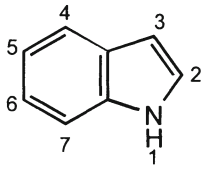
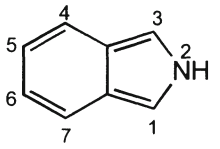


IUPAC name
1*H*-benzo[*b*]pyrrole

Other names
α,β-benzopyrrole
1-azaindene
1-benzazole

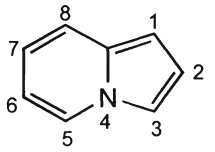
Isoindole (trivial name) : benzene ring fused to 'face c' (3,4-bond) of the pyrrole ring.



IUPAC name
2*H*-benzo[*c*]pyrrole

Other name
1*H*-isoindole

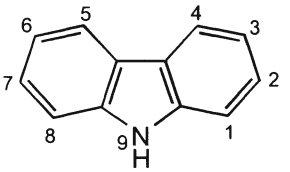
Indolizine (trivial name) : benzene ring fused to 'face a' (1,2-bond) of the pyrrole ring.



IUPAC name
pyrrolo[1,2-*a*]pyridine

Other name
pyrrocoline

Carbazole (trivial name) : fusion of benzene rings to 2,3- and 4,5-bonds of the pyrrole ring.



IUPAC name
Dibenzopyrrole

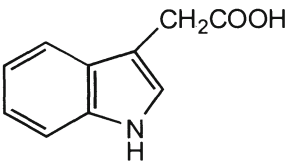
2.1 Indoles[1–7]

2.1.1 General

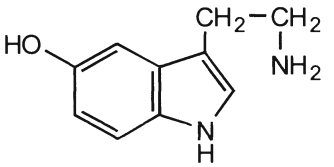
Indole is the most common member of the benzopyrrole class. The chemistry of indole has been and continues to be an attractive field of heterocyclic chemistry

because of the presence of indole structural unit in many of the natural products of varying important physiological activity. Some naturally occuring indoles with their applications are given as follows :

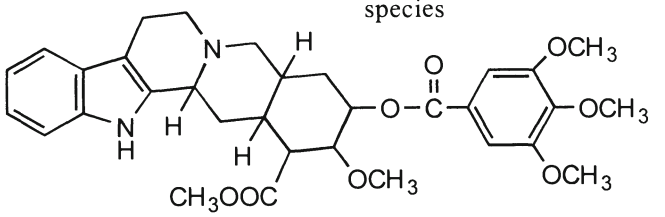
Indole-3-acetic acid — plant growth regulating hormone



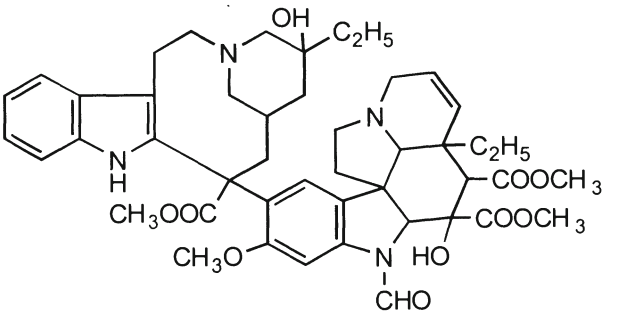
Serotonine — 5-hydroxy derivative of tryptamine and is obtained from tryptophan amino acid by hydroxylation and decarboxylation — vasoconstrictor



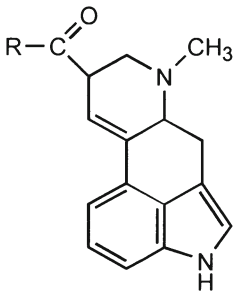
Reserpine — isolated from Rauwolfia serpentine species — tranquillizing and antihypertensive effects



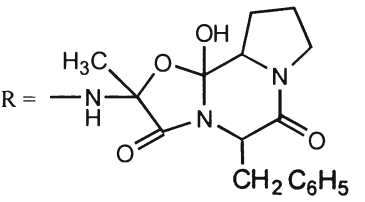
Vincristine (dimeric indole) — isolated from Catharanthus roseus — used in the treatment of leukemia because it arrests mitosis by an interaction with the protein tubulin



Ergotamine

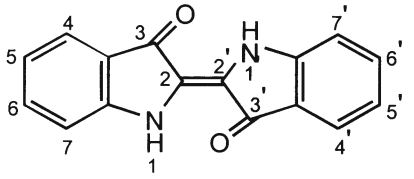


extracted from Clavicepus (grain parasite)



used as vasoconstrictor for treatment of migrain headache

Indigo

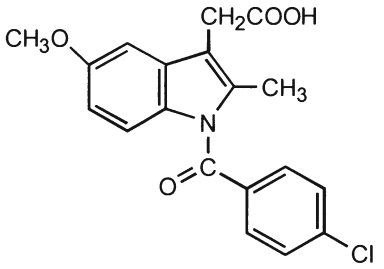


obtained from indican β-glucoside of indoxyl which occurs in plants

vat dye

The synthetic derivatives of indole also exhibit diversified biological activity relating to antiinflammation and antihypertension(CNS) as follows :

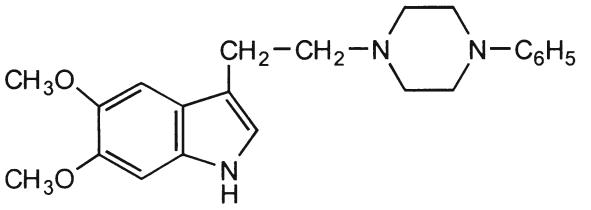
Indomethacin



antiinflammatory agent

used in the treatment of osteoarthritis

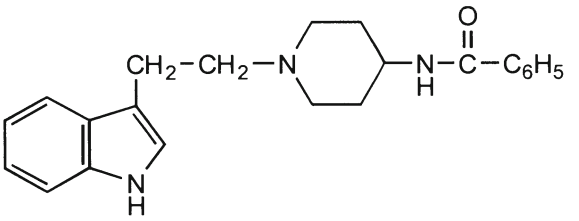
Oxypertine



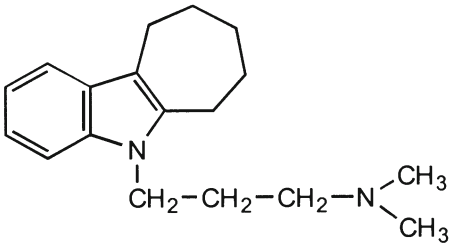
tranquillizer

used in the treatment of mental illness

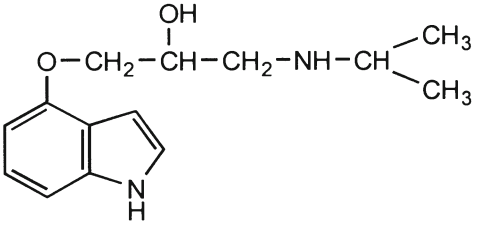
Indoramine — antihypertensive drug — used as an antihypertension agent



Iprindole — neurotransmitters



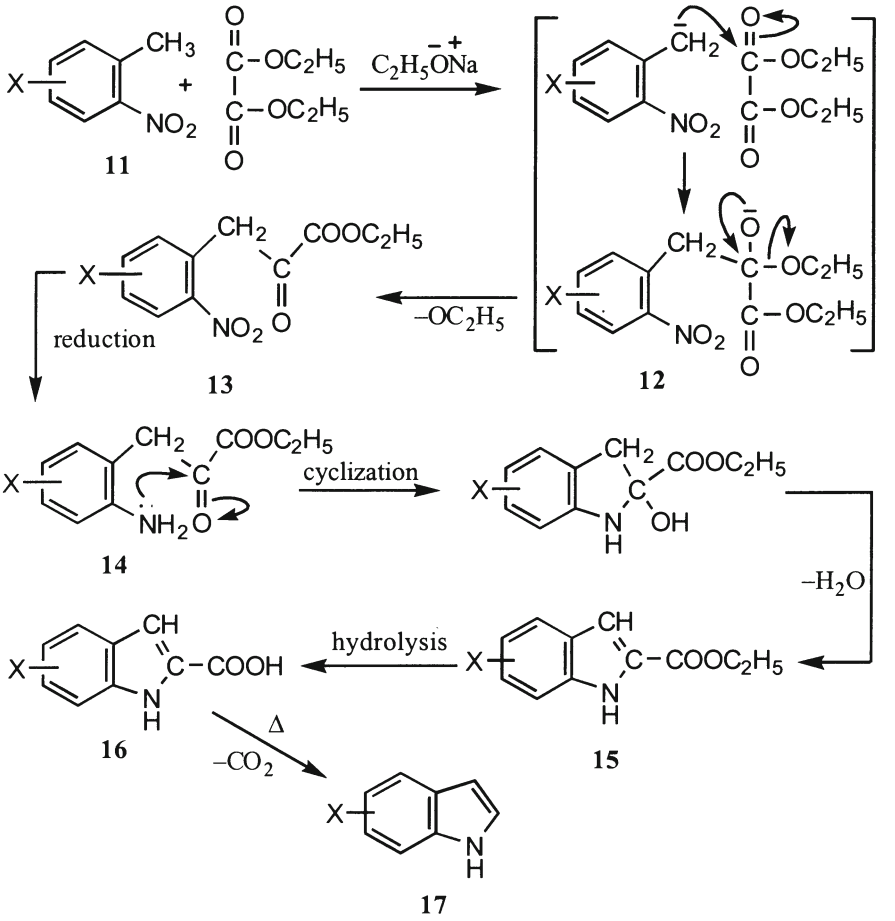
Pindolol — antihypertensive activity — β-blocking agent



2.1.2 Synthesis

2.1.2.1 Reaction of *o*-Nitrotoluene with Diethyl Oxalate (Reissert Indole Synthesis)

The reaction of o-nitrotoluene **11** with diethyl oxalate in the presence of a base (Claisen condensation) gives o-nitrophenylpyruvate **13** which on reductive cyclization followed by dehydration leads to the formation of indole-2-carboxylate **15** via *o*-aminophenylpyruvate **14**. The 2-ethoxycarbonyl substituent in indole may be removed, if required, by hydrolysis and thermal decarboxylation (scheme-1)[8,9].

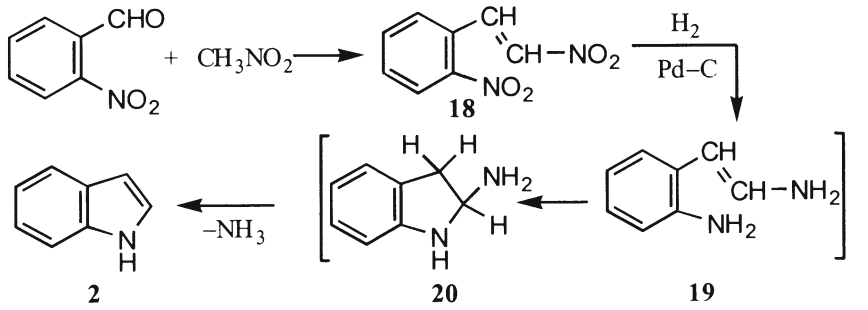


Scheme-1

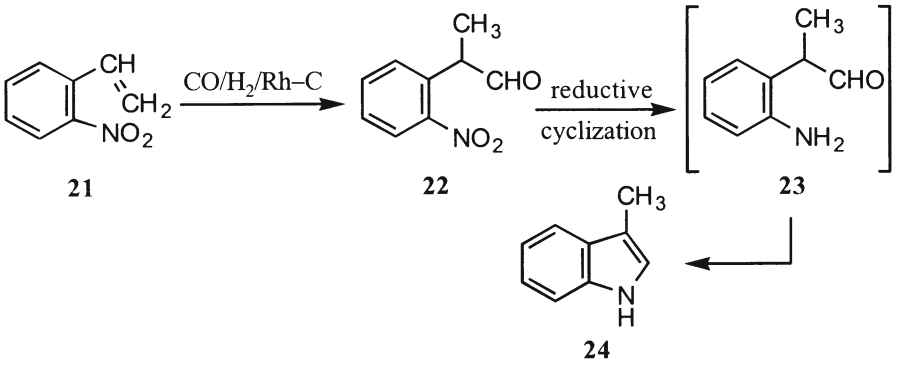
2.1.2.2 From *o*-Nitrophenylnitroethylene (*o*,ω-Dinitrostyrene)

The reductive cyclization of *o*-nitrophenylnitroethylene (*o*,ω-dinitrostyrene) **18**, prepared by the reaction of o-nitrobenzaldehyde with nitromethane, followed by subsequent aromatization with the elimination of ammonia results in the formation of indole involving N–C_2 bond formation (scheme-2)[10-12].

However, the reductive cyclization of aldehyde **22** resulting from the hydroformylation of nitrostyrene **21** provides 3-methylindole (skatole) **24** (scheme-3)[13].



Scheme-2



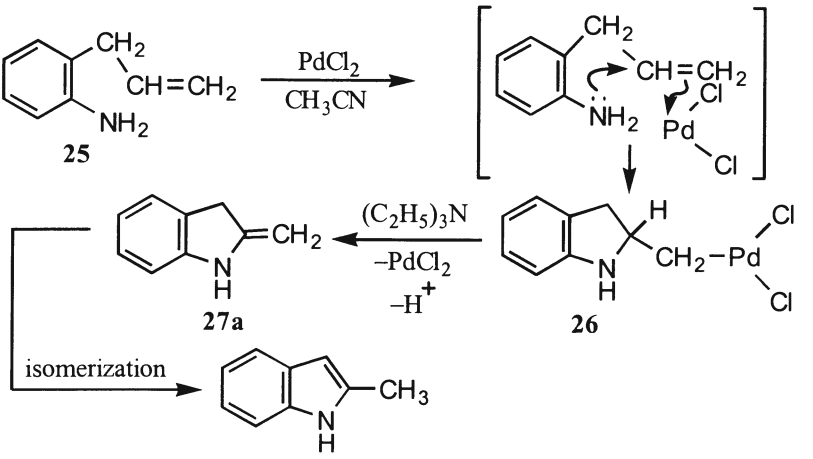
Scheme-3

2.1.2.3 Palladium Catalyzed Cyclization

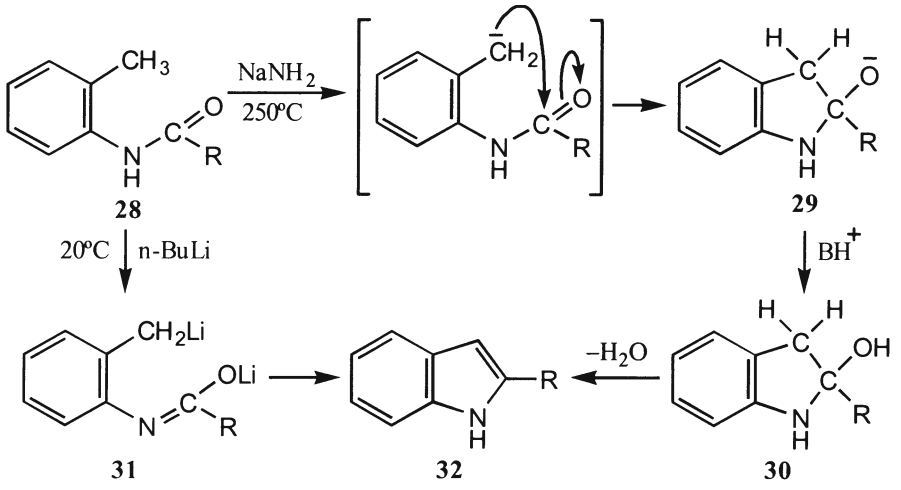
The reaction of *o*-allylaniline **25** with palladium(II) chloride in acetonitrile involves palladium ion catalyzed nucleophilic cyclization and proceeds with the formation of organopalladium intermediate **26** which on subsequent reaction with triethylamine provides 2-methylindole **27** (scheme-4)[14].

2.1.2.4 Madelung Indole Synthesis

It involves intramolecular cyclization of N-acyl-*o*-aminotoluenes (N-acyl-*o*-toluidines or toluamides) **28** with a strong base, sodamide or tert-butoxide, at high temperature. However, the strong bases, n-butyllithium and LDA, cause the reaction to occur relatively at lower temperature (20°C) (scheme-5). The reaction is considered to proceed with the deprotonation of methyl group and the nucleophilic addition to the amide carbon. This reaction is used to synthesize 2-alkyl- and 3-arylindoles.



