Thesis Title Synthetic Studies of Isoindolobenzazepine and
Homoprotoberberine Alkaloids

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ABSTRACT

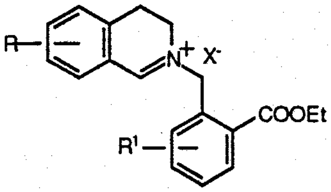
Chapter I

Lennoxamine, the natural isoindolobenzazepine, and its derivatives, were synthesized by two newly developed routes. In the first route, 2-ethoxycarbonylbenzyl-3,4-dihydroisoquinoline derivative was the key intermediate which could be readily synthesized by the N-alkylation of 3,4-dihydroisoquinoline with ethyl 2-chloromethylbenzoate derivative. This key intermediate, 2-ethoxycarbonylbenzyl-3,4-dihydroisoquinoline derivative was then treated with ethanolic potassium hydroxide or sodium hydroxide to give the dehydrolennoxamine derivative which could then be easily converted to the required alkaloid. In the second route, aldehydic lactam was used as the key intermediate. In this approach, the aldehydic lactam was synthesized by bis alkylation-acylation of phenethylamine derivative with ethyl 2-chloromethylbenzoate derivative followed by formylation which was found to be conveniently carried out by the reaction of dichloromethyl methyl ether (Cl_2CHOCH_3). The aldehydic lactam was then further treated with ethanolic potassium hydroxide or sodium hydroxide to give the dehydrolennoxamine derivative which could be transformed to natural lennoxamine by catalytic hydrogenation in good yield. The above approaches could be extended to synthesize various isoindolobenzazepine alkaloids.

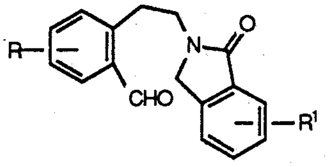
Chapter II

The new approach to the synthesis of homoprotoberberine alkaloids was developed. The key step of the reaction involved the alkylation of the aromatic carbanion with 2-(2-bromoethyl)-1,3-dioxolane. The alkylation product was then converted to the homoprotoberberine alkaloid by cyclization in the presence of formic acid and further reduction with lithium aluminium hydride.

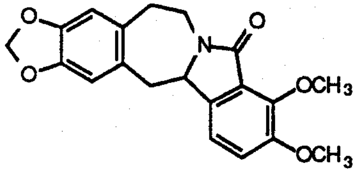
Praziquantel, the pyrazinoisoquinoline skeleton, and its analogue were prepared. The sequence of the reaction involved the condensation of phenethylamine with chloroacetyl chloride and subsequent N-alkylation of 2-aminoacetaldehyde dimethyl acetal with the resulting chloro amide. The amino amide so obtained could be cyclized by sulfuric acid to give the key tricyclic amine. The praziquantel and various other derivatives were easily prepared by amidification of the derived amine with the appropriate acid chlorides.



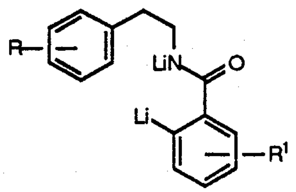
2-ethoxycarbonylbenzyl-3,4-dihydroisoquinolinium salt



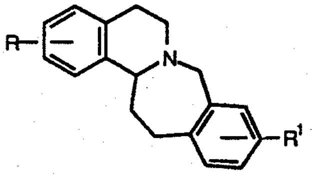
aldehydic lactam



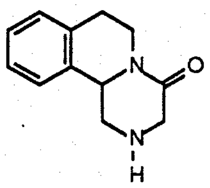
lennoxamine



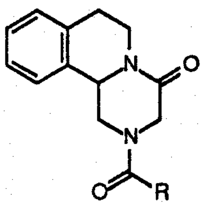
aromatic carbanion



homoprotoberberine



tricyclic amine



praziquantel ($R = C_6H_{11}$)