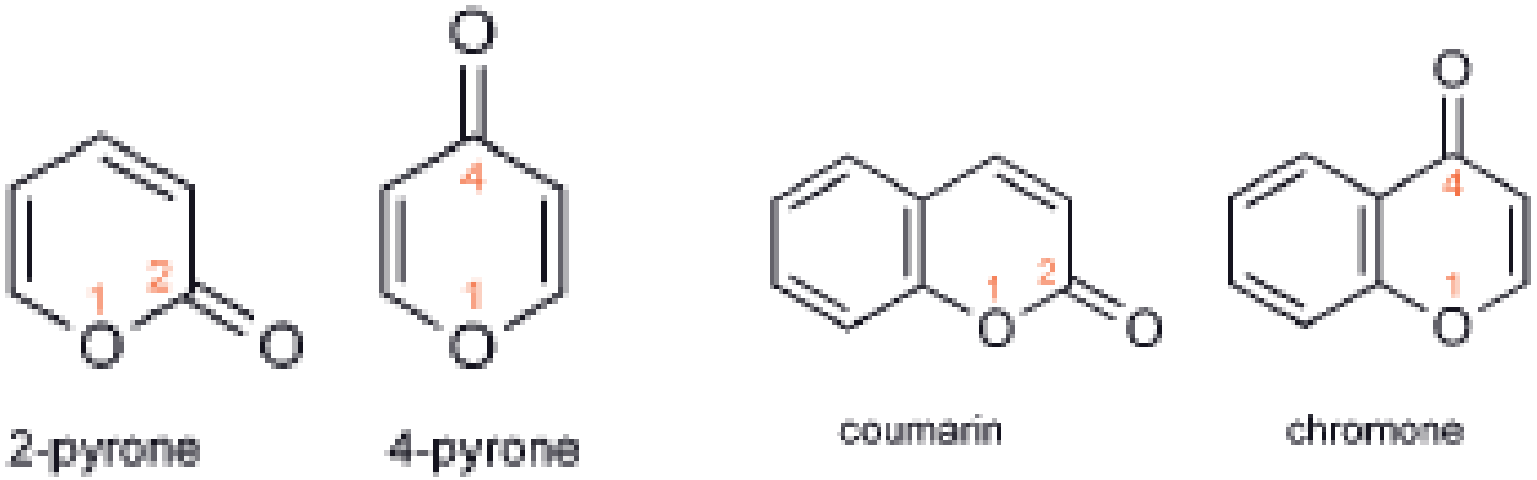
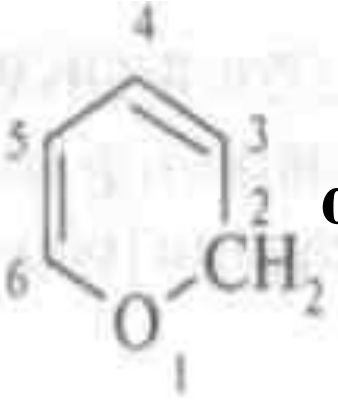
Benzopyrone may refer to either of two ketone derivatives of benzopyran which constitute the core skeleton of many flavonoid compounds

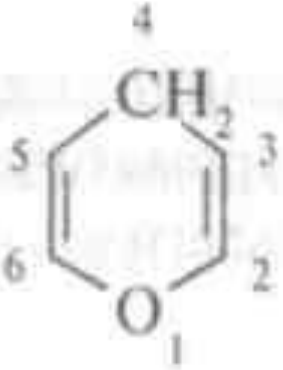
- Chromone (1-benzopyran-4-one)
- Coumarin (1-benzopyran-2-one)



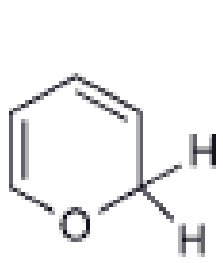
Pyrones or **pyranones** are the class of cyclic chemical compounds. They contain an unsaturated six member ring containing one oxygen atom and a ketone functional group. There are two isomers denoted as 2-pyrone and 4-pyrone. The 2-pyrone structure is found in nature as part of the coumarin ring system. 4-Pyrone is found in some natural chemical compounds such as meconic and helidonic acid



