

**COURSE
GUIDE**

**CHM 421
HETEROCYCLIC CHEMISTRY**

Course Team DR. Gloria Abiodun Ayoola (Developer/Writer)
 - UNILAG
 Prof. Olayinka O. Ajani
 Department of Chemistry
 Covenant University, Ota



NATIONAL OPEN UNIVERSITY OF NIGERIA

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National Open University of Nigeria
Headquarters
University Village
Plot 91, Cadastral Zone
Nnamdi Azikiwe Expressway
Jabi, Abuja

Lagos Office
14/16 Ahmadu Bello Way
Victoria Island, Lagos

e-mail: centralinfo@nou.edu.ng
URL: www.nou.edu.ng

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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 AIM

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 aim, there are some set objectives for the course. Besides, each module and each unit have 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.

By 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

The major components of the course include the following:

1. Course Guide
2. Study Units
3. In-Text Questions
4. Self-Assessment Questions
5. Conclusion
6. Summary
7. Textbooks and References

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, intended learning outcomes, body of the unit, in-text questions, self-assessment questions, conclusion, summary, 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:

Joule, J. A. & Mills, K. (2010). *Heterocyclic Chemistry* (5th ed.). John Wiley and Sons Ltd., United Kingdom.

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.

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.

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 = $10\% \times 4 = 40\%$
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, Pyriliun 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	Week 14	Assignment 14
5	Application of the Coumarin and Chromone Ring Systems in	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 from 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 Questions (SAQs) 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 selftest 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 the 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 you 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; therefore, 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. In order to gain much benefits from course tutorials, prepare a question list before attending them. You will learn a lot from participating actively in group or online discussions.

SUMMARY

Heterocyclic chemistry is a very vast subject; therefore, 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 or bearing 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. In order 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.

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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

UNIT 1 REACTIONS OF QUINOLINES

CONTENTS

1.0	Introduction
2.0	Objectives
3.0	Main Content
3.1	General Physical and Chemical Properties of Quinoline
3.2	Electrophilic Substitution
3.3	Nucleophilic Substitution
4.0	Conclusion
5.0	Summary
6.0	Tutor-Marked Assignment
7.0	References/Further Reading

1.0 INTRODUCTION

Quinolines belong to heterocyclic compounds and are a class of organic compound of the heteroaromatic series which are characterised by a double-ring structure. This ring structure is 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 heteroatom (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 is a heterocyclic base and was first isolated in 1834 by Runge from coal tar and he named it as Leukol. Later in 1842 Gerhard isolated it by heating the alkaloid cinchonine with alkali and named as quinoline.

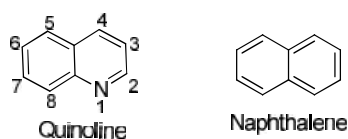


Fig. 1: Structures of Quinoline and Naphthalene (the Hydrocarbon Analogue)

2.0 OBJECTIVES

By 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 with pK_a value of 4.9 as compared with pyridine with pK_a of 5.2. The bp of quinoline at 760 mm was found to be 237.1°C. The density of quinoline at 25°C has been reported to be 1.08981. Quinoline is aromatic with a resonance energy of 47.3

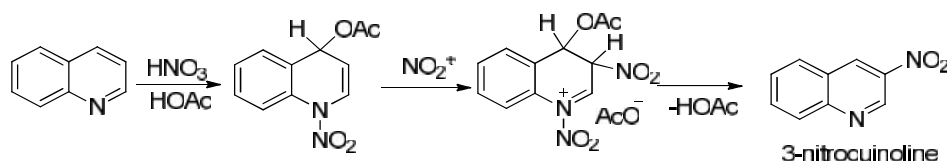
The general properties are based on those of the individual ring structures forming that system. It can be predicted that the benzene ring in quinoline would undergo electrophilic substitution by electrophiles but will be resistant to oxidation and reduction. On the other hand, the heterocyclic portion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

In practice, quinoline is a weak base (pK_a 4.9). It usually undergoes electrophilic substitution at positions 5 and 8 which are on the benzene ring portion of quinoline. Nucleophilic substitution occurs mainly at positions 2 and 4 of the pyridine ring. Reduction of the pyridine ring portion of the quinoline nucleus is comparatively easy but reduction of the benzene ring part is comparatively difficult. However, oxidation of both rings is difficult (Scheme 1).

3.2 Electrophilic Substitution

It has been documented that the reaction of acids and Lewis acids with quinoline occurred at the basic nitrogen atom to form quinolinium salts. Then, there is a question over the nature of the substrate for electrophilic

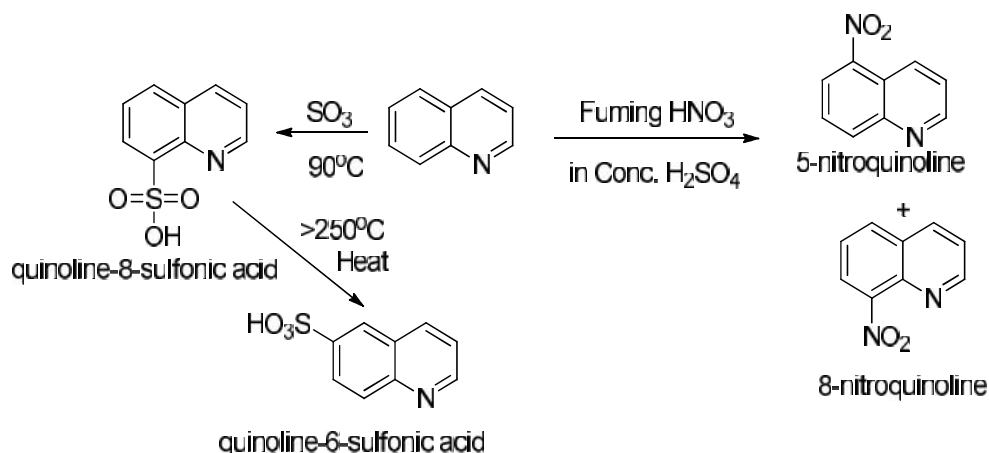
attack, i.e. is it quinoline or the quinolinium cation? The answer is not a simple one and appears to depend upon the reagents and reaction conditions. Thus, whereas acetyl nitrate at 20 °C gives 3-nitroquinoline (Scheme 2), fuming nitric acid in concentrated sulphuric acid containing sulphur trioxide at 15-20 °C yields a mixture of 5-nitroquinoline (35%) and 8-nitroquinoline (43%) as show in 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

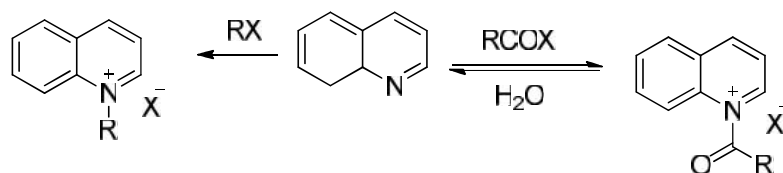
It is interesting to note that the rate of nitration of quinoline in 80-99% of sulphur acid is of the same order as that of N-methylquinolinium salts. This suggests that, here quinolinium cation may be the target for attack.

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). Since at a very high temperature, 6-quinolinesulfonic acid is obtained because the 5-and 8-isomers rearrange to the 6-isomer, then, quinoline-6-sulfonic acid is thermodynamically more stable. This rearrangement is similar to that shown by naphthalene-1-sulphonic acid, the kinetic sulphonation product of naphthalene, which isomerises on heating into the thermodynamic- ally favoured (less hindered) 2-isomer.



Scheme 3: Reaction of Quinoline with Fuming Nitric Acid in Concentrated Sulphuric Acid

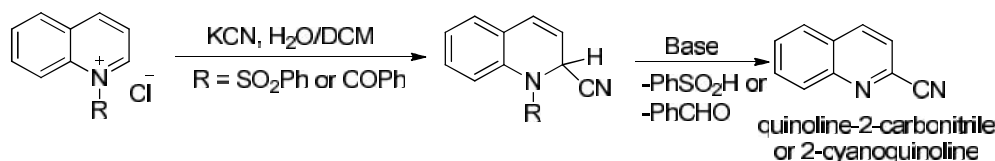
Alkyl and acyl halides react directly with quinoline to give *N*-alkyl or *N*-acylquinolinium salts (Scheme 4), whereas the *N*-alkyl salts are stable and can often be isolated as crystalline solids; the *N*-acyl analogues are unstable and undergo rapid hydrolysis in moist air or in aqueous solution.



Scheme 4: Reactions of Quinoline with Acyl and Alkyl Halides

3.3 Nucleophilic Addition/Substitution

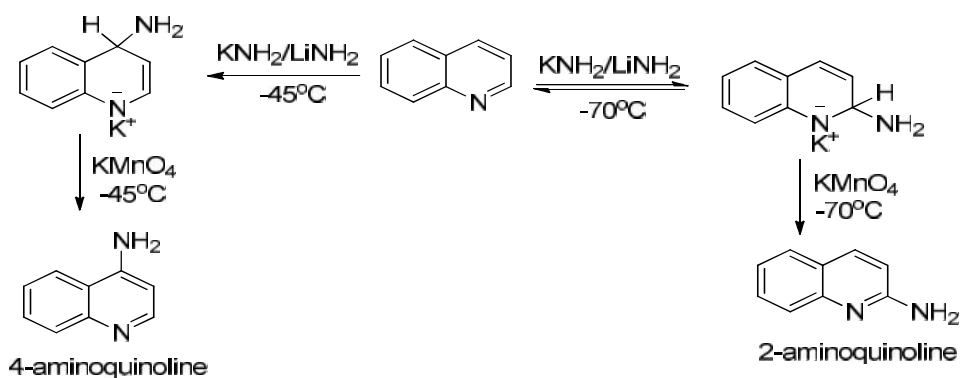
In 1909, Arnold Reissert described the addition of cyanide to 2-position of quinoline which was being activated by acylating agents. *N*-Acyl- or *N*-sulphonylquinolinium salts can be trapped by cyanide ion to form what are known generally as Reissert adducts. The easy removal of the *N*-substituent 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.

Under the Chichibabin type reaction which was reported by Aleksei Chichibabin in 1914, 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. This reaction is also attainable using sodium amide which reacts rapidly and completely with quinoline, even at -45°C to give a dihydro-adducts with initial attack at the C-2 (major) and C-4 (minor). The quinoline 2-adduct rearranges to the more stable 4-aminated adduct at higher temperature.



Scheme 6: Reaction of Quinoline with Potassamide

SELF-ASSESSMENT EXERCISE

- Give a brief account of isolation and discovery of quinoline in history
- Describe the formation of Reissert adducts in quinoline reaction
- Using reaction scheme only, distinguish between formation of 2-cyanoquinoline and 4-cyanoquinoline
- Under what condition will the ring rupturing of quinoline lead to formation of pyrazine-2,3-dicarboxylic acid

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, 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 heterocycle which contains a 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 on 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.
- Ram, V. J.; Sethi, A.; Nath, M. and Prata, R. (2019). Six-Membered Hetero-cycles in: *The Chemistry of Heterocycles*, Elsevier Ltd., pp. 3-391.

