NATIONAL OPEN UNIVERSITY OF NIGERIA

SCHOOL OF SCIENCE AND TECHNOLOGY

COURSE CODE: CHM 421

COURSE TITLE: HETEROCYCLIC CHEMISTRY

**COURSE
GUIDE**

**CHM421
HETEROCYCLIC CHEMISTRY**

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Introduction

CHM421: Heterocyclic Chemistry is a 2 -credit course for B.Sc. Chemistry.

The course is broken down into 3 modules of 15 study units. At the end of this course, a student is expected to be conversant with the chemistry and mechanistic aspects of fused heterocycles, their synthesis and applications in drug synthesis. This course further provides insight into the design of synthetic routes for related heterocyclic compounds.

What You Will Learn in This Course

You will learn about the chemistry and synthesis of some fused heterocyclic systems such as Quinolines, Iso-quinolines, Benzofurans, Benzothiophenes, Indoles, Benzopyrilium salts, Coumarins and Chromones. You will also learn about their applications in drug synthesis.

Course Aims

The aim of this course is for you to understand the chemistry of some fused heterocyclic systems and so you will be able to predict the chemistry of other compounds containing similar ring structures. Also you will have an in-depth knowledge on how to synthesise various fused heterocyclic structures and you will also be able to appreciate why heterocyclic chemistry is so important to mankind.

Course Objectives

In order to achieve the course aims, there are some set objectives for the course. Besides, each module and each unit has their respective objectives which you and your facilitator must constantly refer to, so that no objective is skipped. All the modules and unit objectives are specifics of the course objectives. At the end of the course, you should be able to:

- identify the structures of different types of fused heterocyclic structures
- explain the chemistry and mechanistic aspects of fused heterocyclic structures particularly those of quinolones, Isoquinolones, benzofurans, benzothiophenes, Indoles, Benzopyrilium salts, Coumarins and Chromones
- describe the synthesis of fused heterocyclic systems and design synthetic routes to the synthesis of similar compounds
- explain the application of heterocyclic systems in drug synthesis
- identify heterocyclic structures in certain biologically active compounds.

Working through This Course

This course contains some packages that you will be given at the beginning of the semester: one of them is the course material. Your full participation in both the continuous assessment and the final written examination are two areas expected of you to fulfill at the end of the course. Stated below are the components of this course and what you have to do.

Course Materials

Major course materials for the course are as follows:

1.   Course Guide
2.   Study Units
3.   Assignment Files
4.   Presentation Schedule

Study Units

There are 3 modules and 15 study units in this course. They are:

Module 1   Benzopyridines

Unit 1	Reactions of Quinolines
Unit 2	Synthesis of Quinolines
Unit 3	Application of the Quinoline Ring System in Drug Synthesis
Unit 4	Synthesis and Reactions of Iso-quinolines
Unit 5	Application of the Iso-quinoline Ring System in Drug Synthesis

Module 2   Benzofuran, Benzothiophene and Indoles

Unit 1	Reactions of Benzopyrrole (Indole)
Unit 2	Synthesis of Benzopyrrole (Indole)
Unit 3	Application of Indole in Drug Synthesis
Unit 4	Synthesis and Reactions of Benzofuran and Benzothiophene
Unit 5	Applications of the Benzofuran and Benzothiophene Ring System in Drug Synthesis

Module 3   Dibenzopyrones,   Pyrilium   Salts   and   Other Benzopyrones

Unit   1   Synthesis and Reactions of Coumarins
Unit   2   Reactions of Chromones
Unit   3   Synthesis of Chromones
Unit   4   Synthesis and Reactions of Dibenzopyrilium Salts
Unit   5   Application of the Coumarin and Chromones Ring Systems in Drug Synthesis

From all indications, you should be able to complete two credit units about 15 weeks in a semester. Well spread out in each unit is: Introduction to the unit, specific objectives, body of the unit, conclusion, summary, Tutor-Marked Assignments and References.

Details of the study units have earlier been presented. It is spelt out in modules with corresponding units and titles. You will be expected to spend 2-3 hours in studying a unit.

Textbooks and References

These texts will be of immense benefit to this course:

Norman, R. O. C. & Coxon, J. M. (1993). *Principles of Organic Synthesis* (3rd ed.). Glasgow: Blackie Academic & Professional. An Imprint of Chapman & Hall, pp. 696-723.

Olaniyi, A. A.; Ayim, J. S. K.; Ogundaini, A. O. & Olugbade, T. A. (1998).   *Essential Inorganic and Organic Pharmaceutical Chemistry.* Shaneson C.I. Limited, pp. 363-450.

Sainsbury, M. (2001). *Heterocyclic Chemistry.*   Royal Society of Chemistry, pp. 142.

Assignment File

The assignment file will be given to you in due course. In this file, you will find all the details of the work you must submit to your tutor for marking. The marks you obtain for these assignments will count towards the final mark for the course. Altogether, there are 15 tutor-marked assignments for this course.

Presentation Schedule

The presentation schedule included in this course guide provides you with important dates for completion of each tutor-marked assignment. You should therefore try to meet the deadlines.

Assessment

There are two aspects to the assessment of this course. First, there are tutor-marked assignments and second, the written examination.

You will be expected to complete at least ten assignments by the end of the course. Some of these will be in the form of a project and continuous assessment (CA). You will be expected to write a final examination in the course. The overall score in the course will be a sum of 40% of CA and 60% of written examination.

Tutor-Marked Assignment

There are 15 TMAs in this course. You need to submit all the TMAs. The best 4 will therefore be counted. When you have completed each assignment, send them to your tutor as soon as possible and make sure that it gets to your tutor on or before the stated deadline. If for any reason you cannot complete your assignment on time, contact your tutor before the assignment is due to discuss the possibility of extension. Extension will not be granted after the deadline, unless on exceptional cases.

Final Examination and Grading

The end of course examination for this course will be for about 3 hours and it has a value of 60% of the total course work. The examination will consist of questions, which will reflect the type of self-testing, practice exercise and tutor-marked assignment problems you have previously encountered. All areas of the course will be assessed.

The time between the last unit and the final examination can be used for revision. You might find it useful to review your self-test, TMAs and comments on them before the examination. The end of course examination covers information from all parts of the course.

Course Marking Scheme

Assignment	Marks
Assignments 1-15	15 assignments, 40% for the best 4 Total = 10% x 4 = 40%
End of Course Examination	60% of overall course marks
Total	100% of course materials

Course Overview

This table indicates the units, the number of weeks required to complete them and the assignments.

Unit	Title of Work	Weeks Activity	Assessment (End of Unit)
	Course Guide		
Module 1	**Benzopyridines**		
1	Reactions of Quinolines	Week 1	Assignment 1
2	Synthesis of Quinolines	Week 2	Assignment 2
3	Application of the Quinoline Ring System in Drug Synthesis	Week 3	Assignment 3
4	Synthesis and Reactions of Isoquinolines	Week 4	Assignment 4
5	Application of the Isoquinoline Ring System in Drug Synthesis	Week 5	Assignment 5
Module 2	**Benzopyrrole (Indole), Benzofuran and Benzothiophene**		
1	Reaction of Benzopyrrole (Indole)	Week 6	Assignment 6
2	Synthesis of Benzopyrrole	Week 7	Assignment 7
3	Application of Indole in Drug Synthesis	Week 8	Assignment 8
4	Synthesis and Reactions of Benzofuran and Benzothiophene	Week 9	Assignment 9
5	Applications of the Benzofuran and Benzothiophene Ring System in Drug Synthesis	Week 10	Assignment 10
Module 3	**Dibenzipyrones, Pyrilium Salts and Other Benzopyrones**		
1	Synthesis and Reactions of Coumarins	Week 11	Assignment 11

2	Reactions of Chromones	Week 12	Assignment 12
3	Synthesis of Chromones	Week 13	Assignment 13
4	Synthesis and Reactions of Benzopyrilium and Dibenzopyrilium Salts	Week 14	Assignment 14
5	Application of the Coumarin and Chromone Ring Systems in Drug Synthesis	Week 15	Assignment 15

How to Get the Most from This Course

In distance learning, the study units replace the university lecturer. This is one of the huge advantages of distance learning mode; you can read and work through specially designed study materials at your own pace and at a time and place that suit you best. Think of it as reading form the teacher, the study guide tells you what to read, when to read and the relevant texts to consult. You are provided exercises at appropriate points, just as a lecturer might give you an in-class exercise.

Each of the study units follows a common format. The first item is an introduction to the subject matter of the unit and how a particular unit is integrated with the other units and the course as a whole. Next to this is a set of learning objectives. These learning objectives are meant to guide your studies. The moment a unit is finished, you must go back and check whether you have achieved the objectives. If this is made a habit, then you will significantly improve your chances of passing the course. The main body of the units also guides you through the required readings from other sources. This will usually be either from a set book or from other sources.

Self-assessment exercises are provided throughout the unit, to aid personal studies and answers are provided at the end of the unit. Working through these self-tests will help you to achieve the objectives of the unit and also prepare you for tutor marked assignments and examinations. You should attempt each self test as you encounter them in the units.

The following are practical strategies for working through this course:

1.   Read the course guide thoroughly
2.   Organise a study schedule. Refer to the course overview for more details. Note the time you are expected to spend on each unit and how the assignment relates to the units. Important details, e.g. details of your tutorials and the date of the first day of the semester are available. You need to gather together all these

information in one place such as a diary, a wall chart calendar or an organiser. Whatever method you choose, you should decide on and write in your own dates for working on each unit

3.   Once you have created your own study schedule, do everything you can to stick to it. The major reason that students fail is that they get behind with their course works. If you get into difficulties with your schedule, please let your tutor know before it is too late for help

4.   Turn to unit 1 and read the introduction and the objectives for the unit

5.   Assemble the study materials. Information about what you need for a unit is given in the table of content at the beginning of each unit. You will almost always need both the study unit your are working on and one of the materials recommended for further readings, on your desk at the same time

6.   Work through the unit, the content of the unit itself has been arranged to provide a sequence for you to follow. As you work through the unit, you will be encouraged to read from your set books

7.   Keep in mind that you will learn a lot by doing all your assignments carefully. They have been designed to help you meet the objectives of the course and will help you pass the examination

8.   Review the objectives of each study unit to confirm that you have achieved them. If you are not certain about any of the objectives, review the study material and consult your tutor

9.   When you are confident that you have achieved a unit's objectives, you can start on the next unit. Proceed unit by unit through the course and try to pace your study so that you can keep yourself on schedule

10.   When you have submitted an assignment to your tutor for marking, do not wait for its return before starting on the next unit. Keep to your schedule. When the assignment is returned, pay particular attention to your tutor's comments, both on the tutor marked assignment form and also written on the assignment. Consult your tutor as soon as possible if you have any questions or problems

11.   After completing the last unit, review the course and prepare yourself for the final examination. Check that you have achieved the unit objectives (listed at the beginning of each unit) and the course objectives (listed in this course guide).

Facilitators/Tutors and Tutorials

There are 8 hours of tutorials provided in support of this course. You will be notified of the dates, times and location of these tutorials as well

as the name and phone number of your facilitator, as soon as you are allocated a tutorial group.

Your facilitator will mark and comment on your assignments, keep a close watch on your progress and any difficulties you might face and provide assistance to you during the course. You are expected to mail your Tutor-Marked Assignment to your facilitator before the schedule date (at least two working days are required). They will be marked by your tutor and returned to you as soon as possible.

Do not hesitate to contact your facilitator by telephone or e-mail if you need assistance. The following might be circumstances in which you would find assistance necessary, hence you would have to contact your facilitator if you:

• do not understand any part of the study or the assigned readings.
• have difficulty with the self-tests
• have a question or problem with an assignment, with your tutor's comments or with the grading of an assignment.

You should endeavour to attend the tutorials. This is the only chance to have face to face contact with your course facilitator and to ask questions which are answered instantly. You can raise any problem encountered in the course of your study.

To gain much benefit form course tutorials, prepare a question list before attending them. You will learn a lot from participating actively in discussions.

Summary

Heterocyclic chemistry is a very vast subject so this course has focused on fused heterocyclic systems such as Quinolines, Isoquinolines, Benzofurans, Benzothiophenes, Indoles, benzopyrilium salts, Coumarins and Chromones. The synthesis of drug molecules containing these heterocyclic structures has also been covered. Upon completion of this course, you will be equipped with the basic knowledge of heterocyclic chemistry of fused systems. You will be able to answer the following questions:

• What is a fused heterocyclic system?
• How are quinolines synthesised?
• What are the major reactions of quinolines?
• How are Isoquinolines synthesised?
• What are the major reactions of Isoquinolines?
• How are indoles synthesised?

- What are the major reactions of indoles?
- How are benzothiophenes and benzofurans synthesised?
- What are the major chemical reactions that benzothiophenes and benzofurans undergo?
- How are benzopyrilium salts, Coumarins and Chromones synthesised?
- What are the major reactions of benzopyrilium salts, Coumarins and Chromones?
- What are the advantages of the various synthetic routes for each class of heterocyclic compound?
- What are the importance/applications of the chemistry of these compounds?

Of course, the list of questions that you can answer is not limited to the above list. To gain the most from this course, you should endeavour to apply the principles you have learnt to your understanding of the chemistry of similar heterocyclic compounds.

I wish you success in the course and I hope that you will find it both interesting and useful.

Course Code   CHM421
Course Title   Heterocyclic Chemistry

Course Team   Dr. Gloria Abiodun Ayoola (Developer/Writer) - UNILAG

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Unit 2   Synthesis of Quinolines
Unit 3   Application of the Quinoline Ring System in Drug Synthesis
Unit 4   Synthesis and Reactions of Iso-quinolines
Unit 5   Application of the Iso-quinoline Ring System in Drug Synthesis

UNIT 1   REACTIONS OF QUINOLINES

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       3.3   Nucleophilic Substitution
4.0   Conclusion
5.0   Summary
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1.0   INTRODUCTION

Quinolines are a class of organic compound of the heteroaromatic series characterised by a double-ring structure composed of benzene and a pyridine ring **fused** at two adjacent carbon atoms (Figure 1). The benzene ring contains six carbon atoms, while the pyridine ring contains five carbon atoms and a nitrogen atom (compare with the structure of Naphthalene below). The simplest member of the quinoline family is quinoline itself, a compound with molecular structure C_9H_7N.

Quinoline

Naphthalene

Fig. 1:   Structures of Quinoline and Naphthalene (the Hydrocarbon Analogue)

2.0   OBJECTIVES

At the end of this unit, you should be able to:

- identify the quinoline ring
- explain how the presence of the benzene ring influences the chemistry of quinolines compared to that of pyridine
- write at least three reactions of quinolines with other compounds.

3.0   MAIN CONTENT

3.1   General Physical and Chemical Properties of Quinoline

Quinoline is a colourless hygroscopic liquid with a strong odour. It becomes yellow on exposure to light and later turns brown. Quinoline is only slightly soluble in cold water but dissolves readily in hot water and most organic solvents. Quinoline is a slightly weaker base (pKa 4.9) than pyridine (pKa 5.2).

The general properties are based on those of the individual ring structures forming that system. It can be predicted that the benzene ring in quinoline would undergo electrophilic substitution by electrophiles but be resistant to oxidation and reduction whilst the pyridine ring would act as a base, undergo nucleophilic substitution and reduction but be resistant to oxidation and electrophilic substitution since electrophilic substitution of the benzene ring is easier. Furthermore, by comparison with its aromatic analogue naphthalene, one would expect position 3 to be relatively unreactive.

In practice, quinoline is a weak base (pKa 4.9). It usually undergoes electrophilic substitution at positions 5 and 8 of the benzene ring. Nucleophilic substitution occurs mainly at positions 2 and 4 of the pyridine ring. Reduction of the pyridine ring is comparatively easy but reduction of the benzene ring is comparatively difficult. Oxidation of both rings is difficult. (Scheme 1).
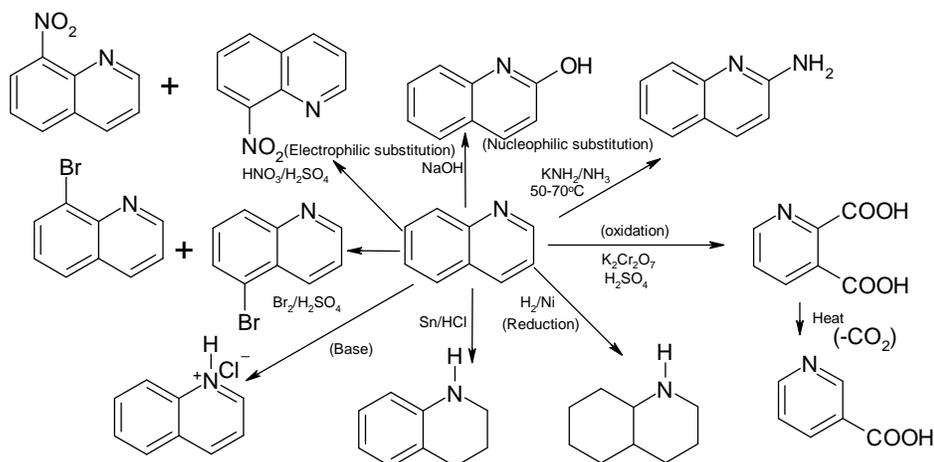
Scheme 1:   Examples of the General Types (in brackets) of Reaction of Quinoline

3.2   Electrophilic Substitution

Acids and Lewis acids react with quinoline at the basic nitrogen atom to form quinolinium salts, and there is a question over the nature of the substrate for electrophilic attack, i.e. is it quinoline or the quinolinium substrate for electrophilic attack. The answer is not a simple one and appears to depend upon the reagents and reaction conditions. Thus whereas acetyl nitrate at 20°C gives 3-nitroquinoline (Scheme 2), fuming nitric acid in concentrated sulphuric acid containing sulphur trioxide at 15-20°C yields a mixture of 5-nitroquinoline (35%) and 8-nitroquinoline (43% - Scheme 3). In the case of acetyl nitrate, the reaction may proceed by the 1,4-addition of the reagent to quinoline, followed by electrophilic attack upon the 1,4-dihydro derivative.
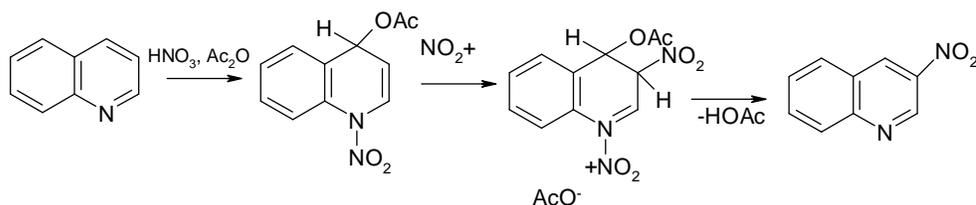
*Scheme 2:*   Reaction of Quinoline with Acetyl Nitrate
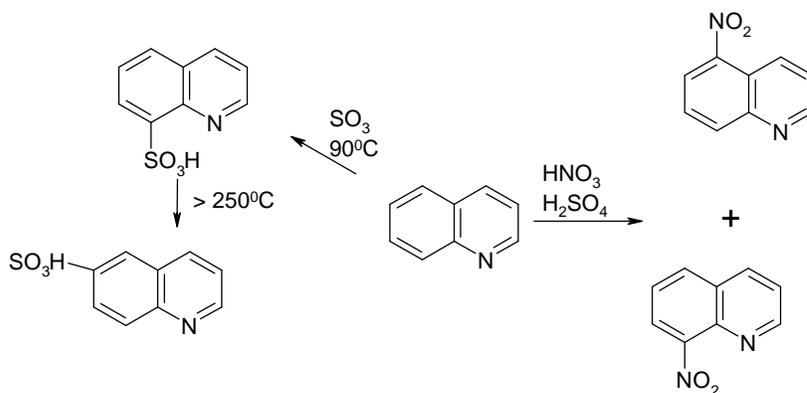
Scheme 3:   Reaction of Quinoline with Fuming Nitric Acid in Concentrated Sulphuric Acid

However, the rate of nitration of quinoline in 80-99% sulphuric acid is of the same order as that of N-methylquinolinium salts, suggesting that here the quinolinium cation may be the target for attack.

Sulphonation with oleum at 90°C affords mainly the 8-sulphonic acid, but as this product is sterically hindered, at higher temperatures it rearranges into the 6-sulphonic acid (Scheme 3). This rearrangement is similar to that shown by naphthalene-1-sulphonic acid, the kinetic sulphonation product of naphthalene, which isomerises on heating into the thermodynamically favoured (less hindered) 2-isomer.

Alkyl and acyl halides react directly with quinoline to give N-alkyl or N-acylquinoliniumm salts (Scheme 4), whereas the N-alkyl salts are stable and can often be isolated as crystalline solids; the N-acyl analogues are unstable and undergo rapid hydrolysis in moist air or in aqueous solution.
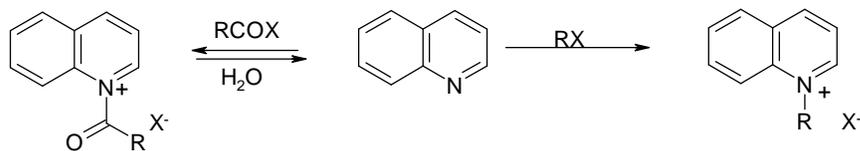
Scheme 4:   Reactions of Quinoline with Acyl and Alkyl Halides

3.3   Nucleophilic Addition/Substitution

N-Acyl- or N-sulphonylquinolinium salts can be trapped by cyanide ion to form what are known generally as Reissert adducts. The easy removal of the N-substituent in a subsequent reaction with a base provides access to 2-cyanoquinoline(Scheme 5).
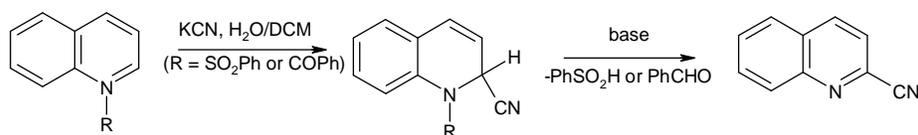
Scheme 5:　　Reaction of Quinoline with Potassium Cyanide

There is a strong similarity between the reactions of pyridines and quinolines towards nucleophiles. Addition occurs mainly at C-2 giving 1,2-dihydroquinolines, but the locus of the reaction can be diverted to C-4, particularly if there is a good leaving group located at this position.

In a Chichibabin-type reaction quinoline reacts with potassamide (KNH$_2$) in liquid ammonia at -70°C to give 2-amino-1,2-dihydroquinoline and this is oxidised by potassium permanganate [manganate(VII)] at the same temperature to yield 2-aminoquinoline (Scheme 6). If the temperature is allowed to increase to -45°C the adduct rearranges into 4-amino-3,4-dihydroquinoline, and upon oxidation this product gives 4-aminoquinoline.
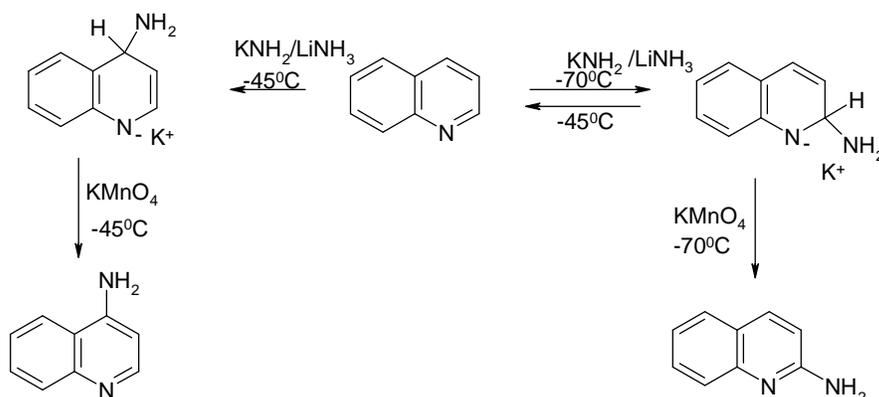
Scheme 6:　　Reaction of Quinoline with Potassamide

4.0　CONCLUSION

In this unit, we have learnt that the quinoline ring is bicyclic consisting of the benzene ring fused to a pyridine ring. We have also learnt that quinolines can undergo electrophilic substitution, Nucleophilic addition/substitution, and oxidation and reduction reactions. You will be exposed to synthesis of quinolines in the next unit.

