CHAPTER ONE

INTRODUCTION

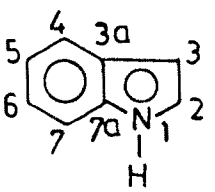
LITERATURE SURVEY

SCOPE OF PRESENT WORK

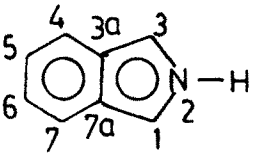
INTRODUCTION AND LITERATURE SURVEY

The indoles is class of heterocyclic compound found in many natural products which are of chemical and biochemical importance.[1] The indole occurs in free state in Jasmine, orange blossoms, citrus fruits and in the form of indican in the indigo plant. In the animal body, indole is found alongwith pus and also in liver, pancreas, brain and bile. Human and animal faces contain indole and skatole. Among several natural products containing indole nucleus, mention may be made of the essential amino acid tryptophan, the plant growth hormone indole-3-acetic acid, alkaloids like gramine, abrine bufotenine, brucine, reserpine, yohimbine and strychnine. The antibiotics like mitomycine and glitoxin contain indole nucleus. A large number of indole derivatives obtained in the laboratories by synthesis which act as therapeutic agents, drugs and dye stuffs.

The indole is commonly called as benzopyrrole in which the benzene ring is fused at 2 and 3 positions of pyrrole ring. The fusion at 3 and 4 positions forms isoindole.

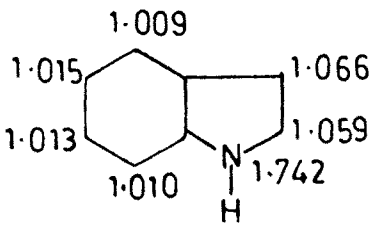


Indole



Isoindole

The electron densities at various atoms in the indole ring system have been calculated by molecular orbital methods[2]



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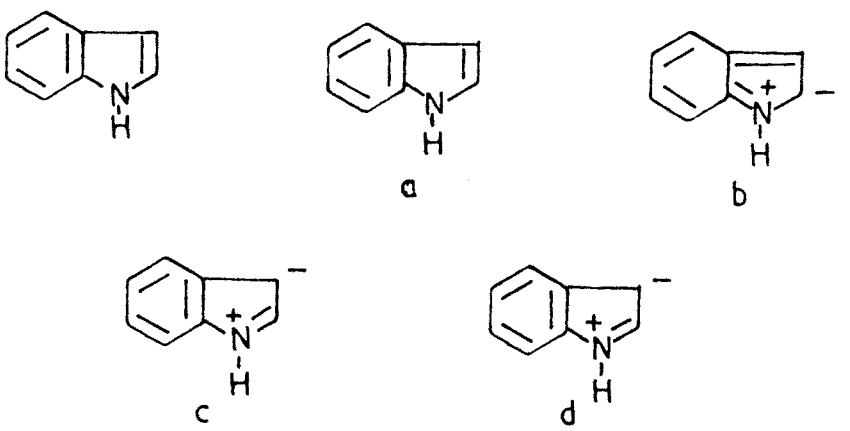
From the above values of electron densities the position 3 is most susceptible for electrophillic attack. The resonance energy of indole calculated from its heat of combustion is 47-49 Kcals/mole. The indole is represented by different resonating structures as

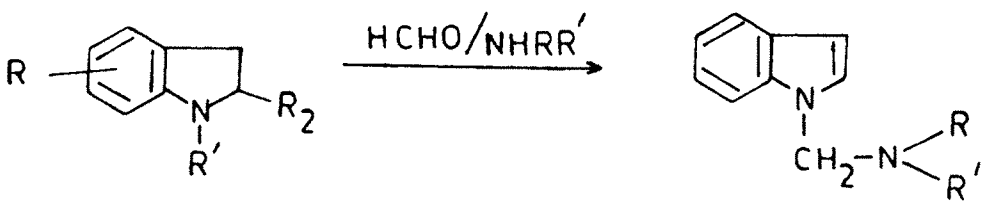


(3)

out of these structures, the structure I is important. In indole the hydrogen at position 1 is appreciably acidic (pKa = 17) and forms anion in the presence of strong base.[3] The indole oxygenated at 2- and at 3- positions are commonly named as oxindole and indoxyl respectively. The indole tautomer in which the hydrogen as moved from nitrogen to C_3 is called as indolinin but it is unstable w.r.t. indole.

