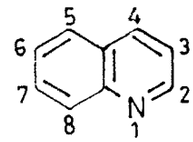
CHAPTER-I

INTRODUCTION

I. Introduction :

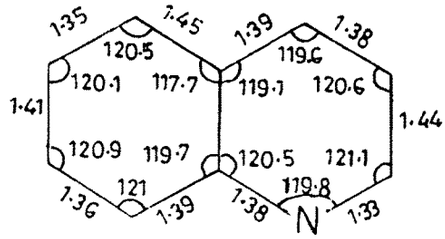
Quinoline is a benzocondensed derivative of pyridine containing one hetero atom as nitrogen. The structure of the quinoline is designed as,



(I)

It is highly stable, high boiling point, liquid rarely used as basic solvent. It was first isolated from coal tar bases in 1834, by Runge[1] and a little later the base was obtained by Gerhardt[2] in 1842 in the alkaline pyrolysis of cinchonamine, an alkaloid closely related to the famous antimalerial alkoloid quinine. The word quinoline in fact is derived from the word quinine, which in turn is derived from quina, a Spanish version of a local south American name for the bark of quinine containing cinchona species.

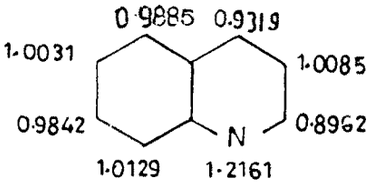
The molecular dimensions of quinoline have not been accurately determined, but an X-ray structure determination of a nickel complex containing quinoline[3] gives the dimensions as shown below,



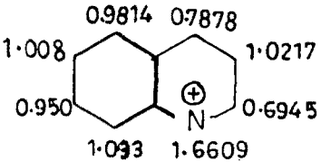
Dimensions of quinoline in Ni $[S_2.PEt_2]C_9H_7N$

Quinoline has proved to be interesting subject for theoretical chemists, since Coulson and Longuet-Higgins first attempted to deduce electron densities for nitrogen heterocycles in 1947.[4] The implications were that there is no interaction between non bonded atoms and that the values given for α_N can be used for any nitrogen heterocycle. The calculations showed very low π-electron densities at position 2- and 4- in quinoline in accord with the known preference 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.[5] The electron-density figures for quinoline and for its protonated form are shown below.



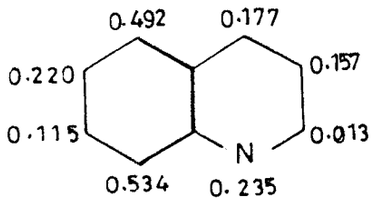
Quinoline



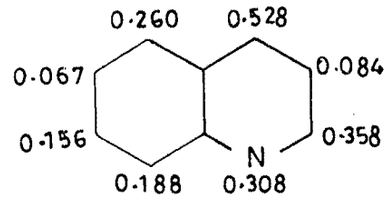
Protonated Quinoline

One alternative theoretical method used in calculations on quinoline is the variable electronegativity SCF approach favoured by Brown and his co-workers[6-8] which has produced good calculated values for dipole moments and another alternative is the "frontier orbitals".

The calculated density of "frontier electrons" for electrophilic and for nucleophilic reactions on quinoline is indicated below :



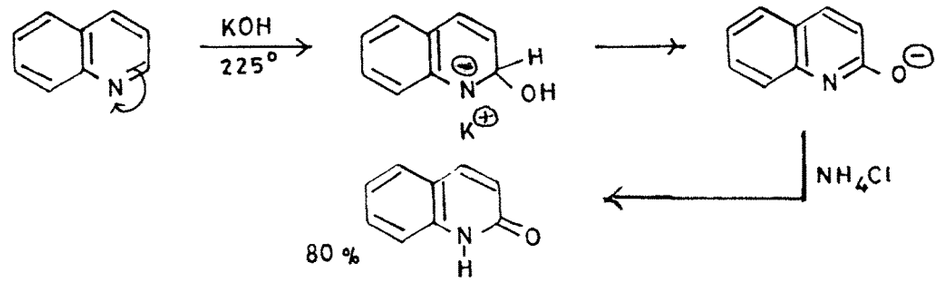
For Electrophillic (A)



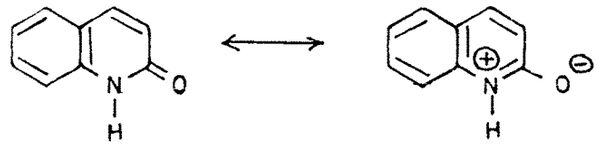
For Nucleophillic (B)

II. Quinoline Derivatives :

Quinolone[9] is 2-Keto derivative of quinoline and is obtained initially by heating quinoline with KOH or NaOH with nearly quantitative yield.