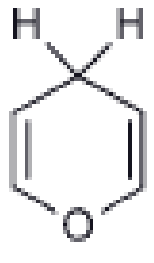
α-pyran



γ-pyran

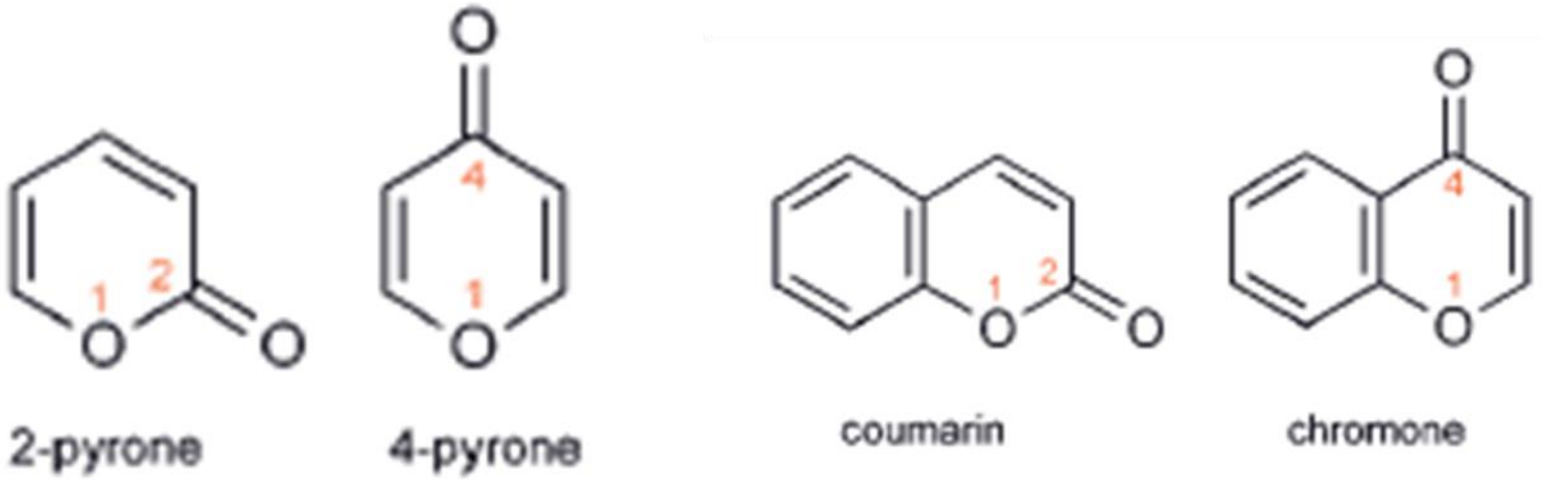


2*H*-pyran



4*H*-pyran

Coumarin is a chemical compound (benzo[b]pyrone-2); a toxin found in many plants, notably in high concentration in the cacao bean, vanilla grass, woodruff, mullein, and bison grass. It has a sweet scent, readily recognised as the scent of newly-mown hay, and has been used in perfumes since 1882. It has clinical medical value as the precursor for several anticoagulants, notably warfarin, and is used as a gain medium in some dye lasers.



Reactions of Coumarins

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

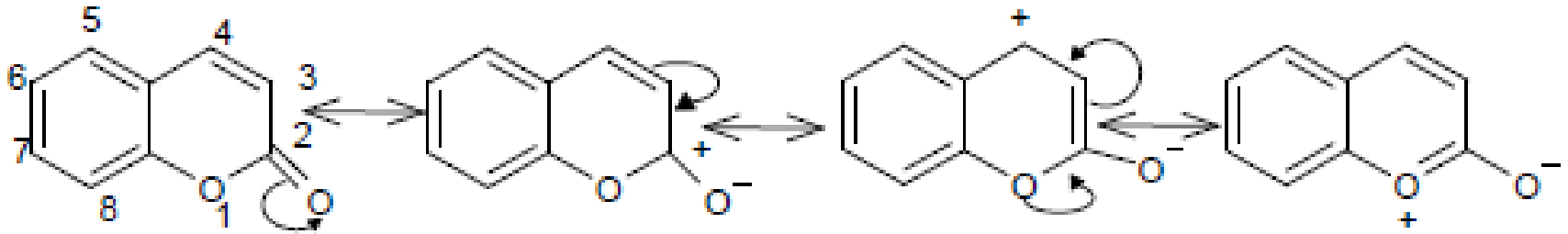
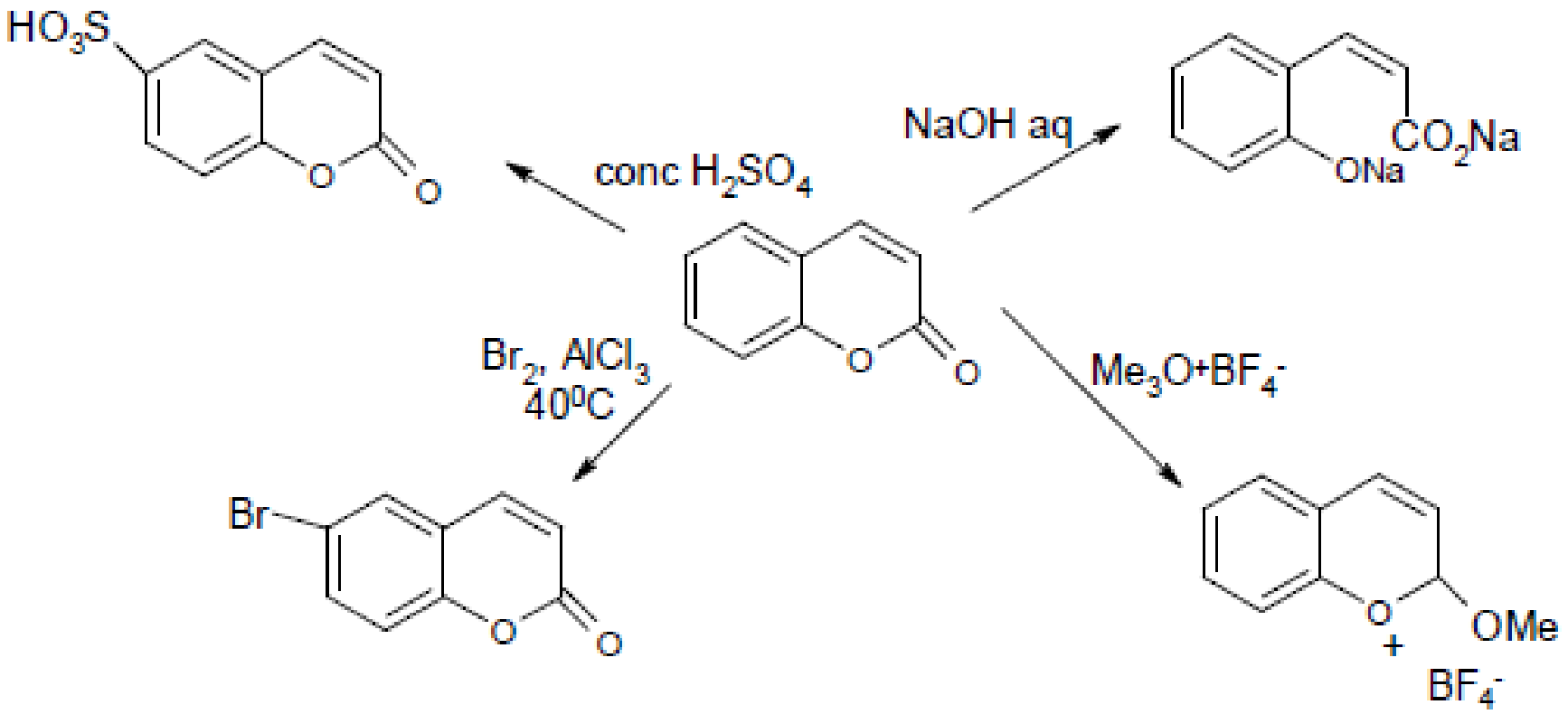


