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SYNTHESIS OF APORPHINES

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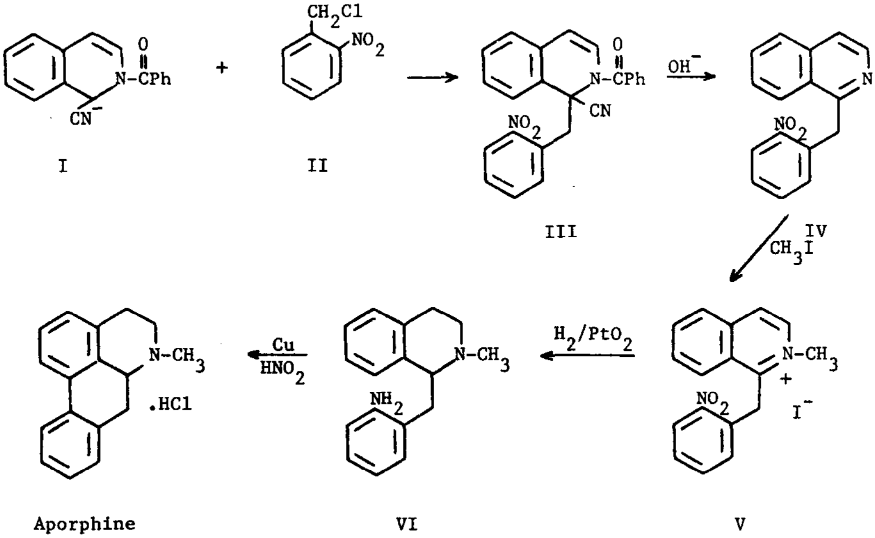
Several recent reports have described novel synthetic approaches to aporphines which are based either on a photocyclization of an aporphine precursor (1, 2, 3) or by a biogenetic type oxidative condensation of a quaternary benzyltetrahydroisoquinoline (4). Previous methods used successfully for preparing aporphine molecules have involved a Bischler-Napieralski cyclization sequence (5) or the Gadamer procedure (6,7) followed by a Pschorr cyclization. We wish to report our findings for a new aporphine synthesis which can be applied also to the synthesis of a number of naturally occurring aporphine alkaloids. The key step in our method involves the generation of 1-(o-nitrobenzyl)isoquinoline (IV) by the reaction of a Reissert compound with o-nitrobenzyl chloride (II), with subsequent reduction and the usual Pschorr cyclization (Scheme 1).

The reaction of Reissert compounds with aldehydes or alkyl halides has proved valuable in the synthesis of a number of benzylisoquinoline alkaloids (8). Alkylation of a Reissert compound with o-nitrobenzaldehyde has yielded o-nitrophenyl-1-isoquinolylmethyl benzoate, but the attempted base hydrolysis to o-nitrophenyl-1-isoquinolylmethanol failed to yield the desired product (9). We attribute this failure to the vigorous basic hydrolysis conditions used in these reactions which, by a mechanism recently proposed (10), can similarly cause a carbon-carbon cleavage in such a system (11).

Our initial attempts at the synthesis of III utilizing ethereal phenyllithium (8) for the generation of the Reissert anion (I) (12) failed to yield any of the desired products. The condensation was successful when sodium hydride in DMF (13) was used to generate the anion I. The reaction was monitored on thin-layer chromatography and the product, 1-cyano-1-(2-nitrobenzyl)-2-benzoyl-1,2-dihydroisoquinoline [III, mp 143-144° (14), λ_{max}^{EtOH} 228 mμ (ε 26,000), 281 (ε 10,000), 294 (ε 9900), 312 (ε 9300)], was isolated in 80% yield after column chromatography on silicic acid and elution with benzene. Careful hydrolysis of III with potassium hydroxide in ethanol yielded 1-(2-nitrobenzyl)isoquinoline [IV, mp 110-111°, λ_{max}^{EtOH} 261 mμ (ε 9200), 268 (ε 8900), 278s (ε 6900), 307 (ε 4300), 321 (ε 4200); picrate mp 182°] in 73% yield. The isoquinoline IV was converted to the methiodide (V, mp 223° dec) in 87% yield. Conversion of V to 1-(2-aminobenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (VI) [isolated as the dihydrochloride, mp 257-258°, λ_{max}^{EtOH} 233 mμ (ε 6300), 287 (ε 1900)] with platinium oxide and hydrogen in ethanol proceeded without difficulty. Compound VI had the same properties as a material obtained by Gadamer, et al. (6) and Govindachari (15). The borohydride reduction of V yielded only cleavage products (10). Pschorr ring closure by standard procedures (7, 16) afforded aporphine hydrochloride in 50% yield.

Scheme 1



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