5.0   SUMMARY

In this unit you have learnt that quinoline ring is bicyclic consisting of the benzene ring fused to the pyridine ring. Quinoline is a weak base and hence reacts with strong acids to give salts. It undergoes electrophilic substitution at positions 5 and 8 of the benzene ring. Electrophilic substitution reaction at position 3 can take place by nitration with acylnitrate via 1,4-addition of the reagent to quinoline followed by electrophilic attack upon the 1,4-dihydro derivative obtained.

You also learnt that nucleophilic substitution occurs mainly at positions 2 and 4 of the pyridine ring. Reduction takes place on the pyridine ring while oxidations of both rings are difficult.

6.0   TUTOR-MARKED ASSIGNMENT

1.   What are the physical properties of Quinoline?
2.   Explain why nitration of quinoline with acetyl nitrate yields 3-nitroquinoline, while nitration with fuming nitric acid and sulphuric acid yields 5 and 8-nitroquinoline. Write the equations for the reactions.
3.   Write 2 nucleophilic addition/substitution reactions of quinoline.

7.0   REFERENCES/FURTHER READING

Olaniyi, A. A.; *et al.* (1998). *Essential Inorganic and Organic Pharmaceutical Chemistry.* Shaneson, C.I. Limited. pp. 363-450.

Sainsbury, M. (2001). Heterocyclic Chemistry. *Royal Society of Chemistry*, pp.42-49.

UNIT 2   SYNTHESIS OF QUINOLINES

CONTENTS

1.0   INTRODUCTION

Quinoline was first extracted from coal tar in 1834 by Friedlieb Ferdinand Runge. Coal tar remains the principal source of commercial quinoline. It can be synthesised by various methods such as the Skraup, Dobner-von Miller Synthesis, Conrad-Limpach, Friedlaender and Pfitzinger synthesis.

2.0   OBJECTIVES

At the end of this unit, you should be able to:

• explain the synthesis of quinolines
• design synthesis of quinoline derivatives.

3.0   MAIN CONTENT

3.1   Skraup Synthesis of Quinoline

Aniline, glycerol, nitrobenzene, iron (II) sulphate and sulphuric acid are mixed and gently heated. A vigorous exothermic reaction occurs which is completed by further heating. After removal of the residual nitrobenzene by distillation in steam, quinoline is liberated from the reaction mixture by basification and is isolated by steam-distillaton. The yield of the purified product is 84-91%.

The reaction involves dehydration of glycerol to propenal (Acrolein), Michael-type addition of aniline to propenal, acid-catalysed cyclisation and dehydrogenation by nitrobenzene (Scheme 7). Iron (II) sulphate acts to moderate the reaction. Propenal itself is not employed because of its tendency to polymerise. The successs of the reaction depends on the rapid addition of aniline to the propenal as it is formed.
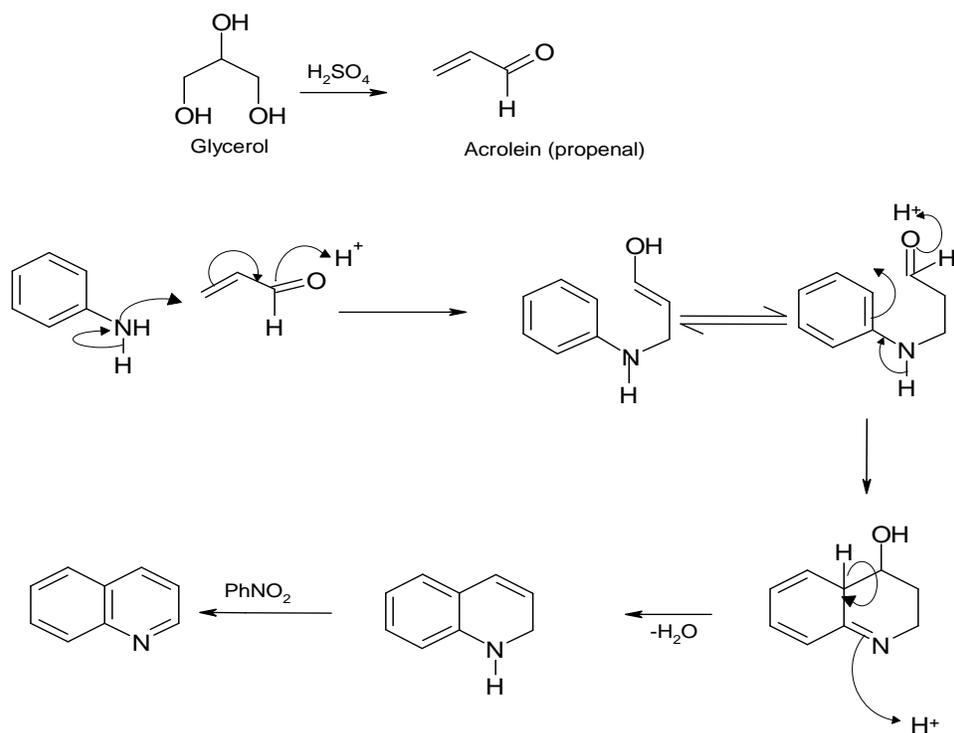

Scheme 7:   Skraup Synthesis of Quinoline

The synthesis is of wide application especially for synthesis of quinoline substituted in the benzene ring. The aniline may contain nuclear substituents: ortho- and para-substituted anilines give 8- and 6-substituted quinolines, respectively, and meta-substituted anilines give mixtures of 5- and 7-substituted quinolines, the latter predomination with activating substituents such as methoxyl and the former predominating with deactivating substituents such as nitro. Propenal may be replaced by 2-butenal giving 2-methylquinolines and by butanone, giving 4-methylquinolines.

3.2   The Döbner-von Miller Synthesis

The reaction uses pre-formed α, β-unsaturated carbonyl compounds instead of acrolein. It is used to provide alkyl and aryl substituents in the "pyridine" half of the quinoline.

The intermediate β-aminocarbonyl compound can be isolated and this shows that the mechanism starts with a conjugate addition. The intermediate may then be subsequently cyclised under a variety of conditions (Scheme 8).
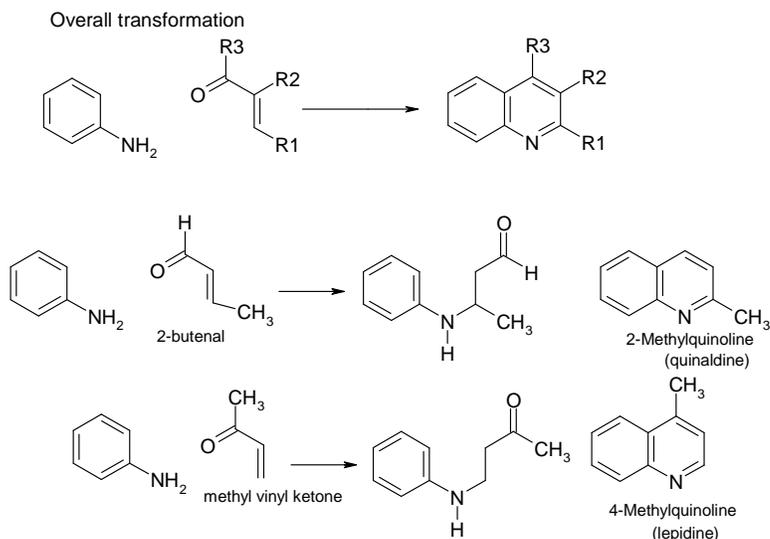
Scheme 8:   Döbner-von Miller Synthesis

3.3   The Conrad-Limpach Synthesis

β-keto esters react with aniline in each of two ways; at low temperatures reaction occurs at the keto-group to give an imine and at high temperatures reaction occurs at the ester group to give an amide. The resulting compounds can each be cyclised to quinolines (see Scheme 9).
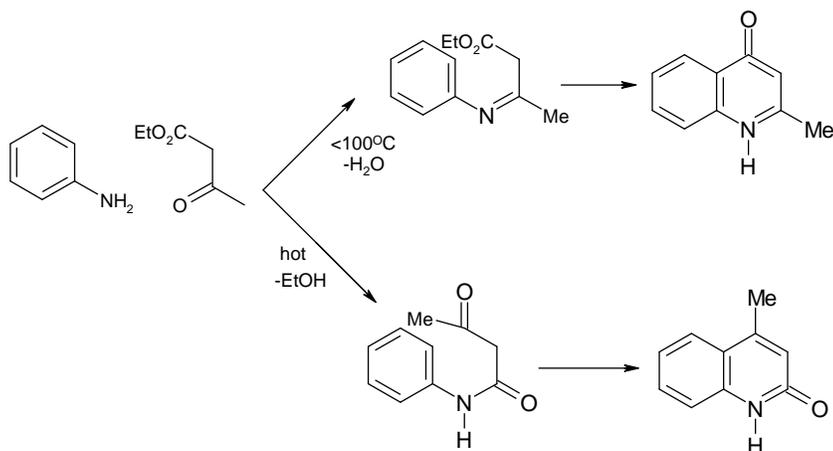

Scheme 9:   The Conrad-Limpach Synthesis

3.4   The Friedlaender Synthesis

An o-aminobenzaldehyde is treated with an aldehyde or ketone in a basic medium; formation of the imine is followed by dehydrative cyclisation (Scheme 10).
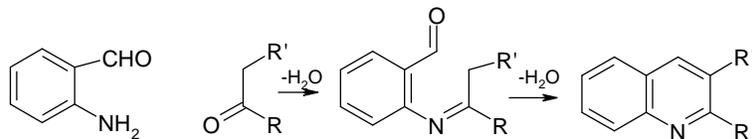

Scheme 10:   Friedlaender Synthesis

The main problem with this synthesis is that o-aminobenzaldehydes are very unstable, readily undergoing self-condensation. One way of overcoming this is to start instead with an o-nitrobenzaldehyde: acid- or base-catalysed reaction gives an intermediate which cyclises spontaneously on reduction (Scheme 11 cf. the Reissert indole synthesis).
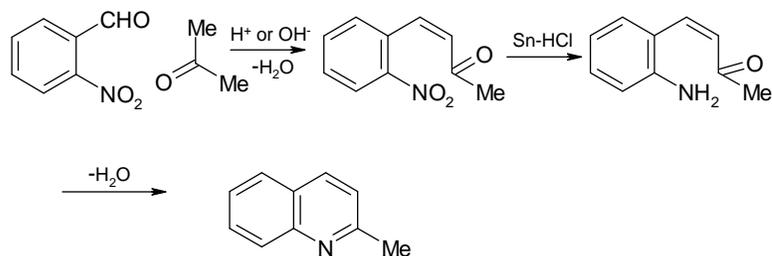
Scheme 11:   Variation of Friedlaender Synthesis

3.5   The Pfitzinger Synthesis

This is a modification of Friedlaender's method and employs isatin in place of 0-aminobenzaldehyde. Reaction with the base gives o-aminobenzoylformate ion which reacts with an aldehyde or ketone to give a 4-carboxyquinoline from which the carboxyl group can be removed thermally (Scheme 12).
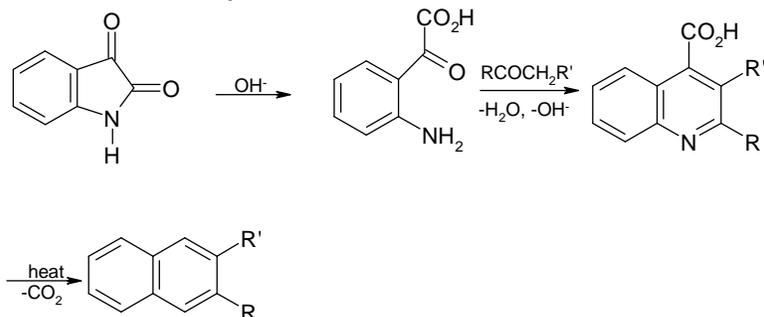
Scheme 12:   Pfitzinger Synthesis

4.0   CONCLUSION

In this unit we have looked at the various methods used in the synthesis of quinoline and its derivatives. These methods normally start from phenylamines or similar compounds with an intact benzene ring.
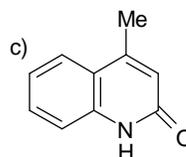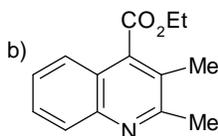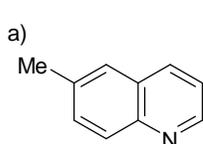
5.0   SUMMARY

In this unit, you have learnt the following.

- Quinolines are synthesised from phenylamines or similar nitrogen containing benzenoid compounds.
- Skraup synthesis, Dobner-von Miller and Conrad-Limpach synthesis involves the use of phenylalanine and a 3-carbon fragment as starting materials.
- Friedlaender and Pfitzinger synthesis involve the use of o-aminobenzaldehydes and o-aminobenzoylformate respectively and a two carbon fragment as starting materials.
- Conrad-Limpach synthesis is used to synthesise quinolone derivatives.

6.0   TUTOR-MARKED ASSIGNMENT

1.   Devise a synthesis of 1-benzyl-1,2,3,4-tetrahydroquinoline from quinoline.
2.   Provide synthetic routes to the following quinoline derivatives (a)-(c).

7.0   REFERENCES/FURTHER READING

Norman, R. O. C. & Coxon, J. M. (1993). Principles of Organic Synthesis (3rd ed.). *Blackie Academic & Professional, Glasgow.* An Imprint of Chapman & Hall. pp. 703-706.

Olaniyi, A. A.; *et al*. (1998). *Essential Inorganic and Organic Pharmaceutical Chemistry.* Shaneson, C.I. Limited. pp. 363-450.

Sainsbury, M. (2001). Heterocyclic Chemistry. *Royal Society of Chemistry*. pp. 42-49.

UNIT 3   APPLICATION OF THE QUINOLINE RING SYSTEM IN DRUG SYNTHESIS

CONTENTS

1.0   INTRODUCTION

Quinoline is used principally for the manufacture of nicotinic acid which prevents pellagra in humans and in the manufacture of other specialty chemicals. Approximately 4 tonnes are produced annually according to a report published in 2005. It is used as a precursor to 8-hydroxyquinoline, which is a versatile chelating agent and precursor to pesticides. Its 2- and 4-methyl derivatives are precursors to cyanine dyes. Oxidation of quinoline affords quinolinic acid (pyridine-2,3-dicarboxylic acid), a precursor of the herbicide sold under the name 'Assert'. The quinoline nucleus is contained in several groups of alkaloids (e.g. quinine), in a number of synthetic materials with important physiological properties such as the antimalarial plasmoquin and chloroquine, in the cyanine dyes and in the analytical reagent, oxine (8-hydroxyquinoline).

2.0   OBJECTIVES

At the end of this unit, you should be able to:

•   identify some biologically active compounds containing the quinoline nucleus
•   describe the synthetic routes to some quinoline derivatives of medicinal importance.

3.0   MAIN CONTENT

3.1   Quinine

Quinine is a natural white crystalline alkaloid having antipyretic (fever-reducing), antimalarial, analgesic (painkilling), anti-inflammatory properties and a bitter taste. It is a stereoisomer of quinidine which, unlike quinine, is an anti-arrhythmic. Quinine contains two major fused-ring systems; the aromatic quinoline and the bicyclic quinuclidine. The aromatic part of the quinine molecule is a quinoline with a methoxy substituent. The amine component has a quinuclidine skeleton and the methylene bridge in between has a hydroxide group. The substituent at the carbon-3 position is a vinyl group. The molecule is optically active with four stereogenic (Figure 2).
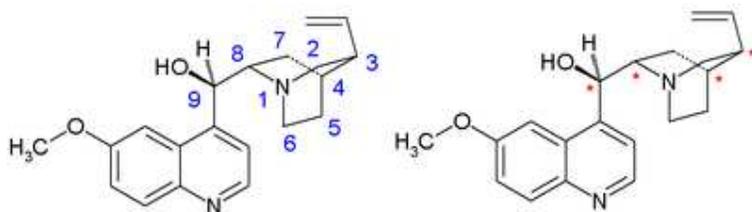

Fig. 2:   Structure of Quinine (the Asymmetric Centres are Shown as *)

Though it has been synthesised in the laboratory, the bark of the cinchona tree is the only known natural source of quinine. The medicinal properties of the cinchona tree were originally discovered by the Quechua Indians of Peru and Bolivia; later, the Jesuits were the first to bring the cinchona to Europe.

Quinine was the first effective treatment for malaria caused by *Plasmodium falciparum*, appearing in therapeutics in the 17th century. It remained the antimalarial drug of choice until the 1940s, when other drugs replaced it. Since then, many effective antimalarials have been introduced, although quinine is still used to treat the disease in certain critical situations.. Quinine is also used to treat lupus and arthritis. Quinine is very sensitive to ultraviolet light (UV) and will fluoresce in direct sunlight, due to its highly conjugated resonance structure.

Quinine is a flavour component of tonic water and bitter lemon. Quinine is also used in photochemistry as a common fluorescence standard, because of its relatively constant and well-known fluorescence quantum yield.

Synthetic quinine

Cinchona trees remain the only economically practical source of quinine. However, under wartime pressure, research towards its synthetic production was undertaken. A formal chemical synthesis was accomplished in 1944 by American chemists R.B. Woodward and W.E. Doering. Since then, several more efficient quinine total syntheses have been achieved, but none of them can compete in economic terms with isolation of the alkaloid from natural sources. The first synthetic organic dye, mauveine, was discovered by William Henry Perkin in 1856 while he was attempting to synthesise quinine.

3.2 Chloroquine

Chloroquine (CQ), N'-(7-chloroquinolin-4-yl)-N,N-diethyl-pentane-1,4-diamine was discovered in 1934 by Hans Andersag and co-workers at the Bayer laboratories who named it "Resochin". It was ignored for a decade because it was considered too toxic for human use. During World War II United States government-sponsored clinical trials for anti-malarial drug development showed unequivocally that CQ has a significant therapeutic value as an anti-malarial drug. It was introduced into clinical practice in 1947 for the prophylactic treatment of malaria.

Uses

a. It has long been used in the treatment or prevention of <u>malaria</u>. After the malaria parasite *Plasmodium falciparum* started to develop widespread resistance to chloroquine new potential utilisations of this cheap and widely available drug have been investigated. Chloroquine has been extensively used in <u>mass drug administrations</u> which may have contributed to the emergence and spread of resistance.

b. As it mildly suppresses the <u>immune system</u>, it is used in some <u>autoimmune disorders</u>, such as <u>rheumatoid arthritis</u> and <u>lupus erythematosus</u>.

c. Chloroquine is in clinical trials as an investigational <u>antiretroviral</u> in humans with <u>HIV-1/AIDS</u> and as a potential <u>antiviral</u> agent against <u>chikungunya</u> fever.

d. The <u>radiosensitising</u> and <u>chemosensitising</u> properties of chloroquine are beginning to be exploited in anticancer strategies in humans.

e. Synthesis

f. Chloroquine can be synthesised using the Conrad-Limpach quinolone method as shown below:
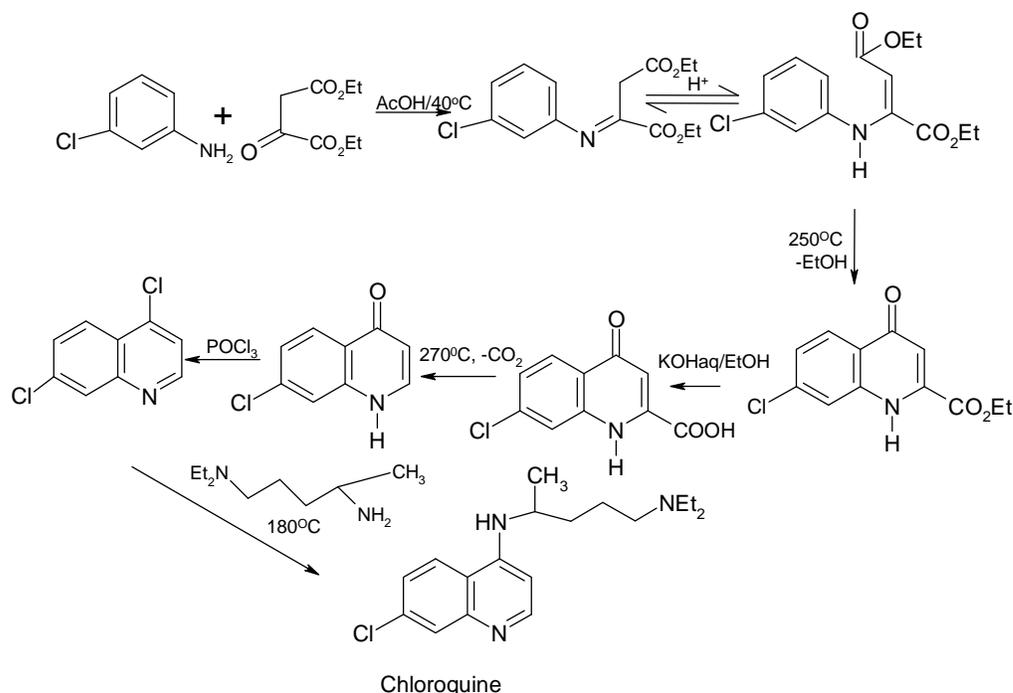
Scheme 13:   Synthesis of Chloroquine
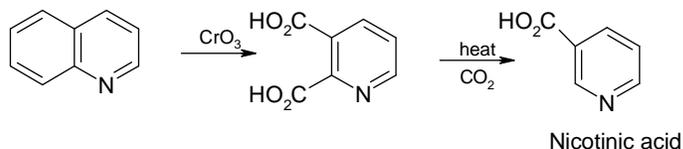

3.3   Nicotinic Acid

Niacin (also known as **vitamin B$_3$**, **nicotinic acid** and **vitamin PP**) is an organic compound with the formula $C_6H_5NO_2$ and, depending on the definition used one of the forty to eighty essential human nutrients. This colourless, water-soluble solid is a derivative of pyridine, with a carboxyl group (COOH) at the 3-position. Other forms of vitamin B$_3$ include the corresponding amide, nicotinamide ("niacinamide"), where the carboxyl group has been replaced by a carboxamide group (CONH$_2$), as well as more complex amides and a variety of esters. The terms niacin, nicotinamide, and vitamin B$_3$ are often used interchangeably to refer to any member of this family of compounds, since they have similar biochemical activity.

Niacin is one of five vitamins associated with a pandemic deficiency disease, niacin deficiency (pellagra), vitamin C deficiency (scurvy), thiamin deficiency (beriberi), vitamin D deficiency (rickets), vitamin A deficiency.

Niacin has been used to increase levels of HDL cholesterol in the blood and has been found to modestly decrease the risk of cardiovascular events in a number of controlled human trials. However, in a recent trial AIM-HIGH, a slow-release form of niacin was found to have no effect on cardiovascular event and stroke risk in a group of patients with LDL

levels already well-controlled by a statin drug, and the trial was halted prematurely on evidence that niacin addition actually increased stroke risk in this group. The role of niacin in treating cardiovascular risk remains under debate.

Nicotinic acid is synthesised by the oxidation of quinoline with Chromium (vi) oxide. Quinoline oxidises to pyridine-2,3-dicarboxylic acid which readily loses the 2-carboxyl-substituent on being heated to form nicotinic acid (Scheme 14).

Scheme 14: Synthesis of Nicotinic Acid from Quinoline

3.4   Other Applications of Quinoline

The quinoline nucleus is also contained in plasmoquin (an antimalarial agent), in cyanine dyes and in the analytical reagent, oxine (8-hydroxyquinoline).

4.0   CONCLUSION

This unit has shown that Quinolines are important because their derivates exhibit useful biological activities. Some of these derivatives like quinine have been recognised for centuries.

5.0   SUMMARY

In this unit, you have learnt that many derivatives of quinolines show very useful biological activities and some have been in use for decades e.g. quinine. Quinine can be obtained naturally from the bark of Cinchona trees.