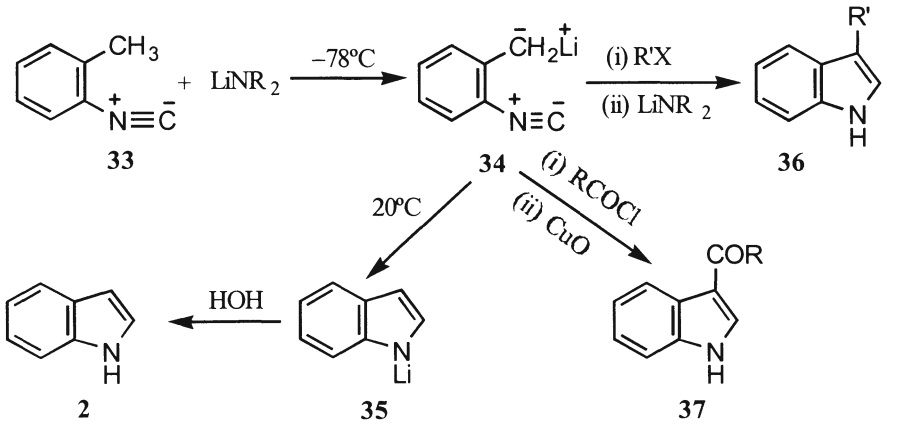
Scheme-4



Scheme-5

2.1.2.5 Isonitrile Cyclization

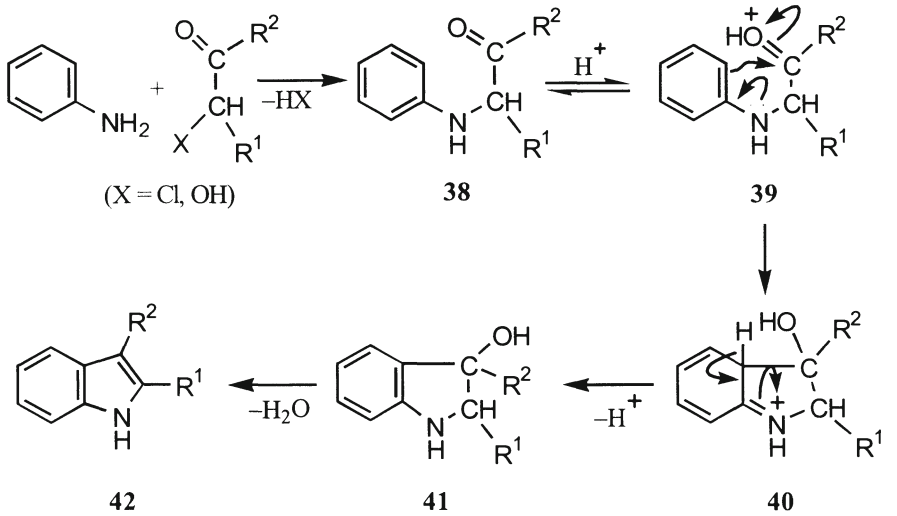
The reaction of *o*-tolyl isocyanide **33** with lithium dialkylamide at –78°C proceeds via lithiation of the methyl group affording lithiated intermediate **34** which (i) on cyclization at room temperature provides lithiated indole **35** and finally indole on hydrolysis, (ii) if treated with alkyl halide and subsequently with additional LDA, the methyl group is alkylated before cyclization affording 3-alkylindole **36** and (iii) with acyl halide in the presence of cupric oxide produces 3-acylindole **37** (scheme-6)[15].



Scheme-6

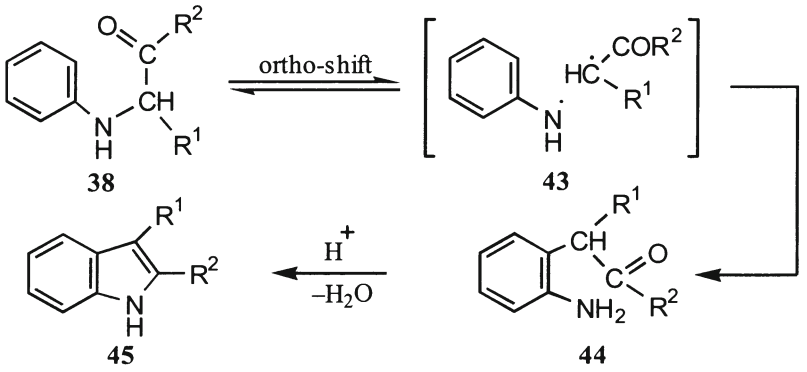
2.1.2.6 Bischler Indole Synthesis

The reaction of α-hydroxy- or α-halo ketones with arylamine in the presence of an acid provides indoles **42** involving (i) N-alkylation, (ii) electrophilic intramolecular cyclization and (iii) aromatization (scheme-7). If the substituents R^1 and R^2 are different, the scrambling of the substituents (migration of the substituents) occurs



Scheme-7

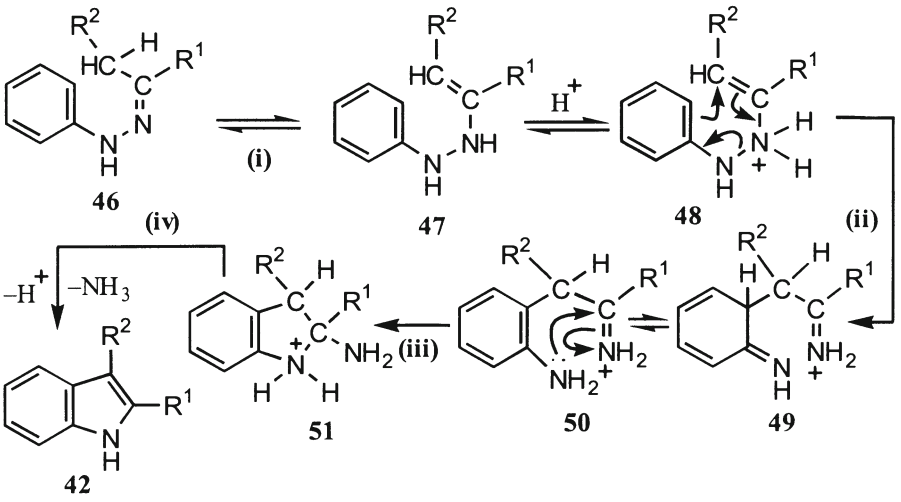
under vigorous conditions (excess of aniline and acid catalyst) with the formation of an isomeric product **45** involving ortho-shift (scheme-8)[16].



Scheme-8

2.1.2.7 Fischer Indole Synthesis

It is the most widely used method for the synthesis of indoles and involves an acid catalyzed cyclization of the arylhydrazones of appropriate aldehydes and ketones with the elimination of ammonia (scheme-9)[17-20]. The most commonly used acid catalysts affecting cyclization are; zinc chloride, boron trifluoride and polyphosphoric acid. However, the choice of the catalyst depends on the structure of arylhydrazone.



Scheme-9

The mechanism of Fischer indole synthesis is considered to involve the following steps :

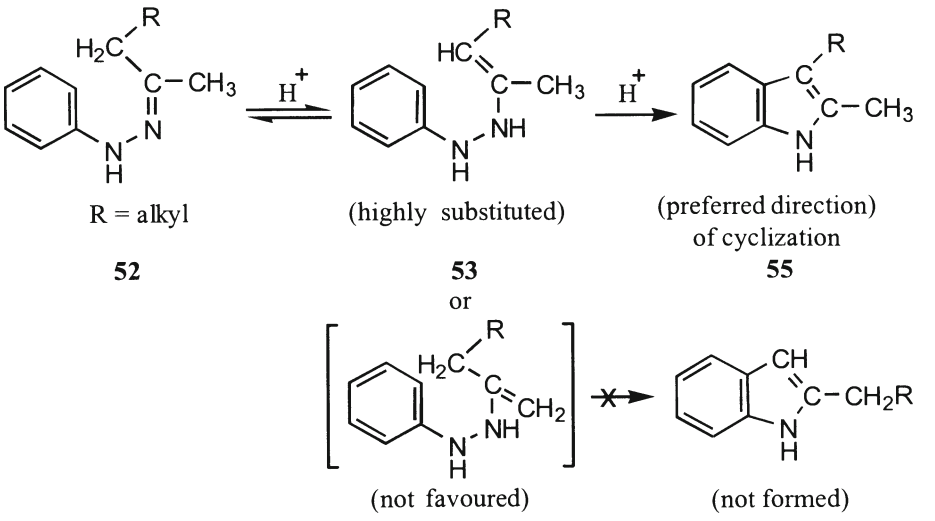
(i) hydrazone-enehydrazine tautomerism,

(ii) Claisen-type rearrangement [(3,3) sigmatropic rearrangement] involving cleavage of N–N bond and formation of C–C bond,

(iii) cyclization involving nucleophilic attack on imine carbon with the formation of N–C_2 bond and

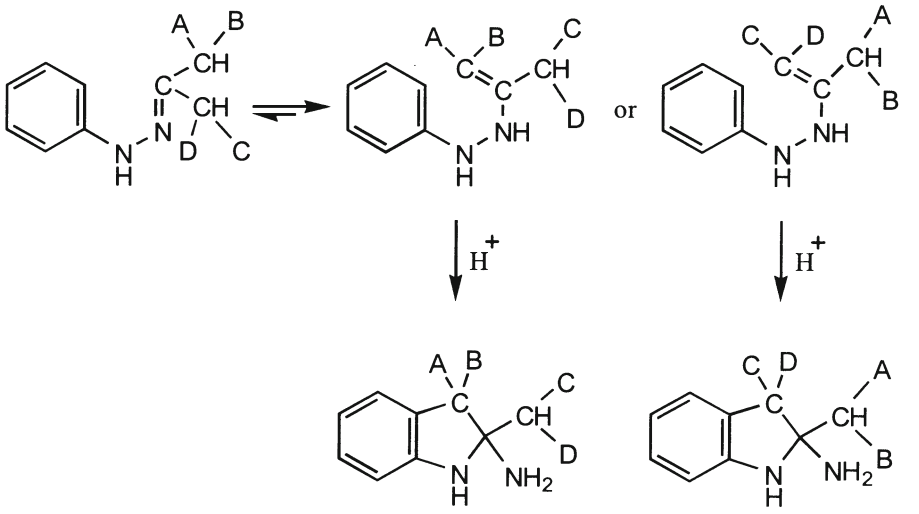
(iv) aromatization with the elimination of ammonia.

The structure of indole so formed depends on the direction of formation and cyclization of the enehydrazine tautomer. The cyclization tends to proceed in the direction of forming more highly substituted enehydrazine. Thus, the arylhydrazone of unsymmetrical ketone produces predominantly the indole derived from shifting of hydrgoen atom (prototropic shift) to the more highly substituted enehydrazine (scheme-10). However, the preferred direction of cyclization varies with the acid catalyst as high acidity and temperature favour cyclization to the less substituted position[21].



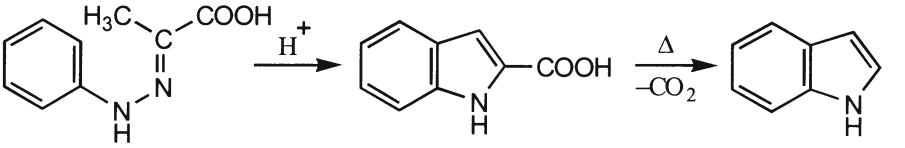
Scheme-10

When the degree of substitution is equivalent, usually the mixture of both possible cyclization products is obtained as illustrated by the generalized Scheme-11.



Scheme-11

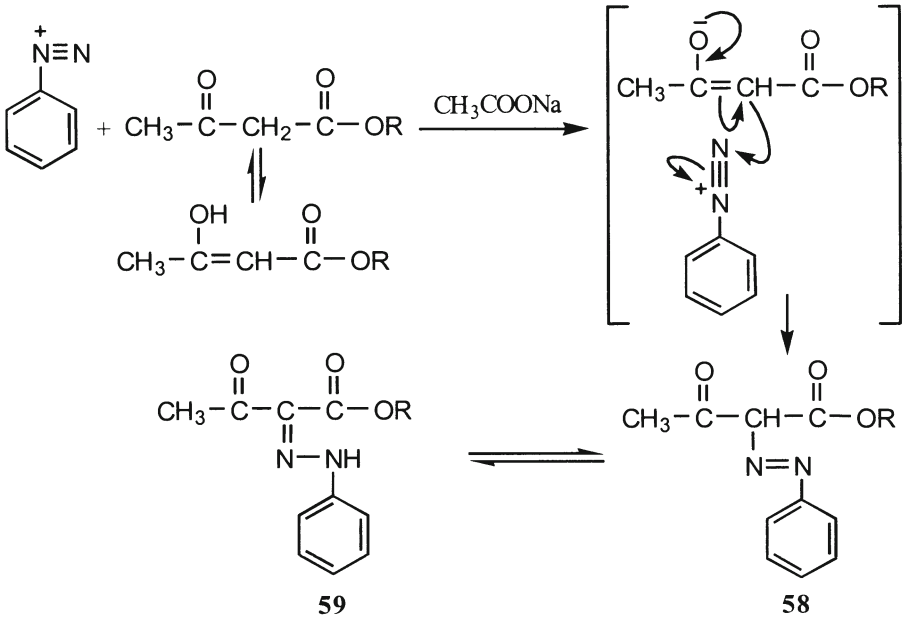
Limitation : Indole itself cannot be prepared directly as this reaction fails with acetaldehyde hydrazone. Indole is prepared indirectly by the Fischer reaction from phenylhydrazone of pyruvic acid involving cyclization and decarboxylation (scheme-12).



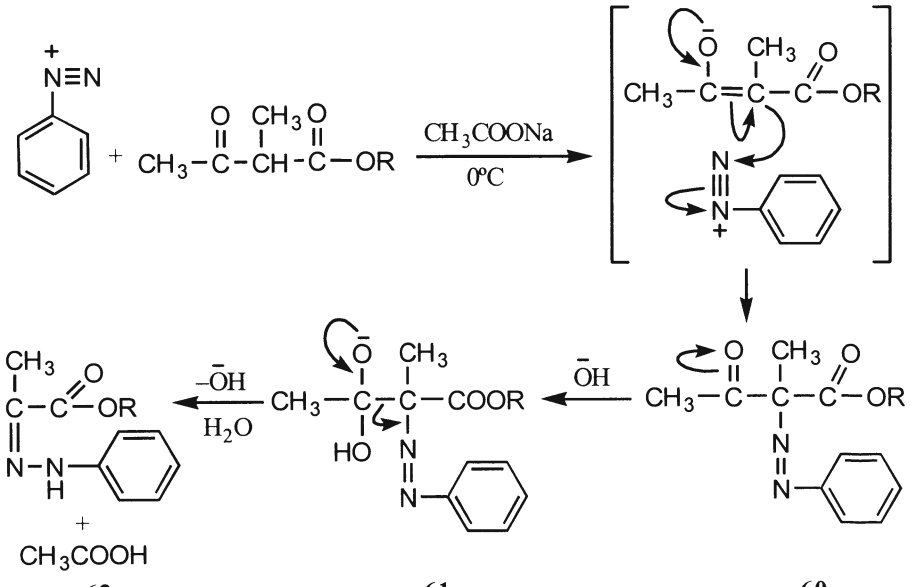
56 **57** **2**

Scheme-12

Extension : Jaap–Klingemann reaction is an excellent method for synthesizing arylhydrazones which are not obtained directly. It involves the coupling of diazonium salts with β-diketones (β-keto acids and β-ketoesters) or with enamines in the presence of a base (scheme-13). However, when the carbon atom at which coupling occurs does not contain hydrogen atom, the prototropic shift is not possible and the reaction proceeds with the cleavage of C–C bond providing arylhydrazone **62** (scheme-14)[22].



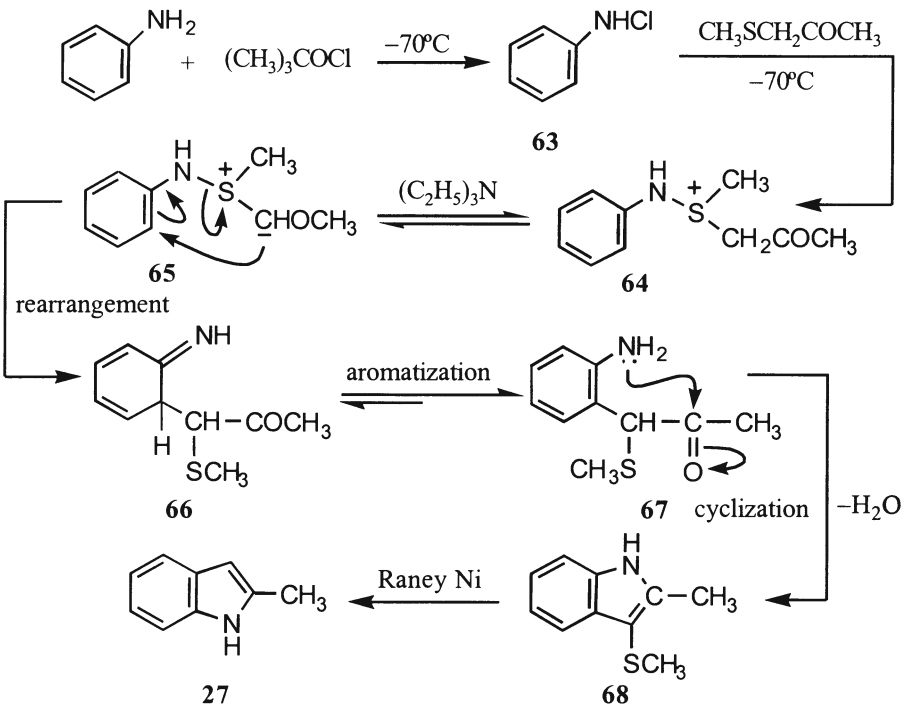
Scheme-13



Scheme-14

2.1.2.8 Gassman Indole Synthesis

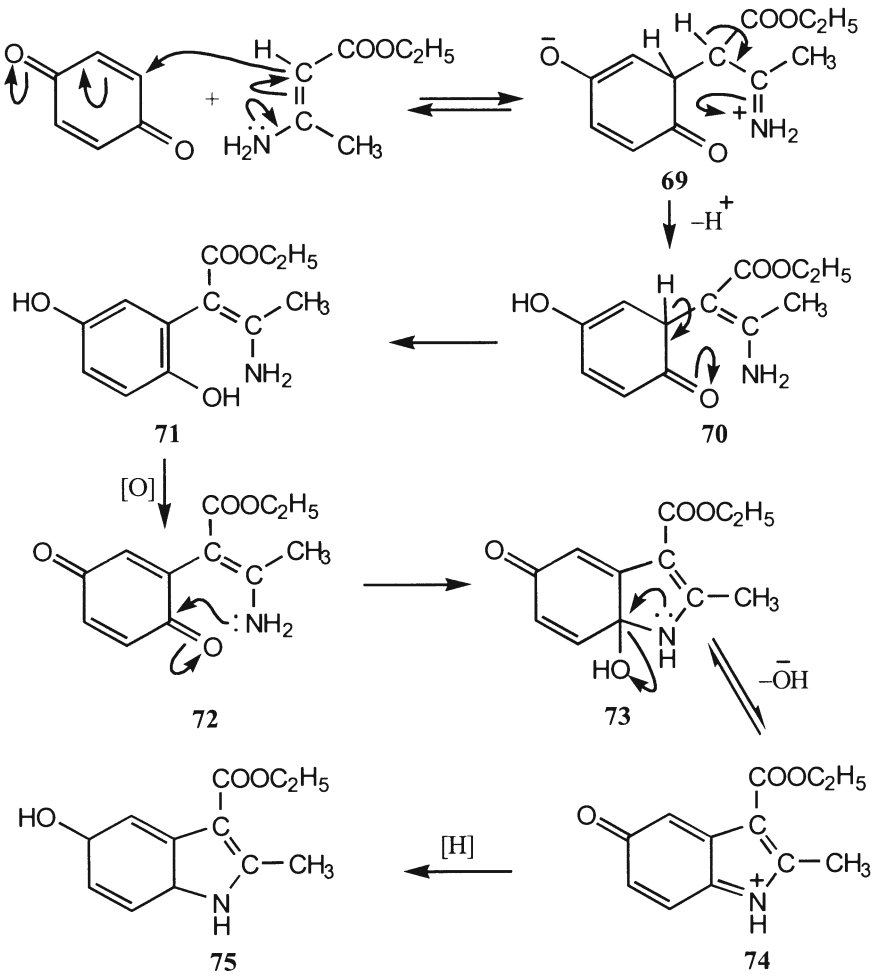
The reaction of aniline with tert-butyl hypochlorite gives N-chloroaniline **63** which on treatment with β-ketosulfide produces azasulfonium salt **64**. The sulfonium salt **64** with a weak base is deprotonated and generates sulfur ylide **65** which undergoes intramolecular rearrangement known as Sommelet–Hauser reaction [(3,2) sigmatropic rearrangement] with the cleavage of N–S bond and the formation of C–C bond providing α-amino ketone **67**. The cyclization of the resulting α-amino ketone affords 3-methylthioindole **68** but the methylthio-group can be easily removed by the reaction with Raney nickel leading to the formation of **27** (scheme-15)[23].