UNIT 2 SYNTHESIS OF QUINOLINES

CONTENTS

- 1.0 Introduction
- 2.0 Objectives
- 3.0 Main Content
 - 3.1 Skraup Synthesis of Quinoline
 - 3.2 Döbner-von Miller synthesis
 - 3.3 Conrad-Limpach Synthesis of Quinolones
 - 3.4 Friedländer Synthesis
 - 3.5 Pfitzinger Synthesis
- 4.0 Conclusion
- 5.0 Summary
- 6.0 Tutor-Marked Assignment
- 7.0 References/Further Reading

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. Although, quinoline occurs naturally, but due to its wide application various attempt and effort have been tailored toward its laboratory synthesis. Some of those synthetic approaches are Skraup, Dobner-von Miller Synthesis, Conrad-Limpach, Friedlaender and Pfitzinger synthesis. These methods are highly commendable in the design and formation of diverse quinoline derivatives of biological relevance.

2.0 OBJECTIVES

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

- explain the synthesis of quinolines
- design synthesis of quinoline derivatives.
- identify reaction condition for diverse named reactions for quinoline synthesis

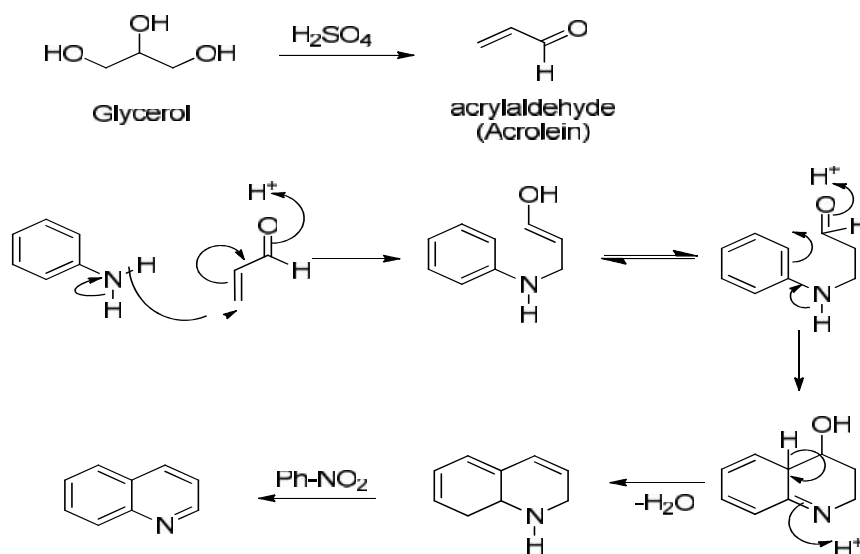
3.0 MAIN CONTENT

3.1 Skraup Synthesis of Quinoline

This synthetic approach is named after the Czech chemist Zdenko Hans **Skraup** (1850-1910). 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 crystallized from the reaction mixture by basification and is isolated by steam-distillation. The yield of purified product is 84-91%.

The reaction involves dehydration of glycerol in conc. H_2SO_4 to afford 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. Success of the reaction depends on rapid addition of aniline to propenal as it is formed.

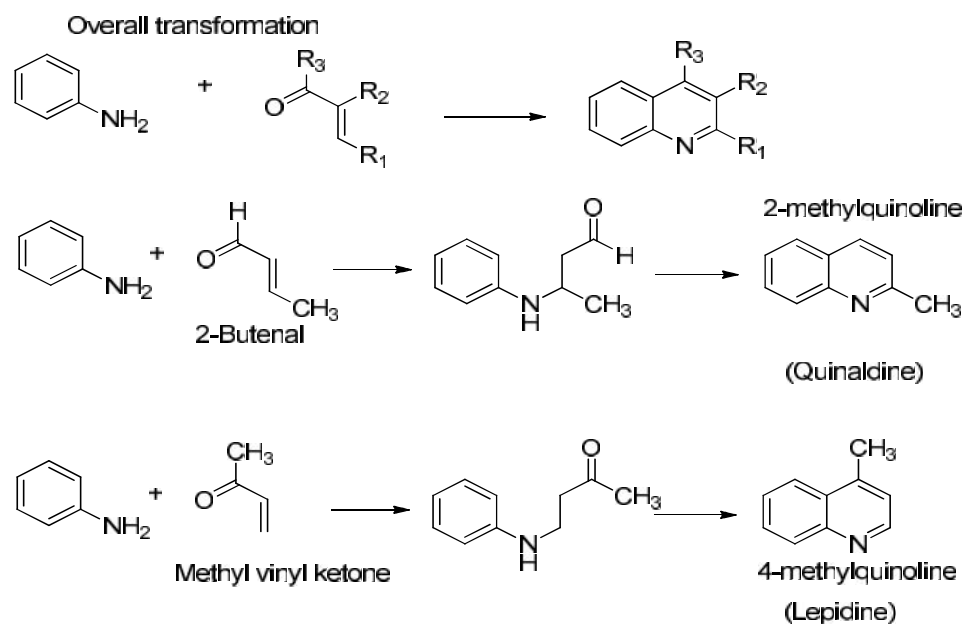


Scheme 7: Skraup Synthesis of Quinoline

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 predominating 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

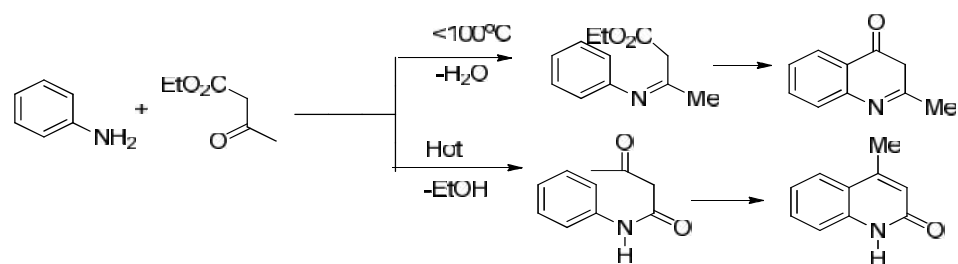
The reaction uses pre-formed α,β -unsaturated carbonyl compounds instead of acrolein. It is used to provide alkyl and aryl substituents in the “pyridine” half of the quinoline. The intermediate β -aminocarbonyl compound can be isolated and this shows that the mechanism starts with a conjugate addition. 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

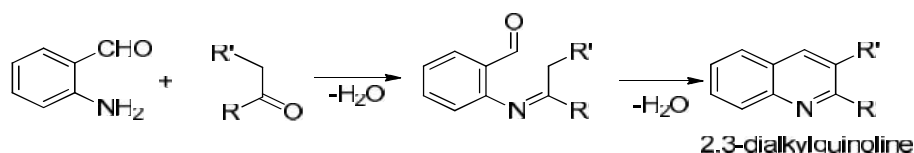
-Keto esters react with aniline in each of two ways; at low temperatures reaction occurs at the keto-group to give an imine and at high temperatures reaction occurs at the ester group to give an amide. The resulting compounds can each be cyclised to quinolines (see Scheme 9). Several alternative aprotic solvents, including 1,2,4-trichlorobenzene, 2-nitrotoluene, and 2,6-di-*tert*-butylphenol could be useful, inexpensive alternative solvents for the preparation of quinoline derivatives on a large scale provided the reaction is conducted at high temperature.



Scheme 9: The Conrad-Limpach Synthesis

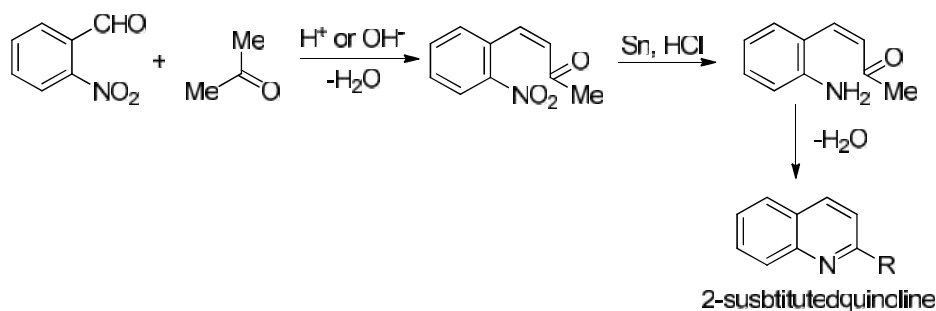
3.4 The Friedländer Synthesis

Friedländer synthetic approach proceeded by the condensation of 2-amino benzaldehydes with ketones to form the quinoline derivatives. 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). It has also been catalyzed using agent such as trifluoroacetic acid (TFA), Lewis acids, iodine and toluenesulfonic acids



Scheme 10: Friedländer Synthesis of Quinoline Derivatives

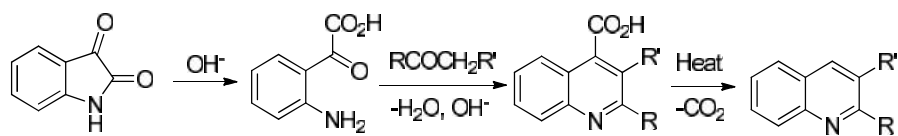
The problem of this approach is that *o*-aminobenzaldehydes are very unstable, readily undergoing self-condensation. One way of overcoming this is to start instead, with an *o*-nitrobenzaldehyde: acid- or base-catalysed reaction gives an intermediate which cyclises spontaneously on reduction (Scheme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



Scheme 11: Variation of Friedländer Synthesis

3.5 The Pfitzinger Synthesis

This is a modification of Friedländer's method and employs isatin in place of *o*-aminobenzaldehyde. It is initiated by hydrolysis of isatin. Reaction with the base gives *o*-aminobenzoylformate ion which reacts with an aldehyde or ketone to give a 4-carboxyquinoline. The carboxyl group at position 4 can then be thermally removed by the process called thermal decarboxylation (Scheme 12).



Scheme 12: Pfitzinger Synthetic Route to 2,3-disubstituted quinoline

SELF-ASSESSMENT EXERCISE

- Highlight one major bottleneck of Friedländer approach for the synthesis of quinoline.
- Identify structural difference between quinaldine and lepidine
- Using Döbner-von Miller Synthesis, what , -unsaturated carbonyl will be required to react with aniline to produce 2,3,4-trimethylquinoline

- iv. With the aid of equation only, show how you will prepare 2,3-dimethyl quinoline via Pfitzinger synthetic approach

4.0 CONCLUSION

In this unit, we have looked at the various named reaction approaches (methods) utilized 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 synthetic approaches involve the use of phenylalanine and a 3-carbon fragment as starting materials.
- Friedlaender and Pfitzinger synthesis involve the use of o-amino benzaldehydes and o-aminobenzoylformate respectively and a two carbon fragment as the starting materials.
- Conrad-Limpach synthesis is used to synthesise quinolone derivatives.

