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CHEMISTRY
Paper No. 14: Organic Chemistry –IV (Advance Organic Synthesis and Supramolecular Chemistry and carbocyclic rings)
Module No. 29: Tropones and Tropolones

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CHEMISTRY

Paper No. 14: Organic Chemistry –IV (Advance Organic Synthesis and Supramolecular Chemistry and carbocyclic rings)

Module No. 29: Tropones and Tropolones

1. Learning Outcomes

After studying this module, you shall be able to

8. Tropone and Tropolone and their structure.
9. Nomenclature of Tropone and Tropolone
10. Synthesis of Tropone and Tropolone
11. Property of Tropone and Tropolone
12. Tropone and Tropolone containing natural product
13. Summary

2. Introduction

Tropones and Tropolones are important development in organic chemistry in recent years and collectively called “non-benzoid aromatic compounds.” Of the small ring compounds, cyclobutadiene is still unknown and generally assumed to be too strained to be stable. Cyclooctatetraene exists in a puckered form, the planar form which would be necessary for aromaticity being again too highly strained. Among them systems may thus be focused on the five- and seven-membered ring systems. These are the anions (a), radicals (b), cations (c) of cyclopentadienyl (I) and cycloheptatrienyl (II) (Figure 1).

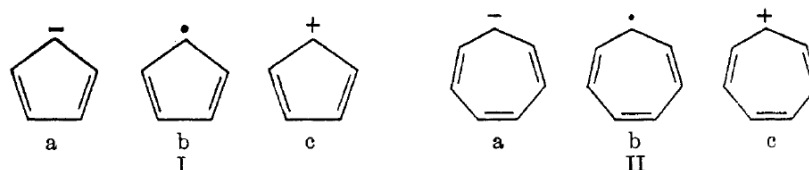
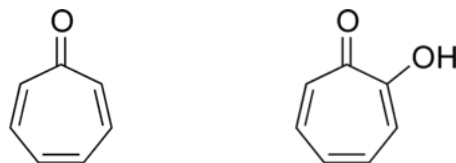


Figure 1:

Further limitation is possible according to molecular orbital theory, which has been used by Huckel (151, 152) to predict that aromaticity will be shown only by those rings having $(4n + 2) \pi$ -electrons. Of the systems mentioned, only the cyclopentadienyl anion and the cycloheptatrienyl cation satisfy this condition.

Tropone or 2,4,6-cycloheptatrien-1-one is a non benzoind organic compound. Tropone consist of a ring of seven carbon atoms with three conjugated alkene group and ketone group. The tropone moiety can be found in biomolecules such as colchicines (medicine commonly used to treat Gout), stipitatic acid and hinokitiol (natural monoterpenoid found in the wood of trees. It has inhibitory effects on Chlamydia Trachomatis – a bacteria responsible for spreading STD).



Tropone

Tropolone

Tropolone or 2-hydroxy-2,4,6-cycloheptatrien-1-one is a derivative of tropone. It has additional alcohol group next to the ketone.

3. Nomenclature of Tropone and Tropolone

The trivial name “tropone” has now been sanctioned by such wide usage that it may be considered as generally accepted. Its IUPAC name is “2-hydroxy-2,4,6-cycloheptatrien-1-one.” As the name indicates, the carbonyl oxygen is always taken to occupy position 1 and the hydroxyl group position 2.

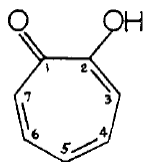
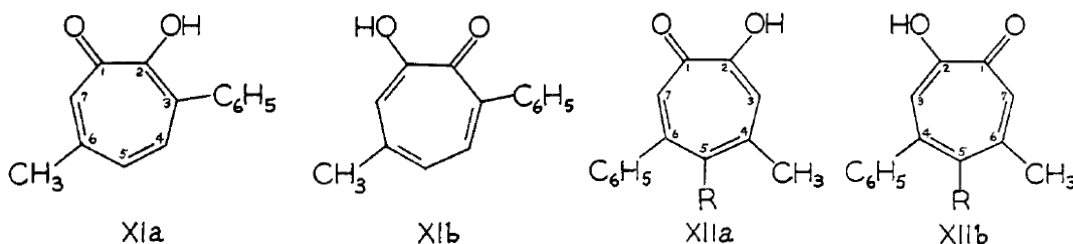


