CHAPTER THREE
THEORETICAL
THEORETICAL PART I

SYNTHESIS OF INDOLE-2-CARBOXALDEHYDES, 2-(2-AMINOETHYL)INDOLES AND 2-(2-AMINOPROPYL)INDOLES
A large number of structural analogues of tryptamine, modelled after serotonin have been found to exhibit antiserotonin activity (Chapter I). Although, the compounds tested so far include various substituted tryptamines, the survey of literature shows that the synthesis and evaluation of biological activity of substituted 2-(2-aminoethyl)-indoles have received comparatively little attention. However, Witkop and co-workers\textsuperscript{1a} tested several indole derivatives for monoamine oxidase inhibition property and found that 5-hydroxy-2-(2-aminoethyl)-indole\textsuperscript{1b} was moderately active in vitro.

Introduction of alkyl group (methyl or ethyl) in the ethylamine side chain of tryptamine had remarkable effect in increasing the drug potency.\textsuperscript{2} Julia and co-workers\textsuperscript{3} have shown that 3-(3-aminopropyl)-2-phenylindoles were more potent serotonin antagonists than the corresponding 2-phenyltryptamines. Recently, Basanagoudar and Siddappa\textsuperscript{4a} prepared several Bz-substituted 3-(3-aminopropyl)- and 1-(3-aminopropyl)-indoles, and evaluated their antiserotonin activity.\textsuperscript{4b} Out of the several compounds screened, some of the 1-(3-aminopropyl)indoles were found to be more potent antagonists of serotonin than BAS.
In view of the above results, it was apparent that the Bz-substituted 2-(2-aminoethyl)- and Bg-substituted 2-(2-aminopropyl)indoles would be of considerable interest and required thorough investigation. The present work, therefore, was undertaken with the object of synthesising various Bg-substituted 2-(2-aminoethyl)- and 2-(2-aminopropyl)-indoles for the evaluation of biological activity.

I. Synthesis of 5-methoxyindole-2-carboxaldehyde, 5-methoxy-2-(2-aminoethyl)indole and 2-(2-aminopropyl)indole

The first objective in the present scheme of work was the synthesis of 5-methoxy-2-(2-aminoethyl)- and 5-methoxy-2-(2-aminopropyl)indoles.

Although, indole-3-carboxaldehydes can be obtained in high yields by the Smith procedure, the indole-2-carboxaldehydes which are the intermediates for the synthesis of the title compounds are not easily accessible. The methods developed in recent years for the synthesis of indole-2-carboxaldehydes are briefly reviewed (Chapter II). In our laboratory, Dambal and Siddappa adopted McFadyen and Stevens procedure for the synthesis
of 5-methyl substituted indole-2-carboxaldehydes, required as the intermediates for the synthesis of biologically important *isoctryptamine* derivatives. Therefore, it was proposed to synthesise 5-methoxy-indole-2-carboxaldehyde according to the above procedure.

Ethyl 5-methoxyindole-2-carboxylate (IV), required as the starting material, was prepared by following the procedure described by Hydon and Siddappa.7a (Chart I). Ethyl pyruvate 5-methoxy-phenylhydrazone (III) was obtained by coupling

**Chart I**

![Diagram showing the synthesis process from I to IV](image-url)
p-anisidine diazonium chloride (I) with ethyl α-methylacetoacetate (II), according to the Japp-Klingemann reaction. This hydrazone underwent Fischer cyclisation in alcoholic sulphuric acid to yield ethyl 5-methoxyindole-2-carboxylate (IV), which was converted almost quantitatively into 5-methoxyindole-2-carboxydrazide (V) on reaction with 100% hydrazine. The carboxydrazide (V) was tosylated to get 5-methoxy-2-toluene-p-sulphon-hydrazidocarbonylindole (VI), which upon alkaline decomposition with anhydrous sodium carbonate in ethylene glycol at elevated temperature, yielded 5-methoxyindole-2-carboxaldehyde (VIII).
The aldehyde obtained by this method contained considerable impurities which had to be removed by repeated chromatographic separation on alumina column. The low yield (about 41%) of the 5-methoxyindole-2-carboxaldehyde (VIII) obtained is probably due to the formation of much azine, along with the aldehyde, during the alkaline decomposition of 5-methoxy-2-toluene-p-sulphon-hydrazidocarbonylindole at elevated temperature.

Since the purification of the aldehyde obtained by McFadyen and Stevens procedure (method A) was cumbersome, the preparation of 5-methoxyindole-2-carboxaldehyde by an alternative method (method B) due to Harley-Mason\(^8\) was attempted with the object of evaluating the preparative value of the two methods.\(^9\) The necessary intermediate 5-methoxy-2-hydroxymethylindole (VII) was prepared by lithium aluminium hydride reduction of ethyl 5-methoxyindole-2-carboxylate (IV), following the procedure of Brehm.\(^10\) Oxidation of 5-methoxy-2-hydroxymethylindole (VII) with activated manganese dioxide\(^11\) yielded 5-methoxyindole-2-carboxaldehyde (VIII). The oxidation reaction was followed by t.l.c. and was found to take about 20-25 hours. The aldehyde
obtained by this method (method B) was in a purer form, and the yield obtained was also good (about 61%). The aldehyde obtained by both the methods was found to be identical [no depression in mixed m.p. and identical t.l.c. behaviour].

5-Methoxy-2-hydroxymethylindole (VII) showed UV maxima at 230 and 274 millimicrons, and IR exhibited strong band at 3185 cm\(^{-1}\) (OH/NH), in agreement with the earlier observation.\textsuperscript{12} 5-Methoxyindole-2-carboxaldehyde (VIII) showed UV maxima at 239 and 315 millimicrons, and IR exhibited a medium strong band at 3205 cm\(^{-1}\) (NH), and a strong band at 1672 cm\(^{-1}\) (CHO).

The condensation of nitropraffins with 3-formylindole is a well investigated reaction.\textsuperscript{13} Ash and Wragg\textsuperscript{2c} studied this reaction under variety of conditions using different catalysts. They concluded that the condensation of nitroethane with 3-formylindole using benzylamine as catalyst and excess of nitroethane as solvent gave a practicable yield of 3-(2-nitropropenyl)indole (51% yield). Heinzelman and co-workers\textsuperscript{2f} used a mixture of ammonium acetate, acetic anhydride and glacial acetic
acid as catalyst for the condensation of nitro-
paraffins with 3-formylindole (50% yield). However, 
they were able to improve the yield of the 
condensation product up to 60% by using dibasic 
ammonium phosphate and acetic acid as catalyst.

During the present work, 5-methoxyindole-
2-carboxaldehyde was condensed with nitromethane 
using ammonium acetate as catalyst, employing excess of nitromethane as solvent, at reflux 
temperature. 5-Methoxy-2-(2-nitrovinyl)indole (IX) separated on cooling as a red crystalline compound in an yield of 65%. The nitrovinylindole was further conveniently reduced with lithium aluminium hydride to get the desired 5-methoxy-2-(2-aminoethyl)-indole (X), and was characterised by preparing its benzoyl derivative.

Similarly, 5-methoxyindole-2-carboxaldehyde (VIII) was condensed with nitroethane using benzyl-
amine as catalyst at reflux temperature, to yield 5-methoxy-2-(2-nitropropenyl)indole (XI), which on subsequent reduction with lithium aluminium hydride, yielded the desired 5-methoxy-2-(2-aminopropyl)indole (XII),
and was characterised as its benzoyl derivative.

II. Synthesis of 5-methoxy-3-methylindole-2-carboxaldehyde, 5-methoxy-3-methyl-2-(2-aminooethyl)indole and 5-methoxy-3-methyl-2-(2-aminopropyl)indole

Sunagawa and co-workers\textsuperscript{14a} reported the
synthesis of 5-methoxy-3-methylindole-2-carboxaldehyde by reducing the corresponding acid chloride with lithium tri-t-butoxyaluminoxydride. In the present investigation, it was thought to prepare this aldehyde by McFadyen and Stevens, and Harley-Mason procedures (Chart III).

The required ethyl 5-methoxy-3-methylindole-2-carboxylate (XV) was prepared according to the procedure described by Hlaikie and Perkin. Ethyl α-ketobutyrate p-methoxyphenylhydrazone (XIV) was obtained by subjecting p-methoxybenzenediazonium chloride (I), to a Japp-Klingemann reaction with ethyl α-ethylacetoacetate (XIII). The hydrazone was then cyclised in alcoholic sulphuric acid to get ethyl 5-methoxy-3-methylindole-2-carboxylate (XV). Ethyl 5-methoxy-3-methylindole-2-carboxylate (XV) was reacted with hydrazine to get 5-methoxy-3-methylindole-2-carbohydrazide (XVI). The carbohydrazide (XVI), on tosylation, furnished 5-methoxy-3-methyl-2-toluene-p-sulphonydrazidocarbonylindole (XVII), which upon alkaline decomposition with anhydrous sodium carbonate in ethylene glycol at elevated temperature yielded 5-methoxy-3-methylindole-2-carboxaldehyde (XIX). The impurities in the crude
product were removed by repeated chromatographic separation on alumina to obtain the pure aldehyde in 50% yield.
The aldehyde (XIX) was also prepared according to the Harley-Mason procedure (method B). 5-Methoxy-3-methyl-2-hydroxymethylindole (XVIII) was conveniently obtained by lithium aluminium hydride reduction of ethyl 5-methoxy-3-methylindole-2-carboxylate (XV) in dry ether. The hydroxymethylindole (XVIII) on subsequent oxidation with activated manganese dioxide in dichloromethane, at room temperature, furnished 5-methoxy-3-methylindole-2-carboxaldehyde (XIX). The oxidation reaction was followed by t.l.c. and was found to take about 20-25 hours. The aldehyde obtained by the alternative route (method B) was in a purer form and the yield was better (71%). The analytical sample of the aldehyde melted at 229-231° (lit. m.p. 213-215°). The aldehyde obtained by both these methods (method A and method B) was found to be identical (no depression in mixed m.p. and identical t.l.c. behaviour).