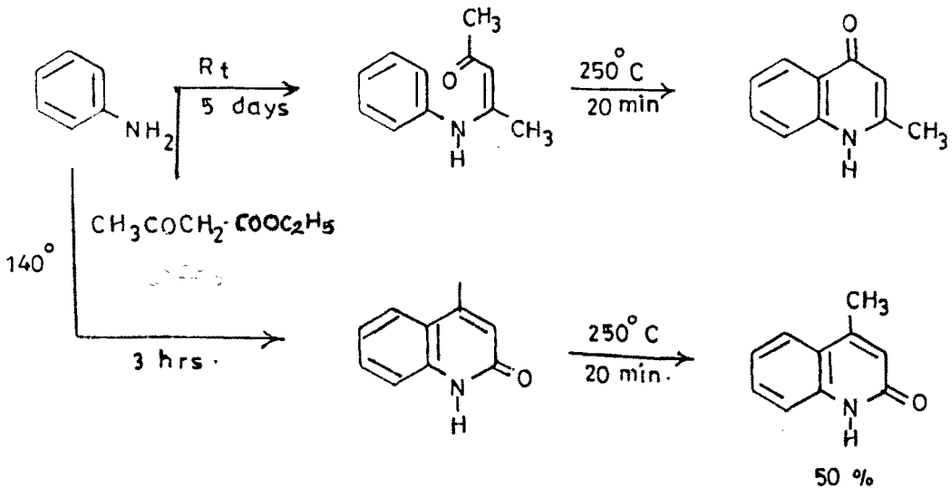


Oxo-quinoline carrying the oxygen at 'C_2' exist for all practical purpose entirely in the carbonyl form.



2-Quinolone

Arylamine condenses with the ketonic carbonyl group at low temperature (kinetic control) and at higher temperature the stabler amide (thermodynamic control) is formed. The second type of condensation product can be cyclized to an isomeric 2-quinolone.[10]

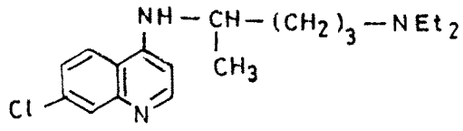


Most of the quinoline derivatives have been prepared by ring formation reaction. Korr[11a] discovered that, acetoacetanilide undergoes cyclisation when it is treated with H_2SO_4 to give methyl quinolone. The IR spectroscopy of the compound is useful to distinguishes between 2-quinolone and 4-quinolone systems.[11b]

III. Importance of Quinoline Derivatives :

The quinoline ring system is important in medicinal plant alkoloids having application in chemotherapy. The cinchoma alkoloids including cinchonine and quinine are useful for the treatment of Maleria.[12] Benzopyridine stimulated the production of synthetic material used as chemotherapeutic agents.

The subsequent importance of quinoline is linked to maleria in the several successful synthetic antimalarial drugs such as chloroquine used in the treatment of amoebic dysentary.



Chloroquine

Quinolines play no part in fundamental metabolism and they occur relatively rarely in plants as secondary metabolites (alkoloids), quinine being much the best known. An important role played by quinoline compounds was that of providing the first photographic film sensitizers, such as the cyanine dye 'ethyl red'. Quinoline derivative have been reported as pharmaceuticals.[13-15] Most of them possess a wide therapeutic activities viz. antiseptic,[16] analgesics,[17] tryphocidal,[18] germicidal,[19] antitubercular,[20] anthelmintics[21] and antiserotonin.[22] Chalcones der. possess anthelmintic[23] and antimicrobial activity.[24] 8-Hydroxy quinoline derivatives and 4- substituted 7-chloro quinolines have been extensively used as powerful antiamoebic drugs.[25-31].

The quinoline and isoquinoline derivatives besides having antifilarial properties[32,33] are efficaceous against many worm infection[34-36] 2- and 8-substituted quinolines containing 1,3,4-thiadiazole residue have been found to possess antimalerial and schistomicidal[37,38] activities.

The 4-amino 7-chloro quinolines[39,40] with phenyl thiazole and phenyl diathiazole are known to exhibit antibacterial and antiviral efficacy.

All the compounds of 4-amino-7-chloro quinolines were evaluated for their antimalerial activity against plasmodium berghei in mice and antifilarial activity against litomosoides cornii in cotton rat and found to be inactive. Some of the compounds were tested for their in vitro growth, inhibitory activity against different strain of bacteria and fungi. Halo derivatives of quinoline are known as antimalerial drugs.[41-42]

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LITERATURE SURVEY

The rapid and efficient synthesis of 1-Aryloxy carbostyrils have been reported by Paquette[1] by heating a mixture of 2-alkoxy quinoline 1-oxide with a benzyl halide 10 hrs. at 100-150^{o} to give 1-benzyloxy carbostyril [1] exhibit CNS stimulatory activity in animals and antifungal activity against Candida-albicans, Microsporum canis and Trichophyton rubrum in animals and Fusarium oxysporum var. cubense in plants.

