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PRELIMINARY NOTE

Synthesis of a Fluoro Seco Phenanthroindolizidine Analogue

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SUMMARY

Synthesis of a fluorine-substituted seco phenanthroindolizidine (VIII) has been accomplished utilizing p-fluorobenzyldehyde and homoveratric acid as building blocks. This is the first report of the preparation of such a fluoro analogue which is a potentially bio-active molecule.

Phenanthroindolizidine alkaloids constitute an interesting group of biologically active secondary metabolites. These have been shown to possess antileukemic [1], antiasthmatic [2], anti bacterial, antifungal [3], antifeedant [4] and antiamoebic [5] activities. The related seco bases such as septicine (IX) [6] and hispidine (X) [7] have also been isolated from natural sources.

Introduction of fluorine in a biologically active substance often enhances its activity or alters the biological

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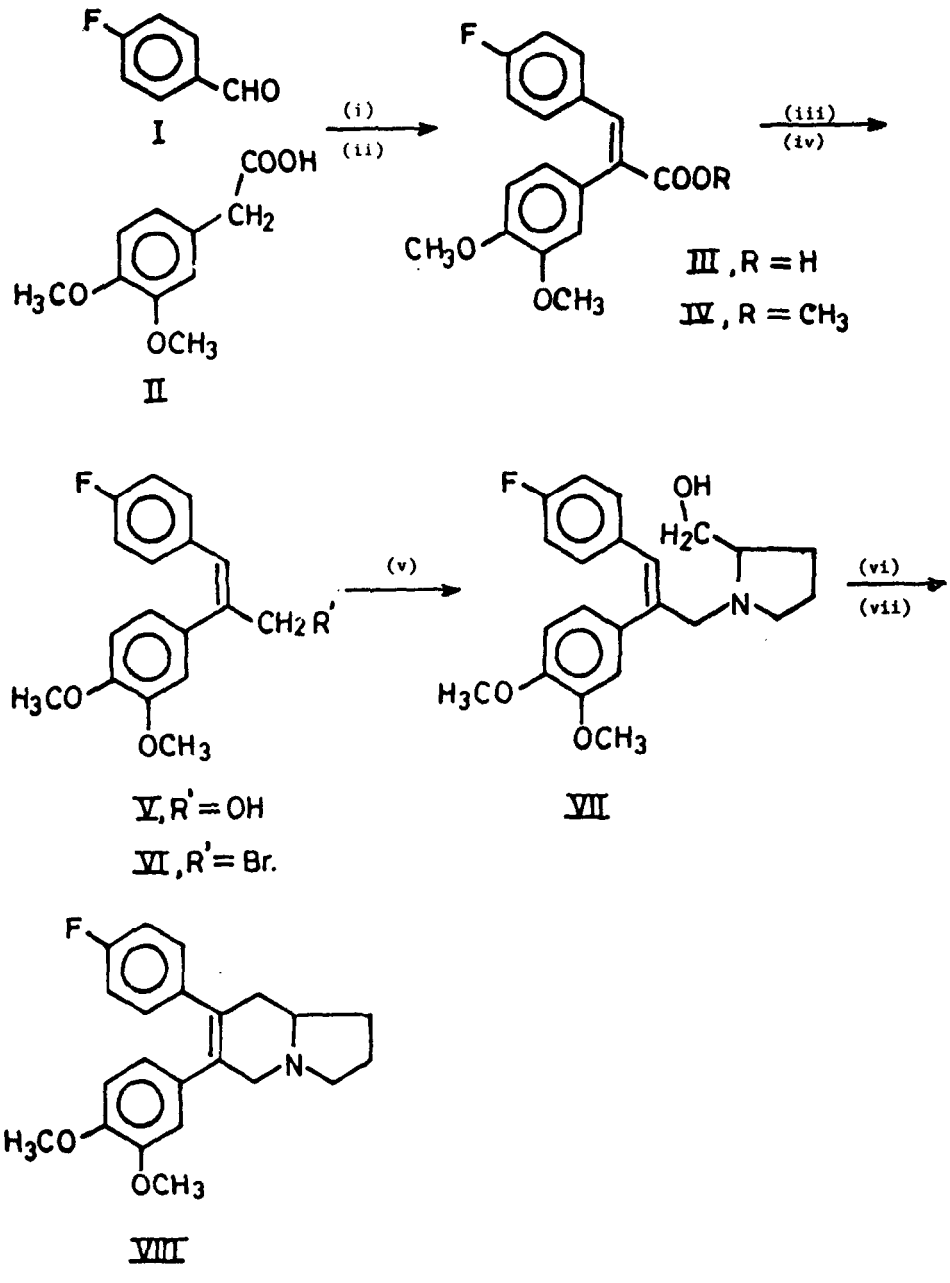
profile in the resultant derivative [8]. In view of this, we carried out the synthesis of a fluorine containing seco phenanthroindolizidine alkaloid which could be further cyclised to the parent phenanthroindolizidine derivative.

