A PROJECT WORK ON

SYNTHESIS OF QUINOLINE-*N*-OXIDE-4-BENZOYLSULPHIDE

SUBMITTED BY

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MAT NO PSC1607115

IN PARTIAL FULFILLMENT FOR THE DEGREE OF

BACHELOR OF SCIENCE (B.Sc.) IN INDUSTRIAL CHEMISTRY

UNDER THE GUIDIANCE OF

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CERTIFICATE

This is to certify that this research work entitled **"Synthesis of Quinoline-*N*-oxide-4-benzoylsulphide",** was done by **Winifred Obehi Inegbedion** with matriculation number **PSC1607115** in the project laboratory of the Department of Chemistry, University of Benin, under the supervision of Dr. Bodunde J. Owolabi in fulfillment of the requirements of the degree of Bachelor of Science in Industrial Chemistry.

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PROF. J.U. IYASELE

DATE

HEAD OF DEPARTMENT

DEDICATION

This work is dedicated to my parent Mr. and Mrs. M.O Inegbedion for their unfaltering love, prayers, support and encouragement throughout this journey.

ACKNOWLEDGEMENT

My heartfelt appreciation goes to everyone who helped made this work a success. First and foremost, I am very grateful to God Almighty, our maker, for His Grace and Favour in my life that got me through all the rough and difficult times when all seemed hopeless.

My sincere gratitude also goes to my project supervisor Dr. Bodunde J. Owolabi for his kind supervision, guidance, and fatherly advice all through this research work.

I also want to thank my HOD, Prof J. U. Iyasele, the staffs and laboratory technicians for all their assistance during the course of this project, and also the Ph.D students of the University of Benin, the likes of Mr. Divine and Mr. Henry. This work would definitely not have been this successful without you both.

And of course my family. I am so grateful to my Parent (Mr. and Mrs. M.O. Inegbedion), for all their supports given to me without any reserve be it financially, spiritually, and morally. Thank you for all your struggles and perseverance. And to my Brothers: Clem, Trikque, Mike_mic, OZ (PS, I know u made me promise you a full page of acknowledgement but just manage this one small), thank you for all your supports, financially and just being there for me. A full page of gratitude will not even come close to express my appreciation for all your influence in my life.

Also to my project colleagues (Floyd and Joy), I appreciate you both for all the long hours and late night spent in the lab, the stress and frustration would not have been so bearable with you both. I am also thankful to Kingsley Chibuzor for always being there and always willing to contribute, and my friends for being encouraging and supportive (Nicholas, Eva and Marian).

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ABSTRACT

Quinoline or benzopyridine, a nitrogen containing compound has been known to possess antimalarial, anti-bacteria, and anti-fungal properties. In this study, a derivative of quinoline-*N*-oxide-4-thiol was obtained by a five step reaction. The compounds synthesized in the stepwise reactions were: quinoline-N-oxide, 4-nitroquinoline-N-oxide, 4-chloroquinoline-N-oxide and quinoline-N-oxide-4-thiol. Furthermore, the latter was coupled with benzoyl chloride under basic condition to obtain quinoline-*N*-oxide-4-benzoylsulphide. The physical properties of the compound obtained are percentage yield 1.86%, melting point 96-98^{o}C, and retention factor value 0.83.

CHAPTER ONE

INTRODUCTION AND LITERATURE REVIEW

1.0 Introduction

Heterocyclic compound is a class of cyclic organic compounds having at least one heteroatom in the cyclic ring system. The most common heteroatoms are nitrogen, oxygen and sulphur (Joule *et al.*, 2000).

Heterocyclic compounds are also found in plants and animal products; and they are one of the essential constituent of natural organic compounds namely alkaloids, natural dyes, drugs, proteins, and enzymes (Finar, 2004).

Heterocyclic compounds are primarily classified as saturated and unsaturated. The saturated heterocyclic compounds behave like the acyclic derivatives with modified steric properties. Piperidine and tetra-hydrofuran are the conventional amines and ethers of this category. However, unsaturated heterocyclic compounds of 5- and 6-member rings have been studied extensively because of their unstrained nature. The unstrained unsaturated heterocyclic compounds include pyridine, thiophene, pyrrole, furan and their benzofused derivatives. Quinoline, isoquinoline, indole, benzothiophene, and benzofuran are some important example of benzofused heterocycles (Gilchrist, 1999).

Quinoline is a versatile bicyclic heterocyclic scaffold with immense therapeutic potential. Some of the compounds containing quinoline nucleus are agents of choice for the treatment of various ailments, particularly cancer and malaria (Hussaini, 2016).

Several molecules containing quinoline skeleton are clinically significant drugs and extensively used for the treatment of various human diseases/disorders. The clinical success of someofthesecompoundsandtheversatilecharacterofthequinolinenucleusattractedmedicinalchemistsinthedevelopmentofnewerchemotherapeuticagents(Yan*etal.*,2013).

Quinolinenotonlyhasawiderangeofbiologicalandpharmacologicalactivitiesbutthereareseveralestablishedprotocolsforthesynthesisofthisring.

Thesynthesisofquinolineshasbeenofconsiderableinteresttochemistsbecausetheiroxygenheterocyclesmaycontributetopotentialantimalarial,antibacterial,antiasthmatic,antihypertensive,antiinflammatory,andantiplateletproperties(Maguire*etal*.,1994).VariousmethodshavebeenreportedforthesynthesisofquinolinessuchastheSkraup,Conrad-Limpach-Knorr,Pfitzinger,Friedlander,andCombesmethods(Fehnel,1966).However,theFriedlandercondensationisstillconsideredasapopularmethodforthesynthesisofquinolinederivatives(Fehnel,1966).

1.1 BackgroundoftheStudy

Heterocyclicchemistryisoneofthemostvaluablesourcesofnovelcompoundswithdiversebiologicalactivitybecauseoftheiruniqueabilityoftheresultingcompoundtomimicthestructureofthepeptidesandtobindreversiblywithproteins(Adreani*etal*.,2008).Amongstheterocycliccompounds,quinolinesysteminavastrangeofmedicinalandindustrialsettingscanbedescribedmainlybyitsversatilityandbroadpotentialforfunctional(Evans*etal*.,1988).Moreover,thequinolineringsystemoccursinvariousnaturalproducts,particularlyinalkaloids,anditsseldomlyusedfortheplanofmanysyntheticcompoundswithvariedpharmacologicalproperties(Matada*etal.,*2021).Theknownquinolinealkaloidsdictamnineandy-fagarineisolatedfromrootsofZanthoxylumulutaienswerereportedtoexhibitmoderateantibacterialactivitywithMICsof30ug\ml(Garcia*etal.,*2012).

Thefusionofseveralringsleadtogeometricallywell-definedrigidpolycyclicstructuresandthusholdsthepromiseofahighfunctionalspecializationresultingfromtheabilitytoorientsubstituentinthreedimensionalspace(Adreani*etal.,*2008).Compoundswithheterocyclicringsareinextricablywovenintothemostbasicbiochemicalprocessesoflife.Ifoneweretochooseastepinabiochemicalpathwayatrandom,therewouldbeaverygoodchancethatoneofthereactantsorproductswouldbeaheterocycliccompound.Eventhoughthisisfalse,participationofheterocycliccompoundsinthereactioninquestionwouldalmostbecertainasallbiochemicaltransformationsarecatalyzedbyemzymes,andthreeofthetwentyaminoacidsfoundinemzymescontainheterocyclicrings.

Manyenzymesfunctiononlyinthepresenceofcertainsmallnon-aminoacidsmoleculescalledcoenzymes(orcofactor),whichmoreoftenthannotareheterocycliccompounds.

Assumingtheenzymeinquestioncontainsnoneofthesecoenzymesorthethreeaminoacidsreferredtoabove,anessentialrolewouldstillbeplayedbyheterocycliccompoundsasallenzymesaresynthesizedaccordingtothecodeinDNA,whichofcourseisdefinedbythesequenceoftheheterocyclicbasesfoundinDNA.Chemotherapyconcernsthetreatmentofinfectious,parasitic,ormalignantdiseasesbychemicalagents,usuallysubstancesthatshowsselectivetoxicitytowardsthepathogen.Thediseasesofbodilydysfunctionandtheagentsemployedaremainlycompoundsthataffectthefunctioningofenzymes,thetransmissionofnerveimpulsesortheactionofhormonesonreceptors.Heterocycliccompoundsareusedforallthesepurposesbecausetheyhaveaspecificreactivity,forexample,epoxides,aziridinesand*B*-Lactams(Adreani*etal.,*2008)becausetheyresembleessentialmetabolitesandcanprovidefalsesymptomsinbiosynthesisprocesses,forexample,antimetabolitesusetreatmentsofcancerandvirusdiseasesbecausetheyfitbiologicalreceptorsandblocktheirnormalwor king,orbecausetheyprovideconvenientbuildingblockstowhichbiologicallyactivesubstituentcanbeattached.Theintroductionofheterocyclicgroupsintodrugsmayaffecttheirphysicalproperties,forexample,thedissociationconstantofsulfadrugs,modifytheirpatternsofabsorption,metabolismortoxicity.Manysignificantdiscoverieshavebeenmade,however,bytherationaldevelopmentofobservationofbiologicalactivitymadebychanceinworkdesignedforotherpurposes(Nagendra*etal.*,2013).Thetheoreticalbasisofmedicinalchemistryhasbecomemuchmoresophisticated,butisnaïvetosupposethatthediscoveryofdrugsismerelyamatterofstructure-activerelationships.Thesuccessofamedicinalagentdependsonthebalancebetweenitsdesirablepharmacologicaleffectsandtheharmitmayotherwisedotoapatient,andthiscannotyetbepredictedwithcertainty.Serendipityandluckwilldoubtlesscontinuetoplayanimportantpartanimportantpartinnewdiscoveries(Nagendra*etal.,*2013).

1.2 StatementoftheProblem

Despitethesubstantialeffortmadebysyntheticchemisttosynthesizecompoundshavingantimalarialpropertiesfordrugdevelopmentinthetreatmentofparasiticinfections,malariacontinuetobeoneofthemajorpublichealthchallengeinprevalentpartoftheworld,particularlyintropicalAfrica(Irungu*etal*.,2012),principallyduetothewell-knownresistanceoftheparasitestoalreadyavailableantimalarialsuchaschloroquineandquinine(Zofou*etal.*,2011).Duetothelimitedsuccessinthedevelopmentofmalariavaccinesandthedestructivereactionsoftheconventionalantimalarialdrugs,thereisanurgentneedtoprovidescientificreportonquinolinebasedagentthatcaninhibitmalariastrain.

1.3 JustificationofStudy

Marella*etal.,*2013reportedthatquinolineanditsderivativespossessantimalarial,antibacterial,anti-inflammatory,anti-fungiactivities.Therefore,tothebestofourknowledgequinolineringsystemhavingbenzoylchloridesubstituenthasnotbeenscientificallysynthesized.

1.4 ScopeoftheWork

Thisresearchworkfocusesonthesynthesisandsomephysicalcharacterizations(percentageyield,colour,state,meltingpointandretentionfactor)ofQuinoline-*N*-oxide-4-benzoylsulphide.

1.5 AimandObjectivesofThesis

Theaimofthisworkistosynthesisquinoline-*N*-oxide-4-benzoylsulphide.

