Homoaporphine Systems and Related Dienones: Isolation, Structure, and Synthesis

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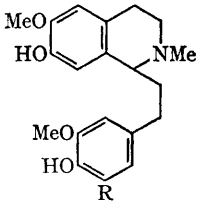
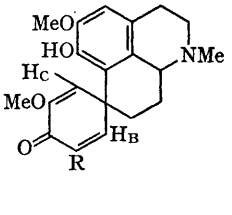
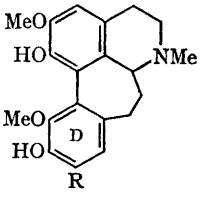
HOMOAPORPHINE alkaloids were recently discovered[1] in *Kreysigia multiflora*, two examples being floramultine (VIII) and multifloramine (V). Synthesis of the latter was achieved[1] from (I) by oxidation to the dienone (III) followed by dienone–phenol rearrangement. The biosynthesis of multifloramine (V) may involve these same steps, and floramultine (VIII) could be generated by a subsequent change of methylation pattern. However, there are other possibilities; among them the sequence (II) → (IV) → (VI) or (VII) and the third oxygen in ring D of the natural alkaloids could be introduced at a later stage, *cf.*, narcotine biosynthesis.[2] Accordingly, the diphenol (II) was synthesised and oxidised with ferricyanide to yield a mixture of two dienones that differ in configuration



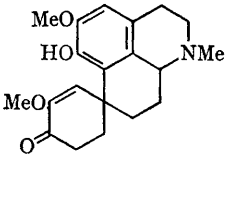
(I) R=OMe
(II) R=H



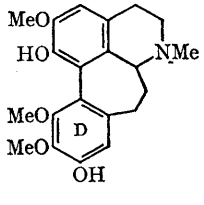
(III) R=OMe
(IV) R=H_A



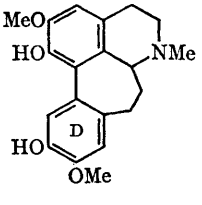
(V) R=OMe
(VI) R=H



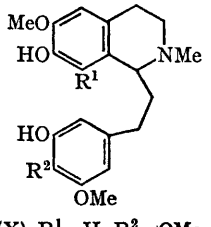
(IX)



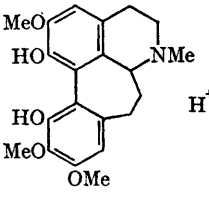
(VIII)



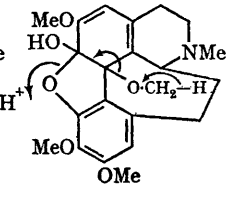
(VII)



(X) R^1=H, R^2=OMe
(XII) R^1=R^2=OMe
(XIV) R^1=H, R^2=OH



(XI)



(XIII)

at the spiro-centre, and they were separated by fractional crystallisation; combined yield 31%. Dienone-I (IV), $C_{20}H_{23}NO_4$, (M^+, 341), m.p. 155° then 194° decomp. showed the following important n.m.r. signals (τ values): 4·05 (d, H_C; J 3 c./sec.) olefinic; 3·72 (d, H_A; J 10 c./sec.) olefinic; 3·17 (d.d, H_B; J 3 and 10 c./sec.) olefinic; 3·48 (s, 1H) aromatic; 6·24, 6·46 (s, 3H each) *O*-methyls; 7·55 (s, 3H) *N*-methyl; also ν_{max} 3550, 1614, 1633, 1659 cm.$^{-1}$ ($CHCl_3$); λ_{max} (EtOH) 214, 243, 287 mμ (log ϵ 4·54, 4·15, 3·78). Similarly, dienone-II (IV), had m.p. 202° decomp. and showed M^+ 341 and the following n.m.r. signals: 4·23 (d, H_A; J 3 c./sec.) olefinic; 3·80 (d, H_A; J 10 c./sec.) olefinic; 3·04 (d.d, H_B; J 3 c./sec.) olefinic; 3·49 (s, 1H) aromatic 6·26, 6·41 (s, 3H each) *O*-methyls; 7·59 (s, 3H) *N*-methyl; also ν_{max} 3500, 1661, 1635, 1609 cm.$^{-1}$ ($CHCl_3$).