5-Methoxy-3-methyl-2-hydroxymethylindole (XVIII) showed strong IR absorption band at 3311 cm\(^{-1}\) (OH/NH). 5-Methoxy-3-methylindole-2-carboxaldehyde (XIX) showed UV maxima at 243 and 321 millimicrons and IR exhibited a medium band at 3311 cm\(^{-1}\) (NH) and a strong band at 1626 cm\(^{-1}\) (CHO).
Sunagawa and co-workers\textsuperscript{14b} were able to condense nitromethane with 5-methoxy-3-methylindole-2-carboxaldehyde (XIX) using butylamine as catalyst. The resulting 5-methoxy-3-methyl-2-(2-nitrovinyl)indole was useful as bactericide. However, in the present investigation, condensation of nitromethane with the aldehyde (XIX) was brought about by using ammonium acetate as catalyst and excess of nitromethane as solvent, at reflux temperature. 5-Methoxy-3-methyl-2-(2-nitrovinyl)indole (XX) separated in a pure form on cooling, in an yield of 66%. The analytical sample melted at 211° (lit. m.p.\textsuperscript{14b} 200-205°). Lithium aluminium hydride reduction of the nitrovinylindole (XX) gave the desired 5-methoxy-3-methyl-2-(2-aminoethyl)indole (XXI). Similarly, the aldehyde (XIX) condensed with nitroethane in presence of benzylamine to yield 5-methoxy-3-methyl-2-(2-nitropropenyl)indole (XXII), which on lithium aluminium hydride reduction furnished the desired 5-methoxy-3-methyl-2-(2-aminopropyl)indole (XXIII) in 69% yield. The several steps involved in the synthesis are presented below (Chart IV).
III. 7-Methoxyindole-2-carboxaldehyde, 7-methoxy-2-(2-aminoethyl)indole and 7-methoxy-2-(2-aminopropyl)indole

The synthesis of 7-methoxyindole-2-carboxaldehyde required ethyl 7-methoxyindole-2-
carboxylate (XXVIII) as the starting material. Ethyl 7-methoxyindole-2-carboxylate (XXVIII) was prepared according to the Reissert method (Chart V). 2-Nitro-

Chart V

3-hydroxytoluene (XXIV) was obtained from m-cresol by disulphonation, nitration and subsequent hydrolysis
IR SPECTRA
according to literature method. 2-Nitro-3-hydroxytoluene was methylated to get 2-nitro-3-methoxytoluene (XXV). Condensation of 2-nitro-3-methoxytoluene with ethyl oxalate gave 2-nitro-3-methoxyphenylpyruvic acid (XXVI), which on reduction with ferrous sulphate and ammonia furnished 7-methoxyindole-2-carboxylic acid (XXVII). This, on esterification with ethanolic sulphuric acid, gave ethyl 7-methoxyindole-2-carboxylate (XXVIII).

Ethyl 7-methoxyindole-2-carboxylate, on reduction with lithium aluminium hydride in dry ether at room temperature, yielded 7-methoxy-2-hydroxymethylindole (XXIX). The hydroxymethylindole in dichloromethane underwent smooth oxidation with activated manganese dioxide (method B) to furnish 7-methoxyindole-2-carboxaldehyde (XXX). The oxidation reaction when followed by t.l.c., was found to take about 20-25 hours, and the aldehyde was obtained in an yield of 66%.

7-Methoxy-2-hydroxymethylindole (XXIX) showed UV absorption maxima at 225 and 264 millimicrons, and the IR spectrum showed strong bands at 3356 cm⁻¹.
and 3226 cm\(^{-1}\) (doublet, OH/NH). 7-Methoxyindole-2-carboxaldehyde (XXX) showed UV absorption maxima at 225 and 307 millimicrons and the IR spectrum exhibited a medium strong band at 3125 cm\(^{-1}\) (NH) and a strong band at 1634 cm\(^{-1}\) characteristic of \(\text{C} = \text{O}\) stretching vibration (CHO).

7-Methoxyindole-2-carboxaldehyde (XXX) condensed with nitromethane in presence of catalytic amount of ammonium acetate to yield 7-methoxy-2-(2-nitrovinyl)indole (XXXI), which on reduction with lithium aluminium hydride gave the desired 7-methoxy-2-(2-aminoethyl)indole (XXXII) in 75\% yield. Similarly, condensation of the aldehyde with nitroethane furnished 7-methoxy-2-(2-nitropropenyl)indole (XXXIII) in 60\% yield. In this case, dibasic ammonium phosphate and glacial acetic acid were used as catalyst and excess of nitroethane as solvent. Lithium aluminium hydride reduction of the nitropropenyl-indole gave the desired 7-methoxy-2-(2-aminopropyl)-
Indole (XXXIV), in 69\% yield.

**Chart VI**

XXX

CH$_3$NO$_2$

XXXI

L$_2$AlH$_4$.

XXXII

CH$_3$NO$_2$

XXXIII

L$_2$AlH$_4$.

XXXIV

Indole (XXXIV), in 69\% yield.
IV. 7-Methoxy-3-methylindole-2-carboxaldehyde and 7-methoxy-3-methyl-2-(2-aminoethyl)indole

The required starting material, ethyl 7-methoxy-3-methylindole-2-carboxylate (XXXVII) was prepared\textsuperscript{15} by a Fischer Indole synthesis (Chart VII).

\textbf{Chart VII}

\begin{equation}
\begin{array}{c}
\text{XXXV} \\
\text{CH}_3 \text{CO CH COOEt} \\
\text{XXXVI} \\
\text{XXXVII} \\
\text{EtOH/H}_2\text{SO}_4 \\
\text{XXXVIII} \\
\text{XXXIX} \\
\text{XLI} \\
\end{array}
\end{equation}
Ethyl α-ketobutyrate o-methoxyphenyl-hydrazone (XXXVI) was prepared by subjecting o-methoxy-benzenediazonium chloride (XXXV) to a Japp-Klingemann reaction\textsuperscript{7b} with ethyl α-ethylacetooacetate (XIII). This was then cyclised with alcoholic sulphuric acid to get ethyl 7-methoxy-3-methylindole-2-carboxylate (XXXVII). Ethyl 7-methoxy-3-methylindole-2-carboxylate (XXXVII) reacted with hydrazine to yield the carbohydrazide (XXXVIII) almost quantitatively. Compound (XXXVIII) was tosylated to get 7-methoxy-3-methyl-2-toluene-p-sulphonhydrazido-carbonylindole (XXXIX), which on decomposition with anhydrous sodium carbonate in ethylene glycol at elevated temperature, gave 7-methoxy-3-methylindole-2-carboxaldehyde (XL), in a crude form. The aldehyde was found to be highly contaminated with impurities which were then removed by repeated chromatographic separation on alumina (48% yield), (method A).

Since the yield of the aldehyde obtained in the above method was not satisfactory and its purification was tedious, the aldehyde was prepared by the alternative route (method B). Ethyl 7-methoxy-
3-methylindole-2-carboxylate (XXXVII) was reduced with lithium aluminium hydride in dry ether at room temperature, to get 7-methoxy-3-methyl-2-hydroxymethylindole (XLI). The compound (XLI) in dichloromethane was subjected to activated manganese dioxide oxidation at room temperature to get 7-methoxy-3-methylindole-2-carboxaldehyde (XL). The oxidation reaction was followed by t.l.c. and was found to take about 20-25 hours. The aldehyde obtained by both these methods was found to be identical (no depression in mixed m.p. and identical t.l.c. behaviour).

7-Methoxy-3-methyl-2-hydroxymethylindole (XLI) showed UV maxima at 228 and 271 millimicrons, and IR exhibited strong bands at 3509 cm\(^{-1}\) and 3226 cm\(^{-1}\) (doublet, OH/NH). 7-Methoxyindole-2-carboxaldehyde (XL) showed UV absorption maxima at 252 and 313 millimicrons, and IR spectrum exhibited strong band at 3289 cm\(^{-1}\) (NH) and another strong band at 1639 cm\(^{-1}\) characteristic of C = O stretching vibration (OHO).

The aldehyde (XL) readily condensed with nitromethane, in presence of catalytic amount of
ammonium acetate to yield 7-methoxy-3-methyl-2-(2-nitrovinyl)indole (XLII) in 69\% yield, which on reduction with lithium aluminium hydride furnished the required 7-methoxy-3-methyl-2-(2-aminoethyl)-indole (XLIII), and was characterised by preparing its benzoylderivative. The steps involved in the synthesis are given below (Chart VIII).

**Chart VIII**

\[ XL \xrightarrow{\text{CH}_3\text{NO}_2} XLII \xrightarrow{\text{LiAlH}_4} XLIII \]

V. 6-Methoxyindole-2-carboxaldehyde

Ethyl 6-methoxyindole-2-carboxylate (XLIX), required as the starting material was prepared following the Reissert Synthesis,\textsuperscript{16} according to Kermack, Perkin and Robinson.\textsuperscript{18} 3-Nitro-\textmu-cresol (XLV)
was prepared from 3-nitro-\(\text{p}\)-toluidine. Compound (XLV), on methylation with dimethyl sulphate in

**Chart IX**

\[
\begin{align*}
\text{XLIV} & \quad \xrightarrow{\text{EtOH/\(\text{H}_2\text{SO}_4\)}} \quad \text{XLV} \quad \xrightarrow{\text{(CH}_3)_2\text{SO}_4} \quad \text{XLVI} \\
\text{XLVIII} & \quad \xrightarrow{\text{FeSO}_4/\text{H}_2\text{O}} \quad \text{XLVII} \\
\text{XLIX} & \quad \xrightarrow{\text{EtOH/\(\text{H}_2\text{SO}_4\)}} \quad \text{L} \\
\text{L} & \quad \xrightarrow{\text{Activated \(\text{MnO}_2\)}} \quad \text{LI}
\end{align*}
\]
aqueous sodium hydroxide gave 2-nitro-4-methoxy-toluene (XLVI), which readily condensed with ethyl oxalate to yield 2-nitro-2-methoxyphenylpyruvic acid (XLVII). This, on reduction with ferrous sulphate and ammonia, gave 6-methoxyindole-2-carboxylic acid (XLVIII). Compound (XLVIII), on esterification with ethanolic sulphuric acid, furnished ethyl 6-methoxyindole-2-carboxylate (XLIX).

The ester (XLIX) was reduced with lithium aluminium hydride to get 6-methoxy-2-hydroxymethylindole (L), which on oxidation with activated manganese dioxide (method B) in dichloromethane at room temperature, furnished 6-methoxyindole-2-carboxaldehyde (LI) in 62% yield. The oxidation reaction was followed by t.l.c. and was found to take about 20-25 hours.

The UV absorption maxima of 6-methoxy-2-hydroxymethylindole (L) was observed at 225, 269 and 295 millimicrons, and the IR spectrum showed strong bands at 3425 cm\(^{-1}\) and 3289 cm\(^{-1}\) (OH/NH). 6-Methoxyindole-2-carboxaldehyde (LI) exhibited a strong IR absorption band at 3279 cm\(^{-1}\) (NH) and another strong band at 1613 cm\(^{-1}\) (CHO).
VI. 5-Ethoxyindole-2-carboxaldehyde, 5-ethoxy-2-(2-aminoethyl)indole and 5-ethoxy-2-(2-aminopropyl)indole

Ethyl 5-ethoxyindole-2-carboxylate (LIV), required as the starting material for the synthesis of the title compounds, was prepared according to the procedure described by Rydon and Siddappa\(^\text{19}\) (Chart X). Ethyl pyruvate p-ethoxyphenylhydrazone (LIII) was obtained by reacting p-ethoxybenzenediazonium chloride (LII) with ethyl \(\alpha\)-methylacetoacetate (II), following the procedure of Japp-Klingemann reaction.\(^\text{7b}\) Compound (LIII), cyclised in ethanolic sulphuric acid, to yield ethyl 5-ethoxyindole-2-carboxylate (LIV).