6.0 TUTOR-MARKED ASSIGNMENT

1. Provide synthetic routes to the quinoline derivatives (a)-(c).
(Time allowed: 12 mins)
2. Using Döbner-von Miller approach how can you synthesize 3,4- dimethyl quinoline (Time allowed: 6 mins)

7.0 REFERENCES/FURTHER READING

Joule, J. A. & Mill, K. (2010). *Heterocyclic Chemistry* (5th ed.). Wiley and Sons Ltd., United Kingdom. pp. 177-203.

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.

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UNIT 3 APPLICATION OF THE QUINOLINE RING SYSTEM IN DRUG SYNTHESIS

CONTENTS

- 1.0 Introduction
- 2.0 Objectives
- 3.0 Main Content
 - 3.1 Quinine
 - 3.2 Chloroquine
 - 3.3 Nicotinic Acid
 - 3.4 Other Applications of Quinoline
- 4.0 Conclusion
- 5.0 Summary
- 6.0 Tutor-Marked Assignment
- 7.0 References/Further Reading

1.0 INTRODUCTION

Quinoline is used principally for the manufacture of nicotinic acid which prevents pellagra in humans. For years, it has been accepted that a number of effective quinoline antimalarial drugs (e.g., chloroquine, quinine, amodiaquine) function by preventing hemozoin crystallization. It is also used in the manufacture of other specialty chemicals. Approximately, four (4) tonnes are produced annually according to a report published in 2005. It is used as a precursor for the production of 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) which is 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 drug which are plasmoquin and chloroquine. Chimanine alkaloids isolated from the bark of *Galipea longiflora* trees are quinoline-based anti-leishmanial drug agents. Quinoline is found in the cyanine dyes and in the analytical reagent, oxine (8-hydroxyquinoline).

2.0 OBJECTIVES

By 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
- list some earlier discovered naturally occurring antimalarial drugs which are quinoline based compounds.

3.0 MAIN CONTENT

3.1 Quinine

Quinine is a natural white crystalline alkaloid possessing antipyretic (fever-reducing), antimalarial, analgesic (pain-killing), 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 its methylene bridge (linker) 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).

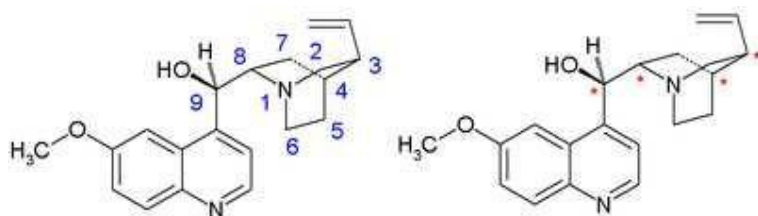


Fig. 2: Structure of Quinine (the Asymmetric Centres are Shown as *)

The bark of the **cinchona** tree is the only known natural source of quinine; although, it has been synthesised in the laboratory. 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 were discovered and were used 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

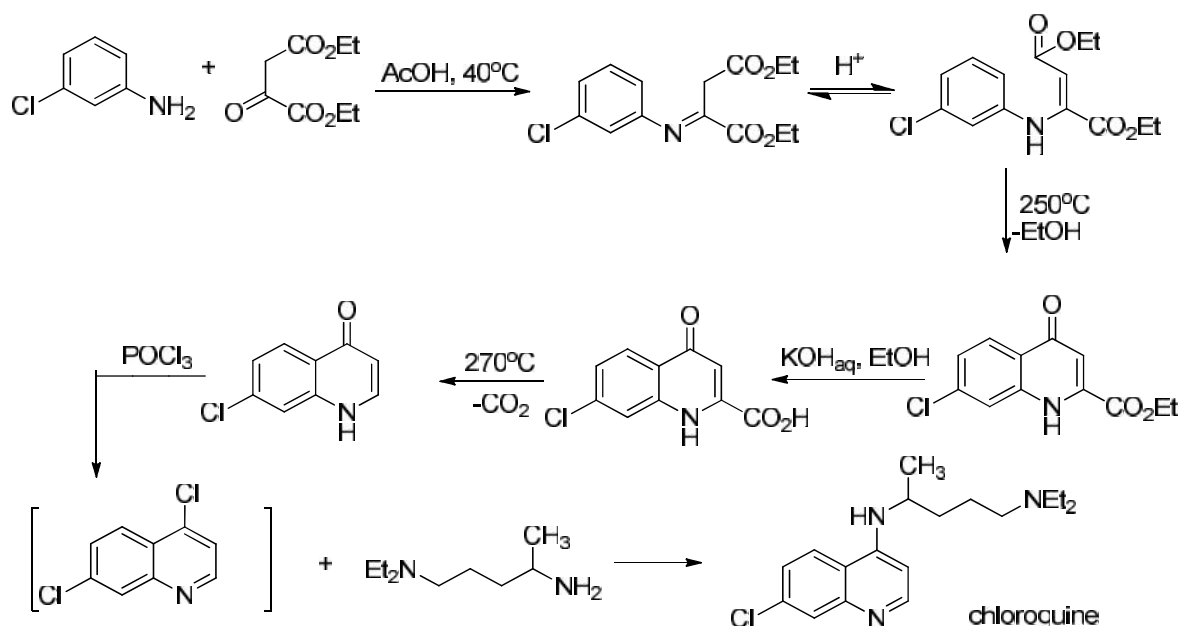
Cinchona trees remain the only economically practical source of quinine. However, under wartime pressure, research towards its synthetic production was undertaken. A formal chemical synthesis was accomplished in 1944 by American chemists R.B. Woodward and W.E. Doering. Since then, several more efficient 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

- It has long been used in the treatment or prevention of malaria. 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 mass drug administrations which may have contributed to the emergence and spread of resistance.
- As it mildly suppresses the immune system, it is used in some autoimmune disorders, such as *Rheumatoid arthritis* and *Lupus erythematosus*.
- Chloroquine is in clinical trials as an investigational antiretroviral in humans with HIV-1/AIDS and as a potential antiviral agent against chikungunya fever.
- The radiosensitising and chemosensitising properties of chloroquine are beginning to be exploited in anticancer strategies in humans.
- Synthesis: Friedländer approach, Conrad-Limpach Approach, etc
- Chloroquine can be synthesised using the Conrad-Limpach quinolone method as shown below:



Scheme 13: Synthesis of Chloroquine via Conrad-Limpach Approach

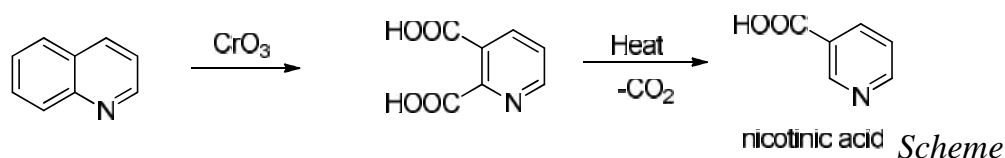
3.3 Nicotinic Acid

Niacin (also known as **vitamin B₃**, **nicotinic acid** and **vitamin PP**) is an organic compound with the formula C₆H₅NO₂ 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 B₃ include the corresponding amide, nicotinamide ("niacinamide"), where the carboxyl group has been replaced by a carboxamide group (CONH₂), as well as more complex amides and a variety of esters. The terms niacin, nicotinamide, and vitamin B₃ 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 starting drug, & 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. However, some of symptoms of niacin deficiency include: memory loss and mental

confusion, fatigue, depression, headache, diarrhea and skin problem. 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 after being heated to form nicotinic acid. This process is called thermal decarboxylation (Scheme 14).



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). Cinchocaine was the first local anesthetic to be synthesized from the quinoline-based group.

SELF-ASSESSMENT EXERCISE

- i. Why is quinine used in photochemistry as fluorescent standards?
- ii. What are two (2) heterocycles that combine to form quinine
- iii. Enumerate four (4) symptoms in patient for confirmation of niacin deficiency
- iv. Under what condition can quinoline be transformed to niacin?
- v. The medicinal term for “fever reducing” in drug chemistry is_____
- vi. The medicinal term for “pain killing” in drug chemistry is_____

4.0 CONCLUSION

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

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 (potent antimalarial). 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 through the Conrad-Limpach synthetic approach. 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. (Time allowed: 7 mins)
2. Outline the synthesis of chloroquine via the Conrad-Limpach synthetic approach. (Time allowed: 6 mins)
3. Outline the synthesis of nicotinic acid from quinoline. What are the medicinal uses of nicotinic acid? (Time allowed: 3 mins)

7.0 REFERENCES/FURTHER READING

- Joule, J. A. & Mill, K. (2010). *Heterocyclic Chemistry* (5th ed.). Wiley and Sons Ltd., United Kingdom. pp. 630-631.
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UNIT 4 SYNTHESIS AND REACTIONS OF ISO-QUINOLINES

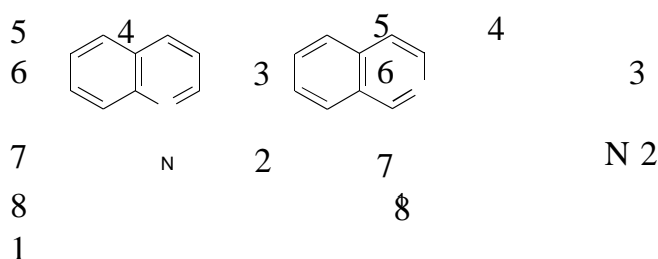
CONTENTS

- 1.0 Introduction
- 2.0 Intended Learning Outcomes
- 3.0 Main Content
 - 3.1 General Physical and Chemical Properties Isoquinoline
 - 3.1.1 Reactions with Electrophiles
 - 3.1.2 Reduction and Reactions with Nucleophiles
 - 3.2 Synthesis of Isoquinoline
 - 3.2.1 Bischler-Napieralski Synthesis
 - 3.2.2 Picket-Spengler Synthesis
 - 3.2.3 The Pomeranz-Fritsch Synthesis
- 4.0 Conclusion
- 5.0 Summary
- 6.0 Tutor-Marked Assignment
- 7.0 References/Further Reading

1.0 INTRODUCTION

Isoquinoline is a heterocyclic aromatic organic compound. It is a **structural isomer** of **quinoline**. Isoquinoline and quinoline are both **benzopyridines**, which is composed of a **benzene** ring fused to a **pyridine** ring. The heteroatomic nitrogen in isoquinoline is on position 2 while the nitrogen heteroatom 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.



Quinoline

Isoquinoline

Fig. 3: Structures of Quinoline and Isoquinoline

2.0 OBJECTIVES

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

- differentiate between isoquinoline 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.