You also learnt that antimalarial agents such as quinine, chloroquine and plasmoquine are quinoline derivatives. Chloroquine can be synthesised via the Conrad-Limpach synthesis. Nicotinic acid known as niacin is used in the treatment of pellagra and hypercholesterolaemia and it can be synthesised by the oxidation of quinoline. The quinoline nucleus is also contained in cyanine dyes and in the analytical agent, oxine (8-hydroxyquinoline).

6.0 TUTOR-MARKED ASSIGNMENT

1. Write briefly on two medicinal agents containing the quinoline nucleus.
2. Outline the synthesis of chloroquine via the Conrad-Limpach synthesis.
3. Outline the synthesis of nicotinic acid from quinoline. What are the medicinal uses of nicotinic acid?

7.0 REFERENCES/FURTHER READING

Norman, R. O. C. & Coxon, J. M. (1993). Principles of Organic Synthesis (3rd ed.). *Blackie Academic & Professional, Glasgow*. An Imprint of Chapman & Hall. pp. 703-706.

Olaniyi, A. A.; *et al.* (1998). *Essential Inorganic and Organic Pharmaceutical Chemistry.* Shaneson, C.I. Limited. pp. 363-450.

Sainsbury, M. (2001). Heterocyclic Chemistry. *Royal Society of Chemistry*. pp. 42-49.

UNIT 4 SYNTHESIS AND REACTIONS OF ISO-QUINOLINES

CONTENTS

1.0 INTRODUCTION

Isoquinoline is a heterocyclic aromatic organic compound. It is a structural isomer of quinoline. Isoquinoline and quinoline are benzopyridines, which are composed of a benzene ring fused to a pyridine ring. The nitrogen in isoquinoline is on position 2 while the nitrogen is on position 1 in quinoline (Figure 3). In a broader sense, the term isoquinoline is used to make reference to isoquinoline derivatives. 1-Benzylisoquinoline is the structural backbone in naturally occurring alkaloids including papaverine and morphine. The isoquinoline ring in this natural compound derives from the aromatic amino acid tyrosine.
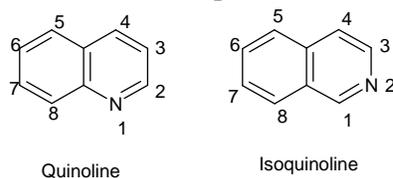

Fig. 3: Structures of Quinoline and Isoquinoline

2.0 OBJECTIVES

At the end of this unit, you should be able to:

- differentiate between isoquiniline and its isomer quinoline
- appreciate the similarities and differences in their physical and chemical properties

- describe the influence of presence of the benzene nucleus on the chemistry of isoquinolines compared to that of pyridine
- explain the main methods used for the synthesis of isoquinolines and their derivatives.

3.0   MAIN CONTENT

## 3.1   General Physical and Chemical Properties Isoquinoline

Isoquinoline is a colourless <u>hygroscopic</u> liquid at room temperature with a penetrating, <u>unpleasant odour</u>. Impure samples can appear brownish, as is typical for nitrogen heterocycles. It crystallises to platelets and have a low <u>solubility</u> in <u>water</u> but dissolve well in <u>ethanol</u>, <u>acetone</u>, <u>diethyl ether</u>, <u>carbon disulphide</u>, and other common <u>organic solvents</u>. It is also soluble in dilute <u>acids</u> as the protonated derivative.

Being an <u>analog</u> of <u>pyridine</u>, isoquinoline is a weak <u>base</u>, with a pK_b of 5.1. It protonates upon treatment with <u>strong acids</u>, such as HCl to form <u>salts</u>.. It forms <u>adducts</u> with <u>Lewis acids</u>, such as BF_3.

Isoquinoline is closely related to quinoline in physical and chemical properties. Modifications are only as a result of the different position of the nitrogen atom relative to the cabocyclic ring.

## 3.1.1 Reactions with Electrophiles

Isoquinoline like quinoline is protonated and alkylated at the nitrogen atom and undergoes electrophilic substitution in the benzene ring. Sulphonation with oleum gives mainly the 5-sulphonic acid, but fuming nitric acid and concentrated sulphuric acid at 0˚C produce a 1:1 mixture of 5- and 8-nitroisoquinolines. Bromination in the presence of aluminium trichloride at 75˚C gives a 78% yield of 5-bromoisoquinoline (Scheme 15).
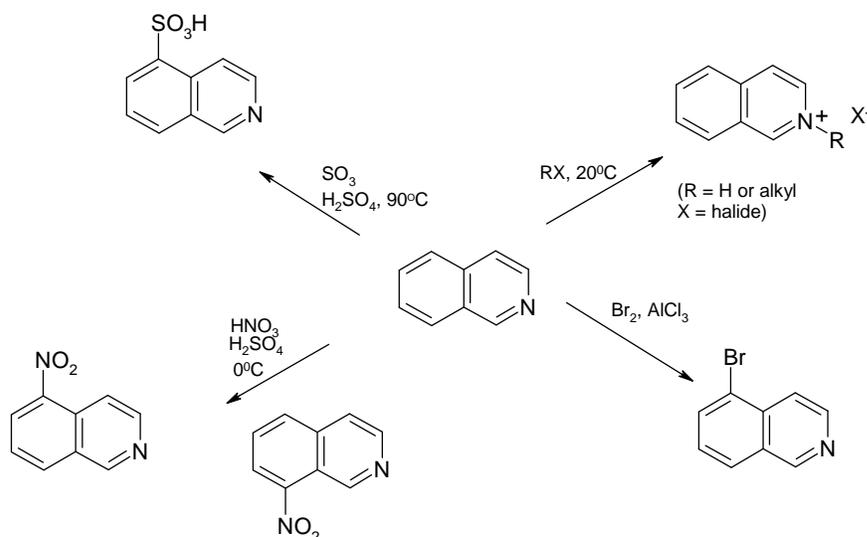
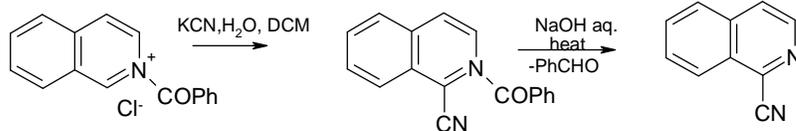*Scheme 15:*   Reactions of Isoquinolines with Electrophiles

3.1.2 Reduction and Reactions with Nucleophiles

Nucleophilic addition takes place at C-1 and this is considerably enhanced if the reaction is carried out upon an isoquinolinium salt. Reduction with lithium aluminium hydride {tetrahydroaluminate(III)} in THF (tetrahydrofuran) for example gives a 1,2-dihydroisoquinoline. These products behave as cyclic enamines and if isoquinolium salts are reacted with sodium borohydride [tetrahydroboronate(III)] in aqueous ethanol, further reduction to 1,2,3,4-tetrahydroisoquinolines is effected through protonation at C-4 and then hydride tranfer from the reagent to C-3 (Scheme 16).
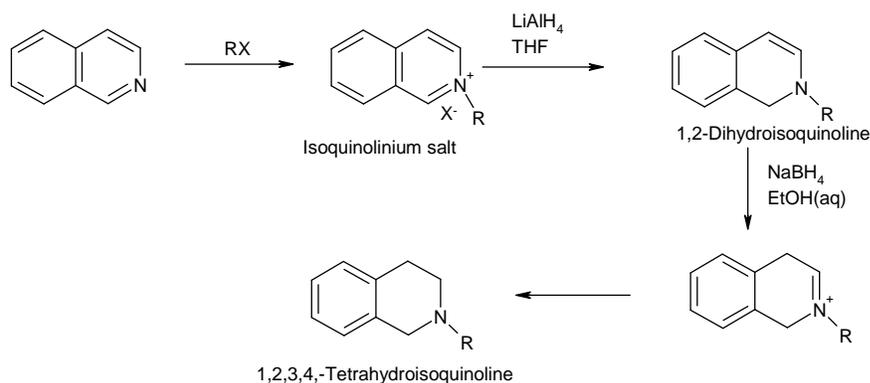
Scheme 16:   Reduction of Isoquinoline

The cyanide anion adds to C-1 in 2-benzoylisoquinolinium salts in water/DCM (dichloromethane), forming Reissert compounds; then, just like their quinoline counterparts, the adducts can be deprotonated by a base with the loss of the N-substituent and the formation of a 1-cyanoisoquinoline (Scheme 17).

Scheme 17:   Reaction of Isoquinoline with Nucleophiles

3.2   Synthesis of Isoquinolines

Isoquinoline was first isolated from <u>coal tar</u> in 1885 by Hoogewerf and van Dorp. They isolated it by fractional crystallisation of the acid sulphate. Weissgerber developed a more rapid route in 1914 by selective extraction of coal tar; exploiting the fact that isoquinoline is more basic than quinoline. Isoquinoline can then be isolated from the mixture by fractional crystallisation of the acid sulphate.

Although isoquinoline derivatives can be synthesised by several methods, relatively few direct methods deliver the unsubstituted isoquinoline. The **Pomeranz-Fritsch reaction** provides an efficient method for the preparation of isoquinoline.

The biological properties of many derivatives have ensured the development of a number of syntheses providing access to all types of isoquinolines, both natural and manmade. Three important routes are the Bischer-Napieralski, Picted-splenger and Pomeranz-Fritsch methods.
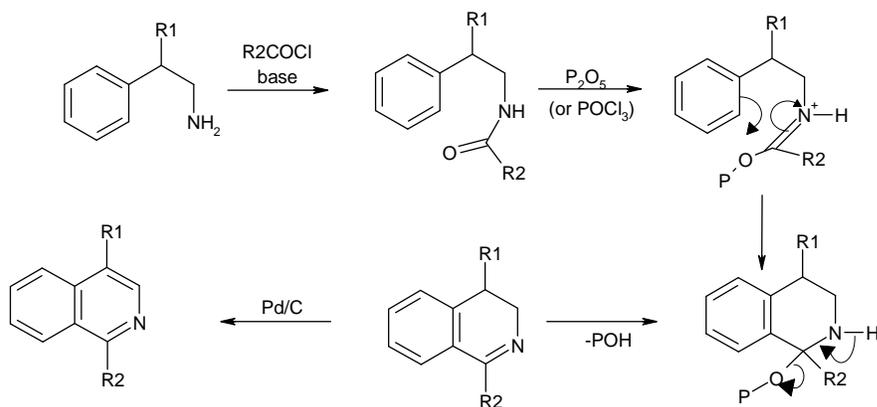
3.2.1 Bischler-Napieralski Synthesis

This method is very useful for the construction of 1-substituted 3,4-dihydroisoquinolines, which if necessary can be oxidised to isoquinolines. A β-phenylethylamine (1-amino-2-phenylethane) is the starting material, and this is usually preformed by reaction of an aromatic aldehyde with nitromethane in the presence of sodium methoxide, and allowing adduct to eliminate methanol and give a β-nitrosytrene (1-nitro-2-phenylethene). This product is then reduced to β-phenylethylamine commonly by the action of lithium aluminium hydride (Scheme 18). Once prepared, the β-phenylethylamine is reacted with an acyl chloride and a base to give the corresponding amide (R1 = H) and then this is cyclised to a 3,4-dihydroisoquinoline by treatment with either phosphorus pentoxide or phosphorus oxychloride. Finally,

aromatisation is accomplished by heating the 3,4-dihydroisoquinoline over palladium on charcoal (Scheme 19).
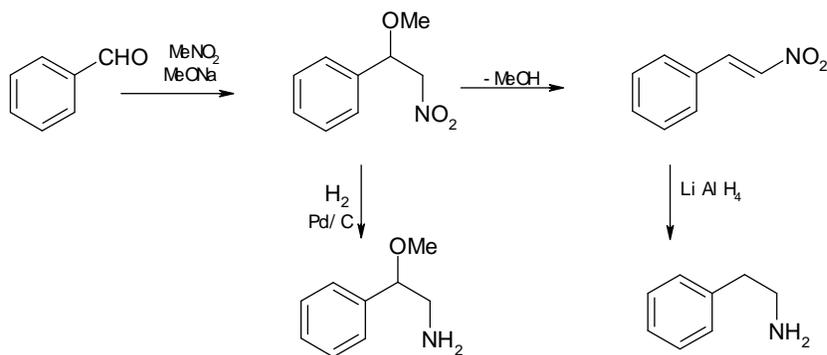

Scheme 18:   Synthesis of β-phenylethylamine

Scheme 19:   Bischler-Napieralski Synthesis of Isoquinoline

Alternatively, a β-methoxy-β-phenylethylamine can be used to circumvent the oxidation step after the conventional Bischler-Naperialski cyclisation. Here, when treated with the phosphorus reagent the amide (R1 = OMe) undergoes both cyclisation and the elimination of methanol to give the isoquinoline (R=H) directly. This is known as the Pictet-Gams modification of the Bischer-Napieralski synthesis.

3.2.2 Picket-Spengler Synthesis

A β-phenylethylamine is treated with an aldehyde in the presence of dilute acid; ring closure occurs by a reaction of Mannish type reaction and the tetrahydroisoquinoline formed is dehydrogenated on palladium (Scheme 20).
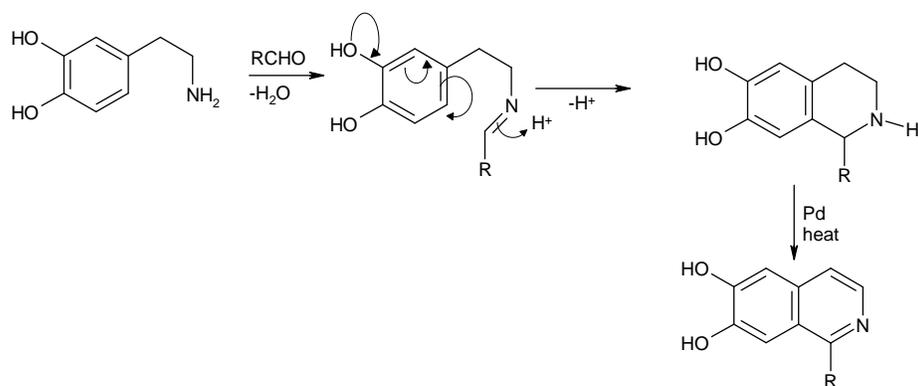
Scheme 20:   Picket-Spengler Synthesis

3.2.3 The Pomeranz-Fritsch Synthesis

Whereas both the previous two routes depend upon a cyclisation of the benzene ring to what becomes C-1 of the heterocycle, the key step in the Pomeranz-Fritsch synthesis is the formation of a bond to C-4. A benzaldehyde is the starting material, and it is reacted with an amino-acetaldehyde dialkyl acetal to form an imine, which is then cyclised directly under relatively severe acidic conditions (e.g. conc. H_2SO_4 at 100°C) to give the isoquinoline. Although the Pomeranz-Fritsch ring-closure conditions permit the cyclisation of unsubstitued imines, the reaction is accelerated greatly if electron-donating groups are present in the benzene ring (Scheme 21).
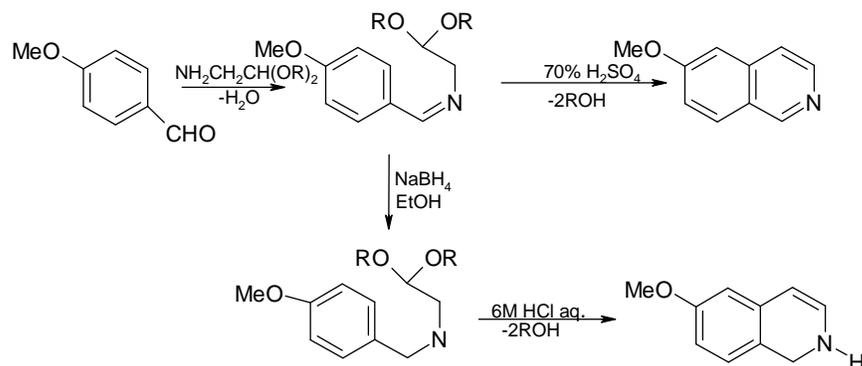
Scheme 21:   Pomeranz-Fritsch Synthesis

Through slight modification the Pomeranz-Fritsch synthesis can be made particularly useful for the preparation of 1,2-dihydroisoquinolines. The imine is first reduced with sodium borohydride in 98% ethanol to the corresponding benzylamine, prior to cyclisation, by treatment with 6M hydrochloric acid. When electron-donating groups (such as a methoxyl) are present in the aromatic unit of the benzylamine, the ring closure step occurs at room temperature to give a 1,2-

dihydroisoquinoline. As 1,2-dihydroisoquinolines are unstable in air, it is customary to carry out the reaction under an atmosphere of oxygen-free nitrogen.

An advantange of the modified Pomeranz-Fritsch synthesis is that the 1,2-dihydroisoquinolinium salts can be reacted in situ with electrophiles, yielding 3,4-dihydroisoquinolinium salts that react with nucleophiles at C-3. Such a 'single pot' procedure can be used to form complex 1,2,3,4-tetrahydroisoquinolines.

4.0   CONCLUSION

In this unit, we have learnt that the isoquinoline ring is bicyclic consisting of the benzene ring fused to a pyridine ring. The nitrogen on the isoquinoline ring is at position 2 compared to position 1 on quinoline. We have also learnt that isoquinolines can undergo similar reactions of quinolines. Synthesis of isoquinolines and derivatives are usually via phenylamines or similar nitrogen containing benzenoid compounds.

5.0   SUMMARY

Isoquinoline ring is bicyclic consisting of the benzene ring fused to the pyridine ring however the nitrogen in the pyridine ring is on position 2 compared to position 1 in quinoline. Isoquinoline like quinoline is a weak base and hence reacts with strong acids to give salts. It undergoes electrophilic substitution at positions 5 and 8 of the benzene ring.

Also nucleophilic substitution occurs mainly at positions 1 compared to positions 2 and 4 of the pyridine ring in quinolines. Reduction takes place on the pyridine ring and oxidation of both rings are difficult. Synthesis is via the reaction of β-phenylethylamine and acyl chloride or an aldehyde in the Bischler-Napieralski synthesis and Picket-Spengler synthesis respectively. Pomeranz-Frisch synthesis also occurred via the reaction of a benzaldehyde with an amino-acetaldehyde.

6.0   TUTOR-MARKED ASSIGNMENT

1.   How does isoquinoline react with fuming nitric acid and sulphuric acid?
2.   Which reagent will you use to synthesise N-methylisoquinolium salt?
3.   Outline the synthesis of 1-methylisoquinoline from benzaldehyde and suitable reagents via a multi-step synthesis.

7.0   REFERENCES/FURTHER READING

Norman, R. O. C. & Coxon, J. M. (1993). Principles of Organic Synthesis (3rd ed.). *Blackie Academic & Professional, Glasgow.* An Imprint of Chapman & Hall. pp. 706-708.

Olaniyi, A. A.; *et al.* (1998). *Essential Inorganic and Organic Pharmaceutical Chemistry.* Shaneson, C.I. Limited. pp. 363-450.

Sainsbury, M. (2001). Heterocyclic Chemistry. *Royal Society of Chemistry*. pp. 50-54.

**UNIT 5   APPLICATION   OF   THE   ISO-QUINOLINE
              RING SYSTEM IN DRUG SYNTHESIS**

CONTENTS

1.0   Introduction
2.0   Objectives
3.0   Main Content
        3.1   Papaverine
        3.2   Morphine
        3.3   Other Applications of Isoquinolines
        3.4   Isoquinoline and Parkinson's disease
4.0   Conclusion
5.0   Summary
6.0   Tutor-Marked Assignment
7.0   References/Further Reading

1.0   INTRODUCTION

Isoquinolines are very important because of their derivatives. A large
proportion of which are alkaloids, show useful biological effects.
Indeed, the medicinal properties of the plants that biosynthesise these
alkaloids have been recognised for centuries, long before the nature of
the compounds responsible was known. Papaverine and morphine are
found in the latex from poppy seed capsules. Papaverine is a vasodilator
while morphine is an analgesic agent. Antihypertensive agents such as
debrisoquine, quinalapril and quinalaprilat all contain the isoquinoline
ring system.

2.0   OBJECTIVES

At the end of this unit, you should be able to:

•   identify various medicinal agents containing the isoquinoline ring
        system
•   list the importance of isoquinoline derivatives in medicine
•   design the synthesis of some of the medicinal agents.

3.0   MAIN CONTENT

3.1   Papaverine

Papaverine is an opium alkaloid that is a vasodilator used primarily in
the treatment of visceral spasm, vasospasm (especially those involving
the heart and the brain), and occasionally in the treatment of erectile
dysfunction. While both are found in the opium poppy, papaverine

differs in both structure and pharmacological action from the analgesic (morphine-related) opium alkaloids (opioids).
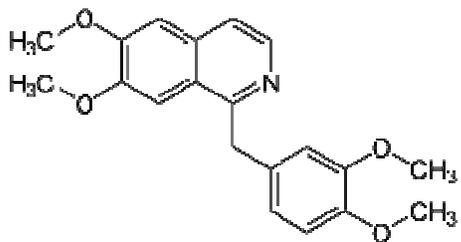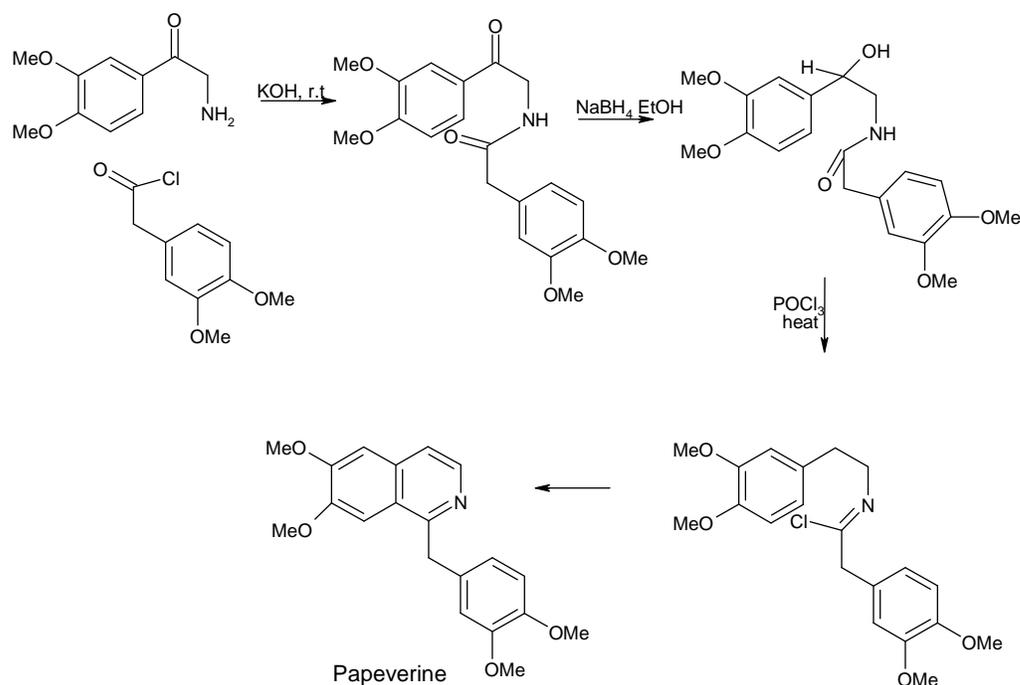

Fig. 4:   Structure of Papaverine

Scheme 22:   Synthesis of Papaverine Based on the Bischler-Napieralski Procedure

3.2   Morphine

Morphine (**MS Contin**, **MSIR**, **Avinza**, **Kadian**, **Oramorph**, **Roxanol**) Morphine is a benzylisoquinoline alkaloid with two additional ring closures. It is a potent opiate analgesic medication and is considered to be the prototypical opioid. It was first isolated in 1804 by Friedrich Sertürner, first distributed by same in 1817, and first commercially sold by Merck in 1827, which at the time was a single small chemists' shop. It was more widely used after the invention of the hypodermic needle in 1857. It took its name from the Greek god of dreams, Morpheus.

Morphine is the most abundant <u>alkaloid</u> found in <u>opium</u>, the dried sap (latex) derived from shallowly slicing the unripe seedpods of the opium, or common edible, poppy, *Papaver somniferum*. Morphine was the first <u>active principle</u> purified from a plant source and is one of at least 50 alkaloids of several different types present in opium, <u>Poppy Straw Concentrate</u>, and other poppy derivatives.