The ester (LIV) reacted with hydrazine to yield 5-ethoxyindole-2-carbohydrazide (LV). This, on tosylation gave 5-ethoxy-2-toluene-p-sulphon-hydrazido-carbonylindole (LVI). Compound (LVI), on decomposition with anhydrous sodium carbonate in ethylene glycol at elevated temperature, furnished 5-ethoxyindole-2-carboxaldehyde (LVIII). The aldehyde contained large quantities of impurities which were removed by repeated chromatographic separation on alumina (43% yield).
Chart I

LII + CH₃ CO CH₃ COOEt \[\xrightarrow{\text{Japp-Klingemann}}\] LIII

\[\xrightarrow{\text{EtOH/H}_2\text{SO}_4}\] LIV

\[\xrightarrow{\text{H}_2\text{N NH}_2}\] LV

\[\xrightarrow{\text{H}_3\text{C- SO}_2\text{Cl}}\] LVI

\[\xrightarrow{\text{LiRIH}_4}\] LVII

\[\xrightarrow{\text{Na}_2\text{CO}_3/\text{Ethylene-glycol}}\] LVIII

\[\xrightarrow{\text{Activated MnO}_2}\] LVIII
FIG. 2 ABSORPTION SPECTRA

- 5-ETHOXY-2-HYDROXYMETHYLINDOLE
- 7-ETHOXY-2-HYDROXYMETHYLINDOLE
With the aim of getting pure aldehyde in improved yield, the alternative method (method B) was attempted (Chart X). Ethyl 5-ethoxyindole-2-carboxylate (LIV) was subjected to lithium aluminium hydride reduction in dry ether at room temperature, to get 5-ethoxy-2-hydroxymethylindole (LVII), in 85% yield. Compound (LVII), on oxidation with activated manganese dioxide in dichloromethane at room temperature, furnished 5-ethoxyindole-2-carboxaldehyde (LVIII), in 61% yield. The oxidation reaction was followed by t.l.c. and was found to take about 20-25 hours. The aldehyde obtained by both these methods was found to be identical in no depression in mixed m.p. and identical t.l.c. behaviour.

5-Ethoxy-2-hydroxymethylindole (LVII) showed UV maxima at 227 and 273 millimicrons, and a strong IR absorption band at 3226 cm\(^{-1}\) (OH/NH). 5-Ethoxyindole-2-carboxaldehyde (LVIII) exhibited two strong IR absorption bands, one at 3311 cm\(^{-1}\) due to N-H stretching vibration of the indole nucleus and the other at 1639 cm\(^{-1}\) characteristic of carbonyl stretching vibration of the aldehyde.
The aldehyde (LVIII) readily condensed with nitromethane in presence of catalytic amount of ammonium acetate to give 5-ethoxy-2-(2-nitrovinyl)indole (LIX) in 75% yield. This, on reduction with lithium aluminium hydride, yielded the desired 5-ethoxy-2-(2-aminoethyl)indole (LX), and was

**Chart XI**

characterised by preparing its benzoyle derivative.
Similarly, the aldehyde (LVIII) condensed with nitroethane in presence of catalytic amount of benzylamine, to give 5-ethoxy-2-(2-nitropropenyl)-indole (LXI), which on reduction with lithium aluminium hydride, furnished the required 5-ethoxy-2-(2-amino-propyl)indole (LXII) in good yield (78%).

VII. Synthesis of 5-ethoxy-3-methylindole-2-carboxaldehyde, 5-ethoxy-3-methyl-2-(2-aminoethyl)indole and 5-ethoxy-3-methyl-2-(2-aminoethyl)indole

The present reported synthesis of 5-ethoxy-3-methylindole-2-carboxaldehyde required ethyl 5-ethoxy-3-methylindole-2-carboxylate (LXIV) as the starting material, and was conveniently prepared by Fischer Indole synthesis, following the literature method20 (Chart XII).

p-Ethoxybensenediazonium chloride (LII) reacted with ethyl α-ethylacetoacetate (XIII), according to Japp-Klingemann reaction,7b to yield ethyl α-ketobutyrate p-ethoxyphenylhydrazone (LXIII). This, on cyclisation with ethanolic sulphuric acid, gave ethyl 5-ethoxy-3-methylindole-2-carboxylate (LXIV).
Chart XII

LII + CH₃ CO CH COOEt \xrightarrow{\text{Jopp-Klingemann}} \text{LXIII}

\text{EtOH/H}_2\text{SO}_4

\text{LXV}

\text{H}_2\text{N NH}_2

\text{LXIV}

\text{H}_3\text{C- SO}_2\text{Cl}

\text{LXVI}

\text{LiAlH}_4

\text{LXVII}

\text{Na}_2\text{CO}_3/\text{Ethylene glycol}

\text{LXVIII}

\text{Activated MnO}_2
FIG 3 ABSORPTION SPECTRA.
Compound (LXIV) reacted with hydrazine to yield the carbohydrazide (LXV) almost quantitatively. The carbohydrazide was tosylated to get 5-ethoxy-3-methyl-2-toluene-$p$-sulphonhydrazidocarbonylindole (LXVI), which on decomposition with anhydrous sodium carbonate in ethylene glycol at elevated temperature, furnished 5-ethoxy-3-methylindole-2-carboxaldehyde (LXVIII). The aldehyde thus obtained was found to contain large quantities of impurities, and hence, required repeated chromatographic separation on alumina (49% yield).

As the purification of the aldehyde obtained by the above procedure (method A) was cumbersome, it was thought to prepare the aldehyde by the alternative method (method B). Ethyl-5-ethoxy-3-methylindole-2-carboxylate (LXIV) was reduced with lithium aluminium hydride in dry ether at room temperature, to get 5-ethoxy-3-methyl-2-hydroxymethylindole (LXVII) in good yield. Compound (LXVII) was then oxidised with activated manganese dioxide in dichloromethane at room temperature to get 5-ethoxy-3-methylindole-2-carboxaldehyde (LXVIII). The aldehyde was obtained in a purer form with a higher yield (70%). The oxidation reaction was followed by t.l.c., and was
found to take about 20-25 hours. The aldehyde obtained by both these methods was found to be identical (no depression in mixed m.p. and identical t.l.c. behaviour).

The UV absorption maxima for 5-ethoxy-3-methyl-2-hydroxymethylindole (LXVII) was observed at 229 and 279 millimicrons, and the IR spectrum showed a strong band at 3333 cm$^{-1}$ and 3185 cm$^{-1}$ (OH/NH). 5-Ethoxy-3-methylindole-2-carboxaldehyde (LXVIII) showed a strong absorption band at 3311 cm$^{-1}$ due to indole N-H stretching vibration and another strong band at 1616 cm$^{-1}$ characteristic of C = O stretching vibration of the aldehydic group.

The aldehyde (LXVIII) readily condensed with nitromethane in presence of ammonium acetate to yield 5-ethoxy-3-methyl-2-(2-nitrovinyl)indole (LXIX), which on reduction with lithium aluminium hydride, gave the required 5-ethoxy-3-methyl-2-(2-aminoethyl) indole (LXX), in 73% yield. Similarly, condensation of the aldehyde with nitroethane in presence of catalytic amount of benzylamine, yielded 5-ethoxy-3-methyl-2-(2-nitropropenyl)indole (LXXI). This, on lithium aluminium hydride reduction, afforded
5-ethoxy-3-methyl-2-(2-aminopropyl)indole (LXXII) in good yield.

Chart XIII

VIII. Synthesis of 7-ethoxyindole-2-carboxaldehyde and 7-ethoxy-2-(2-aminoethyl)indole

The synthesis of the title compounds required
ethyl 7-ethoxyindole-2-carboxylate (LXXIV) as the starting material, and was prepared according to the unambiguous Reissert method\(^\text{16}\) (Chart XIV).

\(\text{m-Cresol was subjected to disulphonation, nitration and hydrolysis, to get 2-nitro-3-hydroxytoluene (XXIV).}\)\(^\text{17}\) Compound (XXIV) was ethylated using diethyl sulphate and aqueous sodium hydroxide, to yield 2-nitro-3-ethoxytoluene (LXXXIII). This readily condensed with ethyl oxalate to give 2-nitro3-ethoxyphenylpyruvic acid (LXXXIV). The phenylpyruvic acid (LXXXIV), on reduction with ferrous sulphate and ammonia, furnished 7-ethoxyindole-2-carboxylic acid (LXXV), which was then esterified using ethanolic sulphuric acid, to get ethyl 7-ethoxyindole-2-carboxylate (LXXXVI).

The ester (LXXXVI) on lithium aluminium hydride reduction, furnished 7-ethoxy-2-hydroxymethylindole (LXXXVII). Compound (LXXXVII) was conveniently oxidised with activated manganese dioxide in dichloromethane at room temperature, to get 7-ethoxyindole-2-carboxaldehyde (LXXXVIII) in a purer form (63% yield). The oxidation reaction was followed by t.l.c. and was found to take about 20-25 hours.
7-Ethoxy-2-hydroxymethylindole (LXXVII) showed UV maxima at 226 and 263 millimicrons, and IR exhibited strong bands at 3448 cm\(^{-1}\) and 3236 cm\(^{-1}\) (OH/NH). 7-Ethoxyindole-2-carboxaldehyde (LXXVIII) showed UV maxima at 246 and 317 millimicrons, and IR exhibited a strong band at 3215 cm\(^{-1}\) characteristic of N-H stretching vibration of indole nucleus and another strong band at 1656 cm\(^{-1}\) due to O = O stretching vibration of aldehydic group.

The aldehyde (LXXVIII) readily condensed with nitromethane in presence of catalytic amount of ammonium acetate to yield 7-ethoxy-2-(2-nitrovinyl)-indole (LXXIX), which on subsequent reduction with lithium aluminium hydride, furnished the required 7-ethoxy-2-(2-aminomethyl)indole (LXXX) in good yield.

Recently, Zherebchenko and co-workers\(^{21}\) studied the relation between the structure and radioprotective activity of methyl and halogen substituted tryptamines. Whittle and Young\(^{22}\) suggested that the substitution in aromatic ring of tryptamine, particularly in 5- and 6-positions, by halogen atom
might be expected to prevent the hydroxylation and conjugation — one of the metabolic pathways of tryptamines. Such a metabolic block should result in sustaining drug action. Further, introduction of halogen atom would also tend to increase the drug persistence by increasing the solubility of the compound in lipoid materials and fat deposits in the body. Some Bz-chloro substituted α-alkyl-tryptamines reported by the above workers were found to possess stimulant and anticonvulsant properties in rodents, and to produce behaviour changes in cats. More recently, some Bz-halo substituted 1-(3-aminopropyl)indoles, synthesised in our laboratory were also found to be more potent serotonin antagonists than BAS.