Toachievethisaim,thefollowingobjectiveswereset:

- Synthesisofquinoline-*N*-oxide
- Synthesisof4-nitroquinoline-*N*-oxide
- Synthesisof4-chloroquinoline-*N*-oxide
- Synthesisofquinoline-*N*-oxide-4-thiol
- Synthesisofquinoline-*N*-oxide-4-benzoylsulphide
- PhysicalCharacterizationoftheSynthesizedCompounds

1.6 LITERATURE REVIEW

Heterocyclic compounds have a wide application in pharmaceuticals, agrochemicals and veterinary products. Many heterocyclic compounds are very useful and essential for human life. Various compounds such as hormones, alkaloids antibiotic, essential amino acids, hemoglobin, vitamins, dyestuffs and pigments have heterocyclic structure (Solomons, 1997).

Based on the structural and electronic arrangement, the heterocyclic compounds may be classified into two categories (Bansal, 1998):

i. aliphatic heterocyclic compounds
ii. aromatic heterocyclic compounds

The aliphatic heterocyclic compounds are the cyclic amines, cyclic amides, cyclic ethers and cyclic thioethers. Aliphatic heterocycles those do not contain double bonds are called saturated heterocycles. The properties of aliphatic heterocycles are mainly affected by the ring strain. Examples of aliphatic heterocyclic compounds are shown in figure 1.

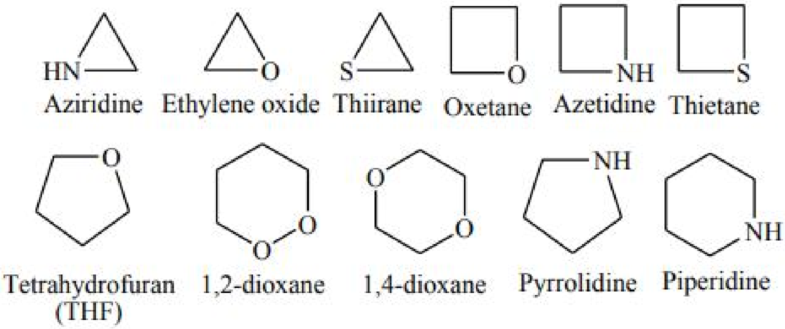


Figure 1. Examples of aliphatic heterocyclic compounds

However, aromatic heterocyclic compounds are analogous of benzene. The aromatic heterocyclic compounds also of follow the Huckel's rule.

AccordingtoHuckel’srule,anaromaticcompoundsmustbecyclicinnaturewithplanargeometryduetoconjugateddoublebondsandmusthave(4n+2)πelectrons.Examplesofaromaticheterocycliccompoundsareshowninfigure2.

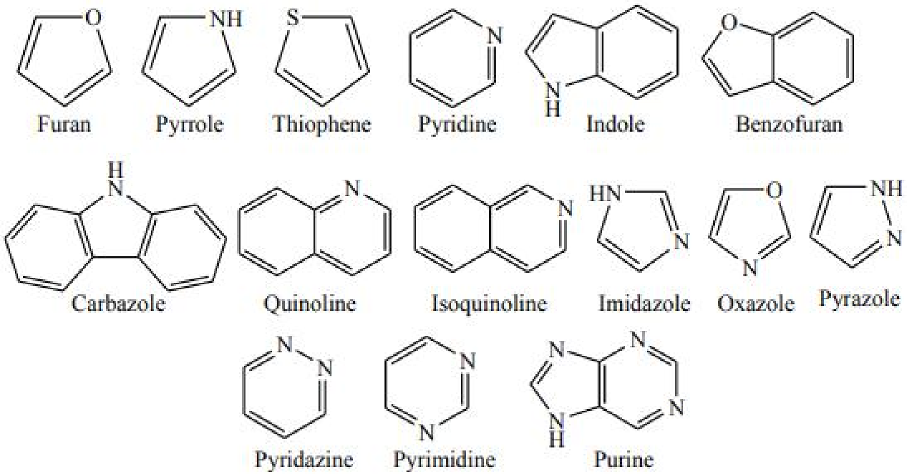


Figure2.Examplesofaromaticheterocycliccompounds

1.6.1 Quinolines

QuinolineisaheterocyclicaromaticorganiccompoundwiththechemicalformulaC$_9$H$_7$N. Itiscolourlesshydroscopic(asubstancethatreadilyattractswaterfromitssurroundingsthrougheitherabsorptionoradsorption)liquidwithastrongodour.Quinolineisonlyslightlysolubleincoldwaterbutdissolvesreadilyinhotwaterandmostorganicsolvent.Itisabicyclicheterocyclehavingabenzeneringfusedwithapyridineringin2,3-position(BahlandBahl,2014).Itderivesitsnamefromthefactthatitwasfirstobtainedbyheatingthefamousantimalarialalkaloid“quinine”,withalkali.Beingaweaktertiarybase,itformssaltswithacidsandexhibitsreactionssimilartobenzeneandpyridine.Itparticipatesinbothelectrophilicandnucleophilicsubstitutionreactions.

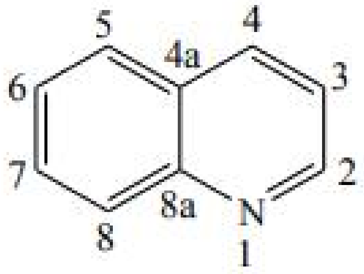
Quinolineisusedmainlyasanintermediateinthemanufactureofotherproducts.Potentialexposuretoquinolinemayoccurfromtheinhalationofcigarettesmoke.Quinolinebreaksdownquicklyintheatmosphereand water.Acute(short-term)inhalationexposuretoquinolinevapoursirritatestheeyes,nose,andthroatandmaycauseheadaches,dizziness,andnauseainhumans.

Informationonthechronic(long-term),reproductive,developmental,orcarcinogeniceffectsofquinolineinhumansisnotavailable.Liverdamagehasbeenobservedinratschronicallyexposedtoquinolinebyingestion.Anincreasedincidenceoflivervasculartumorshasbeenobservedinratsandmiceorallyexposedtoquinoline.

EPAhasprovisionallyclassifiedquinolineasaGroupC,possiblehumancarcinogen(Merck.,1989).

1.6.2 StructureofQuinoline

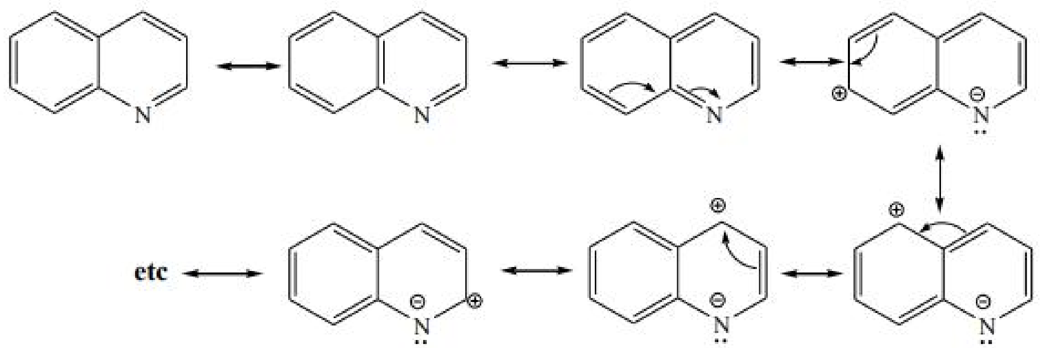
Quinolineisabicyclicheterocyclewhichconsistsofabenzeneringfusedtothealphaandbetapositionsofapyridinering.TheIUPACnameofquinolineisbenzo[b]pyridine.itisbeingtheb-facebenzo-fusedisomer.Theatomsarenumberedasshowninbelowstructure.ThenumberingbeginsfromtheNitrogenatomandgoingcounterclockwisearoundthetwocondensedrings.Thestructureofquinolineisshownasfollow(Bansal,1998).



Quinoline

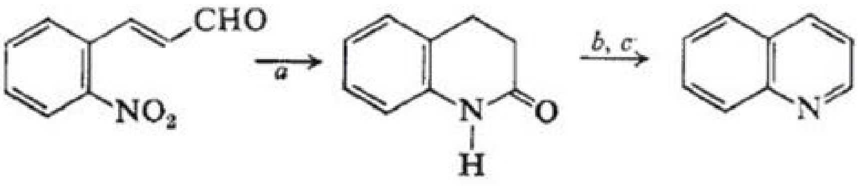
AlltheringatomsinQuinolinearesp2hybridized.Thesp2orbitalsofallcarbonandnitrogenatomoverlapwitheachotherandalsowiththesorbitalsofhydrogentoformC-C,C-N,andC-Hπbonds.Eachringatomalsopossessesaporbital.Theseporbitalsareperpendiculartotheplaneofthering.Lateraloverlapofthesep-orbitalsproduceaπmolecularorbitalcontaining10electrons.QuinolineisanaromaticcompoundsinceitfollowstheHuckel’srule(i.e.4n+2πelectronrule)forn=2.

UnlikeIndole,thelonepairofnitrogenofquinolinedoesnotparticipateinthedelocalization.Quinolineisaresonancehybridofseveralcanonicalformsasshownbelow(Dewar,.1966)



1.6.3 OccurrenceofQuinoline

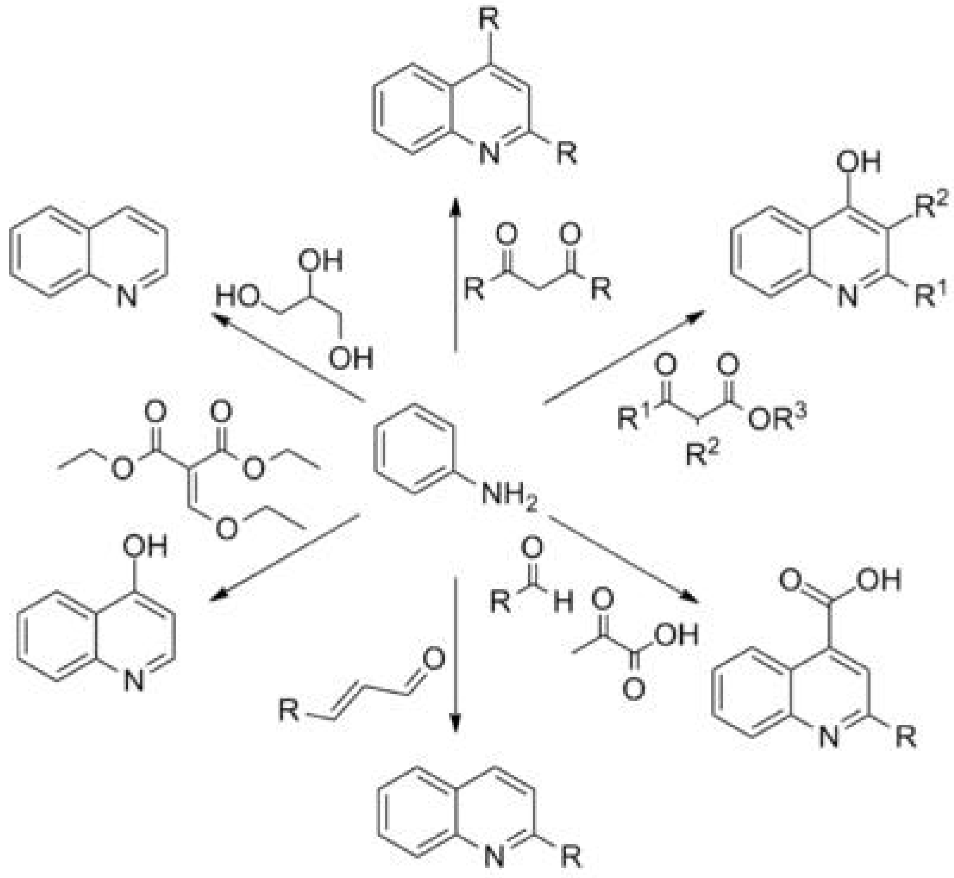
Quinolinewasdiscoveredincoaltardistillatebyrunge(Allan,1971)in1834andnamed" Leukol"(fromoleummeaningwhiteoilinGreek).ThebasewasalsoobtainedbyGerhardt(Koenigs,1879)in1842byalkalinedistillationofquinine,cinchonine,orstrychnine,andwasnamedbyhimas"Chinolein"or"Chinolin".Notuntil1882wastheidentityofleukoland chinolinfirmlyestablished,whenHoogewerffandVanDorp(Koenigs,1880)showedthatthesamplesfromcoaltarandfromalkaloiddistillationhadthesameboilingpoint,formedthesamehydrate($3H_2O$),platinichloride,bichromate,andargentonitrate.Bothspecimens werealsoconvertedbyoxidationintoquinolinicacid,whichwasdecarboxylatedtonicotinicacid.Kornerwascitedasthefirsttoproposethestructuralformulaforquinoline(inDieChemievonPyridinsund*Seiner*DevioatebyA.Calm)butDewar(Mann,1922)in1871suggestedthatquinolineborethesamerelationshiptopyridinethatnaphthaleneboretobenzene. Thestructurebelowwasconfirmedbythesynthesesinwhichallylanilinewaspassedover glowingleadoxide(Koenigs,1879),orfrom*o*-nitrocinnamaldehydeasshowninreactionbelow(Baeyers,1879);