Non oxidative ring closure are the photocyclisation of ∝-methyl acrylic acid [2] to 3,4-dihydro-3-methyl carbostyril [3] have been reported by Cleveland et.al.[2] The synthesis of 4-anilino-8-hydroxyquinolines have been reported by Sen et.al.[3] which were claimed as possible antiamoebic agents. 5-substituted phenanthridiones useful as a antidepressant [4] has been reported[4].

1.CW- piperidino or 1-(piperazinyl alkyl)-3,4-dihydro carbostyrils [5] prepared by Havera and his coworker.[5] Halogenation of [5] over pd/c and treatment with oxalic acid gave the semioxalate.

Migration of ortho substituents in amide [6] on photocyclisation gave [7] which has been reported by Ninomiya et.al.[6] Chlorination of 4-hydroxy-5,6, 7,8-tetrahydro-2-quinolones have been reported by Ziegler et.al.[7] to yield[8] Formation and reactions of N-alkyl-2,2-dichlorobenzoyl acetanilides have been reported by Staskun.[8] The acid-catalysed cyclisation of certain N-isopropylbenzoyl acetanilides to the corresponding 1-isopropyl quinolinones [9] has been observed.

Quinoline 1-nitroamides have been prepared by Katritzky et.al.[9] by treating two-quinolone with NaH in CH_2Cl_2 and then with o-mesitylene sulfonyl hydroxyl amine to give the 1-amino-derivative which was oxidized by $EtONO_2$-NaOEt to give the nitro-amide [10]. Two step carbostyril [11] preparation in the synthesis of dibenzoquinolizines has been reported by Tourwe et.al.[10]

Fungicidal carbostyrils for Oryza sativa have been prepared by Utematsu et.al.[11] The compound $o\text{-}ClC_6H_4.NMe.COCH_2.COMe$ was added to concentrated H_2SO_4 at 70-75° and the mixt. stirred 10 min.at 100°, cooled at room temp. and poured into ice water to give [12]. It prevented growth of Pericularia oryzae by 100% at 100 ppm and Heliminthosporium sigmodeum by 95-96% when given to Oryza sativa at 4-5 leaf stages.

4-Hydroxy-3-sulfonyl quinolin-2(1H)-ones have been recorded by Hardtmann et. al.[12] Antiallergic hydroxy quinolinones [13] and their salts were prepared by treating $MeSO_2CH_2COOEt$ with N-methylisatoic anhydride to furnish [13].

8-Chloro-5,6,7,8-tetrahydro-2-quinolinone [14] as useful dye intermediate have been reported by Meidert et.al.[13] Reaction of 3-quinoline carbonitriles and 6-quinoline carbonitrile with methyl magnesium iodide and PhMgBr gave 55.4% of the 1,4-additional product.[14] Thiocarbostyrils [15] were prepared by Uchida et.al.[15] act as antiulcer, antiasthama, anti-inflammatory and thromboisis inhibiting agents.

Anti-inflammatory activity of 3,4-disubstituted 2-oxo-1,2-dihydroquinolines have been reported by Shridhar et.al.[16] The compound [16] and [17]

were tested for in vitro antibacterial, antifungal and analgesic activities. N^1-substituted carbostyrils have been reported by Guul et.al.[17] Allylation of 4-methyl carbostyril [18] with $Cl_2C = CHCH_2Cl$ gave product with 80% yield.

Carbostyril, &rtheir 3,4-didehydro analogs and their salts [19] useful as ß-adrenergic blocking agents were prepared by Tominaga et.al.[18] The ß-adrenergic blocking activity of 21 compounds was equal to or greater than that of proctolol and Atenolol in dogs. Oxidation of quinolinium salts gave 50-52% of the corresponding quinolone[19] [20].

Carbostyril derivatives and their uses in therapy have been reported by Banno et.al.[20] The compounds [21] and [22] exhibited antihistaminic, anti-aggressive and adrenaline antagonist activity and showed their usefulness as CNS agents. 6-(4-Chlorobutyril)-3,4-dihydrocarbostyril was treated with 1-phenyl piperazine in Me_2CO containing NaI and Et_3N to give 6-|4-(4-Phenyl-1-piperazinyl)butyril|-3,4-dihydro carbostyril.

