RECENT ADVANCES IN THE CHEMISTRY OF TROPONOIDS AND RELATED COMPOUNDS IN JAPAN

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ABSTRACT

Extensively reviewed are recent contributions of Japanese chemists to the development of troponoid chemistry over the past five years. The contents are divided into three parts: (i) reactions of monocyclic troponoids and their benz-analogues (benzologues) towards electrophilic and nucleophilic reagents as well as photochemical and thermal reactions; (ii) syntheses and reactions of heptafulvenes, sesquifulvenes, sesquifulvalenes and azulenes in addition to syntheses of troponoids and azulenes fused with heteroaromatic ring systems; (iii) syntheses of tropone and its simple derivatives and naturally occurring tropolones and finally theoretical discussions concerning the physical properties of troponoids. It is shown that many troponoid compounds react as cyclic polyolefins but some can undergo reactions, clearly typical of aromatic compounds. It is also shown that there remain many interesting and important problems in this field that await further studies.

INTRODUCTION

It is rather unusual for the Chairman of the symposium to accept an invitation to present a lecture. However, because of my involvement with troponoid chemistry for some twenty years, the committee felt that it would be appropriate for me to review the contributions in recent years of Japanese chemists in this field.

Having accepted this important and difficult task, I have attempted to cover the Japanese contributions as widely as possible, even at the sacrifice of some important aspects of individual studies. The literature coverage will be limited to that having appeared since 1965 and some important unpublished results will be included[1]. However, because of limitation of time, I regret that the omission of many papers is inevitable and that contributions from foreign countries are virtually excluded in this presentation.

I think it will be convenient to mention here, the types of compounds which are the subject of this lecture. First, I will describe the chemistry of monocyclic troponoids (I) and their benz-analogues (II). Troponoids are generally

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thought to be aromatic to some extent, by the resonance contribution of the dipolar structure (Ia) having a 6π electronic system. However, substituents (shown by X) and annelation with benzene rings (or a heteroaromatic nucleus) alter to a remarkable extent the properties of individual troponoid compounds.

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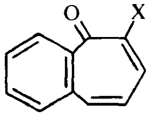
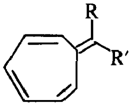


(II)

The second part comprizes heptafulvene (III) and other compounds having a heptafulvenoid chromophore, such as sesquifulvalene (IV), heptafulvalene (V), azulene (VI) and heterocyclic compounds (VII and VIII) having this chromophore. In the third part, I will briefly discuss some problems concerning syntheses of some troponoids, naturally occurring troponoids, and physicochemical and theoretical studies.



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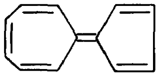

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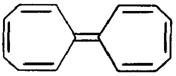

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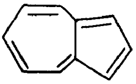

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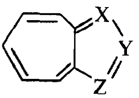

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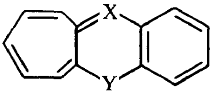


(VIII)

MONOCYCLIC TROPONOIDS AND THEIR BENZ-ANALOGUES

Reaction with the electrophilic reagents

Halogenation

While tropones afford addition products, which yield substituted tropones on subsequent heating, tropolones are easily halogenated at the 3, 5 and 7 positions. However, such trihalotropolones now show considerable unsaturated character, and undergo further halogenation to give, for example, a hexachlorodiketone (IX) or its hydrate (X), which in turn rearrange to give a hexachlorocarboxylic acid (XI); and then finally give rise to chloranil (XIII) through polychlorophenols (XII: R = H or Cl)[2].