Considering these facts, it seemed logical that the synthesis and study of the biological activity of Bz-halo substituted 2-(2-aminoethyl)- and 2-(2-aminopropyl)indoles would be of considerable interest. The present investigation aiming at the synthesis of Bz-halo and halo-methyl 2-(2-aminoethyl)- and 2-(2-aminopropyl)indoles, is presented in the following pages. The biological activity of these compounds was evaluated, and the details are dealt-with in a separate chapter.
IX. Synthesis of 4-chloroindole-2-carboxaldehyde, 4-chloro-2-(2-aminoethyl)indole and 4-chloro-2-(2-aminopropyl)indole

The first objective of the project was the synthesis of 4-chloro-2-(2-aminoethyl)- and 4-chloro-2-(2-aminopropyl)indoles.

The present reported synthesis of the above compounds required 4-chloroindole-2-carboxaldehyde as the intermediate. The aldehyde could be obtained in good yield with the Harley-Mason procedure.

The required starting material for the synthesis of the title compounds was ethyl 4-chloroindole-2-carboxylate (LXXXIV), which was prepared by the Reissert method, according to Uhle (Chart XV).

2-Nitro-6-chlorotoluene (LXXXI) was condensed with diethyl oxalate in presence of sodium ethoxide to get 2-nitro-6-chlorophenylpyruvic acid (LXXXII). This, on reduction with ferrous sulphate and ammonia, yielded 4-chloroindole-2-carboxylic acid (LXXXIII), which on esterification in ethanolic sulphuric acid, furnished ethyl 4-chloroindole-2-carboxylate (LXXXIV).
Compound (LXXXIV) was reduced with lithium aluminium hydride in dry ether at room temperature, to get 4-chloro-2-hydroxymethylindole (LXXXV), which on oxidation with activated manganese dioxide in dichloromethane at room temperature, afforded 4-chloroindole-2-carboxaldehyde (LXXXVI) in a purer form with high yield (76%). The oxidation reaction was
FIG 4 ABSORPTION SPECTRA
followed by t.l.c., and was found to take 15-20 hours.

The UV absorption maxima of 4-chloro-2-hydroxymethylindole (LXXXV) was observed at 227 and 279 millimicrons, and the IR spectrum showed a sharp band at 3535 cm$^{-1}$ and a strong band at 3260 cm$^{-1}$ (OH/NH). 4-Chloroindole-2-carboxaldehyde (LXXXVI) showed UV absorption maxima at 247 and 310 millimicrons and a medium IR absorption band at 3298 cm$^{-1}$ due to H-H stretching vibration of indole nucleus and another strong band at 1675 cm$^{-1}$ characteristic of C=O stretching vibration of aldehydic group.

The aldehyde (LXXXVI) condensed with nitromethane in presence of aqueous sodium hydroxide at 0$^\circ$. The resulting 4-chloro-2-(2-nitrovinyl)indole (LXXXVII) was subjected to lithium aluminium hydride reduction, to get the desired 4-chloro-2-(2-aminovinyl)indole (LXXXIX). Similarly, the aldehyde (LXXXVI) condensed with nitroethane in presence of catalytic amount of dibasic ammonium phosphate and acetic acid, to yield 4-chloro-2-(2-nitropropenyl)indole (LXXXVIII). This, on subsequent reduction with lithium aluminium
hydride, furnished 4-chloro-2-(2-aminopropyl)indole (XI) in good yield.

X. Synthesis of 5-chloroindole-2-carboxaldehyde, 5-chloro-2-(2-aminoethyl)indole and 5-chloro-2-(2-aminopropyl)indole

The synthesis of the title compounds needed ethyl 5-chloroindole-2-carboxylate (XIII) as the
starting material, and was conveniently prepared by Fischer cyclization, according to Rydon and Tweddel.24 (Chart XVIII).

**Chart XVIII**

Ethyl pyruvate p-chlorophenylhydrazone (XCVII) was prepared through Japp-Kingemann reaction7b from ethyl α-methylacetoacetate (II) and p-chlorobenzenediazonium chloride (XI). The hydrazone (XCVII) was then cyclised with polyphosphoric acid at 180°.
for 5 minutes, to get ethyl 5-chloroindole-2-carboxylate (XIII).

Compound (XIII) underwent smooth reduction with lithium aluminium hydride in dry ether at room temperature, to yield 5-chloro-2-hydroxy-methylindole (XIV) in 79% yield. This, on oxidation with activated manganese dioxide in dichloromethane at room temperature, furnished 5-chloroindole-2-carboxaldehyde (XV) in 78% yield. The oxidation reaction was followed by t.l.c., and was found to take about 15-20 hours.

5-Chloro-2-hydroxymethylindole (XIV) showed UV absorption maxima at 230 and 281 millimicrons, and the IR spectrum exhibited a sharp band at 3405 cm\(^{-1}\) and a broad band at 3320 cm\(^{-1}\) (OH/NH). 5-Chloroindole-2-carboxaldehyde (XV) showed UV maxima at 247 and 310 millimicrons, and a medium IR band at 3279 cm\(^{-1}\) due to indole N-H stretching vibration and another strong band at 1661 cm\(^{-1}\) characteristic of C = O stretching vibration of aldehydic group.

The aldehyde (XV) dissolved in methanol,
readily condensed with nitromethane in presence of aqueous sodium hydroxide at 0° or below, to give 5-chloro-2-(2-nitrovinyl)indole \((XCVI)\). The nitrovinylindole \((XCVI)\), on reduction with lithium aluminium hydride, furnished the required 5-chloro-2-(2-aminomethyl)indole \((XCVII)\), in a very good
yield (80%). The water soluble oxalate derivative was prepared for this compound.

Similarly, the aldehyde (XCV) condensed with nitroethane in presence of dibasic ammonium phosphate and acetic acid, to yield 5-chloro-2-(2-nitropropenyl)indole (XCVIII), which on reduction with lithium aluminium hydride, gave the desired 5-chloro-2-(2-aminopropyl)indole (XIX). The oxalate derivative was also prepared for this compound.

XI. Synthesis of 6-chloroindole-2-carboxaldehyde and 6-chloro-2-(2-aminopropyl)indole

The required starting material, ethyl 6-chloroindole-2-carboxylate (ClII), was prepared by the Beissert method, according to Rydon and Twedle²⁴ (Chart XX).

2-Nitro-4-chlorotoluene (0) was reacted with diethyl oxalate in presence of sodium ethoxide, to get 2-nitro-4-chlorophenylpyruvic acid (0I). This, on reduction with ferrous sulphate and ammonia, underwent reductive cyclisation, to
give 6-chloroindole-2-carboxylic acid (CII), which on esterification with ethanolic sulphuric acid, yielded ethyl 6-chloroindole-2-carboxylate (CIII).
FIG 19 ABSORPTION
Ethyl 6-chloroindole-2-carboxylate (OIII) was reduced with lithium aluminium hydride in dry ether at room temperature to get 6-chloro-2-hydroxymethylindole (OIV). On oxidation with activated manganese dioxide, compound (OIV) furnished 6-chloroindole-2-carboxaldehyde (OV) in 71% yield. The oxidation reaction was followed by t.l.c., and was found to take about 15-20 hours.

The IR spectrum of 6-chloro-2-hydroxymethylindole (OIV) showed a sharp band at 3390 cm\(^{-1}\) and broad bands at 3150 cm\(^{-1}\) and 3100 cm\(^{-1}\) (OH/NH). 6-Chloroindole-2-carboxaldehyde (OV) showed UV maxima at 245 and 317 millimicrons, and a medium IR absorption band at 3175 cm\(^{-1}\) due to indole N-H stretching vibration and another strong band at 1667 cm\(^{-1}\) characteristic of C = O stretching vibration of aldehydic group.

Nitromethane condensed with methanolic solution of the aldehyde (OV) in presence of sodium hydroxide at 0\(^{\circ}\) or below, to yield 6-chloro-2-(2-nitrovinyl)indole (OVI), which on reduction with lithium aluminium hydride, furnished the desired 6-chloro-2-(2-aminoethyl)indole (OVII) in good
yield (80%). This compound was converted to the water soluble oxalate derivative.

XII. Synthesis of 7-chloroindole-2-carboxaldehyde, 7-chloro-2-(2-aminoethyl)indole and 7-chloro-2-(2-aminopropyl)indole

Synthesis of the title compounds required ethyl 7-chloroindole-2-carboxylate (OX) as the starting material, and was conveniently prepared according to the literature method\textsuperscript{24} (Chart XXI).

\begin{center}
\textbf{Chart XXI}
\end{center}
o-Chlorobenzenediazonium chloride (CVIII) was coupled with ethyl α-methylacetooacetate (II), to get ethyl pyruvate o-chlorophenylhydrazone (OIX). The phenylhydrazone thus obtained was cyclised with polyphosphoric acid at 190° for 5 minutes, to get ethyl 7-chloroindole-2-carboxylate (OX).

Compound (OX) underwent smooth reduction with lithium aluminium hydride in dry ether at room temperature, yielding 7-chloro-2-hydroxymethylindole (OXI). The hydroxymethylindole was dissolved in dichloromethane, and was subjected to activated manganese dioxide oxidation at room temperature, to get 7-chloroindole-2-carboxaldehyde (OXII) in 71% yield. The oxidation reaction was followed by t.l.c., and was found to take about 10-15 hours.

7-Chloro-2-hydroxymethylindole (OXI) showed UV maxima at 230 and 273 millimicrons, and IR exhibited a medium strong band at 3340 cm⁻¹ (OH/CH). 7-Chloroindole-2-carboxaldehyde (OXII) showed UV absorption maxima at 245 and 305 millimicrons, and IR spectrum exhibited a medium strong band at 3289 cm⁻¹ due to indole N-H stretching vibration and another strong band at 1672 cm⁻¹ characteristic of C = O.
stretching vibration of aldehydic group.

The aldehyde (OXII) condensed with nitromethane in methanol in presence of aqueous sodium hydroxide at 0°, to yield 7-chloro-2-(2-nitrovinyl)indole (OXIII), which on lithium aluminium hydride reduction* furnished the required 7-chloro-2-(2-aminovinyl)indole (OXIV). A stable oxalate
derivative was prepared for this compound. Similarly, condensation of the aldehyde (GXII) with nitroethane in presence of dibasic ammonium phosphate and acetic acid, gave 7-chloro-2-(2-nitropropenyl)indole (CXV) in good yield. This, on reduction with lithium aluminium hydride yielded the desired 7-chloro-2-(2-aminopropyl)indole (CXVI). The oxalate derivative was also prepared for this compound.

XIII. Synthesis of 5-bromoindole-2-carboxaldehyde, 5-bromo-2-(2-aminoethyl)indole and 5-bromo-2-(2-aminopropyl)indole

After the synthesis of all four Bz-chloro substituted indole-2-carboxaldehydes, 2-(2-aminoethyl)- and 2-(2-aminopropyl)indoles, the synthesis of the Bz-bromo analogues was undertaken.

