PREFACE

The work reported in this thesis deals with the elucidation of crystal structure and conformation of seven compounds which are derivatives of 2-carbethoxyindoles. The compounds that are investigated here are important intermediates in obtaining pharmacologically active compounds of the type 1,2,3,4-tetrahydropiperizino(1,2-a)indoles and diazepino(1,2-a)indoles which exhibit CNS depressant, psychotopic, anti-depressant, anti-hypertensive, muscle relaxant and anti-allergic properties. For all the seven compounds the intensity data is collected on an automatic 4 circle diffractometer.

The thesis is divided into 6 chapters.

The first chapter is a brief outline of the theory and practice of single crystal x-ray crystallography. Here, the procedure for collecting the data, the different methods employed in obtaining the structure and refinement are presented with the necessary theory in brief.

In chapter two a brief literature survey on indole derivatives is presented. The interest in the indole derivatives, their origin and importance with emphasis on 2-carbethoxyindoles is briefly discussed.

Chapter three deals with the crystal structure determination of three compounds which are N-substituted 2-carbethoxyindoles and it consists of three parts.
The first part deals with the crystal structure determination of ethyl 5-methoxy-3-phenyl-2-indolecarboxylate which serves as a versatile starting material to synthesize fused indole heterocycles of biological importance. This compound was synthesized by Fisher indolization of ethyl pyruvate-p-methoxy-phenylhydrazone using dry hydrogen chloride gas. The compound crystallizes in monoclinic space group C2/c with a unit cell of dimensions a = 11.689(2), b = 22.934(4), c = 11.592(2) Å and β = 100.16(3)°. The structure was solved by direct methods and refined to an R-value of 0.046. The indole nucleus is folded along C(8)-C(9) bond by 1.7(4)°. The planar phenyl ring attached to C(3) is inclined to the indole rings at an angle 45.8(3)°. The mean plane through the carbethoxy group is inclined to the indole nucleus at an angle 6.1(2)°. The centrosymmetrically related molecules are linked through strong N-H···O bonds.

Second part deals with the crystal structure of ethyl 5-ethoxy-3-phenyl-2-indolecarboxylate which is synthesized by Fisher indolization of ethyl phenylpyruvate-p-ethoxy-phenylhydrazone using dry hydrogen chloride gas. The title compound when made to undergo nucleophilic substitution using chloroacetonitrile in the presence of sodium hydride and dimethyl formamide results in the formation of ethyl 1-cyano methyl-5-ethoxy-3-phenyl-2-indolecarboxylate which is an important precursor for the synthesis of 1,2,3,4-tetrahydropyrazino indoles which show anti-5-hydroxy
tryptamine, anti-histamine and CNS depressant properties. The compound crystallizes in the monoclinic space group \( \text{P2}_1/c \) with 8 molecules in a unit cell of dimensions \( a = 10.322(3) \), \( b = 21.063(5) \), \( c = 15.006(5) \) Å and \( \beta = 92.93(3)^\circ \). The structure was solved by direct methods and refined to an R-value of 0.048. There are two independent molecules in an asymmetric unit. The indole ring system is almost planar with the normals to the five membered ring and six membered ring inclined to each other at an angle of 0.9(2)° in molecule A and 0.4(3)° in molecule B. The ethoxy group attached to C(5) is coplanar with the indole rings. The phenyl ring attached to C(3) is planar in both the molecules and is inclined to the indole ring system at an angle of 47.3(4)° in molecule A and 44.7(4)° in molecule B. The carbethoxy group is inclined to the mean plane of the indole rings at an angle of 4.4(6)° in molecule A and 14.7(7)° in molecule B. The molecules of the asymmetric unit are linked through N-H⋯O bonds.

