

Biogenetic Type Syntheses of Aporphine Alkaloids : Isoboldine and Corydine

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THE key role of reticuline (Ia) in the biosynthesis of the morphine and berberine groups of alkaloids is now well established,¹ but whether it is also the precursor of certain aporphine alkaloids remains to be determined. Recently it has been shown that manganese dioxide oxidation of reticuline gives salutaridine (II) (the precursor of the morphine alkaloids) in 0.024% yield,² and that ferric chloride oxidation of tembeterine (Ib) gives the quaternary aporphine laurifoline (IIIb) in 3% yield.³

We now report that ferricyanide oxidation of reticuline in ammonium acetate solution at about -10° yields (\pm)-isoboldine (IIIa) (0.5%), which forms an amorphous picrate, m.p. 163—165°. The structure of the product was confirmed by spectroscopic methods (especially n.m.r.), and by conversion into (\pm)-glaucine⁴ (IIIc), picrate, m.p. 193—194°. This work thus constitutes the first

synthesis of isoboldine, a new alkaloid only recently isolated from natural sources.⁵

An attempt to synthesise a bromocorytuberine (IVa), (with the isomeric oxygenation pattern—1,2,10,11—to isoboldine and glaucine), by the oxidative coupling of the blocked bromoreticuline (Ic), was unsuccessful. Somewhat surprisingly the bromine was eliminated and the only product isolated was isoboldine (IIIa) in an improved yield (2.5%). The expected coupling may have been inhibited by steric factors, *i.e.* interactions between the oxygen functions at positions I and II in the expected product, or the intermediates in the reaction. (It is well known that oxygen functions in these positions in the twisted biphenyl ring system of aporphines considerably enhance the angle of twist.⁶)

In connection with these results it is interesting

¹ D. H. R. Barton, Hugo Muller Lecture, *Proc. Chem. Soc.*, 1963, 293; A. R. Battersby, Tilden Lecture, *ibid.*, 1963, 189.

² D. H. R. Barton, G. W. Kirby, W. Steglich, and G. M. Thomas, *Proc. Chem. Soc.*, 1963, 203.

³ S. M. Albonico, A. M. Kuck, and V. Deulofeu, *Chem. and Ind.*, 1964, 1580.

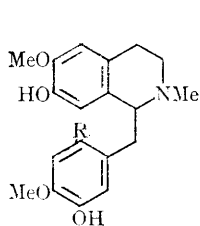
⁴ R. H. F. Manske, "The Alkaloids", Vol. 4, Academic Press, New York, p. 119.

⁵ H. Chikamatsu and M. Tomita, *J. Chem. Soc. Japan*, 1961, 82, 1708, *Chem. Abs.*, 1963, 59, 7571.

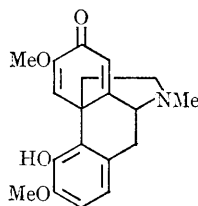
⁶ *cf.* M. Shamma, *Experientia*, 1962, 18, 64, and references cited therein.

to note that the dienone (V) gave isocorytuberine⁷ (IVb), hydrochloride m.p. 221° (67%), on treatment with glacial acetic acid containing concentrated hydrochloric acid, and corydine⁷ (IVc), m.p.

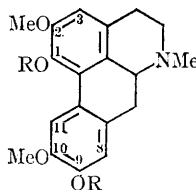
suggestion that aporphine alkaloids with the 1,2,10,11-oxygenation pattern may be derived in nature by dienone-phenol type rearrangements,⁹ rather than by direct coupling of the type observed



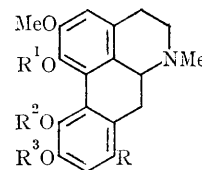
(I)a, R=H
b, Metho-salt of (Ia)
c, R=Br



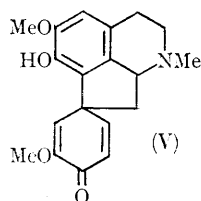
(II)



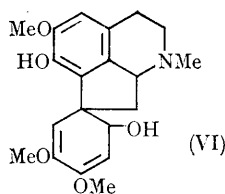
(III)a, R=H
b, Metho-salt of (IIIa)
c, R=Me



(IV)a, R=Br, R¹=R²=H, R³=Me
b, R=R¹=R³=H, R²=Me
c, R=R¹=H, R²=R³=Me



(V)



(VI)

148° (84%), on treatment with dry methanolic hydrogen chloride. The dienone (V), "orientalinone",⁸ was prepared by rearrangement of the dienol⁷ (VI) by treatment with dilute aqueous methanolic hydrochloric acid, and was presumably an intermediate in our previously reported syntheses of isocorytuberine and corydine.⁷

These experiments thus lend support to the

in the isoboldine and laurifoline syntheses. Indeed there seems to be a distinct possibility that the majority of aporphine alkaloids arise in this way,⁹ e.g. alternative rearrangements of orientalinone (V) could give alkaloids of the glaucine type.¹⁰

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⁷ A. H. Jackson and J. A. Martin, *Chem. Comm.*, 1965, 142.

⁸ The orientalinone was identical (m.p., mixed m.p., and spectra) with a sample prepared by the method of A. R. Battersby and T. H. Brown, *Proc. Chem. Soc.*, 1964, 85.

⁹ Professor A. R. Battersby (private communication) has also independently considered these possibilities, and appropriate tracer experiments are already in progress.

¹⁰ H.-G. Boit ("Ergebnisse der Alkaloid Chemie bis 1960", Akademie Verlag, Berlin, 1961, p. 263) has briefly discussed the possibility that all aporphines arise *via* dienones.