Role of Codeinone in the Biosynthesis of Morphine Alkaloids

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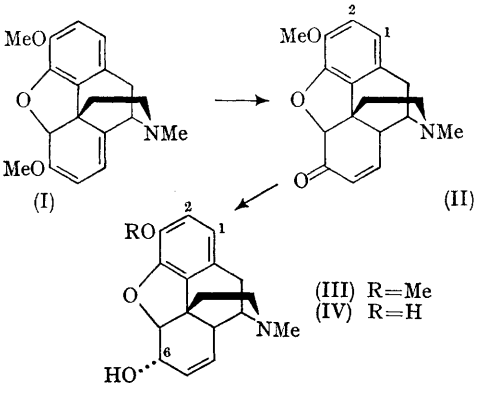
IT is established[1] that the terminal steps in the biosynthesis of morphine involve conversion of thebaine (I) *via* codeine (III) into morphine (IV). Codeinone (II) has been considered on chemical grounds to be a probable intermediate[2] and we now report experiments with specifically-labelled materials which show codeinone to act as a precursor of codeine and morphine.

[2-^{3}H]Morphine (IV) was prepared by base-catalysed exchange[3] and converted by standard methods[4] into [2-^{3}H]codeine (III) and [2-^{3}H]-codeinone (II), the latter being shown by dilution analysis to contain $< 0{\cdot}036\%$ of [2-^{3}H]codeine. Reduction[5] of radio-inactive codeinone with sodium borotritiide gave [6-^{3}H]codeine which was mixed in known proportion with [2-^{3}H]-codeine to give [2,6-$^3H_2$]codeine. This and [2-^{3}H]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-^{3}H]morphine. The incorporation of [2-^{3}H]codeinone into codeine was 4·8% and into morphine 18·4%. Treatment



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

[2,6-$^3H_2$]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-^{3}H]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-^{3}H]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-workers[6] have published work during the preparation of our paper which gives evidence from $^{14}CO_2$ exposures and feeding experiments (generally labelled) that codeinone is an intermediate on the pathway. Our work and theirs interlock.

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