

Phenol-coupling Reactions: The Synthesis of Corydine and Isocorytuberine

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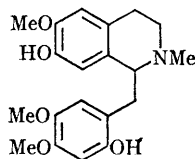
(The Robert Robinson Laboratories, University of Liverpool)

THE importance of phenol-oxidation reactions in the biosynthesis of many benzyloquinoline alkaloids is now well recognised,^{1,2} and has been adequately demonstrated by tracer experiments, particularly in the morphine field.^{3,4} It has been suggested that the dienones formed in some of these reactions are reduced to dienols, further transformations of which can lead to morphine, or aporphine, type alkaloids.³

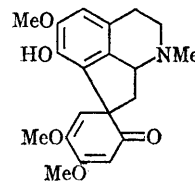
We are currently investigating the potentiality of such phenol-coupling reactions (whether biogenetically likely or not) in the synthesis of benzyloquinoline alkaloids, and we now report new syntheses of (\pm)-corydine (IIIa) and (\pm)-"isocorytuberine" [an isomer of the naturally occurring (+)-corytuberine (IIIc)].

The novel benzyloquinoline (I) [picrate,⁵ m.p. 189° (prepared by application of standard methods)] was oxidised by aqueous potassium ferricyanide in a two-phase system (8% ammonium acetate-chloroform) to a mixture of two isomeric 2,4-dienones (II) (*ca.* 30% yield). On chromatographic separation one dienone was obtained

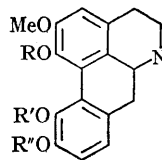
crystalline (10% yield), m.p. 213°, (picrolonate, m.p. 193°). It showed ν_{\max} . 1573, 1626, and 3511



(I)



(II)



(III)

(a); R=H, R'=R''=Me

(b); R=R'=H, R''=Me

(c); R=R''=H, R'=Me

(d); R=R'=R''=Me

¹ R. Robinson, "Structural Relations of Natural Products," Oxford, 1954.

² D. H. R. Barton and T. Cohen in "Festschrift A. Stoll," Birkhauser, Basle, 1957, p. 117.

³ A. R. Battersby, Tilden Lecture, *Proc. Chem. Soc.*, 1963, 189.

⁴ D. H. R. Barton, Hugo Müller Lecture, *Proc. Chem. Soc.*, 1963, 293.

⁵ All crystalline products have been characterised by elemental analysis, and by i.r., u.v., n.m.r. and mass spectra.

cm.⁻¹ (in chloroform); λ_{max} . 288, and 312 m μ (in ethanol); its n.m.r. spectrum (in CDCl₃) showed the expected methyl resonances at τ 7.62 (NCH₃), 6.30, 6.18, and 6.10 (OCH₃) singlets at 4.55 and 4.26 for the olefinic protons, and a singlet at 3.42 for the aromatic proton. The other dienone could also be separated chromatographically but it has not so far been obtained crystalline; however, it formed a picrolonate, m.p. 230°, and was spectroscopically very similar to the other product.

On reduction with sodium borohydride the crystalline dienone afforded a non-crystalline dienol (characterised by i.r. and mass spectra) which underwent dienol-benzene rearrangement in anhydrous methanolic hydrogen chloride to give (\pm)-corydine (IIIa) (80% from the dienone), m.p. 148° [hydrochloride, m.p. 218° (lit.⁶ gives m.p. 228°)]. The identity of the product was confirmed by spectroscopic (i.r., u.v., n.m.r., and mass)

and thin-layer-chromatographic comparison with natural corydine.⁷ Rearrangement of the dienols in aqueous methanolic hydrogen chloride yielded (\pm)-isocorytuberine (IIIb), (65% yield from the dienone) (hydrochloride, m.p. 223°), which was identified by comparison with natural (+)-corytuberine⁷ (particularly by n.m.r.⁸). In addition, methylation of isocorytuberine with diazomethane gave the same product (thin-layer chromatography) as methylation of either corydine or corytuberine, *i.e.* (+)-*O*-methylcorydine (IIIId).

These alkaloid syntheses *via* dienones differ from those previously reported (morphine⁹ and isothebaine¹⁰) in that 2,4-dienones are involved rather than 2,5-dienones. Also, the total yield of dienones (*ca.* 25–30%) in our coupling reaction was much higher than either of the earlier syntheses.

(Received, March 22nd, 1965.)

⁶ D. H. Hey and A. L. Palluel, *J. Chem. Soc.*, 1957, 2926.

⁷ Samples of natural corydine and corytuberine were kindly supplied by Dr. R. H. F. Manske. *Cf.* "The Alkaloids," Ed. R. H. F. Manske and H. L. Holmes, Vol. IV, p. 129–130.

⁸ *Cf.* S. Goodwin, J. N. Shoolery, and L. F. Johnson, *Proc. Chem. Soc.*, 1958, 306; R. C. Bick, J. Harley-Mason, M. Sheppard, and M. J. Vernengo, *J. Chem. Soc.*, 1961, 1896; and W. H. Baarschers, R. R. Arndt, K. Pachler, J. A. Weisback, and B. Douglas, *J. Chem. Soc.*, 1964, 4778.

⁹ D. H. R. Barton, G. W. Kirby, W. Steglich, and G. M. Thomas, *Proc. Chem. Soc.*, 1963, 203.

¹⁰ A. R. Battersby and T. H. Brown, *Proc. Chem. Soc.*, 1964, 85.