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A NOVEL FORMATION OF (±)-GLAZIOVINE THROUGH NITRENIUM INTERMEDIATE

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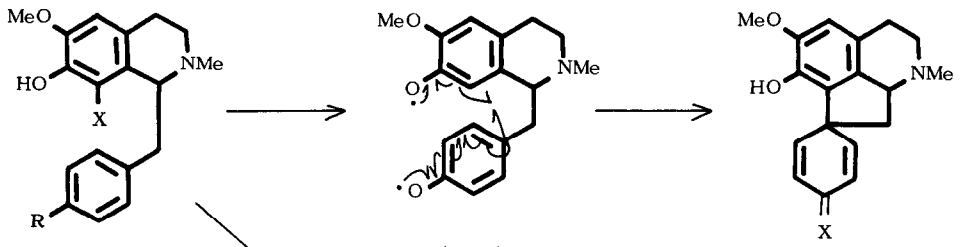
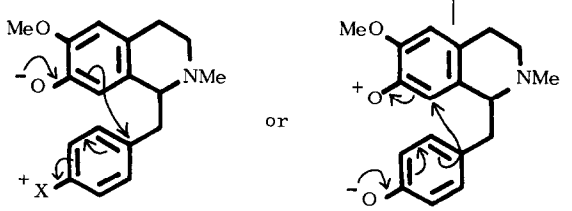
In the course of the proaporphine synthesis, the intervention of a too reactive radical intermediate (VII) in the conventional method (e.g., the phenolic oxidation[1] and the photolytic reaction[2]) made the reaction very complex and the formation of the desired dienone very poor. An improvement of the yield could be expected when the radical intermediate (VII) would be substituted with as ionic intermediate (VIII) or (X).



(I) R=OH, X=H
(II) R=NH_2, X=H
(III) R=NHCl, X=H
(IV) R=$NHCH_2C_6H_5$, X=H
(V) R=NH_2, X=Cl
(VI) R=$NHCH_2C_6H_5$, X=Cl



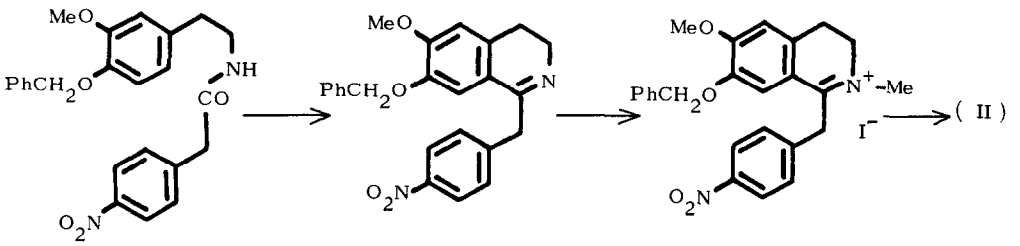
(VIII) X=O
(IX) X=NH

(X)

On this premise, we chose a phenolic 1-(4-chloroaminobenzyl)isoquinoline (III) as a key intermediate, which could generate a phenoxy-nitrenium intermediate (IX) electronically equivalent to VIII on treating with a strong base, since the generation of a phenoxy-phenoxonium intermediate (VIII) could be practically impossible.

The key intermediate (III) was synthesized by a standard method; the amide (XIII), obtained

from 4-benzyloxy-3-methoxyphenethylamine and 4-nitrophenylacetic acid, was cyclized with phosphoryl chloride to give the 3,4-dihydroisoquinoline (XIV), whose methiodide (XV) was converted into II by the reduction with zinc and hot hydrochloric acid.



(XIII) (XIV) (XV)

A phenolic aminoisoquinoline (II) was treated with 1 % sodium hypochlorite in dichloromethane, and then the resulting crude N-chloro base (III) was treated with two molar equivalents of potassium tert-butoxide in tetrahydrofuran. The desired imino compound (XI) was not obtained, but a hydrolysed compound, (±)-glaziovine (XII),[3,4] formed as a minor product in addition to the 1-(4-aminobenzyl)-8-chloro-1,2,3,4-tetrahydro-7-hydroxy-6-methoxyisoquinoline (V) [δ ($CDCl_3$) 6.45 (1H, s, 5 - H), 6.5 (2H, d, J = 8 Hz, 3' - and 5' - H) and 7.02 (2H, d, 2' - and 6' - H)] as a main product. The low yield of XII might be explained from the formation of an azo compound, the structure of which is under examination, since the condition of the synthetic method employed is quite the same as that of azo compounds.[5] Moreover, the N-benzylamino derivative (IV), prepared by a condensation of II with benzaldehyde, followed by reduction, was treated as above, but gave only the corresponding 8-chloro compound (VI) [m/e 226 and 196, δ ($CDCl_3$) 6.5 (1H, s, 5 - H), 6.55 (2H, d, J = 8 Hz, 3' - and 5' - H) and 7.08 (2H, d, 2'- and 6' - H)] . Investigation of its application and modification of this method is in progress.

References

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