^{a} Zn/HCl. ^{b} $POCl_3/PCl_5$. ^{c} HI, AcOH, 240 °C.

1.6.4 SynthesisofQuinoline

Quinolinesareoftensynthesizedfromsimpleanilinesusinganumberof namedreactions(Yan*etal.,*2013).



Goingclockwisefromtop,theseare:

- combesquinolinesynthesis using anilines andβ-diketones.
- conrad-Limpachsynthesis using anilines andβ-ketoesters.
- doebnerreaction using anilines withan aldehyde and pyruvicacid toformquinoline-4-carboxylicacids
- doebner-Millerreaction using anilines andα,βunsaturated carbonyl compounds.
- gould-Jacobsreaction startingfromananilineandethylethoxymethylenemalonate
- Skraupsynthesis using ferroussulfate, glycerol, aniline, nitrobenzene,and sulfuricacid.

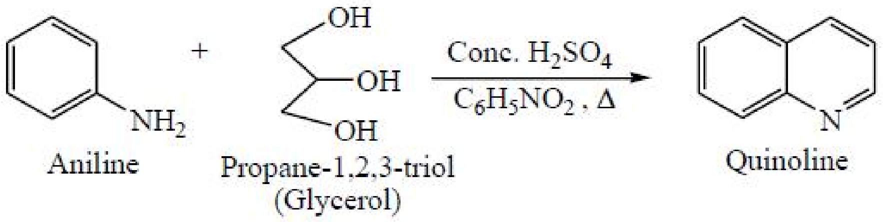
Anumberofotherprocessesexist,whichrequirespecificallysubstitutedanilinesorrelatedcompounds:

- campsquinolinesynthesis usingano-acylaminoacetophenoneandhydroxide
- friedländersynthesis using 2-aminobenzaldehyde and acetaldehyde
- knorrquinolinesynthesis,usingaβ-ketoanilideandsulfuricacid
- niementowskiquinolinesynthesis,usinganthranilicacidandketones
- pfitzingerreaction usingan isatin withbaseandacarbonylcompoundtoyieldsubstitutedquinoline-4-carboxylicacids
- povarovreaction usinganiline,a benzaldehyde andanactivated alkene.

PreparationMethodsofQuinolines

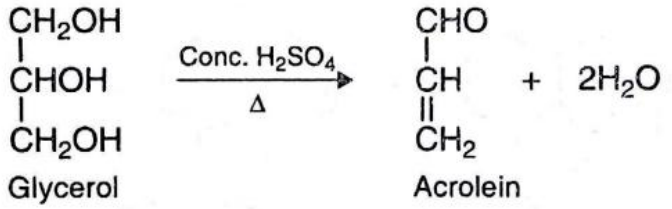
1. **BySkraupSynthesis:(CommercialMethod)**

   Thisisoneofthemostimportantmethodsforthepreparationofquinoline.Inthisreaction,amixtureofanilineandglycerolisheatedinthepresenceofsulphuricacidandamildoxidizingagent,usuallynitrobenzeneorarsenicpentoxide.Thereactionisexothermicandtendstobecomeveryviolent.Ferroussulphateorboricacidisgenerallyaddedtomakethereactionlessviolent(uop.edu.pk\ocontents\Quinoline.pdf).

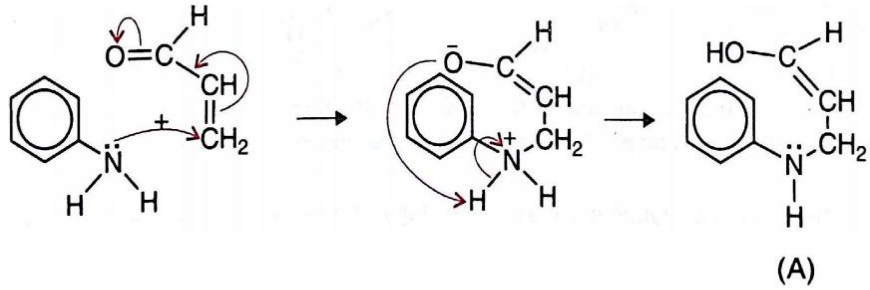


Mechanism

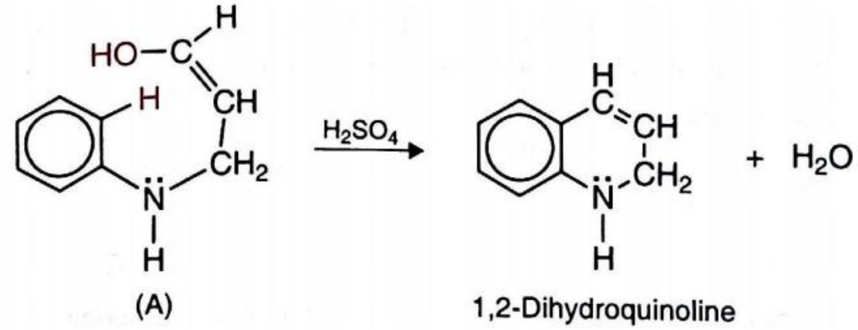
Step1:Glycerolundergoesdehydrationwithsulphuricacidtogiveacrolein.



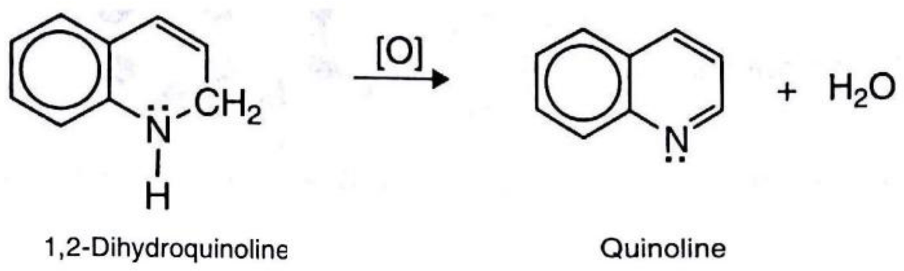
Step2:Anilineaddstoacrolein(1,4-addition)togive(A).



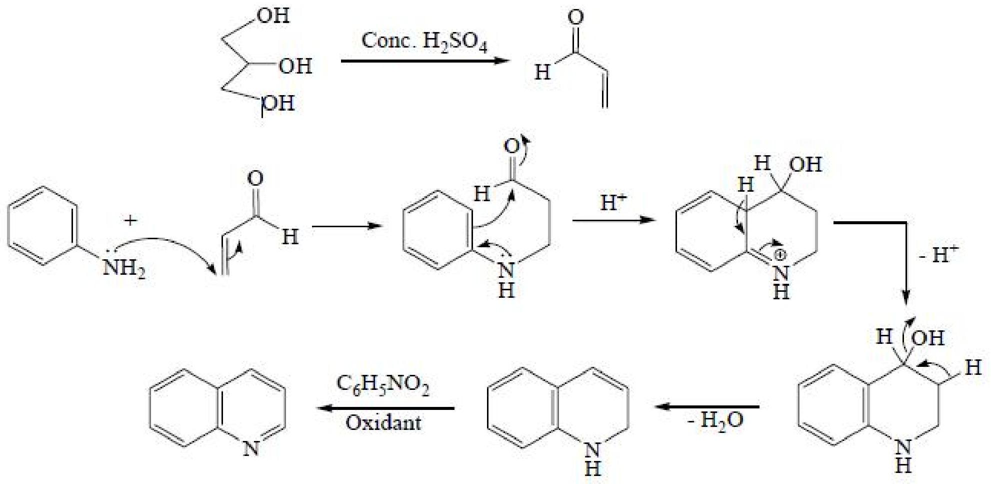
Step3:Compound(A)Undergoesringclosureinthepresenceofsulphuricacidtoform1,2-dihydroquinoline.



Step4:1,2-Dihydroquinolineundergoesoxidationwithnitrobenzenetofinallyyieldquinoline.Nitrobenzeneitselfisreducedtoanilinewhichisreusedinstep(2).

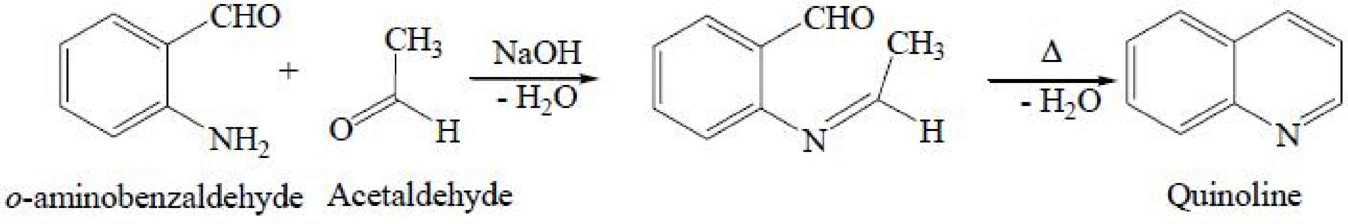


Thestepwiseschemeofthereactionisgivenbelow



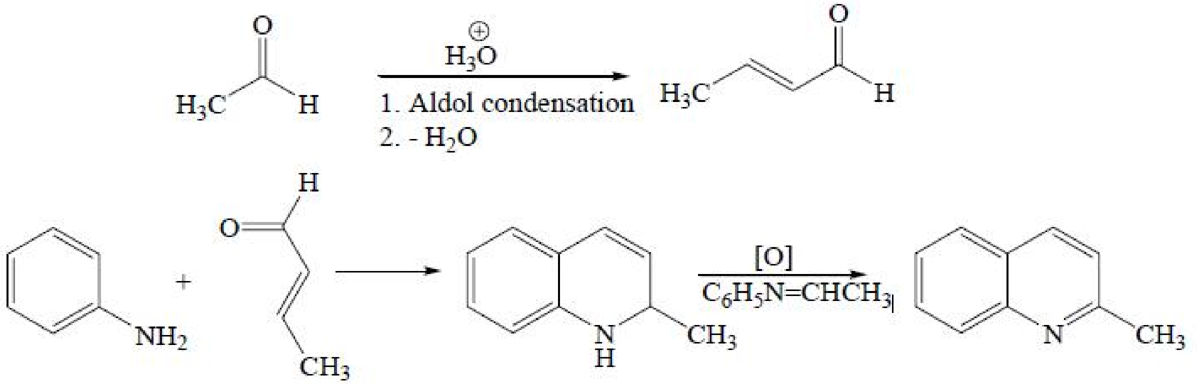
2. **BytheFriedlanderSynthesis:**

   Quinolinecanalsobepreparedbythecondensationofo-aminobenzaldehydewithacetaldehydeinsodiumhydroxidesolution.Thereactionmechanismisshownasfollow(uop.edu.pk\ocontents\Quinoline.pdf).