Carbostyril derivatives [23] were prepared by Ofsuka[21] and had antiinflammatory, analgesic and muscle relaxing activities. Introduction of a functionalized carbon chain at the 3-position and 4-methoxy-2-quinolones vi. photochemical [2+2]-cycloaddition to alkynes and the synthesis of (±)-edulinine have been reported by Naito et.al.[22] Irradiation of 4-methoxy-2-quinolone or its derivatives in MeOH in presence of monosubstituted ethylene gave head to tail adducts e.g. Dihydrocyclobuta-quinolinones [24]. A new method for cleavage of the (C-1) - (C - 8b) bond in the adducts was developed. Thus, the cycloproduct obtained from 4-methoxy-1-methyl-2-quinolone and 2-methyl-3-butan-2-ol was transformed to edulinine [24].

Carbostyril derivatives such as Heterocyclic amido-oximes derivatives [25] useful as antidepressants were reported by Obitz and his co-worker.[23] Carbostyril derivatives as cardiotonics have been reported by Otsuka et.al.[24] The compound [26] was found to be effective cardiotonics at 1-300 µg in isolated dog heart.

Novel carbostyril anchord heterocyles have been prepared by Zoorob et.al.[25] Carbostyril [27] and [28] were prepared from 3-acetyl-1,2,3,4-tetra hydro-1-phenyl-3,4-quinoline dione by heating with HCHO, Et_2NH and HCl in EtOH to give [27]. A mixture of [27], $Ph\text{-}NHNH_2$ and NaOH in NaOAc was heated further to give pyrazolinyl carbostyril deriv [28]. Synthesis and spectral studies of 3-substituted 2H-Pyrano [2,3-b] quinolin-2-ones [29] have been reported by Tilakraj and his co-worker.[26] 3-Phenyl-2H-pyrano [2,3-b] quinoline-2-ones and 3-acetamido-2H-Pyrano [2,3-b]-quinolin-2-ones have been prepared by Perkin type condensation of 3-formyl-2-quinolones with sodium salt of phenylacetic acid and acetylglycine respectively. Mass spectral fragmentation pattern of these compounds have been discussed.

Bergman[27] synthesised 4-amino-2-quinolinones [30]. Addition of Grignard reagent to N-(α-haloacyl)-N-alkyl substituted anthranilonitriles involved the initially the halogen metal exchange reaction e.g. $N\text{-}C_2$-bromo propionyl)-N-methyl-2-cyanoaniline, induced anion formation followed by cyclisation of 4-amino-2-quinolinones e.g. 4-amino-1,3-dimethyl-2-quinolinone [30].

Studies on positive inotropic agents and synthesis of [(4-substituted, 1-piperazinyl) carbonyl]-2(1H)-quinolinone derivatives have been made by

Tominaga et.al.[28] and examined for positive inotropic activity on the canine heart. Among them [31] had potent activity. Benzo (f) quinoline compounds and their medicinal compositions have been reported by Nakao et.al.[29] Compound [32] was used as anti-inflammatory agents. Preparation and reactions of 3,4-dihydro-1-ethyl,4-methylene-3,3,6,8-tetra chloro-2(1H)-quinolinones and their derivatives have been reported by Staskun and his coworkers[30]. Chloroquinolinones [33] were prepared from difluoro-oxyboranes their reactions and interconversions were studied. This cyclic borane was treated with $SOCl_2$ and concentrated H_2SO_4 to give [33].

1-Methyl isatinone flask synthesis of 2-oxo-3-benzoylamino-1,2-dihydroquinolin-4-carboxanilides have been reported by Jain et.al.[31]. The synthetic methodology inovlved the condensation of $PhCONHCH_2COOH$ and PhCNS with isatin to produce [34] which is also prepared by condensation of isatinimine with 2-phenyl-2-oxazolin-5-one. Synthesis and antibacterial activity of some new fatty acid hydrazones have been reported by Kulkarni et.al.[32] C_8-C_{18} falty acid hydrazides were prepared with 4-[(O-formyl phenoxy methyl)] carbostyril [35] to give corresponding hydrazone [36]. The hydrazone [36] exhibited good activity against E.coli bacteria.

Synthesis of some bicyclic and tricyclic quinoline derivatives have been reported by Hogale et.al.[33] 2-Chloroquinoline derivative [37] (R' = isothiocyanato, $PhCH_2CONHNH_2$),triazinoquinoline derivative [38] (R' = Cl) reacted with Ph-CH_2-$CONHNH_2$ to give [37] (R = $PhCH_2CONHNH$, R'=isothiocyanato). Chloro compound when heated with NH_4SCN in acetone followed by the reaction with CH_3CN furnished targetted compound [38].