A large number of methods of synthesis of indoles are available. The most widely used methods of synthesis of indole derivatives are due to Fischer[4-70] and consist of heating aldehyde and ketone with phenyl hydrazine in the presence of anhydrous zinc chloride/BF_3/H_3PO_3 catalyst. The cyclisation of 2-acyl amino toluene with potassium t-butoxide to form indole has quite wide application called as modification of Madelung synthesis.[71-85] The indoles can also be obtained by Bischler's synthesis,[86] by heating α-halo of α-hydroxy ketone with aryl amines. The reaction is acid catalysed and many indoles have been obtained from aniline and N-methyl aniline. Another synthesis[87] which gives good results but have been used less. It involves the reaction of o-nitrotoulene with diethyloxalate in sodium ethoxide followed by the treatment with zinc and acetic acid. The resulting product being 2-carboethoxy indole.

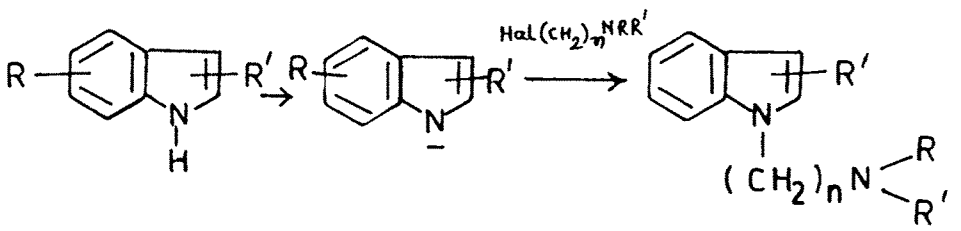
The Mannich reaction[88-91] is the valuable method to substitute an acidic hydrogen of nucleophile by amino methyl group. It involves the condensation of indole with formaldehyde and secondary amine. In the absence of acidic condition 1-Mannich base is obtained.



(4)

Some amino alkyl derivatives of indoles were prepared by treating indole with alkali amides and alkali hydrides or with lithiumalkyl in inert

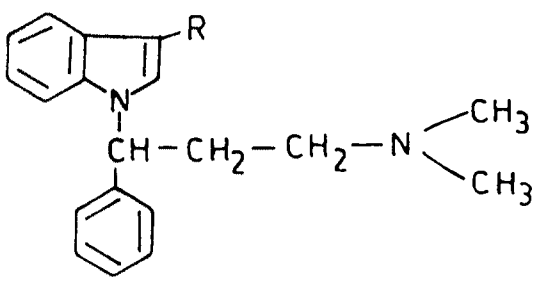
solvent like benzene, toluene, dimethyl formamide or liq. ammonia. The alkylation reaction[92-99] of anions with aminoalkyl halides leads to the corresponding substitution products.



(5)

A study of 1-alkylation versus 3-alkylation for the sodium salt of indole depends on the nature of the halide and solvent.

The alkylation of the Lithium salt of 1-benzyl indole or 1-benzyl-3-phenyl indole with 2-dimethylamino ethyl chloride gives the following basic compound with low yield[100]



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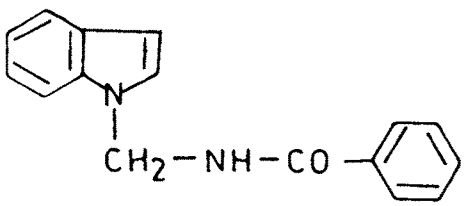
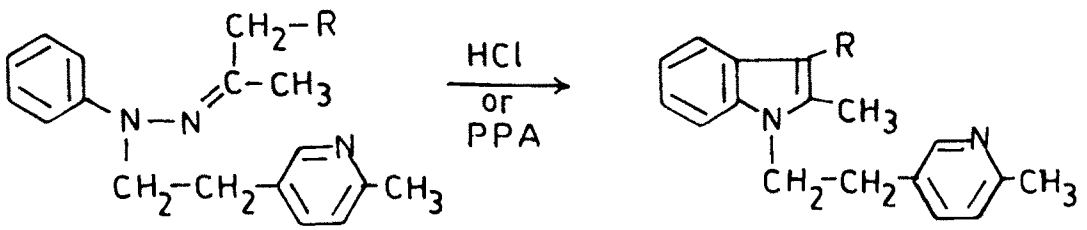
The reaction between indole and benzamide Mannich base in the presence of NaOH gives 1-benzol-aminomethyl indole[101]