In clinical medicine, morphine is regarded as the gold standard, or benchmark, of analgesics used to relieve severe or agonising <u>pain</u> and <u>suffering</u>. Like other opioids, such as <u>oxycodone</u>, <u>hydromorphone</u>, and diacetylmorphine (<u>heroin</u>), morphine acts directly on the <u>central nervous system</u> (CNS) to relieve <u>pain</u>. Unlike many other opioids, morphine is an opiate and a natural product. Morphine has a high potential for <u>addiction</u>; <u>tolerance</u> and <u>psychological</u> <u>dependence</u> develop rapidly, although <u>physiological</u> dependence may take several months to develop.
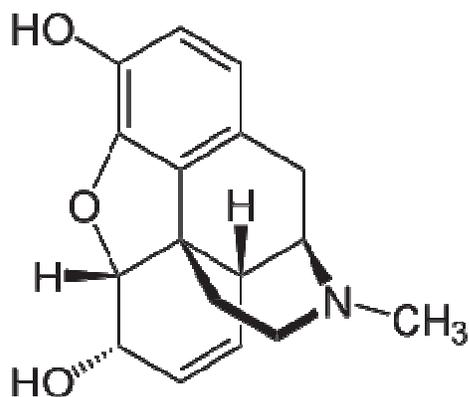

Fig. 5:   Structure of Morphine

3.3   Other Applications of Isoquinolines

anesthetics; <u>dimethisoquin</u> is one example (shown below).
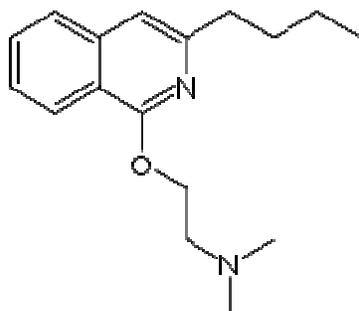

Fig. 6:   Structure of Dimethisoquine

b)   antihypertension agents, such as <u>quinapril</u>, <u>quinapirilat</u>, and <u>debrisoquine</u> (all derived from 1,2,3,4-tetrahydroisoquinoline).

c)   antifungal   agents,   such   as   2,2'-Hexadecamethylenediisoquinolinium dichloride, which is also used as a topical antiseptic. This derivative, shown below, is prepared by N-alkylation of isoquinoline with the appropriate dihalide.
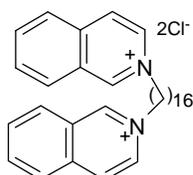

Fig. 7:   Structure   of   2,2'-Hexadecamethylenediisoquinolinium Dichloride

d)   disinfectants, like N-laurylisoquinolinium bromide (shown below), which is prepared by simple N-alkylation of isoquinoline.
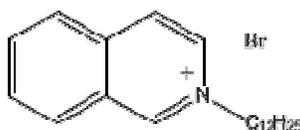

Fig. 8:   Structure of N-laurylisoquinolinium Bromide

Bisbenzylisoquinolinium compounds are compounds similar in structure to <u>tubocurarine</u>. They have two isoquinolinium structures, linked by a <u>carbon</u> chain, containing two <u>ester</u> linkages.

3.4   Isoquinolines and Parkinson's Disease

<u>Parkinson's disease</u>, a slowly progressing movement disorder, is thought to be caused by certain <u>neurotoxins</u>. A neurotoxin called <u>MPTP</u> (1[N]-methyl-4-phenyl-1,2,3,6-<u>tetrahydropyridine</u>), the precursor to MPP+, was found and linked to Parkinson's disease in the 1980s. The active neurotoxins destroy <u>dopaminergic neurons</u>, leading to parkinsonism and Parkinson's disease. Several <u>tetrahydroisoquinoline</u> derivatives have been found to have the same neurochemical properties as MPTP. These derivatives may act as neurotoxin precursors to active neurotoxins.

Other Uses:

- Isoquinolines are used in the manufacture of <u>dyes</u>, <u>paints</u>, <u>insecticides</u> and <u>antifungals</u>. It is also used as a <u>solvent</u> for the <u>extraction</u> of <u>resins</u> and <u>terpenes</u>, and as a <u>corrosion</u> inhibitor.

4.0   CONCLUSION

This unit has shown that Isoquinolines are important because their derivates exhibit useful biological activities. Some of these derivatives like morphine and papaverine have been recognised for centuries.

5.0   SUMMARY

- Many derivatives of isoquinolines show very useful biological activities and some have been in use for decades e.g. morphine and papaverine.
- Papaverine is a vasodilator and can be synthesised based on the Bischler-Napieralski procedure.
- Morphine and papaverine can be obtained naturally from the opium poppy seeds.
- Other medicinal agents containing the isoquinoline ring include dimethisoquine, and anaesthetic agent, quinalapril, debrisoquie and quinalaprilat which are antihypertensive agents.
- Isoquinolines are also used in the synthesis of disinfectants such as N-laurylisoquinolinium bromide.
- Isoquinoline derivatives may act as neurotoxin precursors to active neurotoxins.

6.0   TUTOR-MARKED ASSIGNMENT

1. Show the structures of two medicinal agents containing the isoquinoline ring.
2. Mention the medicinal uses of the compounds mentioned in (i).
3. Outline the synthesis of Papaverine using the Bischler-Naprieski procedure.
4. Design a synthetic route for N-laurylisoquinolinium bromide from isoquinoline.

7.0   REFERENCES/FURTHER READING

Sainsbury, M. (2001). Heterocyclic Chemistry.   *Royal Society of Chemistry.* pp. 50-54.

Olaniyi, A. A.; *et al.* (1998). *Essential Inorganic and Organic Pharmaceutical Chemistry.* Shaneson, C.I. Limited. pp. 363-450.

Norman, R. O. C. & Coxon, J. M. (1993). Principles of Organic Synthesis (3rd ed.). *Blackie Academic & Professional, Glasgow.* An Imprint of Chapman & Hall. pp. 706-708.

MODULE 2   BENZOPYRROLE   (INDOLES), BENZOFURAN AND BENZOTHIOPHENE

UNIT 1   REACTIONS OF BENZOPYRROLE (INDOLE)

CONTENTS

1.0   INTRODUCTION

Indole is an aromatic heterocyclic organic compound. It has a bicyclic structure, consisting of a six-membered benzene ring fused to a five-membered nitrogen-containing pyrrole ring (Figure 9). Indole is a popular component of fragrances and the precursor to many pharmaceuticals. Compounds that contain an indole ring are called indoles. The indolic amino acid tryptophan is the precursor of the neurotransmitter serotonin. Indole is a solid at room temperature. Indole

can be produced by bacteria as a degradation product of the amino acid tryptophan. It occurs naturally in human faeces and has an intense faecal odour. At very low concentrations, however, it has a flowery smell, and is a constituent of many flower scents (such as orange blossoms) and perfumes. It also occurs in coal tar.
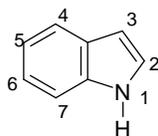

Fig. 9:   Structure of Indole

2.0   OBJECTIVES

At the end of this unit, you should be able to:

- identify and draw the indole structure
- explain the general physical and chemical properties of Indole
- describe the effect that the fusion of a benzene ring has upon the reactions of the pyrrole ring.

3.0   MAIN CONTENT

3.1   General Physical and Chemical Properties of Indoles

Indole is a solid at room temperature with a melting point between 52-54ºC. Unlike most amines, indole is non basic. The bonding situation is completely analogous to that in pyrrole. Very strong acids such as hydrochloric acid are required to protonate indole. The protonated form has a pK_a of −3.6. The sensitivity of many indolic compounds (e.g., tryptamines) under acidic conditions is caused by this protonation.

## 3.2   Electrophilic Substitution

Electrophiles attack indole at C-3, rather than at C-2. This is the opposite result to that observed for pyrroles, but can be explained if the intermediates for each type of reaction are considered. For a reaction at C-3, the energy of activation of the intermediate is lowered because it is possible to delocalise the positive charge through resonance involving the nitrogen lone pair of electrons. This favourable situation is not possible in the corresponding intermediate for attack at C-2. Any attempt to delocalise the positive charge would now disrupt the 6π-electron system of the benzene ring (Scheme 23).
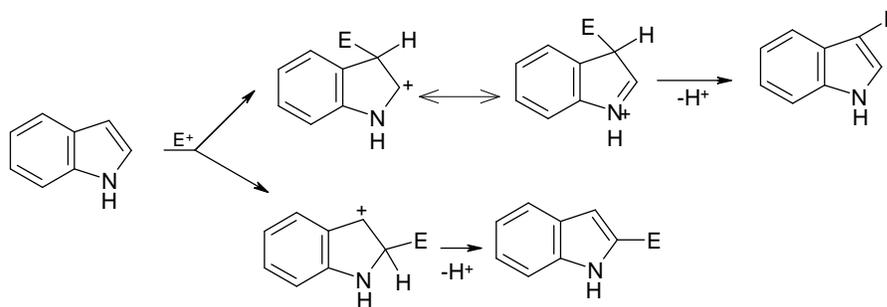
Scheme 23: Electrophilic Substitution of Indole- C-3 versus C-2

3.2.1 3-Substituted Indoles

Sulphonation of indole with pyridinium-N-sulphonate yields indolyl-3-sulphonic acid, and bromine in pyridine at 0°C affords 3-bromoindole (Scheme 19). Acetylation with a heated mixture of acetic anhydride and acetic acid gives 1,3-diacetylindole. Methylation requires heating with methyl iodide in DMF (N,N-dimethylformamide) at 80-90°C and yields 3-methylindole. This compound reacts further, giving 2,3-dimethylindole and finally 1,2,3,3-tetramethyl-3H-indoleninium iodide (Scheme 24).
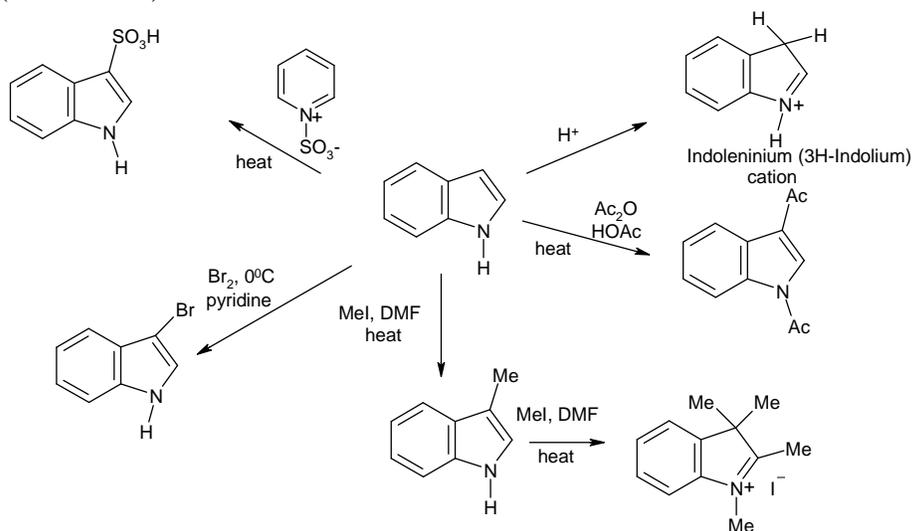

Scheme 24: Reactions of Indole with Electrophiles

3.2.2 Vilsmeier Formylation

When DMF and phosphorus oxychloride are reacted together in the Vilsmeler reaction, the N,N-dimethylamino(chloro)methyleniminium cation is generated, and this reacts with indole at 5°C to give 3-(N,N-dimethylaminomethylene)indolenine. When hydrolysed by treatment

with dilute sodium hydroxide, this gives an excellent yield of 3-formylindole (Scheme 25).
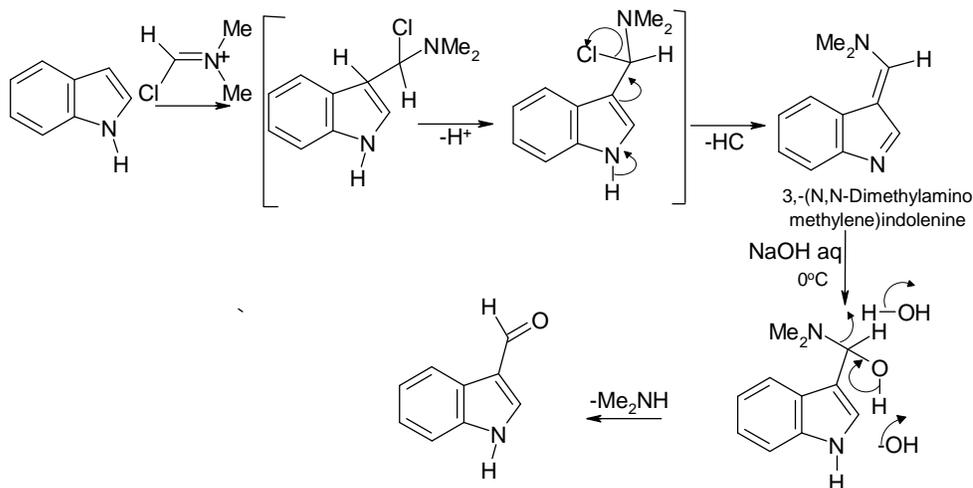
Scheme 25:   Vilsmeier Formylation

3.2.3   Reaction with Triethyl Orthoformate (Triethoxymethane)

Triethyl orthoformate is often used in ractions with enolates and carbanions to form diethyl acetals that on treatment with dilute acid give the corresponding formyl derivatives. However, when indole is heated at 160˚C with triethyl orthoformate the locus of reaction is at N-1 rather than at C-3, and 1-(diethoxymethyl)indole is formed (Scheme 26). The N-substituent is easily removed by acidic hydrolysis to reform indole.
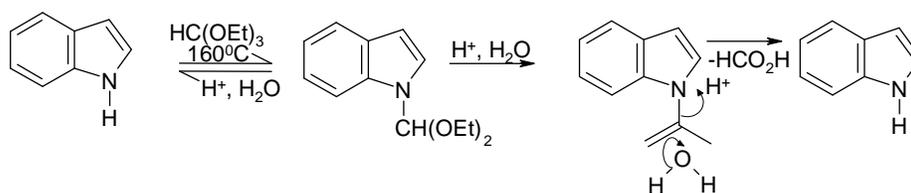

Scheme 26:   Reaction on Indole with Triethyl Orthoformate

3.2.4 Mannish Reaction

The mechanism of the Mannish reaction is similar to that of the Vilsmeier reaction as the electrophile is also a methyleniminium cation, formed this time from a condensation of dimethylamine and formaldehyde in acetic acid solution (Scheme 27). This reacts with indole to yield 3-(N,N-dimethylaminomethyl)indole (although not

shown, it is possible that initial attack occurs at N-1 and rearrangement of the side chain to C-3 takes place as a follow-up step (Scheme 27).
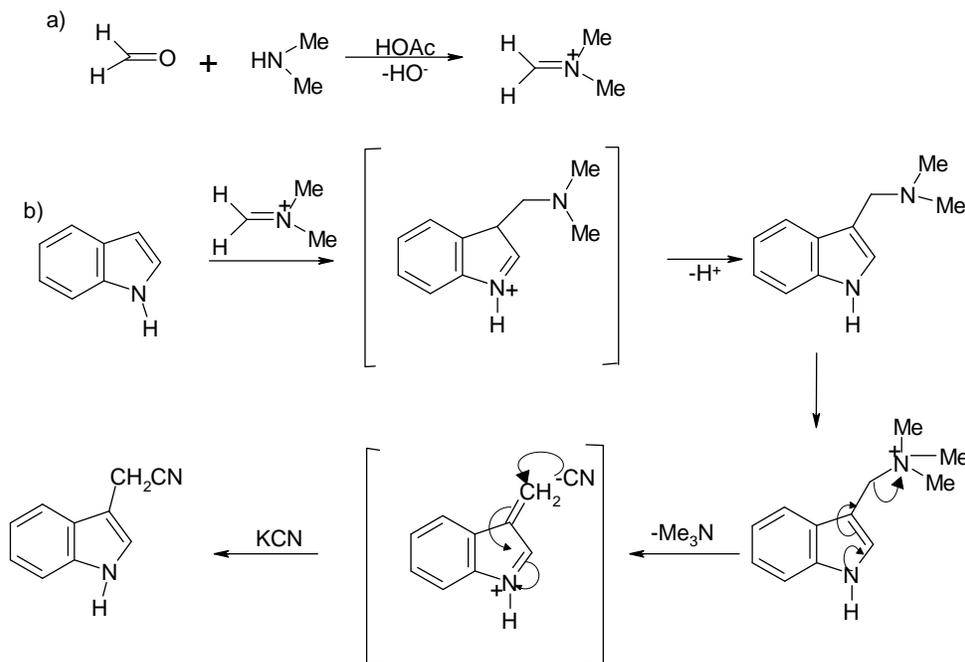

Scheme 27:   Mannish Reaction

3.2.5 Formation of the Indoyl Anion; N-1 versus C-3 Substitution

The indole anion is easily formed by reactions with bases such as sodium hydride, sodamide, Grignard reagents or alkyllithiums. Although the indolyl anion is resonance stabilised, the nature of the cation has an influence upon future reactions (as does the solvent used). Thus, if the conjugate cation is not easily polarised, e.g. a sodium ion (or potassium ion), the indolyl anion is attacked at the site of highest electron density, i.e. at N-1. However, if the metal in the cation is magnesium, then it is assumed that partial covalent bonding to nitrogen prevents attack there. Now the electrophilic attack is diverted to C-3.

N-Alkylation, -acylation and sulphonation are also promoted by a polar solvent, such as HMPA (hexamethylphosphoric triamide), DMF and DMSO. This acts to solvate the ions (promoting dissociation), but in a non-polar solvent like toluene, diethylether or tetrahydrofuran (THF), attack by most carbon electrophiles upon indolylmagnesium bromide proceeds at C-3 (Scheme 28).

E = alkyl, acyl
X = halide

E = alkyl, acyl, PhSO2
X = halide
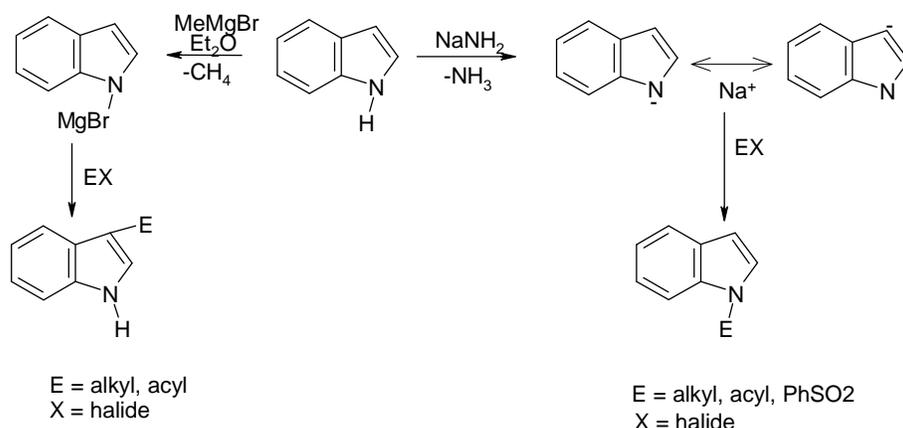
Scheme 28: N-1 versus C-3 Substitution

3.2.6 C-2 Lithiation

Carbon acidity and C-2 lithiation

After the N-H proton, the hydrogen at C-2 is the next most acidic proton on indole. Reaction of N-protected indoles with butyl lithium or lithium diisopropylamide results in lithiation exclusively at the C-2 position. This strong nucleophile can then be used as such with other electrophiles (Scheme 29).

Bergman and Venemalm developed a technique for lithiating the 2-position of unsubstituted indole.
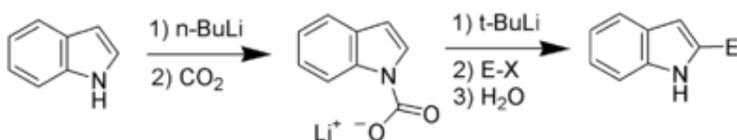
Scheme 29: C-2 Lithiation

3.3   Ring Expansion with Dichlorocarbene

Indole can be reacted with dichlorocarbene to yield 3-chloroquinoline (Scheme 30). Initially, the carbene adds across the C-2- C-3 double bond to form a cyclopropanoindole, this product then ring-expand with the elimination of hydrogen chloride.
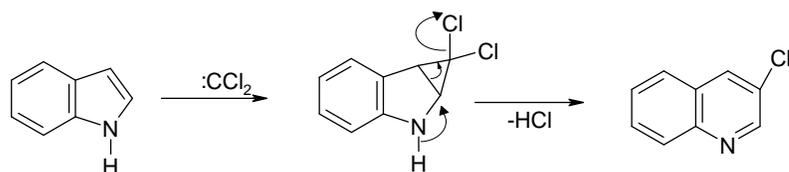
Scheme 30: Ring Expansion of the Indole Ring with Dichlorocarbene

3.4   Reduction

Indole can be reduced under Birch conditions (lithium in liquid ammonia containing a hydrogen donor e.g. methanol) to give a 4:1 mixture of 4,7-di and 4,5,6,7-tetrahydroindoles (Scheme 31a). Sodium cyanoborohydride ($NaBH_3CN$) in acetic acid, however, forms indoline (2,3-dihydroindole). In this reduction, 3-protonation gives the indoleninium salt, which is then 'set-up' to undergo hydride transfer at C-2 from the boron reagent (Scheme 31b).
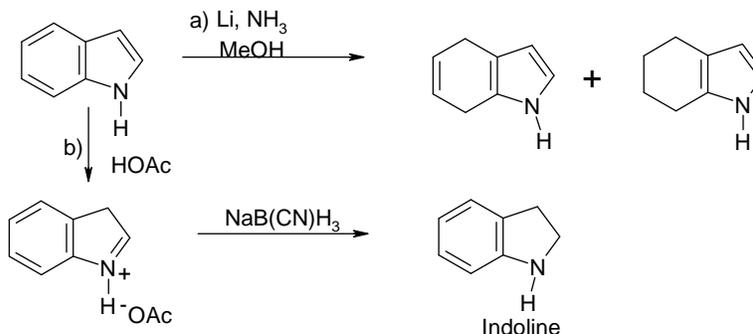
Scheme 31:   Reduction of Indole

3.5   Oxidation of Indole

Due to the electron-rich nature of indole, it is easily oxidised. Simple oxidants such as *N*-bromosuccinimide will selectively oxidise indole **1** to oxindole (**4** and **5**) (Scheme 32).
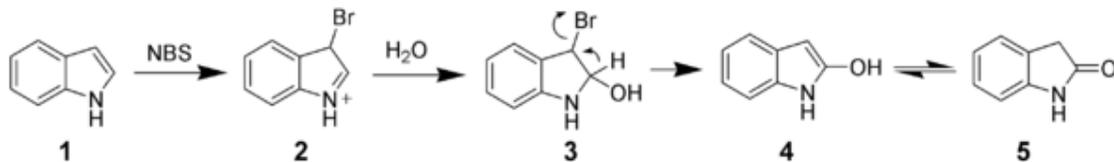
Scheme 32:   Oxidation of Indole

4.0   CONCLUSION

In this unit, we have learnt that the benzopyrrole (indole) ring is bicyclic consisting of the benzene ring fused to a pyrrole ring. We have also learnt that Indole undergo electrophilic substitution reactions, reduction and oxidation reactions.

5.0   SUMMARY

The highlights of this unit are as follows:

- Indole is a solid at room temperature and unlike most amines, it is non-basic.
- Very strong acids such as HCl are required to protonate indole.
- E-substitution reactions take place more readily at position 3 compared to position 2 in pyrrole.
- E-substitution at position 2 can be facilitated via C-2 Lithiation.
- Reduction of indole with lithium in liquid ammonia containing a hydrogen donor e.g. methanol takes place in the benzene ring while reduction with sodium cyanoborohydride ($NaBH_3CN$) takes place in the pyrrole ring.
- Indole can be oxidised to oxindole with N-bromosuccinimide.