Figure 2 : Tropolone

To make possible the assignment of a single unambiguous name, the following rules are proposed: (1) That formula is used which leads to the lowest total for the numbers assigned to the substituents (e.g., compound XI is named as 6-methyl-3-phenyltropolone, corresponding to XIa, and *not* as 4-methyl-7-phenyltropolone (XIb)). (2) Where the above rule is indecisive, that substituent which is named first receives the lower of two possible numbers (e.g., compound XII (R = H) is 4-methyl-6-phenyltropolone (XII a) and *not* 6-methyl-4-phenyltropolone (XII b) ; compound XII (R = Br) is 5-bromo-4-methyl-6-phenyltropolone and *not* **5-bromo-6-methyl-4-phenyltropolone**).



The “Tropone” name is used to designate 2,4,6-cycloheptatrien-1-one, but the use of other trivial name has been kept to minimum.

3. Classes of Tropolones

The few natural tropolones known at present can be divided into three groups:

1. Isopropyltropolones is the simplest tropolones, which have been occur in several conifers (cone bearing plants) and all conifers belonging to the family *Cupressaceae*, examples of this class are α -, β , and γ -thujaplicin (Figure 3) (chemical substances isolated from red cedar tree) (they are known for their potent anti-fungal and anti- bacterial properties. They are also known to be potent anti-oxidants).

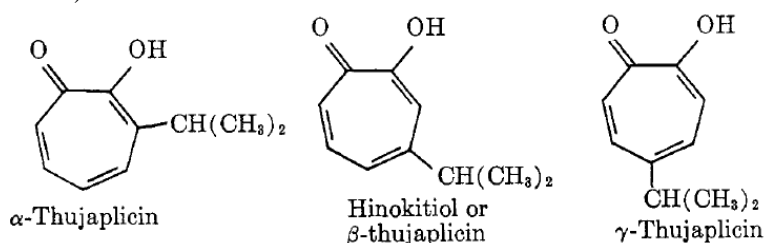


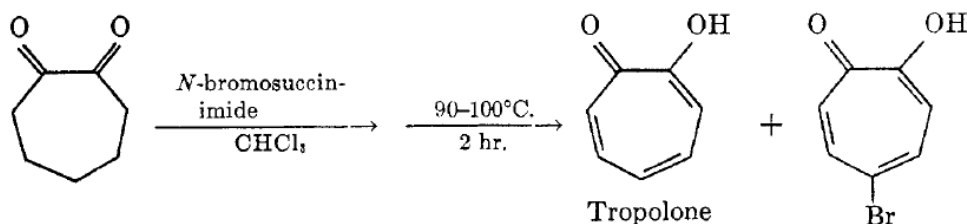
Figure 3: α -, β , and γ -thujaplicin

- The second class is belong to hydroxytropolonecarboxylic acids and have been found only in mould species of the *Panicillium* family.
- Colchicine and a few very closely related compounds have been isolated from various *Liliaceae*, particularly from *Colchicum autumnale* (meadow saffron or autumn crocus) and related species.

4. Synthesis of Tropones and Tropolones

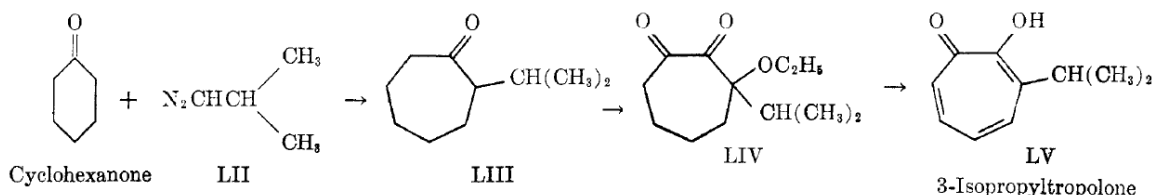
1. From Cycloheptaxone Derivatives :

- A. *From 1,2-cycloheptanediones* : The bromination of 1,2-cycloheptanedione provide mixture of products, which give tropolone and its bromo derivatives with lose of hydrogen bromide on warming.