3,7-Dibromohinokitiol (XIV) gives, through a tribromodiketone (XV), a pentabromodiketone (XVI) which rearranges to a six-membered pentabromo acid (XVII). Similarly, 5,7-dibromohinokitiol (XVIII) is also brominated to a tribromodiketone (XIX) or its hemiketal (XX) in ethanol. The diketone (XIX) does not tautomerize to its enolic form (XXI), but on heating with ethanol, (XIX) reverts to the original compound (XVIII), ethanol being oxidized. However, when *t*-butanol is used, (XIX) is isomerized to tribromohinokitiol (XXI)[2]. Free tribromohinokitiol[3] once it is formed is very stable. Interestingly the 7-membered nucleus of this substance (XXI) exists in a

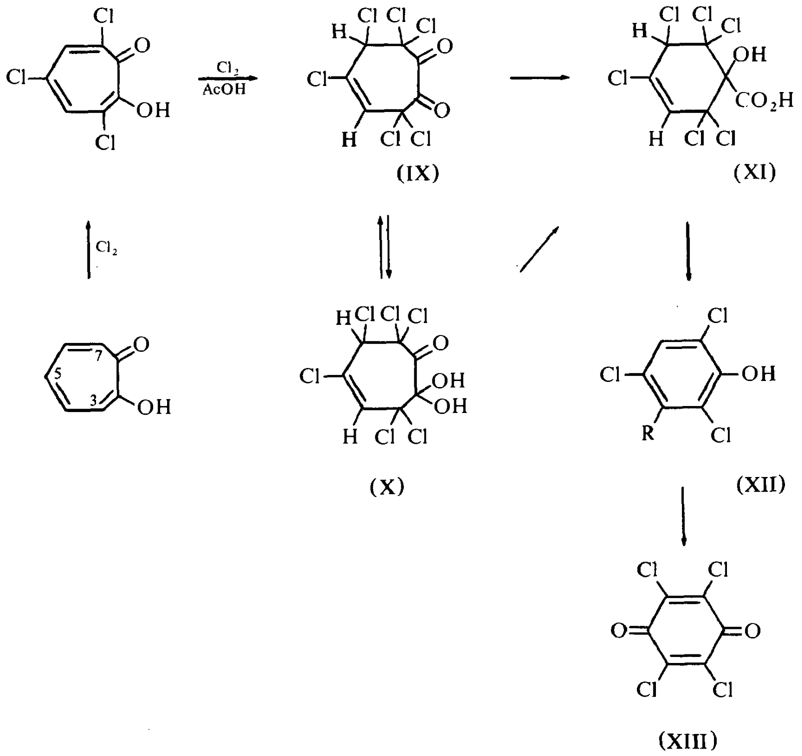


Figure 1. Exhaustive chlorination of tropolone.

boat form because of the steric interaction of these groups as has been shown by x-ray analysis[4].

Nitration

When 2-chlorotropone is treated with concentrated nitric acid, 2-chloro-7-nitrotropone (XXII) is obtained, along with two phenolic compounds (XXIII) and (XXIV). These compounds are derived from the nitrotropone (XXII) by rearrangement, water acting as a base[5]. 2,7-Dinitrotropone (XXV) was obtained by Lin *et al.*[6] as a byproduct in this reaction. It was known that 3,5,7-trinitrotropolone (XXVI) was obtained by the reaction of concentrated nitric acid on tropone[7]. Such nitrated derivatives (XXII, XXV, XXVI) must have been produced by addition–elimination reactions rather than direct nitrations.

Azo-coupling

Recently we have found that the 5-substituted tropolone (XXVII) couples with aryldiazonium ion at the 3-position and the product is the arylhydrazone of 1,2,3-tropoquinone (XXVIIIa)[8].

More than twenty years ago, we found orange-coloured arylazohinokitiol (XXIX) changed to a purple-coloured pigment which we named 'hinopurpurin', and later investigation[9] proved that this pigment had a heterocyclic

