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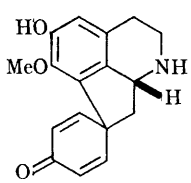
On the Biosynthesis of Crotonosine

By L. J. Haynes and K. L. Stuart
(*University of the West Indies, Jamaica*)
and D. H. R. Barton, D. S. Bhakuni, and G. W. Kirby
(*Imperial College, London, S.W.7*)

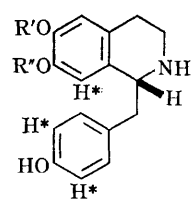
We have recently established the constitution (I) for crotonosine.[1] According to biogenetic theory[2] crotonosine and related dienones[3-5] should be derived in Nature from coclaurine (II; R′ =Me, R″ = H) or *N*-methylcoclaurine. We have now confirmed this experimentally.

(±)-Coclaurine was labelled with tritium, as shown (II), by base-catalysed exchange in tritiated water.[6] Degradation to anisic acid (64% of the total activity) established the uniformity of labelling. This precursor was fed to *Croton linearis* and the derived crotonosine (see Table) converted into diacetylcrotonosine which had the same molar activity. Reduction to the tetrahydro-derivative, treatment with hot methanolic sodium hydroxide, and reacetylation gave inactive diacetyltetrahydrocrotonosine. Thus all the tritium was, as expected, α to the carbonyl group in crotonosine. In a similar experiment (±)-[2-^{14}C]-phenylalanine was also incorporated (0·04%) into crotonosine.

Resolution of (±)-*OO*′-dibenzylcoclaurine, with dibenzoyltartaric acid, gave the (+)- and (−)-forms, $[\alpha]_D$ +24·5° and −26·5° (in chloroform). Hydrogenolysis gave (+)- and (−)-coclaurine hydrochloride, $[\alpha]_D$ +13° and −14° (in methanol). The chirality of the enantiomers was established by



(I)



(II)

methylation with formaldehyde–formic acid to give (−)- and (+)-*N*-methylcoclaurine, $[\alpha]_D$ −120° and +123° (in methanol) (lit. −122° and

[1] L. J. Haynes, K. L. Stuart, D. H. R. Barton, and G. W. Kirby, *Proc. Chem. Soc.*, 1964, 261.
[2] D. H. R. Barton and T. Cohen, "Festschrift A. Stoll," Birkhauser, Basle, 1957, p. 117.
[3] K. Bernauer, *Helv. Chim. Acta*, 1963, **46**, 1783.
[4] M. P. Cava, K. Nomura, R. H. Schlessinger, K. T. Buck, B. Douglas, R. F. Raffanf, and J. A. Weisbach, *Chem. and Ind.*, 1964, 282.
[5] B. Gilbert, M. E. A. Gilbert, M. M. de Oliveira, O. Ribeiro, E. Wenkert, B. Wickberg, U. Hollstein, and H. Rapoport, *J. Amer. Chem. Soc.*, 1964, **86**, 694.
[6] *Cf.* G. W. Kirby and L. Ogunkoya, unpublished work.

+124°).[7] As expected, (+)-coclaurine hydrochloride [absolute configuration (II)] gave (−)-*N*-methylcoclaurine of known[8,9] absolute configuration. Feeding experiments with the labelled (±)-Norcoclaurine (II; R′ = R″ = H), labelled in the usual way, was a rather less efficient precursor of crotonosine than was (±)-coclaurine. This suggests, but does not prove, that demethylation of coclaurine does not precede incorporation. The lack of incorporation of isococlaurine (II; R′ = H, R″ = Me) supports this idea. Experiments are in hand to test the possibility[10] of a methyl migration during crotonosine biosynthesis.

Incorporation of coclaurine derivatives into crotonosine

Precursor	(±)-Coclaurine	(+)-Coclaurine	(−)-Coclaurine	(±)-Norcoclaurine	(±)-Isococlaurine
Incorporation (%)	0·19, 0·20, 0·11*	0·17**	0·00**, 0·00**	0·08, 0·11, 0·07	0·00*

Incorporations are corrected for loss of one tritium;
* and ** indicate feeding experiments performed in parallel.

enantiomers (as above) showed that only (+)-coclaurine was an efficient precursor of crotonosine (see Table). This confirms the absolute configuration of crotonosine (see Cava *et al.*, *loc. cit.*) and shows that the biological conversion is stereospecific.

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[7] H. Yamaguchi, *J. Pharm. Soc. Japan*, 1958, **78**, 678.
[8] C. Ferrari and V. Deulofeu, *Tetrahedron*, 1962, **18**, 419.
[9] M. Tomita and J-I. Kunitomo, *J. Pharm. Soc. Japan*, 1962, **82**, 734.
[10] D. H. R. Barton, *Pure Appl. Chem.*, 1964, **9**, 35.