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SYNTHETIC APPROACH TO PAKISTANAMINE BY PHENOLIC OXIDATIVE COUPLING

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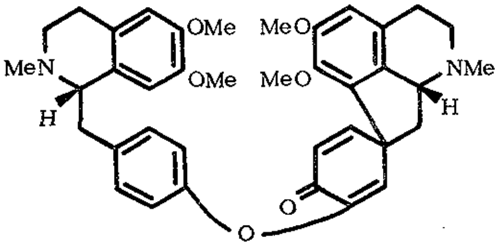
The synthesis of a racemic mixture of pakistanamine (I) by oxidation of a racemic mixture of berbamunine (magnoline) (III) with potassium ferricyanide is described.

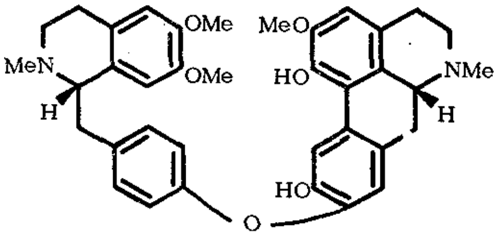
Recently, Shamma and co-workers have reported the isolation and characterization of pakistanamine (I), the first known proaporphine-benzylisoquinoline dimer, and pakistanine (II), the aporphine-benzylisoquinoline dimer, which were found in *Berberis baluchistanica* Ahrendt.[1] Shamma has suggested that the latter alkaloid (II) could be biosynthesized from the above proaporphine-benzylisoquinoline dimer which is derived from bisbenzylisoquinoline berbamunine (III) by phenolic oxidative coupling.[2]

We now wish to report the phenolic oxidation of a racemic mixture of berbamunine (magnoline) (III) to give a racemic mixture (IV) of pakistanamine (I). The bisbenzylisoquinoline (III) was prepared as follows: diazoketone (V), prepared by treating the biscarboxylic acid (VI) with thionyl chloride and diazomethane, was subjected to the Arndt-Eistert reaction with phenethylamine (VII) in the presence of silver oxide to afford the bisamide (VIII), which was converted into the bisbenzylisoquinoline (III) in four steps. Namely, Bischler-Napieralski reaction of VIII, followed by iodomethylation, sodium borohydride reduction and debenzylation,[3] gave (III), The triphenolic bisbenzylisoquinoline (III) was oxidized by vigorous shaking with potassium ferricyanide, buffered by 1 N ammonium acetate in chloroform, under nitrogen for 4 h at room temperature. Purification, which involved silica gel chromatography using $CHCl_3$–MeOH (25 : 1) as an eluant, gave the expected proaporphine-bisbenzylisoquinoline dimer (IX) as an oily substance. The ir spectrum [ν max ($CHCl_3$) 3550, 1665, 1640 cm^{-1}] was in accord with the expected dienone system.[1,2] Methylation of dienone (IX) with diazomethane gave a pale brown caramel, which was purified by preparative thin layer chromatography to give a racemic mixture (IV) of pakistanamine (I). The ir spectrum [ν max ($CHCl_3$) 1670, 1640 cm^{-1}] was almost superimposable with that of a natural sample of (I). The high resolution mass spectrum also showed a molecular ion peak at m/e 622.3031 (M^+) (Calcd. 622.3042).

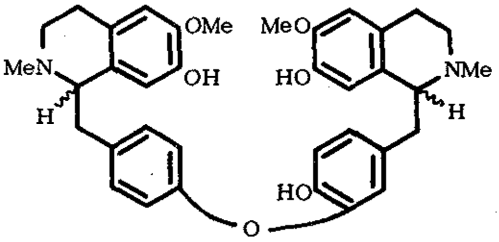
Since compound (IV) is a racemic mixture of pakistanamine (I) and the stereochemistry of the spiro center remains unclear, the synthesis of pakistanamine (I) using the optical active compounds is now under examination.



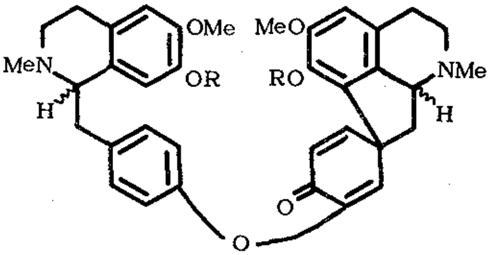
(I)



(II)

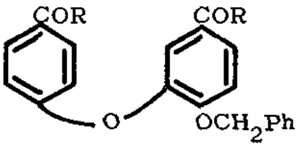


(III)



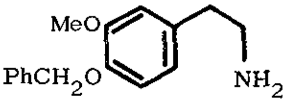
(IV) R=Me

(IX) R=H

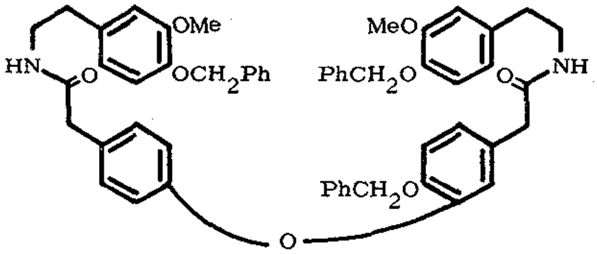


(V) R=CHN$_2$

(VI) R=OH



(VII)



(VIII)

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