(7)

Indole with substituents in position 3 forms corresponding 1-pyridyl-ethylindole on reaction with 4-vinylpyridine in acidic solution. Indole with ethylenediamine in the presence of CS_2 has been described in a patent.[102] An alternative procedure for the synthesis of 1-pyridylethyl indoles has involved by Fischer cyclization of phenylhydrazones.[103,104]



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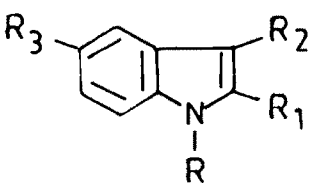
Woolley and Shaw[105] have synthesised various indole derivatives and screened for their antiserotonin activity on isolated tissue preparations. Medmain (9b) (2-methyl-3-ethyl-5-dimethylamino indole) and methylmedmain (9c) has been shown high degree of antiserotonin activity



(9)

	R	R_1	R_2	R_3
a	H	CH_3	C_2H_5	NH_2
b	H	CH_3	C_2H_5	$N(CH_3)_2$
c	CH_3	CH_3	C_2H_5	$N(CH_3)_2$
d	CH_3	CH_3	$COOC_2H_5$	OH

Grinev et. al.[106] have reported that dimekerbene (9d) 1,2-dimethyl-3-carbethoxy 5-hydroxy indole and its analoguos possess strong serotonin antagonistic activity. Dimerkabene in conjuction with another drug is used for effective treatment of hypertension.[106]

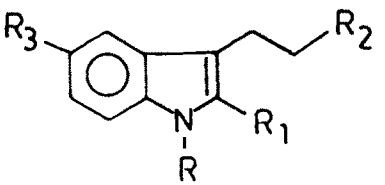
The nitroindoles are also gaining importance as intermediate for the synthesis of various compounds of pharmacological interest. Raymond et. al.[107] tested 5 and 6 nitro indoles and reported them to possess anthelmintic activity. Siddappa and co-workers[108] have synthesised Bz substituted nitro and amino indoles to evaluate for their biological activities.

Gaddum and co-workers[109] have screened several methyl substituted indoles for their antiserotonin activity. The antagonism was observed as unspecific and decreasing order of activity for different positions of methyl group in the indole molecule were to be 5, 7, 4, 3.

Bonnycastle and co-workers[110] have shown that the elevation of brain serotonin in a consequence of the administration of various central nervous system (CNS) depressant. On the other hand many simple derivatives show predominantly excitory properties.

Some derivatives of tryptamine having structural analogy with serotonin are found to antagonise serotonin induced effects of the several synthetic tryptamine analogue, 1-benzyl-2-methyl-5-methoxytryptamine commonly known as BAS, when fed to dogs in doses 1 mg/kg exhibited strong activity[111] against pressor action of serotonin. Though BAS reduced

the blood pressure level in hypertensive patients,[112] the side effects produced could not be neglected.[113] The N, N-dimethyl analogue of BAS is a bufotenin derivative having strong antiserotonin action on isolated rat uterus and also on serotonin induced diarrhoea and in mice.[114] However, BAS is less potent than LSD against serotonin induced rise of blood pressure in the dogs.[115]



(10)