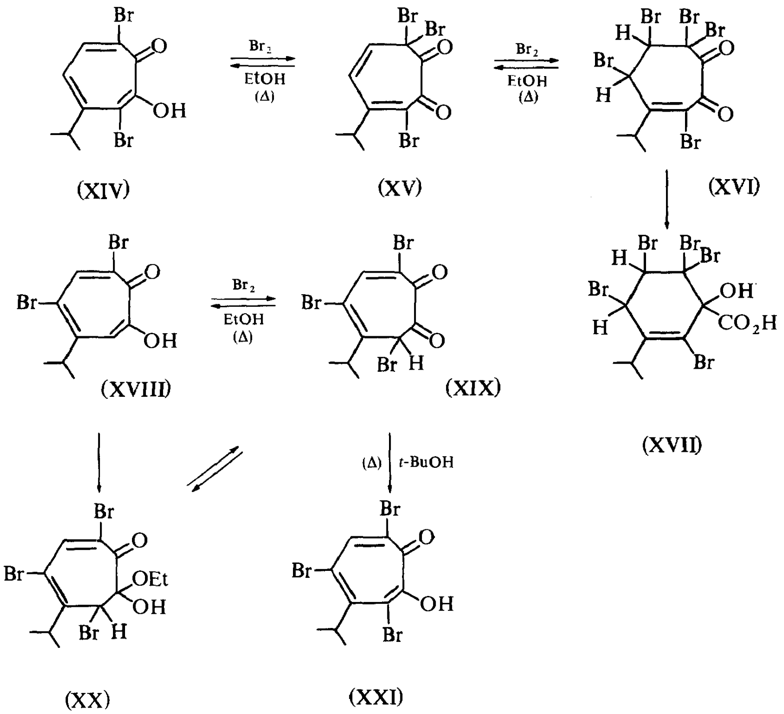
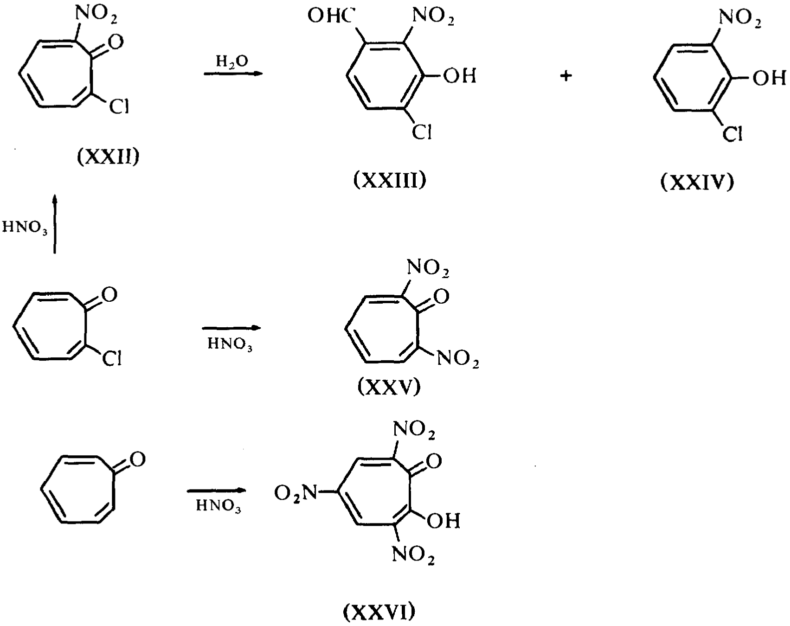
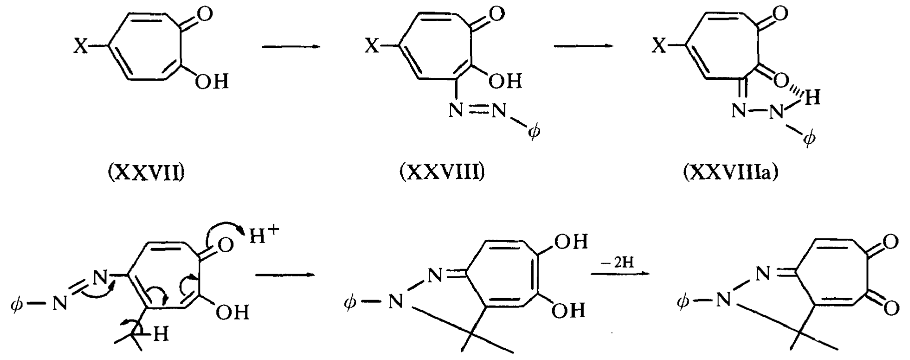


Figure 2. Exhaustive bromination of hinokitiol.