Fig. 14: Resonance structures of Coumarin

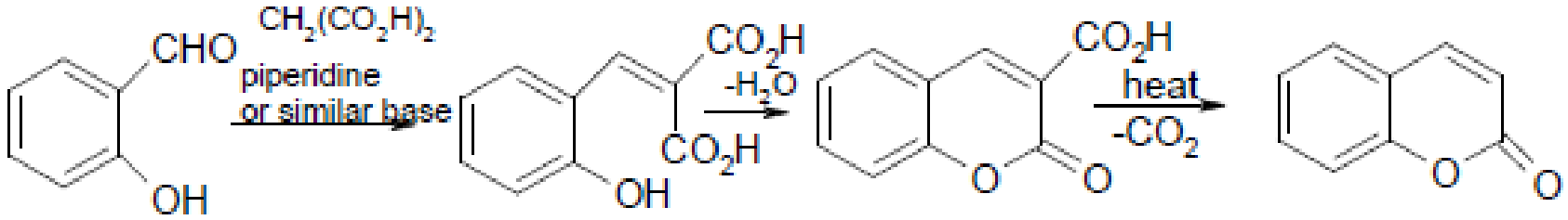
Nucleophilic addition occurs mainly at the carbon atom of the carbonyl group causing ring opening. Similarly, electrophilic reagents containing an element capable of forming a strong bond to oxygen (oxophiles) bind to the oxygen atom of the carbonyl group; thus silanes, for example, give 2-(o-silyl)benzopyrilium salts. Other less oxophilic electrophiles give C-6 substituted coumarins.

In the presence of a Lewis acid e.g. AlCl3, bromine reacts with coumarin to form 6-bromocoumarin, however in the absence of a lewis acids, bromine adds across the 3,4-double bond to give 3,4-dibromo-3,4- dihydrocoumarin. In the presence of pyridine a dehydrobromination reaction takes place, leading to 3-bromocoumarin as the favoured Product.