The molysis of [39] (R = $-CH_2$ = $CH-CH_2O$, R'=F) in tetralin at 212^oC for 48 hours gave 69% of the Claisen-rearrangement product [40] in which 'N' is the migration terminus.[34]

Preparation of heterocyclic carbostyril derivatives as inhibitors of thrombocyte adhension have been reported by Nishi et.al.[35] The compound [41] and their salts were prepared as blood platelet aggregation inhibitors. A direct synthesis of pyridinyl-2 (1H)-quinolinones via palledium catalysed Inter-coupling reaction have been reported by Bell et.al.[36] Pyridinyl zinc chloride was treated with 6-halo quinolinones in presence of catalytic amount of tetrakis (triphenyl phosphine) palledium to give the corresponding 6-pyridinyl quinolinones in moderate to high yielded product [42].

Synthesis of some new 3-substituted 4-hydroxy-1-methyl quinolin-2-one derivatives [43] as potential antibacterial and antifungal agents have been reported by Girger et al.[37] 3-Acetyl-4-hydroxy-1-methyl quinoline-2-one and its bromoderivatives were treated with different reagents to prepare new quinoline derivatives that have different heterocycles at position-3. The anti-bacterial and antifungal activities were evaluated. 3-Alkyl-4-methyl carbostyrils and their sulphur analogs have been reported by Gyulbudagyan and his co-workers.[38] Quinolinethione [44] was prepared in79% yield from $MeCOCH_2CONHPh$ in four steps by alkylation with EtBr, cyclisation with polyphosphoric acid and H_2SO_4, chlorination by $POCl_3$ to obtain chloroquinone [45].

Preparation of 2-oxoquinoline derivatives [46] as antiarrhythemic agents have been reported by Tafusa et.al.[39] Preparation of N-halo-o-alkyl hydroxamic acids have been reported by Kakakawa.[40] N-alkoxy N-hetero-

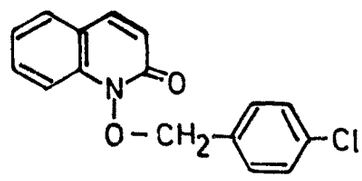
cyclic compounds were prepared by intramolecular cyclisation of $Br(CH_2)_n$-CONXOR in neutral solvents in the presence of Zn salts. $Ph(CH_2)_3CONCl$, OMe,$MeNO_2$ under reflux for 5 min. formed 93.8% carbostyril deriv [47]. Synthesis of p-methyl-2-oxo-1,2-dihydro, 3-quinolino carbonitriles have been reported by Tilak and his co-worker.[41] The compds. [48] were prepared from quinoline carboxaldehyde by methylation followed by oximation with $HONH_2$ and dehydration by treating with P_2O_5.

Preparation of (heterocyclylmethoxy phenyl) tetrahydropyrans [49] and related compds. as lipoxygenase inhibitor have been reported by Crawley et.al.[42] Preparation of 2,4-dihydroxy quinolines as an agrochemical and pharmaceutical intermediates have been reported by Franaki et.al.[43] The compounds [50] was prepared and claimed to have antiasthmatic activity. Carbostyrils as antiarrhythmics, their preparation and formulations have been done by Tafusa et.al.[44] The reaction of 3-(1-chloro-1-phenylmethyl)-8-methyl carbostyril and $Me_3.C.NH_2$ in MeCN under refluxing condition for 1 hr. gave [51] on acidification with HCl.

Synthesis of 5H-quinolin-[3,4-b] [1,4]-benzothiazin-6-ones have been reported by Jayshree et.al.[45] The reaction of 4-hydroxy quinoline-2-ones and 7-aminothiophenol in dioxane in the presence of p-toluene sulphonic acid furnished compound involving dehydration and oxidative cyclisation. The synthesis of benzofuroquinolines and some halobenzofuro [2,3-c] quinoline derivatives [52] (R = F, Br) by photocyclisation of N-benzyl-N-(p-halophenyl)-2-benzofuran carboxamides has been reported by Yamaguchi et.al.[46] An efficient synthesis of 8-methoxy and 8-hydroxy-1-methyl carbostyril has been reported by Gesto et.al.[47].

Studies on Vilsmeir-Haack reaction , a new route to 2-chloro quinoline-3-carboxyaldehydes [53] has been reported by Pawar et.al.[48] to yield 3-carboxyaldehyde, 6-methyl quinoline-2(1H)-one [54]. Some new sulphides [56] and [57] from 4-Bromoethyl-carbostyril [55] have been reported by Kulkarni et.al.[49] Regio selectivity of radical cyclisation of 6-exo/7-endo and 7-exo/8-endo of N-(O-alkenyl phenyl)-2,2-dichloroacetamides have been reported by Tatsunori et.al.[50] The regiochemistry of the radical cyclisation of the title compound was shown. Thus 2-(CH_2 = CH).C_6H_4-$NHCH_3$ when treated with Bu_3SnH and AIBN to give 49% dihydrodimethyl quinolinone [58].