The title compounds required ethyl 5-bromoindole-2-carboxylate (CXIV) as the starting material, and was conveniently prepared by Fischer cyclization according to Cavallini and Revanna25 (Chart XXIII).
p-Bromobenzenediazonium chloride (CXVII) was reacted with ethyl \( \alpha \)-methylacetoacetate, to get ethyl pyruvate p-bromophenylhydrazone (CXVIII), by a Japp-Klingemann reaction. The hydrazone obtained was cyclised with polyphosphoric acid at
FIG 21  ABSORPTION SPECTRA.

(I) 5-Bromoindole-2-carboxaldehyde
(II) 7-Chloroindole-2-carboxaldehyde
(III) 5-Chloro-7-methylindole 2-carboxaldehyde
180° for 5 minutes, to get ethyl 5-bromoindole-2-carboxylate (CXIV).

Compound (CXIV), when reduced with lithium aluminium hydride, yielded 5-bromo-2-hydroxymethylindole (CXV). The hydroxymethylindole (CXV) was then oxidised with activated manganese dioxide in dichloromethane at room temperature, to get 5-bromoindole-2-carboxaldehyde (CXVI), in 70% yield. The oxidation reaction was followed by t.l.c., and was found to take about 10-15 hours.

The UV absorption maxima for 5-bromo-2-hydroxymethylindole (CXV) was observed at 227 and 284 millimicrons, and IR spectrum showed a sharp band at 3418 cm⁻¹ and a broad band at 3320 cm⁻¹ (OH/NH). 5-Bromoindole-2-carboxaldehyde (CXVI) showed UV maxima at 246 and 311 millimicrons and IR spectrum exhibited a medium strong band at 3290 cm⁻¹ due to N-H stretching vibration of indole nucleus and another strong band at 1660 cm⁻¹ characteristic of C = O stretching vibration of aldehydic group.

The aldehyde (CXVI) condensed with nitromethane in methanol in presence of aqueous sodium
hydroxide at 0° or below, to give 5-bromo-2-(2-nitrovinyl)indole (CXVII), which upon lithium aluminium hydride reduction, furnished the required

\[ \text{Chart XXIV} \]

\[ \text{Br} \]

\[ \begin{array}{c}
\text{CH}_3\text{NO}_2 \\
\rightarrow \\
\text{CH} = \text{CH} \cdot \text{NO}_2 \\
\text{CXVII}' \\
\downarrow \\
\text{Br} \\
\text{CXVIII}' \\
\end{array} \]

\[ \text{CXVI} \]

\[ \begin{array}{c}
\text{CH}_3\text{NO}_2 \\
\rightarrow \\
\text{CH} = \text{C} \cdot \text{NO}_2 \\
\text{CXIX} \\
\downarrow \\
\text{CXX} \\
\end{array} \]

\[ \text{LiAlH}_4 \]

5-bromo-2-(2-aminomethyl)indole (CXVIII). This, gave the oxalate derivative. Similarly, the aldehyde (CXVI), on condensation with nitroethane in presence
of dibasic ammonium phosphate and acetic acid yielded 5-bromo-2-(2-nitropropenyl)indole (OXX). The nitropropenylindole, on reduction with lithium aluminium hydride furnished 5-bromo-2-(2-aminopropyl) indole (OXX). Its oxalate derivative was also prepared.

XIV. Synthesis of 7-bromoindole-2-carboxaldehyde, 7-bromo-2-(2-aminomethyl)indole and 7-bromo-2-(2-aminopropyl)indole

The present synthesis of the title compounds required ethyl 7-bromoindole-2-carboxylate (OXXXII) as the starting material. It was conveniently prepared, following the method of Pappalardo and Vitali

Ethyl pyruvate α-bromophenylhydrazone (OXXXIII) was prepared by a Japp-Klingemann reaction, from ethyl α-methylacetooacetate (II) and α-bromo-benzenedisodium chloride (OXXI). The hydrazone was then cyclised with polyphosphoric acid at 170° for 5 minutes, to obtain ethyl 7-bromoindole-2-carboxylate (OXXXIII).
Chart XXV

Ethyl 7-bromoindole-2-carboxylate (CXXIII) was reduced with lithium aluminium hydride in dry ether at room temperature, to get 7-bromo-2-hydroxymethylindole (CXXIV), in 70% yield. It was then oxidised with activated manganese dioxide, to get 7-bromoindole-2-carboxaldehyde (CXXV) in 60% yield. The oxidation reaction was followed by t.l.c.,
and was found to take about 12-15 hours.

7-Bromoindole-2-carboxaldehyde (CXXV) showed UV absorption maxima at 247 and 307 millimicrons, and IR spectrum exhibited a strong band at 3228 cm\(^{-1}\) due to indole-N-H stretching vibration and another strong band at 1675 cm\(^{-1}\) characteristic of C=O stretching vibration of aldehydic group.

**Chart XXVI**

```
CH\(_3\)NO\(_2\)

\[\text{CXXV} \rightarrow \begin{array}{c}
\text{CXXVI} \\
\text{CXXVII} \\
\text{CXXVIII} \\
\text{CXXIX}
\end{array}\]
```

---

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FIG 20 ABSORPTION SPECTRA

(1) 7-Bromo-2-(2-nitropropenyl) indole
(II) 5-Methyl-7-bromo-2-(2-nitropropenyl) indole
(III) 5-Chloro-7-methyl-2-(2-nitropropenyl) indole

$\varepsilon$ vs. $\log c$
The methanolic solution of the aldehyde (CXXV) condensed with nitromethane in presence of aqueous sodium hydroxide (50%), at 0°, to yield 7-bromo-2-(2-nitrovinyl)indole (CXXVI). The nitrovinylindole (CXXVI) was conveniently reduced with lithium aluminium hydride to obtain the required 7-bromo-2-(2-aminoethyl)indole (CXXVII). Its oxalate derivative was prepared. Similarly, condensation of the aldehyde (CXXV) with nitroethane in presence of dibasic ammonium phosphate and acetic acid, gave 7-bromo-2-(2-nitropropenyl)indole (CXXVIII), which on subsequent reduction with lithium aluminium hydride, furnished the desired 7-bromo-2-(2-amino propyl)-indole (CXXIX). The oxalate derivative was prepared for this compound.

Recently, Ambekar and Siddappa27 synthesised several Bz-methyl and halo substituted 3-(3-aminoethyl)-indoles and their N-substituted derivatives. Those tryptamines showed inhibition to serotonin contractile action in a wide range of concentrations. The most active drug of the series was 5-chloro-7-N,N-trimethyl-tryptamine, causing 50% inhibition to serotonin action in as low a concentration as 0.7 μg./ml.276
Encouraged by these results, it was desirable to prepare some 2-halo and methyl substituted 2-(2-aminoethyl)- and 2-(2-aminopropyl)-indoles for the evaluation of their antiserotonin activity. Therefore, under the present scheme, the synthesis of 5-methyl-7-chloro-2-(2-aminoethyl)- and 2-(2-aminopropyl)indoles, 5-chloro-6-methyl-2-(2-aminoethyl)- and 2-(2-aminopropyl)indoles, and 5-methyl-7-bromo-2-(2-aminoethyl)- and 2-(2-aminopropyl)-indoles were undertaken and their antiserotonin activity was evaluated.

XV. Synthesis of 5-methyl-7-chloroindole-2-carboxaldehyde, 5-methyl-7-chloro-2-(2-aminoethyl)indole and 5-methyl-7-chloro-2-(2-aminopropyl)indole

The synthesis of 5-methyl-7-chloroindole-2-carboxaldehyde required as the intermediate for the synthesis of the desired isotryptamines was first undertaken. The necessary starting material, ethyl 5-methyl-7-chloroindole-2-carboxylate (CXXXIV), was prepared by the Fischer method, according to Ambekar and Siddappa. 27a 2-Chloro-4-methylaniline (CXXXII) was obtained by the chlorination of p-acetamido-
toluene and subsequent hydrolysis$^{28}$ (Chart XXVII).

**Chart XXVII**

CXXX
\[ \text{Acetylation} \]
\[ \text{Chlorination} \]

CXXXI

Hydrolysis

CXXXII

Japp-Klingemann

CXXXIII

PPA

CXXXIV

L$_2$AIH$_4$

CXXXV

Activated
MnO$_2$

CXXXVI
FIG 5 ABSORPTION SPECTRUM

--- 5-METHYL-7-BROMO-2-HYDROXYMETHYL-DC ---
--- 5-METHYL-7-CHLORO-2-HYDROXYMETHYL-DC ---
--- 5-CHLORO-7-METHYL-2-HYDROXYMETHYL-DC ---
Ethyl puruvate 2-chloro-4-methylphenylhydrazone (OXXXIII) was readily obtained by subjecting 2-chloro-4-methylaniline to a Japp-Klingemann reaction with ethyl \( \alpha \)-methylacetooacetate. The hydrazone (OXXXIII) was then cyclised with polyphosphoric acid at 90° for 10 minutes, to get ethyl 5-methyl-7-chloroindole-2-carboxylate (OXXXIV).

Compound (OXXXIV) was conveniently reduced with lithium aluminium hydride in dry ether, at room temperature, to get 5-methyl-7-chloro-2-hydroxymethylindole (OXXXV). This compound was then oxidised with activated manganese dioxide in dichloromethane, to obtain 5-methyl-7-chloroindole-2-carboxaldehyde (OXXXVI), in 66% yield. The oxidation reaction was followed by t.l.c., and was found to take about 12-15 hours.

The UV absorption maxima for 5-methyl-7-chloro-2-hydroxymethylindole (OXXXV) was observed at 226 and 276 millimicrons, and IR exhibited a sharp band at 3448 cm\(^{-1}\) and a broad band at 3318 cm\(^{-1}\) (OH/NH). 5-Methyl-7-chloroindole-2-carboxaldehyde (OXXXVI) showed UV maxima at 248 and 309 millimicrons.
and IR spectrum exhibited a strong band at 3318 cm\(^{-1}\) due to N-H stretching vibration of indole nucleus and another strong band at 1665 cm\(^{-1}\) characteristic of C = O stretching vibration of aldehydic group.