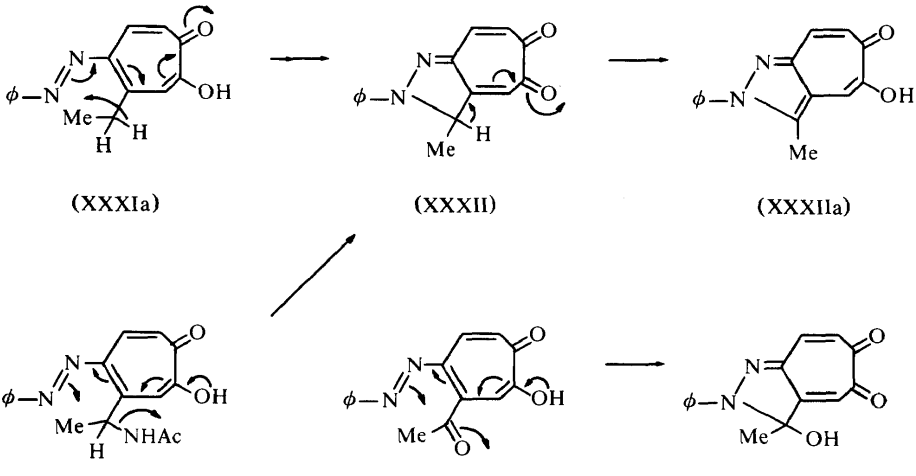
(XXVII) (XXVIII) (XXVIIIa)

(XXIX) (XXX)

structure of the 1,2,5-tropoquinonoid form (XXX). Arylazo compounds of 4-ethyl- and 4-acetamidoethyltropolone (XXXI a, b) easily cyclize to afford a heterocyclic compound (XXXII), which exists in the yellow-coloured enolic form (XXXIIa)[10]. The sodium derivative of 4-acetyltropolone (XXXIc) instantly cyclizes on acidification to give a purple-coloured pigment (XXXIIb) (*Figure 3*).

Benzotropolones

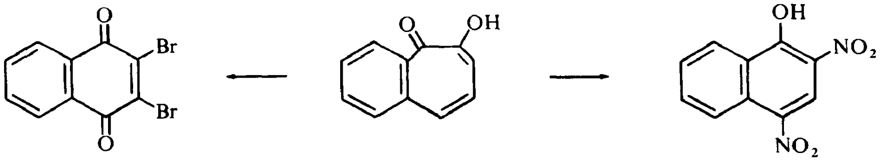
Reactions of benzotropolones towards electrophilic reagents are similar to those of monocyclic tropolones, but the former compounds rearrange more readily to afford benzenoid compounds. For example, 3,4-benzotropolone (XXXIII) gives dibromonaphthoquinone (XXXIV) on exhaustive



(XXXIa) (XXXII) (XXXIIa)

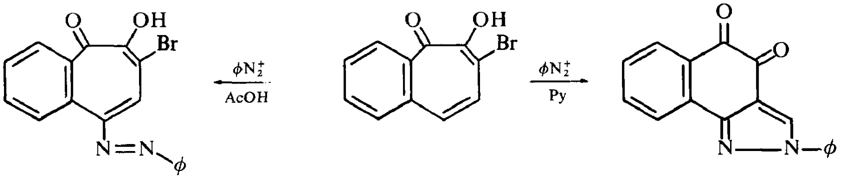
(XXXIb) (XXXIc) (XXXIIb)

Figure 3. Cyclization of 5-arylazotropolone derivatives.