The foregoing dienones were then used as standards for a chromatographic examination of the minor alkaloids from *K. multiflora* which led to the isolation of dienone-I (IV) as a natural product, named kreysiginone. The synthetic and natural materials were proved identical, apart from optical activity, by full spectroscopic and chromatographic comparison. In addition, the dihydro-derivative (IX) $C_{20}H_{25}NO_4$, (M^+, 343), m.p. 217—222° decomp., was isolated and showed the following n.m.r. signals: 4·26 (s, 1H) olefinic; 3·46 (s, 1H) aromatic; 6·16, 6·46 (s, 3H each) *O*-methyls; 7·43 (s, 3H) *N*-methyl; also ν_{max} 3500, 1678, 1635, 1610 cm.$^{-1}$ ($CHCl_3$); λ_{max} (EtOH) 220, 269 mμ.

It is probable that the dihydro-material corresponds in configuration at the spiro-centre to kreysiginone (IV), but there is as yet no direct evidence. This co-occurrence of a dienone with the dihydro-derivative has precedent, *e.g.*, orientalinone and dihydro-orientalinone[3] in *Papaver orientale*.

Rearrangement of (±)-kreysiginone (IV) and dienone-II, under a variety of conditions gave diphenols of the homoaporphine type. The structures of these rearrangement products are being investigated and will be used to screen the minor alkaloids of *K. multiflora*. Whether or not one of these diphenols and the dienone (IV) are intermediates in the pathway to the natural alkaloids (V) or (VIII) is being tested by tracer experiments.

Ferricyanide oxidation of (X), which is the biological precursor of colchicine,[4] gave a homoaporphine system (XI) directly by *ortho–ortho*-coupling (25%), $C_{21}H_{25}NO_5$ (M^+, 371). The n.m.r. spectrum showed no high-field methoxy-signal and eliminates the alternative *ortho–para*-coupling which would be floramultine (VIII).

Even with the systems (XII), the same direction of coupling was favoured over *ortho–para*-coupling to give a product, $C_{22}H_{27}NO_6$ (M^+, 401), no carbonyl absorption in the infrared spectrum, and showed n.m.r. signals at 3·81 (s, 1H) aromatic; 5·25 (s, 1H) olefinic; 6·13, 6·21, 6·35, 6·87 (s, 3H each) *O*-methyls; 7·53 (s, 3H) *N*-methyl. This substance, obtained in 50% yield, is assigned the structure (XIII) on the foregoing spectroscopic evidence and because it is rearranged by isopropenyl acetate–toluene-*p*-sulphonic acid to yield the diacetate of (XI). The illustrated fragmentation may rationalise this change.

Very ready oxidation of the catechol (XIV) occurred with ferricyanide to give a coupled product, $C_{20}H_{23}NO_5$ (M^+, 357), m.p. 230°, which is being further examined since it corresponds to none of the products expected by straightforward coupling.

Further studies on phenol coupling of 1-phenethylisoquinolines are in progress, particularly aimed at the androcymbine skeleton.[5]

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[1] A. R. Battersby, R. B. Bradbury, R. B. Herbert, M. H. G. Munro, and R. Ramage, *Chem. Comm.*, **1967**, 450.
[2] A. R. Battersby, and M. Hirst, *Tetrahedron Letters*, **1965**, 669.
[3] A. R. Battersby and T. H. Brown, *Chem. Comm.*, **1966**, 170.
[4] A. R. Battersby, R. B. Herbert, E. MacDonald, R. Ramage, and J. H. Clements, *Chem. Comm.*, **1966**, 603.
[5] A. R. Battersby, R. B. Herbert, L. Pijewska, and F. Šantavý, *Chem. Comm.*, **1965**, 228.