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RATE STUDY ON THE INCORPORATION OF TYROSINE INTO MORPHINE, CODEINE AND THEBAINE

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MUCH is now known about the early[1,2] and intermediate[3] stages of morphine biosynthesis and there is considerable interest in the later stages. By feeding [2-^{14}C] tyrosine to Papaver somniferum plants it has been established[1,2] that two molecules of tyrosine are built into morphine (I). Purification of the codeine (II) and thebaine (III) fractions from our feeding experiments has yielded codeine (3.1×10^5 counts per min. per millimole) and thebaine (1.1×10^5 counts per min. per millimole). Morphine from the same plants had an activity of 4.5×10^5 counts per min. per millimole. Tyrosine can thus serve as the precursor of all three alkaloids. This finding allows [2-^{14}C] tyrosine to be used to follow the rate of incorporation of activity into the bases (I), (II), and (III).

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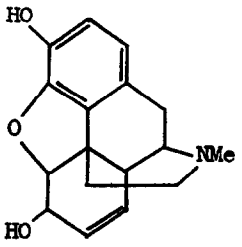
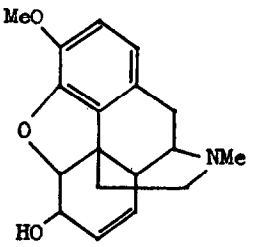
[1] A. R. Battersby and B. J. T. Harper, Chem. & Ind. 363 (1958); A. R. Battersby, R. Binks and D. J. LeCount, Proc. Chem. Soc. 287 (1960).

[2] E. Leete, Chem. & Ind. 977 (1958); E. Leete, J. Amer. Chem. Soc. 81, 3948 (1959).

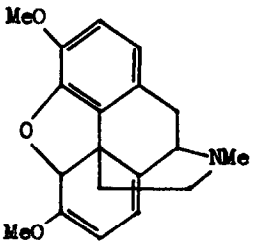
[3] A. R. Battersby and R. Binks, Proc. Chem. Soc. 360 (1960).



I



II



III

Forty five mature poppy plants (1958 season) were fed over 0.5 hr. with [2-^{14}C] tyrosine and at set times after the feeding, groups of five plants were harvested. The alkaloids were extracted and the morphine, codeine and thebaine were isolated by partition chromatography on Whatman No. 1 paper in dioxan, water, 99% formic acid (90, 9.5, 0.5 by volume) for determination of their activities.

We find that the total amounts of alkaloid and the relative amounts of the bases (I), (II) and (III) vary from plant to plant; in addition, these quantities are known to depend upon the stage of development of the

plant.[4] It is therefore necessary to express a result for a given alkaloid as total activity; this gives a measure of the amount of that alkaloid formed from [2-^{14}C] tyrosine which is still present in the plant at the time of harvesting. In order to deal with variations in the total

Time after Feeding	Total Activities x 10^{-3} (counts per 100 sec.)			Ratio Codeine/Morphine	Ratio Thebaine/Morphine
	Morphine	Codeine	Thebaine		
4 hours	7.3	14	33	1.9	4.5
8 hours	24	60	53	2.5	2.2
25 hours	76	77	53	1.0	0.7
2 days	75	91	52	1.2	0.7
3 days	86	36	19	0.4	0.2
5 days	270	55	27	0.2	0.1
8 days	145	29	10	0.2	0.07
11 days	204	25	11	0.1	0.05
14 days	195	21	9	0.1	0.05

incorporation (e.g. apparently more efficient incorporation has occurred in the 5 day experiment) the ratios of activities of the three alkaloids are given. High accuracy is not claimed for these figures, but the experimental error is small compared with the very large changes in activity.

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[4] R. Miriam and S. Pfeifer, Scienta Pharmaceutica 27, 34 (1959); A. R. Battersby and B. J. T. Harper, unpublished work.

The results show a rapid incorporation of activity into thebaine followed by a rise in the codeine activity and then a steady fall in the activities of these two alkaloids relative to that of morphine. Obviously the simplest interpretation of these facts is that the biosynthetic pathway runs from tyrosine to thebaine which is converted into codeine and that morphine is the end product of the synthesis. Feeding experiments using high activity specifically labelled thebaine are planned.

The above studies are complementary to the recent work of Rapoport et al.[5] who grew poppy plants in ^{14}C-carbon dioxide; they proved that the activities residing in the thebaine, codeine and morphine skeletons (i.e. lacking methyl groups) changed with time as in the experiments above. Rapoport et al. also regard their results as evidence for the pathway thebaine → codeine → morphine.

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[5] H. Rapoport, F. R. Stermitz and D. R. Baker, J. Amer. Chem. Soc. 82, 2765 (1960).