Condensation of p-fluorobenzaldehyde (I) and homoveratric acid (II) gave the fluorostilbene acid (III) in satisfactory yields. Its IR spectrum showed the presence of a carboxyl group while the UV spectrum indicated the presence of a stilbene system. The ^{1}H NMR spectrum of (III) confirmed the presence of two methoxyls and accounted for all the aromatic protons. The acid (III) was esterified with diazomethane to furnish the corresponding methyl ester (IV) in quantitative yield. The mass spectrum of (IV) showed the molecular ion peak at m/z 316 while the IR spectrum indicated the presence of an ester function. Reduction of (IV) with lithium aluminumhydride gave the stilbene alcohol (V) in moderate yields. The molecular ion peak in the mass spectrum of (V) was located at m/z 288. The presence of an alcohol was confirmed from its IR spectrum. In the ^{1}H NMR of (V), signals for two methoxyls (6H,s) and aromatic protons (7H,m) were observed. The bromination of (V) with phosphorus tribromide yielded the corresponding bromo derivative (VI) which was immediatly condensed with L-prolinol to give the base (VII) in good yields. The mass spectrum of (VII) revealed the molecular ion peak at m/z 371. The IR spectrum of (VII) indicated the presence of the hydroxyl group while the UV spectrum suggested the stilbene chromophore. The ^{1}H NMR of this base showed the presence of aliphatic protons of the pyrrolidine ring as



Reagents : (i) Ac_2O/Et_3N; (ii) CH_2N_2; (iii) $LiAlH_4$; (iv) PBr_3; (v) L-Prolinol; (vi) CH_3SO_2Cl; (vii) NaH.

Scheme

multiplets in the up-field region . The signals for two methoxyls and seven aromatic protons were also observed. The basic character of (VII) was confirmed by a positive Dragendorff test [9]. The foregoing aminoalcohol (VII) was mesylated with methane sulphonylchloride and the resultant mesyl derivative was immediately cyclised using sodium hydride [10]. From the crude reaction product, the seco derivative (VIII) was isolated by preparative layer chromatography. The mass spectrum of this seco base (VIII) showed the parent ion peak at m/z 353 and a base peak at m/z 284 (M-69) due to the retro Diels -Alder cleavage of the indolizidine moiety. The absence of hydroxyl group in (VIII) was evident from its IR spectrum. The UV spectrum of (VIII) resembled that of hispidine (X). The ^{1}H NMR spectrum of (VIII) exhibited the signals for methoxyls (6H,s) and aromatic protons (7H,m) as expected for the structure (VIII)*.

Attempts to cyclise (VIII) by the known methods viz., photolysis and oxidative coupling using reagents like vanadium oxyfluoride and thallium trifluoroacetate [11] failed to yield the corresponding fluoro phenanthroindolizidine derivative.

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*The presence of a fluorine atom in all the synthetic derivatives was confirmed by ^{19}F NMR.

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