CHAPTER -I

INTRODUCTION

CHAPTER-I

INTRODUCTION AND LITERATURE SURVEY

1.1 Introduction **Pyrazole** and literature survey

1.2 Introduction **Quinoline** and literature survey

1.3 Scope of the present work

1.1 INTRODUCTION AND LITERATURE SURVEY :

A study of heterocyclic compounds has contributed to a great deals towards the knowledge of chemistry. Number of heterocycles have been patented for their varying pharmacological and biological properties.

The pyrazoles or pyrazoline, pyranopyrazoles, quinoline and quinolinopyrazoles are very important classes of heterocycles and are of industrial importance.[31-34]

For the synthesis of many drugs and dyes pyrazoles form an intermediates and act as anasthetics.[1,2] Some compounds with pyrazole ring system find their use as insecticides and plant growth stimulators.[3] Because of persistant of odour, alkyl pyrazoles from their use in perfumary. some alkyl and aryl pyrazoles have showed sedative action on central nervous system[6,7]. Aminopyrazoles are highly active pharmacological agents.[8-9] Recently, it has been pointed out that when benzopyran ring is directly attached to the heterocyclic ring enhances the pesticidal activity. So, it was connsidered worthwhile to synthesise series of new pyrazoles.

As compared with imidazoles indoles benzamidazoles, pyrazoles and their derivatives are less biological significance due to difficulty for living organism to construct the N-N bond, but they have marked pharmacological properties and hence, find applications in drug synthesis despite the recent tendency

to suppress the compound containing N=N bond in human medicine.

Pyrazole important ring compounds containing two nitrogen atom in pentacyclic ring which belongs to the family azoles. They are classified depending upon the number of endocyclic and exocyclic double bonds are non aromatic and can be represented as (1,2). The pyrazoles with two endocyclic double bonds exhibits aromatic characters while some of their derivatives are non aromatic (3-5).

Burton and finar[10] calculated a comparative electronic density on pyrazole ,its anion and cation. Orgel[11] calculated π-electron density of pyrazole by HMO method (6-8) while the charge densities in anion and cation by different positions were calculated by different methods and optimised geometry by MNDO method [12] (9)

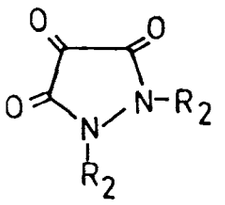
The molecular structure of pyrazole was proposed for first time by Ehrlisch[13] and later on correct structure of pyrazole was established by Rasmussen[14-15] by neutron diffraction (10) and X-ray diffraction studies (11)

Infrared spectra of pyrazoles in concentrated solution show broad absorption band corresponding to the N-H group region 3500-3100 cm^{-1} (2.7-3.0μ)due to intramolecular hydrogen bonding.[16] Another prominent band occur at 1600 cm^{-1} due to >C=C< . The IR spectra of pyrazoles are given in chemical literature.[17]

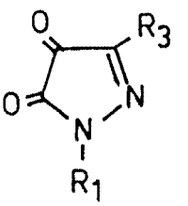
The ultraviolet spectra[18] of pyrazoles recorded in different solvents and various pH are well studied. Alkyl pyrazoles showed

CHART – I

STRUCTURES OF PYRAZOLES



(1) Pyrazolidine-3,4,5-trione



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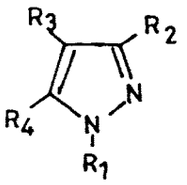
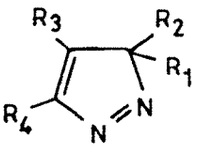
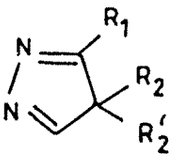


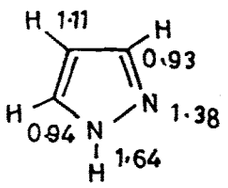
(3) Pyrazole



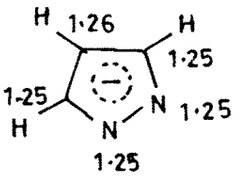
(4) Pyrazolinine
3-H-Pyrazole



(5) Isopyrazole
4-H-Pyrazole



(6)



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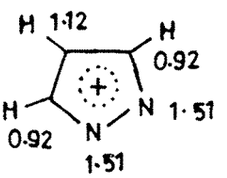

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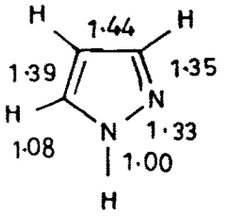

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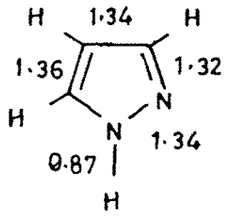

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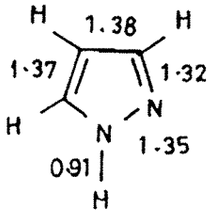


(11)

the absorption maxima in the region 210-225 mμ (log ε_{max} 3.5-4.0). The maxima for aryl pyrazoles lie between 250 - 280 mμ (log ε_{max} 3.4-4.2). The presence of chromophoric group such as $-COOC_2H_5$, $-NO_2$ -CHO, -COR, in alkyl pyrozoles show bathochromic shift of the order 25-40 mμ .