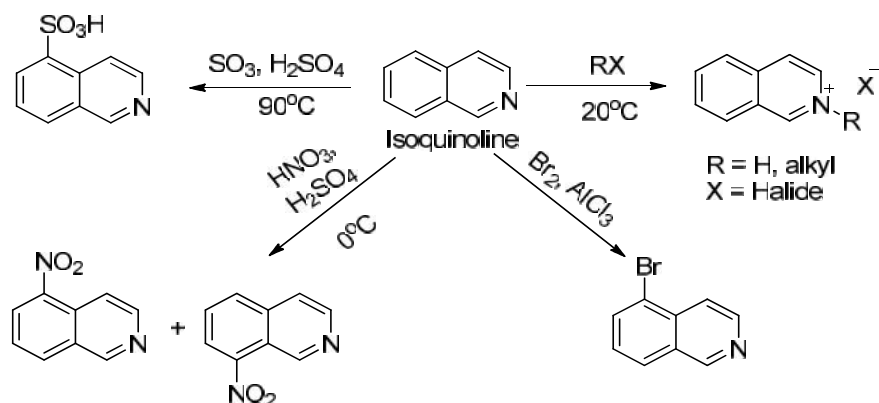
3.0 MAIN CONTENT

3.1 General Physical and Chemical Properties Isoquinoline

Isoquinoline is a colourless **hygroscopic** liquid at room temperature with a penetrating, unpleasant odour. Impure samples can appear brownish, as is typical for nitrogen heterocycles. It crystallises to platelets and have a low **solubility** in **water** but dissolve well in **ethanol, acetone, diethyl ether, carbon disulphide**, and other common organic solvents. It is also soluble in dilute acids as the protonated derivative. Isoquinoline is a weak base, with a pK_b of 5.1 being an analog of pyridine. It protonates upon treatment with strong acids, such as HCl to form salts. It forms adducts with Lewis acids, 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 carbocyclic ring.

3.1.1 Reactions with Electrophiles

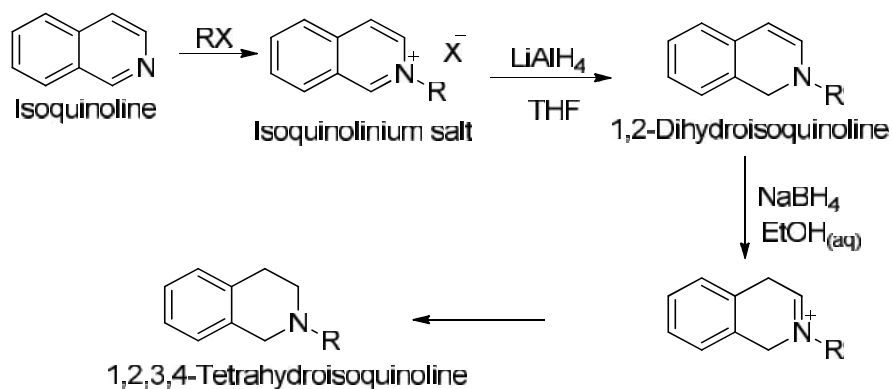
Isoquinoline like quinoline is protonated and alkylated at the nitrogen atom and undergoes electrophilic substitution in the benzene ring. Sulphonation with oleum gives mainly the 5-sulphonic acid, but fuming nitric acid and concentrated sulphuric acid at 0°C produce a 1:1 mixture of 5- and 8-nitroisoquinoline derivatives. Bromination in the presence of aluminium trichloride ($AlCl_3$) at 75°C gives a 78% yield of 5-bromo isoquinoline (Scheme 15).



Scheme 15: Reactions of Isoquinolines with Electrophiles

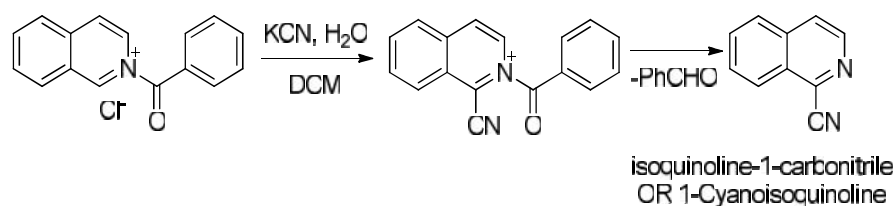
3.1.2 Reduction and Reactions with Nucleophiles

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 isoquinolinium 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 transfer 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

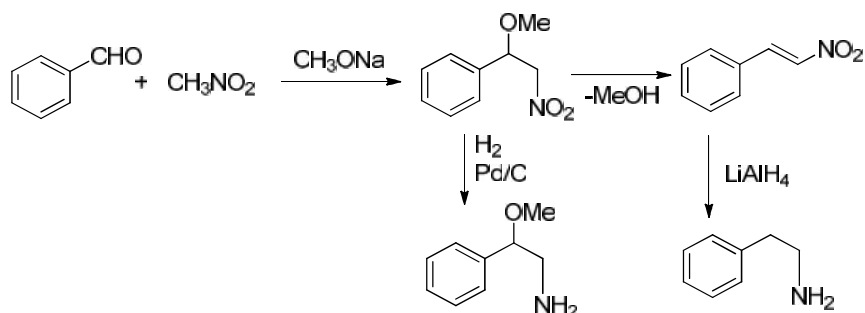
Isoquinoline was first isolated from **coal tar** in 1885 by Hoogewerf and van Dorp. They isolated it by fractional crystallisation of the acid sulphate. Weissgerber developed a more rapid route in 1914 by selective extraction of coal tar; exploiting the fact that isoquinoline is more basic than quinoline.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

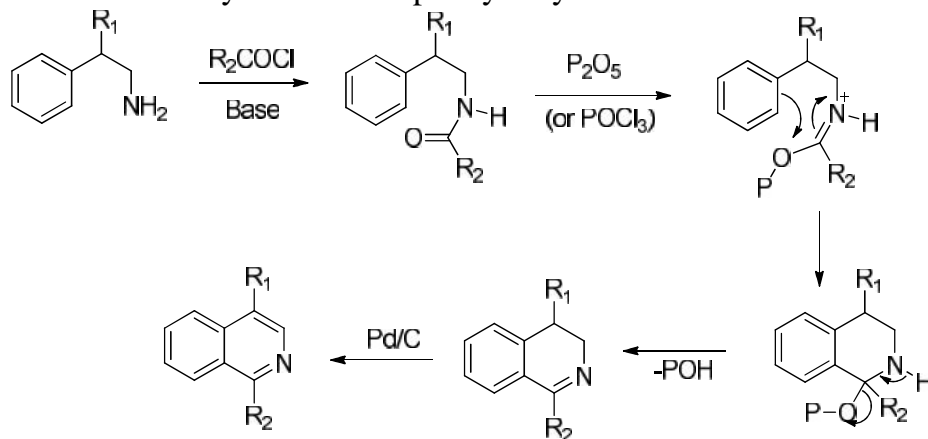
The biological properties of many derivatives have ensured the development of a number of syntheses providing access to all types of isoquinolines, both natural and man-made. Three important routes are the Bischer-Napieralski, Pictet-splenger and Pomeranz-Fritsch methods.

3.2.1 Bischler-Napieralski Synthesis

This method is very useful for the design and preparation of 1-substituted 3,4-dihydroisoquinolines, which if necessary can be oxidized 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 -nitrosyrene (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 ($R_1 = H$) 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 -phenylethylamine

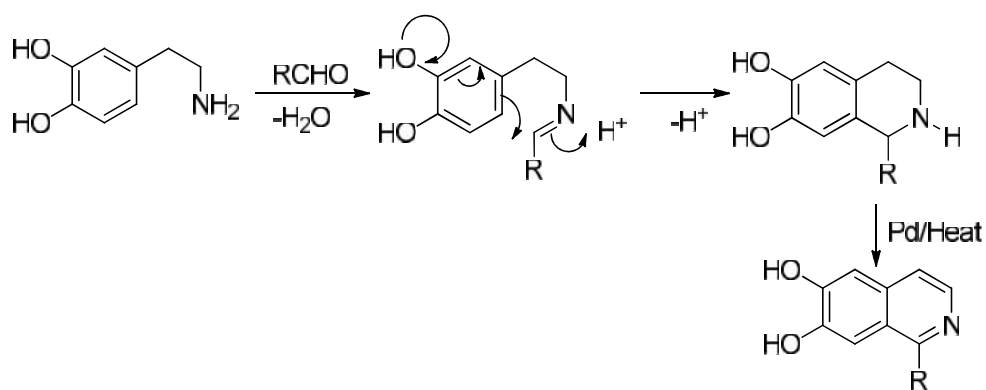


Scheme 19: Bischler-Napieralski Synthesis of Isoquinoline

Alternatively, a -methoxy- -phenylethylamine can be used to circumvent the oxidation step after the conventional Bischler-Napieralski cyclisation. Here, when treated with the phosphorus reagent the amide ($R_1 = \text{OMe}$) undergoes both cyclisation and the elimination of methanol to give the isoquinoline ($R = \text{H}$) directly. This is known as the Pictet-Gams modification of the Bischler-Napieralski synthesis. It involves conducting Bischler-Napieralski sequence with a potentially unsaturated aryl ethanamine thereby resulting in the formation of a fully aromatic isoquinoline directly.

3.2.2 Picket-Spengler Synthesis

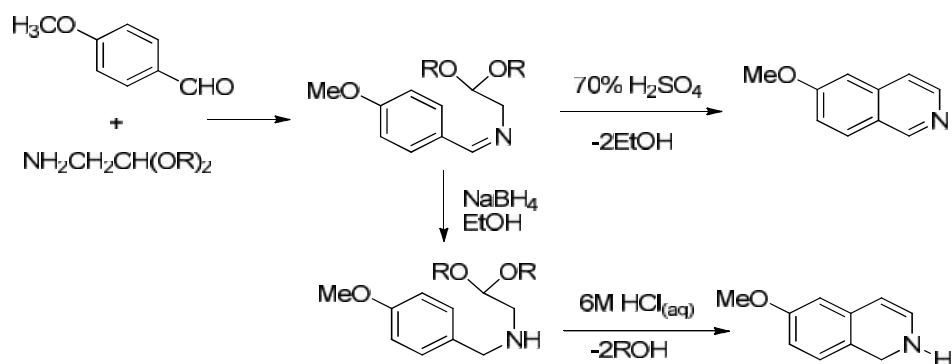
A -phenylethylamine is treated with an aldehyde in the presence of dilute acid; ring closure occurs by a reaction of Mannish type reaction and the tetrahydroisoquinoline formed is dehydrogenated on palladium (Scheme 20).



Scheme 20: Pickett-Spengler Synthesis

3.2.3 The Pomeranz-Fritsch Synthesis

The synthesis is carried out in two stages. At first an aryl aldehyde is condensed with amino acetal to form an aryl aldimine and it proceeds in high yield under mild conditions. The second stage involved cyclization of the aldimine by treating it with strong acid. 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 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 unsubstituted 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 advantage 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.

