

THE TOTAL SYNTHESIS OF (±)-DECININE

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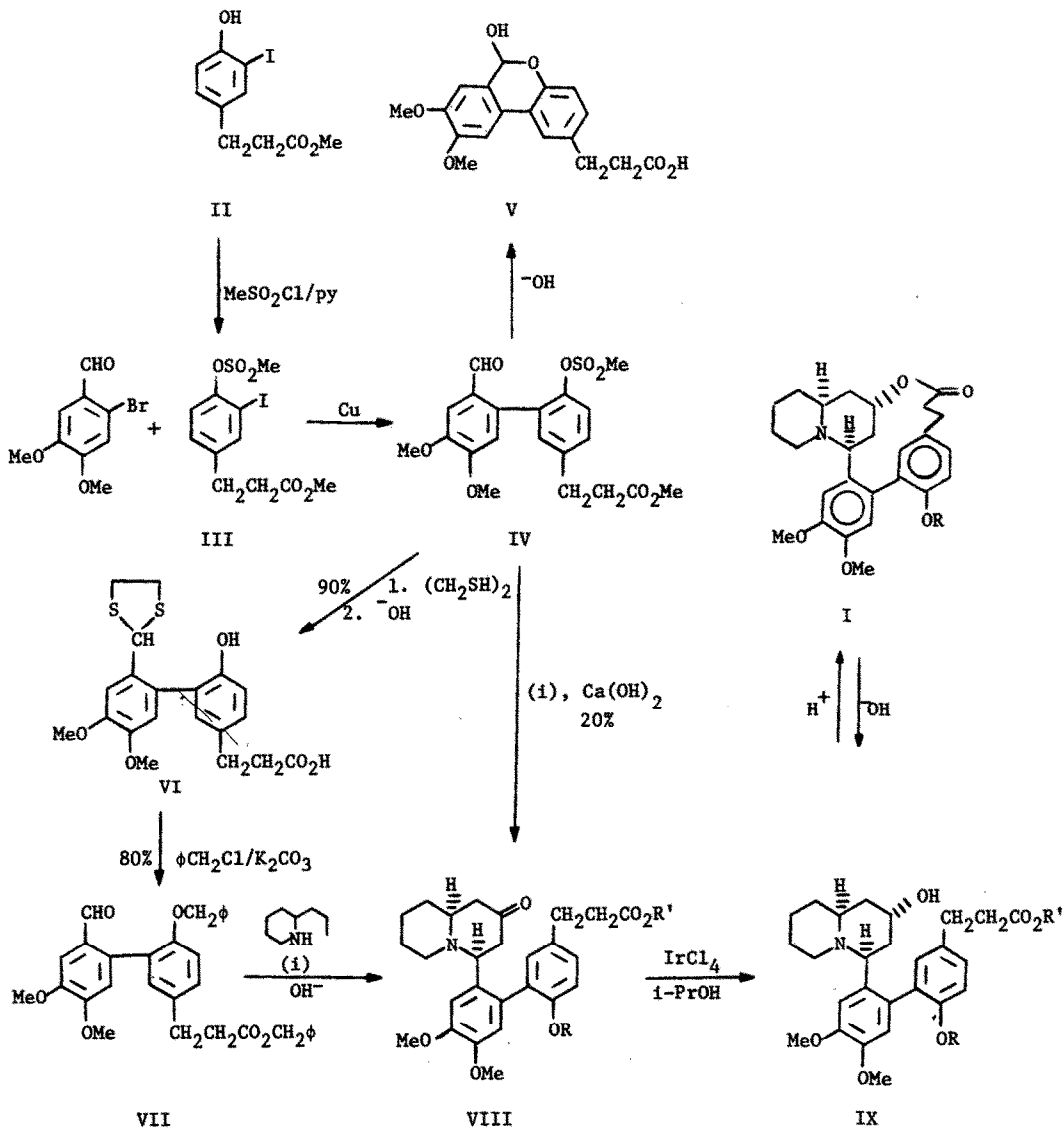
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Recent papers on the Lythracea alkaloids have described the synthesis of methyl ether of (±)-decinine^{1,2} (I, R=Me-) and of the related diphenyl ether containing alkaloids (±)-decaline³ and (±)-vertaline⁴. Thus far none of the methods of synthesis has been applicable to the synthesis of a Lythracea alkaloid containing a free phenolic hydroxyl group. We now wish to report such a method and the first synthesis of such a free phenolic compound, (±)-decinine (I, R=H).

The synthesis, based in part on our previous scheme¹, required finding a group to block the hydroxyl group in methyl 2-(4'-hydroxy-3'-iodophenyl) propionate (II) which, at the same time would allow the coupling reaction to proceed and would also be stable to the subsequent alkaline conditions of condensation, and yet which could be removed at the end of the reaction. These conditions were difficult to fulfill as most alkaline stable protecting groups prevented the Ullmann coupling⁵ (ϕSO_2^- , allyl, benzyl), while groups that permitted the reaction were alkaline labile.