The ^1H NMR spectra of pyrazolinones play an important role in tautomeric studies.[19] NMR studies of delta-pyrozolines are useful for determination of stereochemistry of C-atoms at C_3, C_4, C_5 and calculation of the ring puckering.[20-21] Substituted pyrazones like 1-phenyl, 3-methyl-5-pyrazolone[22] exist in two tautomeric forms of comparable energy in which -OH (12) and -NH (13) tautometer co-exist in the crystalline form.

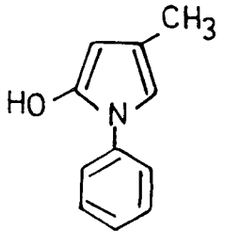
The ^1H NMR spectra of pyrazoles have been available along with other heterocycles[23] for symmetrical system where $R_3=R_5= -CH_3$ in N^1-substituted derivatives (14) to assign methyl signal at 3-and 5- position equivalent.

J.Van Thuijl[24-25] have done a lot of work on the mass spectral study of pyrazole derivatives. The molecular ion peak of pyrazole itself is more intense because pyrazole being aromatic are extremely stable under electronic impact.[27]

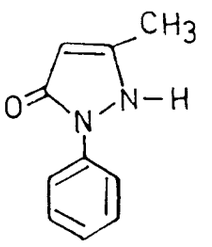
There are number of methods available in the chemical literature for the synthesis of pyrazoles which involve the treatment of variously substituted esters with hydrazine hydrate.[28-29] E.Schyaufstaetter has synthesised some pyrano-pyrazole derivatives

CHART–II

STRUCTURES OF PYRAZOLES AND ITS DERIVATIVES



(12)



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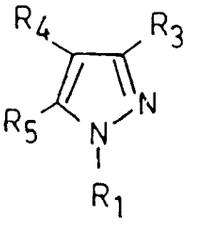
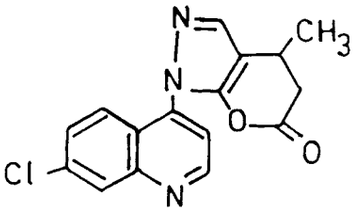
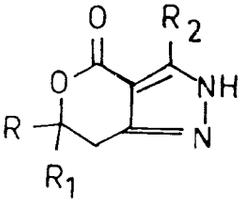


(14)



(15)

(16)



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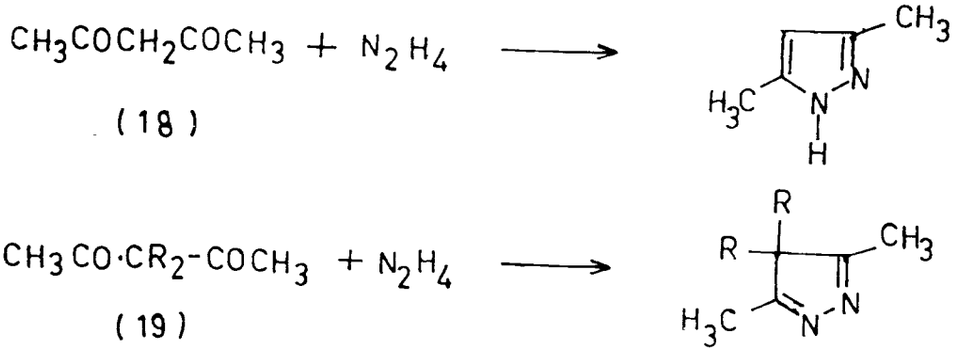
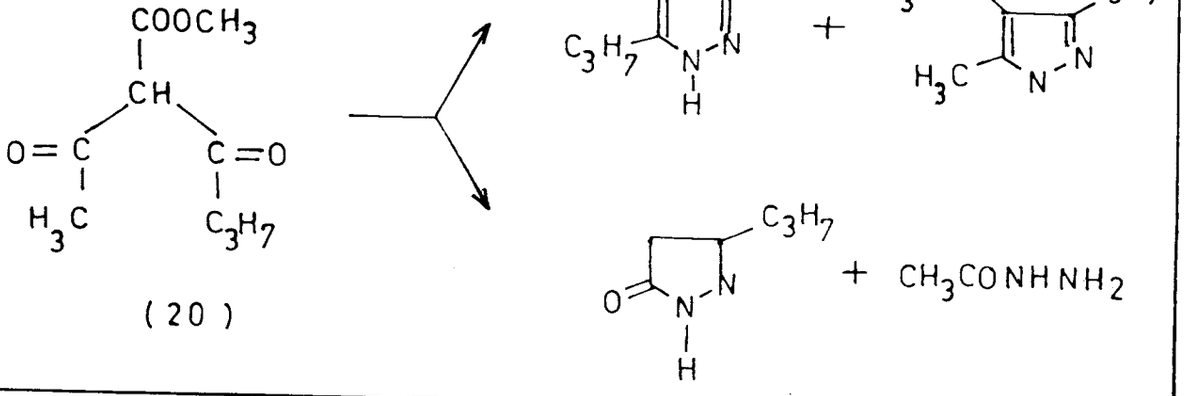