The aldehyde (CXXXVI) dissolved in methanol, readily condensed with nitromethane in presence of aqueous sodium hydroxide at 0\(^{\circ}\), to yield 5-methyl-7-chloro-2-(2-nitrovinyl)indole (CXXXVII). This on reduction with lithium aluminium hydride, furnished 5-methyl-7-chloro-2-(2-aminomethyl)indole (CXXXVIII). The oxalate derivative for this compound was prepared. Similarly, condensation of the aldehyde (CXXXVI) with nitroethane in presence of dibasic ammonium phosphate and acetic acid, yielded 5-methyl-7-chloro-2-(2-nitropropenyl)indole (CXXXIX), which on lithium aluminium hydride reduction, gave the required 5-methyl-7-chloro-2-(2-aminopropyl)indole (CXL) in good yield. The oxalate derivative of this compound was also prepared. The steps involved in the synthesis of these compounds are given (Chart XXVIII).
XVI. Synthesis of 5-chloro-7-methylindole-2-carboxaldehyde, 5-chloro-7-methyl-2-(2-aminoethyl)indole and 5-chloro-7-methyl-2-(2-aminopropyl)indole

The required starting material for the synthesis of the title compounds was ethyl 5-chloro-
7-methylindole-2-carboxylate (OXLV). 2-Methyl-4-chloroaniline, needed for the synthesis of ethyl 5-chloro-7-methylindole-2-carboxylate was prepared from o-toluidine (CXL) by acetylation, chlorination and hydrolysis, following the procedure of Kaufmann. From this aniline, ethyl 5-chloro-7-methylindole-2-carboxylate (OXLV) was prepared by the Fischer cyclisation, following the procedure described by Ambekar and Siddappa27b (Chart XXIX).

Ethyl pyruvate 2-methyl-4-chlorophenyl-hydrazone (CXLIV) was synthesised by a Japp-Klingemann7n reaction from ethyl α-methylacetoacetate and 2-methyl-4-chlorobenzene diazonium chloride. The hydrazone (CXLIV) was cyclised with polyphosphoric acid at 95° for 30 minutes, to obtain ethyl 5-chloro-7-methylindole-2-carboxylate (OXLV).

Compound (OXLV), on mild reduction with lithium aluminium hydride, gave 5-chloro-7-methyl-2-hydroxymethylindole (CXLVI). This, on oxidation with activated manganese dioxide, yielded 5-chloro-7-methylindole-2-carboxaldehyde (CXLVII) in 67% yield. The oxidation reaction was followed by t.l.c.
5-Chloro-7-methyl-2-hydroxymethylindole (CXLVI) showed UV maxima at 228 and 274 millimicrons. 5-Chloro-7-methylindole-2-carboxaldehyde (CXLVII) showed UV maxima at 248 and 311 millimicrons, and IR spectrum exhibited a strong band at 3348 cm⁻¹ due
to N–H stretching vibration of indole nucleus and another strong band at 1675 cm\(^{-1}\) characteristic of C = O stretching vibration of aldehydic group.

The aldehyde (OXLVII) reacted with nitromethane in presence of aqueous sodium hydroxide (50%) at 0\(^{\circ}\), to yield 5-chloro-7-methyl-2-(2-nitrovinyl)-indole (OXLVIII), which on reduction with lithium aluminium hydride, furnished the desired 5-chloro-7-methyl-2-(2-aminoethyl)indole (OXLIX) in 85% yield. The stable oxalate derivative was prepared for this compound. Similarly, nitroethane condensed with the aldehyde (OXLVII) in presence of ammonium phosphate and glacial acetic acid, to yield 5-chloro-7-methyl-2-(2-nitropropenyl)indole (OL), which on reduction with lithium aluminium hydride, gave the required 5-chloro-7-methyl-2-(2-aminopropyl)indole (OLI) in 73% yield. Its oxalate derivative was prepared. The steps involved in the synthesis are given (Chart XXX).
XVII. Synthesis of 5-methyl-7-bromoindole-2-carboxaldehyde, 5-methyl-7-bromo-2-(2-aminoethyl)indole, and 5-methyl-7-bromo-2-(2-aminopropyl)indole

Ethyl 5-methyl-7-bromoindole-2-carboxylate

(CLV), required as the starting material for the
synthesis of the desired compounds, was prepared from 2-bromo-4-methylaniline (GLIII). The aniline (OLIXI) was obtained from p-toluidine (OXXX) by acetylation, bromination and subsequent hydrolysis, according to the procedure given by Johnson and Saundbern. Ethyl 5-methyl-7-bromoindole-2-

**Chart XXXI**

\[
\begin{align*}
\text{CXXX} & \xrightarrow{1) \text{Acetylation}} \text{CLII} & \xrightarrow{2) \text{Bromination}} \text{CLIII} & \xrightarrow{\text{Hydrolysis}} \text{CLV} & \xrightarrow{\text{LiNH}_2} \text{CLVI} \\
\text{CLV} & \xrightarrow{\text{P P R}} \text{CLIV} & \xrightarrow{\text{Activated MnO}_2} \text{CLVII}
\end{align*}
\]
carboxylate (OLV) was then prepared by the Fischer cyclisation, following the procedure described by Ambekar and Siddappa.\textsuperscript{27b}

2-Bromo-4-methylbenzenediazonium chloride was reacted with ethyl α-methylacetoacetate (II) by a Japp-Klingemann reaction,\textsuperscript{7b} to get ethyl pyravato 2-bromo-4-methylphenylhydrazone (OLIV). The hydrazone (OLIV), on cyclisation with polyphosphoric acid at 95° for 30 minutes, gave ethyl 5-methyl-7-bromoindole-2-carboxylate (OLV).

Compound (OLV) was reduced with lithium aluminium hydride in dry ether at room temperature, to get 5-methyl-7-bromo-2-hydroxymethylindole (OLVI) in 75\% yield. It was then subjected to manganese dioxide oxidation in dichloromethane, to yield 5-methyl-7-bromoindole-2-carboxaldehyde (OLVII) in 63\% yield. The oxidation reaction was followed by t.l.c., and was found to take about 15-20 hours.

The UV absorption maxima for 5-methyl-7-bromo-2-hydroxymethylindole (OLVI) was observed at 225 and 275 millimicrons, and IR exhibited a sharp band at 3438 cm\(^{-1}\) and a broad band at 3320 cm\(^{-1}\) (OH/\text{N-H}).
5-Methyl-7-bromoindole-2-carboxaldehyde (OLVII) showed UV absorption maxima at 246 and 309 millimicrons, and IR spectrum exhibited a medium strong band at 3330 cm\(^{-1}\) due to N-H stretching vibration of indole nucleus and another strong band at 1675 cm\(^{-1}\) characteristic of C = O stretching vibration of aldehydic group.

The aldehyde (OLVII) condensed with nitromethane in presence of aqueous sodium hydroxide at 0\(^{\circ}\), to yield 5-methyl-7-bromo-2-(2-nitrovinyl)indole (OLVIII), which on reduction with lithium aluminium hydride, furnished the required 5-methyl-7-bromo-2-(2-aminoethyl)indole (OLIX) in 61% yield. Its oxalate derivative was prepared for screening purpose. Similarly, nitroethane condensed with the aldehyde (OLVII), in presence of ammonium acetate and glacial acetic acid, to yield 5-methyl-7-bromo-2-(2-nitropropenyl)indole (OLX). This, on reduction with lithium aluminium hydride, gave the desired 5-methyl-7-bromo-2-(2-aminopropyl)indole (OLXI) in good yield. Its oxalate derivative was prepared.
Chart XXXII

\[
\begin{align*}
\text{CLVII} & \quad \text{CH}_3\text{NO}_2 \\
\text{CLVIII} & \quad \text{CH}_3\text{CHO} \\
\text{CLIX} & \quad \text{CH}_2\text{CH}_2\text{NH}_2 \\
\text{CLXI} & \quad \text{CH}_3\text{NH}_2
\end{align*}
\]
THEORETICAL PART II

SYNTHESIS OF 3,4-DIHYDRO-5H-PYRIDO[4,3-b]INDOLES
AND 3,4-DIHYDROPYRIMIDO[3,4-g]INDOLES
As the carboline ring system forms the major structural unit of several Rauwolfia and related alkaloids, a large number of research workers have evinced active interest in the synthesis and study of the biological activity of these compounds. Among the four types of carboline ring systems, the $\tau$-carboline system gained increasing interest during the last decade as a source of biologically active compounds.

Some $\text{N}_2$-quaternary salts of $\tau$-carbolines reported in the literature have been found to possess potential curarising effect. Horlein and co-workers have synthesised some 5-alkyl-, substituted alkyl-, aryl alkyl- and aryl-$\tau$-carbolines. Out of these several $\tau$-carboline derivatives, 2-methyl-5-benzyl-1,2,3,4-tetrahydro-$\tau$-carboline was found to exhibit prolonged antihistaminic activity with little sedative effect in man. Spicke showed that 2-methyl-1,2,3,4-tetrahydro-$\tau$-carboline and the 8-bromo derivative blocked the conditional avoidance response in rats. Several $\tau$-carboline derivatives synthesised by Pawel and co-workers were tested for monoamine oxidase inhibition in rat brain mitochondria in vitro. Experiments with guinea pigs revealed that some tetrahydro-$\tau$-carboline
derivatives when fed to the animal (1 mg./kg.), prevented their death even after giving several lethal doses of histamine. It was postulated that this activity was related either to a high catalytic activity of carboline relative to the break down of histamine, or to a competition for a receptor site. Several 1,2,3,4-tetrahydro-\( \alpha \)-carboline derivatives have also been shown to possess anticoagulant, analgesic and antidepressant effects.

Recently, Cohen and co-workers\(^\text{39}\) reported the synthesis of several 2,3,4,5-tetrahydro-1H-prido[4,3-b]indoles and evaluated their antiserotonin activity \textit{in vitro} on isolated rat uterus and colon. The halogen substituted, \( N \)-alkyl derivatives of such tetrahydro-\( \alpha \)-carbolines showed high degree of anti-serotonin activity.

Considering the pronounced biological activity of these tetrahydro-\( \alpha \)-carboline derivatives, it seemed of interest to prepare some dihydro-\( \alpha \)-carboline derivatives for the assessment of their biological activity. The synthesis of these dihydro-\( \alpha \)-carboline derivatives is discussed briefly in the following pages.
I. Synthesis of 6-chloro-1-phenyl-3,4-dihydro-
\[\text{\textalpha-carboline} \]

The Bischler-Napieralski reaction is one of the reactions widely used for the synthesis of several dihydro-\[\text{\textalpha-carboline} \] derivatives. Ashabina and Osada were the first to introduce this reaction for the synthesis of 3,4-dihydro-\[\text{\textalpha-carboline} \]. Spath and Lederer further developed this reaction. The reaction consists of cyclodehydration of an N-acyltryptamine derivatives by making use of phosphorous pentoxide, phosphorous oxychloride or polyphosphoric acid to obtain 3,4-dihydro-\[\text{\textalpha-carboline} \]. Recently, Kanaoka, Sato and Ban reported the use of a new cyclodehydrating agent viz., polyphosphate ester (PPE) in the Bischler-Napieralski reaction to obtain dihydro-\[\text{\textalpha-carboline} \] from tryptamine N-acyl derivatives.

During the present course of investigation polyphosphate ester (PPE) was used for the cyclodehydration of the benzoyl derivative of 7-chloro-2-(2-aminoethyl)indole to obtain 6-chloro-1-phenyl-3,4-dihydro-\[\text{\textalpha-carboline} \].