Scheme 43: Some Reactions of Coumarin

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

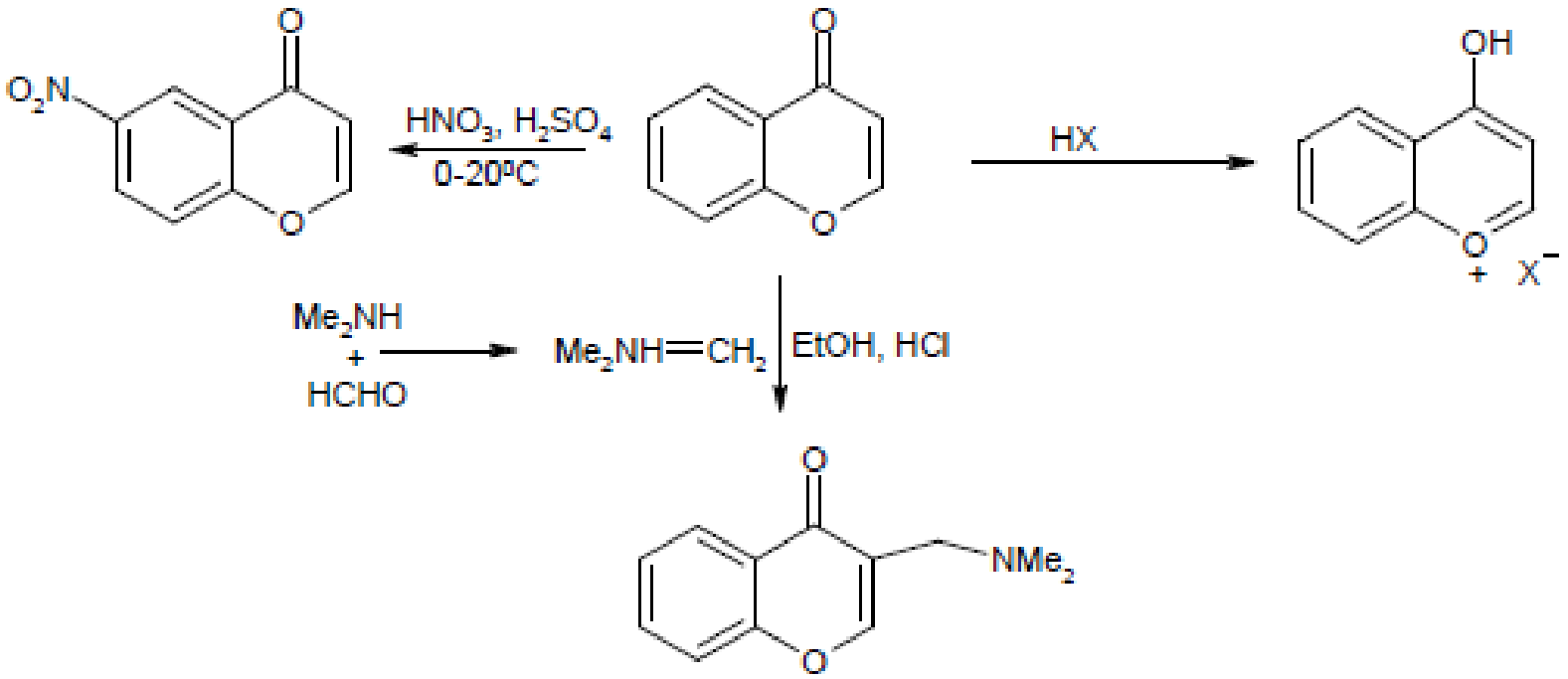


Scheme 44: Synthesis of Coumarin

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

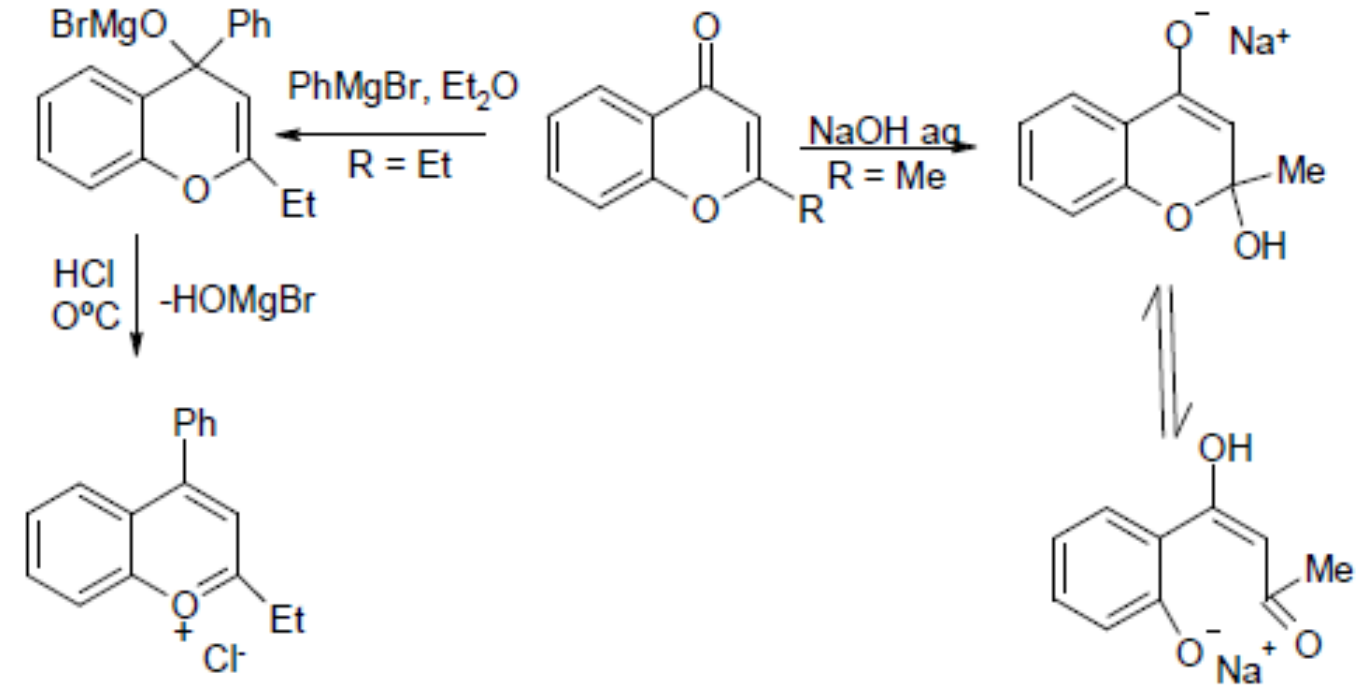