	R	R_1	R_2	R_3
a	$-CH_2-C_6H_5$	$-CH_3$	$-NH_2$	$-OCH_3$
b	$-CH_2-C_6H_5$	$-CH_3$	$-N-(CH_3)_2$	$-OCH_3$
c	H	$-CH_3$	$-NH_2$	$-OCH_3$
d	$-CH_3$	H	$-NH_2$	$-OCH_3$
e	$-CH_2-C_6H_5$	$-CH_3$	$-NHCH_3$	-OH
f	$-CH_2-C_6H_4-OCH_3$	$-CH_3$	$-N-(CH_3)_2$	$-OCH_3$
g	$-CH_2-C_6H_4-OCH_3$	$-CH_3$	$-N-(CH_3)_2$	-OH
h	$-CH_2-C_6H_4-OCH_3$	$-CH_3$	$-N-(CH_3)_2$	$-OCH_3$
i	$-CH_2-C_6H_4OCH_3$	$-CH_3$	$-NH_2$	$-OCH_3$
j	H	$-CH_3$	$-NH_2$	-OH
k	$-CH_2-C_6H_4-OCH_3$	$-CH_3$	$-NH_2$	-OH

2-Methyl serotoninmethyl ether (10_c) administered either intraveneously or orally inhabited. The blood pressure rise in dog caused by excess of serotonin. But compound (10 d) exhibited serotonin like activity on isolated rat uterus[116] while compound 10 c-j displayed strong antiserotonin activity,[105-117] compound (10 k) was 25 times as strong as active BAS. Several 1-substituted-2-methyl-3-(dialkylamino alkyl) indoles possessing remarkable antiserotonin activity.[118]

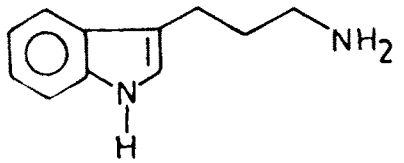
Hunt and Brimblecombo[119] have synthesised tryptamines having hydroxy methoxy or benzoloxy substituents in 5, 6 - or 7 positions. Majority of these compound evoke hyperthermia in rabbits, which tends to parallel psychotomimetic (LSD like) activity in man. These compounds were also found to be effective in changing the pattern of behaviour of rats in the open field situation. The pharmacological activity of several substituted hydroxy, methoxy, or benzyloxy tryptamines have been reported by Julia and co-workers.[120a] Psychotomimetric activity for some of these compounds was recorded.[120b,d] The tests on rabbit hear[120c] exhibited coronary dialation of the same order of magnitude as papavarine. 2-Aryt-5-methoxy tryptamines[121] synthesised have been shown to possess weak antiserotonin activity, but lasting hypotensive activity and the muscular flaecidity caused by some of these drugs are remarkable.

Recently, 5-methoxy 3(2--benzyl aminoethyl)indole has been synthesised and screened[122] on isolated rat fundal stomach preparations, guinea pig uterus, ileums and ganglion free faenia coli preparation and has been shown to be potent inhibition of serotonin.

Siddappa and co-workers[123] synthesised some 2-phenyl 6,7-benztryptamines and 2-phenyl 4,5-benztryptamines possessing anti-serotonin activity. Several Bz substituted tryptamines and linear benztryptamines prepared by Ambekar and Siddhappa[124] exhibited moderate antiserotonin activity. To evaluate the biological activities Hiremath and Siddappa[125] have synthesised some Bz substituted 2-phenyl-5-methoxy trptamines and the results of screening for their antiserotonin activity have also been reported.[126,127a] Basangoudar and Siddappa synthesised several 3-(-3-aminopropyl) indoles and 1-(3-amino propyl) indoles possessing higher degree of antiserotonin activity[127]. Several Bz substituted 2-(2-aminopropyl) indoles[128] and 2-(2-aminoethyl) indoles[128b,129d] have shown higher degree of potency than BAS. Various Bz substituted 2-(2-aminoethyl) indoles[130,131] prepared by Hiremath and co-workers were evaluated for their biological activities.