7-Chloro-2-(2-aminoethyl)indole (CXIV) required
as the starting material was conveniently prepared according to the procedure described earlier (cf. p. 120).

The 2-isotryptamine (CXIV) was reacted with benzoyl chloride to get benzoyl derivative (CLXII), which underwent the Bishler-Napieralski type cyclodehydration in presence of polyphosphate ester (PPE) to yield the required 6-chloro-1-phenyl-3,4-dihydro-\(\alpha\)-carboline (CLXIII) in 64% yield.

The dihydro-\(\alpha\)-carboline (CLXIII) showed UV absorption maxima at 227, 277, 317 and 384 millimicrons.
of N-H stretching vibration of the indole molecule.

II. Synthesis of 6-bromo-1-phenyl-3,4-dihydro-5H-pyrrolo[4,3-b]indole

Synthesis of the title compound required 7-bromo-2-(2-aminoethyl)indole (CXXVII) as the starting material and was conveniently obtained according to the procedure described earlier (cf. p. 123). The 2-isotryptamine (CXXVII) was reacted with benzoyl chloride to get the benzoyl derivative (CLXIV) which

![Chart XXXIV]

**Chart XXXIV**

\[
\text{CXXVII} \quad \text{C}_{6}H_{5} \text{CO Cl} \quad \text{Ar, NaOH} \quad \text{CLXIV}
\]

- \[
\text{CHCl}_{3} / \text{PPE}
\]

- \[
\text{CLXY}
\]
on cyclodehydration in presence of polyphosphate ester (PPE) gave the desired 6-bromo-1-phenyl-3,4-dihydro-r-carboline (CLXV) in 58% yield.

The 3,4-dihydro-r-carboline (CLXV) showed UV absorption maxima at 226, 280, 321 and 378 millimicrons (cf. fig. 17). The absorption curve was similar to that of the 6-chloro derivative (CLXIII), with slight variations in the absorption maxima (cf. fig. 17). Similarly, IR spectrum exhibited a medium strong band at 3180 cm⁻¹, characteristic of N-H stretching vibration of indole part of the molecule.

III. Synthesis of 8-methyl-6-bromo-1-phenyl-3,4-dihydro-r-carboline (8-Methyl-6-bromo-1-phenyl-3,4-dihydro-5H-pyrido[4,3-b]indole)

After the synthesis of 6-chloro- and 6-bromo-1-phenyl-3,4-dihydro-r-carbolines, the next object in the scheme was to introduce a methyl group on the benzenoid ring to obtain 8-methyl-6-bromo-1-phenyl-3,4-dihydro-r-carboline. This required 5-methyl-7-bromo-2-(2-aminoethyl)indole (CLIX) as the starting material. The 2-isotryptamine (CLIX) was reacted with benzoyl chloride to get the benzoyl derivative (CLXVI),
which underwent smooth cyclodehydration in presence of polyphosphate ester (PPE) to yield the required 8-methyl-6-bromo-1-phenyl-3,4-dihydro-α-carboline (CLXVII) in 58% yield.

The dihydro-α-carboline (CLXVII) showed UV absorption maxima at 226, 283, 328 and 379 millimicrons (cf. fig. 18). The UV absorption curve was similar to the absorption curves of the other two dihydro-α-carbollines described earlier (cf. fig. 17). The IR
absorption spectrum exhibited a medium strong bend at 3182 cm\(^{-1}\) due to N-H stretching vibration of the indole part of the molecule (cf. fig. 16b). The IR absorption spectra of both the compounds (Compound CLXIII and CLXVII) are compared (cf. fig. 16b).

IV. Synthesis of 10-bromo-2-phenyl-4,5-dihydroindole-
diazine (1:3): (7-Bromo-1-phenyl-3,4-dihydro
pyrimido\(^3,4-a\) indole)

The next object in the scheme was the synthesis of 8-bromo-1-phenyl-3,4-dihydro-\(\gamma\)-carboline (CLXIX). The required starting material 5-bromo-2-(2-aminoethyl)-indole (CXVIII) was obtained in good yield according to the procedure described earlier (cf. p. 144). The 2-\(\text{iso}\)-tryptamine (CXVIII) was reacted with benzoyl chloride to get the benzoyl derivative (CLXVIII). The Bischler-Napieralski cyclodehydration of this benzoyl derivative (CLXVII) in the presence of polyphosphate ester (PPE) gave an yellow solid with a high melting point (m.p. 226-227\(^0\)).

* The name "indolediazine" has been suggested for such type of compounds by Robinson and co-workers.\(^{13b}\)
The UV spectrum of the cyclised product showed absorption maxima at 223, 280, 325 and 373 millimicrons (cf. fig. 18). The UV absorption curve was similar to the absorption curves of other dihydro-alpha-carboline derivatives (cf. figs. 17 and 18). The IR spectrum of this compound was also taken. Surprisingly, the N-H absorption frequency was absent in the IR spectrum (cf. fig. 16a). Nevertheless, the elemental analysis of this compound was in full agreement with the presumed...
FIG. 22. NMR SPECTRUM

[Diagram of NMR spectrum with peaks labeled 2.29 to 3.15, 6.15, and 7.08]
dihydro-γ-carboline (CLXIX) structure. So, the only possibility to account for the absence of N-H absorption in the IR as well as for the correct analysis, was to assign structure (CLXX) to the compound, cyclisation taking place at position 1 of the indole nucleus. The assignment of this structure is fully supported by the NMR spectrum (cf. fig. 22) of this compound. The NMR spectrum (100 MHz) in deuterated dimethylsulphoxide taking tetramethylsilane as reference standard showed, as expected, two 1:2:1 triplets at \( \nu 7.08 \) and 6.15 respectively due to the two adjacent methylene protons present in the dihydropyrimidine ring, and the nine protons in the aromatic region from \( \nu 2.29 \) to 3.15.

Out of the nine aromatic protons, five are from the phenyl group attached to the dihydropyrimidine ring and the three from the benzene ring of the indole nucleus. Obviously, the ninth proton is the \( \beta \) -proton of the heterocyclic ring of indole, the location of which could not be traced due to its being shifted to downfield and being buried in the complex aromatic signals because of the polar solvent effect of the dimethylsulphoxide. Moreover, if the ninth proton were N-H, it would be in DMSO, have appeared far below \( -1.00 \) \( \nu \) - the fact which indeed is supported by the absence of N-H absorption band in IR.
FIG. 23. NMR SPECTRUM

\[
\begin{align*}
&\text{Cl} \quad \text{Ph} \\
\end{align*}
\]

\[\text{DMSO}\]

\[\text{TMS}\]

\[2.43 \quad 6.20 \quad 7.05\]

\[\text{2.30 to 3.38}\]
The coupling constants of the methylene protons threw more light on the position of this ninth proton. In addition to its coupling with the adjacent methylene group with a coupling constant of 8.00 Hz, the higher field methylene protons (at $\tau$ 7.08) were further split by a small coupling of 2.00 Hz indicating meta coupling with a $-\text{CH}$ proton. This observation could be correctly accounted for only by the free $\text{p}$-proton which is in meta relationship with the higher field methylene group of the dihydropyrimidine ring system (CLXX).

In order to accomplish the basis for the above arguments and to enunciate a complete discussion of the subject, the NMR of the above compound was compared with that of one of the dihydro-$\text{p}$-carbolines discussed earlier. The NMR of 6-chloro-1-phenyl-3,4-dihydro-$\text{p}$-carboline (CLXIII, cf. fig. 23), exhibited, as required, only the eight protons in the aromatic region ranging from $\tau$ 2.30 to 3.38 (unlike the nine protons as in the case of the NMR spectrum of compound described above [fig. 22]). The five protons present on the pyridine ring of the carboline system together appeared as a singlet ($\tau$ 2.43), accounting for a spacially occupied phenyl ring without any steric hindrance, confirming
FIG 24. NMR SPECTRUM

Ph
2.43

\[ \text{FIG 24. NMR SPECTRUM} \]
The cyclisation to have taken place at position 3 of the indole nucleus. Similarly, the NMR spectrum of 6-bromo-1-phenyl-3,4-dihydro-carboline (CLXV, fig. 24), also exhibited the presence of eight protons in the aromatic region ($\tau$ 2.32 to 3.45), five of which appeared as a sharp singlet at $\tau$ 2.43 and the remaining three protons ranged from $\tau$ 2.70 to 3.45, confirming once again, the cyclisation taking place at $\beta$ -position of the indole ring. Very recently, Cohen and Co-workers have reported the synthesis of some pyrimido[3,4-a]indoles, directly by the Fischer cyclisation of 1,3-disubstituted 4-piperidone phenylhydrazone or by the cyclisation of 2-isotryptamine derivatives heating with benzaldehyde. Our observations are in agreement with the discussions of the NMR spectra of dihydropyrimido-indoles reported by these authors.

V. Synthesis of 10-chloro-2-phenyl-4,5-dihydroindole-diazine (I:3)(7-Chloro-1-phenyl-3,4-dihydro pyrimido[3,4-a])

Synthesis of the title compound required 5-chloro-2-(2-aminoethyl)indole (XCVII) as the starting material. It was prepared conveniently according to the procedure described earlier (cf. p. 14). The
2-isotryptamine (XCVII) was reacted with benzoyl chloride to get the benzoyl derivative (CLXXI), which underwent cyclodehydration in presence of polyphosphate ester (PPE) to yield 7-chloro-1-phenyl-3,4-dihydropyrimido \[3,4-a\]indole (CLXXXIII) in 65% yield.

The UV absorption spectra of the dihydro pyrimido \[3,4-a\]indole (CLXXXIII) showed maxima at 225, 280, 329 and 370 millimicrons (cf. fig. 18). The
UV absorption curve of this compound was similar to those of the dihydro-$\pi$-cerbolines and the other 7-bromopyrimido-$\gamma$-$3,4$-a$\gamma$-indole (cf. figs. 17 and 18). The IR spectrum of the compound did not show N-H absorption band, further confirming the structure (CLXXIII) for the cyclised product.

VI. Synthesis of 9-chloro-2-phenyl-4,5-dihydro-endolediazine (1:3):(6-Chloro-1-phenyl-3,4-dihydropyrimido-$\gamma$-$3,4$-a$\gamma$-indole)

Synthesis of the title compound required 4-chloro-2-(2-aminoethyl)indole (LXXXIX) as the starting

Chart XXXVIII

![Chemical diagram]
material and was obtained in good yield by the procedure already described (cf. p. no). The 2-isotryptamine (LXXXIX) thus obtained was reacted with benzoyl chloride to get the benzoyl derivative (CLXXXIV) which upon the Bischof-Napiersalski cyclodehydration in presence of polyphosphate ester (PPE) gave 6-chloro-1-phenyl-3,4-dihydropyrimido[3,4-a]indole (CLXXVI) in 61% yield.