3. **TheDobner-MillerSynthesis:**

   ThisisamodifiedformoftheSkraupsynthesis.Inthisreaction,thesimplealdehydesandketonesactasprecursorofα,β-unsaturatedcarbonylcompounds.ThereactionfollowsthesimilarreactioncourseasintheSkraupsynthesistoproducederivativesofquinoline.Whenacetaldehydeisusedasprecursorofα,β-unsaturatedcarbonylcompound2-methylquinolineisformed.Thereactionmechanismisshownasfollow(Joule*etal.*, 2000)



1.6.5 PhysicalPropertiesofQuinolines

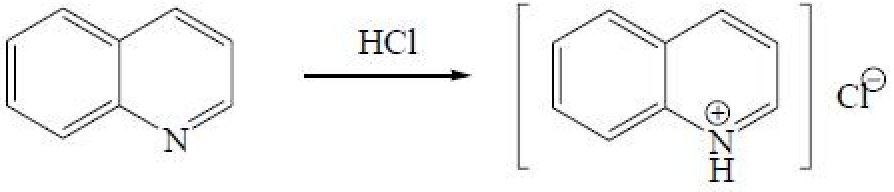
Quinolineisacolourlesshygroscopicliquid,boilingpoint238^{O}C,havingadisagreeable,pyridine-likeodour.Itissolubleinwaterandcompletelymisciblewithalcohol,ether,acetoneandcarbondisulphide.Quinolineisaliquidwithapeculiarodour,slightlydenserthanwater,Ithasamolarmassof129.16g/mol,densityof1.093g/ML.Itisacolourlessoilyliquidwithameltingpointof-15^{o}candboilingpointof237^{O}C.

Contactwiththeskinmayirritatetheskinandeyes.Onexposuretoair,quinolineturnsintoyellowcoloured.Itismiscibleinorganicsolvents.Quinolineishighlyaromaticinnatureandithasresonanceenergy47.3kcal/mole.QuinolineisaweakbasehavingpKa4.94.Thebasicityofquinolineisintermediatebetweenaniline(pKa4.58)andpyridine(pKa5.17)(Finar, 2004).

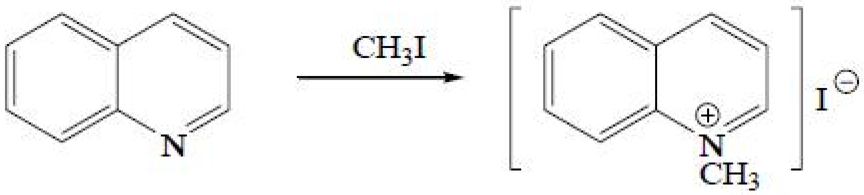
1.6.6 ChemicalPropertiesofQuinoline

1. **Basicity:**Duetoavailabilityoflonepairofelectronsonnitrogen,quinolineactsasabaseandformssaltswithacidsandquaternarysaltswithalkylhalides.

    a) Reactionwithacids:



    b) Reactionwithmethyliodide:

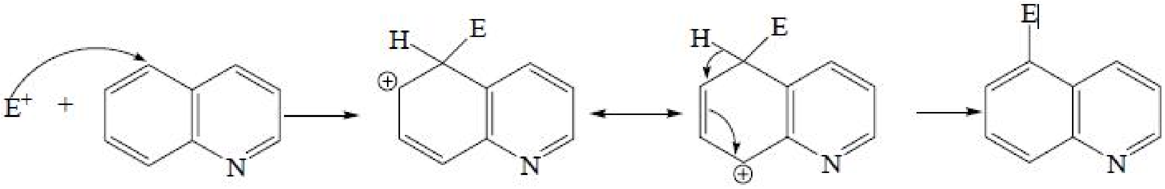


2. **ElectrophilicSubstitutions**

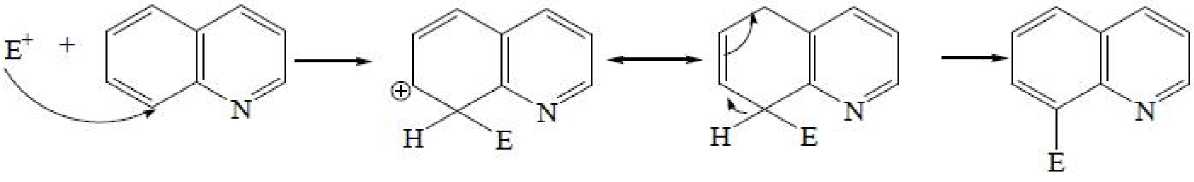
Outofthetwofusedringsinquinoline,thecarbocyclic(benzene)ringisrelativelymore electronrichandresemblesbenzeneringwhilethenitrogencontainingring(lesselectronrich)resembleswithpyridinering.

Therefore,theelectrophilicsubstitutioninquinolinetakesplacemorereadilyatbenzenering(atposition5and8ofbenzenering)ratherthanthepyridinering.Thus,ifboththe positionsinbenzeneringarevacantthanmixtureofsubstitutedproductisobtained.The generalmechanismofelectrophilicsubstitutiononquinolineisshownbelow.

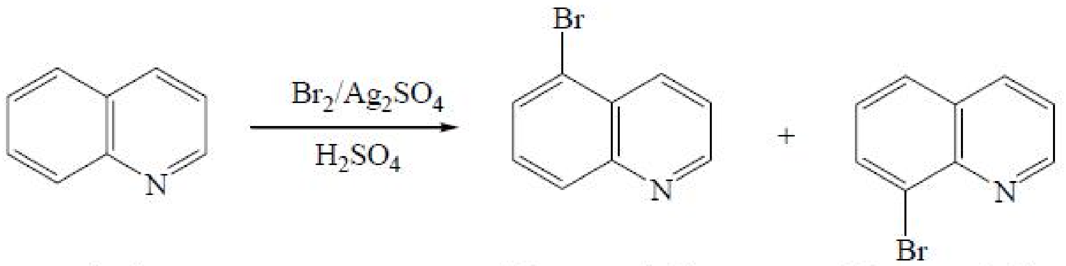
Atposition5



Atposition8

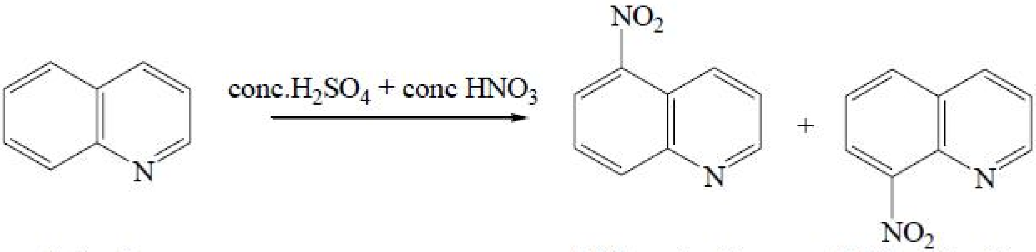


Bromination: QuinolineundergoesbrominationwithBr$_2$inpresenceofsilversulphate(Ag$_2$SO$_4$)andH$_2$SO$_4$.Brominationoccursatposition5and8hencemixtureofproductsisformed.



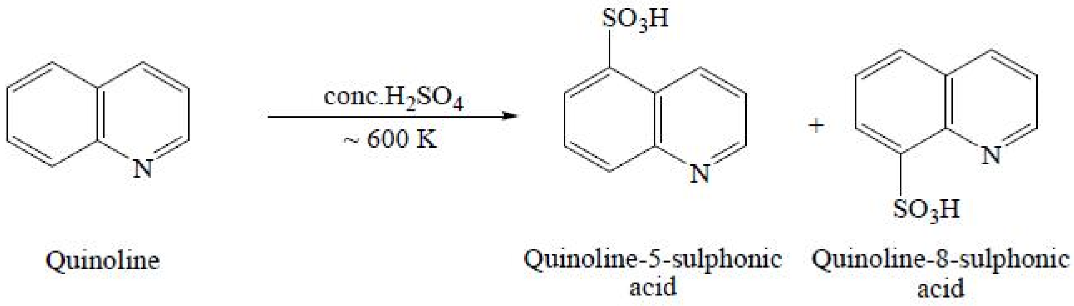
Quinoline 5-Bromoquinoline 8-Bromoquinoline

Nitration: Quinolinecanundergonitrationbyreactingwiththewell-knownnitratingagent(Conc.H$_2$SO$_4$+conc.HNO$_3$).Nitrationofquinolineoccursatposition5and8.



Quinoline 5-Nitroquinoline 8-Nitroquinoline

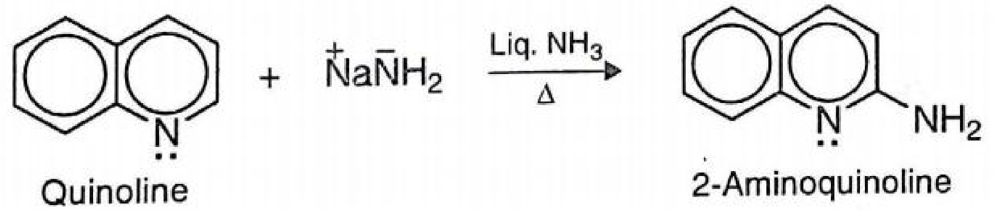
Sulphonation: InpresenceofConc.H_2SO_4athightemperature(~600K)sulphonationofquinolinetakesplace.Likenitrationorbromination,thesulphonationofquinolineoccursatposition5and8.