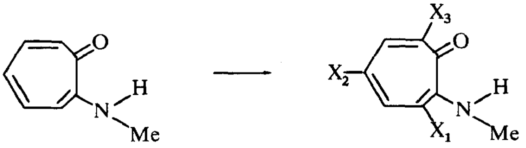
(XXXIV) (XXXIII) (XXXV)

bromination, and 2,4-dinitro-1-naphthol (XXXV) on treatment with an excess of concentrated nitric acid[11]. It is interesting to note that azo-coupling of the 7-bromo derivative (XXXVI) leads to an unrearranged compound (XXXVII) in acetic acid; but in sharp contrast, a rearranged product (XXXVIII) is obtained in pyridine[12].

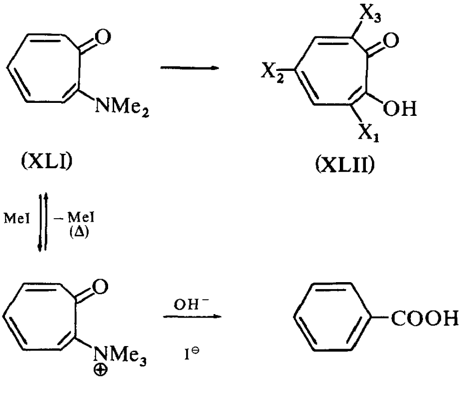


(XXXVII) (XXXVI) (XXXVIII)

Reactions of 6-hydroxy-2,3-benzotropone[13] and 4,5-benzotroponecarboxylic acids[14] were also studied.



(XXXIX) (XL)



(XLI) (XLII)

(XLIII)

Aminotropones

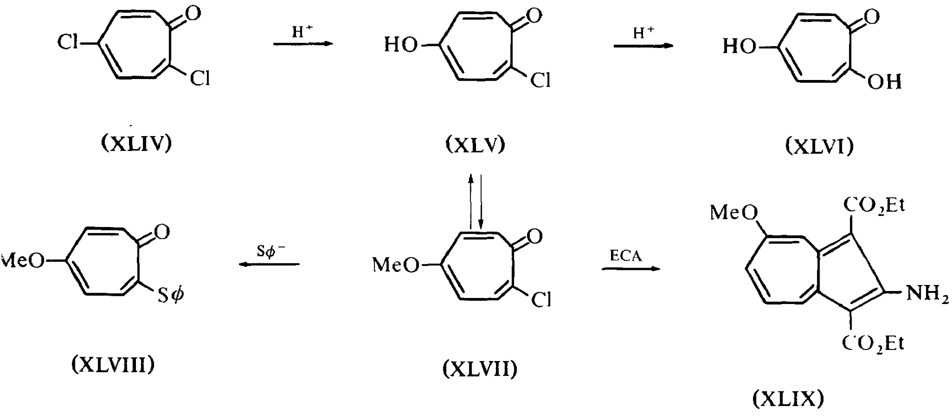
2-Methylaminotropone (XXXIX) behaves in a manner very similar to tropolone and 2-aminotropone toward electrophilic reagents and gives the substituted products (XL), and 2-dimethylaminotropone (XLI) affords substituted tropolones (XLII) wherein the dimethylamino group has been substituted by a hydroxyl group. On the contrary, the trimethylammonium derivative of tropone (XLIII) resembles 2-chlorotropone, rather than methylamino- and dimethylaminotropone[15].

Physical and chemical properties of 3-aminotropone[16], 4-aminotropone[17] and aminotropolones[18] have also been studied recently.