The part three of this chapter deals with the crystal structure of ethyl 5-ethoxy-3-methyl-2-indolecarboxylate. The compound was synthesized by Fisher indolization of ethyl methylpyruvate of p-ethoxyphenylhydrazone using dry hydrogen chloride gas. The compound crystallizes in the triclinic space group \( \text{P}2_1 \) with two molecules in a unit cell of dimensions \( a = 7.855(2) \), \( b = 8.669(1) \), \( c = 11.115(2) \) Å, \( \alpha = 70.38(1)^\circ \), \( \beta = 69.39(1)^\circ \) and \( \gamma = 73.97(1)^\circ \). The structure
solved by direct methods is refined to an R-value of 0.0598. The indole ring system is highly planar with a maximum deviation of 0.006(2) Å from the least-squares mean plane containing the two rings. The normals to the two rings are inclined to each other at an angle of 0.4(2)°. The methyl group at C(3) is coplanar with the indole rings and the ethoxy group at C(5) is almost coplanar with the indole rings. The mean plane through the carboxyloxy group is inclined to the indole rings at an angle of 2.7(2)°. The centrosymmetrically related molecules are held together by strong N-H⋯O bonds across the centre of symmetry.

Chapter four has two parts and deals with the crystal structure of two compounds which are 3,5-disubstituted ethyl 1-cyanomethyl-2-indolecarboxylates.

The first part deals with the crystal structure of ethyl 1-cyanomethyl-5-chloro-3-phenyl-2-indolecarboxylate. This compound is an important precursor to physiologically active piperidineindole and it can be readily converted into 8-chloro-10-phenyl-1,2,3,4-tetrahydropiperidine(1,2-a)indole in a single step by reductive cyclization using lithium aluminium hydride. The title compound was synthesized by treating ethyl 5-chloro-3-phenyl-2-indolecarboxylate with chloroacetonitrile in the presence of sodium hydride. The compound crystallizes in triclinic space group P̅1 with 4 molecules in a unit cell having dimensions a = 13.984(2), b = 10.069(2), c = 13.248(1) Å, α = 72.61(1)°, β = 82.60(1)° and
\[ \gamma = 69.27(2)^\circ \]. The structure was solved by direct methods and refined to an R-value of 0.066. There are two molecules in an asymmetric unit. The indole nucleus is not planar in both the molecules with the normals to the two rings inclined to each other at an angle of 2.1(3)° in molecule A and 3.0(4)° in molecule B. The bond length C(4)–C(5) is shorter than the standard aromatic C-C bond and does not agree with the corresponding values in similar structures. The phenyl ring is planar in both the molecules and is inclined to the indole rings at an angle 52.6(5)° in molecule A and 49.9(5)° in molecule B. The mean plane through the carbethoxy group is inclined to the indole rings at an angle of 25.3(5)° in molecule A and 14.7(3)° in molecule B. The C=C=N chain is linear in both the molecules. There are no hydrogen bonds, the crystal structure is stabilized mainly by van der Waals forces.

The part two of this chapter deals with the crystal structure of ethyl 1-cyanomethyl-5-methoxy-3-phenyl-2-indolecarboxylate. The compound can be effectively converted into 8-methoxy-10-phenyl-1,2,3,4-tetrahydropirazino(1,2-a) indole which exhibits marked CNS depressant and muscle relaxant activities. The title compound is the condensation product of ethyl 5-methoxy-3-phenyl-2-indolecarboxylates and chloroacetonitrile in the presence of sodium hydride. The compound crystallizes in the orthorhombic space group Pbca with 8 molecules in a unit cell of dimensions \( a = 7.179(3)\),
b = 33.014(3) and c = 14.847(1)Å. The structure was solved by direct methods and refined to an R-value of 0.049. The indole ring system is planar with the normals to the two rings inclined to each other at an angle of 0.6(3)°. The methoxy group is coplanar with the indole rings and has a maximum deviation of 0.015(3) Å from the mean plane of the indole ring system. The planar phenyl ring attached to C(3) is inclined to the indole rings at an angle of 55.1(3)°. The mean plane through the carbethoxy group is inclined to the indole rings at an angle of 25.4(6)°. The cyanomethyl chain attached to N(1) is linear. There are no hydrogen bonds and the crystal structure is stabilized mainly by van der Waals forces.

Chapter five consists of two parts and deals with the crystal structure of two compounds which are 3,5-disubstituted ethyl 1-2′cyanoethyl-2-carboxylates.