6.0   TUTOR-MARKED ASSIGNMENT

1. Explain why electrophilic substitution on the indole ring is favoured at the C-3 position compared to C-2 in pyrrole.
2. Describe an indirect method that can be used to facilitate electrophilic substitution reaction on the indole ring at the C-2 position.
3. Outline the synthesis of 2-acetyl-1-(phenylsulfonyl)indole starting from indole.

7.0   REFERENCES/FURTHER READING

Olaniyi, A. A.; *et al.* (1998). *Essential Inorganic and Organic Pharmaceutical Chemistry.* Shaneson, C.I. Limited. pp. 363-450.

Sainsbury, M. (2001). Heterocyclic Chemistry. *Royal Society of Chemistry.* pp. 97-105.

UNIT 2   SYNTHESIS OF BENZOPYRROLE (INDOLE)

CONTENTS

1.0   INTRODUCTION

Indole is a major constituent of coal-tar, and the 220–260°C distillation fraction is the main industrial source of the material. Indole and its derivatives can also be synthesised by a variety of methods. The main industrial routes start from aniline. Other methods of synthesising indole include the Fischer Indole, the Reissert, Wender and the Leimgruber-Batcho synthesis.

2.0   OBJECTIVES

At the end of this unit, you should be able to:

- explain the synthesis of quinolines
- design synthesis of quinoline derivatives.

3.0   MAIN CONTENT

3.1   Industrial Synthesis of Indole

Illustrative of such large-scale syntheses, indole (and substituted derivatives) forms via vapour-phase reaction of aniline with ethylene glycol in the presence of catalysts (Scheme 33).
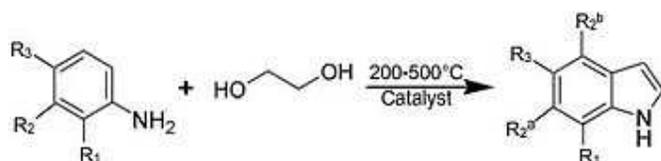
Scheme 33:   Industrial Synthesis of Indole

In general, synthesis is conducted between 200 and 500°C. Yields can be as high as 60%. Other precursors to indole include formyltoluidine, 2-ethylaniline, and 2-(2-nitrophenyl) ethanol, all of which undergo cyclisations. Many other methods have been developed that are applicable.

3.2   Fischer-Indole Synthesis

One of the oldest and most reliable methods for synthesising substituted indoles is the Fischer indole synthesis, developed in 1883 by Emil Fischer (Scheme 34). Although the synthesis of indole itself is problematic using the Fischer indole synthesis, it is often used to generate indoles substituted in the 2- and/or 3-positions. Indole can still be synthesised, however, using the Fischer indole synthesis by reacting phenylhydrazine with pyruvic acid followed by decarboxylation of the formed indole-2-carboxylic acid. This has also been accomplished in a one-pot synthesis using microwave irradiation
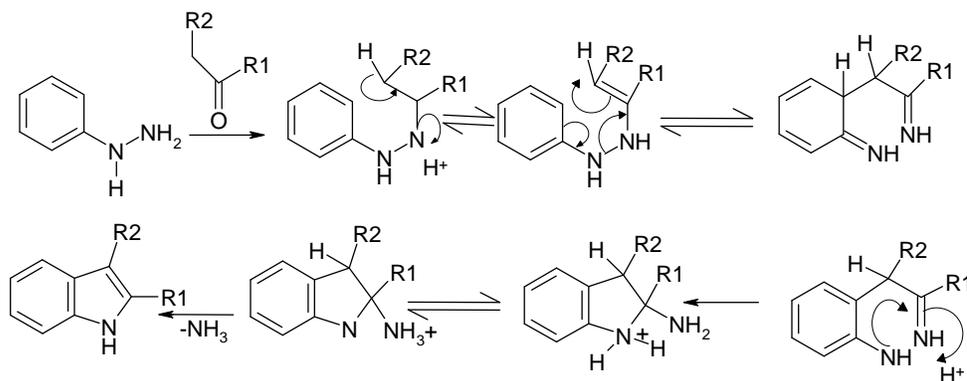
Scheme 34:   Fischer Indolisation Reaction

Phenylhydrazine is first reacted with an aldehyde, or ketone carrying α-methylene group (not acetaldehyde). The corresponding hydrazone is heated with an acid catalyst such as boron trifluoride, zinc chloride or polyphosphoric acid. The reaction is analogous to the benzidine rearrangement. Ring closure occurs through a [3,3]-sigmatropic change and ammonia (as the ammonium cation) is lost. For example, acetaphenone phenylhydrazone (R1-Ph, R2=H), treated with zinc

chloride at 170°C gives 2-phenylindole in up to 80% yield however, the reaction fails with acetaldehyde phenyl hydrazone (R1,R2 = H) so that indole itself must be made indirectly. A simple method is to carry out the Fischer reaction on the phenylhydrazone of pyruvic acid (R1 = COOH, R2 = H) and to decarboxylate the resulting indole-2-carboxylic acid thermally.

Substituent on the phenyl ring of the hydrazone influence the regiochemistry of the [3,3-rearrangement. For example, electron-releasing meta-substituents give mainly 6-substituted indoles (i.e. para ring closure) whereas electron-attracting substituents give mainly 4-substituted indoles (i.e. ortho ring closure).

3.3   The Reissert Synthesis

An o-nitrotoluene is reacted with diethyl oxalate in the presence of a base. The nitro group of the resulting α-keto-ester is reduced to amino and cyclisation then occurs spontaneously. The ester substituent in the indole may be removed, if required by hydrolysis and thermal decarboxylation (Scheme 35).
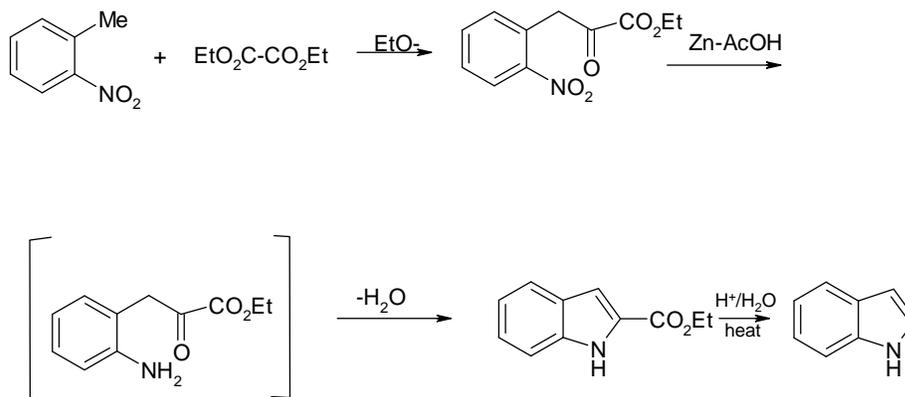
Scheme 34:   Reissert Synthesis

3.4   The Wender Synthesis

In this synthesis, 2-bromo-N-(trifluoroacetyl) aniline in THF is deprotonated by butyllithium and then in the same pot, reacted with tert-butyllithium to effect halogen metal exchange to give the dilithiated derivative. To this intermediate is added α-bromo ketone. A carbon-carbon bond is established first between the reactants, and then cyclisation occurs to form a hydroxyindoline. Finally, dehydration generates the indole (Scheme 36).
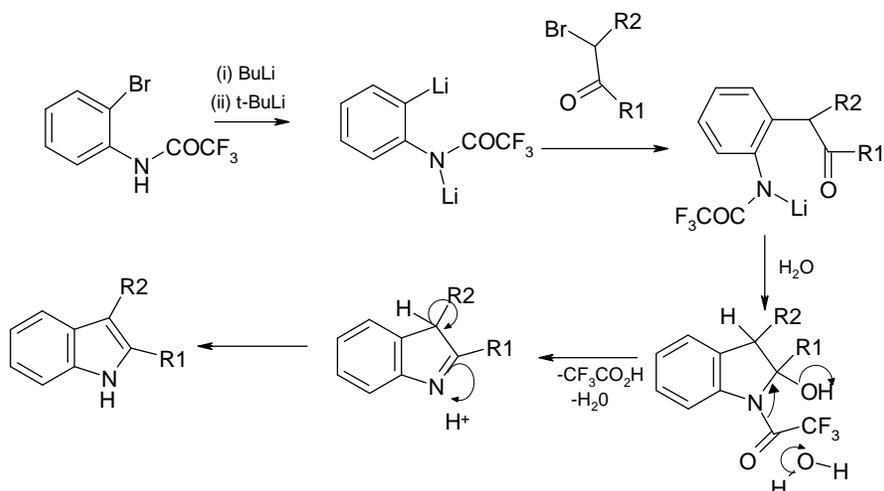
Scheme 36:   Wender Synthesis

3.5   Leimgruber-Batcho indole Synthesis
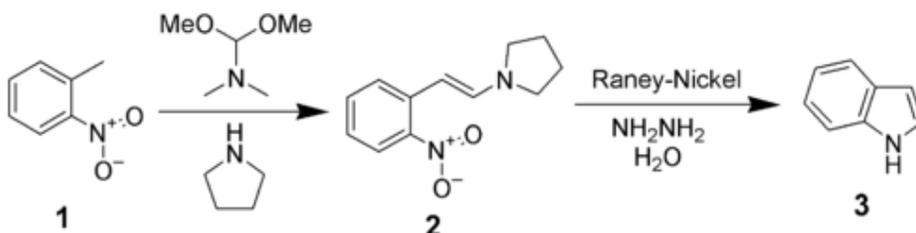
Scheme 37:   Leimgruber-Batcho Indole Synthesis

The Leimgruber-Batcho indole synthesis is an efficient method of sythesising indole and substituted indoles (Scheme 37). Originally disclosed in a patent in 1976, this method is high-yielding and can generate substituted indoles. This method is especially popular in the pharmaceutical industry, where many pharmaceutical drugs are made up of specifically substituted indoles. The method utilises o-nitrotoluene, which when heated in a mixture containing the base pyrrolidine and N,N-dimethylformamide dimethyl acetal (DMFDMA) gives the corresponding β-(N,N-dimethylaminophenylethene. Reduction of this product form the appropriate indole.

4.0   CONCLUSION

In this unit we have looked at the various methods used in the synthesis of indole and its derivatives. These methods normally start from nitrogen containing benzenoid compound.

7.0   SUMMARY

- Indole is a major constituent of coal tar and can be obtained from fractional distillation of coal tar.
- Indole is obtained on a large-scale by the vapour phase reaction of aniline with ethylene glycol in the presence of catalyst and at high temperatures.
- Fischer-Indole reaction involves the formation of a corresponding hydrazone from a phenylhydrazine and an aldehyde or ketone followed by treatment of the hydrazone with an acid.
- Reissert synthesis involves the reaction of o-nitrotoluene with diethyloxalate in the presence of a base followed by the reduction of the α-ketoester formed.
- Wender synthesis involves the reaction of 2-bromo-N-(trifluoroacetyl) aniline in THF with butyllithium followed by tert-butyllithium to yield the dilithiated derivative. Treatment with α-bromoketone gives the indole.
- Leimgruber-Batcho synthesis involves heating o-nitrotoluene with DMFDMA in pyridine to give β-N,N-dimethylaminophenylethene. Reduction of this product gives the indole.
- A variety of methods are used to synthesise indoles; the most versatile for indoles substituted in the benzene ring is still the Fischer indolisation process.
- The Leimgruber-Batcho synthesis is good for the synthesis of indoles unsubstituted in the heterocyclic ring.

8.0   TUTOR-MARKED ASSIGNMENT

1.   Outline the synthesis of 2-ethyl-3-methylindole using the Fischer Indole reaction.
2.   Explain the mechanism of reaction in (i)
3.   Outline a feasible route for the synthesis of serotonin

7.0   REFERENCES/FURTHER READING

Norman, R. O. C. & Coxon, J. M. (1993). Principles of Organic Synthesis (3rd ed.). *Blackie Academic & Professional, Glasgow*. An Imprint of Chapman & Hall. pp. 703-706.

Olaniyi, A. A.; *et al*. (1998). *Essential Inorganic and Organic Pharmaceutical Chemistry*. Shaneson, C.I. Limited. pp. 363-450.

Sainsbury, M. (2001). Heterocyclic Chemistry. *Royal Society of Chemistry*. pp. 42-49.

UNIT 3   APPLICATION OF INDOLE IN DRUG SYNTHESIS

CONTENTS

1.0   Introduction
3.0   Objectives
3.0   Main Content
        3.1   Indomethacin
        3.2   Vinca Alkaloids
        3.3   Other Applications of Indole
4.0   Conclusion
5.0   Summary
6.0   Tutor-Marked Assignment
7.0   References/Further Reading

1.0   INTRODUCTION

Indole is the parent of a very large number of alkaloids and medicinally important compounds. The indole ring system is found in Indomethacin (anti-inflammatory agent) vinca alkaloids, used in the treatment of various cancers, reserpine (an antihypertensive agent), serotonin (a neurotransmitter) and tryptophan (an essential amino acid) to mention but few.

2.0   OBJECTIVES

At the end of this unit, you should be able to:

•   state the importance of the indole nucleus in medicine
•   trace the synthetic route of some of these indole containing medicinal agents
•   design the synthesis of some of the medicinal agents containing indole nucleus.

3.0   MAIN CONTENT

3.1   Indomethacin

Indomethaciun is a non-steroidal anti-inflammatory drug (NSAID) discovered in 1963. It is a non-selective inhibitor of cyclooxygenase 1 and 2 (COX1 and COX2) enzymes that participate in biosynthesis of prostaglandins from arachidonic acid. Prostaglandins are hormone-like molecules which have a wide variety of effects, some of which lead to pain, fever and inflammation. It is commonly used to reduce <u>fever</u>, <u>pain</u>, stiffness, and <u>swelling</u>. It is marketed under many trade names,

including **Indocin**, **Indocid**, **Indochron E-R**, and **Indocin-SR**. Indomethacin can be synthesised using the Fischer indole synthesis (Scheme 38).
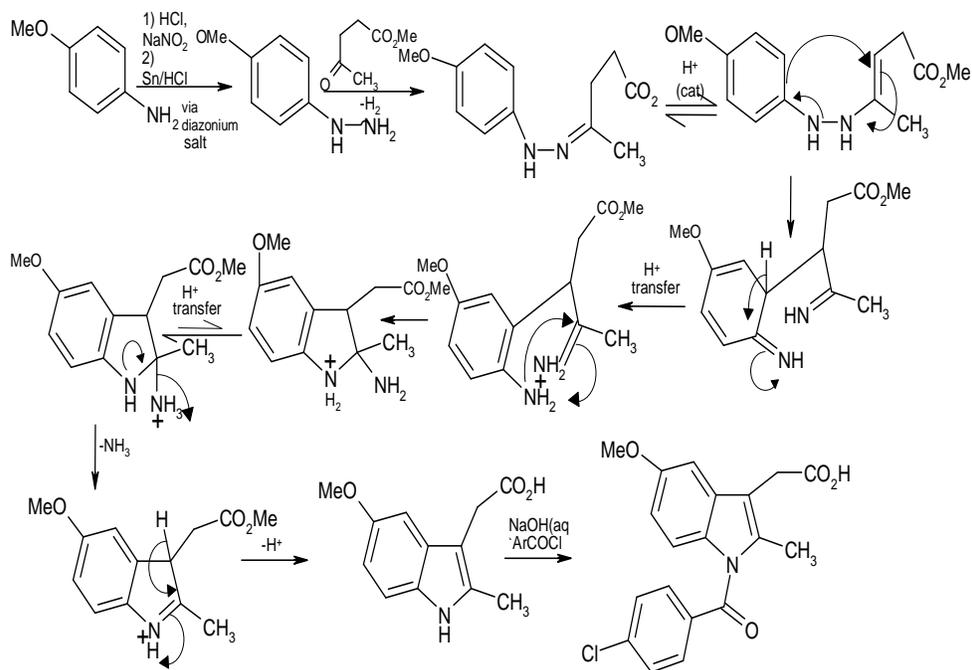
Scheme 38:   Synthesis of Indomethacin

3.2   Vinca Alkaloids

Serotonin or **5-hydroxytryptamine (5-HT)** (Figure 10) is a monoamine neurotransmitter. Biochemically derived from tryptophan, serotonin is primarily found in the gastrointestinal (GI) tract, platelets, and in the central nervous system (CNS) of animals including humans. It is a well-known contributor to feelings of well-being; therefore it is also known as a "happiness hormone" despite not being a hormone.

Approximately 80% of the human body's total serotonin is located in the enterochromaffin cells in the gut, where it is used to regulate intestinal movements. The remainder is synthesised in serotonergic neurons in the CNS where it has various functions. These include the regulation of mood, appetite, sleep, as well as muscle contraction. Serotonin also has some cognitive functions, including memory and learning. Modulation of serotonin at synapses is thought to be a major action of several classes of pharmacological antidepressants.

Tryptophan (L-Trp or D-Trp; sold for medical use as **Tryptan**) is one of the 20 <u>standard amino acids</u>, as well as an <u>essential amino acid</u> in the <u>human</u> diet. It is encoded in the standard <u>genetic code</u> as the <u>codon</u> *UGG*. Only the L-<u>stereoisomer</u> of tryptophan is used in <u>structural</u> or <u>enzyme</u> proteins, but the D-<u>stereoisomer</u> is occasionally found in naturally produced <u>peptides</u> (for example, the marine venom <u>peptide</u> <u>contryphan</u>). The distinguishing structural characteristic of tryptophan is that it contains an <u>indole</u> functional group. It is an essential amino acid as demonstrated by its growth effects on <u>rats</u>.

For many organisms (including humans), tryptophan is an essential amino acid. This means that it cannot be synthesised by the organism and therefore must be part of its diet. Amino acids, including tryptophan, act as building blocks in protein biosynthesis. In addition, tryptophan functions as a biochemical precursor for the following compounds (see also Figure10).

Serotonin (a neurotransmitter), synthesised via tryptophan hydroxylase. Serotonin, in turn, can be converted to melatonin (a neurohormone), via N-acetyltransferase and 5-hydroxyindole-O-methyltransferase activities. Niacin is synthesised from tryptophan via kynurenine and quinolinic acids as key biosynthetic intermediates.

Auxin (a phytohormone) when sieve tube elements undergo apoptosis tryptophan is converted to auxins.

The disorders fructose malabsorption and lactose intolerance cause improper absorption of tryptophan in the intestine, reduced levels of tryptophan in the blood and depression.

3.3   Other Applications of Indole

Other indoles of biological importance include tryptophan which is the precursor of two hormones; serotonin, a vasoconstrictor, and melatonin (Figure 10), which is involved in the control of circadian rhythm. In addition the amino acid tryptophan is an essential component of proteins and anxin (Indole-3-acetic acid) is a plant hormone that co-ordinates many growth and behavioural processed in the life of a plant. Others include, ergot alkaloids, reserpine and vinca alkaloids.
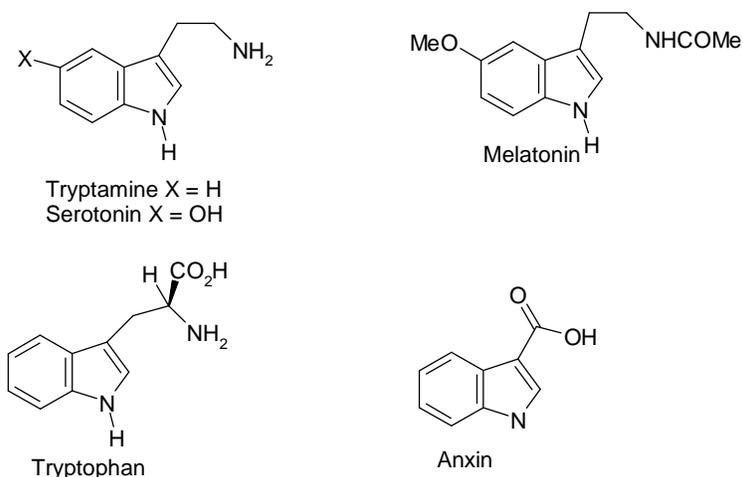
Fig. 10:   Some Important Derivatives of Indole

4.0   CONCLUSION

This unit has shown that indoles are important because their derivates exhibit useful biological activities. Some of these derivatives like the vinca alkaloids are used in the treatment of various cancers.

7.0   SUMMARY

- There are various indole derivatives that are of medicinal importance
- Indomethacin is an anti-inflammatory agent that can be synthesised via the Fischer Indole method.
- Serotonin a monoamine oxidase neurotransmitter is an indole derivative.
- Tryptophan, an essential amino acid is an indole derivative.
- The vinca alkaloids such as Vincristine, Vinorelbine from *Catharanthus roseus* contain the indole nucleus and these are potent anticancer agents.
- Other indole derivatives that are biologically active include reserpine, melatonin and tryptamine.

8.0 TUTOR-MARKED ASSIGNMENT

1.   Write briefly on two indoles of medicinal importance. Include their chemical structures.
2.   Highlight the synthesis of indomethacin via the Fischer Indole synthesis.

7.0   REFERENCES/FURTHER READING

Norman, R. O. C. & Coxon, J. M. (1993). Principles of Organic Synthesis (3rd ed.). *Blackie Academic & Professional, Glasgow*. An Imprint of Chapman & Hall. pp. 703-706.

Olaniyi, A. A.; *et al.* (1998). *Essential Inorganic and Organic Pharmaceutical Chemistry*. Shaneson, C.I. Limited. pp. 363-450.

Sainsbury, M. (2001). Heterocyclic Chemistry. *Royal Society of Chemistry*. pp. 42-49.

UNIT 4   SYNTHESIS AND REACTIONS OF BENZOFURAN AND BENZOTHIOPHENE

CONTENTS

1.0   INTRODUCTION

Benzofuran is a heterocyclic compound consisting of fused benzene and furan ring. This colourless solid is a component of coal tar. Benzofuran is the "parent" of many related compounds with more complex structures. For example, psoralen is a benzofuran derivative that occurs in several plants. **Benzothiophene** A bicyclic aromatic heterocycle in which a benzene ring is fused to that of a thiophene molecule; with a molecular formula C_8H_6S and an odour similar to naphthalene (mothballs). It occurs naturally as a constituent of petroleum-related deposits such as lignite tar. Benzothiophene has no household use. It is used primarily in industry and research.

The aromaticity of benzothiophene makes it relatively stable, although as a heterocycle, it has reactive sites which allow for functionalisation.

2.0   OBJECTIVES

At the end of this unit, you should be able to:

- draw the structure of benzofuran and benzothiophene and identify compounds containing these structures
- state general physical and chemical properties of benzofuran and benzothiophene
- explain the effect of the fusion of a benzene ring upon the reactions of a five –membered parent heterocycle
- predict the chemistry of compounds containing the benzofuran or benzothiophene structure
- describe the syntheses of benzofuran and benzothiophene.