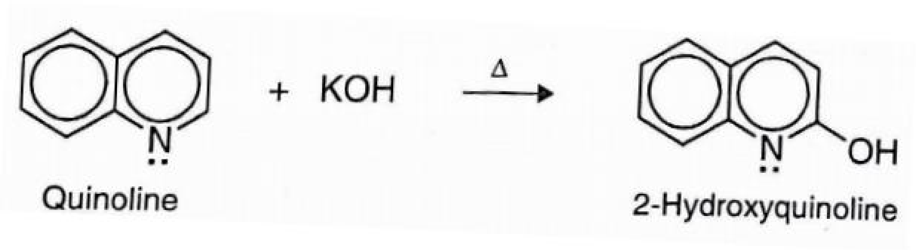
3. NucleophilicSubstitutions

Quinolinealsogivesnucleophilicsubstitutionreactions.Since,pyridineringofquinolineiscomparativelylesserelectronrichincomparisontothebenzenering,therefore,nucleophilicsubstitutioninquinolinetakesplaceonpyridinering.Thenucleophilicsubstitutiononpyridineringtakesplaceatposition2ofpyridinering.Ifposition2isoccupied,thenthesubstitutiontakesplaceatposition4.

a) ReactionwithSodamide:Quinolinereactswithsodamide,astrongbaseinliquidammoniaatabout100°Ctoform2-aminoquinoline

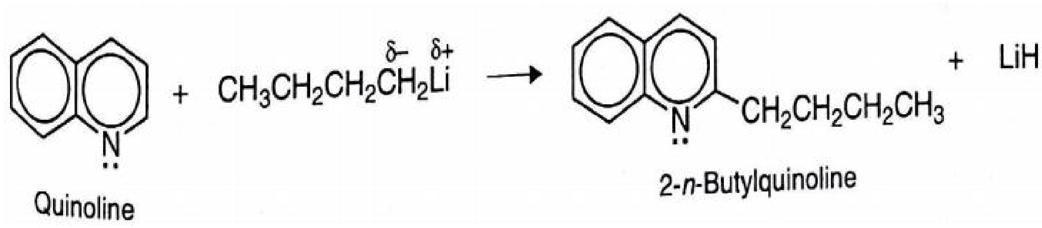


b) ReactionwithPotassiumHydroxide.Quinolinereactswithpotassiumhydroxideat220°Ctogive2-hydroxyquinoline.



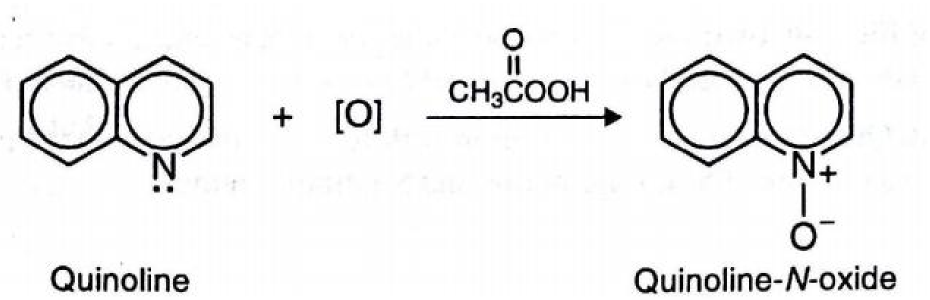
c) Reactionwithn-Butyl-lithium

Quinolinereactswithn-butyl-lithiumtoyield2-n-butylquinoline.



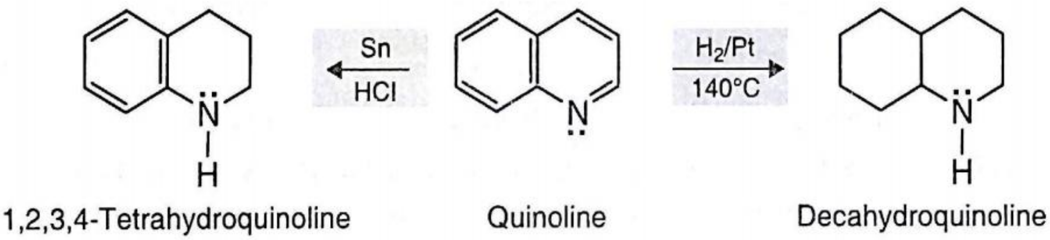
4. Oxidation.

Quinolineisoxidizedbyperaceticacidtogivequinoline-*N*-oxide.



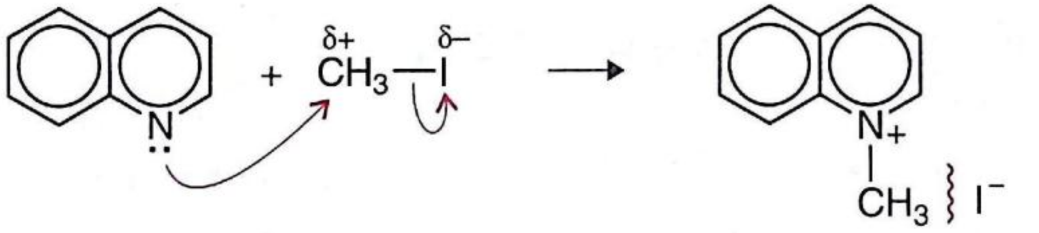
5. Reduction

Mildreductionofquinolinewithtinandhydrochloricacidgives1,2,3,4-tetrahydroquinoline.And,reductionwithhydrogenandplatinumcatalystproducesdecahydroquinoline.



6. ReactionwithAlkylhalides:

QuinolinegivesN-alkylquinoliniumhalidesbyreactingwithalkylhalides.Forexample,withmethyliodideitgivesN-methylquinoliniumhalide.



Quinoline

N-Methylquinolium iodide
(1-Methylquinolium iodide)

1.7 NitrationofQuinoline

Quinoline*N*-oxideismoreeasilynitratedthanpyridine1-oxide(Ochiai,.1953).Amixtureofnitricandsulfuricacidsat65-70°ctogive4-nitroderivativein60-70%yields.Forproofofitsstructure,itwasconvertedinto4-ethoxyquinoline1-oxidebytreatmentwithsodiumethoxide;thiswasidenticalwithasamplepreparedbyoxidationof4-ethoxyquinoline.

Asby-productsofnitration,smallamountsof5-and8-nitroquinoline1-oxideswereobtained.Bothofthelatterwereconvertedbyheatingwithsulphurylchlorideintothecorresponding2-chloronitroquinolinesandthesewweretransformedbycatalyticreductionintotheknown5-and8-aminoquinolines.

Thepositiontakenbynitrogrouponnitrationofquinoline*N*-oxideshowsastrikingtemperaturedependence.At0-10°,onlythe5-and8-nitroderivativesareformed.Above40°C,thereactivityofthe4-

positionbecomesevident,andat65-70°Cmainly,the4-nitroderivativeisproduced.Above100°,deoxygenationoftheN-oxidefunctionbeginstooccur,andat120-130°Ctheformationofthe4-nitroderivativeismuchdecreasedwithsimultaneousformationofquinoline5-and8-nitroquinolineinsmallamounts.Again,ifoneallowsquinoline1-oxidetostandalongtimeatroomtemperaturewithpotassiumnitrateinfumingsulfuricacid(10%$S0_3$),oneobtains4,8-dinitroquinoline1-oxidebesidesthe5-and8-nitroderivatives.

4-and5-Nitroquinoline1-oxidesgiveonanalogousnitrationthesame4,5-dinitroderivativeand6-and8-nitroquinoline1-oxidessimilarlyyieldthe4,6-and4,8-dinitroderivatives.Bothofthelattergive,onheatingwithphosphorusoxychloride,thecorresponding2,4-dichloroquinolineswhichwereconvertedbycatalyticreductionintotheknown6-and8-aminoquinolines;thisestablishedtheirstructures.

NITRODERIVATIVESOFQUINOLINE-*N*-OXIDE

QUINOLINE-*N*-OXIDE	**PROPERTIES**	**MELTINGPOINT(^{O}C)**
4-Nitro	Yellowneedlesorplatelet	154
4-Nitro,2-ethyl	Yellowneedles	155-157
8-Nitro	Yellowprisms	180-181
5-Nitro	Yellowplatelet	161
4,5-Nitro	Yellowprisms	260-262
4,8-Nitro	Orange-yellowrhombs	233
4,6-Nitro	Orange-yellowprisms	218

TABLE1.1:NITRODERIVATIVESOFQUINOLINE*N*-OXIDE

Quinoline*N*-oxideisnitratedat65-70°toa4-nitroderivative.Bytreatmentwithsodiumethoxide,itwastransformedintothecorrespondingethoxyquinaldine*N*-oxidewhichwasrecognizedas4-ethoxyquinaldine1-oxidebydirectcomparisonwithasamplepreparedfrom4-chloroquinaldineviaitsamineoxide.InthenitrationofN-oxidesofthequinolineseries,theformationof2-nitroderivativeswasneverobserved.

4-Nitroquinoline1-oxide (alsoknownas4-NQO,4NQO,4Nqo,NQOandNQNO)isa quinoline derivativeanda tumorigenic compoundusedintheassessmentoftheefficacyof diets, drugs,andproceduresinthepreventionandtreatmentof cancer in animalmodels.ItinducesDNAlesionsusuallycorrectedby nucleotideexcisionrepair.

4-nitroquinoline1-oxide(4NQO)isaquinoline,acarcinogenicandmutagenicchemical.Quinolines,like4N

QO,possessaheterocyclicaromaticstructureandthesamebasicchemicalformulaofC_9H_7N.

4NQOmaynaturallyoccurintheenvironmentbutistypicallymanufacturedforresearchpurpose. 4NQOisknowntomimicthebiologicaleffectsofultravioletlightonvariousorganisms.

Both4NQOanditsreducedmetabolite4-hydroxyaminoquinoline1-oxide(4HAQO)bindcovalentlytocellularmacromoleculessuchasnucleicacidsandproteins.

4NQOhasbeenshowntotraptopoisomeraseIcleavagecomplexes.ItmayalsoinduceDNAdamagethroughtheproductionofreactiveoxygenspeciesthoughttoarisefromenzymaticreductionofitsnitrogroup,althoughitsexactmechanismisunknown. 4NQO’sreactiveoxygenspeciesmayserveasabyproductofDNAdamageorsignalingmoleculefromdamage. Inresponsetodamagefrom4NQO,cellsattempttorepairandinitiateatranscriptionalresponsetodetoxifythecellfrom4NQOanditsmetabolites.

4-NitroquinolineN-oxidehasthechemicalformula$C_9H_6N_2O_3$,Molarmassof190.60g/mol.Itformsayellow-browncrystalorpowderanditisslightlysolubleinwater.

1.8BiologicalImportanceofQuinolineandItsDerivatives

Quinolinehasbeendiscoveredtopossesspotentialapplicationsinmajorfieldnamelyinmedicine.Severalquinoline-derivedcompoundslikequinolonesareusedasdrugs,targetingavarietyofdiseases,e.g.bacterialinfections,cancer,hepatitis,HIV,herpes,fungalinfections,immunodepression,neurodegenerativediseases,tuberculosisormalaria.(Horta*etal.,*2019)

1.8.1 Quinolines as Antimalarial Agents

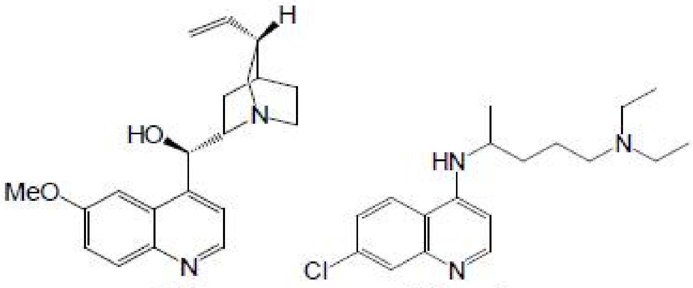
Malaria is a deadly infectious disease that has affected mankind for several millennia. It is caused by a protozoan parasite of the *Plasmodium* genus and transmission of the parasite occurs *via* the bite of an infected female *Anopheles* mosquito (vector).

The control of malaria has long been, and remains, a priority, especially because of the fast development of parasites resistant to almost all available antimalarial drugs.

The use of quinoline derivatives as antimalarial drugs in Europe goes back to the beginning of the 17th century, when Jesuit priests returning from Peru introduced an extract from *Cinchona*, a tree originally found in the high hills of South America, as a treatment for malaria. The bark of this tree was later found to be a mixture of about 35 alkaloids, from which the antimalarial drug quinine would be isolated.

