

Role of Codeinone in the Biosynthesis of Morphine Alkaloids

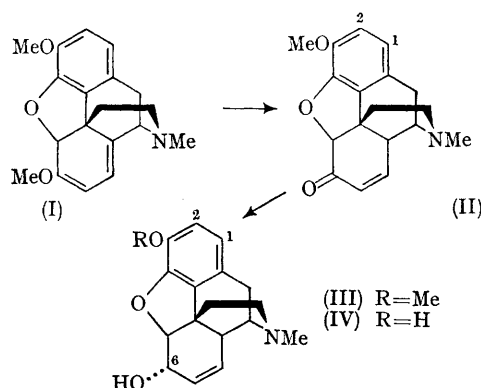
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It is established¹ that the terminal steps in the biosynthesis of morphine involve conversion of thebaine (I) *via* codeine (III) into morphine (IV). Codeinone (II) has been considered on chemical grounds to be a probable intermediate² and we now report experiments with specifically-labelled materials which show codeinone to act as a precursor of codeine and morphine.

[2-³H]Morphine (IV) was prepared by base-catalysed exchange³ and converted by standard methods⁴ into [2-³H]codeine (III) and [2-³H]-codeinone (II), the latter being shown by dilution analysis to contain <0.036% of [2-³H]codeine. Reduction⁵ of radio-inactive codeinone with sodium borotritide gave [6-³H]codeine which was mixed in known proportion with [2-³H]-codeine to give [2,6-³H₂]codeine. This and [2-³H]codeinone were fed separately to *Papaver somniferum* plants and after two weeks, these were worked for alkaloids by a method shown not to cause exchange from [2-³H]morphine.

The incorporation of [2-³H]codeinone into codeine was 4.8% and into morphine 18.4%. Treatment



of the isolated morphine with aqueous base removed 98% of its ³H-activity proving specific labelling at C-2 as in the precursor.

[2,6-³H₂]Codeine was converted efficiently by the plants into morphine (34%) and part was recovered (5.8%). If reversal of the reduction of codeinone to codeine occurs to a significant extent in the living system, then [2,6-³H]codeine will lose tritium from C-6 and this will be evident in the morphine formed from it. Base-catalysed exchange of the isolated morphine allowed the labelling at C-2 to be determined and the material after exchange was converted by *O*-methylation and oxidation into codeinone. The ketone carried <1% of the original activity. In this way the ratio of the 2-label:6-label in the morphine was found to be 1.12:1 (*cf.* 1.13:1 in [2,6-³H]codeine

fed). Similarly, the ratio in the recovered codeine was shown to be 1.15:1. There is thus no significant reversal of the reductive step in the poppy plants used.

The foregoing data give strong support for the sequence thebaine (I) → codeinone (II) → codeine (III) → morphine (IV).

Rapoport and co-workers⁸ have published work during the preparation of our paper which gives evidence from ¹⁴CO₂ exposures and feeding experiments (generally labelled) that codeinone is an intermediate on the pathway. Our work and theirs interlock.

(Received, April 3rd, 1967; Com. 321.)

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² D. H. R. Barton and T. Cohen, "Festschrift A. Stoll," Birkhauser, Basle, 1957, p. 117; D. H. R. Barton, G. W. Kirby, W. Steglich, G. M. Thomas, A. R. Battersby, T. A. Dobson, and H. Ramuz, *J. Chem. Soc.*, 1965, **2423**.

³ G. W. Kirby and L. Ogunkoya, *J. Chem. Soc.*, 1965, **6914**.

⁴ V. M. Rodinov, *Bull. Soc. chim. France*, 1926, **39**, 305; R. J. Highet and W. C. Wildman, *J. Amer. Chem. Soc.*, 1955, **77**, 4399.

⁵ M. Gates, *J. Amer. Chem. Soc.*, 1953, **75**, 4340.

⁶ G. Blaschke, H. I. Parker, and H. Rapoport, *J. Amer. Chem. Soc.*, 1967, **89**, 1540.