3.0   MAIN CONTENT

3.1   General Physical and Chemical Properties

The aromaticity of benzofuran is weaker than in indole and this ring is easily cleaved by reduction and oxidation. Electrophilic reagents tend to react with benzofuran at C-2 in preference to C-3 (Scheme 39), reflecting the reduced ability of the heteroatom to stabilise the intermediate for 3-substitution. Attack in the heterocycle is often accompanied by substitution in the benzenoid ring. Nitration with nitric acid in acetic acid gives mainly 2-nitrobenzofuran, plus the 4-,6-,7-isomers. When the reagent is N_2O_4 in benzene maintained at 10˚C, both 3- and 2- nitrofurans are formed in the ratio 4:1. Under Vilsmeier reaction conditions, benzofuran gives 2-formylbenzofuran in 40% yield. Chlorine or bromine add across the C=C bond of the furan ring giving 2,3-dihalo-2,3-dihydrobenzo-furans.Base-promoted ehydrohalogenation of the dihalides affords mixture of the corresponding 2-and 3-halobenzofurans.
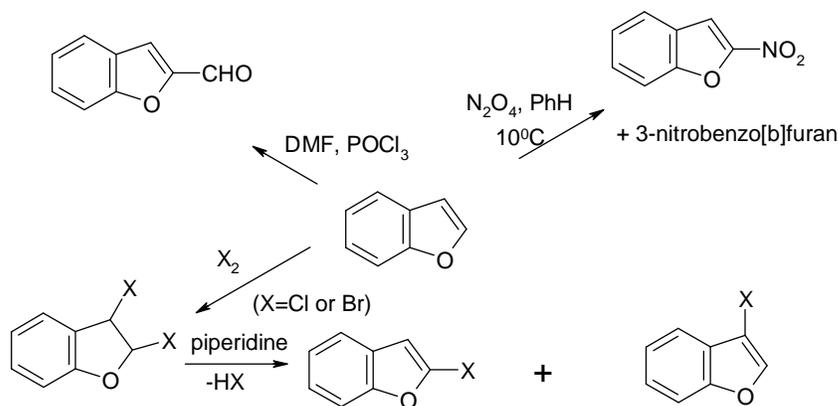
Scheme 39:   Reactions of Benzofuran

For benzothiophene the heterocycle is rather more resistant to ring opening and oxidation with hydrogen peroxide in acetic acid at 95˚C, for example, gives the 1,1-dioxide. Reduction with either sodium and ethanol or triethylsilane in trifluoroacetic acid affords 2,3-dihydrobenzothiophene. Electrophiles give mainly 3-substituted benzothiophenes, although these products are often accompanied by smaller amounts of the 2-isomers (Scheme 40).
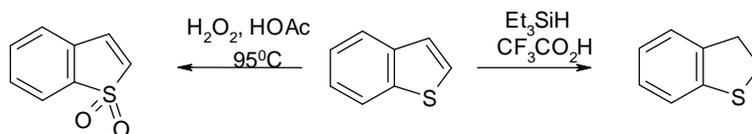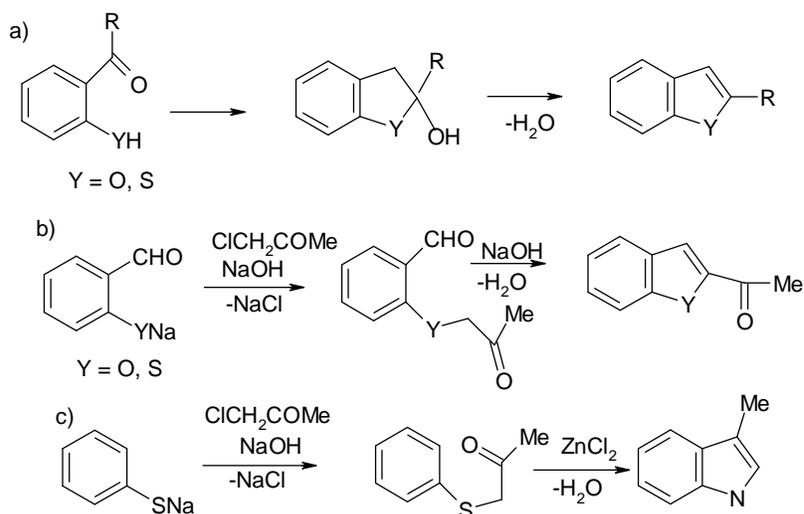
Scheme 40:   Reactions of Benzothiophene

3.2   Synthesis of Benzofurans and Benzothiophenes

A general route to both benzofurans and benzothiophenes depends upon the cyclodehydration of either 2-hydroxyl or 2-sulfanylbenzyl ketones or aldehydes (Scheme 41a). 2-Acetylbenzofuran can be obtained by reacting sodium salt of 2-formylphenolwith chloroacetone (chloropropanone) (Scheme 41b). A similar reaction using sodium 2-formylbenzenethiolate yields 2-acetylbenzothiophene.

3-Methylbenzothiophene is available through the interaction of sodium benzenethiolate and chloracetone, followed by the cyclisation of the initial product by the action of a Lewis acid, zinc chloride (Scheme 41c).

Scheme 41:   Synthesis of Benzofuran and Benzothiophene

4.0   CONCLUSION

In this unit, we have learnt that the benzofuran ring is bicyclic consisting of the benzene ring fused to a furan ring, while the benzothiophene ring consists of the benzene ring fused together to a thiophene. Benzothiophenes and Benzofurans mainly undergo electrophilic

substitution reactions. A general synthetic approach is via dehydration of 2-hydroxyl or 2-sulphanyl benzylketones or aldehydes.

5.0   SUMMARY

In this unit, you have learnt that benzofuran is a bicyclic heterocyclic compound consisting of fused benzene and furan ring. It is less aromatic compared to benzopyrrole and easily cleaved by reduction and oxidation. Benzothiophene is a bicyclic compound consisting of fused benzene and thiophen ring. It is oxidised to the 1,1-dioxide with hydrogen peroxide in acetic acid at 95°C and reduced to dihydrobenzothiophene with reducing agents.

You also learnt that electrophilic substitution reaction takes place at C-2 in benzofurans, while e-substitution reactions takes place at C-3 position in benzothiophenes. Chlorine and bromine add across the C=C bond of furan giving 2,3-dihalo-2,3-dihydrobenzo furans. Base promoted dehyrohalogenation of dihalides affords mixture of the corresponding 2 and 3-halobenzofurans. Synthesis depends on cyclodehydration of either 2-hydroxyl or 2-sulfanylbenzyl ketones or aldehydes.

Also the reaction of chloroacetone with the sodium salt of 2-formylphenol or 2-formylbenzene thiole yields 2-acetylbenzofuran and 2-acetylbenzothiophene respectively. Reaction of chloroacetone with sodium benzenethiolate followed by cyclisation of the initial product with a lewis acid ($ZnCl_2$) gives 3-Methylbenzothiophene.

6.0   TUTOR-MARKED ASSIGNMENT

1. Write an equation for the reaction of benzofuran with
2. nitric acid in acetic acid and
3. N_2O_4 in benzene at 10°C.
4. Write an equation for the reaction of benzofuran with chlorine.
5. What is the name given to this type of reaction?
6. What is the oxidation product obtained by oxidising thiophene with hydrogen peroxide in acetic acid at 95°C?
7. Outline the synthesis of:

a) benzofuran and
b) benzothiophene starting from a suitable aldehyde or ketone.

7.0   REFERENCES/FURTHER READING

Norman, R. O. C. & Coxon, J. M. (1993). Principles of Organic Synthesis (3rd ed.). *Blackie Academic & Professional, Glasgow.* An Imprint of Chapman & Hall. pp. 706-708.

Olaniyi, A. A.; *et al.* (1998). *Essential Inorganic and Organic Pharmaceutical Chemistry.* Shaneson, C.I. Limited. pp. 363-450.

Sainsbury, M. (2001). Heterocyclic Chemistry.   *Royal Society of Chemistry*. pp. 50-54.

UNIT 5   APPLICATIONS OF THE BENZOFURAN AND BENZOTHIOPHENE RING SYSTEM IN DRUG SYNTHESIS

CONTENTS

1.0   Introduction
3.0   Objectives
3.0   Main Content
      3.1   Amiodarone
      3.2   Sertaconazole
      3.3   Raloxifene
4.0   Conclusion
5.0   Summary
6.0   Tutor-Marked Assignment
7.0   References/Further Reading

1.0   INTRODUCTION

Being <u>heterocyclic</u> compounds, benzofuran and benzothiophene find use in research as starting materials for the synthesis of larger, usually bioactive structures. They are found within the chemical structures of pharmaceutical drugs such as amiodarone, <u>raloxifene</u>, <u>zileuton</u>, and <u>sertaconazole</u>. Benzothiophene is also used in the manufacturing of dyes such as thioindigo.

2.0   OBJECTIVES

At the end of this unit, you should be able to:

* explain how certain pharmacological active compounds are derived from benzofuran and benzothiophene structure
* state the importance of benzofuran and benzothiophene derivatives in medicine.

3.0   MAIN CONTENT

3.1   Amiodarone

Amiodarone (Figure 11) is an <u>antiarrhythmic agent</u> (medication used for irregular heart beat), used for various types of tachyarrhythmias (fast forms of irregular heart beat), both ventricular and supraventricular (atrial) arrhythmias. Discovered in 1961, it was not approved for use in the <u>United States</u> until 1985. Despite relatively common <u>side-effects</u>, it is used in arrhythmias that are otherwise difficult to treat with medication. Related newer compounds, such as <u>dronedarone</u> that contain

the benzofuran ring system, have lower <u>efficacy</u>. But they have reduced rate of side-effects. It contains the benzofuran ring system.
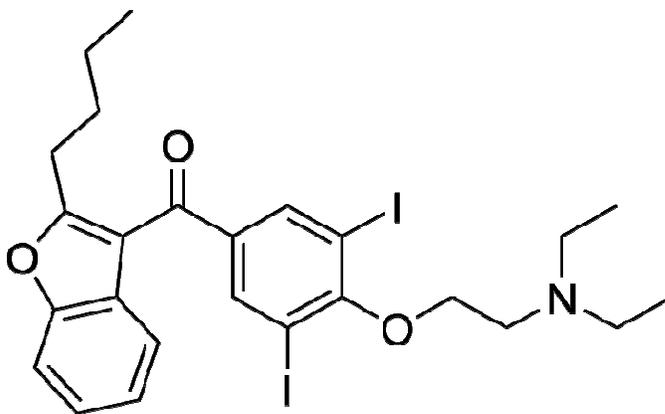

Fig. 11:   Structure of Amiodarone (2-{4-[(2-butyl-1-benzofuran-3-yl) carbonyl]-2,6-diiodophenoxy}ethyl)diethylamine

3.2   Sertaconazole

Sertaconazole nitrate (**Ertaczo**, Dermofix) is an antifungal medication of the <u>imidazole</u> class. It is available as a cream to treat skin <u>infections</u> such as <u>athlete's foot</u>. It contains the benzothiophene ring system.
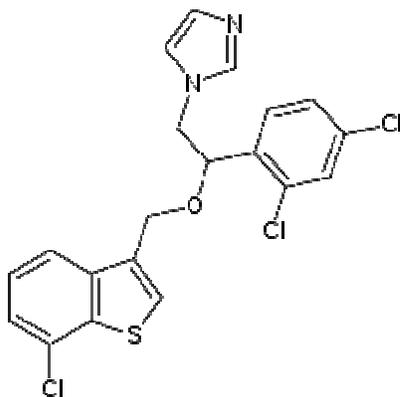

Fig. 12:   Setraconazole   (1-{2-[(7-chloro-1-benzothiophen-3-yl)methoxy]-2-(2,4-dichlorophenyl)ethyl}-1*H*-imidazole)

3.3   Raloxifene

Raloxifene (marketed as **Evista** by Eli Lilly and Company) is an oral selective estrogen receptor modulator (SERM) that has estrogenic actions on bone and anti-estrogenic actions on the uterus and breast. It is used in the prevention of osteoporosis in postmenopausal women.

In 2006, the National Cancer Institute announced that raloxifene was as effective as tamoxifen in reducing the incidence of breast cancer in postmenopausal women at increased risk. A major adverse effect of tamoxifen is uterine cancer; raloxifene had fewer uterine cancers. Tamoxifen increased the risk of cataracts, but raloxifene did not. Both groups had more blood clots in veins and the lungs, but that side effect was more common with tamoxifen than raloxifene. On September 14, 2007, the U.S. Food and Drug Administration announced approval of raloxifene for reducing the risk of invasive breast cancer in postmenopausal women with osteoporosis and in postmenopausal women at high risk for invasive breast cancer.

Raloxifene hydrochloride (HCl) has the empirical formula $C_{28}H_{27}NO_4S \cdot HCl$, which corresponds to a molecular weight of 510.05 g/mol. Raloxifene HCl is an off-white to pale-yellow solid that is slightly soluble in water. Its synthesis is shown in scheme 42.
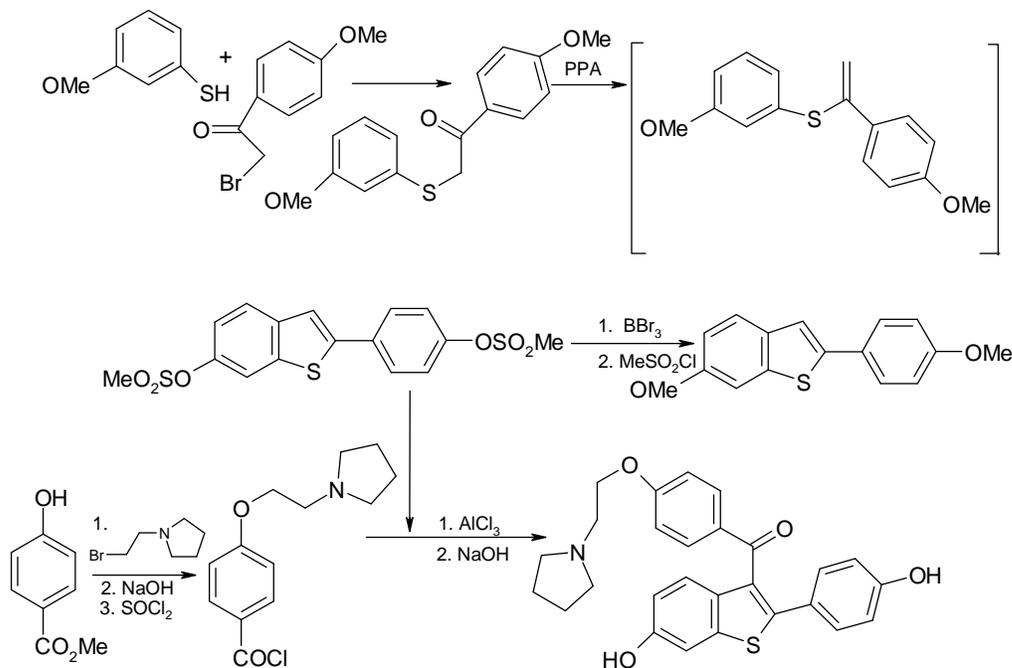
Scheme 42: Synthesis of Raloxifene

4.0   CONCLUSION

This unit has shown that benzofurans and benzothiophenes are important because their derivates exhibit useful biological activities though they are less common compared to benzopyrroles.

5.0   SUMMARY

- There are various benzofuran and benzothiophene derivatives that are of medicinal importance
- Amiodarone is an antiarrhythmic agent containing the benzofuran nucleus.
- Sertaconazole is an antifungal agent that is a derivative of benzothiophene.
- Raloxifene is used to treat invasive breast cancer in women with osteoporosis; it is a derivative of benzothiophene.
- Raloxifene is also used in the prevention of osteoporosis in postmenopausal women.

6.0   TUTOR-MARKED ASSIGNMENT

1. Outline the synthesis of raloxifene and write briefly on its medicinal use.
2. Mention two medicinal agents containing the benzothiophene structure. Draw the chemical structure of the compounds and mention their uses.
3. Give the name and structure of one medicinal agent containing the benzofuran structure. Mention its medicinal use.

7.0   REFERENCES/FURTHER READING

Olaniyi, A. A. (2005). *Essential Medicinal Chemistry* (3rd ed.). Ibadan, Nigeria: Hope Publications. pp.313-314.

Victor, V.; Constantino, V. & Wickerman, L. (2006). "Effects of Tamoxifen vs. Raloxifene on the Risk of Developing Invasive Breast Cancer and Other Disease Outcomes". *The Journal of the American Medical Association,* 295 (23), 2727–2741.

MODULE 3 DIBENZOPYRONES, PYRILIUM SALTS AND OTHER BENZOPYRONES

Unit 1 Synthesis and Reactions of Coumarins
Unit 2 Reactions of Chromones
Unit 3 Synthesis of Chromones
Unit 4 Synthesis and Reactions of Benzopyrilium and Dibenzopyrilium Salts
Unit 5 Applications of the Coumarins and Chromone Ring System in Drug Synthesis

UNIT 1 SYNTHESIS AND REACTIONS OF COUMARINS

CONTENTS

1.0 Introduction
2.0 Objectives
3.0 Main Content
    3.1 General Physical and Chemical Properties of Coumarins
        3.1.1 Reactions of Coumarins
    3.2 Synthesis of Coumarin
4.0 Conclusion
5.0 Summary
6.0 Tutor-Marked Assignment
7.0 References/Further Reading

1.0 INTRODUCTION

Benzopyrone may refer to either of two ketone derivatives of benzopyran which constitute the core skeleton of many flavonoid compounds:

- Chromone (1-benzopyran-4-one)
- Coumarin (1-benzopyran-2-one)

Coumarin (*2H*-chromen-2-one) is a pleasantly fragrant chemical compound (specifically, a benzopyrone) found in many plants, notably in high concentration in the tonka bean (*Dipteryx odorata*), vanilla grass (*Anthoxanthum odoratum*), sweet woodruff (*Galium odoratum*), mullein (*Verbascum* spp.), sweet grass (*Hierochloe odorata*), Cassia cinnamon (*Cinnamomum aromaticum*) and sweet clover. The name comes from a French word, *coumarou*, for the tonka bean.

Coumarin

Chromone

Fig. 13: Comparisons of the Structures of Coumarin and Chromone

2.0 OBJECTIVES

At the end of this unit, you should be able to:

* identify the coumarin structure
* state the physical and chemical properties of Coumarins
* predict the chemical reactions of a coumarin derivative
* explain the synthesis of coumarins.

3.0 MAIN CONTENT

3.1 General Physical and Chemical Properties of Coumarins

Coumarin has a sweet odour, readily recognised as the scent of newly-mown hay, and has been used in perfumes since 1882. Sweet woodruff, sweet grass and sweet clover in particular are named for their sweet smell, which is due to their high content of this substance. It has been used as aroma enhancer in pipe tobaccos and certain alcoholic drinks, although it is generally banned as a flavorant food additive, due to concerns about hepatotoxicity coumarin causes in animal models. In high concentrations in foods, coumarin is a somewhat bitter-tasting appetite suppressant, and is probably produced by plants as a defense chemical to discourage predation.

3.1.1 Reactions of Coumarins

Resonance within the unsaturated lactone unit of coumarin gives a strong hint as to its likely reactivity. Thus, the oxygen atom of the carbonyl group receives electron density both via the enone chromophore from the internal resonance of the lactone group (Figure 11).
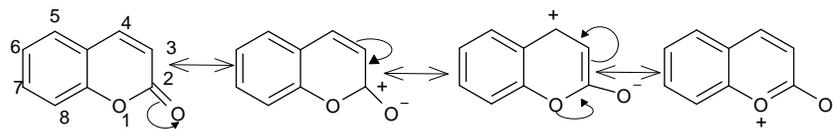

Fig. 14: Resonance structures of Coumarin

Nucleophilic addition occurs mainly at the carbon atom of the carbonyl group causing ring opening. Similarly, electrophilic reagents containing an element capable of forming a strong bond to oxygen (oxophiles) bind to the oxygen atom of the carbonyl group; thus silanes, for example, give 2-(o-silyl)benzopyrilium salts.

Other less oxophilic electrophiles give C-6 substituted coumarins, but it is unclear whether the substrate for such reactions is the free coumarin or a cation formed by protonation or bonded by a Lewis acid at the carbonyl oxygen. Some typical reactions are shown below (Scheme 43).
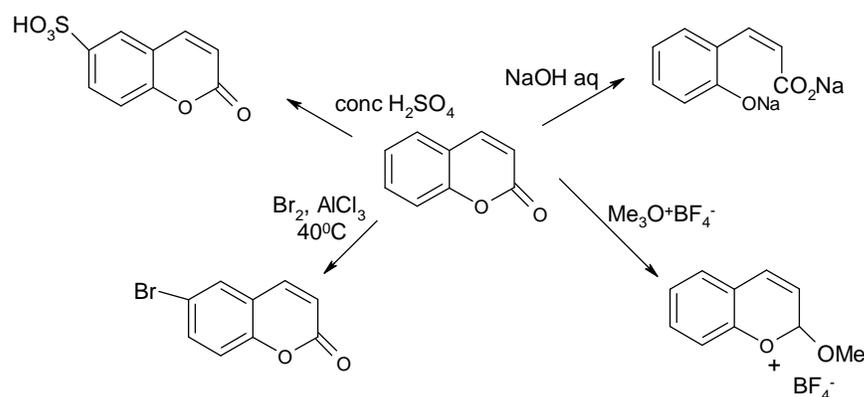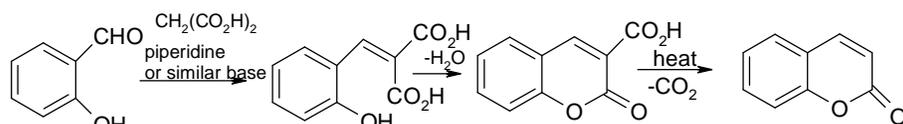

Scheme 43:   Some Reactions of Coumarin

In the presence of a Lewis acid e.g. $AlCl_3$, bromine reacts with coumarin to form 6-bromocoumarin, however in the absence of a lewis acids, bromine adds across the 3,4-double bond to give 3,4-dibromo-3,4-dihydrocoumarin. In the presence of pyridine a dehydrobromination reaction takes place, leading to 3-bromocoumarin as the favoured product.
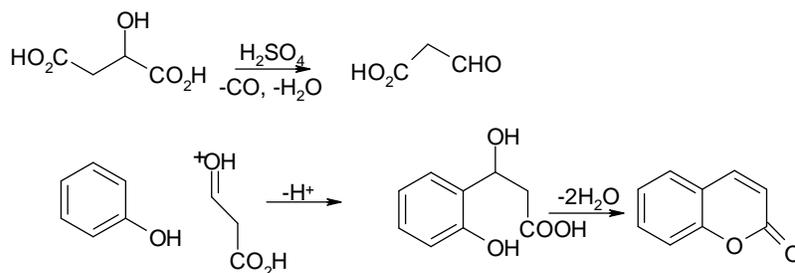
3.2   Synthesis of Coumarins

One approach is to use a 2-hdroxybenzaldehyde to form all but two atoms of the molecule. The remaining atoms are supplied by malonic acid (Propain-1,3-dioic acid), which combines with the aldehyde in a Knoevanagel condensation step, before cyclisation (lactonisation) and decarboxylation occur (Scheme 44).
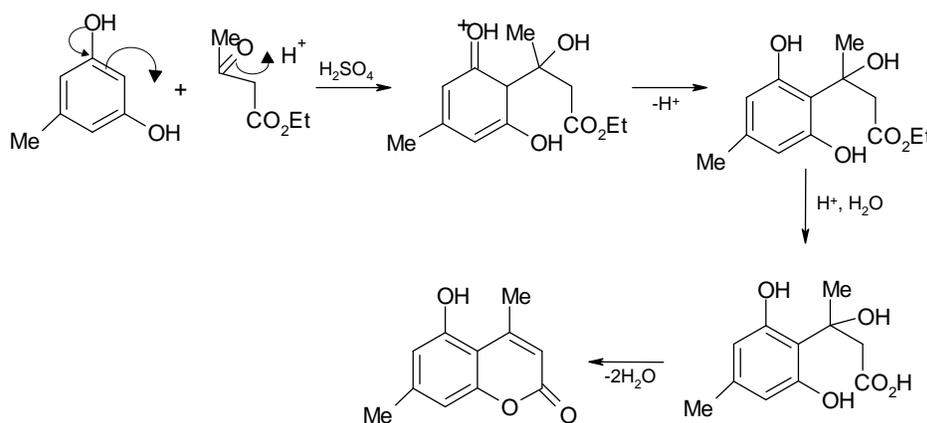

Scheme 44: Synthesis of Coumarin

Coumarins can also be synthesised by the von Pechmann reaction from Phenol, malic acid and concentrated sulphuric acid.

Scheme 45:   Synthesis of Coumarins by von Pechmann Reaction

4-Methylcoumarins bearing hydroxy and other electron-donating groups can be synthesised from the corresponding phenols by reaction with ethyl acetoacetate in the presence of sulphuric acid. Hydrolysis of the ester group in the product then allows the lactone ring of the coumarin to form (Scheme 46).

Scheme 46:   Synthesis of 4-Methylcoumarins

4.0   CONCLUSION

In this unit, you have learnt that coumarin is a bicyclic heterocyclic compound consisting of benzene fused to pyran-2-one. Coumarins undergo nucleophilic and electrophilic reactions; the product depends on the reagent used. Synthesis is from 2-hydroxybenzaldehyde and malonic acid or via the von Pechmann reaction from phenol, malic acid and conc sulphuric acid.