condensed at 4;1-position of 7-chloro quinoline. The formation of the desired compound involved the reaction of 4-hydrazino-7-chloroquinoline with excess of ethyl acetoacetate (15). The pyranopyrazoles (16) and (17) were obtained by treating pyrandiones with substituted hydrazines. These compound showed analgesic activity at 100-200 mg/kg s.c. in the tail flick test in mice.[30]

The reaction of 1,3-diketones with hydrazine and its derivatives leads to the formation of pyrazoles. During the synthesis of pyrazoles, acetates, hemiacetals, chlorovinyl ketones and tetrahalides etc. can be used. 3,5-dimethyl pyrazole can be obtained in 85% yields by reacting acetyl acetone with hydrazine hydrate [57-59] (18).

The linear 1,3-diketones and their derivatives gave corresponding pyrazoles with hydrazine have been listed,[59,60-66]

The reaction of 1,3-diketone proceeds through the formation of monohydrazone intermediate[67]. The bis-hydrazones have been formed when pyrazoles were heated with excess of hydrazine [68-74]. The number of pyrazoles were synthesised using alkyl substituted hydrazines[75]. Aryl substituted hydrazines,[76-83] sulphonyl hydrazides[84], semicarbazides,[85,88] acyl hydrazines [89-92] and amino guanidines[93-99]. The dialkyl acetyl acetone reacts with hydrazine hydrate rapidly to form pyrazole [100-101] (19).

The pyrazoles or pyrazolines can be obtained from diketone, carboxylic acids and ester under different conditions[102-113] (20).

Number of pyrazoles were obtained by azo-coupling of acetoacetic ester derivative followed by cyclization[114-124](21)

Fusco and Rossi[125] used the same method for the synthesis of 3-nitropyraazole. The synthesis of spiro-bis-pyrazolines from 1,3,5-triketone and phenyl hydrazine[126] . The synthesis of pyrazoles with various heterocyclic substituents have been reported in the chemical literature.[127-129] When unsymetrical 1,3-diketone used for synthesis of pyrazoles, then the mixture of pyrazoles were obtained.[130]

Minnuni[131] synthesised 4-carbethoxy pyrazoles starting with acetoacetic ester and phenyl hydrazones of aromatic aldehyde through beta amino crotonic ester (22). One of the most important sulfonamide drug "orisul" was prepared by condensing 1-phenyl-5-amino-pyrazole with sulphonilamide[132-133](23). In 1905 Stolle[134] prepared pyrazolocoumarin from dehydroacetic acid with phenyl hydrazine (24). Pyrazole with 3-substituent formed from 2,6-dimethyl-gama-pyrone and hydrazine through intermediate product [135-136](Fig.25).