3-(3-amindpropyl) indoles and 1-(3-aminopropyl) indoles

3-(3-aminopropyl) indoles are the next homologus of tryptamines. Zherebchemko and co-workers[132] have studied the effect of monoamine oxidase of 3-(3-amino propyl) indole in vitro and found that 3-(3-amino-propyl) indole was strongly inactivated by the enzyme. Further, 3-(3-dimethyl aminopropyl) indole completely inhibited[133] in vitro oxidative deamination of tryptamine and serotonin in the presence of monoamine oxidase in the interpenducular nucleus of rat brain



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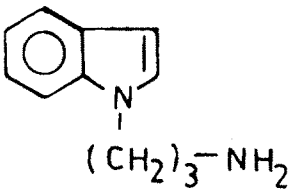
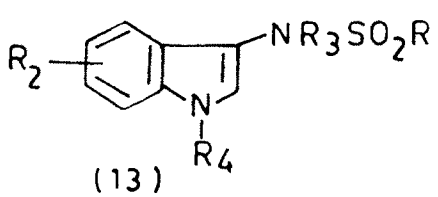


(12)

Julia et. al.[121] have made a comparative study of the antiserotonin activity of 3-(3-aminopropyl) 2-phenyl indoles and 3-(2-aminoethyl)2-phenyl indoles on the rat uterus. They observed that 3-(3-aminopropyl) indoles were more active than the 3-(2-aminoethyl) 2-phenyl indoles. Siddappa et al.[132] have synthesised several 3-(3-aminopropyl) indoles and 1-(3-amino propyl) indoles (12) and tested for their serotonin antagonistic activity. It was observed that the 1-(3-amino propyl) indoles (12) were more potent serotonin antagonistics than the 3-(3-amino propyl) indoles. Recently, Basangoudar et al.[131b] have synthesised some 1-(3-amino propyl) 2-hydroxyl methyl indole to evaluate their biological activity.

Some indoles act as catcher in the synthesis of desirable developer oxidation products. About 15 indole derivatives are described for the use as scavangers of undesirable oxidation products in both black and white colour photographic materials. The use of these compounds improves the image quality.



(13)

R = H or SO_2R_5 where R_5 is noncoloured organic group.

R = H, -OH, alkyl, aryl, carbamoyl

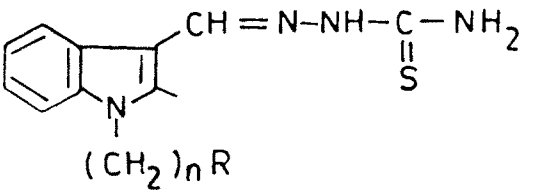
R_2 = (H, alkyl, aryl, arylalkyl, halogen, CN, CO_2H, substituted CO_2H, carbamoyl, SO_3H, sulfamoyl acylamido OH, alkyl sulfonyl (F_3SO_2, aryl sulfonyl).

The good method for synthesis of indole derivative starting with 2-Halo-N-allyl aniline to indole via palladium oxidative addition insertion reaction has been reported by Odle et.al.[134] By this procedure 3-methyl indole, 1-allyl-3-methyl-indole, 3-ethyl indole, 3-isopropylindole, 3,5 dimethyl indole, 3-methyl-5-carbethoxy indole, 3-methyl, 5,6, dimethoxyl indole and 3-3-carbethoxyquinoline were prepared in fair good yield.

1-Substituted, 2-phenyl-3-formyl indoles were synthesised by Tanaka et. al.[135] in good yields. The new modification of the E.Fischer[136] reaction involves the synthesis of N-alkyl indole under basic catalytic condition. The N-alkyl 2-phenyl indoles prepared by this method in about 40% yields.

The indole derivatives[137] with alkyl, alkoxy, alkoxy carbonyl, alkyl, alkoxy, alkoxy carbonyl, arylalkyl were prepared by reductive cyclisation of notrobenzyl nitriles. Some nitroindoles were synthesised[138] by cyclisation of $2,4\text{-}(NO_2)_2.C_6H_3NH\ N = C(R)CH_2R'$ by heating in the presence of HCO_2H (1:1) and CCl_4.