Scheme-15

2.1.2.9 Nenitzescu Indole Synthesis

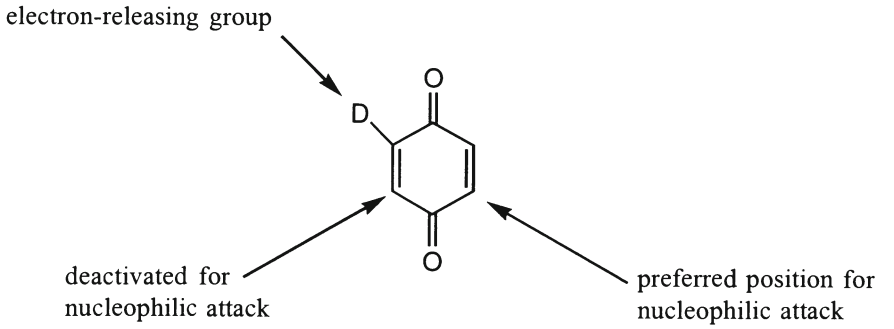
The reaction of *p*-benzoquinone with β-aminocrotonates results in the formation of 5-hydroxyindoles **75**. The reaction is considered to proceed with an enamine addition to α,β-unsaturated ketone, followed by cyclization involving oxidative-reductive transformations (scheme-16).



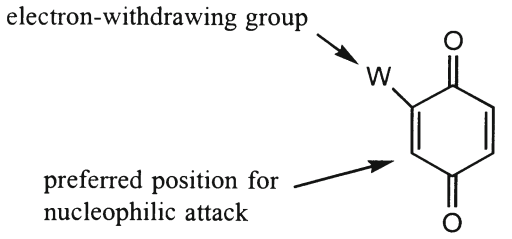
Scheme-16

However, in unsymmetrically substituted *p*-benzoquinones, the directing effects of the substituents depend on the electronic and steric effects and can be generalized as follows :

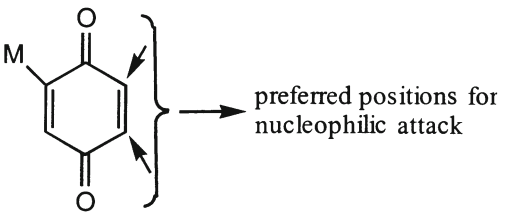
(i) the presence of electron-releasing group (D = OH, OR) at the position-2 of *p*-benzoquinone deactivates C-3 but directs the attack of nucleophile preferably to C-5 due to more electrophilic character of the carbonyl carbon-1.



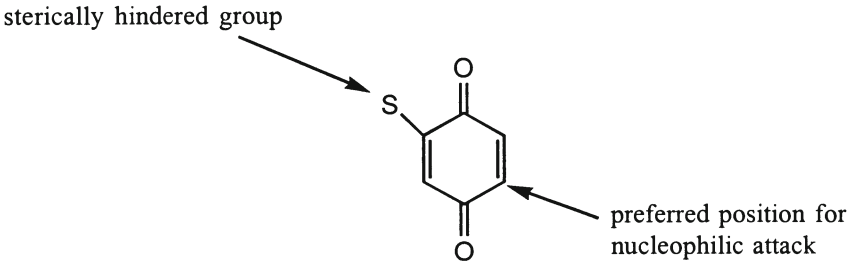
(ii) the electron- withdrawing group (W = CF_3, COOR) at the position-2 causes nucleophilic attack at carbon-3.



(iii) the small group with moderate electron-releasing effect (M = CH_3, Cl, Br, I) directs the nucleophile either to C-5 or C-6 giving a mixture of indoles.

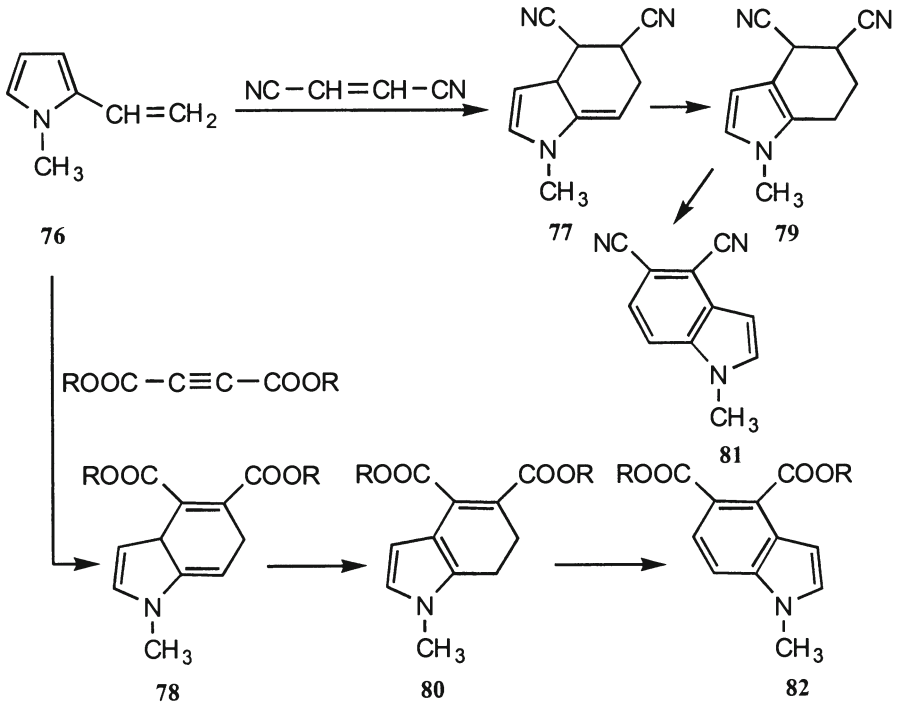


(iv) the sterically hindered group at the position-2 causes nucleophilic attack at C-5. The steric effects are superimposed on the electronic effects.



2.1.2.10 From Pyrroles

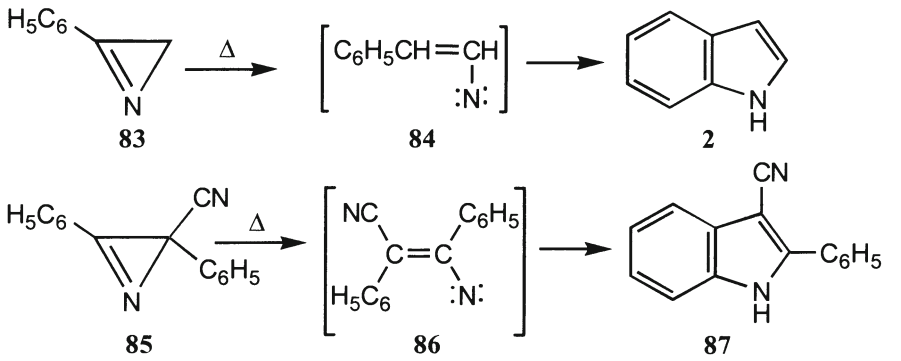
The reaction of 2- or 3-vinylpyrroles **76** with π-electron deficient alkenes and alkynes leads to the formation of the corresponding tetrahydro- **77** and dihydro- **78** indoles involving (4 + 2) cycloaddition reaction. The resulting tetrahydro- and dihydro-indoles can be easily aromatized to indoles **81** and **82**, respectively (scheme-17)[24,25].



Scheme-17

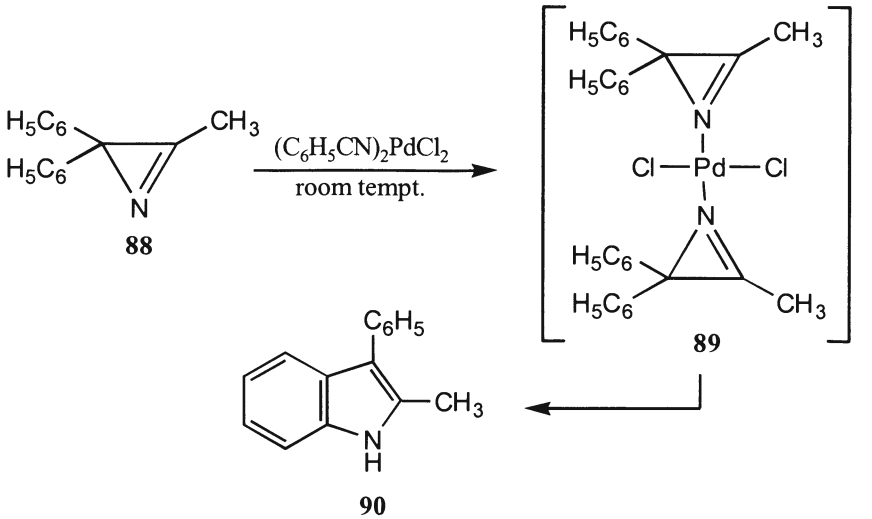
2.1.2.11 From Azirines

2*H*-Azirines are thermally transformed to indoles involving nitrene formation with the cleavage of carbon–nitrogen bond (scheme-18)[26,27]. Thermally initiated



Scheme-18

reactions, however, can be effected even at room temperature in the presence of transition metal catalyst. The reaction of 2*H*-azirines **88** with palladium complex at room temperature proceeds via complexation of azirine with palladium complex **89** with the formation of indoles **90** (scheme-19)[28].



Scheme-19

2.1.3 Structure

Indole is a planar molecule with sp^2-hybridized atoms (carbon atoms and nitrogen atom). The sp^2- hybrid orbitals of the carbon and nitrogen atoms overlap axially with each other and with s orbitals of the hydrogen atoms forming C–C, C–N, C–H and N–H σ-bonds. The unhybridized p-orbitals on the carbon and nitrogen atoms (perpendicular to the plane of σ-bonds) overlap laterally forming a π-molecular orbital with 10π-electrons (two electrons are contributed by nitrogen atom and eight electrons by carbon atoms) (Fig. 2). Indole is considered to be

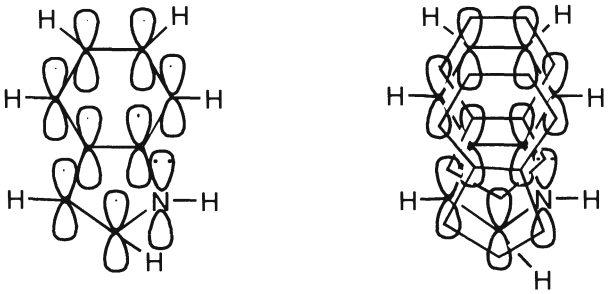
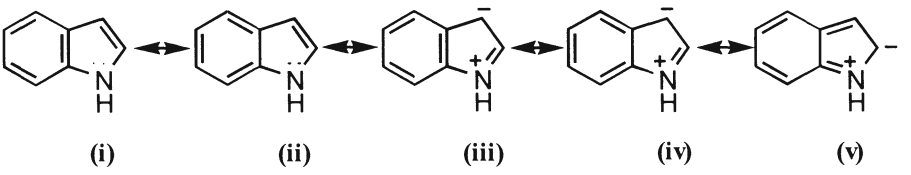


Fig. 2. Molecular orbital structure of indole

resonance hybrid of the following resonating structures (Fig. 3). Thus, indole is an aromatic heterocycle as it is cyclic planar with delocalized 10π electrons.



(i) **(ii)** **(iii)** **(iv)** **(v)**

Fig. 3. Resonating structures of indole

2.1.4 Reactions

Indole is constructed by the fusion of a benzene ring to the π-excessive pyrrole ring. The reactivity of indole is thereofore expected to be similar to that of pyrrole. But the fusion of a benzene ring to the 'β-face' of a pyrrole ring deactivates the position-2 of the resulting indole towards electrophilic attack (reverse of pyrrole).

Although in resonating structure (v) the position-2 is negatively charged (electron rich centre), the benzenoid character of the benzene ring is disturbed and does not contribute significantly to the resonance hybrid. The effect of the fusion of a benzene ring to the 'β-face' of a pyrrole ring is therefore to change the position of the greatest electron density of pyrrole from the position-2 to position-3.

2.1.4.1 Reactions with Electrophiles

The π-electron excessive character of indole makes it extremely susceptible to undergo electrophilic substitution reactions. The electrophilic substitution at the position-3 (β-substitution) is preferred over the substitution at the position-2 (α-substitution). The preferential β-substitution over α-substitution in the pyrrole ring of indole is rationalized by the comparable stabilities of the σ-complexes (transition states) resulting from the electrophilic attack at the positions -2 and -3 (Fig. 4).

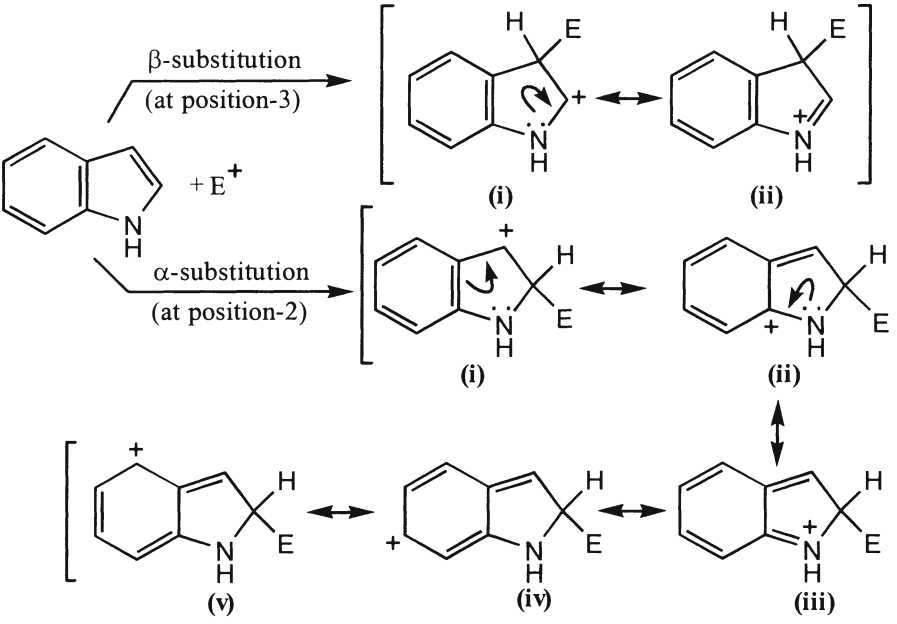


Fig. 4. Electrophilic substitution in indole

The σ-complex resulting from the electrophilic attack at the position-3 is contributed by the resonating structures involving effective stabilization due to the involvement of lone pair on nitrogen without disruption of the benzenoid structure. But, in contrast, the σ-complex resulting from the electrophilic attack at

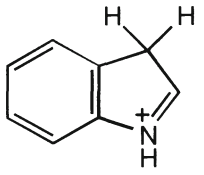
the position-2 (α-substitution) involves resonating structures with the charge distribution over the benzene ring disrupting the benzenoid structure. Thus, the stabilizing influence of nitrogen on σ-complex (transition state) is more effective if resonating structure is with benzenoid structure (β-substitution) than that in which benzenoid structure is not retained (α-substitution).