Polymer stabilizing[137] and corrosion inhibitor[138] activity has been reported by Wallace et. al in pyrazolone carboxaldehyde and sected poly(oxyalkylated) pyrazoles respectively. A new method of 3-pyrazolone preparation has been achieved (18,22,26) with 40% yield.[139]

CHART-III

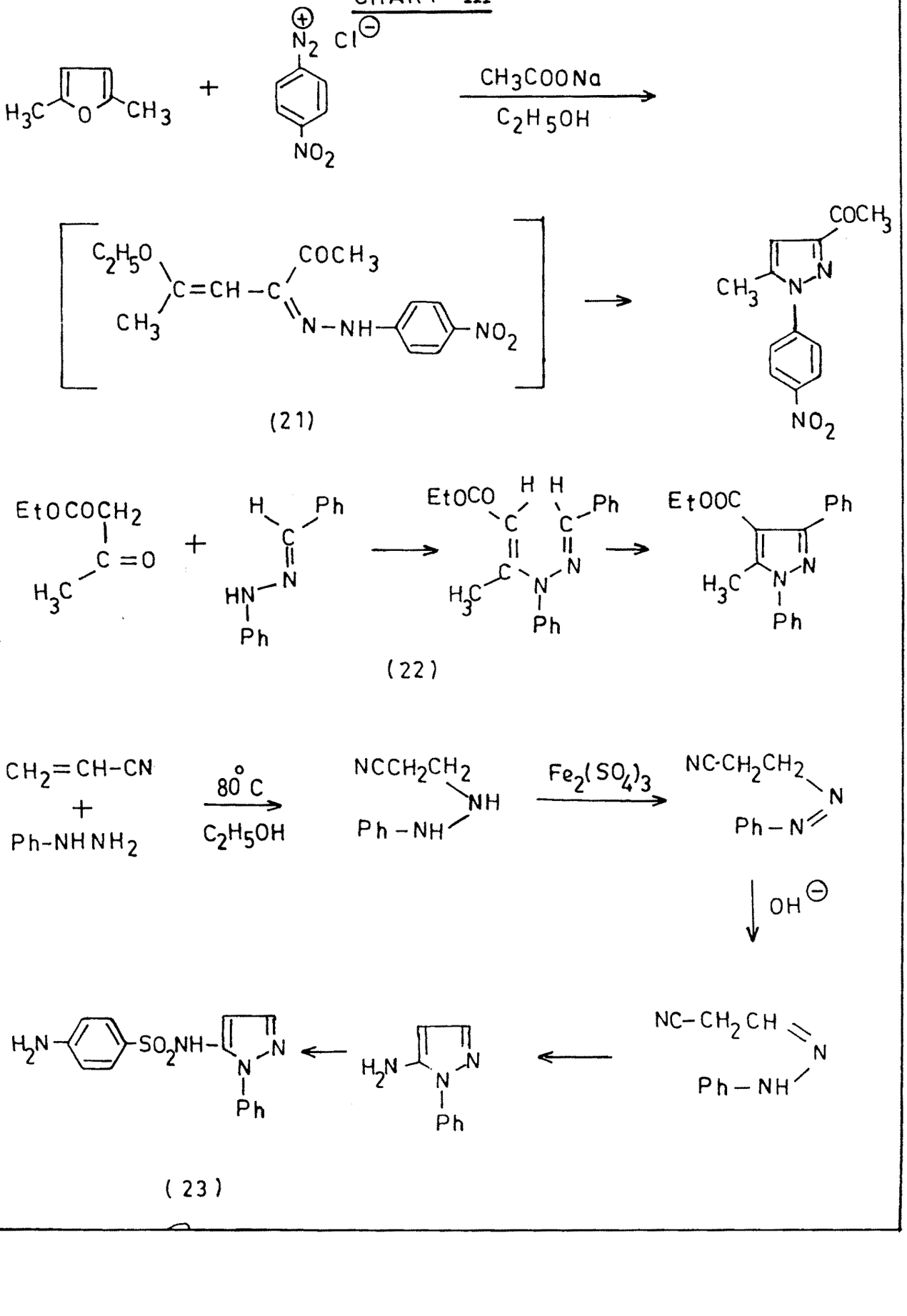
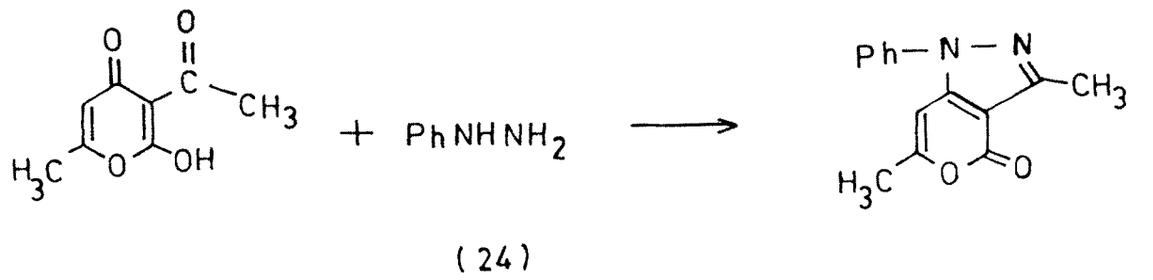
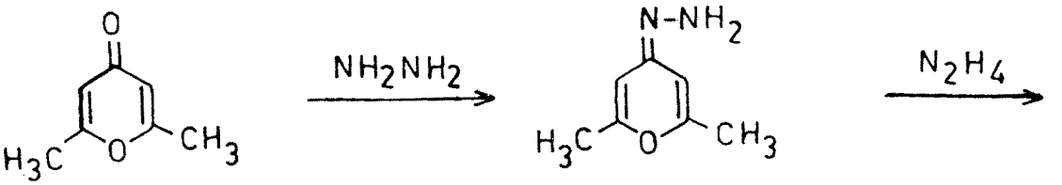
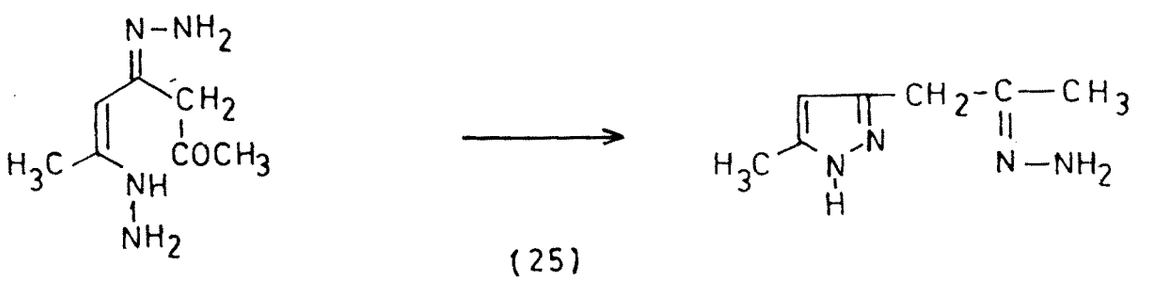