The discovery of methylene blue by the end of the 19th century led to the synthesis of 8-aminoquinolines (pamaquine, mepacrine) and 4-aminoquinolines with potent toxicity against *Plasmodium spp.* Chloroquine, the first antimalarially active 4-aminoquinoline obtained from synthesis, was reported in 1934. This drug demonstrated to be highly effective against *Plasmodium* parasites, well tolerated by humans (less toxic and more effective than quinine) and, in addition, was cheaper than other contemporary antimalarial drugs.

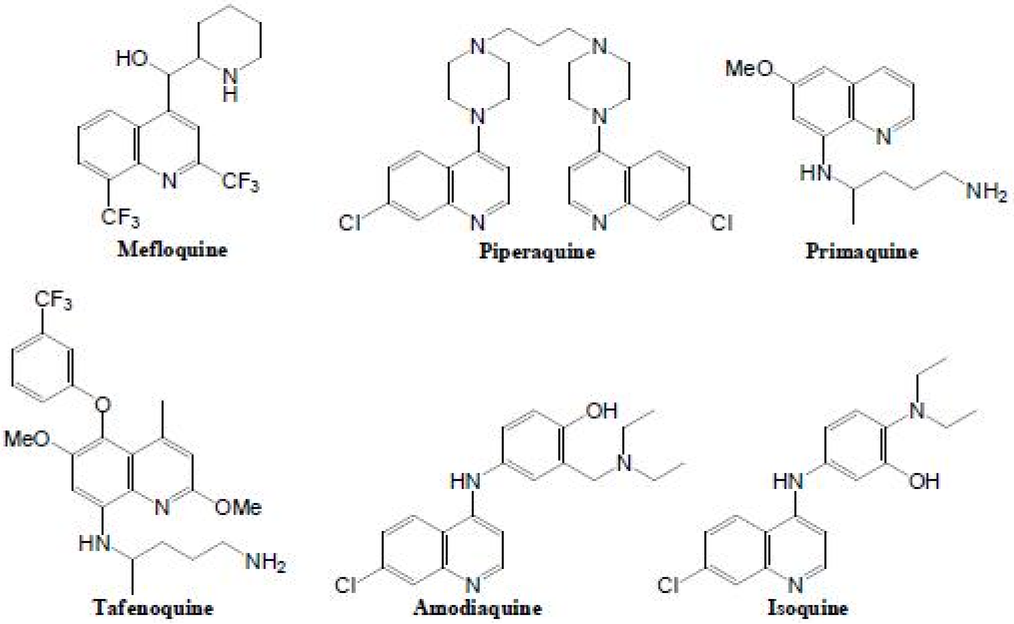
However, resistance of erythrocytic asexual forms of *P. falciparum* to chloroquine has been described shortly after its discovery and is currently common in all endemic areas around the world. Despite these limitations, chloroquine is still used for prophylaxis and treatment of malaria in the few African regions where *P. falciparum* remains sensitive to this drug.



Quinine **Chloroquine**

StructuralrepresentationofQuinineandChloroquine

Theeffortstothediscoveryofnewantimalarialseffectiveagainstchloroquine-resistantstrainsof*Plasmodium*spp.resultedinthedevelopmentofvariousquinolinederivedddrugs,(mefloquine,piperaquine,primaquine,tafenoquine,amodiaquineandisoquine).However,someofthesenewdrugsevidencedlimitations,mainlyrelatedtotoxicityandcost,andweresoonovershadowedthroughthedevelopmentofdrugresistancebytheparasite. Nowadays,quinineremainsanalternativeantimalarialdrugtotreatinfectionscausedbyparasitestrainsresistanttootherdrugs(e.g.chloroquine),althoughsideeffectsrelatedtoits usearekknown.



Mefloquine **Piperaquine** **Primaquine**

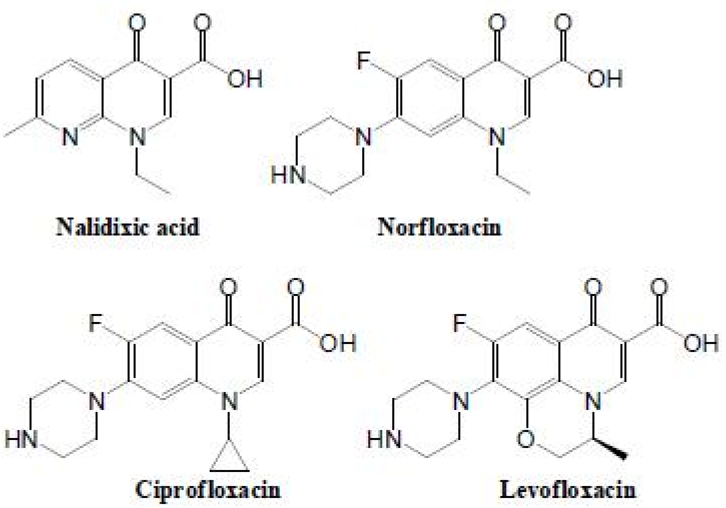
Tafenoquine **Amodiaquine** **Isoquine**

StructuralRepresentationofQuinolinebasedAntimalarialDrugswithHistoricaland/or currentRelevanc

1.8.2QuinolineasanAntibacterialAgent

Theuseofquinolinesasantibacterialagents(awell-establishedclassofantibiotics)beganin1963,withthediscoveryofnalidixicacid,a1,8-naphthyridone3-acid,duringthesynthesisoftheantimalarialagentchloroquine.Nalidixicacid,thefirstsyntheticquinolone-basedantibacterialagent,wasusedagainstsomeentericbacteriainthetreatmentofurinarytractinfections.Itisa*first-generationquinolone*presentingfavourablestructuralfeatures,suchastheethylgroupat *N*-1position,andgoodGram-negativeactivity.

However,nalidixicacidneverbecameausefulagenttotreatsystemicinfections,duetoitsnarrowspectrumofaction,poortissuepenetrability,rapidemergenceofbacterialresistanceandfrequentadverseeffectsinthecentralnervoussystem.


Nalidixic acid Norfloxacin
Ciprofloxacin Levofloxacin

StructuralrepresentationofQuinolinesusedasantibacterialagents

1.8.3QuinolinesasanAnti-mycobacterialAgent

Tuberculosis(TB)isaninfectiousbacterialdiseasecausedby*Mycobacteriumtuberculosis*(MTB)and,mostcommonly,affectsthelungs,causingcough(sometimeswithsputumorblood),chestpain,weakness,weightloss,feverandnightsweats.DespitetheavailabletreatmentsTBtreatmentremainsaglobalhealthproblem,sinceresearchanddevelopmentregardingthisdiseasehasnotevolvedformanyyearsuntilrecentlyandthepathogenicagent hasevidencedanincreasedprevalenceofmultiandextensivedrug-resistantstrains(MDRandXDR,respectively).

Theresistancephenomenonmayresult,mostly,fromthemisuseofcurrentanti-tuberculosischemotherapeuticregimens,whichinvolvecombinationsof,atleast,threedifferentdrugsandtherapeuticregimensofsixmonthsorlonger,withthepossibilityofsomecharacteristicsideeffects.

Overthepastyears,severalsubclassesof4-oxo-quinolinederivatives,incorporatingvarioussubstituentsinthestructureofthequinolinecore,havedemonstrateddiversebioactivities,includinghighactivityagainstbacterialpath ogens.Particularly,gatifloxacinandmoxifloxacinareunderevaluationinthisfield,assubstitutesforisoniazidandasapossibilityofshorteningtheoverallregimenduration,providinggreatersafetyandtolerabilityprofilesinTBtreatment.

Inadditiontothepreexistingquinolonedrugsunderinvestigation,severalotherquinolonesarebeingdesignedfortheirpotentialasanti-tuberculosisagents.

Someanaloguesincorporatingvariationsonthe4-quinolonecoreofthefluoroquinolonedrugsresultedinaseriesofdifferentanalogueswithgoodactivity.

1.8.4 QuinolineasAnticancerAgents

Cancerdefinesagroupofdiseasescharacterizedbyrapidandabnormaldivisionofcells,whichcanoccurinanypartofthebodyandinvadesurroundingtissuesorevenspreadthroughoutthebodyafterreachingthebloodstream.Whenthisaberrantcelldivisionoriginates,amassoftissuethatresultsiscalledasolidtumor.

DNAtopoisomerasesplayakeyroleincancersincetheyregulatecelldivisionthroughmodulationofDNAsupercoilingprocessduringreplication.QuinolinesareknownforahighinhibitorycapacitytowardseukaryotictopoisomerasesthusemergingasthepotentialleadsforthetreatmentandcontrolofsolidtumorS.

Basedonthepreexistingfluoroquinolones,whichshowedactivityonhumantopoisomeraseIIwhileusedfortheirantibacterialeffect,Foroumadi*etal.*evaluatedtheintroductionof *N*-substitutedpiperazinylgroupsatC-7positionoftheciprofloxacinandnorfloxacincore.Theemployedmodificationschangedthebiologicalactivitiesofthesequinolonedrugs,fromantibacterialtocytotoxicagents.

Themostexpressiveresultwasobtainedforthe*O*-methyloximederivative(a6-fluoro-4-oxo-quinolinederivative,compound,thatshowed95-foldincreasedactivity(IC50=2.5μM)inMCF-7cells(breastcancer),comparedtoitsparentquinolone,norfloxacin.

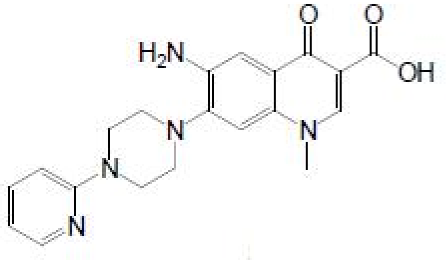
1.8.5 Quinolineswithantiviralactivity

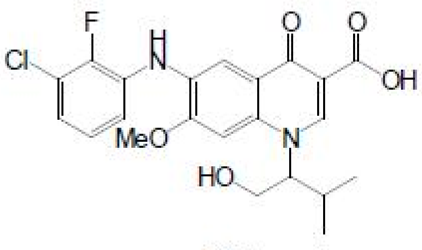
Viralinfectionsarestillamajorhealthissueworldwide.TheHIV(HumanImmunodeficiencyVirus)representsoneofthemostdangerousvirusesaffectingpublichealth,sinceitcausesanincurablediseaseandmorethan36millionpeoplearecurrentlyinfected.

Althoughtherapeuticadvancestransformedthisdeadlydiseaseintoachronicone,manyissuesregardingHIVtherapyremain,includingdrugresistancethatpromotesgraduallossofefficacyofhighlyactiveantiretroviraltherapycombinations,oftenduetopoorpatientcompliance,andcost.

Integraseinhibitorsemergedrecentlyasanovelanti-HIVdrugclass,andquinolone-typecompoundsplayanimportantroleinthisclasssincetheyshowedgoodactivityagainsttheviralDNAstrandtransferstepmediatedbyintegraseenzymes(IN).

Morerecently,quinoloneantibioticderivativesprovedtobepotentagainstthestrandtransferstepofintegraseactivityandtheuseofthedrug,Elvitegravir,wasapprovedforthisindication.Moreover,thequinolonescaffoldalsoshowedinteractionwithviralReverseTranscriptase(RT),whichmakesitapromisingstructurefordual-mechanismdevelopment81orsolelyagainstviralretro-transcriptase.