Fig. 15: Chromone Conjugation

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



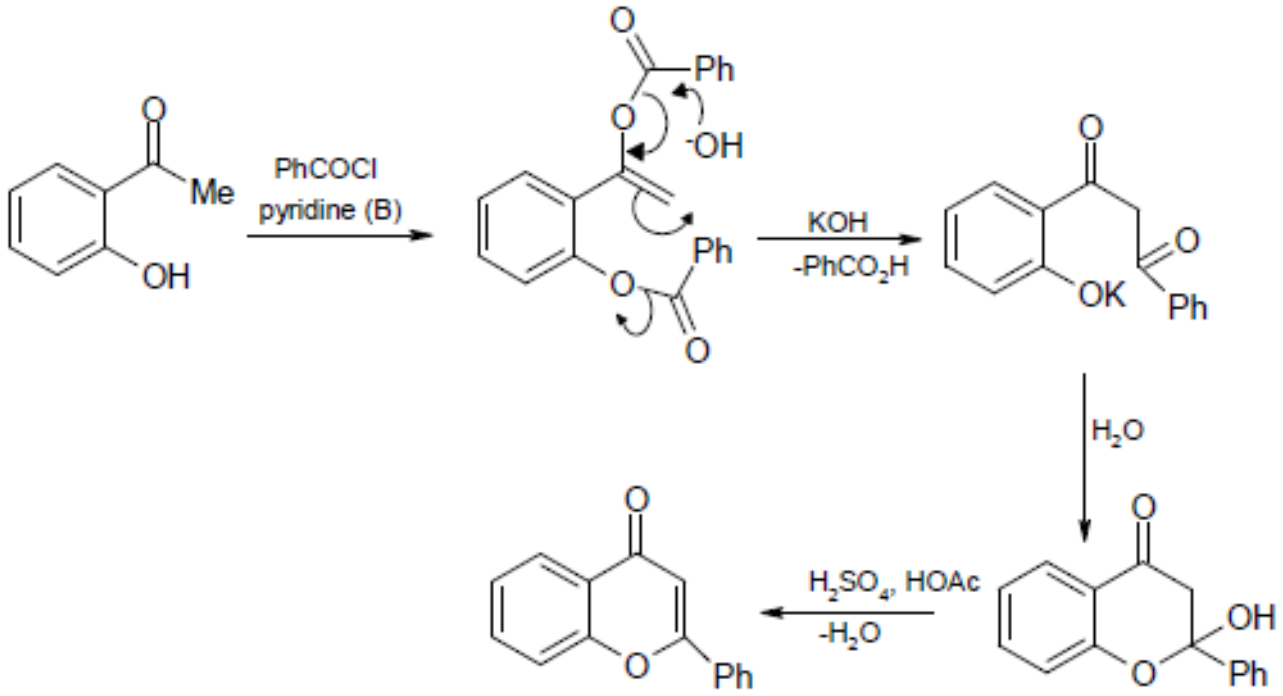
Scheme 47: Reaction of Chromones

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: Reactions of Chromones with Nucleophiles