STRUCTURES



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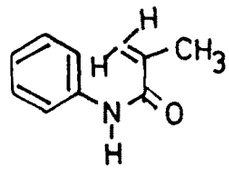

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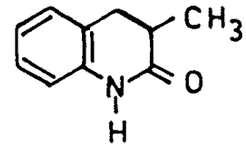

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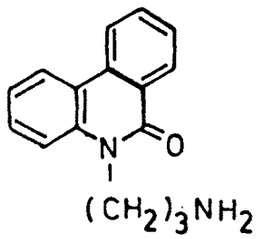

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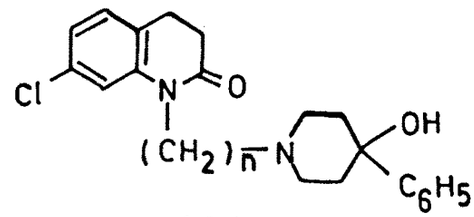

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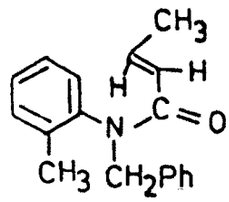

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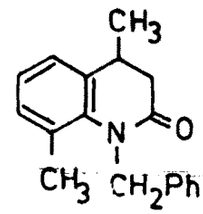

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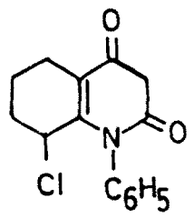

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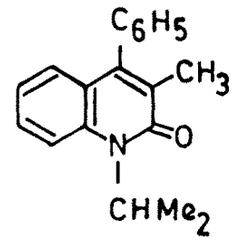

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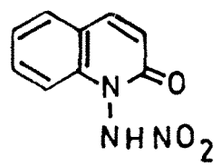

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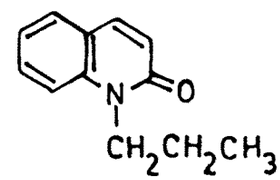

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STRUCTURES

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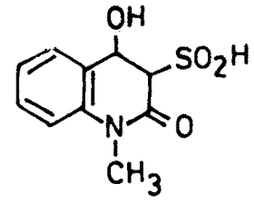

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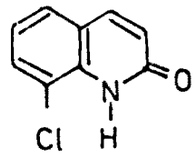

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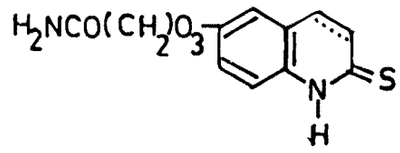

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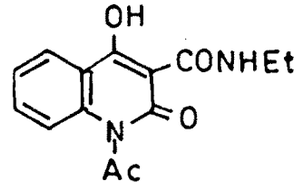

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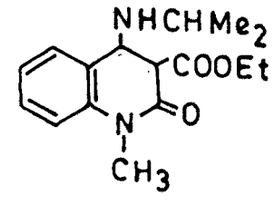

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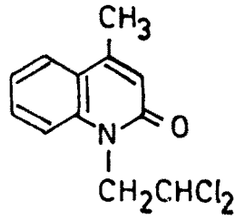

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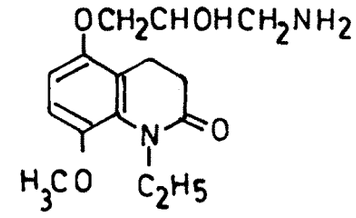

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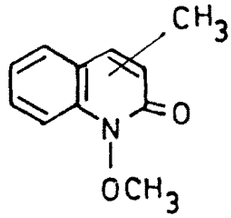

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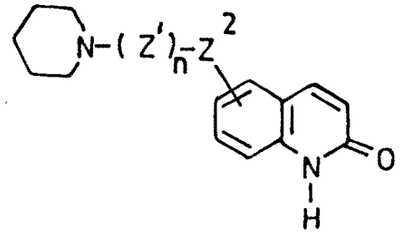
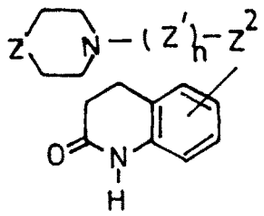


Z = N-Phenyl imino

(21)