Scheme 1 : Synthesis of Tropolone.

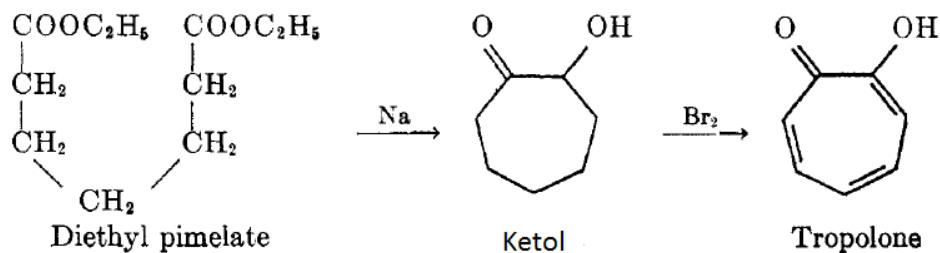
The synthesis of substituted tropolones by this method requires a source of substituted cycloheptanones. Two methods have been widely used for their preparation : (1) cyclization of the appropriately substituted suberic acids, (2) ring enlargement of the corresponding cyclohexanone with diazomethane. The conversion to the diketone is always effected with selenium dioxide. The ring expansion of 2-isopropylcyclohexanone with diazomethane fails, but the desired ketone (LIII) is obtained from the ring expansion of cyclohexanone by reaction with diazoisobutane (LII). Its oxidation by selenium dioxide in ethanol yields LIV rather than the simple dione, but this loses ethanol during the remaining stages and affords the desired product (LV) (Scheme 2).



Scheme 2: Synthesis of Tropolone derivatives.

- B. *From 2-hydroxycycloheptone* :

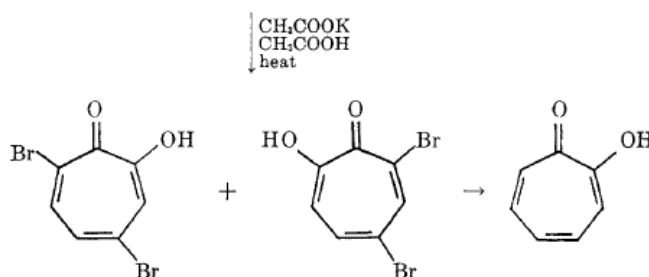
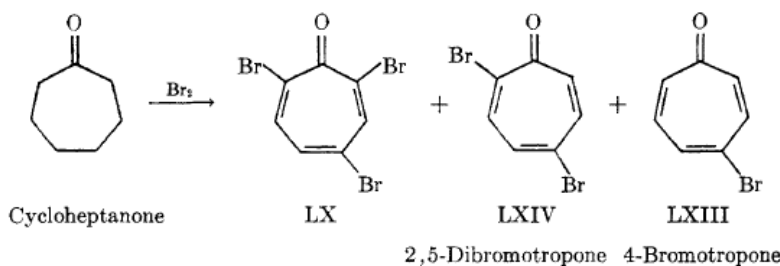
Unsubstituted tropolone has been obtained from diethyl pimelate by acyloin condensation to the ketol followed by bromination. The bromo derivatives leads smoothly to tropolone after the bromination of the diketone (which therefore cannot be an intermediate) (Scheme 3).



Scheme 3: Synthesis of unsubstituted Tropolone.