However, if position-3 is already substituted, the electrophilic substitution in indole occurs at the position-2 initially with the formation of 3,3-disubstituted 3*H*-indole which then rearranges to 2,3-disubstituted indole. The presence of electron-withdrawing substituents at the position-1, -2 or -3 of the pyrrole ring deactivates the pyrrole ring of indole towards electrophilic attack and the substitution occurs in the benzene ring in the positional reactivity order : 6 > 4 > 5 > 7. The electron-releasing substituents on the benzene ring exert normal directional influence on the electrophilic substitution[29].

2.1.4.1.1 Protonation

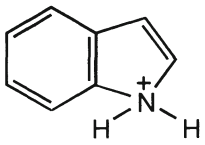
2.1.4.1.1.1 Reaction with Proton Acids

Protonation of indole in a dilute acid produces stable 3*H*-indolium cation **91**, but in strong acidic conditions the protonation can also occur at the positions-1 and -2 with the formation of 1*H*-indolium- **92** and 2*H*-indolium- **93** cations.



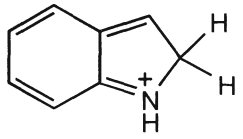
3*H*-Indolium cation

91



1*H*-Indolium cation

92



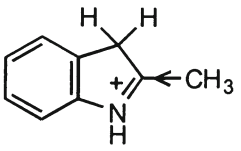
2*H*-Indolium cation

93

The thermodynamic stability of 3*H*-indolium cation **91** over 1*H*-indolium cation **92** and 2*H*-indolium cation **93** is attributed to its resonance stabilization with the retention of benzenoid character of the benzene ring and the delocalization of the positive charge over nitrogen and carbon-2. 1*H*-Indolium cation **92** resulting from the protonation at nitrogen, although retains the benzenoid structure, involves localization of positive charge on nitrogen causing instability to the cation. The instability of 2*H*-indolium cation **93** is due to the disruption of benzenoid structure and the localization of positive charge on nitrogen.

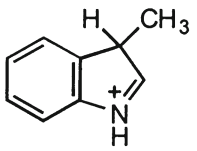
2.1.4.1.1.2 Basicity

Indoles are very weak bases. The pKa values for indoles are: indole (–3.6), 1-methylindole (–2.3), 2-methylindole (–0.3) and 3-methylindole (–4.6). Thus, it is evident that the methyl groups at the positions-1 and -2 enhance basicity by 1000 times. But the methyl group at the position-3 exerts unusual effect and decreases basicity by approximately 1.0 pKa. The enhanced basicity of 2-methylindole is attributed to the stabilization of 2-methyl-3*H*-indolium cation **94** due to electron-releasing effect of the methyl group at the position-2, while the lower basicity of 3-methylindole than indole is because of its stabilization in unprotonated form due to the hyperconjugative stabilizing effect exerted by the methyl group at the position-3. Moreover, the greater hyperconjugative stabilization of 2-methyl-3*H*-indolium cation **94** due to two hydrogen atoms at the position-3 than that of 3-methyl-3H-indolium cation **95** involving only one hydrogen at the position-3 is also considered the cause of stronger base strength of 2-methylindole.



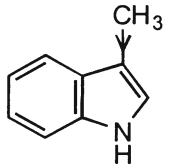
2-Methyl-3*H*-indolium cation

94



3-Methyl-3*H*-indolium cation

95

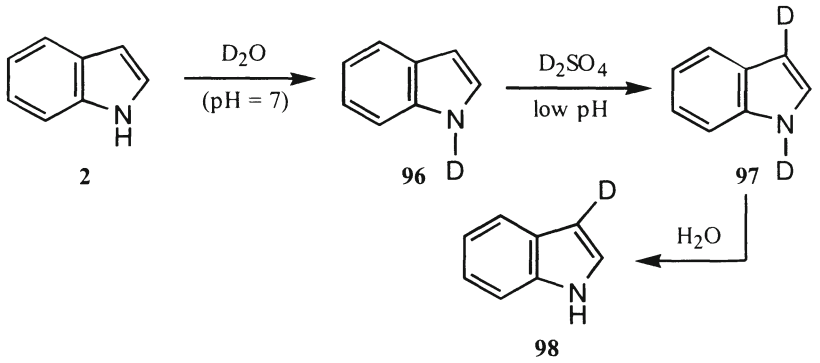


3-Methylindole

24

2.1.4.1.1.3 H $\rightleftharpoons$ D Exchange

The exchange of hydrogen attached to nitrogen in indole is most rapid when treated with weakly acidic D_2O (deuterium oxide). The exchange of hydrogen at carbon does not occur at an appreciable rate (pH=7). The ratio of exchange rates is; 300 : 1 (N-H : C_3–H). The higher exchange rate of N–H than C_3–H is attributed to the lower activation energy of N–H bond breaking than that of C–H bond breaking, thus making N–H exchange more favourable than that at carbon-3 (C–H exchange). However, with increasing acidity (low pH), the exchange of hydrogen at carbon-3 is very much faster than at other carbon atom (scheme-20)[30]. Although N–H exchange is most rapid in the acid solution also, the concentration is very low and the equilibrium is shifted to the side of unprotonated indole.



Scheme-20

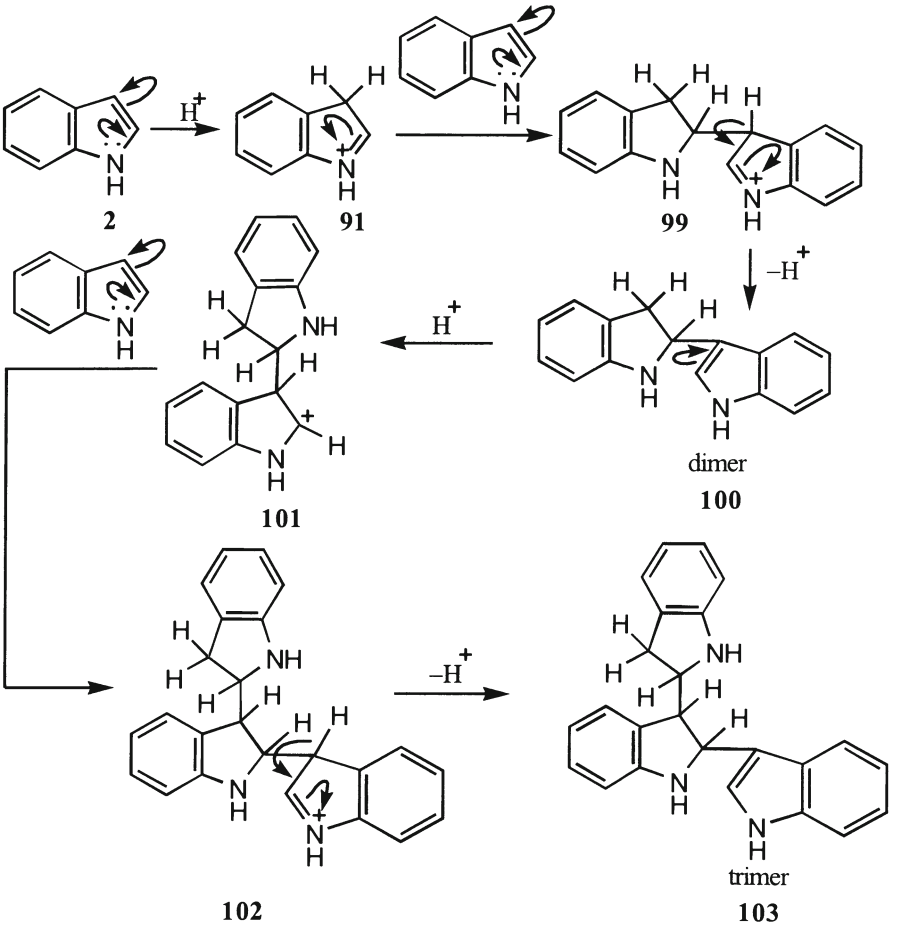
2.1.4.1.1.4 Dimerization and Trimerization

Indole undergoes acid-catalyzed dimerization and produces dimer, 2-(3-indolyl) indoline **100**. The dimerization proceeds via 3*H*-indolium cation **91** which acts as an electrophile and attacks the second molecule of indole providing dimer **100.** The protonation of dimer **100** produces an electrophilic species **101** which with another molecule of indole provides a trimer **103** (scheme-21)[31].

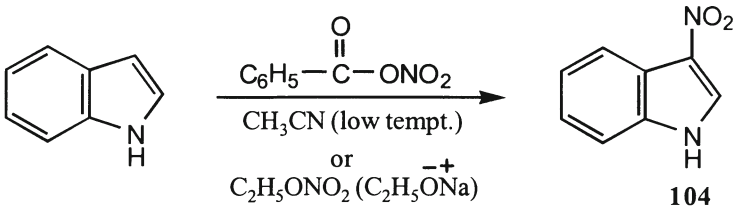
2.1.4.1.2 Nitration

Because of the acid sensitivity of indole nucleus, the products of nitration of indoles with different nitrating agents depend upon the reaction conditions. The nitration of indole in strongly acidic conditions with normal nitrating agents (conc. HNO_3 + conc. H_2SO_4) results in the formation of polymeric products. But the nitration of indole with benzoyl nitrate in acetonitrile or with ethyl nitrate in the presence of sodium ethoxide at low temperature provides 3-nitroindole **104** (scheme-22)[32].

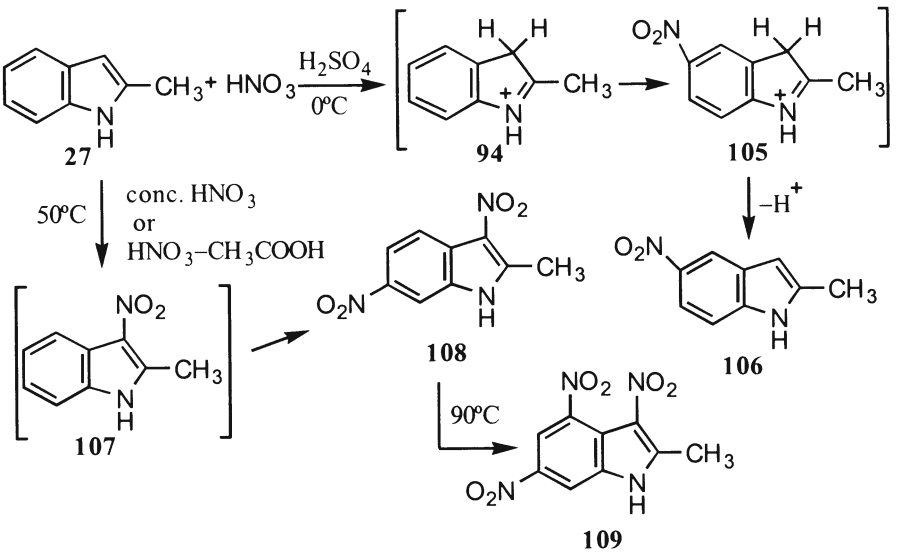
However, 2-methylindole **27** because of its increased acid stability due to the presence of methyl group at the position-2 requires vigorous conditions for the nitration. The nitration of 2-methylindole with concetrated nitric acid in the presence of concetrated sulfuric acid at 0°C affords 2-methyl-5-nitroindole via 2-methyl-3*H*-indolium cation **94** rather than substitution at C-3 because the protonation of position-3 deactivates indole for further electrophilic attack and substitution occurs at C-5 (similarly as *m*-nitration of aniline involving nitration of cation). However, with concetrated nitric acid alone or with nitric acid-acetic acid at 50°C, the nitration occurs at the positions-3 and -6 with the formation of 3,6-dinitro derivative via 2-methyl-3-nitroindole **107**. If the reaction temperature is raised to 90°C, 3,4,6-trinitro derivative **109** is obtained (scheme-23).



Scheme-21

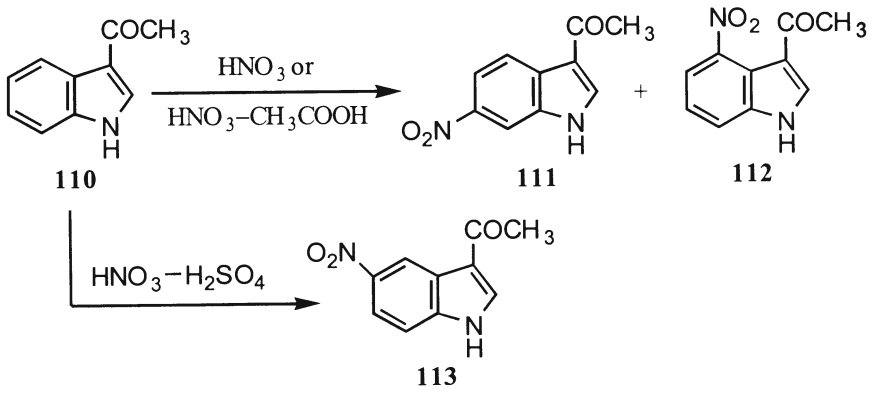


Scheme-22

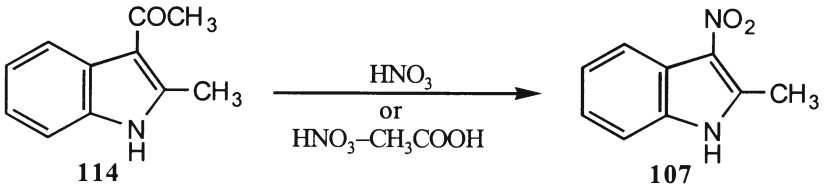


Scheme-23

The presence of electron-withdrawing substituent at the position-3 deactivates the heterocyclic ring and directs the attack of nitronium ion on the benzene ring (scheme-24). However, the presence of methyl group at position-2, in addition to the acyl group at the position-3, facilitates the substitution of acyl group by nitro group (*ipso-* substitution) involving nitro-deacylation by enhancing the reactivity of position-3 towards electrophilic attack of nitronium ion due to its electron-releasing effect (scheme-25)[32].



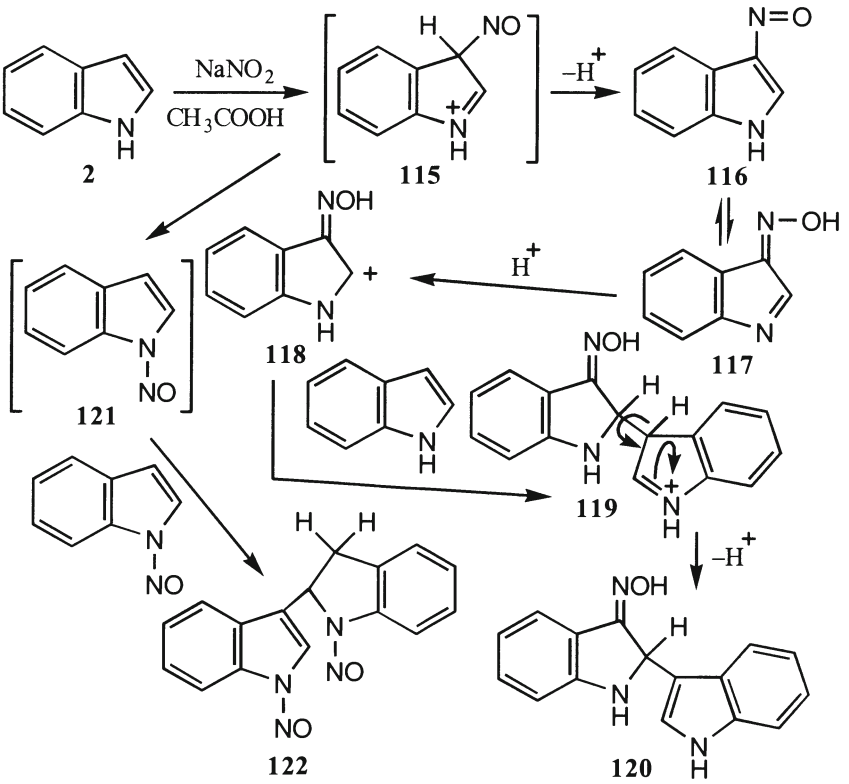
Scheme-24



Scheme-25

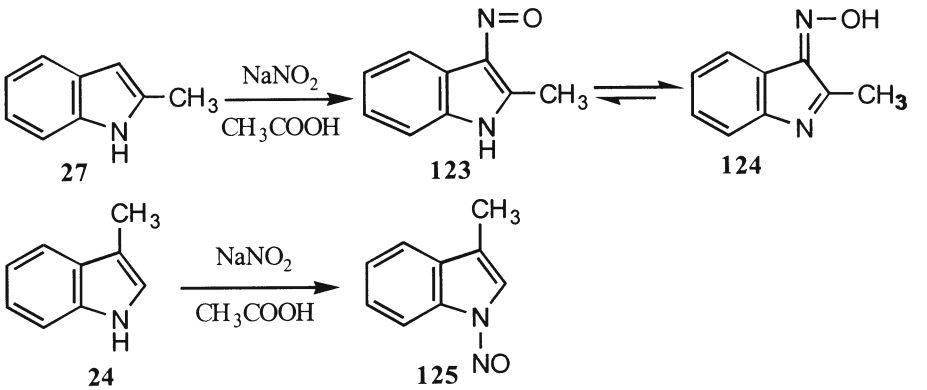
2.1.4.1.3 Nitrosation

The reaction of indole with nitrous acid proceeds rapidly via 3-nitroso-3*H*-indolium intermediate **115** with the formation of a complex mixture containing dimeric products **120** and **122** alongwith 3-nitrosoindole **116**, which exists in equilibrium with its stable tautomeric form 3-oximino-3*H*-indole **117**. If indole is treated with amyl nitrite and sodium ethoxide, the nitrosation results in 3-oximino-3*H*-indole **117** exclusively (scheme-26)[32].



