

The Synthesis of Glaucine, *O*-Methylcorydine, and Pseudocorydine via Phenolic Oxidative Coupling

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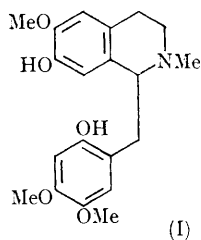
JACKSON and MARTIN have very recently reported that phenolic oxidative coupling of the benzylisoquinoline (I) leads to two isomeric 2,4-dienones (IIa), one crystalline and one oily. Sodium borohydride reduction of the crystalline isomer followed by treatment with aqueous methanolic HCl gave isocorytuberine (IIIa); alternatively, reaction under anhydrous conditions (HCl-MeOH) gave corydine (IIIb), the product of a dienol-benzene rearrangement.¹

We now report our independent investigations with the same benzylisoquinoline (I) which have resulted in:

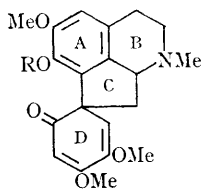
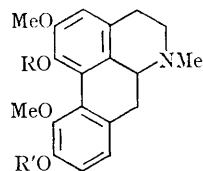
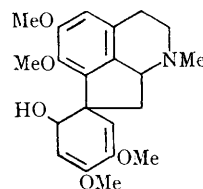
- The isolation of a proaporphine 2,5-dienone intermediate in the conversion sequence: benzylisoquinoline \rightarrow 2,4-dienone \rightarrow 2,4-dienol \rightarrow 2,5-dienone \rightarrow aporphine, and
- The demonstration that both 1,2,9,10- and 1,2,10,11-tetrasubstituted aporphines can arise from the same 2,4-dienone proaporphine precursor through reduction followed by acid-catalysed rearrangements.

The oily benzyltetrahydroisoquinoline (I), picrate m.p. 187–189° (decomp.), obtained in 28% yield, along with \pm -1-hydroxy-2,9,10-trimethoxyaporphine in 22% yield, by diazotisation of the appropriate amine precursor² was oxidized with aqueous potassium ferricyanide and ammonium acetate to give, after purification of the product by column chromatography over Woelm basic alumina, the oily 2,4-dienone (IIa), C₂₀H₂₃NO₅, molecular ion at *m/e* 357, in 52% yield. Treatment of (IIa) with diazomethane afforded the amorphous tetramethoxy-base (IIb), C₂₁H₂₅NO₅, molecular ion at *m/e* 371, with singlets in the n.m.r. spectrum at τ 7.65 (1 *N*-methyl), τ 6.12, 6.21, 6.33, and 6.37 (4 methoxyls), τ 4.29 and 4.59 (2 vinylic protons), and τ 3.39 (1 aromatic proton). Sodium borohydride reduction of (IIb) yielded a mixture of diastereoisomeric 2,4-dienols (IV), C₂₁H₂₇NO₅, which were not separated.

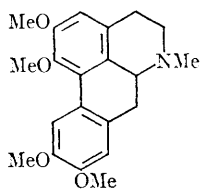
Rearrangement of the dienols (IV) using anhydrous methanolic HCl gave (\pm)-glaucine (V) in 26% yield, and (\pm)-*O*-methylcorydine (IIIc) in 5% yield. On the other hand, rearrangement



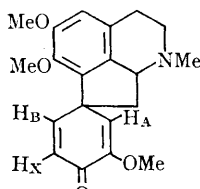
(I)

(II) a; R=H
b; R=Me(III) a; R=R'=H
b; R=H, R'=Me
c; R=R'=Me
d; R=Me, R'=H

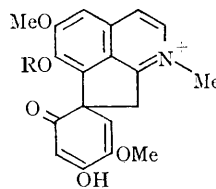
(IV)



(V)



(VI)

(VII) a; R=H
b; R=Me

¹ A. H. Jackson and J. A. Martin, *Chem. Comm.*, 1965, 142.

² M. Shamma and W. A. Slusarchyk, *Tetrahedron Letters*, 1965, 1509.

(MeOH-10% aq. HCl, 1:1) of the 2,4-dienols (IV) over a period of one hour resulted in formation of (\pm)-pseudocorydine (IIId) in 29% yield, and the 2,5-dienone (VI), $C_{20}H_{23}NO_4$, in 10% yield. Base (VI) was obtained as an oil which exhibited $\lambda_{\max}(\text{EtOH})$ 287 $m\mu$, $\log \epsilon$ 3.74, and showed i.r. bands (CHCl_3) at 6.04, 6.14, and 6.23 μ . As expected for a 2,5-dienone of that type, the n.m.r. spectrum of (VI) had a doublet at τ 3.98 (1 proton, H_A , $J_{AB} = 2$ c./sec.), a doublet at τ 3.05 (1 proton, H_X , $J_{BX} = 10$ c./sec.), and a quartet at τ 3.40 (1 proton, H_B , coupled to H_A and H_X).³

The aporphines (IIIc), (IIId), and (V), produced above were in each case identified by means of i.r., u.v., and t.l.c. R_f -comparisons with authentic specimens. Additionally, rearrangement of the dienone (VI) with methanolic hydrochloric acid yielded (\pm)-pseudocorydine (IIId).

The above series of transformations shows that both 1,2,9,10- and 1,2,10,11-tetrasubstituted aporphines can be obtained from 2,4-dienones of type

(IIb). The total yield of dienone (IIb) (52%) after purification of the product of oxidative coupling is also exceptionally high.⁴

In a recent communication,⁵ Tomita and co-workers have found that the base peaks in the mass spectra of the 2,5-dienone proaporphines pronuciferine and stepharine also corresponded to the molecular-ion peaks. Such is not the case with the 2,4-dienones (IIa) and (IIb). In both of these cases the base peaks came at m/e ($M - 17$) indicating the favoured formation of what are most probably ions (VIIa) and (VIIb), formed by the overall loss of a methyl group and two hydrogens from each of the molecular ions. In the 2,5-dienone series⁵ two favourite modes of cleavage were the retro-Diels-Alder reaction involving ring-B, and the loss of CO from ring-D. We have noticed similar cleavages with the dienones (IIa), (IIb), and (VI).

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³ A. R. Battersby and T. H. Brown, *Proc. Chem. Soc.*, 1964, 85.

⁴ All amorphous intermediates were found to be in agreement with their expected i.r., u.v., n.m.r., and mass spectra. All n.m.r. spectra were run at 60 Mc./sec., in CDCl_3 solution, with Me_4Si as an internal standard.

⁵ M. Tomita, A. Kato, T. Ibuka, H. Furukawa, and M. Kozuka, *Tetrahedron Letters*, 1965, 2825.