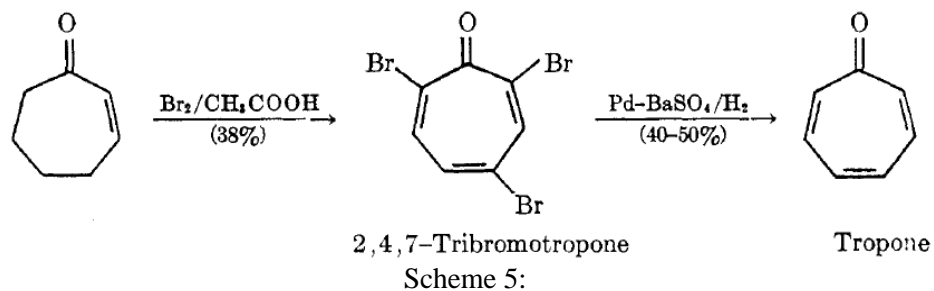
C. From cycloheptanones, cycloheptenones, and cycloheptadienones :

The bromination of cycloheptanone provide a intermediate tribromocycloheptanone and tetrabromocycloheptanone may be isolated. Furthermore, its bromination in acetic acid provide 2,4,7-tribromotropone in 50% yield and 4-bromotropone and 2,5-dibromotropone have been identified as byproducts. It was also observed that tribromosubstitutedtropone provide mixture of 3,5- and 3,6-dibromotropolones by refluxing with potassium acetate in acetic acid or butanol (Scheme 4).

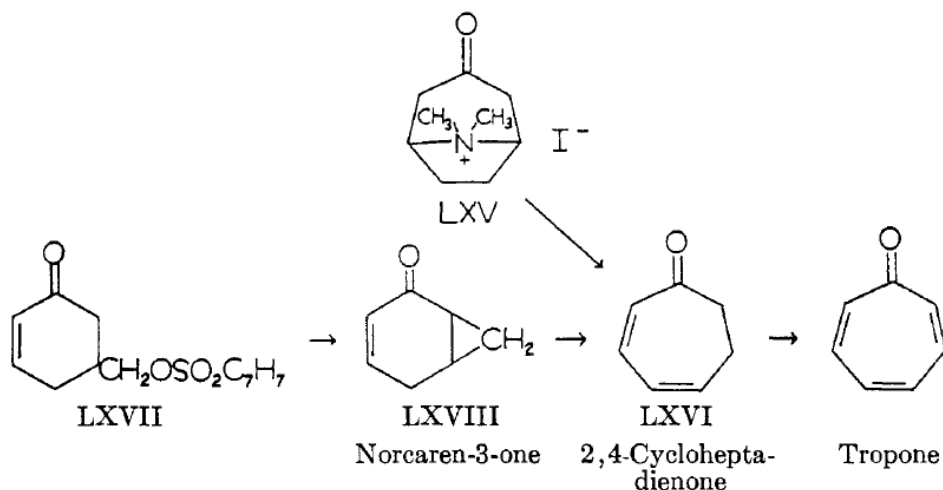


Scheme 4: Synthesis of Tropone and Tropolone.

Furthermore, the tropone can be synthesized by the bromination of 2-cyclohepten-1-one with four molecules of bromine in acetic acid, yielded 2,4,7-tribromotropone. This tribromotropone further convert to tropone by the hydrogenolysis in the presence of poisoned catalyst (palladium on barium sulfate) and interruption of the reaction after the uptake of three molecules of hydrogen. Incomplete hydrogenolysis has yielded 2,7-dibromotropone (Scheme 5).



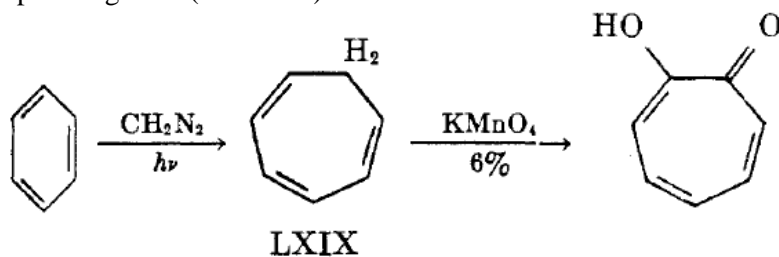
Two routes have been described for the synthesis of tropone, in which 2,4-cycloheptadienon is the key intermediate. In the first route, a mixture of cycloheptadienones was to be produced in one step by Hofmann degradation of tropinone methiodide and converted into tropone by reaction with bromine in carbon tetrachloride. In the second route, the p-toluenesulfonate of 5-hydroxymethylcyclo-2-hexen-1-one was prepared and converted to the unsaturated ketone by treatment with sodium hydroxide. This reaction is considered to proceed *via* norcaren-3-one.