5.0   SUMMARY

The highlights of this unit are as follows:

- Coumarins are fused aromatic heterocycles consisting of benzene fused to pyran-2-one.
- Coumarins have a sweet smell and they are often used in perfumes, aroma enhancer in pipe tobaccos and certain alcoholic drinks.
- Nucleophilic addition reactions occur at C-2 of the carbonyl and results in ring opening.
- Electrophilic reaction takes place on the oxygen atom of the carbonyl group for strong oxophiles e.g. silane, however less oxophililc electrophiles give C-6 substituted coumarins.
- Halogenation in the presence of a lewis acid gives the C-6 substituted product while in the absence of a lewis acid, 3,4-addition products are obtained.
- In the presence of pyridine debromation of the 3,4-addition product occurs giving the 3-halogenated product.
- Synthesis is via the reaction of 2-hydroxybenzaldehyde and malonic acid (propane-1,3-dioic acid) in a Knoevenagel condensation step, followed by cyclisation and decarboxylation reactions.
- Reaction of Phenol, malic acid and conc Sulphuric acid also yields coumarin in the von Pechmann reaction.
- 4-Methylcoumarins can be synthesised from a corresponding phenol by reaction with ethyl acetoacetate in the presence of sulphuric acid, followed by hydrolysis of the ester formed.

6.0   TUTOR-MARKED ASSIGNMENT

1.   Suggest a possible mechanism for the conversion of coumarin into 3-bromocourmarin.
2.   Write the equation for the conversion of coumarin to 6-bromocoumarin.
3.   What is the product formed by reacting coumarin with NaOH?
4.   What is the name given to the reaction in iii?

7.0   REFERENCES/FURTHER READING

Norman, R. O. C. & Coxon, J. M. (1993). Principles of Organic Synthesis (3rd ed.). *Blackie Academic & Professional, Glasgow.* An Imprint of Chapman & Hall. pp. 711-712.

Olaniyi, A. A.; *et al.* (1998). *Essential Inorganic and Organic Pharmaceutical Chemistry.* Shaneson, C. I. Limited. pp. 363-450.

Sainsbury, M. (2001). Heterocyclic Chemistry. *Royal Society of Chemistry*. pp.70-72.

UNIT 2   REACTIONS OF CHROMONES

CONTENTS

1.0   Introduction
2.0   Objectives
5.0   Main Content
          3.1   General Chemical Reactions of Chromones
4.0   Conclusion
5.0   Summary
6.0   Tutor-Marked Assignment
7.0   References/Further Reading

1.0   INTRODUCTION

Chromone (or **1,4-benzopyrone**) is a derivative of benzopyran with a substituted keto group on the pyran ring. Derivatives of chromone are collectively known as *chromones*. Most, though not all, chromones are also phenylpropanoids.

2.0   OBJECTIVES

At the end of this unit, you should be able to:

• identify the chromone structure
• write at least two chemical reactions of chromones
• predict the chemical reactions of a chromone derivative.

3.0   MAIN CONTENT

3.1   General Chemical Reactions of Chromones

Chromones differ marginally in their chemistry from coumarins (benzopyran-2-ones) because the carbonyl group is now conjugated with the oxygen atom via the double bond of the heterocycle.   This conjuagation does not involve the benzene ring (Figure 15).

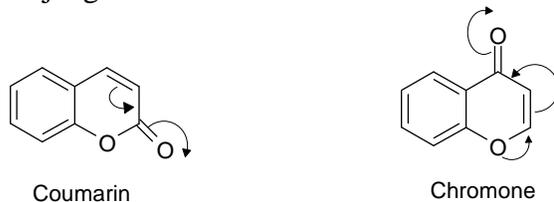Coumarin   Chromone

Fig. 15:   Chromone Conjugation

As a result, chromones are rather more basic, and strong acids readily protonate the carbonyl oxygen atoms, forming crystalline benzopyrilium salts. Once protonated, the molecule should be resistant to further electrophilic attack, but with fuming nitric acid and concentrated sulphuric acid at between 0˚C and room temperature, chromone gives the 6-nitro derivative (Scheme 47). Chromone also undergoes a Mannish-type reaction (Scheme 47) with dimethylamine and formaldehyde (methanal) in hydrogen chloride and ethanol; here the product is 3-(N-N-dimethylaminomethyl)chromone.
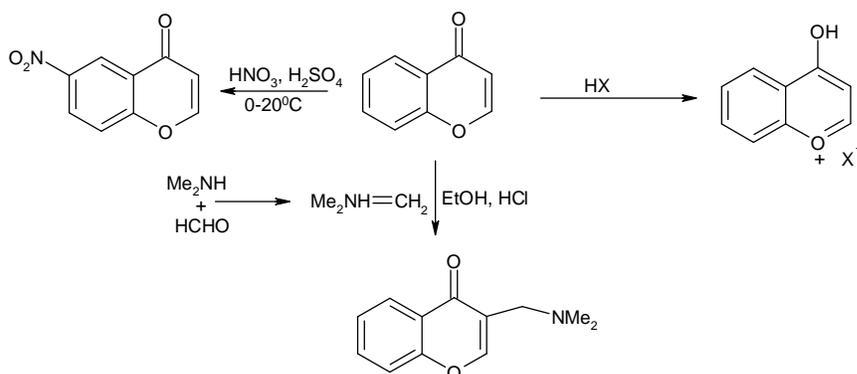
Scheme 47:   Reaction of Chromones

Relatively hard nucleophiles, such as Grignard reagents, may attack at the carbonyl carbon, whereas softer nucleophiles, e.g. hydroxide ion, combine at C-2 by conjugative addition, and this may then cause ring opening (Scheme 48).
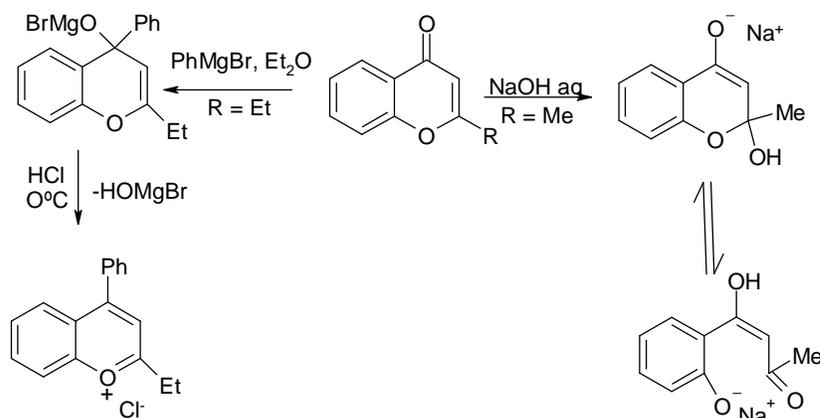
Scheme 48:   Reactions of Chromones with Nucleophiles

66

4.0 CONCLUSION

From this unit, you know that chromone is a bicyclic heterocyclic compound consisting of benzene fused to pyran-4-one. Moreover, it is now clear why the reactions of chromones differ from that of coumarins despite the similarities in their structures. Chromones undergo electrophilic substitution and nucleophilic addition reactions and forms salts with strong acids.

9.0 SUMMARY

- Indole is a major constituent of coal tar and can be obtained from Chromones are bicyclic heterocyclic compounds consisting of a benzene ring fused to a pyrane-4-one ring.
- The presence of a benzene unit fused to a pyrone ring affects the chemistry of both chromones and coumarins, but there are subtle differences in the reactivity of the two types of compounds.
- Chromones are more basic compared to coumarins so they are readily protonated to form benzopyrilium salts. Once protonated the molecule is resistant to further electrophilic attack.
- E-substitution with fuming nitric acid and concentrated sulphuric acid takes place at C-6.
- Reaction with strong nucleophiles such as Grignard reagents take place at position 2 to give the 2-substituted product, while softer nucleophiles attack at C-2 by conjugative addition followed by ring opening.

10.0 TUTOR-MARKED ASSIGNMENT

1. What is the reaction product when chromone is reacted with EtMgBr?
2. Explain why chromone is more basic compared to coumarin.
3. How does chromone react with NaOH?
4. What is the product of the reaction of chromone with hydrochloric acid?

7.0 REFERENCES/FURTHER READING

Olaniyi, A. A.; *et al*. (1998). *Essential Inorganic and Organic Pharmaceutical Chemistry.* Shaneson, C.I. Limited. pp. 363-450.

Sainsbury, M. (2001). Heterocyclic Chemistry. *Royal Society of Chemistry.* pp. 42-49.

UNIT 3   SYNTHESIS OF CHROMONES

CONTENTS

1.0   INTRODUCTION

Chromone is a parent member of a group of plant colouring pigments, the flavones (2-arylchromones), which are found both free and as glycosides. 2,3-substituted chromones can be synthesised from salicylic acid derivatives and from 2-hydroxyphenyl ketones. 3-substituted chromones can be synthesised via the condensation of the enolate of 2-hydroxyphenyl ketone and ethyl formate.

2.0   OBJECTIVES

At the end of this unit, you should be able to:

•   explain the synthesis of chromones
•   design the synthesis of some chromone derivatives

3.0   MAIN CONTENT

3.1   Synthesis of Chromones

Synthesis of 2- and 3- substituted chromones normally start from 2-hydroxyphenyl ketones. In the first of two examples, a route to flavone is shown in Scheme 49 using 2-hydroxyacetophenone (2-hydroxyphenylethanone) and benzoyl chloride as starting materials. Initially, the phenolic group of the acetophenone is O-acylated by benzoyl chloride, using pyridine as a base (a Schotten-Baumann type reaction). Under these conditions, the O-benzoyl derivative immediately enolises and is O-acylated again to yield a dibenzoate. Without isolation, this product is cyclised by treatment with aqueous potassium hydroxide to yield 2-hydroxy-2,3-dihydroflavone. Dehydration to flavone is then affected by the action of glacial acetic acid containing sulphuric acid.
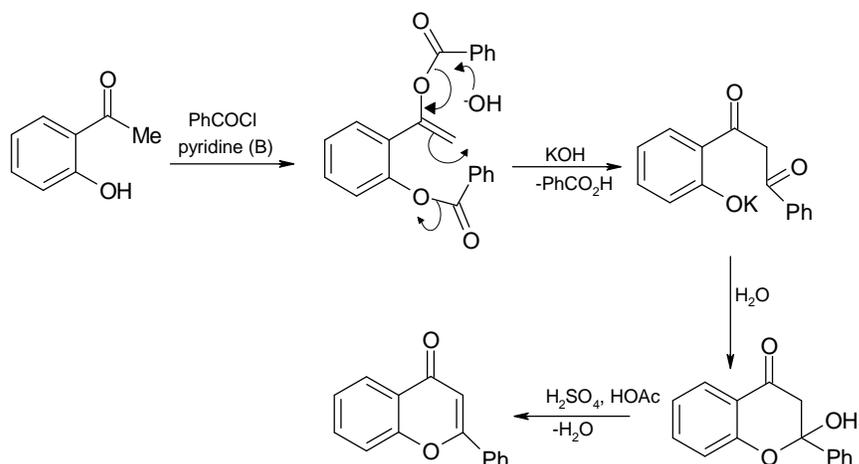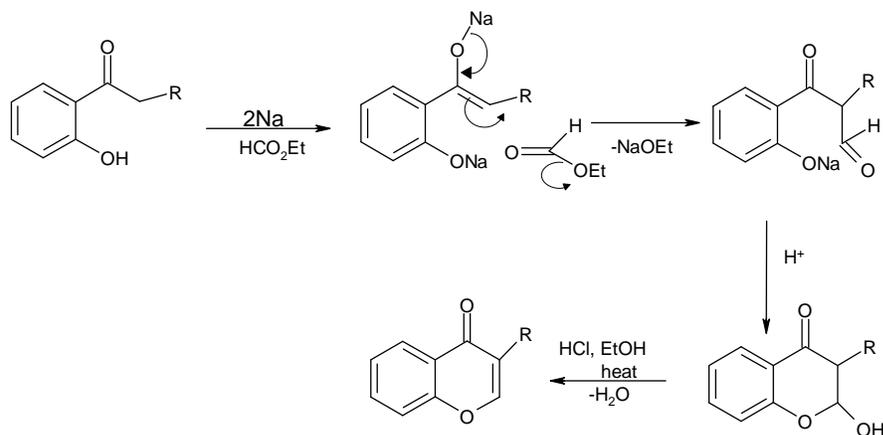
Scheme 49:   Synthesis of 2-substituted Chromones

2- substituted chromones can also be synthesised from salicylic acid derivatives (Scheme 50).
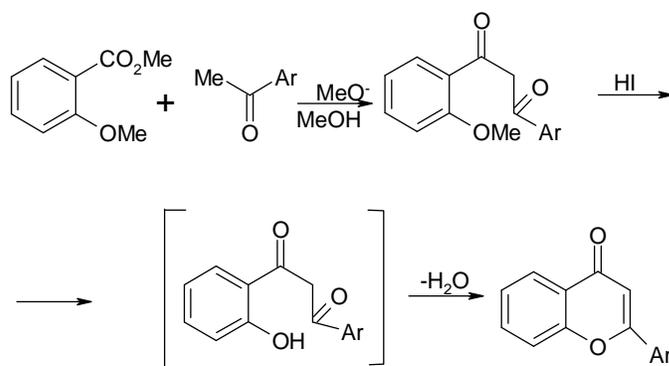
Scheme 50:   Synthesis of 2-substituted Chromones from Salicylic Acid
                Derivatives

A similar route to 3-substituted chromones and isoflavone (R=Ph) relies upon a Claisen-like condensation between the enolate of a 2-hydroxyphenyl ketone and ethyl formate (methanoate) (Scheme 51). This affords a 2-hydroxydihydrochromone that, as in the first example is subjected to an acid-promoted dehydration in the final step.

Scheme 51:   Synthesis of 3-substituted Chromones

4.0   CONCLUSION

In this unit, you have learnt how to synthesise 2- and 3-substituted chromones.

9.0   SUMMARY

- 2-substituted chromones can be synthesised from the reaction of 2-hydroxyphenylketones with suitable acid chloride.
- 2-substituted chromones can also be synthesised from salicylic acid derivatives with a suitable ketone.
- 3-substituted chromones and isoflavones can be synthesised via a Claisen-like condensation between the enolate of 2-hydroxyphenyl ketone and ethyl formate.

10.0   TUTOR-MARKED ASSIGNMENT

1. Devise a synthesis for 3-methylchromone and 3-phenylchromome (isoflavone).
2. Devise a synthesis for 2-methylchromone via 2-hydroxyphenylketone.

7.0   REFERENCES/FURTHER READING

Norman, R. O. C. & Coxon, J. M. (1993). Principles of Organic Synthesis (3rd ed.). *Blackie Academic & Professional, Glasgow*. An Imprint of Chapman & Hall. pp. 703-706.

Olaniyi, A. A.; *et al.* (1998). *Essential Inorganic and Organic Pharmaceutical Chemistry*. Shaneson, C.I. Limited. pp. 363-450.

Sainsbury, M. (2001). Heterocyclic Chemistry. *Royal Society of Chemistry*. pp. 42-49.

UNIT 4 SYNTHESIS AND REACTIONS OF BENZOPYRILIUM AND DIBENZOPYRILIUM SALTS

CONTENTS

1.0 INTRODUCTION

There are numerous examples of benzopyrilium salts, benzopyrones and benzopyranones and frequently they have trivial names that reflect their long history (Figure 16).
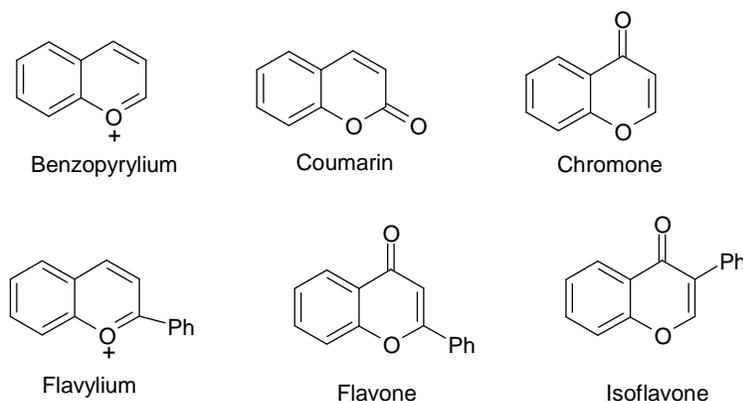

Fig. 16: Structures of Benzopyrilium Salts, Coumarins, Chromones and Flavonoids

Many natural products and frequently these compounds contain hydroxyl or alkoxy groups (sometimes in the form of a sugar residue). Polyhydroxylated natural products based upon 2-phenylbenzopyrilium (flavylium) salts and with ether linkages to sugars are called anthocyanins, whereas without their sugars they are known as anthocyanidins.

2.0   OBJECTIVES

At the end of this unit, you should be able to:

- design the structures of other benzopyrilium salts and dibenzopyrilium salts
- state the general properties of benzopyrilium salts
- describe how prylium salts can be synthesised
- describe how benzopyrilium salts and dibenzopyrilium salts are synthesised.

3.0   MAIN CONTENT

3.1   General Properties of Benzopyrilium Salts

Anthocyanins, in association with other compounds, such as flavones, are responsible for the colour of certain flowers. An anthocyanin found in rose petals is cyanin; it can be isolated as its chloride. The corresponding anthocyanidin, cyanidin, exists as the pentahydroxy salt in acidic media, but as the pH increases it gives first a quinone and then an anion. Each of these forms have different colours (Scheme 52).
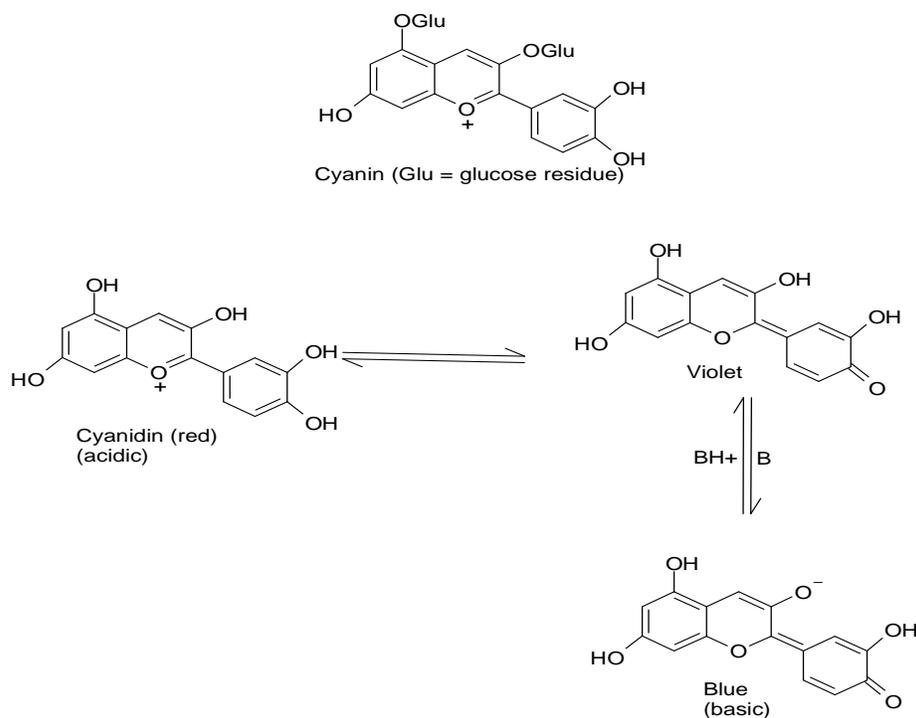

Scheme 52:   Effect of pH on Cyanidin

Other natural products in the group are built up by ring fusions of several types of ring systems. They include the garden insecticide rotenone (sometimes sold in crude form as derris powder, the pulverised bark of the plant *Derris elliptica*).
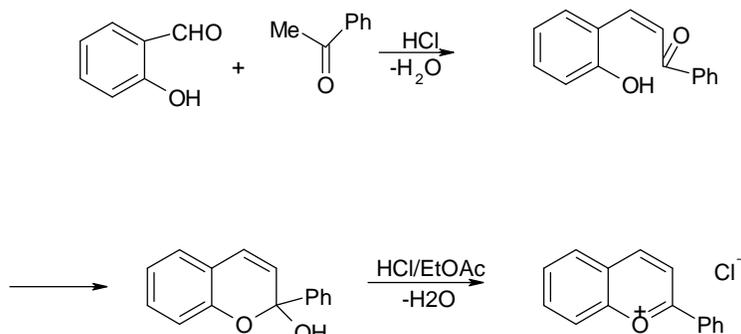
3.2   Synthesis of Pyrilium Salts

Salts of the type $R_3O^+X^-$ are normally unstable and cannot be isolated unless X^- is an especially stable (non-nucleophilic) anion such as BF_4^-. However, the oxonium salts derived by oxidation of the pyran nucleus are comparatively stable because the cation possesses aromatic stabilisation energy which is lost when an anion bonds covalently to it. The parent member of the series, the pyrilium ion is formed by acidification of the sodium salt of glutaconic aldehyde at low temperatures (Scheme 53).
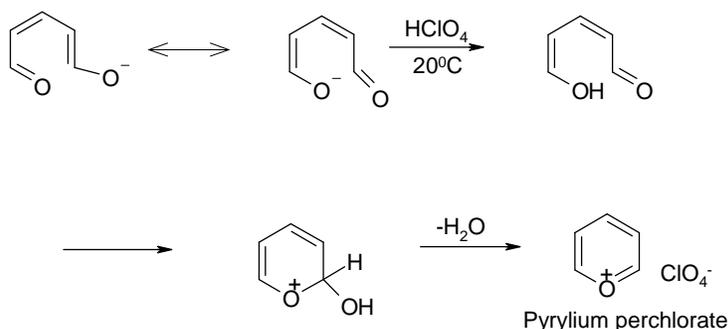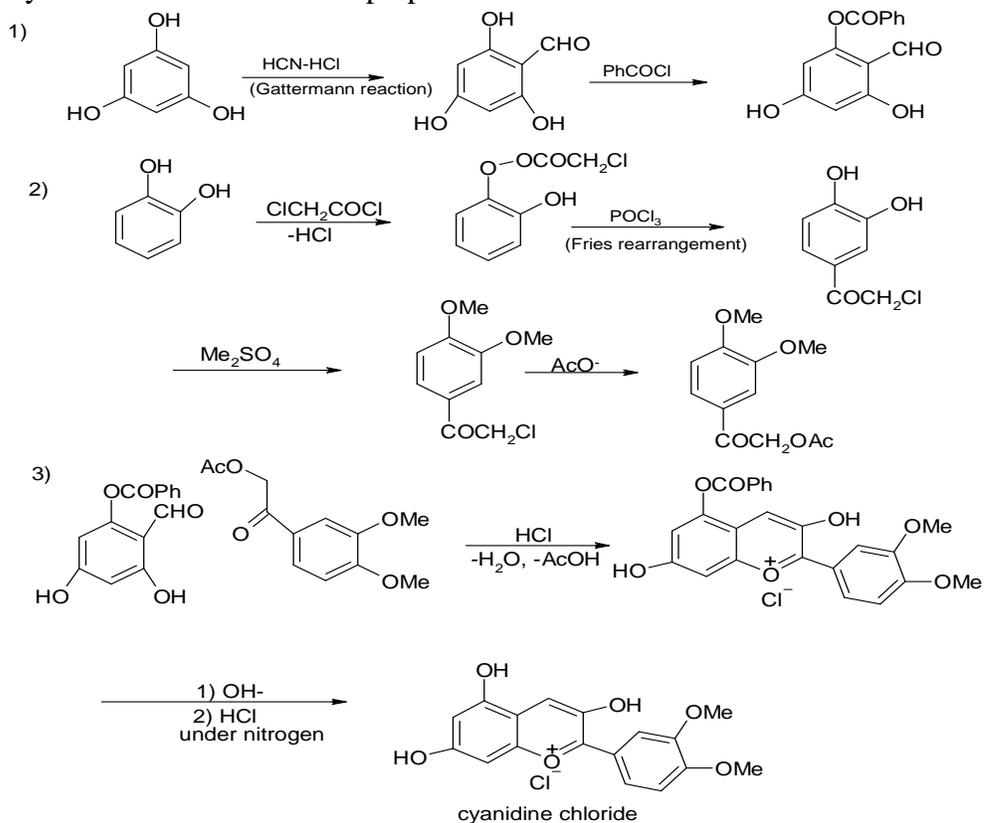

Scheme 53:   Synthesis of Pyrilium Salts

3.3   Synthesis of Anthocyanidin and Cyanidin Chloride

The glycosides of a number of 2-arylbenzopyrlium salts occur naturally as plant colouring matters, the anthocyanins. The parent salts, the anthocyanidins, are synthesised form salicylaldehydes and acetophenones by an acid-catalysed aldol reaction followed by ring closure in ethylacetate solution.
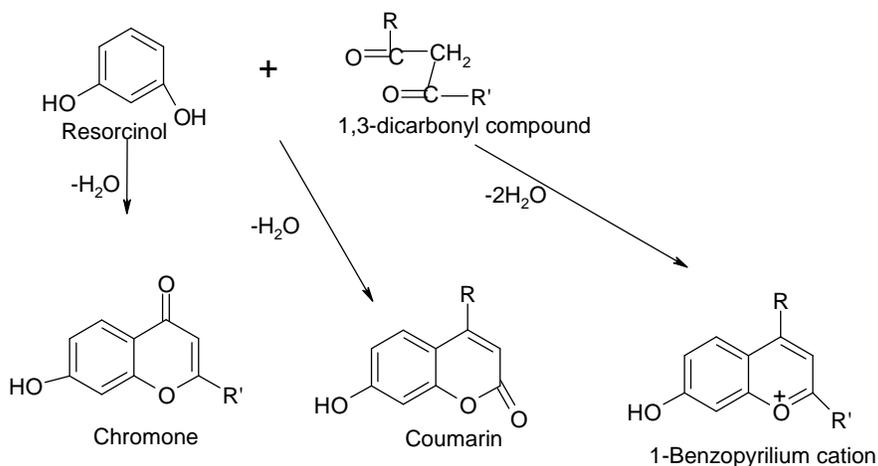

Scheme 54:   Synthesis of 2-arylbenzopyrlium Salts (anthocyanidins)

Cyanidin chloride has been prepared as follows:

1) HCN-HCl (Gattermann reaction) → PhCOCl →

2) ClCH₂COCl, -HCl → POCl₃ (Fries rearrangement) →

Me₂SO₄ → AcO⁻ →

3) HCl, -H₂O, -AcOH →

1) OH⁻
2) HCl under nitrogen →

cyanidine chloride

Scheme 55: Synthesis of Cyanidin Chloride

The general method of synthesis of the three ring systems is shown in Scheme 56 using phenols and 1,3-dicarbonyl compound as starting materials.

