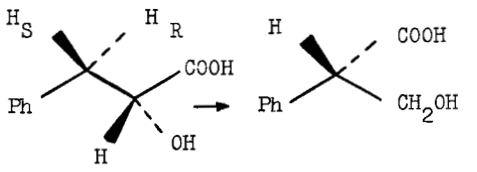
# THE BIOSYNTHESIS OF TROPIC ACID: THE TRANSCARBOXYLATION STEP

S. C. Woodland and J. G. Woolley, School of Pharmacy, Leicester Polytechnic, Leicester LE1 9BH

Tropic acid is the acid moiety of the medicinally useful tropane alkaloids hyoscine and hyoscyamine. Preliminary results on its biosynthesis have been reported previously (Ansarin & Woolley 1978) and recent work (Ansarin 1980) has shownthat it is formed by the intramolecular rearrangement of 2R phenyllactic acid.

The present report highlights work in progress to elucidate the mechanism of this process which inevitably leads to the displacement of one of the two C(3) protons (pro S or pro R) of phenyllactic acid.




The synthesis of stereospecifically labelled C(3) phenyllactic acid (deuterium and tritium) has been accomplished using benzaldehyde-[1-D] prepared by low temperature exchange of the dithian derivative with $D_2O$. (Battersby et al 1972 & 1973).

1. Benzaldehyde was condensed with N-benzoylglycine to give the oxazolinone and cleavage with alkali gave trans benzamidocinnamic acid-[3-D]. Hydrogenation over palladium/C followed by hydrolysis afforded a racemic mixture of 2S 3R and 2R 3S phenylalanine-[3-D].

2. Benzaldehyde was reduced to 1S benzyl alcohol-[1-D] using liver alcohol dehydrogenase and thence to benzyl chloride by the action of thionyl chloride or triphenylphosphine in carbon tetrachloride. The former reagent produced 1S whereas the latter gave 1R benzyl chloride by inversion of configuration. Both chlorides readily condensed with ethyl acetamidocyanoacetate to give 2S 3R + 2R 3R phenylalanine and 2S 3S + 2R 3S phenylalanine labelled at C(3).

The configurations at C(3) for phenylalanine-[3-D] were shown by NMR spectroscopy. Phenylalanine shows a well defined ABX twelve line system which collapses into a double doublet in the amino acid prepared via the oxazolinone. By contrast the enzyme based synthesis gave products showing three doublets at $\delta$ 3·35 (0·5 H), 3·61 (0·5 H) and 4·61 (1H) since the configuration at C(3) is independent of that at C(2). The amino acids have been resolved by means of the selective hydrolysis of the N-chloroacetyl derivatives with carboxypeptidase.

Phenylalanine has been deaminated using nitrous acid, a process which proceeds with retention of configuration at both centres, the L amino acid giving the 2R (+) hydroxy acid. NMR analysis of the variously produced phenyllactic acids showed exactly the same splitting of signals which were observed in the amino acid.

(±)-Phenyllactic acid has been resolved via the morphine salt and thus the dextro acid labelled in either the 3S or 3R position has been prepared.

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