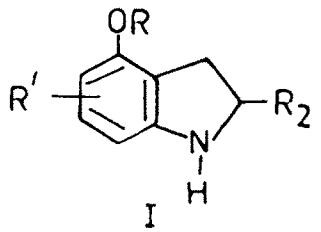
Antiviral activity of some thiosemicarbazones of 1-[(dialkylamino) = (alkyl)]-2-chloro-3-formylindoles has been studied by Gatti R. et.al.[139] The general structure of the compound is represented as follows :



(1 4)

The herbicidal activity of 2-phenyl indole has been recorded in the chemical literature.[140] Thus 25 g 2-phenyl indole/10 acre controlled broad leaf weed in rice and wheat. Novel 2-substituted -3-heterocyclyl indoles were synthesised for their pharmaceutical activity by Steinman et.al.[141]

The piperidyl indole derivatives were synthesised and evaluated for their antidepressant, antiemetic and antiparkinson[142] activities. 4-Hydroxy and 4-alkoxy indole derivatives were prepared by cyclisation of II at 100°C in the presence of strong base[143]



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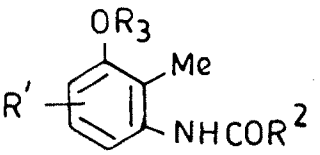

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(15)

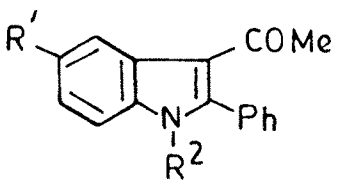
A novel synthesis of indole derivatives by intramolecular nucleophilic aromatic substitution has been carried out by Kametani et.al.[144] The synthesis of some N-substituted 2,3-dihydro indole derivatives has been reported and tested for fungicidal activities.[145]. The synthesis of indoles from N-(trifluoroacetyl)-2-anilino acetals has been reported.[146] Some 1-(3-dimethylaminopropyl)-2-phenyl indole hydrochlorides were prepared and tested for antidepressant activities and it is found that their derivatives act as potential antidepressant.[147]

5-Methoxy-3-aryl azoindoles[148] have synthesised which act as anti-tubercular compound. 3-|2-(4-piperidyl)-1-alkyl| indoles were synthesised[149] by Le Fur et.al. and their uses have been reported in the pharmaceutical

preparations. The synthesis and antimicrobial activity of 1-(α-alkoxyethyl) indoles has been recorded. These indole derivatives showed minute bacteriostatic activity[150] against S.aureus and E.colli at 5 mg/ml. Conc. 2-Hydroxyphenyl indoles were prepared and tested for antiphlogistics, antiestrogens and in the treatment of hormone dependent tumor.[151]

Alkenylation of 1-acyl indole with olefins bearing electron withdrawing substituents and palladium acetate has been carried out by Itahara, Toshio et.al.[152] Recently, some azepinoindoles[153] were synthesised and tested for their pharmaceutical activities.

An antitumor formulations contain indole derivatives and their salts.[154] The antitumor activity of I against sarcoma-180 was demonstrated in mice



(16)

Some indoles were synthesised for allergic and inflammatory[155] diseases. Indole (2,1-C)(1,4)-benzodiazepines were synthesised by HO et.al.[156] and tested for antiallergic activities.

Houlihan et.al.[157] have synthesised some C_2 substituted indoles by reacting the substituted anilines with suitable electrophilic aldehyde or ester.

Recently, a new method for construction of the indole nucleus has been described in the chemical literature by Smith et.al.[158]

SCOPE OF THE PRESENT WORK

The study of indoles has been in a very active state of development since many years because of their significant biological activities having drug potentialities. It is evident from general review that a very little information is available regarding correlationship between chemical constitution and anti-infective properties of indoles.

Present work covers more extensive study along the same line i.e. a study of relationship between antimicrobial activity and chemical constitution of indole derivatives.

In the selection of the compounds or series of the compounds to be prepared the work was naturally guided by the data already reported and reviewed. Most of the compounds are not described in the chemical literature. They are to be synthesised newly and properly characterised. The introduction of the alkylamino, methyl, phenyl groups in the indole nucleus will be carried out by following usual methods. The details of the procedure followed have been described.

The Schiff's bases of N-alkylamino indoles will be prepared, so as to find out the effect of unsaturation on antimicrobial activity whether it increases or decreases. Comparison of the bacteriostatic activity brings one to the same conclusion.