Elvitegravir

Additionally,studiesshowanotherpromisinguseforthequinoloneclassinanti-HIVtherapy,withthediscoveryofastronginteractionof6-desfluoroquinoloneswiththeTARregionofviralRNA,inhibitingitsinteractionwithTatprotein,whichisessentialfortheviralRNAtranscriptionprocess.

Severalviralinfectionscontinuetoaffectpopulationsworldwide.HepatitisC(HCV)and *Herpessimplex*(HSV)virusesrepresenttwoexampleswherenovelandmoreefficienttherapeutictoolsareneededforanimprovedoutcome.

CurrenttreatmentforHCVinfectionsconsistsofacombinationofonce-a-weeksubcutaneouspegylatedInterferon(peg-IFN)alphainjectionsandtwice-dailyoralRibavirin.

However,thesefailtoprovidefulltreatmentinmorethan50%ofpatientsandtheincidenceofsevereadverseeffectsishigh.HCVNS5Bpolymeraseenzymedisplaysahighactive-sitesimilaritywithHIVintegrase'sactivesite.

Since4-quinolone-3-carboxylicacidsexhibitsuchgoodactivitiesagainstHIVintegrase,theycouldalsorepresentapromisingscaffoldforinteractionwithHCVpolymerase.

However,inthiscase,structure-activityrelationshipsshowthatbestanti-HCVactivityisachievedthroughsubstitutionatC-6witharomaticmoieties,whilesubstitutionatC-7positionseemstobedetrimentalforactivity.Giventhepositiveresultsobtainedfromthesemolecules,itisofmaininteresttofurtherexplorethe4-quinolone-3-carboxylicacidscaffoldforuseinthisfield.

Instudiescarriedoutby(Chen*etal.,*2012),itwasobservedthatquinolonederivativeswithaC-7substitutionpatternwereinactive,whereassomeisomerssubstitutedatC-6showedsignificantactivity,especiallythosebearinganaromaticgroupassubstituent.RelativelytotheN-1position,unsubstitutedorsimplealkylN-1substitutedanaloguesshowednoactivitywhilehydroxyethylandhydroxypropylgroupsweresubstantiallybetterforinhibition.Thebestinhibitoryactivitywasachievedwith2-benzothiophene9and2-benzofuransubstitutedanalogues.Notably,theN-1hydroxypropylsubstitutedanaloguewasconsiderablylesspotent.Nevertheless,thebestcompoundsclearlyshowedbetterinhibitoryactivitytowardHCVthanRibavirin,suggestingthatthequinolone-3-carboxylicacidscaffoldbearspotentialforantiviraldiscoveryagainstHCV.

HSV-1virusiscausativeoffacial,oralandsometimesgenitallesionsinhumansanditscurrenttreatmentreliesontheuseoforalortopicantiviraldrugs,suchasAcyclovir,Famciclovir,andValacyclovir.Drug-resistancedevelopmentbytheHSVvirusraisestheneedfornewalternativetreatments,effectiveagainstresistantstrains.Quinolone-basedacycloviranaloguesareapromisingclassofnovelanti-HSV-1drugs.

Thesemaintainthe1-(2-hydroxy-ethoxy)methylsubstituent,butalterthepurinecoretoaquinoloneone,allowingforsmallsubstituentsatC-6orC-7.

Anevaluationoftheantiviralactivityofquinolonecarboxylicacidsandtheircorrespondingestersshowedthatalmostallofthecompoundsreducedtheviralloadin70-99%,beingtheacids,ingeneral,moreeffectiveinhibitorsthantheircorrespondingesters.

1.8.6 QuinolineswithAntifungalActivity

Quinoline-derivativequinolonesweréalsoshowntoactagainstfungalinfections,eitherbytheirsynergisticeffectwithotherantifungaldrugsorashybriddrugs,containingCiprofloxacinandanantifungalFluconazolelinkedtothe7-positionofthequinolonecore.ThispositionisknowntoallowforchemicaldiversityandthepossibilityofoptimizationassociatedwithbroadspectrumandgoodpharmacokineticpropertiesasreportedbyWang*etal.,*(2012).

CHAPTER2

MATERIALSANDMETHODOLOGY

2.1 Materials

Thematerialsusedduringthecourseofthisworksincludereagents,glasswares,apparatusandinstruments.

2.1.1 Reagents

Thefollowingreagentsusedinthesynthesisandtheirsourcesare

REAGENTS	SOURCES
QuinolineJDH	
Hydrogenperoxide(H_2O_2)	BDH
Glacialaceticacid(CH_3COOH)	BDH
Sodiumcarbonate(Na_2CO_3)Kermel	
Chloroform($CHCl_3$)	JDH
ConcentratedSulphuricacid(H_2SO_4)BDH	
Potassiumnitrate(KNO_3)Kermel	
ConcentratedHydrochloricacid(HCl)BDH	
Thiourea	Sigma
Benzoylchloride	JDH
DistilledWaterUniversityofBeninChemistryLaboratory	
AbsoluteEthanol	JDH
SilicagelLOBA	

TABLE2.1:REAGENTSANDTHEIRSOURCE

2.1.2 GLASSWARES

Theglasswaresusedinthesynthesisandsourcesaregivenbelow

GLASSWARES	SOURCE
Condenser	UniversityofBeninChemistryLaboratory
Roundbottomflasks	UniversityofBeninChemistryLaboratory
Flatbottomflasks	UniversityofBeninChemistryLaboratory
Drechselbottle	UniversityofBeninChemistryLaboratory
Separatingfunnel	UniversityofBeninChemistryLaboratory
Conicalflasks	UniversityofBeninChemistryLaboratory
Beakers	UniversityofBeninChemistryLaboratory
Measuringcylinder	UniversityofBeninChemistryLaboratory
Funnel	UniversityofBeninChemistryLaboratory

TABLE2.2:GLASSWARESANDTHEIRSOURCE

2.1.3. APPARATUSANDINSTRUMENTS

Theapparatusandinstrumentsusedduringthesynthesisandtheirssourcesareasfollows

APPARATUS/INSTRUMENT	SOURCE
Retortsstandandclamps	UniversityofBeninChemistryLaboratory

Filterpaper	UniversityofBeninChemistryLaboratory
Litmuspaper	UniversityofBeninChemistryLaboratory
Weighingbalance	UniversityofBeninChemistryLaboratory
Oven	UniversityofBeninChemistryLaboratory
Capillarytube	UniversityofBeninChemistryLaboratory
Glassslide	UniversityofBeninChemistryLaboratory
Magneticstirrerandbar	UniversityofBeninChemistryLaboratory
Heatingmantle	UniversityofBeninChemistryLaboratory
Hotplate	UniversityofBeninChemistryLaboratory
Vacuumpump	UniversityofBeninChemistryLaboratory
Waterbath	UniversityofBeninChemistryLaboratory
Meltingpointinstrument	UniversityofBeninChemistryLaboratory

TABLE2.3:APPARATUS/INSTRUMENTUSEDANDTHEIRSOURCES

2.2 METHODSOFCHARACTERIZATIONANDIDENTIFICATION

2.2.1 ThinLayerChromatography(TLC)

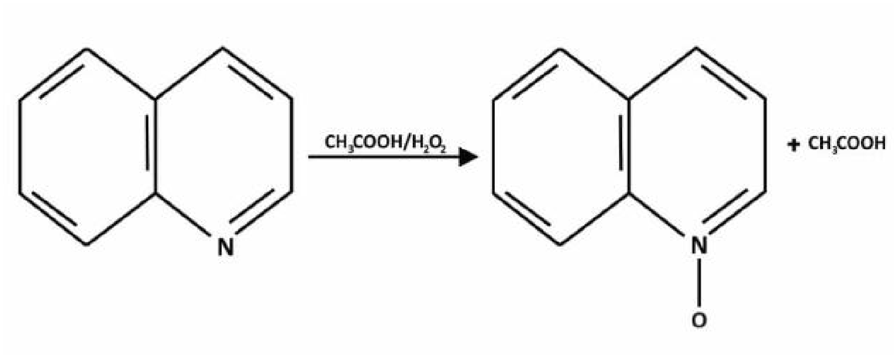
TheascendingTLCwasrunonsilicagelpre-coatedplatesforcheckingthepurityoftheproductsaswellasmonitoringtheprogressofthe reaction.Thefinalproductsweredetectedbyreactingwithiodinevapour.

2.2.2 MeltingPointDetermination

FofferMeltingPointApparatuswasusedtodetermineallthemeltingpointsreportedinthis work.Thiswasdoneusingopenglasscapillaries.

2.3. METHODOLOGY

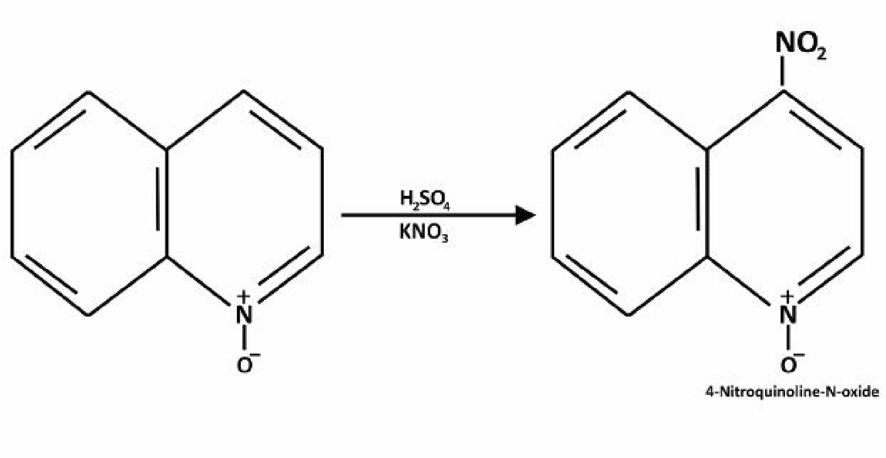
2.3.1 SYNTHESISOFQUINOLINE*N*-OXIDE(COMPOUNDI)



QUINOLINE **QUINOLINE-*N*-0XIDE**

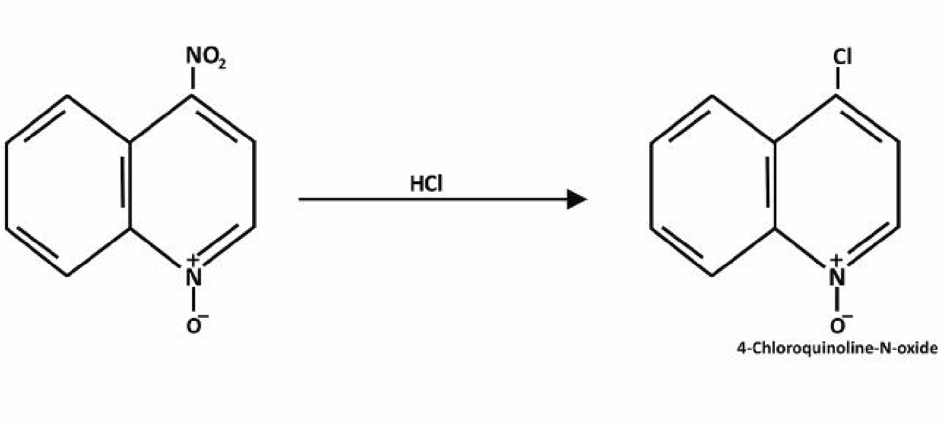
A20mlofdistilledquinolinewasdissolvedin53.3mlglacialaceticacid.8.3mlofhydrogen peroxidewasaddedandthemixturewasheatedat70-80^{o}Cfor6hours.5mlofhydrogenperoxidewasfurtheradded,andthentheprocedurerepeated.Themixturewasconcentratedunderreducedpressureasmuchaspossible,then,thebrownsyrupobtainedwastreatedwithconcentratedsodiumcarbonatesolutionuntilstronglyalkaline.Themixturewasextractedwithchloroform(25mlx5),anddriedwithsodiumcarbonateanhydrous.Aftertheremovalofthesolvent,theproductwasallowedtostandforab outadayforsolidification.Thefollowingdayitwasbrokenupinetherandpowderedtoobtaintheresultingproduct.