CH3COONa
C2H5OH
(21)
EtOCOCH2
EtOCO
EtOOC
(22)
CH2=CH-CN
+
Ph-NHNH2
80° C
C2H5OH
NCCH2CH2
Ph-NH
Fe2(SO4)3
NC-CH2CH2
Ph-N
OH⊖
NC-CH2CH
Ph-NH
H2N
SO2NH
(23)

CHART-IV

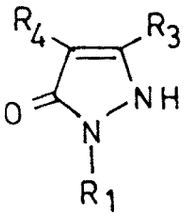


(24)



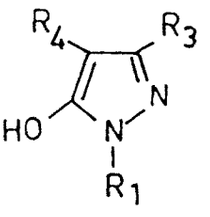


(25)



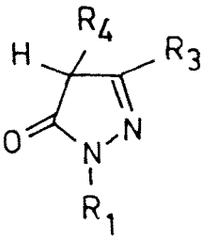
(NH form)

(27)



(OH form)

(26)



(CH form)

(28)

Pyrazole ring system being present in many biologically active molecules, it was considered worthwhile to synthesise series of compounds by incarporating pyrazole moiety as possible antibacterial agents.

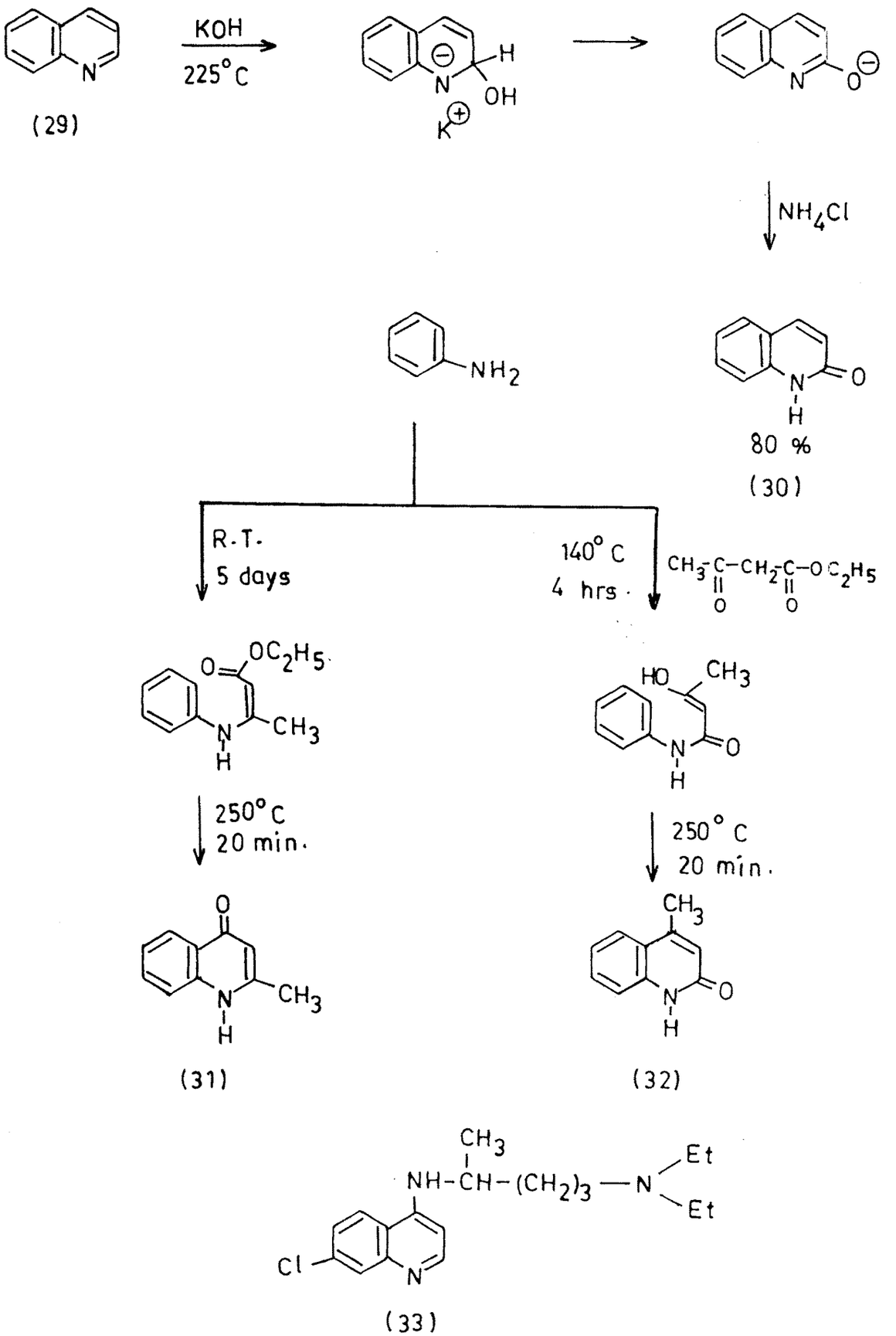
1.2 INTRODUCTION LITERATURE SURVEY OF QUINOLINE

Quinoline is benzocondensed derivatives of pyridine containing one heteroatom as a nitrogen. The structure of quinoline is designed as (29) and has proved to be interesting subject for theoretical chemists. Since Coulson and Longuet Higgins first attempted to deduce electron densities for nitrogen hetrocycles in 1947[35]. Quinolone[36] is 2-keto derivatives of quinoline (30) and is obtained initially by heating quinoline with KOH or NaOH with nearly quantitative yield.

Aryl amine condensed with ketone carbonyl group at low temperature (kinetic control) and high temperature (Thermodynamic control) is formed. The second type of condensed product can be cyclised by an isomeric 2-quinolone. Most of the quinoline derivatives have been prepared by ring formation reaction. Korr[37] discovered that acetoacetanilide undergoes cyclisation when it is treated with A R H_2SO_4 to give methyl quinolone. The infrared spectroscopy of the compound is useful to distinguish between 2-quinolone (31) and 4-quinolone (32) systems.[38]

The importance of quinoline is linked to maleria in the several successful synthetic antimalarial drugs, such as

CHART-V


KOH
225°C
(29)
NH4Cl
80 %
(30)
R.T.
5 days
140° C
4 hrs.
250°C
20 min.
250° C
20 min.
(31)
(32)
(33)

chloroquine (33) which is used in treatment of amoebic dysentry. Most of them possess wide therapeutic activities viz. antiseptic[42] analgesics[43], trypocidal[44], germicidal[45], antitubercular[46] and anthelmintic[47]. Their chalcone derivatives possess anthelmintic[48] and antimicrobial activity.[49] 8-Hydroxy quinoline and 4-substituted-7-chloro quinoline derivatives have been extensively used as powerful antiamoebic drug.[50-56] Quinoline compounds are used in photographic films as sensitizers such as cyanine dye ethyl red. Quinolone derivatives have been reported to be pharmaceuticals agents.[39-40]