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



Scheme 49: Synthesis of 2-substituted Chromones

Derivatives of chromone

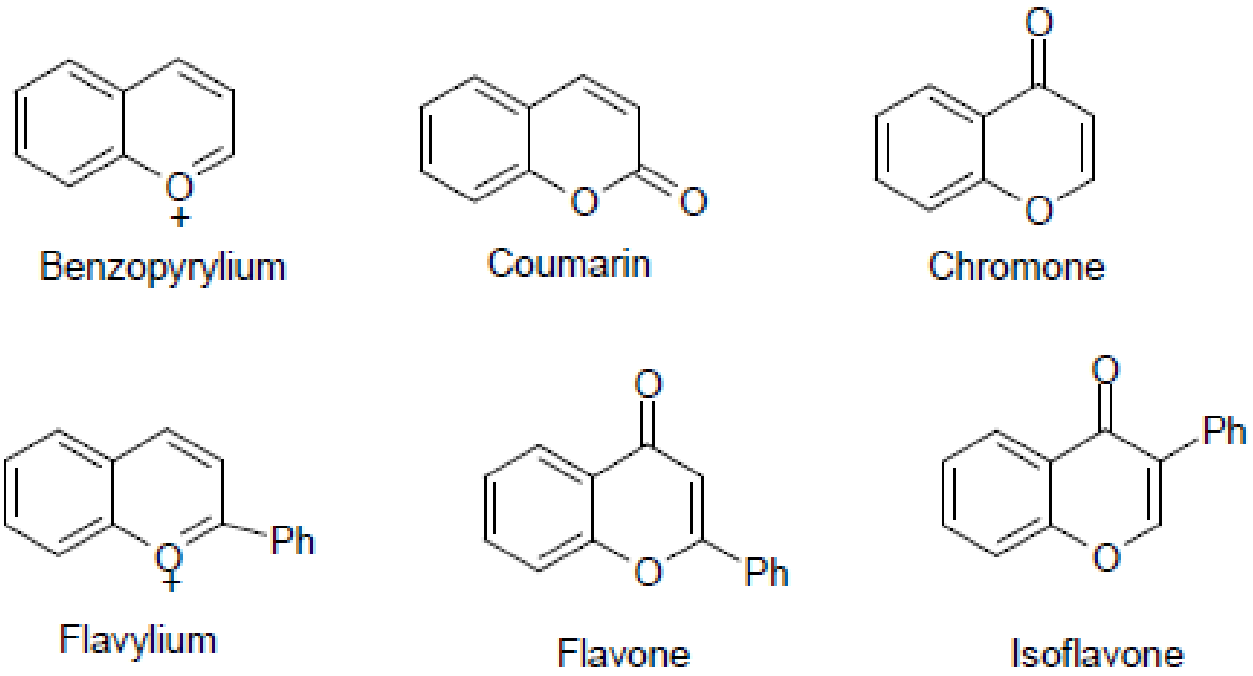
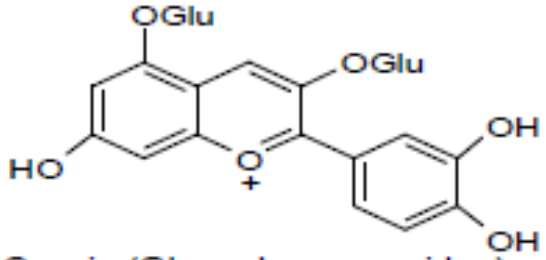
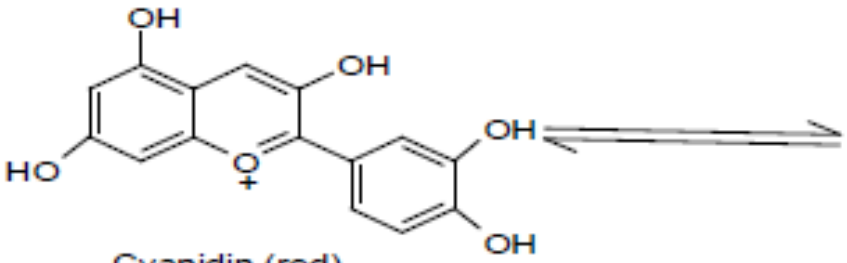