The methane sulfonate group was especially advantageous for our sequence. Not only did its stability permit the Ullmann coupling reaction to take place, it yielded a highly crystalline product, it had sufficient alkaline stability to permit another sequence to occur and sufficient alkaline lability to assure efficient removal.

Iodoester III smoothly yielded biphenyl carboxaldehyde IV (40%, mp. 114-4½°) when coupled with bromoveratraldehyde under previously¹ described conditions (neat, 200°). However, all attempts to prepare keto acid VIII (R'=H, R=MeSO₂- or H) by condensation of IV with isopelletierine (i) by warming in aqueous sodium hydroxide were unsuccessful due to the hydrolytic



- a) $\text{R}=\text{MeSO}_2^-$, $\text{R}'=\text{H}$
 b) $\text{R}=\text{MeSO}_2^-$, $\text{R}'=\text{Me}$
 c) $\text{R}=\phi\text{CH}_2^-$, $\text{R}'=\text{H}$

- a) $\text{R}=\text{MeSO}_2^-$, $\text{R}'=i\text{-Pr}$
 b) $\text{R}=\text{H}$, $\text{R}'=\text{Me}$
 c) $\text{R}=\text{H}$, $\text{R}'=\text{H}$

lability of the methanesulfonyl group under these conditions, yielding solely the very stable hemiacetal V.

In order to introduce a base stable group in place of the methanesulfonate, the aldehyde was transformed into a dithiolane ($\text{BF}_3 \cdot \text{Et}_2\text{O}$), and the phenolic group was benzylated ($\phi\text{CH}_2\text{Cl}$, $\text{DMF}/\text{K}_2\text{CO}_3$). Subsequent unmasking of the carboxaldehyde (HgO , $\text{BF}_3 \cdot \text{Et}_2\text{O}$) resulted in the newly protected biphenyl compound VII. After an extensive study of the condensation of this carboxaldehyde VII with isopelletierine it was found that $\text{Ca}(\text{OH})_2$ successfully catalyzes the reaction giving keto acid VIIIc (albeit in low yield, 5%). It was also subsequently found that this particular base permitted the condensation of IV and isopelletierine to VIIIa (20% yield) without the hydrolytic removal of the methanesulfonate group. Compound VIIIa was thoroughly characterized as its methyl ester VIIIb (mp. $175-6^\circ$) obtained by treatment with diazomethane. The trans stereochemistry of the quinolizidine ring junction was indicated by Bohlmann bands⁷ at 2800 and 2760 cm^{-1} (CHCl_3) and the keto and ester functions show separate bands at 1740 and 1725 cm^{-1} respectively. The nmr spectrum of VIIIb features three $\text{CH}_3\text{O}-$ groups at 3.95, 3.85, and 3.68 p.p.m. and the CH_3SO_2- group at 2.75 p.p.m. downfield from TMS.

Catalytic reduction of VIIIa with iridium tetrachloride⁸ resulted in the axial alcohol IXa⁹ (80% yield, as the isopropyl ester) as the major product. Alkaline hydrolysis followed by diazomethane gave IXb identical spectroscopically to authentic compound derived from natural decinine by hydrolysis and esterification. The total synthesis of (\pm)-decinine (I, R=H, mp. $194-5^\circ$) was completed by acid catalyzed cyclization of IXc (40% yield). The synthetic compound thus obtained was identical [ir (CHCl_3), nmr, ms, vpc] with the natural product.

By an analogous sequence of reactions (reduction, hydrolysis, cyclization), without isolation of the intermediates the benzyl protected keto acid VIIIc yielded I (R= ϕCH_2 , 35%) spectroscopically identical to the compound obtained from natural decinine by benzylation, and yielding (\pm)-decinine upon Pd/C catalyzed hydrogenolysis.

References

- All compounds have been characterized by combustion and spectral analyses except in the case of the benzyl protected compounds (VIIIc; I; R= ϕ CH₂-) whose structures were confirmed by conversion to the known compound decinine.
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 - (3) M. Hanaoka, N. Ogawa, and Y. Arata, Tetrahedron Letters, 2355 (1973) J. T. Wrobel and W. M. Golebiewski, Tetrahedron Letters, 4293 (1973).
 - (4) M. Hanaoka, N. Agawa, and Y. Arata, Chem. Pharm. Bull., 22, 973 (1974).
 - (5) Although the Ullmann reaction has been extensively studied [P. E. Fanta, Chem. Rev. 38, 139 (1946); 64, 613 (1964)], there is remarkable little in the nature of the groups (protective or otherwise) which may be present when carrying out an Ullmann type of coupling, Our studies regarding these will be presented elsewhere.
 - (6) NaOH catalysis leads to an entirely different product; this work will be described elsewhere. We are especially thankful to Dr. Liu of SK&F Labs. for bringing this catalyst to our attention.
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 - (9) The mixture of isomeric alcohols was acetylated (Ac₂O, py) and the esters were assayed by vpc. The product ratio (α : β) was found 8:1, and the nmr signal for the carbinol methine proton at 5.10 p.p.m. with a half-height width of 9.0 cps in the spectrum of acetyl-IXa clearly indicated the axial configuration.