SELF-ASSESSMENT EXERCISE

- i. Name and briefly describe the reaction known to be modification of Bischler-Napieralski synthesis
- ii. Outline the scheme for the synthesis of 6-methoxyisoquinoline
- iii. What ring synthesis method is suitable for the synthesis in SAQ 4.2.

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 α -phenylethylamine and acyl chloride or an aldehyde in the Bischler-Napieralski synthesis and Pictet-Spengler synthesis respectively. Pomeranz-Fritsch 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? (Time allowed: 3 mins)
2. Which reagent will you use to synthesise *N*-methylisoquinolium salt? (Time allowed: 1 min)
3. Outline the synthesis of 1-methylisoquinoline from benzaldehyde and suitable reagents via a multi-step synthesis. (Time allowed: 3 mins)

7.0 REFERENCES/FURTHER READING

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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 wide reported applications of their derivatives. A large proportion of isoquinoline motifs are alkaloids, and they 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 isoquinoline-based heterocyclic compounds which are found naturally 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 in their skeletal framework.

2.0 OBJECTIVES

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

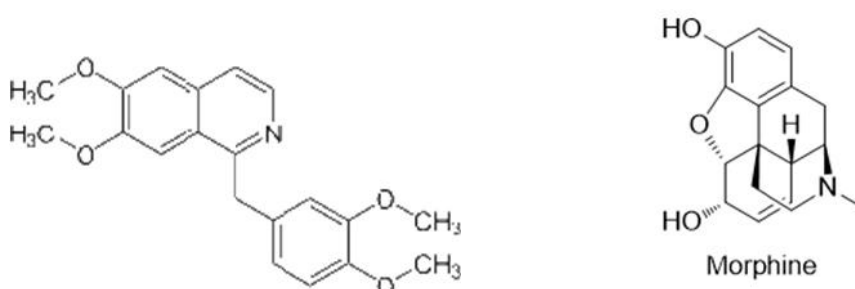
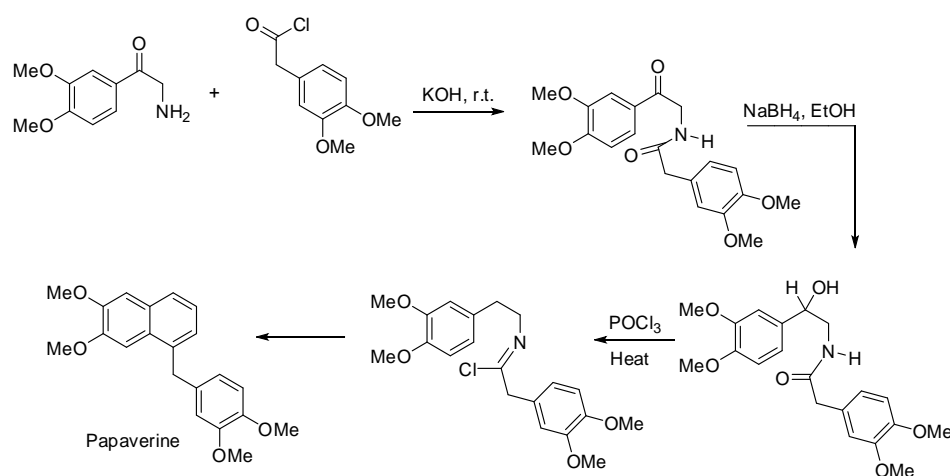


Fig. 4: Structure of Papaverine



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. It was

commercially sold first by **Merck** in 1827, which at that 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 alkaloid found in opium, the dried sap (latex) derived from shallowly slicing the unripe seedpods of the opium, or common edible, poppy, *Papaver somniferum*. Morphine was the first **active principle** purified from a plant source and is one of at least 50 alkaloids of several different types present in opium, **Poppy Straw Concentrate**, and other poppy derivatives.

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

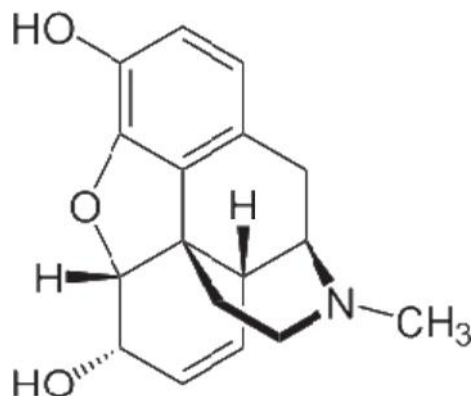


Fig. 5: Structure of Morphine

3.3 Other Applications of Isoquinolines

- a) anesthetics; dimethisoquin is one example (shown below).

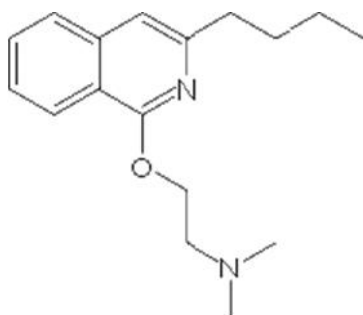


Fig. 6: Structure of Dimethisoquine

- b) antihypertension agents, such as quinapril, quinapirilat, and debrisoquine (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.

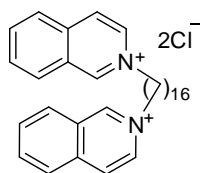


Fig. 7: Structure of 2,2'-Hexadecamethylenediisoquinolinium Dichloride

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

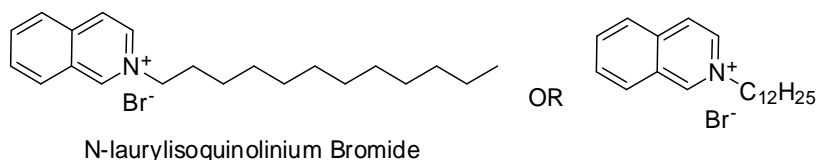


Fig. 8: Structure of N-laurylisoquinolinium Bromide

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

3.4 Isoquinolines and Parkinson's Disease

Parkinson's disease is a slowly progressing movement disorder which is thought to be caused by certain **neurotoxins**. A neurotoxin called MPTP (1[N]- methyl-4-phenyl-1,2,3,6-tetrahydropyridine), the precursor to MPP+, was found and linked to Parkinson's disease in the 1980s. The active neurotoxins destroy dopaminergic neurons, leading to parkinsonism and Parkinson's disease. Several tetrahydroisoquinoline 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 **dyes, paints, insecticides** and **antifungals**. It is also used as a solvent for the extraction of **resins** and **terpenes**, and as a **corrosion inhibitor**.

SELF-ASSESSMENT EXERCISE

- i. Itemize three (3) commercially available antihypertensive drugs which possess isoquinoline ring derivatives.
- ii. What is the historical origin of the name “morphine”?
- iii. Distinguish between papaverine and morphine based on the medicinal use.
- iv. With the aid of structure only, differentiate between morphine and heroin

4.0 CONCLUSION

This unit has shown that Isoquinolines are important because their derivatives 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, debrisoquine 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 (Time allowed: 3 mins)
2. Mention medicinal uses of agents in Activity 1.13. (Time allowed: 4 mins)

7.0 REFERENCES/FURTHER READING

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

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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 Intended Learning Outcomes
- 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 (2*H*-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.

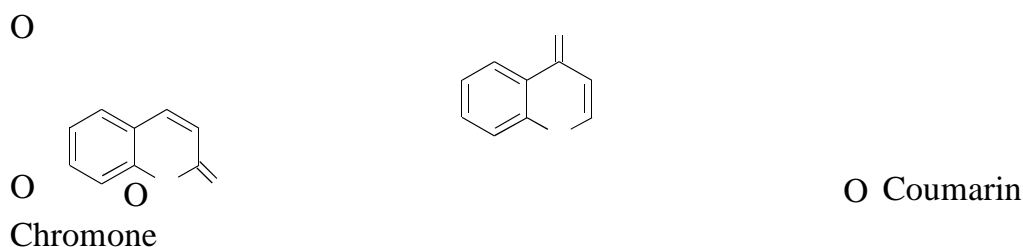


Fig. 13: Comparisons of the Structures of Coumarin and Chromone

2.0 OBJECTIVES

By 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 is a colourless crystalline solid with a sweet odour resembling that of vanilla and a bitter taste. It 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, oxygen atom of carbonyl group receives electron density both via the enone chromophore from the internal resonance of the lactone group (Figure 11)

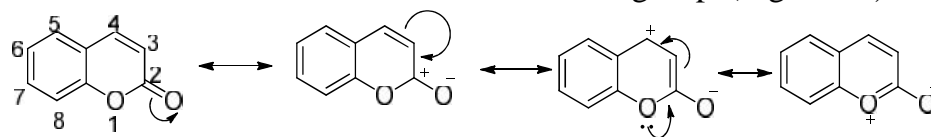
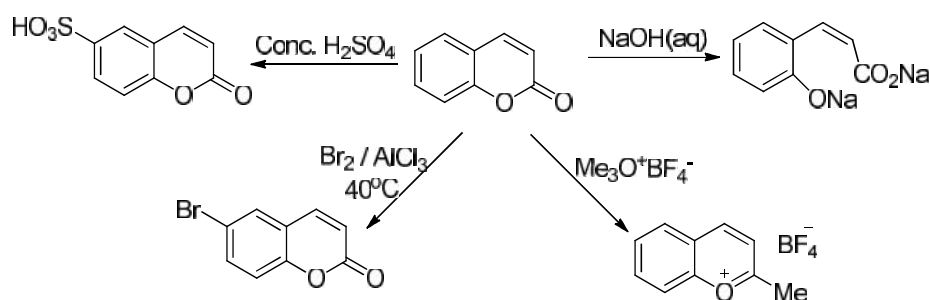


Fig. 14: Resonance structures of Coumarin

Nucleophilic addition occurs mainly at the carbon atom of the carbonyl group thereby resulting into 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).

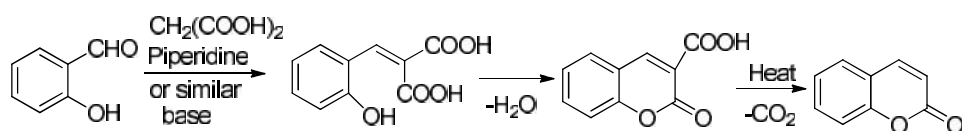


Scheme 43: Some Reactions of Coumarin

In the presence of a Lewis acid e.g. AlCl_3 , bromine reacts with coumarin to form 6-bromocoumarin; however, in the absence of 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.