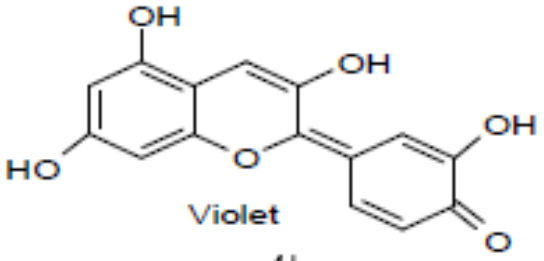
Fig. 16: Structures of Benzopyrilium Salts, Coumarins, Chromones and Flavonoids



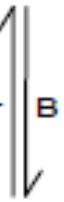
Cyanin (Glu = glucose residue)

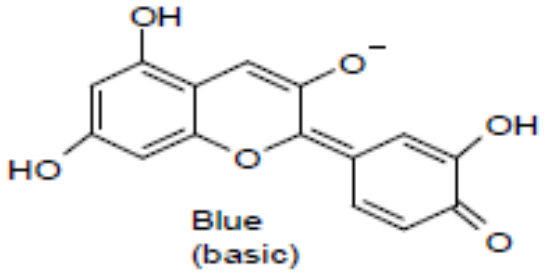


Cyanidin (red)
(acidic)



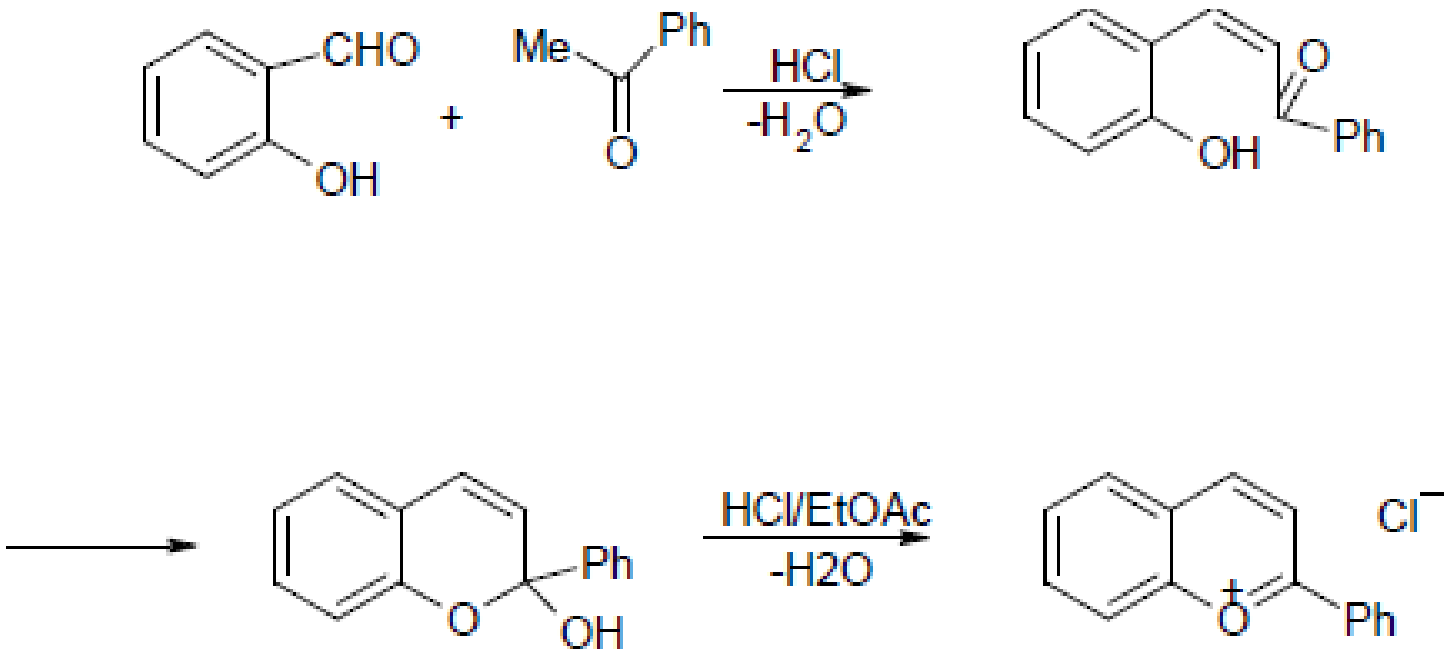
Violet



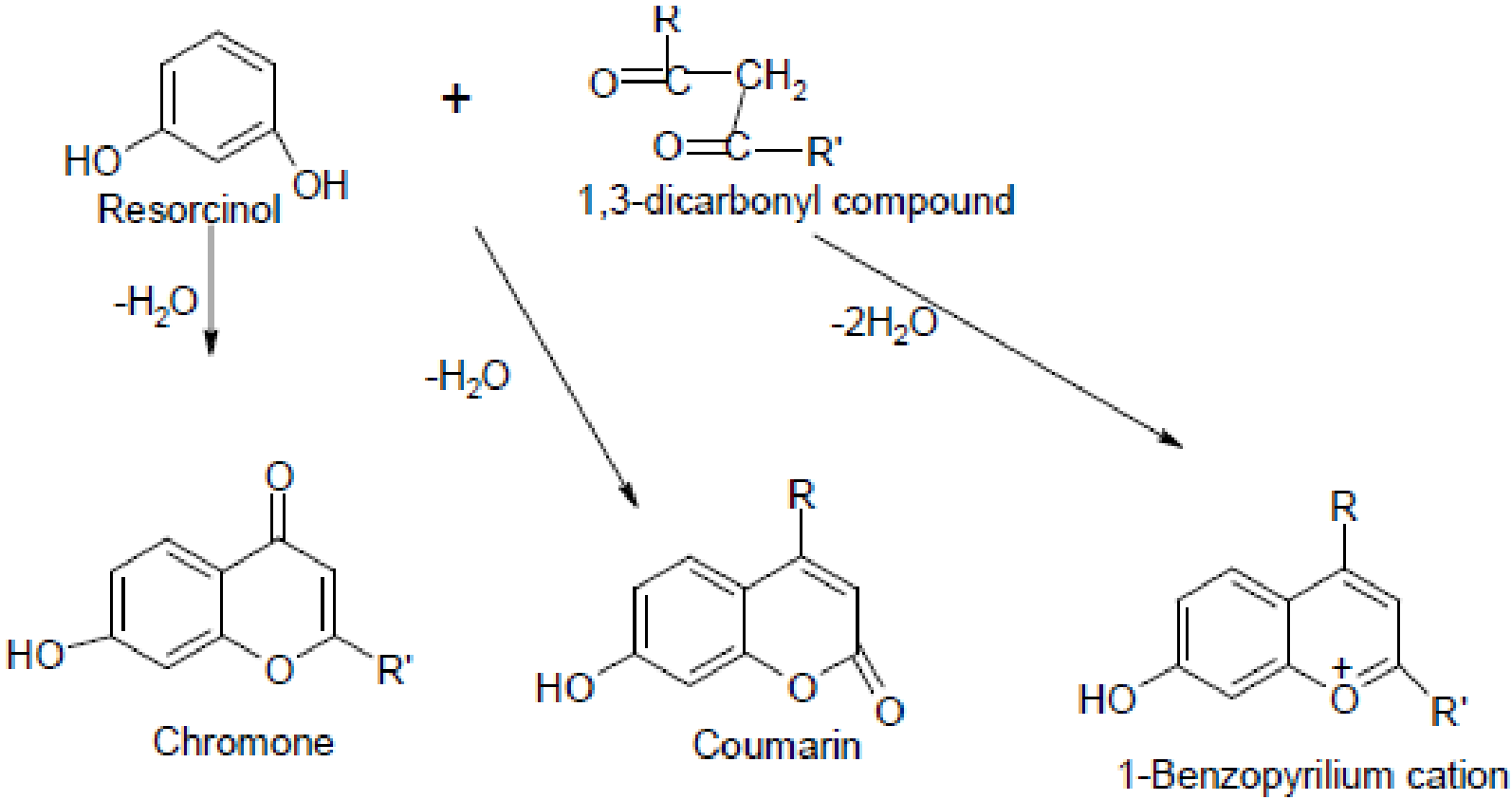


Blue
(basic)