Reaction with the nucleophilic reagents

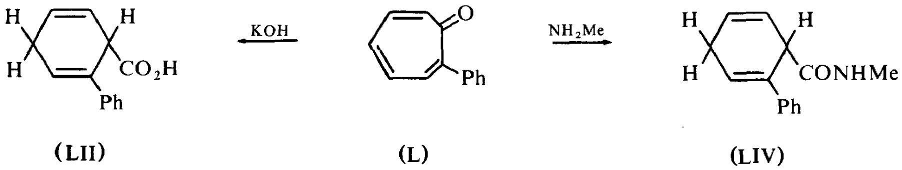
Sulphuric acid

2-Chlorotropones are converted to tropolones with hot sulphuric acid[1]. In the case of 2,5-dichlorotropone (XLIV), the chlorine atom at the 5-position is preferentially hydrolysed by the acid to give 2-chloro-5-hydroxytropone (XLV), and gradually is converted to 2,5-dihydroxytropone (XLVI) under more severe conditions. A hydroxide ion attacks at C-5 of the methyl ether (XLVII) of this compound, whereas its (XLVII) reaction with phenylmercaptide affords a 2-mercapto compound (XLVIII)[19]. An enolate anion such as derived from ethyl cyanoacetate attacks at C-7 to provide a 5-methoxyazulene derivative (XLIX)[19].

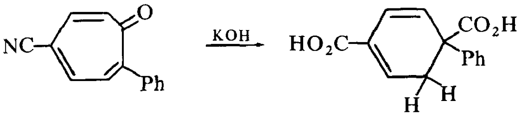


Hydroxide or methylamine

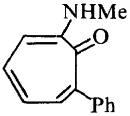
2-Phenyltropone (L) or its 5-cyano derivative (LI) rearrange to dihydrobenzoic acid derivatives (LII) and (LIII) respectively[20]. The former (L)



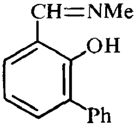
affords the dihydrobenzamide derivative (LIV) on heating with methylamine [21b]. On the other hand treatment of phenyltropone (L) with methylamine in the presence of the copper ammine complex, affords a mixture of 7-phenyl-2-methylaminotropone (LV) and a rearranged product (LVI)[21a].



(LI) (LIII)

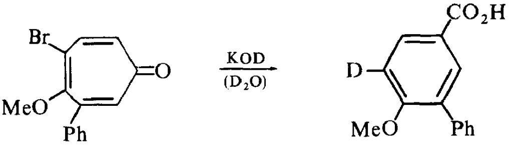


(LV)



(LVI)

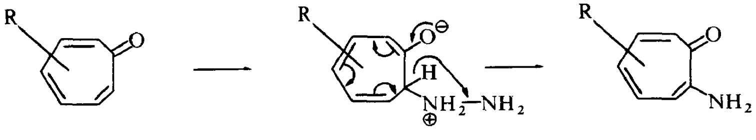
Not only 2-halotropones[1], but the 4-bromotropone derivative (LVII) is also rearranged to benzoic acid derivative by alkali. The mechanism of this reaction was studied using heavy water and potassium deuterioxide[22], and the product was found to have the structure (LVIII).



(LVII) (LVIII)

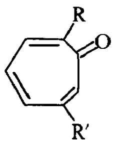
Hydrazine

It is well known that tropones are easily aminated by hydrazine hydrate to give 2-aminotropones (LX) presumably through an intermediate (A)[1d, e].

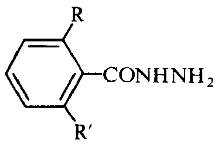


(LIX) (A) (LX)

In the case of the reaction of hydrazine with sterically hindered 2,6-disubstituted tropones (LXI), only rearranged products (LXII) were obtained[23].



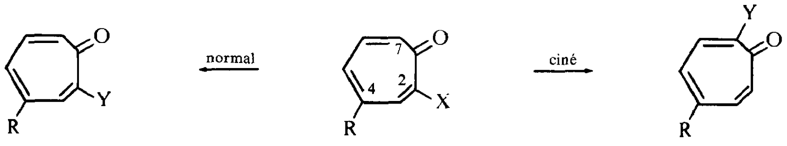
(LXI)



(LXII)

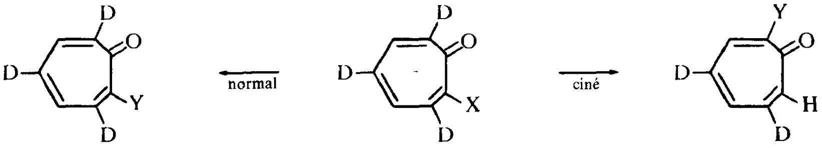
Ciné substitution

Reactive troponoids (LXIII) having a good leaving group at position-2, undergo substitution to give either of two types of substitution products (LXIV and LXV), or rearrange to benzenoid compounds. Such normal or ciné-substitutions in troponoids are generally believed to proceed through intermediates by addition–elimination reactions. When troponoids having a sidechain at position-4 (or 3) are used, we could easily differentiate the position of newly introduced substituents[1d, e].