2.3.2 SYNTHESISOF4-NITROQUINOLINE-*N*-OXIDE(COMPOUNDII)



QuinolineN-oxide(10g)wasdissolvedinicecoldconcentratedH_2SO_4(23.3ml).Potassiumnitrate(8.66g)wasaddeddropwiseoveraperiodof35-40minutesat65to70°candheatedforanextratwohourswithfrequentstirring.Thereafter,themixturewascooledandpouredintoexcessicewater.Thecrudeproductwasfiltered,washedthoroughlywithwater,sodiumcarbonatesolutionandfinallywithwater.Afterdrying,thecrudeproductwasrecrystallizedfromacetone.

2.3.3 SYNTHESISOF4-CHLOROQUINOLINE*N*-OXIDE(COMPOUNDIII)

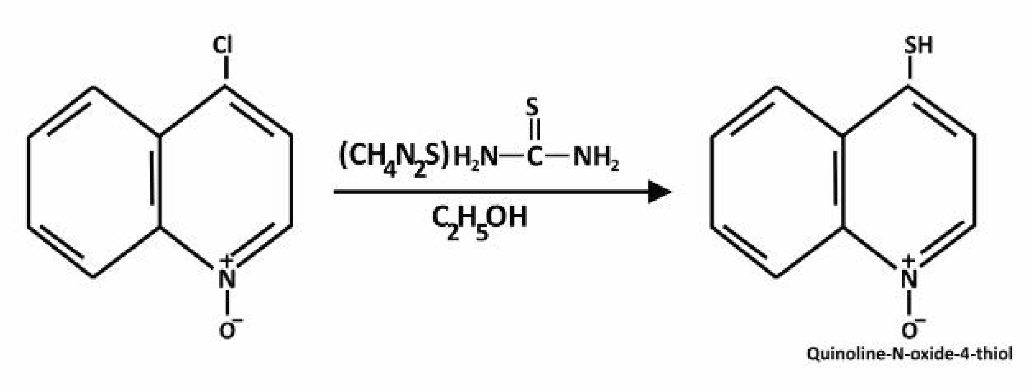


A5gof4-nitroquinoline*N*-oxidewasdissolvedinhydrochloricacidandevaporatedtodrynessatlowtemperature.Thesolidobtainedwasthendissolvedinwaterandprecipitatedusingsodiumhydroxidesolutionuntilstronglyalkaline.Thereactionmixturewasthenfilteredundervacuumtoobtainacolourlessproduct.

2.3.3.1 SYNTHESISOFQUINOLINE-*N*-OXIDE-4-THIOURONIUMCHLORIDE

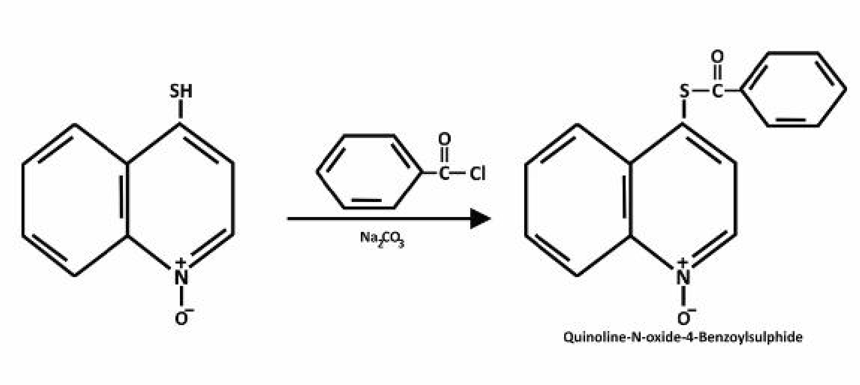
4-chloroquinoline*N*-oxide(0.65g)andthiourea(0.29g)weredissolvedinabsoluteethanol(6.5ml),andrefluxedfor1hour.Aftercooling,itwasfiltered,toobtainquinoline-*N*-oxide-4-thiouroniumchlorideaslightyellowneedles.

2.3.4 SYNTHESISOFQUINOLINE-*N*-OXIDE-4-THIOL



Thesynthesizedthiouroniumchloridewassuspendedin1.95mlofwaterand3mlof10%sodiumhydroxidesolutionwasadded,whereuponthecrystalsdissolvedtoformanorange-redsolution.Thesolutionwasfiltered,acidifiedwithaceticacid,andtheresultingorange-redcrystalswascollectedandwashedwithdistilleddater.

2.3.5 SYNTHESISOFQUINOLINE-*N*-OXIDE-4-BENZOYLSULPHIDE



A0.03gofQuinoline*N*-oxide-4-thiolwasdissolvedinsodiumcarbonateandthencoupledwithbenzoylsulphide(6ml).Themixturewasstirredcontinuouslyfor3hours.Thereafter,thesolidwasextractedusingbenzene.

CHAPTER3

RESULTS

3.1 RESULTS

3.1.1 PhysicalCharacterizationoftheSynthesizedCompounds

3.1.1.1Determinationofmeltingpoint,percentageyieldandappearance

Themeltingpoints,percentageyieldandappearanceofthesynthesizedcompoundsareshownintable3.1

Table3.1PhysicalDataoftheSynthesizedCompounds

Properties	CompoundI	CompoundII	CompoundIII	CompoundIV	CompoundV
NameofCompound	Quinoline-*N*-oxide	4-Nitroquinoline-*N*-oxide	4-Chloroquinoline-*N*-oxide	Quinoline-*N*-oxide-4-thiol	Quinoline-*N*-oxide-4-benzoylsulphid
State	Oily	Solid	Solid	Solid	Solid
Colour	Brown	Yellow	Yellow	Orange-red	Paleyellow
Meltingpoint\Boilingpoint(^{o}c)	53	154-156	133-135	142-144	96-98
PercentageYield(%)	44.48	38.17	13.80	9.38	1.86

3.1.1.2ThinLayerChromatography

Thetable3.2showstheR$_F$valuesofthesynthesizedintermediatesandfinalcompounds,whichshowssingleroundspotafterexposingthechromatogramstoiodinevapourindicatingthepurityofthecompoundsandthecompletionofthereaction.

RetentionFactor(R$_F$)=$\frac{\text{Distance moved by compound}}{\text{Distance moved by solvent}}$

ComparativeR$_F$valuesofallsynthesizedcompound.

Compounds	R$_F$Values	Solvents
CompoundI	0.63	Chloroform
CompoundII	0.79	Chloroform
CompoundIII	0.90	Chloroform
CompoundIV	0.94	Chloroform
CompoundV	0.83	Benzene/Ethanol(1:1)

3.2 Conclusion

Attheendofthisresearchwork,quinoline-*N*-oxide-4-benzoylsulphidewassuccessfullysynthesized.ThiswasconfirmedbyTLCandmeltingpointdetermination.However,theanalyticalcharacterisationofthecompoundscouldnotbeascertained.

3.3Recommendation

Analyticalcharacterisationofthesynthesizedcompoundshouldbedone.Furthermore,thecompoundshouldalsobetestedforitsantimicrobialpotential.

3.4Limitation

Analyticalcharacterisationofthesynthesizedcompoundscouldnotbeascertainedduetolimitedtimeandnoneavailabilityofanalyticalinstrumentssuchas^{1}HNMR,^{13}CNMR,FT-IR,andGC-MS.

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APPENDIX

CALCULATIONFORTHEPERCENTAGEYIELDOFCOMPOUND I-COMPOUNDV

COMPOUNDI

1moleofQuinolone=1moleofQuinolone-*N*-oxide

129g/mol=145g/mol

20g=X(g)

X=$\frac{145\ x\ 20}{129}$=22.48g.

Hence,theoreticalyield=22.48g

Theoreticalyield=22.48g

Actualyield=10g

Percentageyield(%)=$\frac{actual\ yield}{theoretical\ yield}\ x\ \frac{100}{1}$

%yield=$\frac{10}{22.48}\ x\ \frac{100}{1}$

%yield=44.48

COMPOUNDII

1moleQuinoline-*N*-oxide=1mole4-nitroquinoline-*N*-oxide

145g/mol=190g/mol

10g=X

X=$\frac{190\ X\ 10}{145}$

X=13.30g

Theoreticalyield=13.10g

Actualyield=5g

Percentageyield(%)=$\frac{actual\ yield}{theoretical\ yield}\ x\ \frac{100}{1}$

%yield=$\frac{5}{13.10}x\frac{100}{1}$

%yield=38.17

COMPOUNDIII

1mole4-nitroquinoline-*N*-oxide=1moleof4-chloroquinoline-*N*-oxide

190g/mol=179g/mol

5g=X

X=$\frac{179\ x\ 5}{190}$

X=4.71g

Theoreticalyield=4.71g

Actualyield=0.65g

Percentageyield(%)=$\frac{actual\ yield}{theoretical\ yield}\ x\ \frac{100}{1}$

%yield=$\frac{0.65}{4.71}x\frac{100}{1}$

%yield=13.80

COMPOUNDIV

1moleof4-chloroquinoline-*N*-oxide=1moleofquinoline-*N*-oxide-4-thiol

179g/mol=177g/mol

0.65g=X

X=$\frac{177\ x\ 0.65}{179}$

X=0.64g

Theoreticalyield=0.64g

Actualyield=0.25g

Percentageyield(%)=$\frac{actual\ yield}{theoretical\ yield}\ x\ \frac{100}{1}$

%yield=$\frac{0.25}{0.64}x\frac{100}{1}$

%yield=9.38

COMPOUNDV

1moleofquinoline-*N*-oxide-4-thiol=1moleQuinoline-*N*-oxide-4-bezoylsulphide

256.7g/mol=140.6g/mol

0.057g=X

X=$\frac{0.057\ X\ 140.6}{256.7}$

X=0.03g

Theoreticalyield=0.03g

Actualyield=5.76g

Percentageyield(%)=$\frac{actual\ yield}{theoretical\ yield}\ x\ \frac{100}{1}$

%yield=$\frac{5.76}{0.03}x\frac{100}{1}$

%yield=1.86

RETENTIONFACTORFORALLCOMPOUNDS

Retentionfactor=$\frac{distance\ moved\ by\ compound}{distance\ moved\ by\ eluent\ (solvent)}$

COMPOUNDI

R_F(Chloroform)=$\frac{5.0}{8.0} = 0.63$

COMPOUNDII

R_F(Chloroform)=$\frac{5.4}{6.8} = 0.79$

COMPOUNDIII

R_F(Chloroform)=$\frac{6.5}{7.2} = 0.90$

COMPOUNDIV

R_F(Chloroform)=$\frac{6.0}{6.4} = 0.94$

COMPOUNDV

R_F(Benzene/Ethanol)=$\frac{6.6}{8.0} = 0.83$