2. From Benzene derivatives :

Ring enlargement of benzene derivatives has been accomplished by reaction with diazoalkanes. The reaction of benzene with diazomethane takes place under the influence of ultraviolet light and

the cycloheptatriene yielded from benzene. This cycloheptatriene can be oxidize to tropolone by using potassium permanganate (Scheme 7).

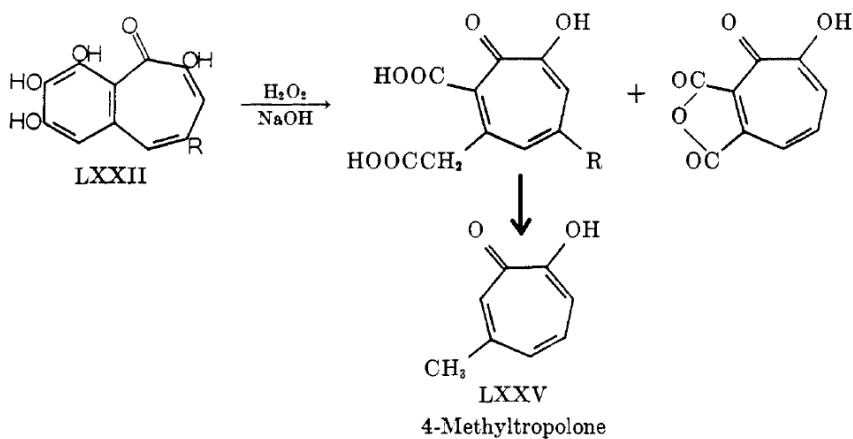


Cycloheptatriene

Scheme 7: Synthesis of Tropolone from benzene.

3. From Purpurogallin :

Pyrogallol is use for the synthesis of purpurogallin. The oxidation of purpurogallin provide the 30-35% yield of dicarboxylic acid derived with small amount of other product. The acidic derivative loses carbon dioxide at its melting point and smoothly converted to 4-methyltropolone (Scheme 8).



Scheme 8: Synthesis of 4-Methyltropolone from purpurogallin.

5. Properties of Tropone and Tropolone

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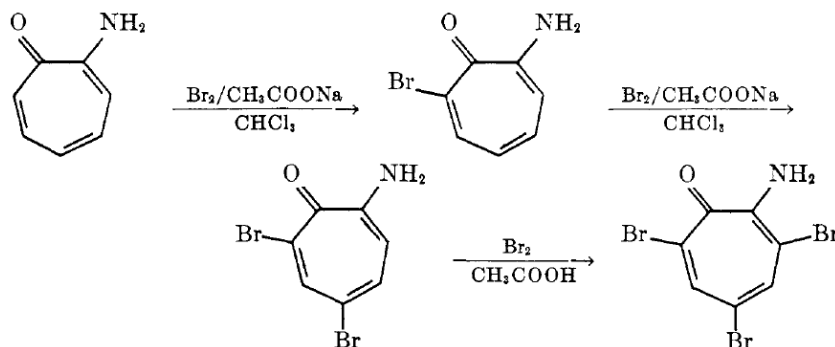
Azo Coupling: A large number of tropolone derivatives are reported in which there is free 5-position have been successfully coupled in alkaline solution with diazotized p-toluidine and several other diazonium salts. 4-tert-butyltropolone is exception, where steric hindrance may be too great, all of these substances give coupling products.

Nitrosation: Nitrous acid (in glacial or aqueous acetic acid solution) converts tropolones to the 5-nitroso derivatives. The reaction proceeds in high yield and reduction of the nitroso compound thus obtained provides the best route to the corresponding 5-aminotropolone in the absence of interference from other substituents. When the 5-position is blocked, substitution at the 3-position may be possible, but 5-methyl-3-nitrosotropolone, the only product of this type reported.