Scheme-26

The nitrosation of 2-methylindole **27** with sodium nitrite in the presence of acetic acid occurs at the position-3 with the formation of only 3-oximino-2-methylindole **124**, stable tautomeric form of 3-nitroso-2-methylindole **123**. If 3-methylindole is nitrosated, N-nitroso-3-methylindole **125** is obtained (scheme-27)[32]. The formation of N-nitroso derivative substantiate the kinetic studies on 2-methylindole that C-nitrosation proceeds via N-nitrosation[33,34].

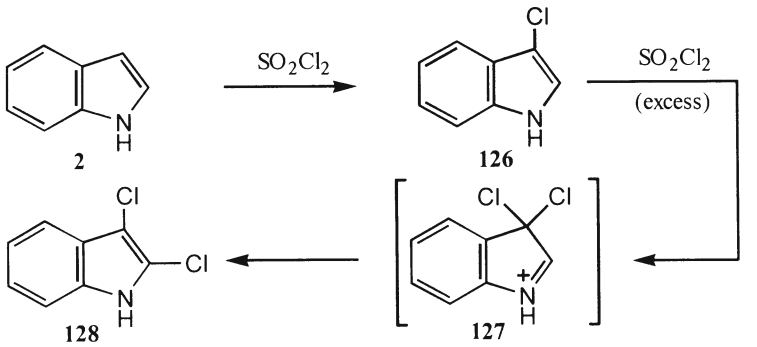


Scheme-27

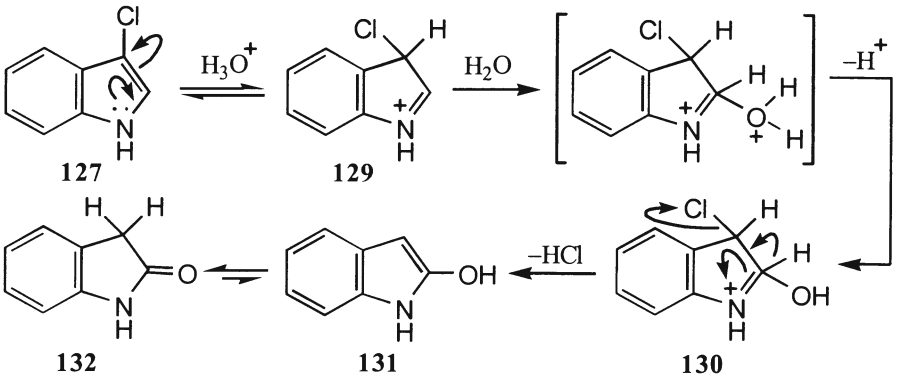
2.1.4.1.4 Halogenation

2.1.4.1.4.1 Chlorination

Chlorination of indole with sulfuryl chloride affords 3-chloroindole **126**. But with an excess of sulfuryl chloride 3-chloroindole so produced reacts further with sulfuryl chloride and provides 2,3-dichloroindole **128** via 3,3-dichloro-3H-indole **127** (scheme-28)[35]. 3-Chloroindole **126** is stable at high pH, but under acidic conditions it is hydrolyzed to oxindole **132**. (scheme-29)[36].

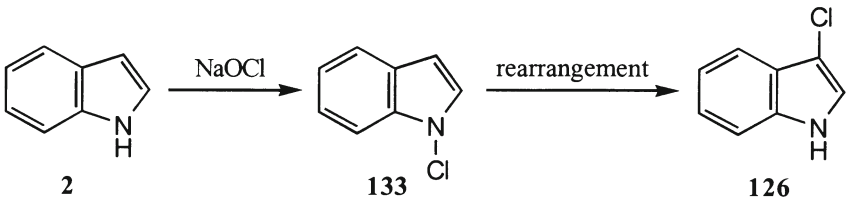


Scheme-28

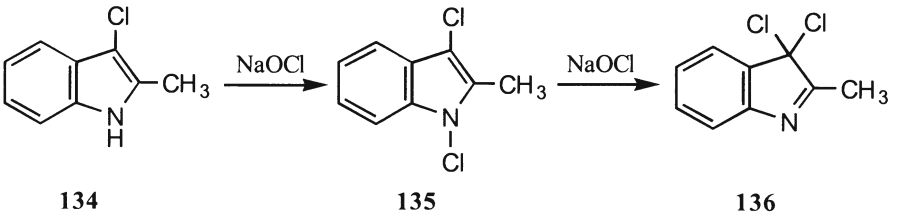


Scheme-29

The chlorination of indole with sodium hypochlorite, however, proceeds to involve N-chloroindole **133** which subsequently rearranges to 3-chloroindole **126** (scheme-30)[37,38]. If methyl group is present at the position-2, 3-chloro-2-methylindole **134** produced reacts with an excess of sodium hypochlorite and results in 3,3-dichloro-2-methyl-3*H*-indole **136** via the rearrangement of 1,3-dichloro-2-methylindole **135** (scheme-31)[37].



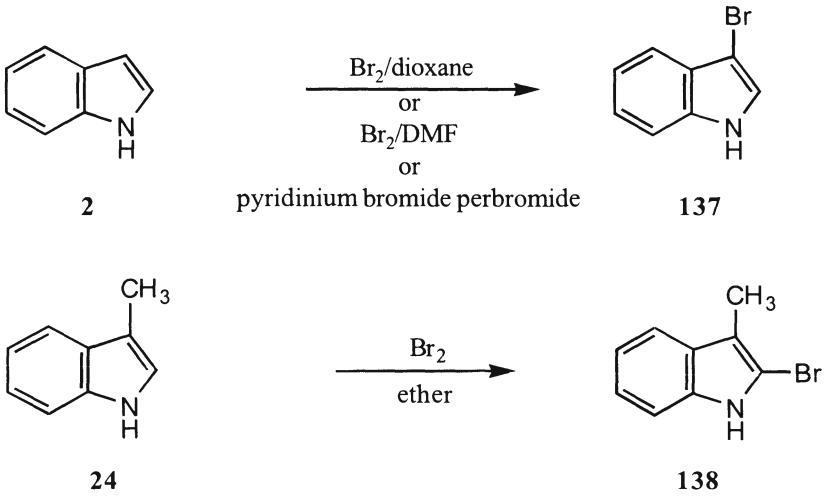
Scheme-30



Scheme-31

2.1.4.1.4.2 Bromination

Bromination of indole occurs at the position-3 with the formation of 3-bromoindole **137.** If the position-3 of indole is already substituted, the bromination takes place at the position-2 (scheme-32)[39].

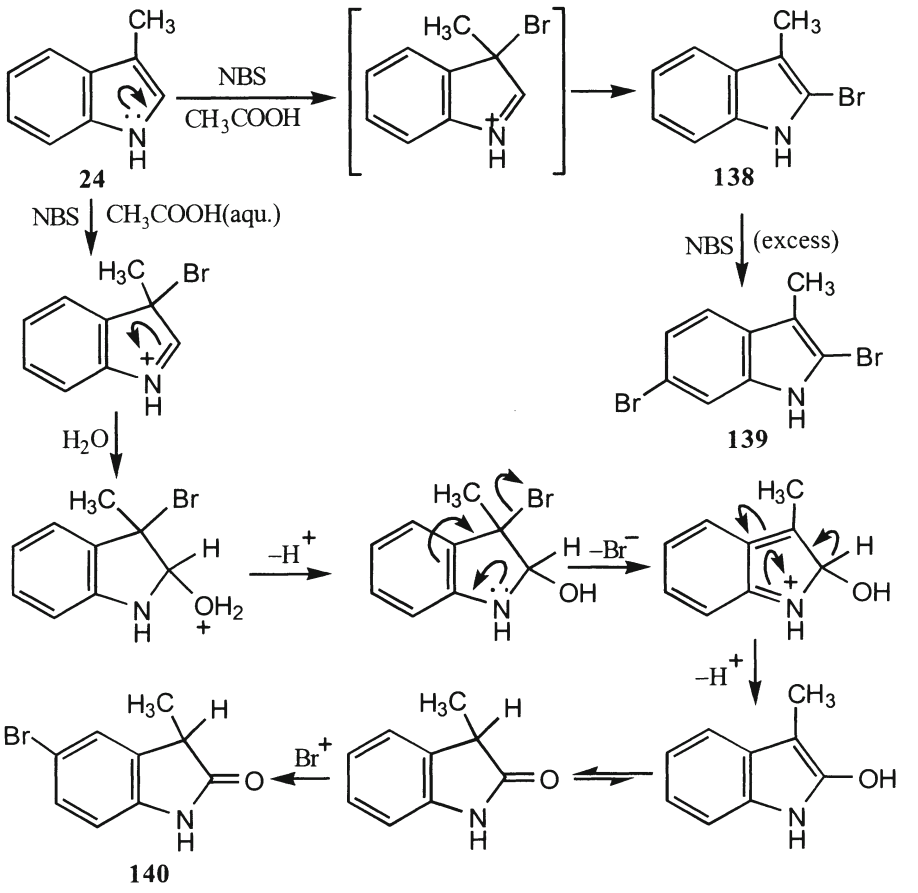


Scheme-32

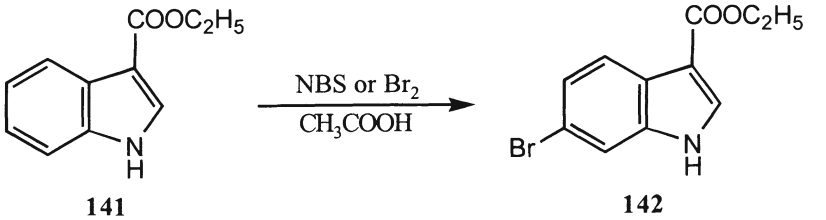
Bromination of 3-methylindole **24** with N-bromosuccinimide in the presence of acetic acid gives 2-bromo-3-methylindole **138** which further reacts with an excess of N-bromosuccinimide with the formation of 2,6-dibromo-3-methylindole **139**. If reaction is carried out in aqueous or alcoholic media, 5-bromo-3-methyloxindole **140** is produced (scheme-33)[36,40]. Thus, the reactions not only depend on the directive influence of the substituent already present, but also upon the reaction conditions. If the position-3 is occupied by an electron-withdrawing substituent, the heterocyclic ring is deactivated for the electrophilic attack and the bromination occurs in the benzene ring (scheme-34)[41].

2.1.4.1.4.3 Iodination

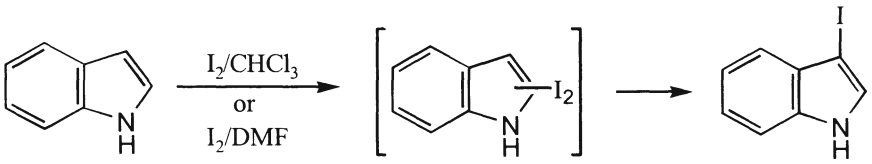
The reaction of indole with iodine in the presence of chloroform at low temperature produces 1:1 charge-transfer complex **143** which collapses to 3-iodoindole **144** (scheme-35). If the position-3 is occupied, iodination takes place at the position-2.



Scheme-33



Scheme-34

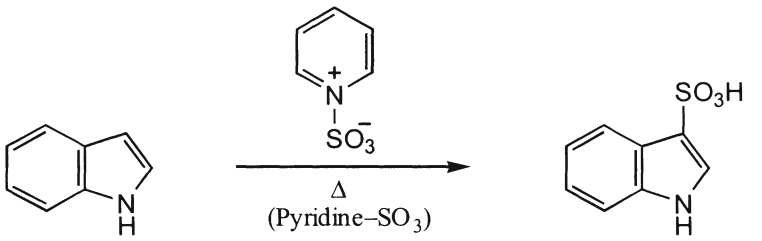


1:1 complex
143 **144**

Scheme-35

2.1.4.1.5 Sulfonation

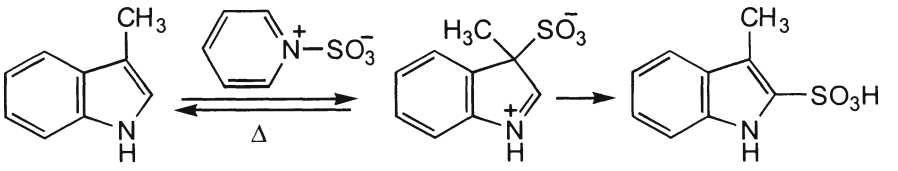
Indole, because of its acid sensitivity, is sulfonated with pyridine–sulfur trioxide complex and provides indole-3-sulfonic acid **145**[42] instead of indole-2-sulfonic acid as erroneously reported earlier in the literature (scheme-36)[43].



2 **145**

Scheme-36

If the position-3 is already occupied, the sulfonation occurs at the position-2 via an initial reversible sulfonation at the position-3 (scheme-37).



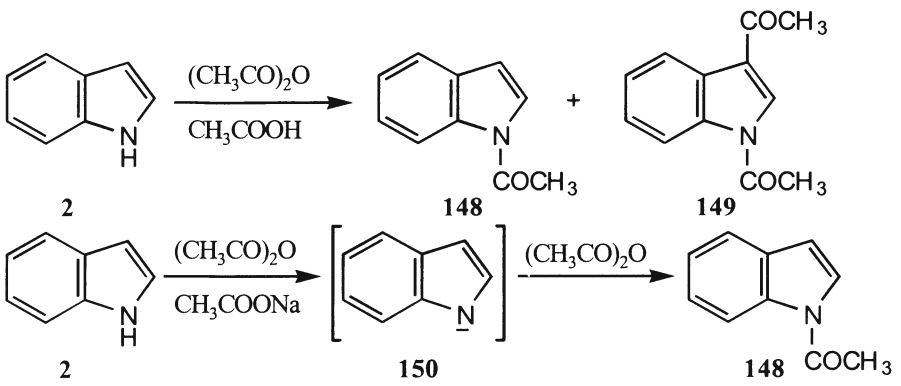
24 **146** **147**

Scheme-37

2.1.4.1.6 Acylation

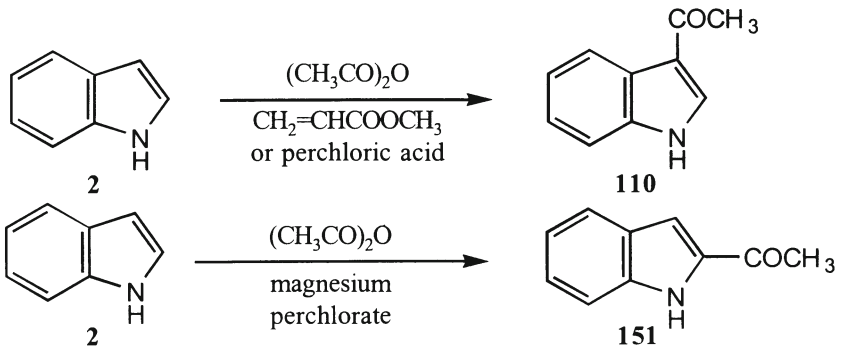
2.1.4.1.6.1 Friedel–Crafts Acylation

Indoles substituted with electron-withdrawing substituents undergo Friedel–Crafts acylation. However, indole with acetic anhydride in the presence of acetic acid produces 1-acetyl- **148** and 1,3-diacetyl- **149** indoles. But with acetic anhydride in the presence of sodium acetate, the reaction proceeds via an anion **150** with the formation of 1-acetylindole exclusively (scheme-38).



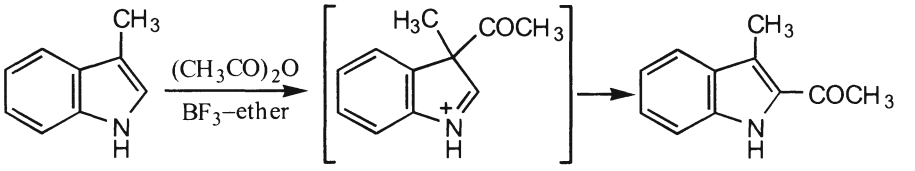
Scheme-38

The reaction of indole with acetic anhydride in the presence of vinyl acetate or perchloric acid produces 3-acetylindole **110**. If indole is treated with acetic anhydride in the presence of magnesium perchlorate, 2-acetylindole **151** is obtained (scheme-39)[41]. If the position-3 of indole is already substituted, acylation



Scheme-39

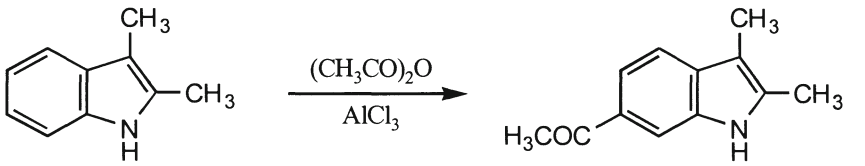
occurs at the position-2 involving rearrangement of initially formed 3-acetyl-3-substituted indolium ion **152** (scheme-40). However, if both the positions in



24 **152** **153**

Scheme-40

heterocyclic ring of indole are substituted by the methyl groups, the acylation with acetic anhydride in the presence of anhydrous aluminium chloride takes place on the benzene ring (scheme-41)[41].