Scheme 52: Effect of pH on Cyanidin

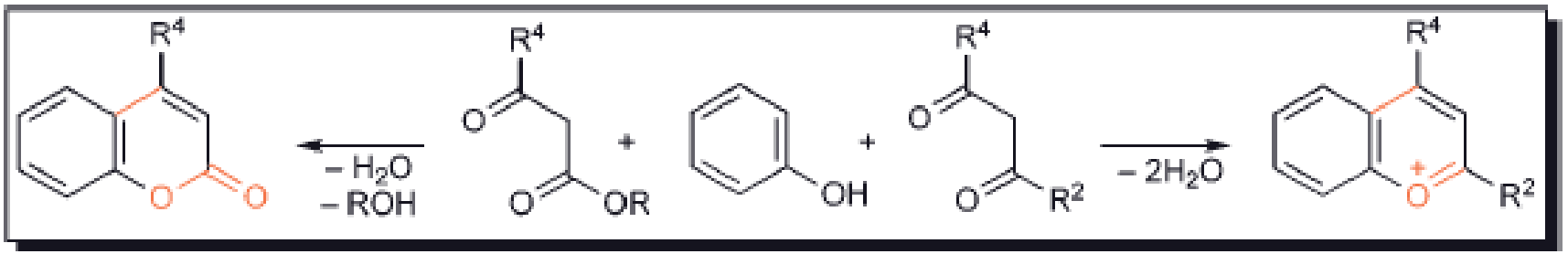


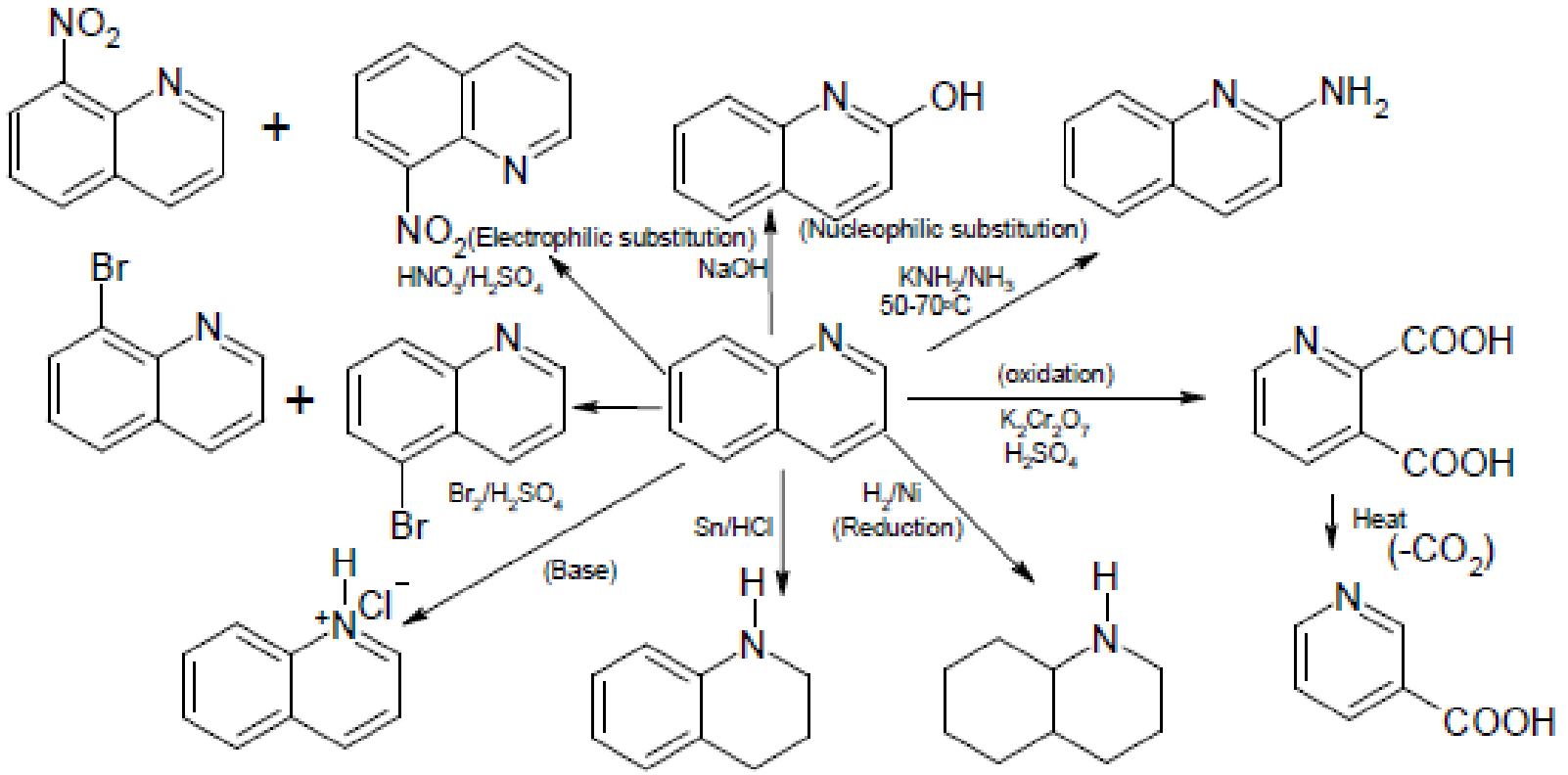
Scheme 54: Synthesis of 2-arylbenzopyrlium Salts (anthocyanidins)



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

There are three important ways of putting together 1 - benzopyryliums, coumarins and chromones; all begin with phenols. The isomeric 2 - benzopyrylium and isocoumarin nuclei require the construction of an *ortho* - carboxy - or *ortho* - formyl - arylacetaldehyde (homophthalaldehyde). Subject to the restrictions set out below, phenols react with 1,3 - dicarbonyl compounds to produce 1 - benzopyryliums or coumarins, depending on the oxidation level of the 1,3 - dicarbonyl component.





Scheme 1: Examples of the General Types (in brackets) of Reaction of Quinoline

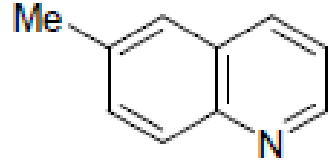
6.0 TUTOR-MARKED ASSIGNMENT

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.

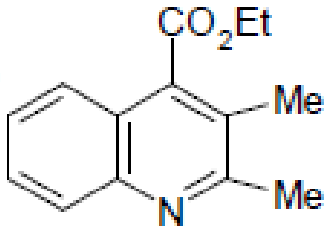
6.0 TUTOR-MARKED ASSIGNMENT

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

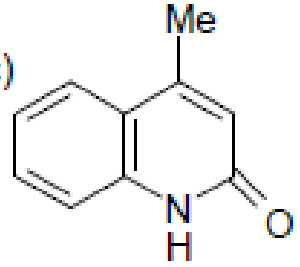
a)



b)



c)



6.0 TUTOR-MARKED ASSIGNMENT

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

6.0 TUTOR-MARKED ASSIGNMENT

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

6.0 TUTOR-MARKED ASSIGNMENT

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

6.0 TUTOR-MARKED ASSIGNMENT

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

8.0 TUTOR-MARKED ASSIGNMENT

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

8.0 TUTOR-MARKED ASSIGNMENT

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

6.0 TUTOR-MARKED ASSIGNMENT

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

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

6.0 TUTOR-MARKED ASSIGNMENT

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

6.0 TUTOR-MARKED ASSIGNMENT

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

10.0 TUTOR-MARKED ASSIGNMENT

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

10.0 TUTOR-MARKED ASSIGNMENT

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

6.0 TUTOR-MARKED ASSIGNMENT

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

6.0 TUTOR-MARKED ASSIGNMENT

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