Nitration: Nitric acid (in glacial acetic acid) used for the nitration reaction. Some time, cupric nitrate in acetic acid can be used.). The main product, 5-nitrotropolone, is accompanied by a smaller amount of the 3-isomer. The nitration of 4-methyltropolone similarly produces 5-, 7-, and 3-nitro derivatives in yields decreasing in that order.

Sulfonation: The sulfonation of tropolone with sulfamic acid leads to the 5-sulfonic acid, possibly accompanied by the 3,5-disulfonic acid. When the 5-position and 4-position is blocked by an alkyl group or by halogens, the reaction takes place equally readily in the 3-position. 4-methyltropolone yield a product, 6-methyltropolone-3-sulfonic acid after couple with p-tolyldiazonium chloride.

Halogenation: The mono-, di- and tri substitution of tropolones with halogen has been studied extensively. Only 3-mono and 3,7-disubstituted has been observed with the unsubstituted tropolones. Only diiodotropolone is doubtful case, in which the position of second iodine is unknown. Two reactions have been reported, which yield predominantly the 5-halogen derivative: (a) 5-bromotropolone obtained after the reaction of cupric complex of tropolones with bromine; (b) The sodium salt of tropolone reacts with iodine monochloride giving a mixture of 5-chlorotropolone and a complex from which 3-iodotropolone is obtained by the action of water. 3- and 7-substituted halogen derivatives of tropolones also occurred after the reaction of alkyl substituted tropolones with halogen, but a small amount of 5-substituted tropolones also obtained. When 3- and 7- positions are blocked, 5-substitution occurs readily and 3,5,7-trihalogen derivatives are readily obtained.



Scheme 9: Halogenation of Tropolone.

Hydroxylation: Oxidation of tropolones with alkaline persulfate yields a mixture of the 3- and 5-hydroxy derivatives in which the latter predominates. The 5-hydroxytropolones and their ethers are also obtained after diazotization and hydrolysis or alcoholysis of the corresponding 5-aminotropolones.

Hydroxymethylation: Hydroxymethylation reaction carried out with alkaline formaldehyde solution at 60-65 °C, 3-substituted product formed as a major product. Disubstituted and Trisubstituted products also formed during the reaction. Identification of the products has been carried out by reduction of the hydroxymethyl compounds with hydriodic acid to the corresponding methyltropolones and rearrangement of the latter to methylbenzoic acids.

6. Tropone and Tropolone containing Natural products

The tropone moiety has been found in several natural products. Alkoxy group and α -hydroxy group containing tropolones also common in nature. The simplest tropolone isolated from *Pseudomonas lindbergii* ATCC 31099 and *Pseudomonas plantarii* ATCC 43733. The simplest tropone is not a naturally occurring compound, it has been used as basic building block in various cycloaddition. Naturally occurring tropolones are relatively rare. The simplest tropone is nezukone and it was isolated from *Thuja standishii* (Figure 1). Some tropone have amino or thio group rather than hydroxyl group i.e. *Manicoline A*, has a amino group and it was isolated from *Dulacia guianensis*. Antibiotics tropodithietic acid and its valence tautomer, thiotropocin, have either thiosubstituents or a carbonesulfur double bond (Figure 1).

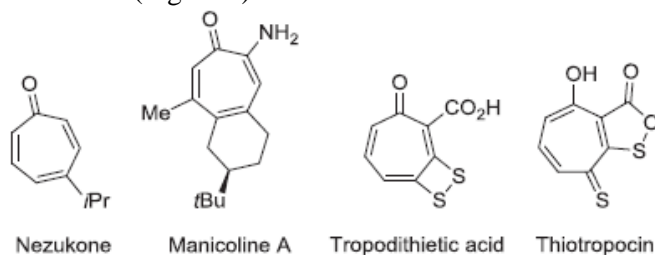


Figure 4: Naturally occurring Tropone.

A unique fused tetracyclic carbon skeleton was found in diterpenoid tropolones. Some diterpenoid tropolones have been isolated and characterized thus far: harringtonolide, hainanolidol, fortunolide A, fortunolide B, and 10-hydroxyhainanolidol (Figure 5).