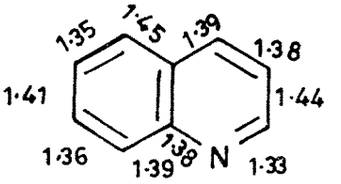
The molecular dimensions of quinoline have not been accurately determined, but an X-ray structure determination of nickel complex containing quinoline[140] gives dimensions as shown in (34). Coulson and Higgins first attempted to deduce electron densities for nitrogen heterocycles in 1947.[35] The implication were that there is no interaction between non bonded atoms and that the values given for N can be used for any nitrogen heterocycle. The calculation showed very low π-electron densities at position 2-and 4-in quinoline in acord with the known preferance for nucleophilic attack at these positions and electrophilic attack at the position 5 and 8 was performed under protonating conditions. Since 1947, many other calculations based on simple HMO treatment and a review of the literature has been extensively recorded. The electron density figures for quinoline(35) and for its protonated form (36) are given.

One alternative theoretical method used in calculations on quinoline is the variable electro-negativity SCF approach favoured by Brown and his co-workers,[142-144] wich has produced good calculated values for dipole moments and another alternative is the "Frontier orbital". The calculated densities of "Frontier electrons" for electrophilic and nucleophilic reactions on quinoline is indicated in (37) and (38).

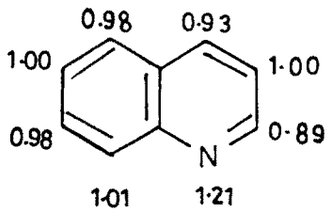
Methods of synthesis of quinoline derivatives have been reported. Non-oxidative ring closure are the polycylisation of α -methyl acrylic acid (39) to 3,4-dihydro-3-methyl carbostyril (40) have been reported by Cleveland et al.[145] The synthesis of 4-anilino-8-hydroxyquinolines have been reported by Sen et. al.[146] which were claimed as possible antiamoebic agents. 5-Substituted phenanthridiones useful as antidepressant (41) has been reported.[147]

Fungicidal carbostyrils for Oryzae Sativa have been prepared by Utematsu et. al.[148]. The compound $o.-ClC_6H_4N.MeCOCH_2COMe$ was added to the concentrated H_2SO_4 at 70-75°C and the mixture stirred for 10 min at 100 C, cooled at room temperature and poured into ice water to give (42). It prevented growth of Pericularia Oryzae by 100% at 100 PPM and Heliminthosporium Sigmodeum by 95-96% when given to Oryzae Sativa at 4-5 leaf stages. 8-Chloro-5,6,7,8-tetrahydro-2-quinolinone (43) as useful dye intermediate have been reported by Meidert et al[149] . Reaction of 3-quinolinocarbonitriles and 6-quinolinocarbonitrile

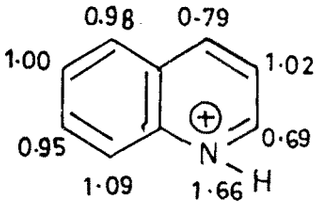
CHART–VI



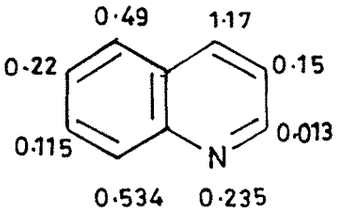
(34) Dimensions of quinoline in Ni $[S_2PEt_2]$ C_9H_7N



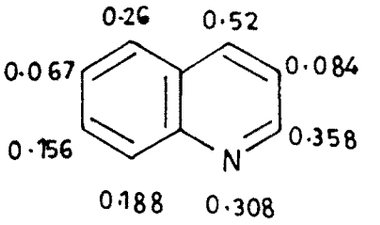
Quinoline (35)



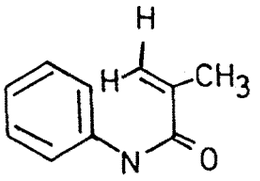
Protonated quinoline(36)



For Electrophilic (37)



For Nucleophilic (38)



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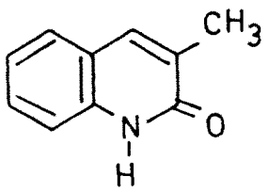

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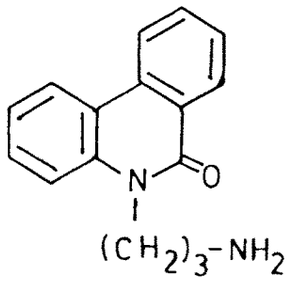

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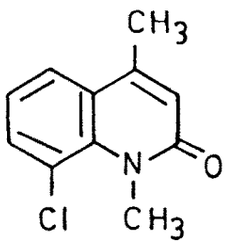
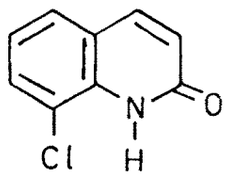


