# On the Biosynthesis of Isothebaine

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THE large group of aporphine alkaloids (skeleton as IV) are regarded[1,2] as being formed by oxidative cyclisation of 1-benzylisoquinolines. A plausible account of most bases can be given by direct phenol coupling, but for others further steps involving dienone–phenol or dienol–benzene rearrangements are postulated.[2] It was suggested[3] that isothebaine is biosynthesised from orientaline (as I) by phenol oxidation to give orientalinone (II) followed by reduction to the dienol (III) and dienol–benzene rearrangement as indicated; the synthesis of (+)-isothebaine by this sequence has been achieved.[4,5] We now report tracer studies carried out with oriental poppies; the figures after

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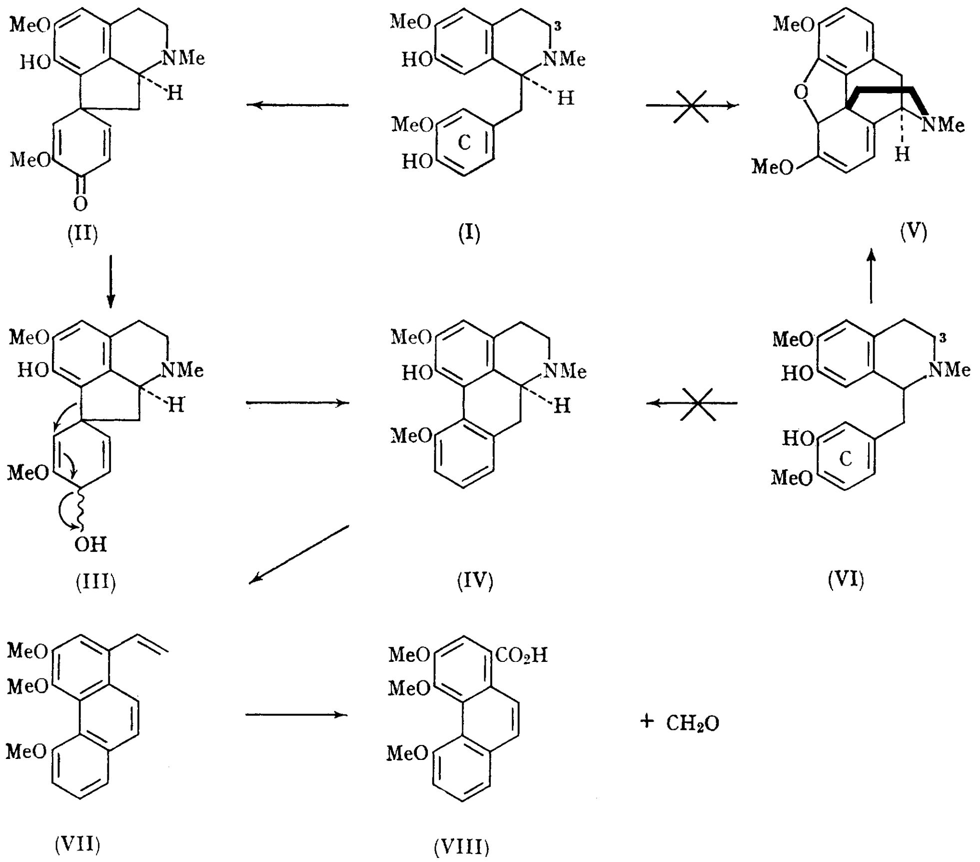
[1] Sir R. Robinson, "The Structural Relations of Natural Products," Clarendon Press, Oxford, 1955.
[2] D. H. R. Barton and T. Cohen, *"Festschrift A. Stoll,"* Birkhauser, Basle, 1957, p. 117.
[3] A. R. Battersby, Tilden Lecture, *Proc. Chem. Soc.*, 1963, 189.
[4] A. R. Battersby and T. H. Brown, *Proc. Chem. Soc.*, 1964, 85.
[5] A. R. Battersby, T. H. Brown, and J. H. Clements, *J. Chem. Soc.*, 1965, in the press.



the formulae numbers record relative radioactivities.

(±)-$[3\text{-}^{14}\mathrm{C}]$Orientaline (as I) was incorporated (1·6%) by *Papaver orientale* plants into isothebaine (IV; 1·00 C*) which was degraded by methylation and Hofmann's method[6] to the vinylphenanthrene (VII; 1·00 C*). This was cleaved by ozone to yield formaldehyde (0·99 C*) and oxidised to the acid[6] (VIII; 0·01 C*). That no fission of the ring-C methoxyl group of orientaline occurs in the biosynthesis was established using (±)-orientaline (as I) doubly labelled with $^{14}\mathrm{C}$ at C-3 (56% of total) and at the ring-C methoxyl group (44%). This material was similarly incorporated into isothebaine which yielded methyl iodide (as $\mathrm{Et_3N^+MeI^-}$; 0·43 C*) by Zeisel's method. Degradation of the alkaloid as above afforded formaldehyde (0·55 C*) and the acid (VIII; 0·43 C*).

The illustrated absolute stereochemistry of (+)-isothebaine (IV) has been established by chemical methods[5]; this agrees with earlier optical studies[7] and corresponds to that of (+)-orientaline[5] (I). (+)-$[^{3}\mathrm{H}]$Orientaline and (−)-$[^{3}\mathrm{H}]$orientaline were prepared[5] and the former was incorporated twenty-eight times more efficiently (1·9%) than the latter (0·067%). The expected relationship thus obtains between precursor and product.

Thebaine (V) also occurs in *P. orientale*[6,8] and its biosynthesis from isothebaine (IV) has been claimed.[9] Such a biosynthetic step goes against

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[6] W. Klee, *Arch. Pharm.*, 1914, **252**, 211.

[7] C. Djerassi, K. Mislow, and M. Shamma, *Experientia*, 1962, **18**, 53.

[8] G. Kleinschmidt, *Arch. Pharm.*, 1961, **294**, 254.

[9] S. Gross and R. F. Dawson, *Biochemistry*, 1963, **2**, 186.

much tracer evidence[10] concerning the biosynthesis of the morphine group of alkaloids and the problem has therefore been re-investigated. (±)-[3-$^{14}$C]-Reticuline (VI) was incorporated (0·2%) into thebaine (V) in *P. orientale* (as it is in the opium poppy[10]), but the isothebaine (IV) isolated from the same plants was virtually radio-inactive ($<7 \times 10^{-4}$% incorpn.). In a parallel experiment, (±)-(3-$^{14}$C]orientaline (as I) was incorporated by *P. orientale* plants into isothebaine (1·6%) but not significantly into thebaine (V; $<2 \times 10^{-3}$% incorpn.). Both alkaloids are clearly being biosynthesised during these experiments and we conclude that the conversion of isothebaine (IV) into thebaine (V) does not occur to any significant extent. The reverse conversion of thebaine into isothebaine has also been eliminated.[11] The (±)-precursors (I) and (VI) differ only in the methylation pattern of ring C and our experiments demonstrate that biosynthesis is directed to different final skeletons, at least in part, by *O*-methylation.

(*Received, April* 15*th*, 1965.)

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[10] A. R. Battersby, R. Binks, R. J. Francis, D. J. McCaldin, and H. Ramuz, *J. Chem. Soc.*, **1964**, 3600; 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; A. R. Battersby, D. M. Foulkes, and (in part) R. Binks, *J. Chem. Soc.*, **1965**, in the press, and refs. therein.

[11] F. R. Stermitz and H. Rapoport, *J. Amer. Chem. Soc.*, 1961, **83**, 4045.