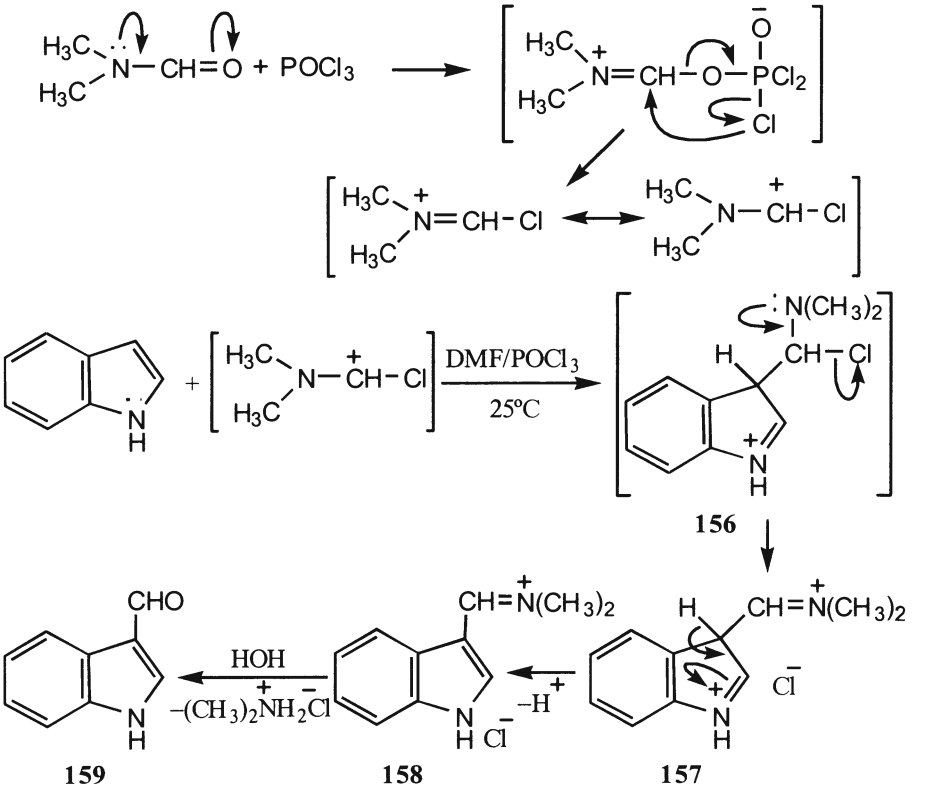
154 **155**

Scheme-41

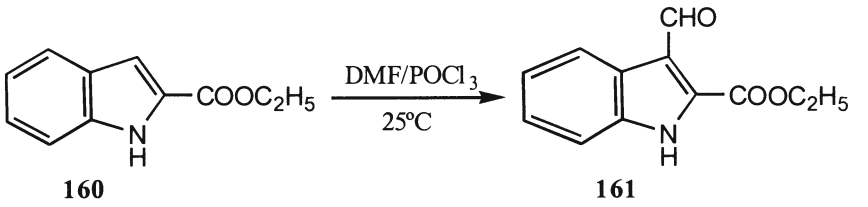
2.1.4.1.6.2 Vilsmeier–Haack Formylation

Indole undergoes Vilsmeier-Haack formylation with the formation of 3-formylindole **159** when treated with N,N-dimethylformamide (DMF) in the presence of phosphorus oxychloride. The reaction is considered to involve the attack of immonium chloride electrophile at the position-3 and proceeds as in (scheme-42).

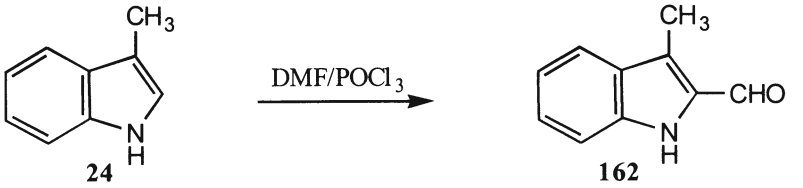
However, indoles substituted even with electron-withdrawing substituents at the position-2 undergo formylation at the position-3 under Vilsmeier–Haack conditions (scheme-43). If position-3 is substituted with an electron-withdrawing substituent, the formylation at the position-2 is difficult. The presence of an electron-releasing substituent at the position-3, however, facilitates formylation at the position-2 (scheme-44)[41].



Scheme-42



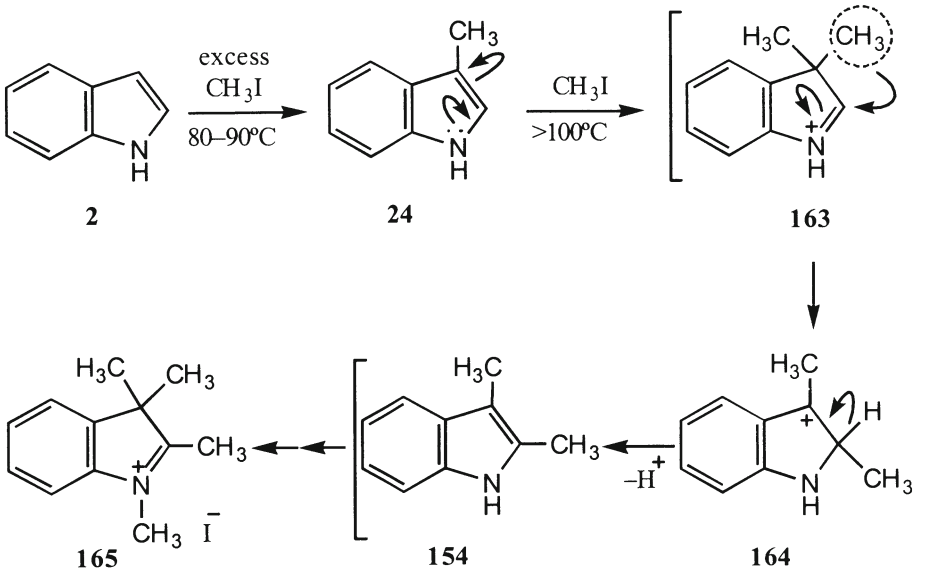
Scheme-43



Scheme-44

2.1.4.1.7 Alkylation

The reaction of indole with an excess of methyl iodide in the presence of DMF at 80-90°C produces 3-methylindole **24**. But at an elevated temperature (>100°C) further methylation proceeds via 3,3-dimethyl-3*H*-indolium ion **163** with the formation of 2,3-dimethylindole **154** which on methylation finally leads to the formation of 1,2,3,3-tetramethyl-3*H*-indolium iodide **165** (scheme-45).

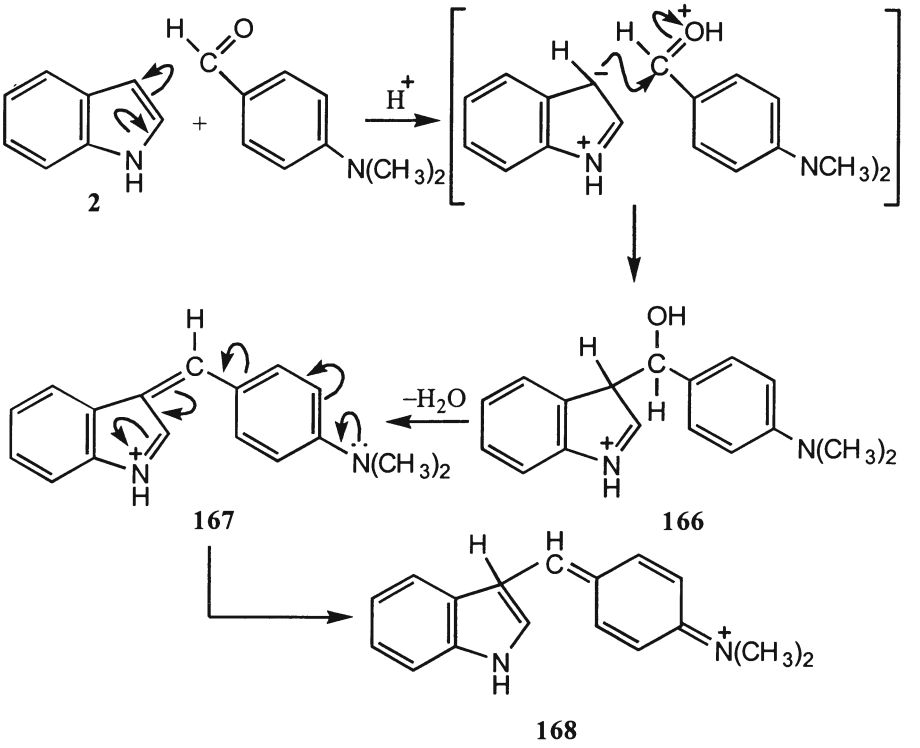


Scheme-45

2.1.4.1.8 Reactions with Aldehydes and Ketones

2.1.4.1.8.1 Ehrlich Test

The acid catalyzed reaction of *p*-N,N-dimethylaminobenzaldehyde with indoles unsubstituted at the position-3 (free reactive position) produces purple-red colouration which is attributed to the formation of coloured salt **168** (scheme-46)[29,44,45]. If the position-3 is substituted, the reaction takes place at the position-2 but very slowly. The sensitivity of the reaction (Ehrlich test) depends upon the substituents on the heterocyclic ring. The electron-withdrawing substituents retard the reaction, while electron-releasing substituents enhance the rate of the reaction by stabilizing the resulting cation **168**.



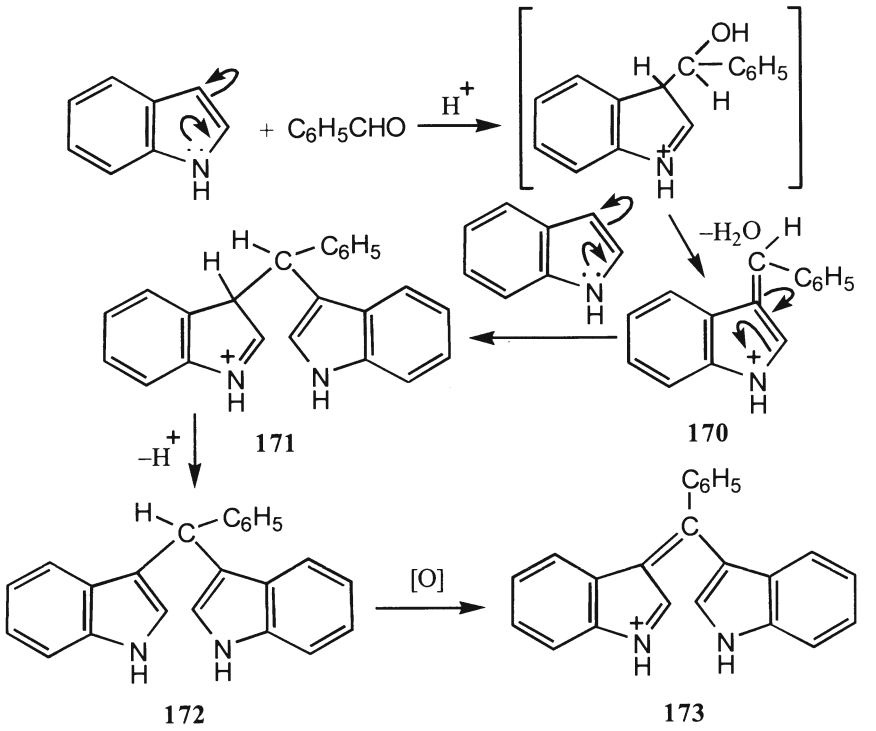
Scheme-46

2.1.4.1.8.2 With Aromatic Aldehydes and Ketones

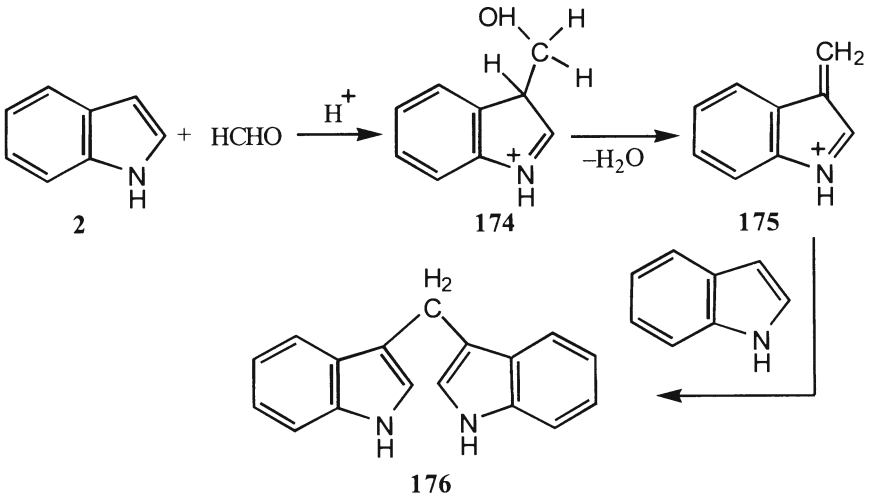
The reaction of indole with aromatic aldehydes or ketones in the presence of hydrochloric acid also produces similar type of coloured cation as with *p*-N,N-dimethylaminobenzaldehyde. The resulting cation **170** is stabilized if the aromatic aldehydes or ketones bear electron-releasing substituents otherwise subsequently reacts with a second molecule of indole providing colourless bisindolylmethane **172** which can be oxidized to a coloured cation **173** (scheme-47).

2.1.4.1.8.3 With Aliphatic Aldehydes and Ketones

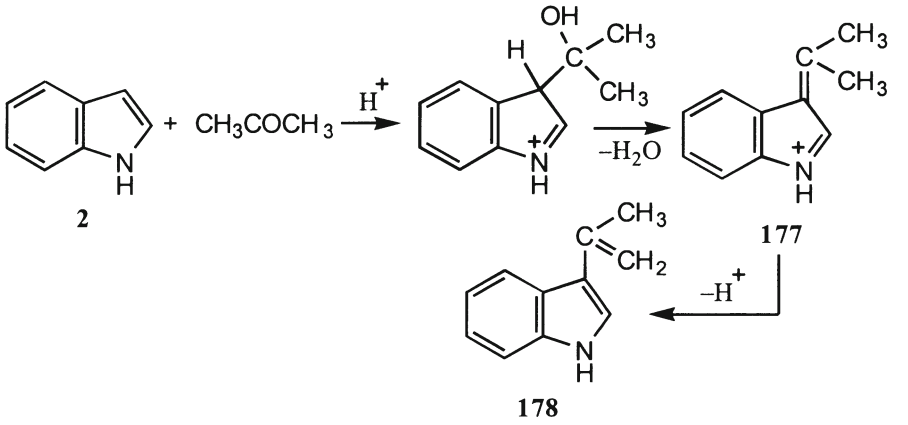
The reaction of indole with aliphatic aldehydes is similar to that with aromatic aldehydes and produces the corresponding unstable cation **175** which subsequently with a second molecule of indole produces bisindolylmethane **176** (scheme-48). But with aliphatic ketone, 3-vinylindole derivative **178** is formed (scheme-49).



Scheme-47



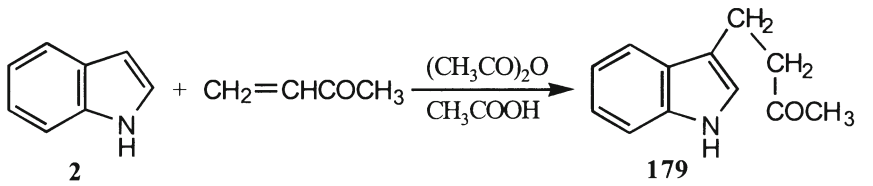
Scheme-48



Scheme-49

2.1.4.1.8.4 With α,β-Unsaturated Ketones

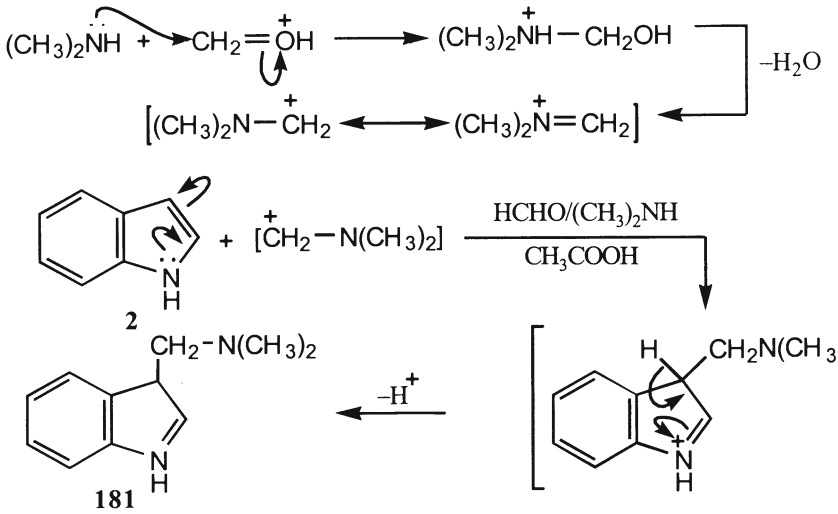
The reaction of indole with α,β-unsaturated ketone involves Michael type addition at the position-3 of indole providing α,β-alkylated product **179** (scheme-50).



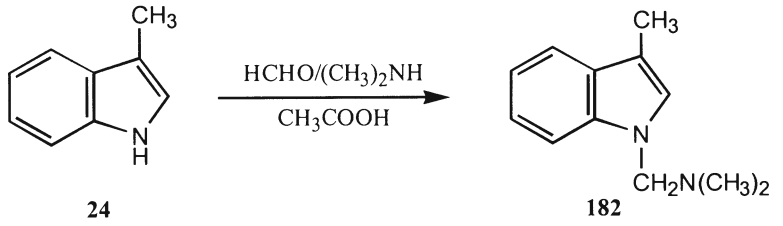
Scheme-50

2.1.4.1.9 Mannich Reaction

The reaction of indole with formaldehyde and N,N-dimethylamine in the presence of a weak acid results in aminomethylation with the formation of 3-N,N-dimethylaminomethylindole (gramine) **181**. The reaction involves β-attack of an elctrophile immonium ion, generated by the reaction of formaldehyde with N,N-dimethylamine, and proceeds as depicted in (scheme-51)[36]. When the position-3 is occupied, the aminomethylation occurs at the position-1 rather than at the position-2, thus indicating the low reactivity of the position-2 (scheme-52)[46].