STRUCTURES



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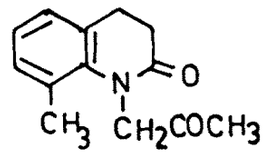

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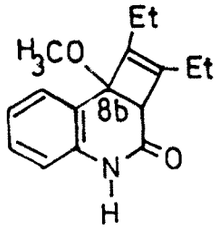

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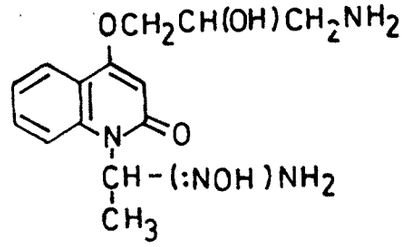

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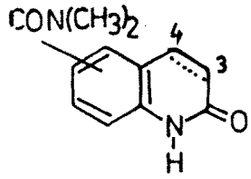

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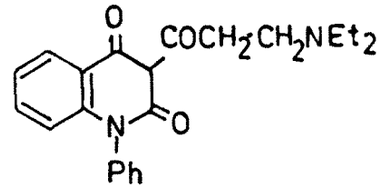

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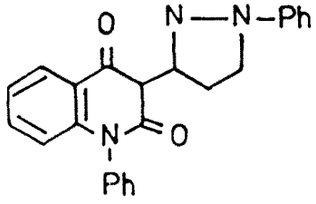

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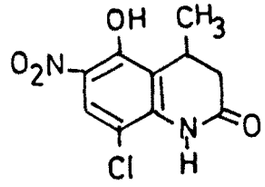

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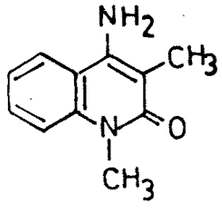

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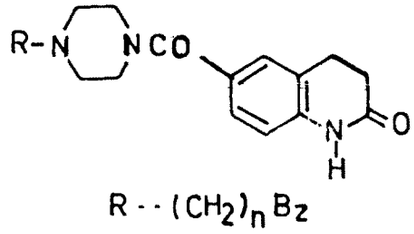

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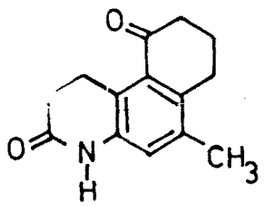
STRUCTURES



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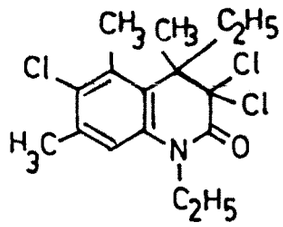

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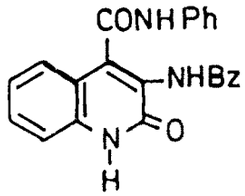

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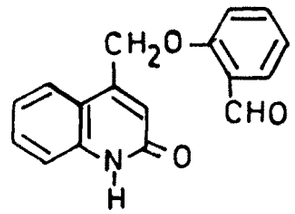

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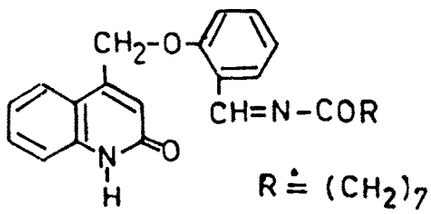
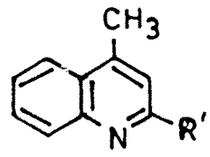


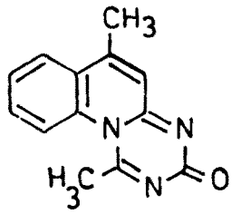
R = $(CH_2)_7$

(36)



R' = Cl

(37)



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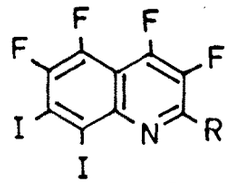
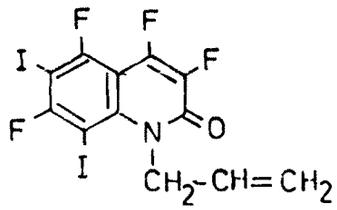


R = CH_2=CH-CH_2O

(39)



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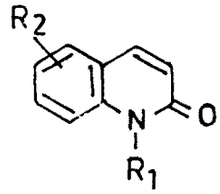
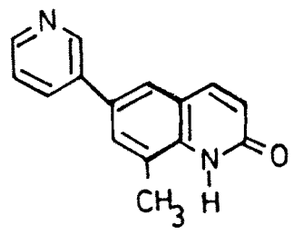


R_1 = H, alkyl, phenyl

R_2 = H, alkoxy, alkyl sulfo-, hydroxy

(41)