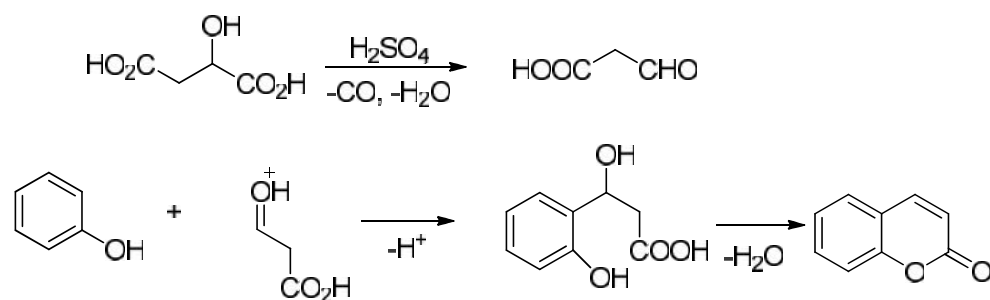
3.2 Synthesis of Coumarins

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



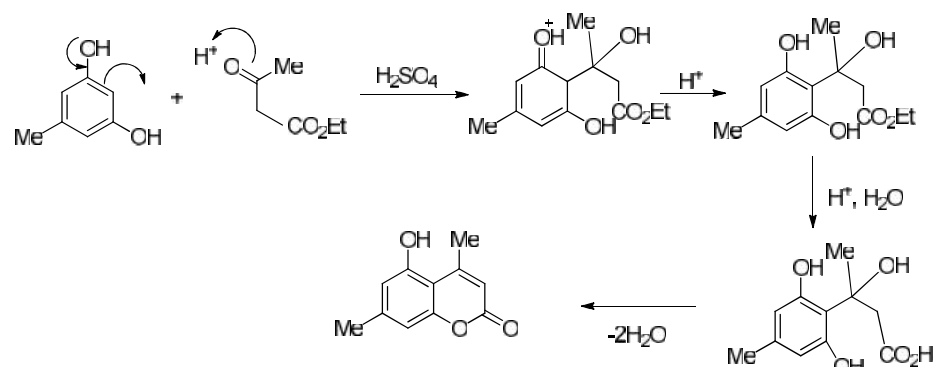
Scheme 44: Synthesis of Coumarin

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

SELF-ASSESSMENT EXERCISE

- With the aid of chemical reaction only, show what happens when bromination of coumarin was carried out in the absence of Lewis acid followed by addition of pyridine to the intermediate?
- Using von Pechmann approach, outline the synthesis of coumarin
- With the aid of structure, only distinguish between coumarin and chromone

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; although, the product depends on the reagent used. Synthesis is from 2-hydroxybenzaldehyde (salicylaldehyde) 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 oxophilic 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, dehydrobromination 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-bromocoumarin.
2. What is the product from the reaction of coumarin with NaOH?

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.
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UNIT 2 REACTIONS OF CHROMONES

CONTENTS

- 1.0 Introduction
- 2.0 Intended Learning Outcomes
- 3.0 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

By 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 conjugation does not involve the benzene ring (Figure 15).

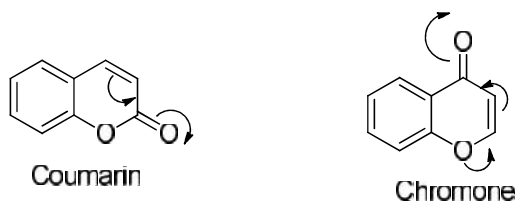
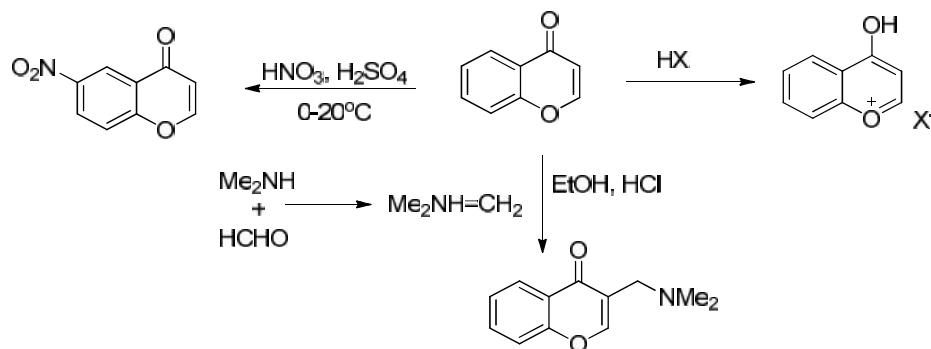


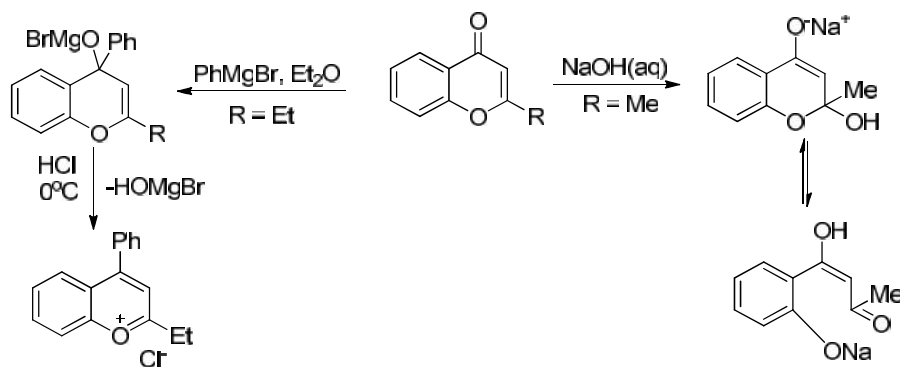
Fig. 15: Chromone Conjugation

As a result, chromones are rather more basic, and strong acids readily protonate the carbonyl oxygen atoms, thereby resulting in the formation of crystalline benzopyrylium 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

SELF-ASSESSMENT EXERCISE

- Under what condition will chromone produce 6-nitrochromone?
- Explain why chromone is more basic compared to coumarin.

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.

5.0 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.

6.0 TUTOR-MARKED ASSIGNMENT

1. What is reaction product when chromone is reacted with EtMgBr? (Time allowed: 2 mins)
2. How does chromone react with NaOH? (Time allowed: 3 mins)
3. What is the product of the reaction of chromone with hydrochloric acid? (Time allowed: 2 mins)

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
- 2.0 Intended Learning Outcomes
- 3.0 Main Content
 - 3.1 Synthesis of Chromones
- 4.0 Conclusion
- 5.0 Summary
- 6.0 Tutor-Marked Assignment
- 7.0 References/Further Reading

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-Disubstituted chromones can be synthesised from salicylic acid derivatives and from 2-hydroxyphenylketones. 3-Substituted chromones can be synthesised via the condensation of the enolate of 2-hydroxyphenyl ketone and ethyl formate.

2.0 OBJECTIVES

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

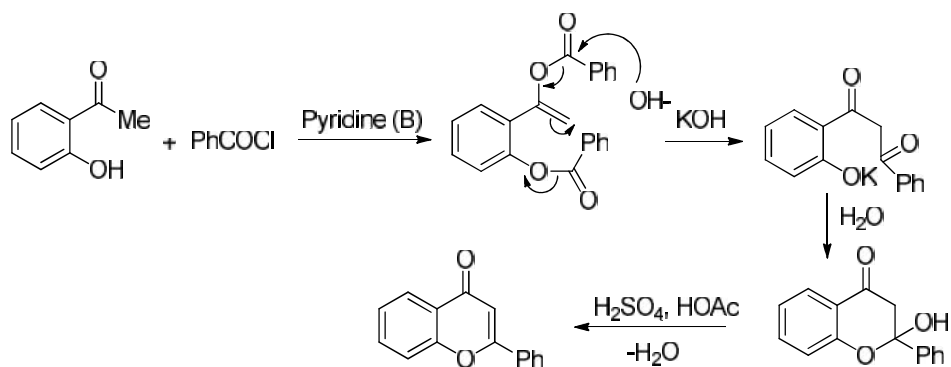
- explain the synthesis of chromones
- design the synthesis of some chromone derivatives

3.0 MAIN CONTENT

3.1 Synthesis of Chromones

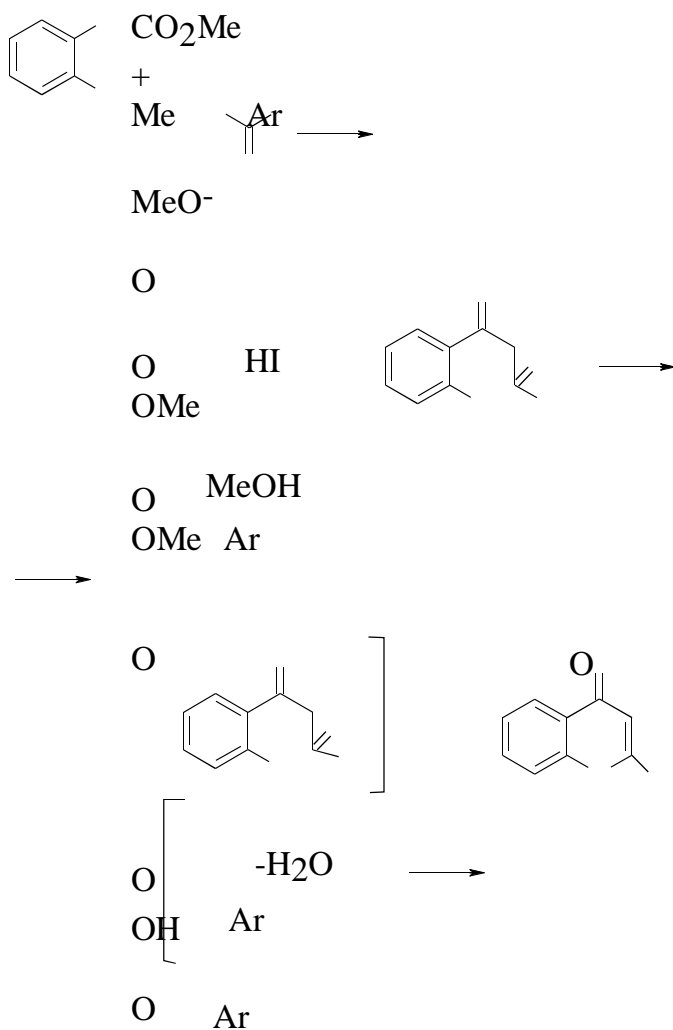
Synthesis of 2- and 3-substituted chromones normally start from 2-hydroxyphenyl ketones. In the first of two examples, a route to flavone is shown in Scheme 49 using 2-hydroxyacetophenone (2-hydroxyphenylethanone) and benzoyl chloride as starting materials. Initially, the phenolic group of the acetophenone is *o*-acylated by benzoyl chloride, using pyridine as a base (a Schotten-Baumann type reaction). The **Schotten–Baumann reaction** is a method to synthesize amides from amines and acid chlorides: Sometimes the name for this reaction is also used to indicate the reaction between an acid chloride and an alcohol to form an ester. 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 effected by the action of glacial acetic acid containing sulphuric acid.