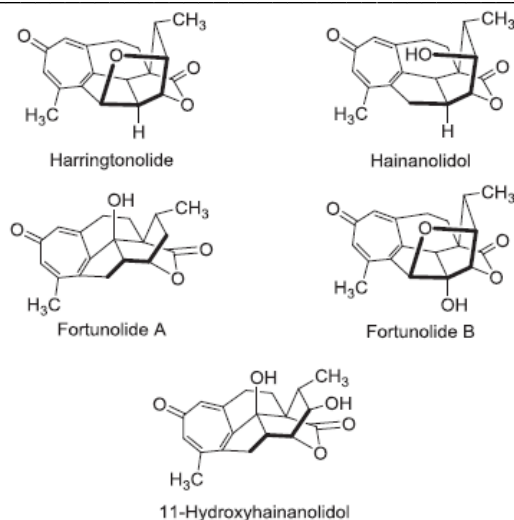


Figure 5: Diterpenoid Tropones.

Harringtonolide was first found to inhibit the growth of beans and tobacco. Subsequently, more interesting biological activities have been discovered, such as antiviral, anti-fungal, and anti-cancer activities.

Benzotropolone contain a benzo-fused tropolones core (Figure 6). Purpurogallin is the most common compound of this family. It is a reddish crystalline substance isolated from nutgalls and oak bark. It is used as anti-oxidant in non-edible oil, fuels and lubricants. Theaflavins family have also benzotropolone skeleton and the benzene unit is often part of a flavones moiety. Theaflavins are found in black tea leaves.

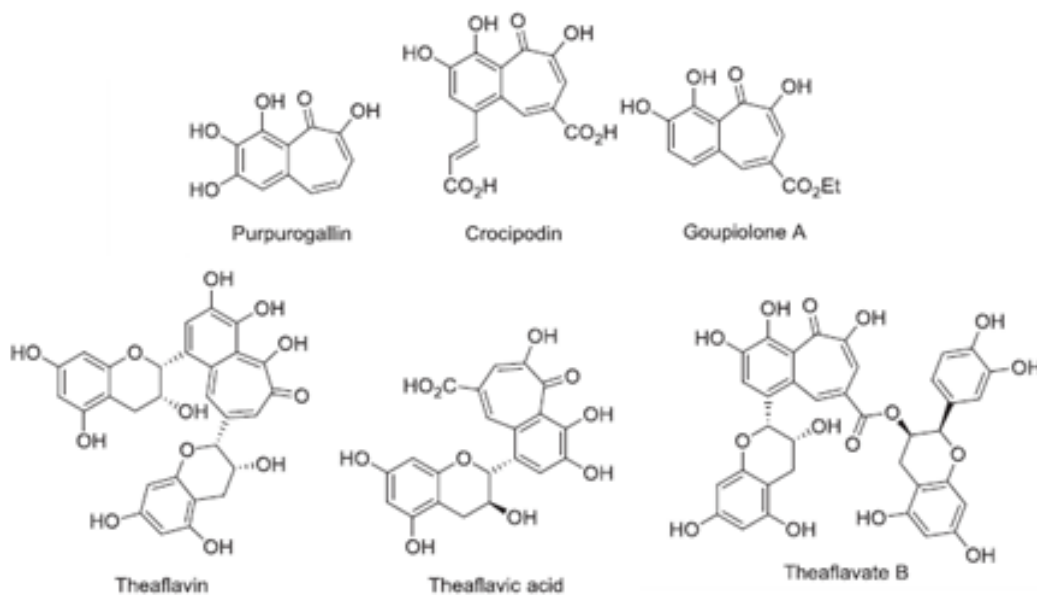


Figure 6: Benzotropolones

7. Summary

1. Tropones and tropolones refer to non-benzenoid seven-membered aromatic compounds with a carbonyl group, which are also called troponoids or tropolonoids.
2. Tropolones are classified on the basis of their naturally isolation.
3. Tropones and Tropolones show various type of reaction such as Azo-Coupling, Halogenation, Hydroxylation, hydroxymethylation etc.
4. Tropones and Tropolones are present in various natural products.