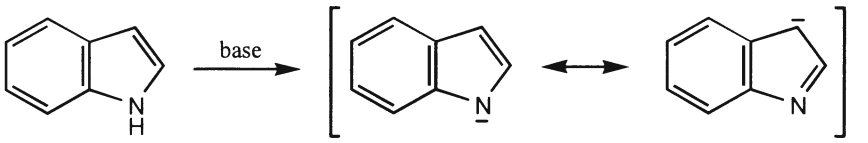
Scheme-51



Scheme-52

2.1.4.2 Reactions on Carbon and Nitrogen Anionic Species

The pKa value for N–H dissociation of indole (20.95) is comparable with that of pyrrole (23.05)[47]. Like pyrrole, indole undergoes deprotonation when treated with sodamide, potassium hydroxide, n-butyllithium or Grignard reagents with the formation of N-indolyl salts. The resulting salts exist as contact ion pairs or solvent separated ion pairs (with alkali metals) or with high N–metal covalent character (heavier metals). These characteristics of the salts control the reactions of N-indolyl anion. The N-indolyl anion **150a** produced by the abstraction of hydrogen atom by a base is stabilized by resonance (scheme-53). Because of the ambident nature of an indolyl anion the attack of an electrophile occurs at the nitrogen atom or at the carbon atom depending on the nature of the metal ion, attacking reagent, solvent and temperature.

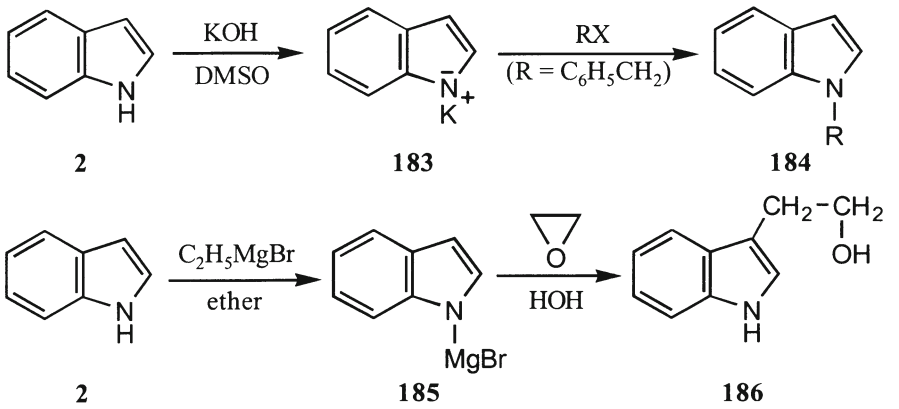


2 **150a** **150b**

Scheme-53

2.1.4.2.1 Alkylation

The site of alkylation in the indolyle salts is generalized on the basis of the 'hard-soft acid-base' concept. The salts of the soft cations (Na^+, K^+) which exist as solvent separated ion pairs or contact ion pairs produce predominantly N-alkylated products, whereas the salts of the harder cations (Mg^{+2}) lead to substitution preferentially at carbon-3 (scheme-54)[48].

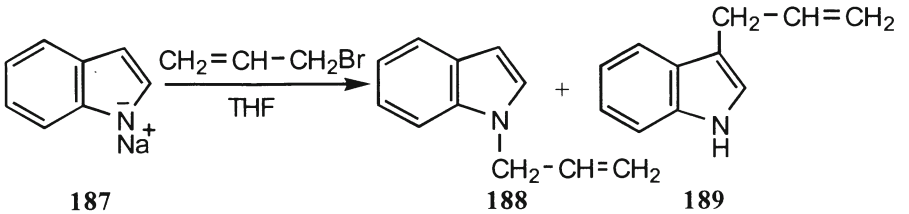


2 **183** **184**

2 **185** **186**

Scheme-54

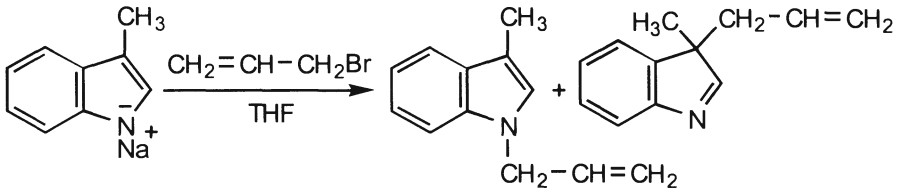
The alkylating agents such as allyl halides which are capable of producing electrophile very readily favour C-alkylation (scheme-55)[36]. If the position-3 is



187 **188** **189**

Scheme-55

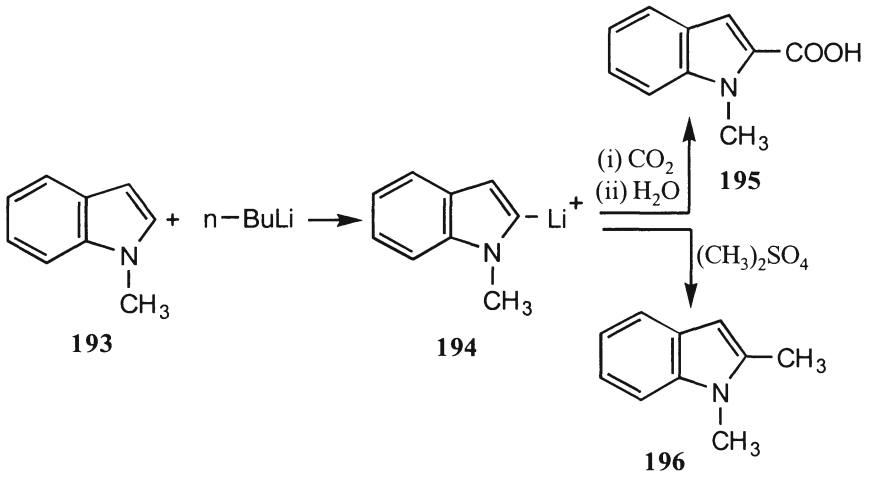
substituted, 3-substituted 1-allylindole **191** and 3,3-disubstituted-3*H*-indole **192** are obtained (scheme-56)[49].



190 **191** **192**

Scheme-56

N-Alkylindoles are selectively lithiated at the position-2 when treated with n-butyllithium (scheme-57).



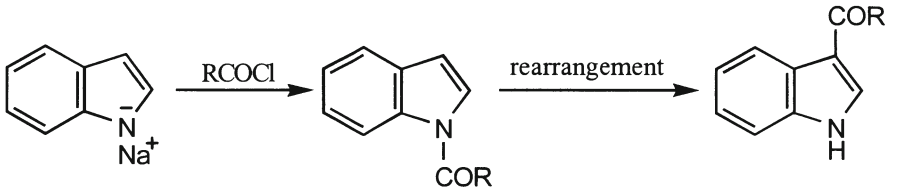
193 **194**

Scheme-57

The alkylation of indole at higher temperature and pressure favours substitution at carbon-3. The presence of electron-withdrawing substituents at the α- or β-position of indole increases its acidity and the mild conditions are required for the alkylation.

2.1.4.2.2 Acylation

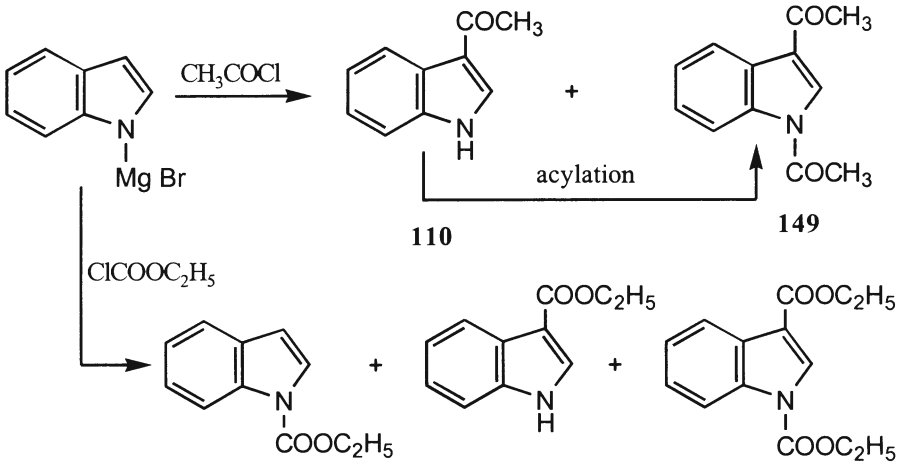
Similarly as in alkylation, the acylation of the indolyl salts with soft cations produces N-acylated products which thermally rearrange readily to the corresponding C-acylated products (scheme-58)



187 **193** **37**

Scheme-58

The acylation of indolylmagnesium halides with acylating reagents is complicating as compared to the alkylation reactions and the formation of the products depends upon the nature (stronger) of acylating regents. The acylation of indolylmagnesium halide with acyl chlorides produces 3-acyl- **110** and 1,3-diacyl- **149** indoles, while with ethylchloroformate acylation occurs at the position-1 providing ethyl indole-1-carboxylate **194** alongwith ethyl indole-3-carboxylate **141** and indole-1,3-dicarboxylic ester **195** (scheme 59)[50]. The change in the site of acylation depends



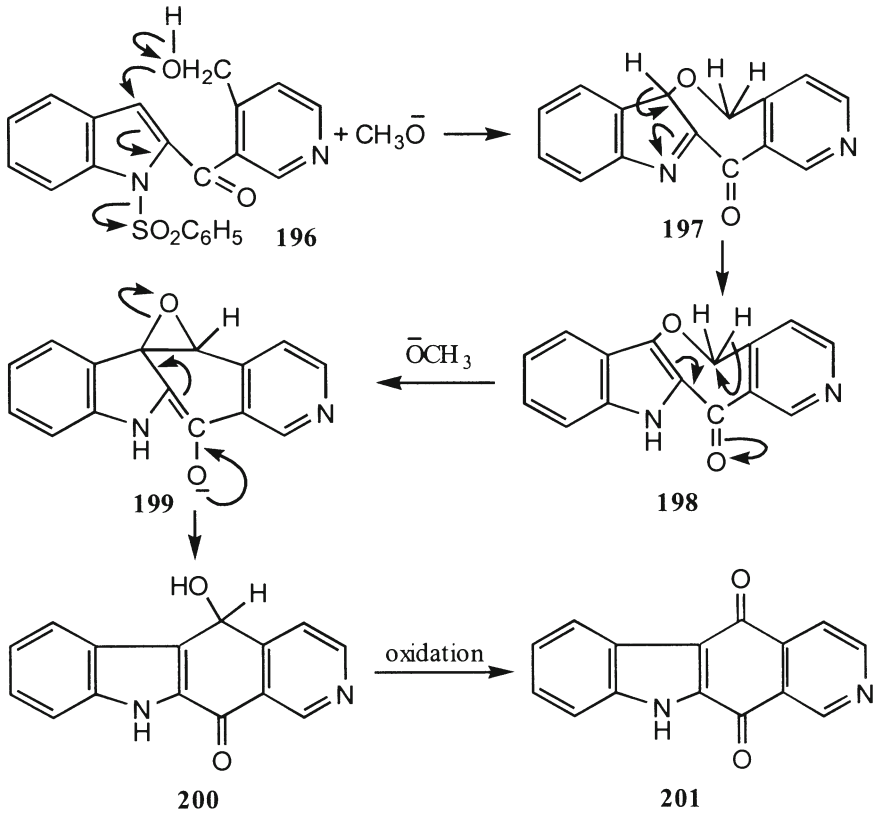
194 **141** **195**

Scheme-59

upon the ability of changing nature of the metal ion and its association with an indolyl anion. However, the presence of electron-withdrawing substituents on an indolyl anion stabilizes the anion and reduces its association with the metal cation which causes acylation to occur preferentially at the nitrogen atom. But with electron-releasing substituents C-acylation is preferred[36].

2.1.4.3 Reactions with Nucleophiles

π-Electron excessive character of indole makes it relatively inert towards nucleophilic attack. However, indoles substituted with electron-withdrawing substituents at the nitrogen atom undergo nucleophilic substitution reactions. Suitably substituted 2-acyl-1-benzenesulfonylindoles **196** undergo intramolecular nucleophilic substitution at C-3 in the presence of a base with the elimination of benzenesulfonyl group providing indolyl ethers **198** which on base catalyzed reaction yield quinones **201** related to the anticancer alkaloid ellipticine (scheme-60)[51-53].

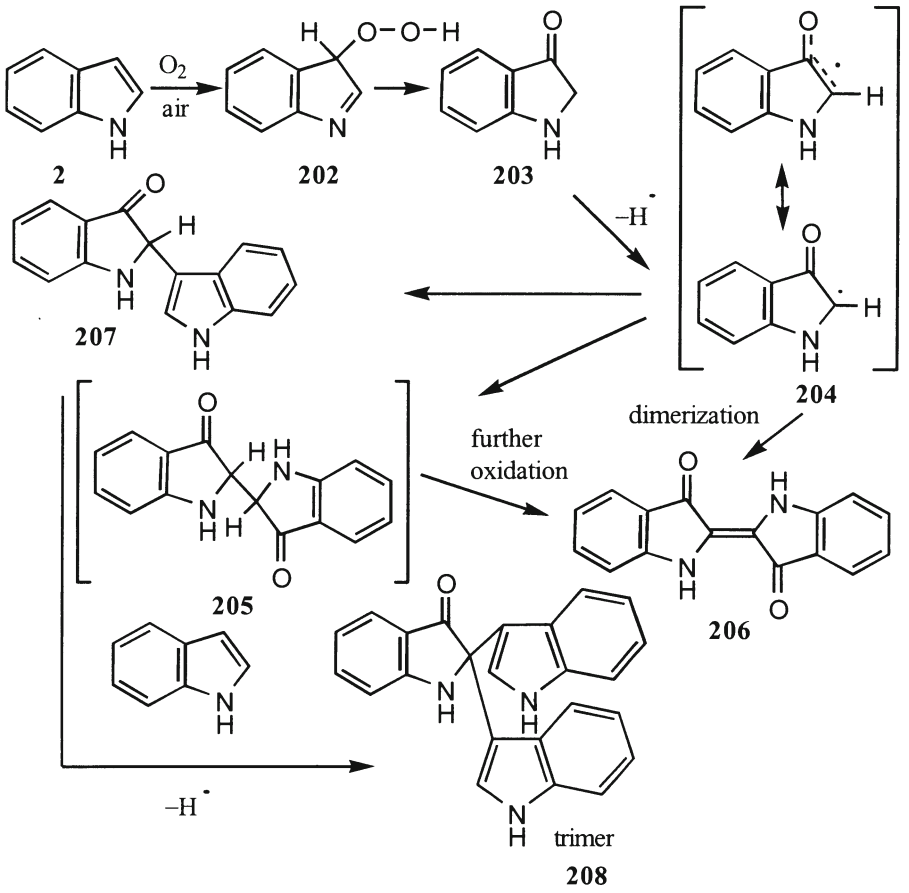


Scheme-60

2.1.4.4 Oxidation

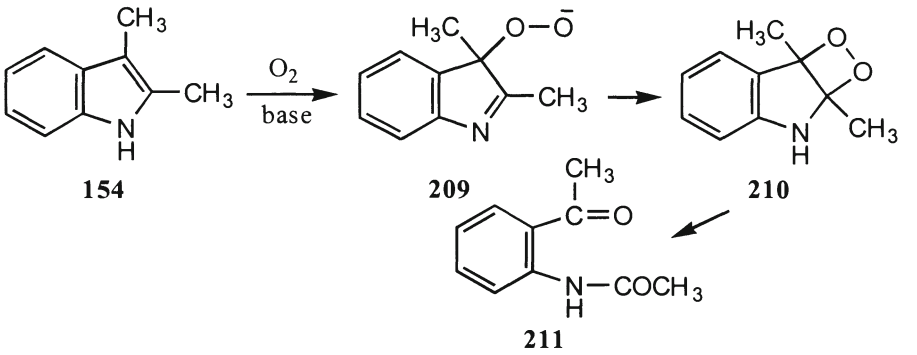
Indoles are comparatively less susceptible than pyrrole towards oxidation and produce monomeric, dimeric and trimeric oxidation products. The presence of electron-releasing substituents enhances the susceptibility of indoles towards oxidation, while indoles with electron-withdrawing substituents are relatively inert.

Indole is oxidized by air with the formation of indolin-3-one (indoxyl) **203** via 3-hydroperoxy-3H-indole **202**. The radical **204** formed by the abstraction of hydrogen atom from the position-2 of indolin-3-one **203** is stabilized and can dimerize to produce indigo **206** or can react further with the formation of **207** and **208**. The formation of **207** and **208** can be rationalized in terms of nucleophilic attack by non-oxidized indoles upon the oxidized intermediate at the position-2 (scheme-61)[29].