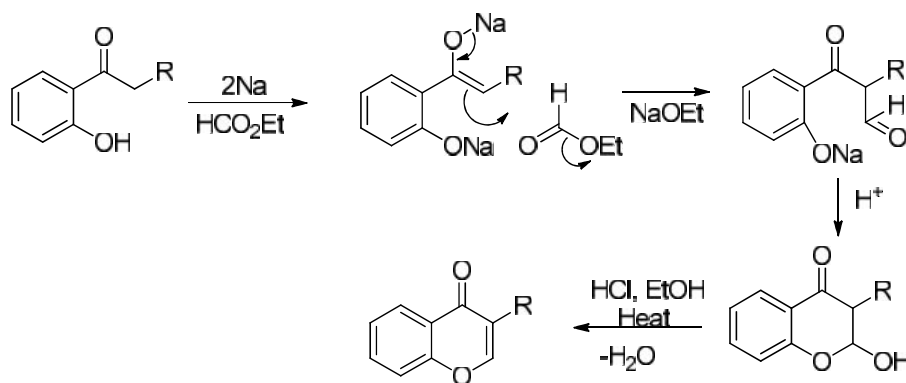
Scheme 49: Synthesis of 2-Phenylchromone (Flavone)

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-hydroxyl phenylketone and ethyl formate (ethyl 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

SELF-ASSESSMENT QUESTIONS (SAQs)

- What is the general name for 2-phenylchromone
- Outline the scheme for the synthesis of 2-phenylchromone from reaction of 2-hydroxy with benzoyl chloride
- Why is the reaction in SAQ 4.2 referred to as Schotten–Baumann type reaction?.

4.0 CONCLUSION

In this unit, you have learnt how to synthesise 2- and 3-substituted chromones and also recognized 2-phenylchromone to be generally called flavones.

5.0 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-hydroxyl phenyl ketone and ethyl formate.

6.0 TUTOR-MARKED ASSIGNMENT

1. Devise a synthesis for 3-methylchromone and 3-phenyl chromone (isoflavone). (Time allowed: 9 mins)
2. Devise a synthesis for 2-methylchromone via 2-Hydroxyphenylketon (Time allowed: 9 mins)

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.
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- 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
- 2.0 Intended Learning Outcomes
- 3.0 Main Content
 - 3.1 General Properties of Benzopyrilium Salts
 - 3.2 Synthesis of Pyrilium Salts
 - 3.3 Synthesis of Anthocyanidins (cyanidin Chloride)
- 4.0 Conclusion
- 5.0 Summary
- 6.0 Tutor-Marked Assignment
- 7.0 References/Further Reading

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).

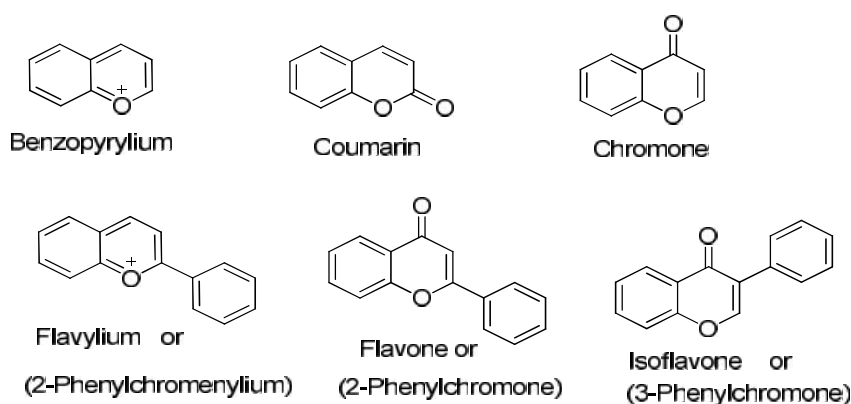


Fig. 16: Structures of Benzopyrilium Salts, Coumarins, Chromones and Flavonoids

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

By 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 pyrilium salts can be synthesized
- 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 has different colours (Scheme 52).

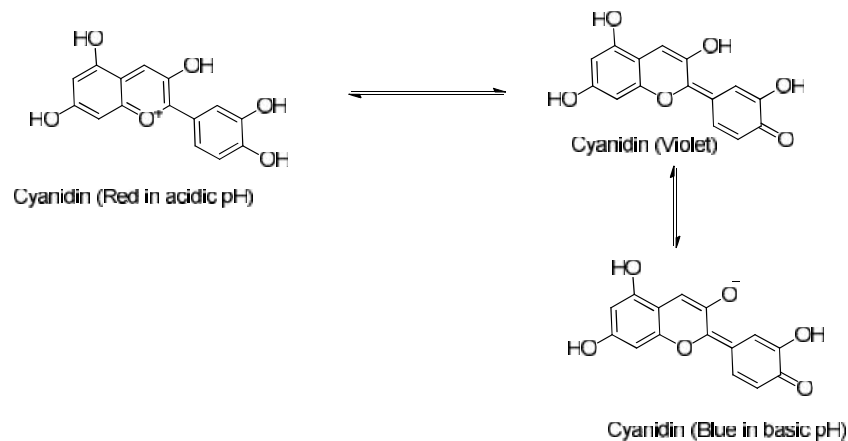
OGlu

OGlu

OH HO

O⁺

OH Cyanin (Glu = glucose residue)

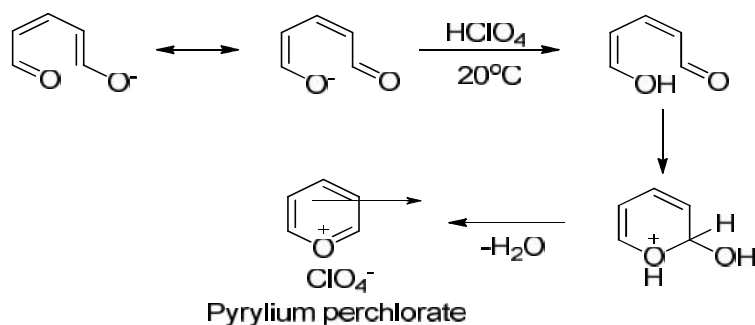


Scheme 52: Effect of pH on Cyanidin

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, which is the pulverised bark of the plant *Derris elliptica*).

3.2 Synthesis of Pyrilium Salts

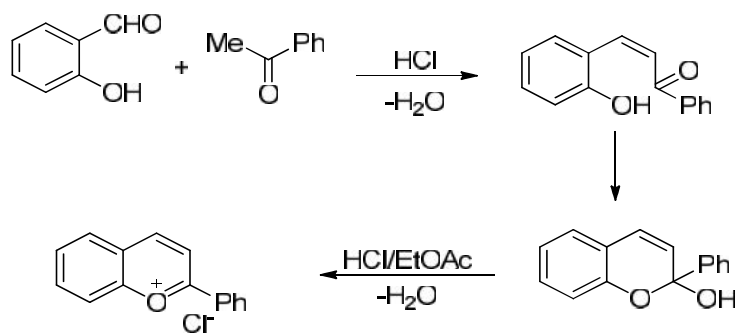
Salts of the type $R_3O^+X^-$ are normally unstable and cannot be isolated unless X^- is an especially stable (non-nucleophilic) anion such as BF_4^- . However, the oxonium salts derived by oxidation of the pyran nucleus are comparatively stable because the cation possesses aromatic stabilisation energy 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

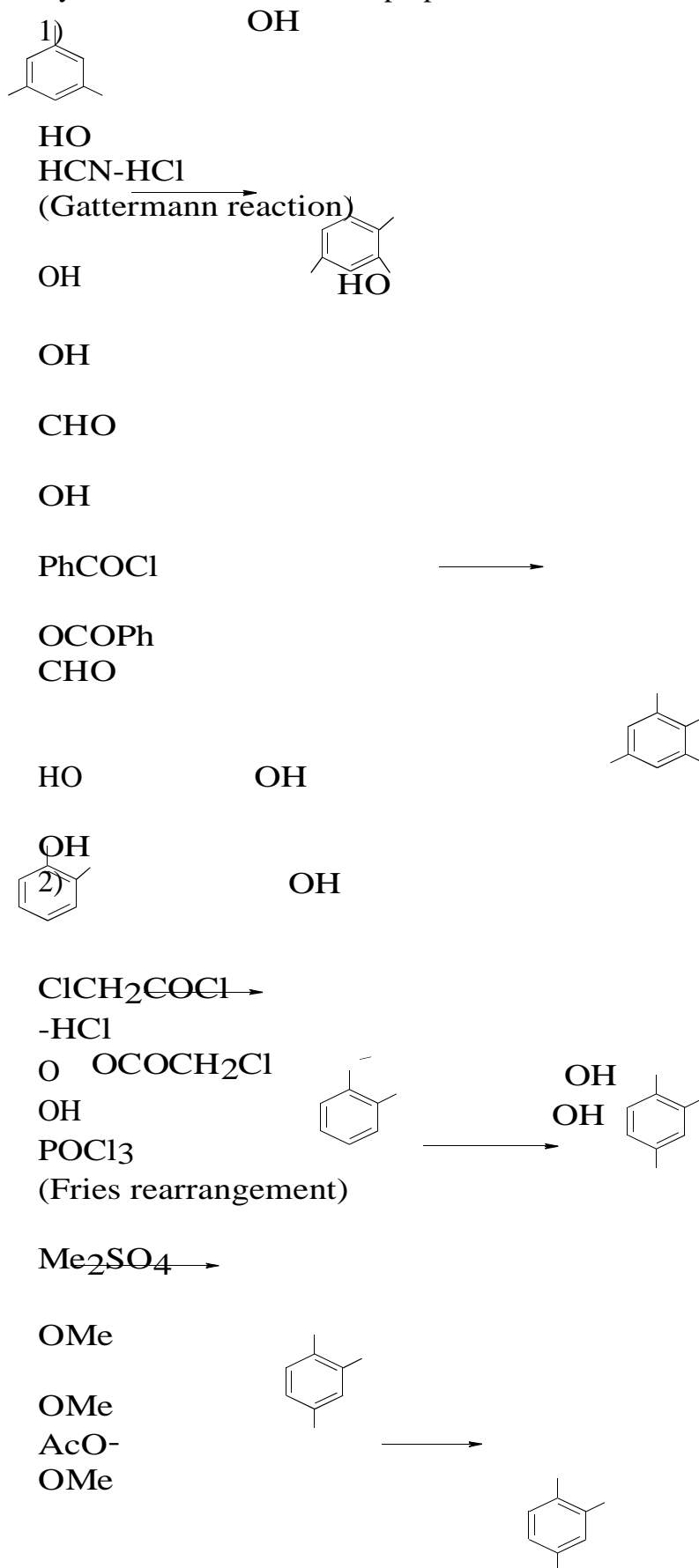
3.3 Synthesis of Anthocyanidin and Cyanidin Chloride

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



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

Cyanidin chloride has been prepared as follows:



