On the Biosynthesis of Sinomenine

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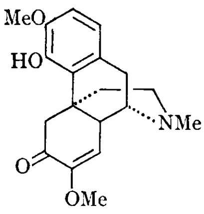
IT has been suggested[1] that protosinomenine (III) is the biological precursor of sinomenine (I). An alternative proposal[2] invokes the oxidative cyclisation of (+)-reticuline (IV) to the dienone (II), which is then transformed into sinomenine. We now present experimental support for the second pathway.

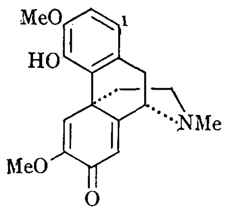
The alkaloid sinoacutine has recently been isolated, along with sinomenine, from *Sinomenium acutum*.[3] Through the good offices of Prof. W.-Y. Huang, and at the suggestion of Prof. Chu, we have shown, by direct comparison with the morphine precursor salutaridine,[4] that sinoacutine has the stereochemistry and constitution summarised in (II).

Sinoacutine, heated at 100° in dimethylformamide containing tritiated water, gave [1-^{3}H]sinoacutine.[5] This selectivity was confirmed by deuterium oxide exchange (nuclear magnetic resonance control) on sinoacutine and by bromination of [1-^{3}H]sinoacutine to inactive 1-bromosinoacutine. The labelled sinoacutine was efficiently converted (1·0% incorporation) into sinomenine in *S. acutum*; 35% of the precursor was recovered from the plant in this experiment. Bromination of the biosynthetic sinomenine to give 1-bromosinomenine,[6] or base-catalysed exchange in aqueous dimethylformamide, removed all (>97%) of the tritium from the alkaloid.

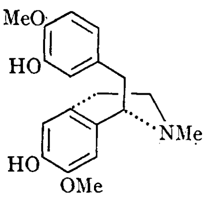
(±)-Reticuline (IV) was labelled with tritium in the positions *ortho* and *para* to the phenolic hydroxyl groups by exchange in alkaline solution and fed earlier in the season to a small *S. acutum* plant. Incorporation (0·007% allowing for the loss of one-third of the tritium) into sinomenine was observed. Bromination of the alkaloid gave 1-bromosinomenine containing 54% of the original activity. The remaining phenolic bases from this experiment were diluted with inactive sinoacutine. This alkaloid was re-isolated and, after rigorous purification, found to be radioactive (0·006% incorporation of reticuline). Bromination gave 1-bromosinoacutine which retained 44% of the activity. The difference between these figures and the expected values of 50% is not significant at the low activities used. Thus the biosynthetic sequence reticuline (IV) → sinoacutine (II) → sinomenine (I) has been established in *S. acutum*.



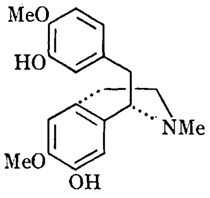
(I)



(II)



(III)



(IV)

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[1] R. Robinson and S. Sugasawa, *J.*, 1931, 3163; 1932, 789.

[2] D. H. R. Barton and T. Cohen in "Festschrift A. Stoll," Birkhauser A.-G., Basel, 1957, p. 117; D. H. R. Barton, *Pure Appl. Chem.*, 1964, **9**, 35.

[3] J.-H. Chu, S.-Y. Lo, and Y.-L. Chou, *Acta Chim. Sinica*, 1964, **30**, 265.

[4] D. H. R. Barton, G. W. Kirby, W. Steglich, and G. M. Thomas, *Proc. Chem. Soc.*, 1963, 203.

[5] Cf. G. W. Kirby and L. Ogunkoya, unpublished observations.

[6] K. Goto and T. Nambo, *Bull. Chem. Soc. Japan*, 1930, **5**, 165.