Scheme-61

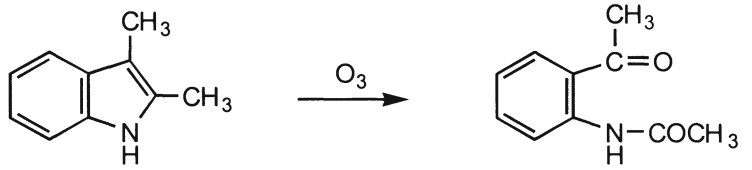
The base catalyzed autoxidation of indoles leads to the cleavage of C_2–C_3 bond with the formation of 2-acylaminophenyl ketones **211** via dioxetane derivatve **210** involving the attack of electrophilic oxygen at the position-3 followed by the nucleophilic attack of the peroxide anion at the position-2 (scheme 62).



154 **209** **210** **211**

Scheme-62

Oxidation of indoles with ozone also results in the cleavage of C_2–C_3 bond with the fomation of 2-acylaminophenyl ketones **211** (scheme-63)[54].



154 **211**

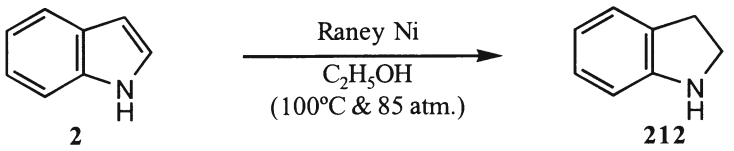
Scheme-63

Oxidation of indoles with hydrogen peroxide under weakly acidic conditions produces indigo **206** and 2,2-di(3-indolyl)indolin-3-one **208**. These products are considered to be obtained via the initial formation of indolin-3-one **203.**

2.1.4.5 Reduction

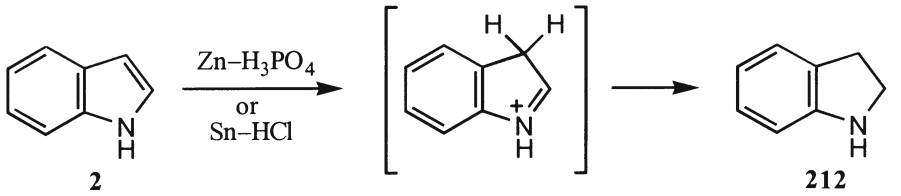
Indoles are generally selectively reduced either in the six-membered ring or in the five-membered ring with different reducing agents.

(i) Indole can be catalytically hydrogenated to indoline **212** (selectively five-membered ring leaving six-membered ring intact), when indole in ethanol is passed over Raney nickel at high temperature and high pressure (scheme-64). However, ruthenium catayzes the hydrogenation of indole to octahydroindole. The catalytic reduction of indole at room temperature and atmospheric pressure in the presence of an acid also provides indoline **212** via 3*H*-indolium salt.



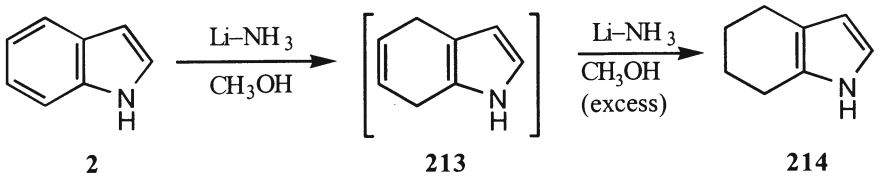
Scheme-64

(ii) Indoles are easily reduced to indolines by zinc–phosphoric acid or tin–hydrochloric acid via 3*H*-indolium cation (scheme-65)[29,55,56].



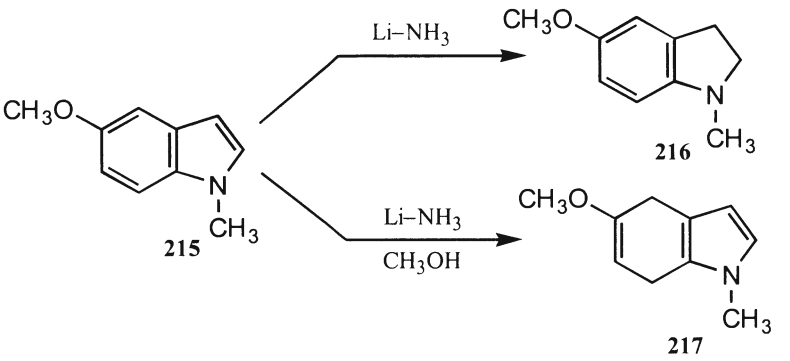
Scheme-65

(iii) N-Unsubstituted indoles are reduced in the six-membered ring providing 4,7-dihydroindoles **213** and finally 4,5,6,7-hydroindols **214**, when treated with lithium or sodium in liquid ammonia in the presence of methanol (Birch reduction) (scheme-66). N-Substituted indoles are also similarly reduced to 1-substituted 4,7-dihydroindoles.



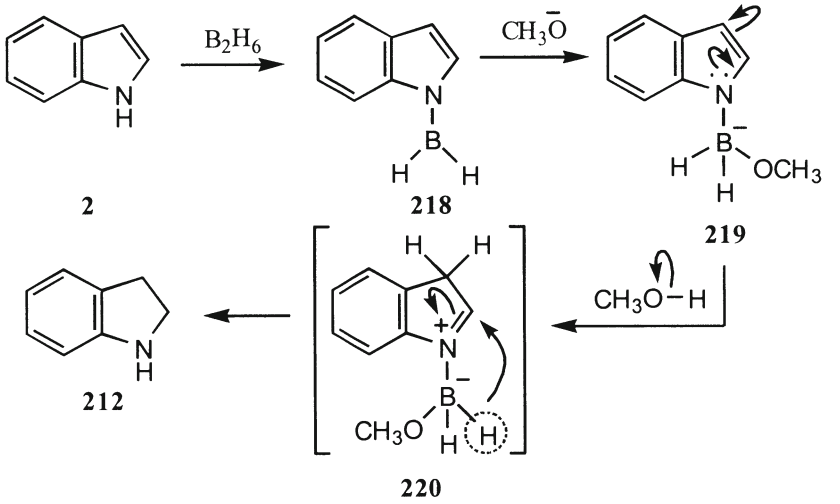
Scheme-66

The reduction of 5-methoxy-1-methylindole **215** with lithium–ammonia (liquid) in the absence of alcohol produces very slowly 5-methoxy-1-methyl-2,3-dihydroindole **216**, whereas in the presence of alcohol 4,7-dihydroindole **217** is obtained (scheme-67).



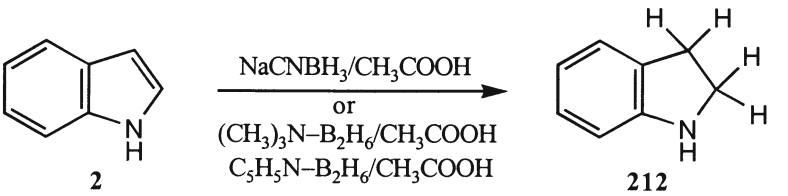
Scheme-67

(iv) Because of the π-excessive character, indoles are not reduced by hydride-transfer reagents (lithium aluminium hydride, sodium borohydride and diborane). N-Unsubstituted indoles can also be reduced to indolines with diborane under basic conditions involving protonation at the position-3 (scheme-68).[63] The reduction of indoles can be effected in excellent yields



Scheme-68

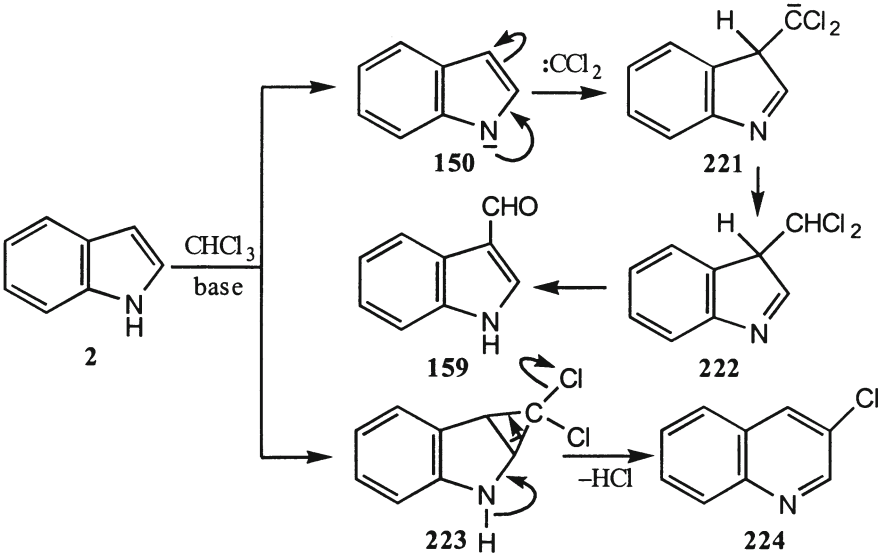
by sodium cyanoborohydride in the presence of acetic acid or by trimethylamine–diborane / pyridine–diborane in the presence of acid medium with the formation of indolines (scheme-69)[57-62].



Scheme-69

2.1.4.6 Reactions with Electron-Deficient Species

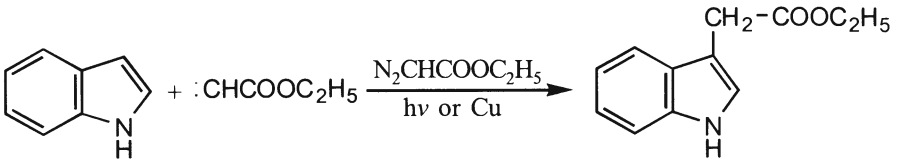
Indole undergoes Reimer–Tiemann reaction when treated with dichlorocarbene, generated from chloroform and strong base, with the formation of a mixture of indole-3-carbaldehyde **159** and ring expanded product, 3-chloroquinoline **224**. The ratio of the products depends on the mode of generation of carbene. Approximately equal amounts of the products are obtained with strong base, but under weakly basic conditions the ring expanded product is favoured. The formation of the products has been rationalized by two reaction pathways (scheme-70).



Scheme 70

The reaction pathway leading to indole-3-carbaldehyde **159** involves electrophilic attack of dichlorocarbene upon an indolyl anion **150**, whereas the second reaction pathway involves insertion of carbene into C_2–C_3 bond of indole and proceeds via cyclopropyl intermediate **223**.

The reaction of indoles with carbenes, generated from copper or light catalyzed decomposition of diazo esters and diazo ketones, produces the corresponding 3-indolyl esters and ketones without the formation of ring expanded product (scheme-71)[29].

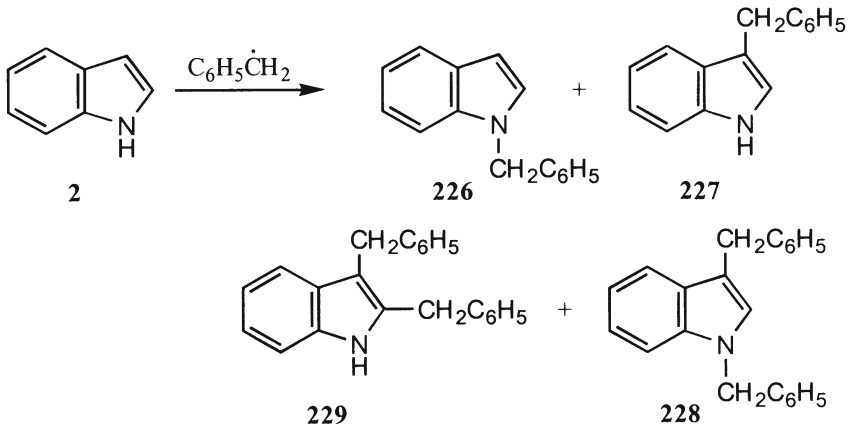


2 **225**

Scheme-71

2.1.4.7 Reactions with Free Radicals

The reaction of indole with benzyl radical, generated by thermal decomposition of tert-butylperoxide in toluene, produces a mixture of benzylated indoles involving benzylation at the carbon and nitrogen atoms in the five membered ring (scheme-72)[64].



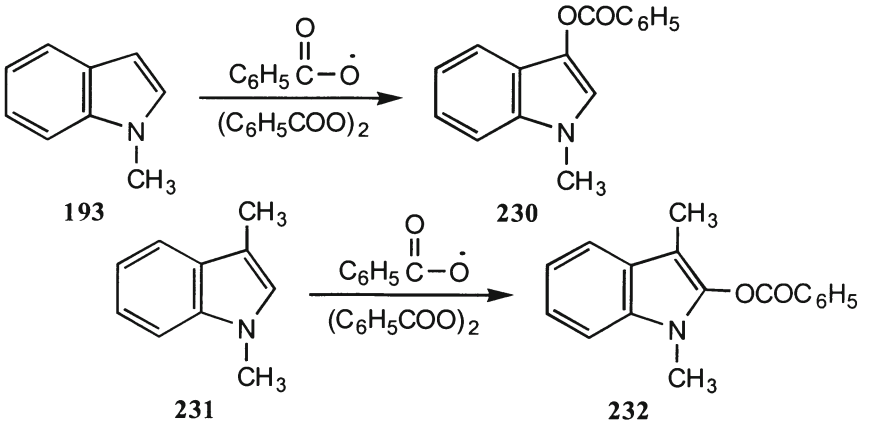
2 **226** **227**

229 **228**

Scheme-72

When N-methylindole reacts with benzoylperoxy radical, free radical attack occurs at the position-3 with the formation of 3-benzoyloxy-1-methylindole **230**.

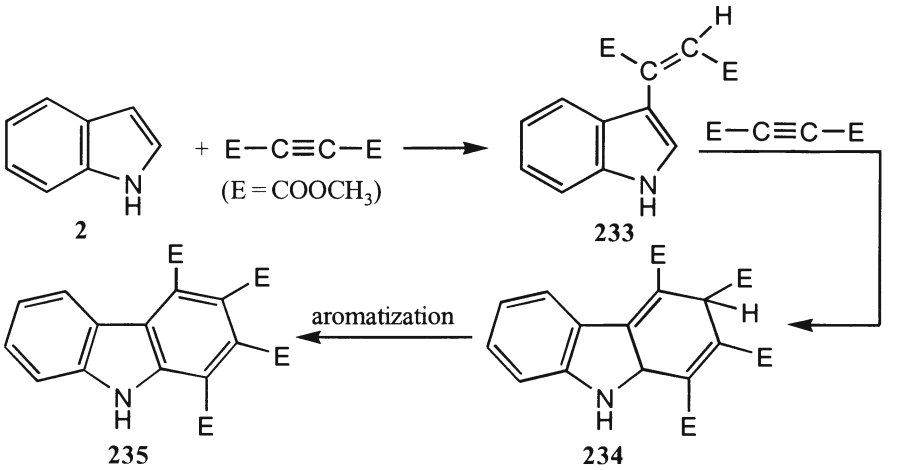
If the position-3 is already substituted, the radical substitution takes place at the position-2 (scheme-73)[65].



Scheme-73

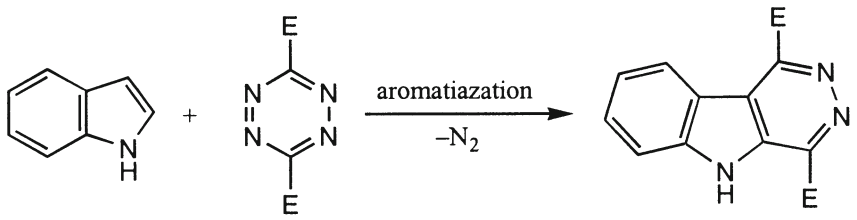
2.1.4.8 Cycloaddition Reactions

Indoles do not participate in Diels–Alder cycloaddition reactions, but undergo Michael addition reaction with π-deficient alkenes and alkynes involving attack at the position-3 of the indole nucleus. The reaction of indole with dimethyl acetylene dicarboxylate (DMAD) gives 3-vinylindole **233** which with second molecule of DMAD provides (4 + 2) cycloaddition product **234** involving exocyclic double bond (scheme-74)[66,67].



Scheme-74

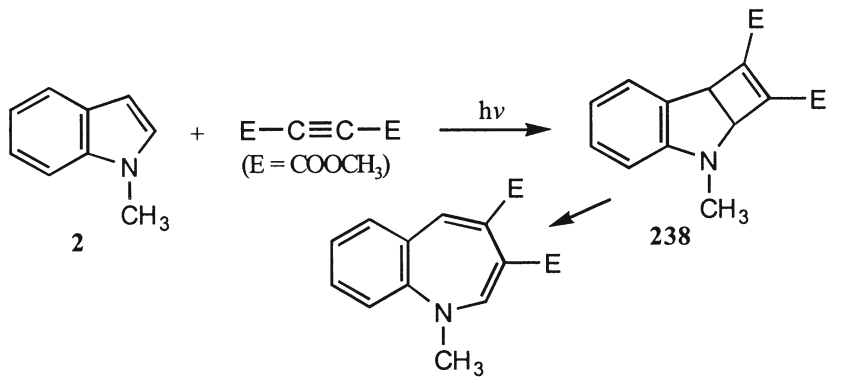
However, indole with 1,2,4,5-tetrazines provides indolepyridazines via (4 + 2) cycloaddition followed by extrusion of nitrogen and aromatization (scheme-75)[68].



2 **236** **237**

Scheme-75

Photocyclization of 1-methylindole with DMAD proceeds to involve (2 + 2) cycloaddition providing cycloadduct **238** which is thermally transformed into benzazepine **239** (scheme-76)[69,70].



2 **238** **239**

Scheme-76

2.2 Isoindoles (Benzo[*c*]pyrroles)[56]

2.2.1 General

Isoindole is an isoelectronic with indole i.e. 10π-electron system, and retains appreciable aromatic character with substantial resonance energy (48.6 kJ/mol) as