A Total Synthesis of (±)-Glaziovine by Phenolic Oxidative Coupling

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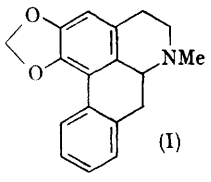
IT has been appreciated for many years that aporphine alkaloids would occur in Nature by phenolic oxidative coupling. Considering the biogenesis of roemerine (I) as an apparently abnormal alkaloid, Barton and Cohen[1] suggested that the precursor (II) was initially oxidized to dienone (III) and reduction of this dienone to the corresponding dienol (IV), followed by catalytic rearrangment with acid, would then furnish the above roemerine (I).

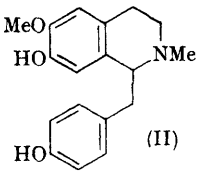
In fact, the best evidence for the general scheme has been given by Barton and his co-workers[2] with the biosyntheses of crotonosine (V) and roemerine (I) from radioactive coclaurine, norcoclaurine, and *N*-methylcoclaurine.

We are currently investigating the possibility of such phenolic oxidative coupling reactions in the syntheses of several isoquinoline alkaloids, and we report a novel total synthesis of (±)-glaziovine (III),[3] the major alkaloid of *Ocotea glaziovii*.

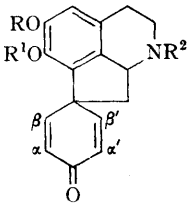
(±)-*N*-Methylcoclaurine (II) hydrochloride (prepared according to the usual methods)[4] was oxidized by potassium ferricyanide in a two-phase system (8% ammonium acetate–chloroform) to give, after purification by column chromatography on alumina, (±)-glaziovine (III), $C_{18}H_{19}NO_3$, m.p. 227 ~ 228° (decomp.) in about 1% yield. Our synthetic sample (III) showed ν_{max} 1657 and 1619 cm.$^{-1}$ (in chloroform); λ_{max} 235 and 288 mμ (in ethanol) (ε 23,870 and 3907, respectively), and λ_{max} 308 mμ (in ethanol–KOH) (ε 5584). The n.m.r. spectrum* of (III) showed the signal of the protons of the *N*-methyl group at 2·40 p.p.m. (3H), those of the methoxyl group at 3·85 p.p.m. (3H), the vinyl protons at 6·26 ~ 6·60 p.p.m. (αα′-position) and 6·70 ~ 7·30 p.p.m. (ββ′-position) as two AB-type quartets with fine structure and one aromatic proton at 6·65 p.p.m. as a singlet.

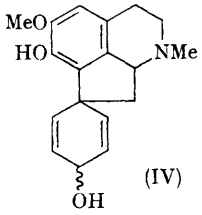


(I)



(II)





(IV)

(III) R=R²=Me, R¹=H
(V) R=R²=H, R¹=Me
(VI) R=R¹=R²=Me

The mass spectrum of (III) showed a molecular ion at *m/e* 297. Furthermore, *M*−1, *M*−17, *M*−29, *M*−43, *M*−58, *M*−71, *M*−86, and *m/e* 165 were shown, and all the peaks could be interpreted quite reasonably.

These spectral data were completely identical with those of the literature.[3] Furthermore, analytical values confirmed the oxidized product to be (±)-glaziovine (III).

Further methylation of the above (±)-glaziovine (III) with diazomethane gave (±)-pronuciferine, m.p. 147 ~ 150° (lit.,[5] m.p. 148 ~ 151°) which was identified by comparison with natural (+)-pronuciferine† (VI) on a thin-layer chromatogram.

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* N.m.r. spectrum was run at 60 Mc./sec. in $CDCl_3$ solution, with Me_4Si as an internal standard.

† Sample of natural (+)-pronuciferine was kindly supplied by Dr. K. Bernauer, Hoffmann-La Roche & Co. AG., Basel.

[1] D. H. R. Barton and T. Cohen, "Festschrift Arthur Stoll", Birkhauser, Basel, 1957, p. 117.
[2] L. J. Haynes, K. L. Stuart, D. H. R. Barton, D. S. Bhakuni, and G. W. Kirby, *Chem. Comm.*, 1965, 141; D. H. R. Barton, D. S. Bhakuni, G. M. Chapman and G. W. Kirby, *ibid.*, 1966, 259.
[3] B. Gilbert, M. E. A. Gilbert, M. M. De Oliveira, O. Ribeiro, E. Wenkert, B. Wickberg, U. Hollstein, and H. Rapoport, *J. Amer. Chem. Soc.*, 1964, **86**, 694.
[4] J. Finkelstein, *J. Amer. Chem. Soc.*, 1951, **73**, 550; T. Kametani, H. Yagi, and S. Kaneda, *Chem. and Pharm. Bull. (Japan)*, 1966, **14**, 974.
[5] K. Bernauer, *Experientia*, 1964, **20**, 380.