The first part deals with the structure of ethyl 1-2′cyanoethyl-3,5-dimethyl-2-indolecarboxylate. This compound is an important precursor in the synthesis of 1,2,3,4-tetrahydropyrazinoindoles which show excellent anti-histamine and CNS depressant properties. The title compound was synthesized in two steps. In the first step the indole derivative was synthesized by the reaction of ethyl methylpyruvate of p-tolylphenylhydrazine with dry hydrogen chloride gas and this compound was made to react with β-chloroethylcyanide and sodium hydride. The compound
crystallizes in the triclinic space group $P\overline{1}$ with two molecules in a unit cell of dimensions $a = 5.925(2)$, $b = 8.321(1)$, $c = 16.126(3)$ Å, $\alpha = 103.41(1)^\circ$, $\beta = 98.85(2)^\circ$ and $\gamma = 99.51(2)^\circ$. The structure was solved by direct methods and refined to an R-value of 0.0701. The indole ring system is planar with the normals to the two rings inclined to each other at an angle of $0.7(7)^\circ$ and the two methyl groups at C(3) and C(5) are coplanar with the indole ring system. The carbethoxy group attached to C(2) is planar and the mean plane through this group is inclined to the indole rings at an angle of $11.5(5)^\circ$. The C-C\_N chain is linear. There are no hydrogen bonds and the crystal structure is stabilized mainly by van der Waals forces.

The second part of this chapter deals with the crystal structure of ethyl 1-2'cyanoethyl-5-methoxy-3-methyl-2-indolecarboxylate. The reduction of this compound in the presence of lithium aluminium hydride and cyclization of the resulting amino compound yields a novel compound 9-methoxy-11-methyl-1,2,3,4-tetrahydro-1H-1,4-diazepino(1,2a)indole which exhibits marked tranquilizing property. The title compound was synthesized by treating ethyl 5-methoxy-3-methyl-2-indolecarboxylate with acrylonitrile in the presence of a basic catalyst Triton-8. The compound crystallizes in the triclinic space group $P\overline{1}$ with four molecules in a unit cell of dimensions $a=9.120(5)$, $b=11.954(2)$, $c = 14.877(2)$ Å, $\alpha = 105.65(1)^\circ$, $\beta = 102.16(2)^\circ$ and $\gamma = 78.84(2)^\circ$. The
structure was solved by direct methods and refined to an R-value of 0.0649. There are two independent molecules in the asymmetric unit. The indole ring system is planar in both the molecules with the normals to the two rings inclined to each other at an angle of 0.6(6)° in molecule A and 0.8(9)° in molecule B. The methyl group at C(3) and the ethoxy group at C(5) are coplanar with the indole rings in both the molecules. The mean plane through the carbethoxy group is inclined to the indole rings at an angle of 13.7(6)° in molecule A and 18.5(6)° in molecule B. The mean plane through the cyannethyl group is inclined to the indole rings at an angle of 89.9(9)° in A and 89.0(8)° in B. There are no hydrogen bonds and the structure is stabilized mainly by van der Waals forces.

Chapter six deals with comparison of some important geometric parameters of the molecules with the reported values. The modifications in the crystalline form of compounds belonging to one class are reflected in some of the molecular parameters and in this chapter an attempt is made to explain the observed variations in the molecular parameters of the substituted 2-carbethoxyindoles in terms of various factors. A comparative study of the orientations of groups like methoxy, ethoxy, phenyl, carbethoxy etc., is presented here. In the present work it is found that the phenyl group is oriented at an angle between 45-55° to the indole nucleus which is the most favourable conformation which facilitates minimum strain due to the steric and
electronic interactions. Substituents on indole nitrogen are expected to cause significant changes in the mode of packing of the molecules in the solid state and this fact is highlighted using the information based on the present work.

Based on the work reported in this thesis, the following papers have been published or under publication.


2. Structure of Ethyl 5-ethoxy-3-phenyl-2-indolecarboxylate


5. Structure of Ethyl 5-methoxy-3-phenyl-2-indolecarboxylate

6. Structure of ethyl 5-ethoxy-3-methyl-2-indolecarboxylate
   [To be submitted to Acta Crystallographica-C]

7. Structure of ethyl 1-2'cyanoethyl-3,5-dimethyl-2-indole carboxylate [To be submitted to Acta Crystallographica-C]