STRUCTURES



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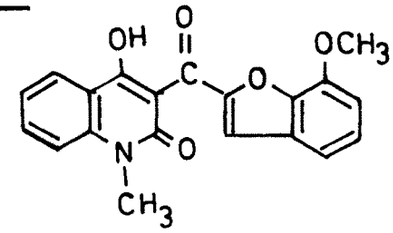

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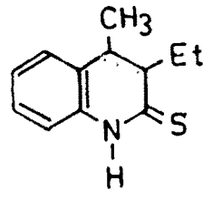

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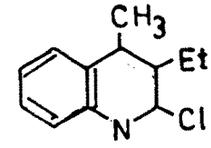

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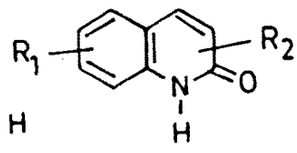
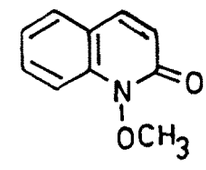


R_1 = H
R_2 = $-CH_3$

(46)



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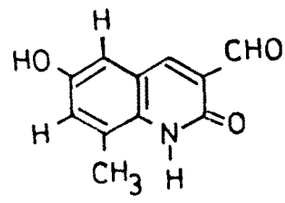

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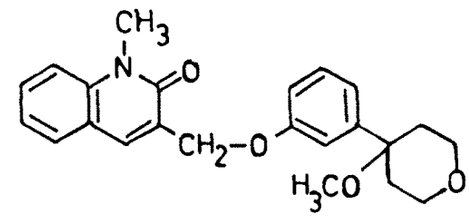

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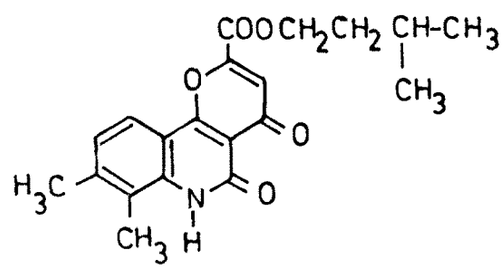

(50)

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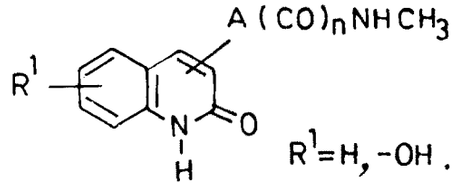
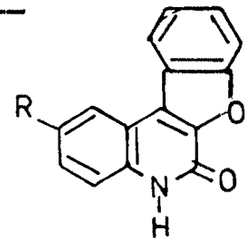


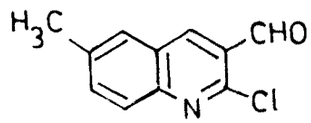
R^1=H, -OH.

(51)



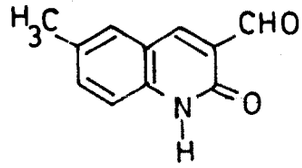
R = F, Br, Cl.

(52)



(53)

6N HCl →



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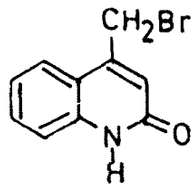
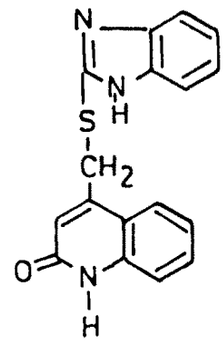


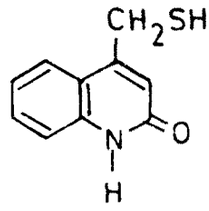
(55)

2-mercapto-Benzimidazole →



(56)

Thiourea
C_2H_5OH →



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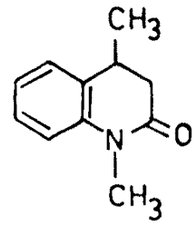

(58)

SCOPE OF THE PRESENT WORK

The quinolines being pharmaceutically important class of the compounds the problem on the synthesis of some new quinoline derivatives is undertaken. The substitution of alkyl group at N^1- position of the quinoline nucleus markedly affect the biological activity of the compound. Therefore, we thought, it proper to introduce hydrazido link at N^1-position of the quinoline ring to see whether these compounds exhibit the promising antimicrobial activity or not. These hydrazides will be converted into thiosemi-carbazides as key intermediate and cyclised to N^1-substituted five membered heterocycles such as triazole, oxadiazoles and thiadiazolees. Further these compounds will be tested against gram +ve and gram -ve bacteria to find out structure activity relationship.

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