The dihydropyrimido[3,4-a]indole (CLXXVI) showed UV absorption maxima at 224, 279, 324 and 381 millimicrons (cf. fig. 17), similar to the dihydro-γ-carbolines and dihydropyrimidinoindoles (cf. figs. 17 and 18). Such similarity was also observed by Cohen and co-workers. Compound (CLXXVI) did not exhibit N-H absorption band which proved that the cyclisation had taken place at position 1 of the indole nucleus so as to form 3,4-dihydropyrimido[3,4-a]indole ring system.

From the above discussions it is evident that, whenever the benzoyl derivative of 7-halogen substituted (Cl or Br) 2-(2-aminoethyl)indole was subjected to the Bischof-Napiersalski cyclodehydration in presence of polyphosphate ester (PPE), cyclisation took place at position 3 of the indole nucleus so as to form
The other possibility, viz., the cyclisation at position 1 of the indole nucleus did not take place probably due to steric hindrance produced by the bulky halogen substituent (Cl or Br) present at position 7 of 2-isotryptamine benzoyl derivative (cf. compounds CLXIII, CLXV and CLXVII). On the other hand, if the 7 position of the 2-isotryptamine benzoyl derivative was not halogen substituted, cyclisation took place at position 1 of the indole nucleus (Compounds CLXX, CLXXXIII and CLXXXVI).
THEORETICAL PART III

SYNTHESIS OF 2-ISOTRYPTOPHANES AND
INDOLE-2-ACETIC ACID
Considerable interest has been evinced in recent years in the synthesis of several tryptophan analogues. These compounds, due to their structural similarity with tryptophan, exhibited antimetabolite properties. The inhibition of growth of *B. typhosum* by methyl substituted indoles and tryptophans was thoroughly investigated by Fildes and Rydon.\(^4\) They found that 4-, 5-, 6-, and 7- methyl tryptophans inhibited the growth of *B. typhosum* in the order of \(4 > 5 > 6 > 7\). Kornfeld\(^48\) noticed that, shift of the alanine side chain in tryptophan from position three to two, produced antagonistic action on tryptophan. It has been shown that 2-*isotryptophan* possessed considerable monoamine oxidase inhibition property also.\(^1\) Synthesis of methyl substituted tryptophans having alanine side chain in various positions of the pyrrole portion of the indole nucleus has also been reported, viz., 3-methyl-2-*isotryptophan*,\(^49\) 3-methyl-1-*isotryptophan*,\(^5\) 5-hydroxy-2-*isotryptophan*,\(^1\) and 6-methyl-2-*isotryptophan*.\(^5\)

In view of the antimetabolite properties associated with the above mentioned methyl substituted *isotryptophans*, it was thought of interest to synthesise some 3-methyl-2-*isotryptophan* derivatives with Bz-methyl, methoxy and ethoxy-substituents. The synthesis
of these isotryptophan derivatives, described in the following pages, was according to the method first reported by Kornfeld and later improved by Snyder and Cook.

I. Synthesis of \( \alpha \)-amino-\( \beta \)-(3,5-dimethyl-2-indole)propionic acid

As a first object of the scheme, the synthesis of \( \alpha \)-amino-\( \beta \)-(3,5-dimethyl-2-indole)propionic acid was undertaken. 3,5-Dimethylindole-2-carboxylic acid (CLXXX), required as the starting material for the synthesis of the title compound, was prepared by Fischer synthesis according to the procedure described by Dambal and Siddappa (cf. chart XXXIX).
p-Methylbenzenediazonium chloride (CLXXVII) and ethyl $d'$-ethylacetoacetate (XIII), were subjected
to a Japp-Klingemann reaction, to get ethyl $d'$-ketobutyrate
p-methylphenylhydrazone (CLXXXVII). This, on Fischer
cyclisation in ethanolic sulphuric acid, gave ethyl

**Chart XI**

![Chemical Diagram]

- **CLXXX**: $\text{H}_3\text{C} - \text{CH}_3$ 
- **CLXXXI**: $\text{H}_3\text{C} - \text{CH}_3$ 
- **CLXXXII**: $\text{H}_3\text{C} - \text{CH}_3$ 
- **CLXXXIII**: $\text{H}_3\text{C} - \text{CH}_3$ 
- **CLXXXIV**: $\text{H}_3\text{C} - \text{CH}_3$ 
- **CLXXXV**: $\text{H}_3\text{C} - \text{CH}_3$ 
- **CLXXXVI**: $\text{H}_3\text{C} - \text{CH}_3$
3,5-dimethylindole-2-carboxylate (OLXXX), which on subsequent hydrolysis with alcoholic potassium hydroxide yielded 3,5-dimethylindole-2-carboxylic acid (OLXXX).

Starting from 3,5-dimethylindole-2-carboxylic acid (OLXXX), the various steps involved in the synthesis of the title compound are given in the chart XL. 3,5-Dimethylindole-2-carboxylic acid (OLXXX) in dry ether, reacted with thiouyl chloride to give the acid chloride (CLXXXI), which readily reacted with dimethylamine to yield 3,5-dimethylindole-2-carboxylic acid dimethylamide (OLXXXII) in 70% yield. This amide (OLXXXII) on reduction with lithium aluminium hydride, furnished 2-dimethylaminomethyl-3,5-dimethylindole (OLXXXIII) in 68% yield. Compound (OLXXXIII) reacted with methyl iodide to yield 2-dimethylaminomethyl-3,5-dimethylindole methiodide (OLXXXIV). This quaternary salt (OLXXXIV) was used for the alkylation of acetamidomalonic ester. The alkylated product was not the expected melonic ester derivative, but was found to be ethyl α-acetamido-β-(3,5-dimethyl-2-indole)propionate (OLXXXV). During the alkylation process, one of the carbethoxy groups had been cleaved and the substituted
propionic ester (CLXXXV) was obtained in 68% yield. This observation was well in agreement with the observations made by Snyder and Cook. The propionic ester was saponified to get the desired L-amino-\(\beta\)-(3,5-dimethyl-2-indole)propionic acid (CLXXXVI) in (CLXXXVII) in 62% yield.

II. Synthesis of L-amino-\(\beta\)-(5-methoxy-3-methyl-2-indole)propionic acid

5-Methoxy-3-methylindole-2-carboxylic acid (CLXXXVII) required as the starting material for the synthesis of the title compound, was obtained from the hydrolysis of ethyl 5-methoxy-3-methylindole-2-carboxylate (IV). This compound was prepared by a Fischer synthesis as described earlier (cf. p. 80). The synthesis of the substituted 2-iso-tryptophan was carried out according to the scheme given in the chart XLI.
5-Methoxy-3-methylindole-2-carboxylic acid (CLXXXVII) was treated with thionyl chloride to get the acid chloride (CLXXXVIII), which readily reacted with dimethyl amine to yield the 5-methoxy-3-methylindole-2-carboxylic acid dimethylamide (CLXXXIX). The amide underwent lithium aluminium hydride reduction to give 5-methoxy-3-methyl-2-dimethylaminomethylindole (CXO). This 2-isogramine (CXO) reacted with methyl iodide to furnish 5-methoxy-3-methyl-2-dimethylaminomethylindole methiodide (CXOI). The stable quaternary salt (CXOI) thus obtained was employed for alkylating the acetamidomalic ester. The reaction product, ethyl L-acetamido-β-(5-methoxy-3-methyl-2-indole)propionic ester (CXOII), was obtained in 68% yield. The propionic ester (CXOII) was conveniently saponified to get L-amino-β-(5-methoxy-3-methyl-2-indole)propionic acid (CXOIII) in good yield (77%).

III. Synthesis of L-amino-β-(5-ethoxy-3-methyl-2-indole)propionic acid and 5-ethoxy-3-methylindole-2-acetic acid

The synthesis of the title compounds required 5-ethoxy-3-methylindole-2-carboxylic acid (CXIV) as the starting material. This was conveniently obtained from ethyl 5-ethoxy-3-methylindole-2-carboxylate (LXIV)
by alkaline hydrolysis in alcohol. Preparation of the compound (LXIV) is described earlier (cf. p. 99).

Starting from 5-ethoxy-3-methylindole-2-carboxylic acid (OXIV), the synthesis of the required $\alpha$-amino-$\beta$-(5-ethoxy-3-methyl-2-indole)propionic acid was undertaken according to the scheme given in the chart XLII.

5-Ethoxy-3-methylindole-2-carboxylic acid (OXIV) was treated with thionyl chloride in dry ether to get the acid chloride (OXV) which was then reacted with dimethylamine to obtain 5-ethoxy-3-methylindole-2-carboxylic acid dimethylamide (OXVI). This amide on reduction with lithium aluminium hydride in dry ether, furnished 5-ethoxy-3-methyl-2-dimethylaminomethylindole (OXVII). This was reacted with methyl iodide to get 5-ethoxy-3-methyl-2-dimethylaminomethylindole methiodide (OXVIII). This stable quaternary salt (OXVIII) was used for the alkylation of the acetamidomelonic ester. Ethyl $\alpha$-acetamido-$\beta$-(5-ethoxy-3-methyl-2-indole)propionate (OXIX) was obtained in 63% yield. This propionic ester (OXIX) on saponification gave the desired $\alpha$-amino-$\beta$-(5-ethoxy-3-methyl-2-indole)propionic acid (X) in good yield (63%).
Chart XLII

LXIV \(\xrightarrow{\text{EtOH/NaOH}}\) CXCV

\(\xrightarrow{\text{Ether/\text{SOCl}_2}}\) CXCV

\(\xrightarrow{\text{HN(\text{Me})}_2}\) CXCVI

\(\xrightarrow{\text{LiAlH}_4}\) CXCVII \(\xrightarrow{\text{CH}_3\text{I}}\) CXCVIII

\(\xrightarrow{\text{Raq, NaOH}}\) CXCIX

EtO

CH₃

COOEt

N

HC

NH

CO

CH₃

EtO

CH₃

COOEt

N

HC

NH

CO

CH₃
5-Ethoxy-3-methylindole-2-acetic acid

Since the discovery of indole-3-acetic acid as a naturally occurring plant growth hormone, numerous substituted derivatives of this auxin have been synthesised in the hope of finding biological antagonists and to study the effect of substitution on the biological activity. Schindler\textsuperscript{52} synthesised 5-hydroxyindole-2-acetic acid and evaluated its phytohormonal activity.

It was therefore desirable to synthesise 5-ethoxy-3-methylindole-2-acetic acid for the evaluation of its biological activity. The quaternary salt (CXXVIII), obtained as the key intermediate in the synthesis of the 2-isotryptophan, described earlier, was made use of in the synthesis of 5-ethoxy-3-methylindole-2-acetic acid. The schematic presentation of the synthesis is shown in the chart XLIII.
The methiodide (CIXVIII) was reacted with sodium cyanide to get 5-ethoxy-3-methylindole-2-acetonitrile (CII). The nitrile (CII) on refluxing with aqueous potassium hydroxide (10%), gave the desired 5-ethoxy-3-methylindole-2-acetic acid (CIII) in 58% yield.
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