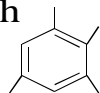
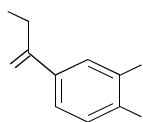
COCH₂Cl

OMe

3)

OCOPh

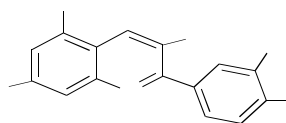
AcO

COCH₂ClCOCH₂OAc

OCOPh

CHO

O



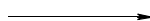
HO

OH

OMe

OMe

HCl

-H₂O, -AcOH HO

OH

OMe

+

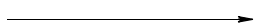
O

OMe

Cl

-

1) OH-



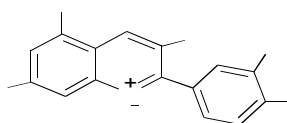
2) HCl

under nitrogen

OH

HO

O Cl

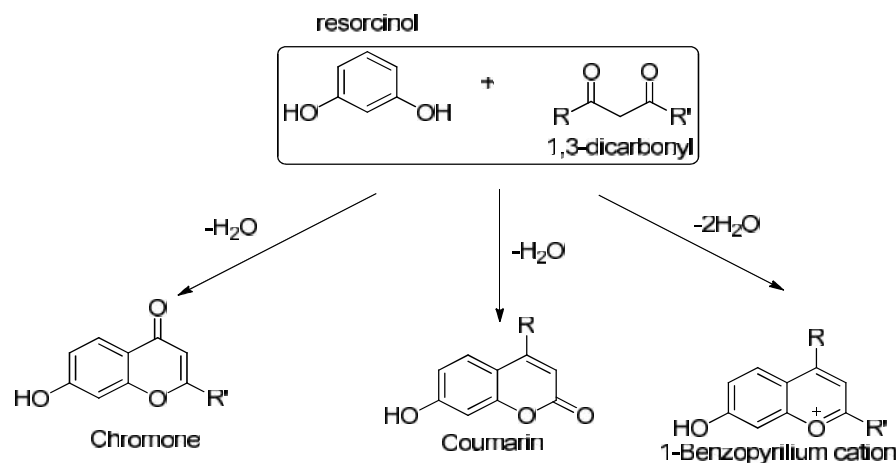


OH OMe

OMe
cyanidine chloride

Scheme 55: Synthesis of Cyanidin Chloride

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



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

SELF-ASSESSMENT QUESTIONS (SAQs)

- Pyrilium salts are generally not stable. As a chemist, how can you enforce stability on this salt type?
- Provide the structure and colour of cyanidin to highlight pH dependent nature of cyanidin
- With the aid of word expression distinguish between anthocyanine and anthocyanidine

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 from 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, coumarin and chromones (Time allowed: 3 mins).
2. Differentiate between the structure of flavylium, flavones and isoflavone. (Time allowed: 3 mins).
3. Illustrate the effect of pH on cyanidin (Time allowed: 3 mins)..
4. Devise a synthesis for 2-phenylbenzopyrilium salt from salicylaldehyde and acetophenone (Time allowed: 5 mins).

7.0 REFERENCES/FURTHER READING

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

CONTENTS

- 1.0 Introduction
- 2.0 Objectives
- 3.0 Main Content
 - 3.1 Warfarin
 - 3.2 Sodium Cromoglycate
- 4.0 Conclusion
- 5.0 Summary
- 6.0 Tutor-Marked Assignment
- 7.0 References/Further Reading

1.0 INTRODUCTION

Although, coumarin has no anti-coagulant activity, it is transformed into the natural anti-coagulant **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 anti-coagulant **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 **anti-coagulant** 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

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

- Ñ list the importance of chromones and coumarins in medicines
- Ñ 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.

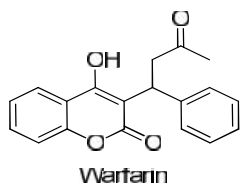
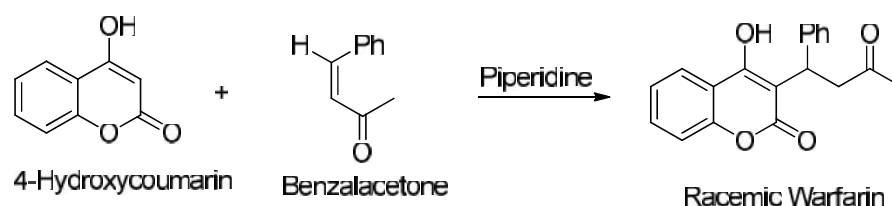


Fig. 17: Structure of Warfarin

Warfarin is used to decrease the tendency for **thrombosis** or as secondary prophylaxis (prevention of further episodes) in those individuals that have already formed a blood clot (**thrombus**). Treatment with Warfarin can help prevent formation of future blood clots and help reduce the risk of **embolism** (migration of a thrombus to a spot where it blocks blood supply to a vital organ).

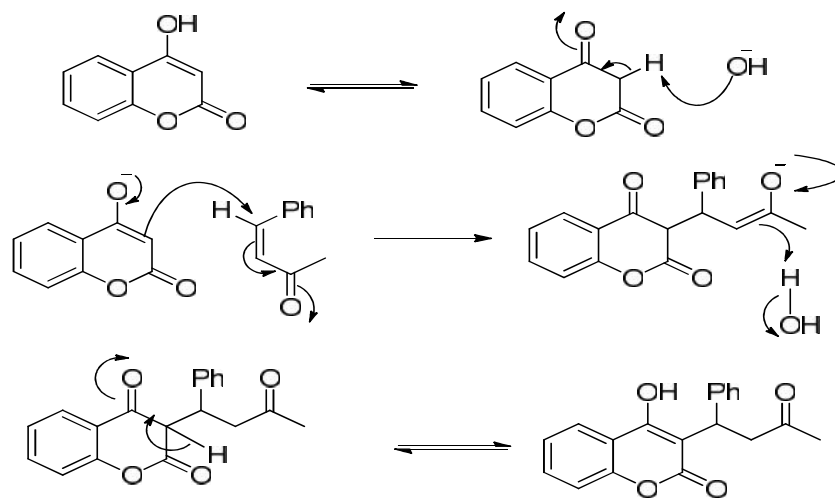
Racemic synthesis

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

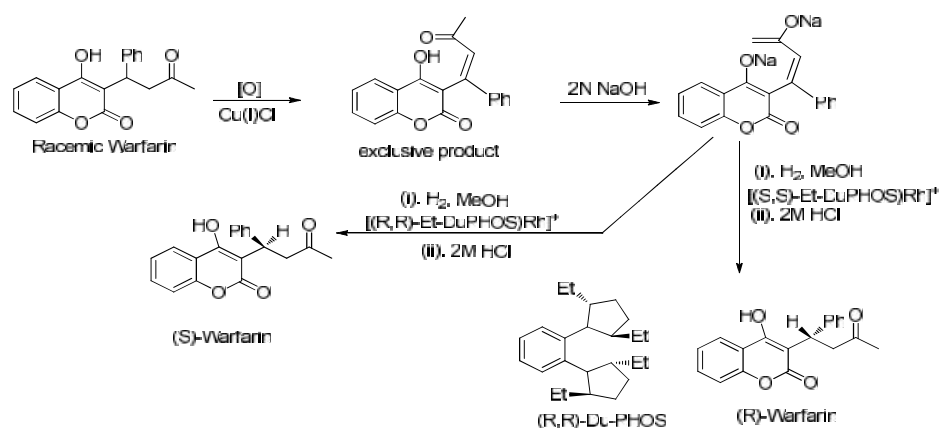
separation. However, these methods are limited to small scale preparations.

1. Asymmetric hydrogenation

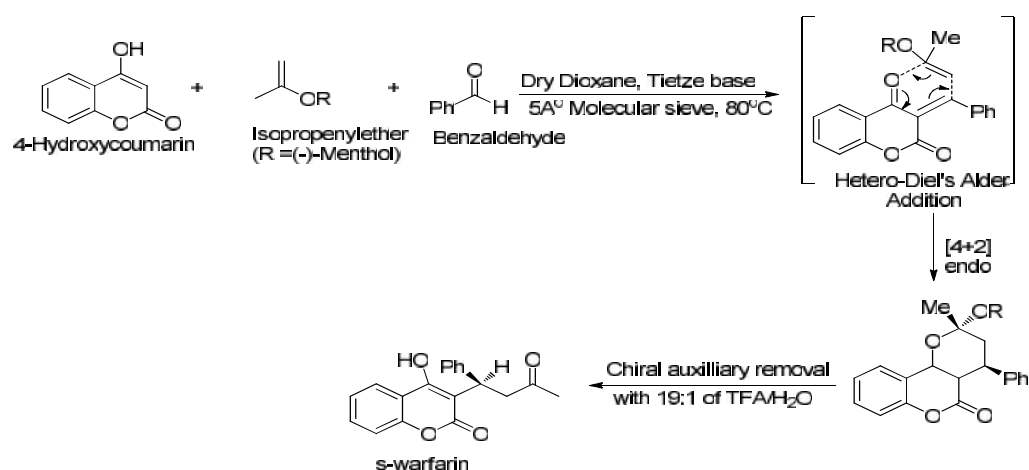
In 1996, researchers at the Dupont Merck pharmaceutical company developed a practical asymmetric synthesis of R- and S-warfarin starting from the racemate and using DuPHOS-Rh(I) catalysed hydrogenation (Scheme 58). Using this method, S-warfarin was obtained in 83% enantiomeric excess (e.e), and R-warfarin 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 (USAN) (also referred to as **cromglicic acid** (INN), **cromoglycate** (former BAN), or **cromoglicate**) is traditionally described as a mast cell stabiliser, and is commonly marketed as the sodium salt **sodium cromoglicate** or **cromolyn sodium**. This drug prevents the release of inflammatory chemicals such as histamine from mast cells.

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

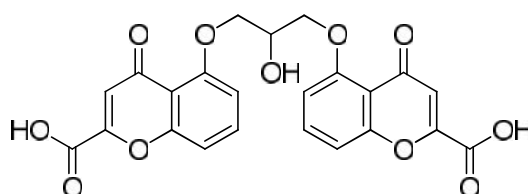


Fig. 18: Sodium Cromoglycate (5,5 -(2-hydroxypropane-1,3-diyl)bis(oxy)bis(4-oxo-4*H*-chromene-2-carboxylic acid)

SELF-ASSESSMENT EXERCISE

- Draw the structure of cromoglycate and indicate its medicinal uses.
- List five (5) other brand names for warfarin
- Compare the anticoagulant potency of (S)-warfarin to that of (R)-Warfarin

4.0 CONCLUSION

In this unit, you have learnt that coumarins 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 elution 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 (Time allowed: 5 mins)
2. Suggest two methods for asymmetric synthesis of warfarin. (Time allowed: 6 mins)
3. What is the medicinal use of warfarin?

7.0 REFERENCES/FURTHER READING

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