Resorcinol + 1,3-dicarbonyl compound

-H₂O → Chromone

-H₂O → Coumarin

-2H₂O → 1-Benzopyrilium cation

Scheme 56: General Methods of Synthesis of 2-Benzopyrilium Salts, Chromone and Coumarin

4.0   CONCLUSION

You will now be familiar with the structures of benzopyrilium salts and some 2-phenylbenzopyrilium salts such as anthocyanidins and cyanidine chloride. Synthesis of 2-phenylbenzopyrilium salts is usually via salicylaldehydes and acetophenones.

5.0   SUMMARY

- Polyhydroxylated natural products based upon 2-phenylbenzopyrilium (flavylium) salts and with ether linkages to sugars are called anthocyanins, whereas without their sugars they are known as anthocyanidins.
- Cyanidins change colour with pH, changing from red to blue as the pH increases.
- Pyrilium salts are normally unstable and cannot be isolated unless X$^-$ is an especially stable anion such as BF$_4^-$.
- The pyrilium ion is formed by acidification of the sodium salt of glutaconic aldehyde at low temperatures.
- Anthocyanidins are synthesised form salicylaldehydes and acetophenones by an acid-catalysed aldol reaction followed by ring closure in ethylacetate solution.
- 2-benzopyrilium cation, chromones and coumarins can also be synthesised using phenols and 1,3-dicarbonyl compounds as starting materials.

6.0   TUTOR-MARKED ASSIGNMENT

1.   Differentiate between the structures of benzopyrilium ion, courmarin and chromones.
2.   Differentiate between the structure of flavylium, flavones and isoflavone.
3.   Illustrate the effect of pH on cyanidin.
4.   Devise a synthesis for 2-phenylbenzopyrilium salt from salicylaldehyde and acetophenone.

7.0 REFERENCES/FURTHER READING

Norman, R. O. C. & Coxon, J. M. (1993). Principles of Organic Synthesis (3rd ed.). *Blackie Academic & Professional, Glasgow.* An Imprint of Chapman & Hall. pp. 706-708.

Olaniyi, A. A.; *et al.* (1998). *Essential Inorganic and Organic Pharmaceutical Chemistry.* Shaneson, C.I. Limited. pp. 363-450.

Sainsbury, M. (2001). Heterocyclic Chemistry. *Royal Society of Chemistry*. pp. 50-54.

UNIT 5   APPLICATIONS OF THE COUMARINS AND CHROMONE RING SYSTEM IN DRUG SYNTHESIS

CONTENTS

1.0   INTRODUCTION

Although coumarin has no anticoagulant activity, it is transformed into the natural anticoagulant dicoumarol by a number of species of fungi. This occurs as the result of the production of 4-hydroxycoumarin, then further (in the presence of naturally occurring formaldehyde) into the actual anticoagulant dicoumarol, a fermentation product and mycotoxin. This substance was responsible for the bleeding disease known historically as "sweet clover disease" in cattle eating moldy sweet clover silage.

Coumarin is used in the pharmaceutical industry as a precursor molecule in the synthesis of a number of synthetic anticoagulant pharmaceuticals similar to dicoumarol, notably warfarin (Coumadin) and some even more potent rodenticides that work by the same anticoagulant mechanism.

The drugs, cromolyn sodium (or cromolyn) and nedocromil, are commonly grouped together as chromones (also called cromoglycates). Strictly speaking, cromolyn is a chromone, whereas nedocromil belongs to the structural class of pyranoquinolines. Both agents contain a chromone ring configuration (one ring in nedocromil, two in cromolyn) and they share many clinical characteristics.

Cromolyn was first introduced in Great Britain in the early 1970s for severe allergic asthma. Since then, recommendations for its use have shifted to milder asthma, where the agent gained greater acceptance. The chromones are currently listed as alternate initial controller therapies for mild asthma in national and international guidelines, although inhaled glucocorticoids (also known as inhaled corticosteroids or ICS) are the

preferred agents. The low incidence of side effects compared to ICS is a leading reason some patients prefer chromones over ICS.

2.0 OBJECTIVES

At the end of this unit, you should be able to:

- list the importance of chromones and coumarins in medicines
- identify some biologically active compounds containing the chromones and coumarin derivatives.

3.0 MAIN CONTENT

3.1 Warfarin

Warfarin is a white crystalline compound, $C_{19}H_{16}O_4$, used as a rodenticide and as an anticoagulant. (Also known under the brand names **Coumadin**, **Jantoven**, **Marevan**, **Lawarin**, **Waran**, and **Warfant**) is an anticoagulant. It is most likely to be the drug popularly referred to as a "blood thinner," yet this is a misnomer, since it does not affect the thickness or viscosity of blood. Instead, it acts on the liver to decrease the quantity of a few key proteins in blood that allow blood to clot.

It was initially marketed as a pesticide against rats and mice and is still popular for this purpose, although more potent poisons such as brodifacoum have since been developed. A few years after its introduction, warfarin was found to be effective and relatively safe for preventing thrombosis and embolism (abnormal formation and migration of blood clots) in many disorders. It was approved for use as a medication in the early 1950s and has remained popular ever since; warfarin is the most widely prescribed anticoagulant drug in North America.

Despite its effectiveness, treatment with warfarin has several shortcomings. Many commonly used medications interact with warfarin, as do some foods (particularly fresh plant-based foods containing vitamin K), and its activity has to be monitored by blood testing for the international normalised ratio (INR) to ensure an adequate yet safe dose is taken.
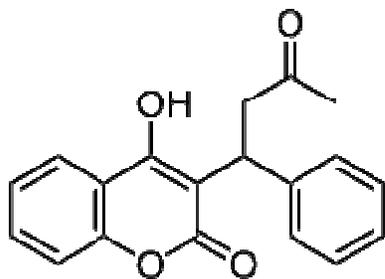
Fig. 17:   Structure of Warfarin

Warfarin is used to decrease the tendency for <u>thrombosis</u> or as secondary prophylaxis (prevention of further episodes) in those individuals that have already formed a blood clot (<u>thrombus</u>). Warfarin treatment can help prevent formation of future blood clots and help reduce the risk of <u>embolism</u> (migration of a thrombus to a spot where it blocks blood supply to a vital organ).
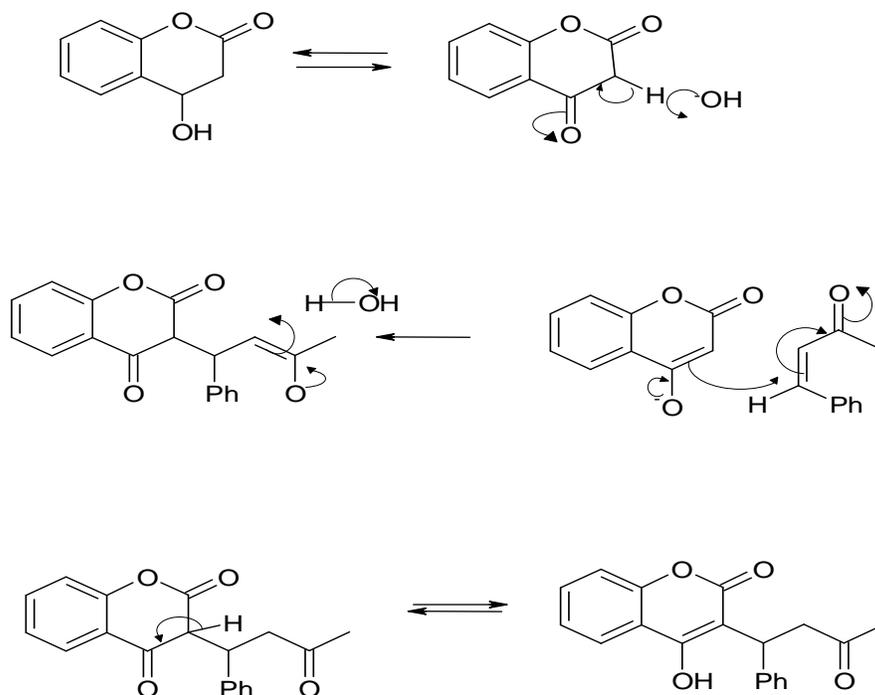
Racemic synthesis
A classic way of synthesising racemic warfarin is by the base (or acid) catalysed Michael condensation reaction of 4-hydroxycoumarin with benzalacetone either in water or piperidine.
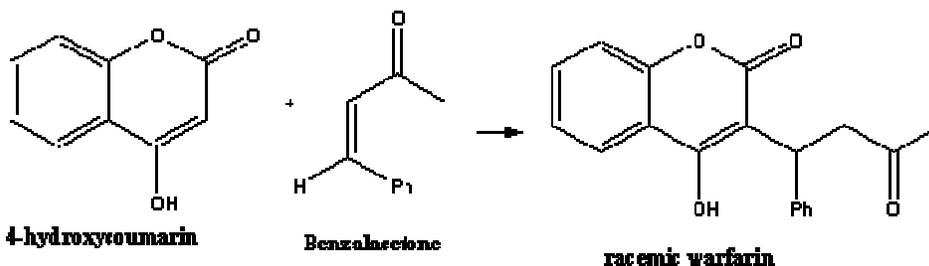
Scheme 57:   Synthesis of Racemic Warfarin

The mechanism for this reaction is as follows:

The yield for this synthesis when carried out in water (4-8 h reflux) is typically 40 %. Higher yields can be obtained by carrying out the reaction in methanol (20 h reflux), isolating the product formed and hydrolysing with acid. Typical yields are 93 %.

There has been increasing interest in the pharmaceutical industry to replace existing racemic drugs by their pure enantiomeric form due to the fact that one enantiomer often has a pharmacological profile superior to the racemate. In this case, S-warfarin is found to be 5 times more potent as an anticoagulant than R-warfarin. Preparation of enantiomerically pure warfarin can be made by the classical resolution of the racemate using quinidine/quinine salts or chromatographic separation. However, these methods are limited to small scale preparations.

1.   Asymmetric hydrogenation

In 1996, researchers at the Dupont Merck pharmaceutical company developed a practical asymmetric synthesis of R- and S- warfarin starting from the racemate and using DuPHOS-Rh(I) catalysed hydrogenation (Scheme 58).

Using this method, S-warfarin was obtained in 83% enantiomeric excess (e.e),   and   R-warfarin   in   86%   e.e

2.   Hetero-Diels-Alder cycloaddition

The previous synthesis used racemic warfarin as its starting material. A novel approach to asymmetric synthesis of warfarin using simpler starting materials was developed in 2001. It proceeds by a hetero-Diels-Alder cycloaddition (Scheme 59).
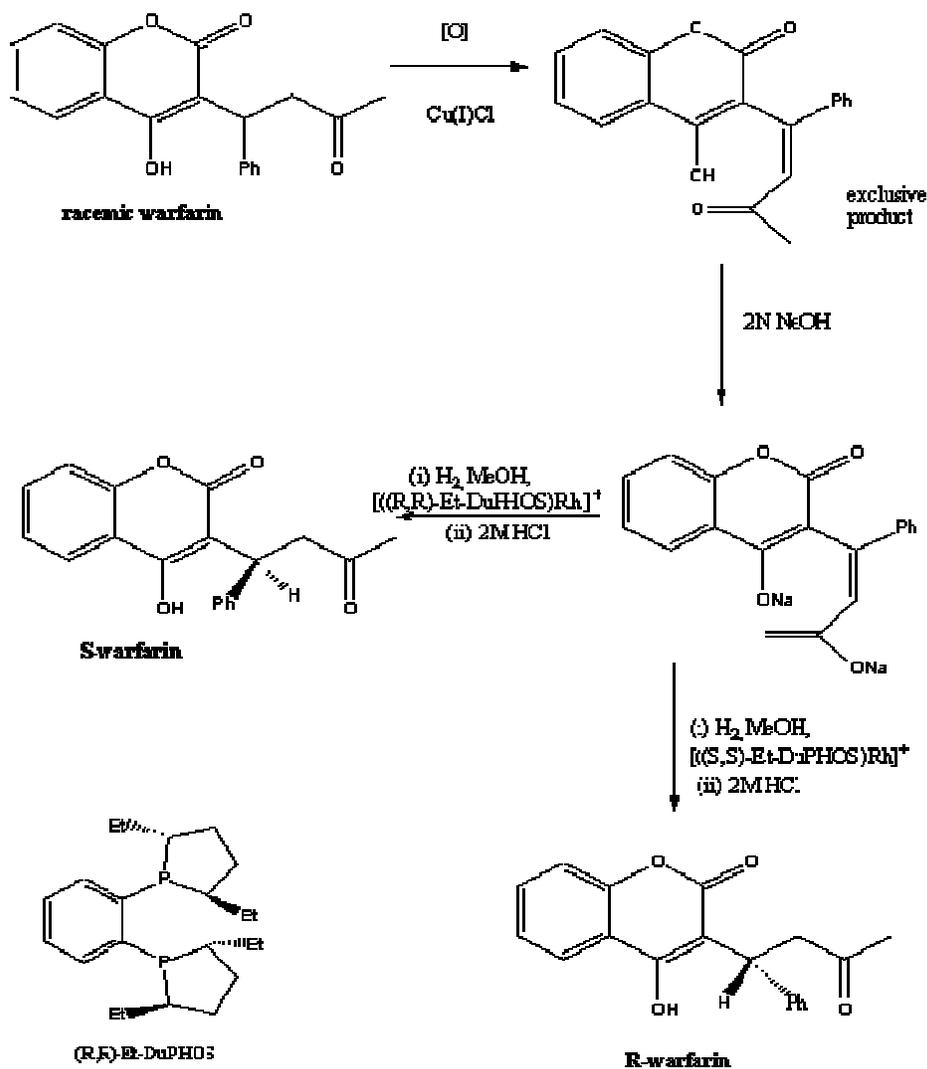
Scheme 58:   Asymmetric Synthesis of R- and S-Warfarin
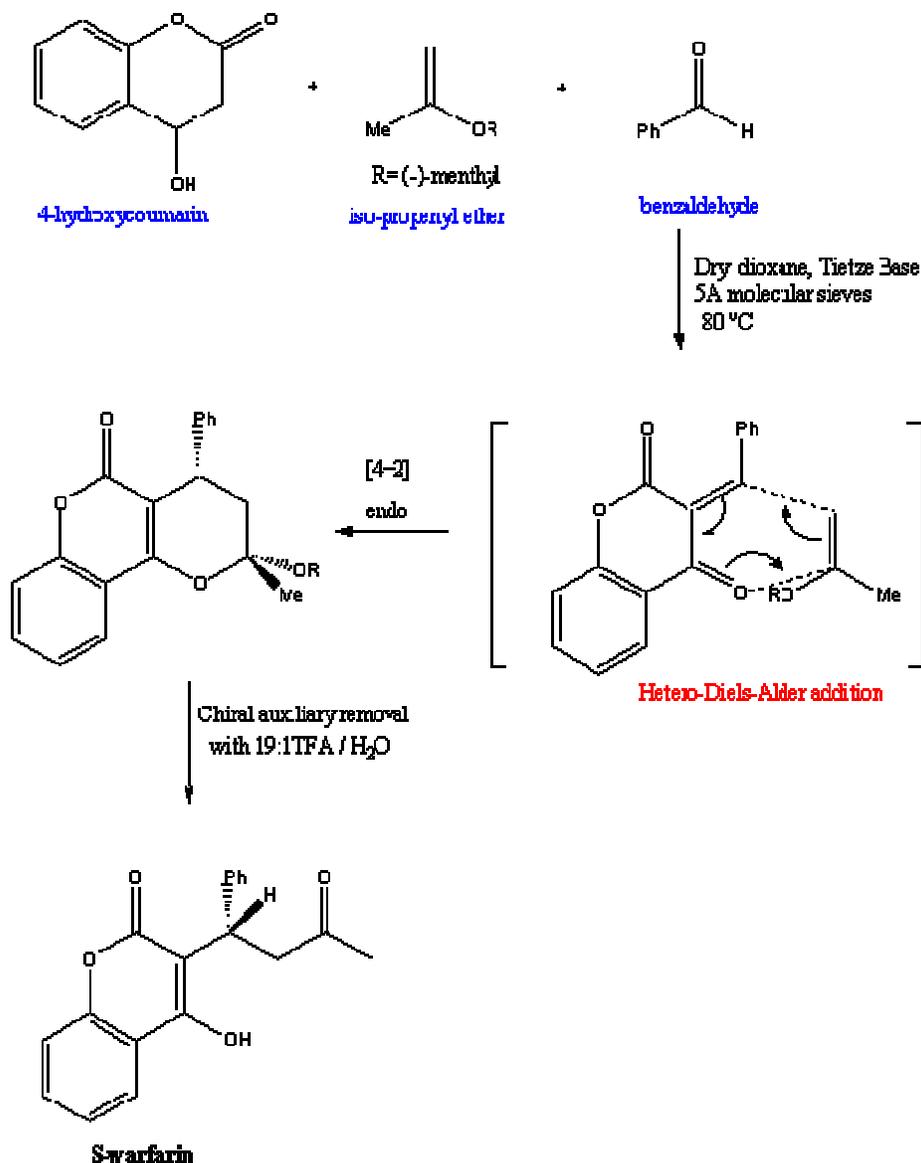
Scheme 59:   Asymmetric Synthesis of Warfarin by Hetero-Diels-Alder Cycloaddition

In this reaction, S-warfarin was obtained in 95 % e.e

3.2   Sodium Cromoglycate

Cromolyn, a synthetic compound, inhibits antigen-induced bronchospasms and, hence, is used to treat asthma and allergic rhinitis. Cromolyn is used as an ophthalmic solution to treat conjunctivitis and is taken orally to treat systemic mastocytosis and ulcerative colitis.

Cromolynn (<u>USAN</u>) (also referred to as **cromglicic** acid (<u>INN</u>), **cromoglycate** (former <u>BAN</u>), or **cromoglicate**) is traditionally described as a <u>mast cell stabiliser</u>, and is commonly marketed as the sodium salt **sodium cromoglicate** or **cromolyn sodium**. This drug prevents the release of <u>inflammatory</u> chemicals such as <u>histamine</u> from <u>mast cells</u>.

Because of their convenience (and perceived safety), <u>leukotriene receptor antagonists</u> have largely replaced it as the non-<u>corticosteroid</u> treatment of choice in the treatment of <u>asthma</u>. Cromoglicic acid requires administration four times daily, and does not provide additive benefit in combination with inhaled corticosteroids.
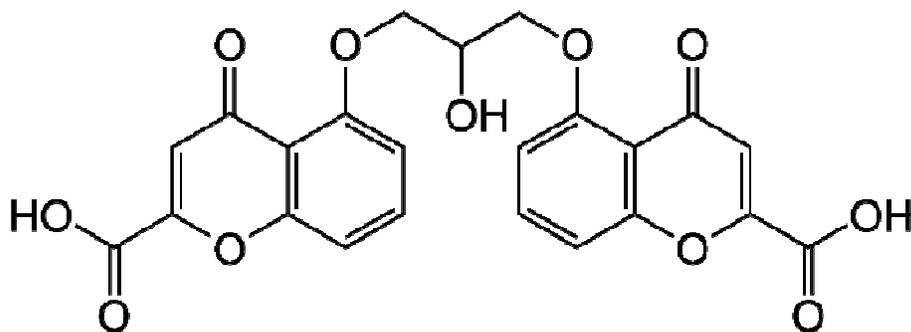

Fig. 18:   Sodium Cromoglycate (5,5′-(2-hydroxypropane-1,3-diyl)bis(oxy)bis(4-oxo-4*H*-chromene-2-carboxylic acid)

4.0   CONCLUSION

In this unit, you have learnt that courmarins are applicable in the synthesis of anticoagulants such as warfarin while chromones are applicable to the synthesis of cromoglycates.

5.0   SUMMARY

- Coumarins have important applications in the synthesis of anticoagulants such as warfarins though it has no anticoagulant activities in itself.
- Racemic warfarin can be prepared by catalysed Michael condensation reaction of 4-hydroxycoumarin with benzalactone in water or piperidine.
- S-warfarin is found to be 5 times more potent as an anticoagulant than R-warfarin.
- Enantiomerically pure warfarin can be prepared by classical relution of the racemic using quinidine/quinine salts or by chromatographic separation.

- A novel approach to the asymmetric synthesis of warfarin proceeds by hetero-Diels-Alder cycloaddition.
- Chromones have important applications in the synthesis of cromoglycates and nedocromil, used in the treatment of asthma and allergic rhinitis.

6.0   TUTOR-MARKED ASSIGNMENT

1. Highlight the synthesis of racemic warfarin from 4-hydroxycoumarin.
2. Suggest two methods for the asymmetric synthesis of warfarin.
3. What is the medicinal use of warfarin?
4. Draw the structure of cromoglycate and indicate its medicinal uses.

7.0   REFERENCES/FURTHER READING

Cravotto, G.; *et al.* (2001). "An Asymmetric Approach to Coumarin Anticoagulants via Hetero Diels-Alder Cycloaddition". *Tetrahedron. Asymm.* 12, 707-709.

Fanta, C. H. (2009). "Asthma". *New England Journal of Medicine.* 360 (10): 1002–14.

Olaniyi, A. A. (2005). *Essential Medicinal Chemistry* (3rd ed.). Ibadan, Nigeria: Hope Publications, pp. 313-314.

Schwartz, H. J.; Blumenthal, M.; Brady, R. and *et al.* (1996). "A Comparative Study of the Clinical Efficacy of Nedocromil Sodium and Placebo. How does Cromolyn Sodium Compare as an Active Control Treatment?"*Chest* 109 (4), 945–52.