(42)



(43)

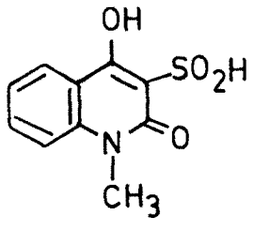
with methyl magnesium iodide and phenyl magnesium bromide/55.4% gave of 1,4-addition product.[150]

4-Hydroxy-3-sulphonyl quinolin-2(1H)-ones have been recorded by Hardtmann et al.[151] Antiallergic hydroxy quinolones (44) and their salts were prepared by treating $MeSO_2CH_2COOEt$ with N-methylisatoic anhydride to furnish (44).

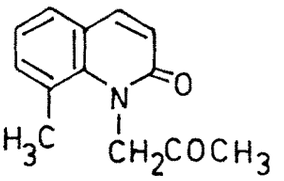
Carbostyril derivatives (45) were prepared by Ofsuka[152] and had antiinflamnatory, analgesic and muscle relaxing activities. Synthesis of some bicyclic and tricyclic quinoline derivative has been reported by Hogale et. al.[153]. 2-Chloroquinoline derivative (46) (R'=isothiocynato, $pHCH_2CONHNH_2$), triazinoquinoline derivative (47) (R'=Cl) reacted with $pHCH_2CONHNH_2$ to give (46))R=$pHCH_2 \cdot CONHNH_2$, R'=isocynato). Chloro-compound when heated with NH_4SCN in acetone followed by reaction with CH_3CN furnished a targetted molecule (47).

Studies on Vilsmeir-Haack reaction, a new route to 2-chloro quinoline-3-carboxyaldehyde [48] has been reported by Pawar et, al.[154] to yield 3-carboxyaldehyde, 6-methyl quinoline-2(1H) one (49). Some new sulphides (51) and (52) from 4-bromoethyl-carbostynil (50) have been reported by Kulkarni et al.[155]

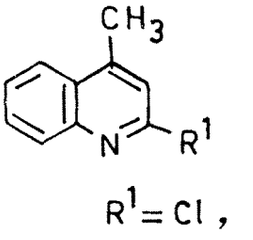
CHART-VII



(44)

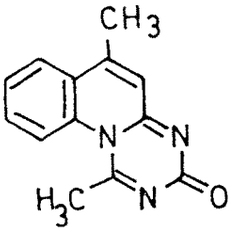


(45)

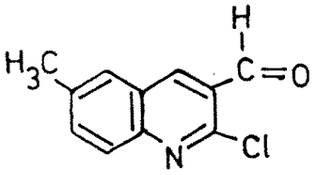


$R^1 = Cl$,

(46)

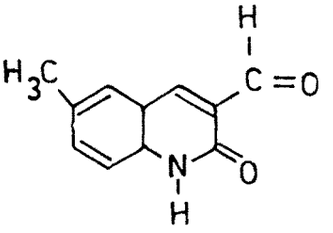


(47)

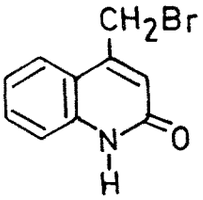


(48)

6N HCl

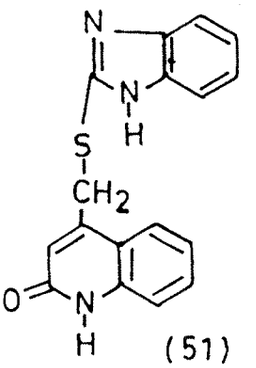


(49)



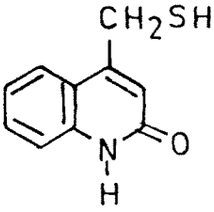
(50)

2 — Mercapto
— Benzimidazole



(51)

Thiourea
C_2H_5OH



(52)

1.3 SCOPE OF THE PRESENT WORK :

The pyrazoles, pyranopyrazoles and quinolino pyrazoles being pharmaceutically important class of compounds, the problem on the synthesis of some new pyranopyrazoles and N^1-substituted quinolino pyrazoles derivatives is undertaken.

Recently, it has been pointed out that when benzopyran ring is directly attached to the heterocyclic ring enhances the pesticidal activity. So it was considered worthwhile to incarporate hectrocyclic moleties in N^1-position of quinoline nucleus to study the effect of N^1 - substitution on antimicrobial and antifungal activities may find use in the pharmaceutical preparations. The research methodology adopted in the synthesis of desired compounds has been depicted in Scheme I, II and III .