(LXIV) (LXIII) (LXV)

It is interesting to note that in the troponoid field, ciné-substitution occurs very often, especially when the leaving group is a halogen or tosyloxy group, rather than a methoxyl group. Deuterated troponoids (LXVI) are now conveniently used to distinguish between these two routes (*Figure 4*)[24]. Very recently 2-fluorotropone was found to show quite similar properties to 2-methoxytropone with respect to the nucleophilic reactions[25].



(LXVI)

Figure 4. Normal and ciné substitution.

Dehydrotropone intermediates

Treatment of the three isomeric bromotropolones (LXVII a–c) with sodium methoxide in dimethylsulphoxide provided isomeric methoxytropolones (LXVIII a–c) as shown in *Figure 5*, indicating the involvement of dehydrotropolone anions (A and B) as intermediates. Existence of the dehydrotropolone intermediates (A and B) is supported by trapping experiments as shown in *Figure 6*[26a]. Similar reactions are recorded in the case of isomeric bromo-2-methylaminotropones (LXIX and its isomers), an example of which is shown in *Figure 7*[26b].

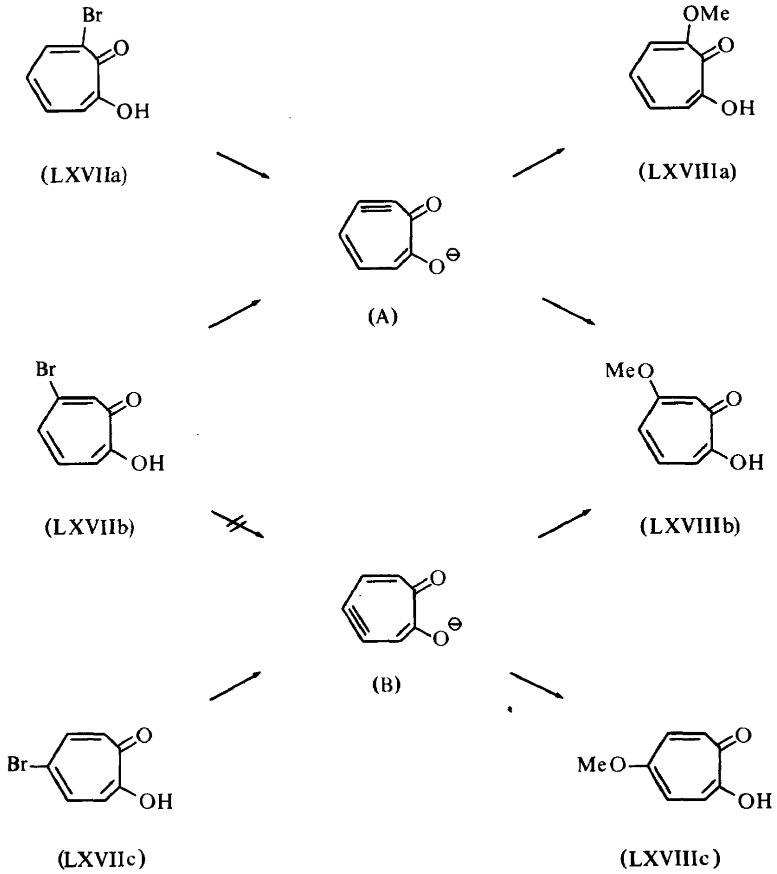


Figure 5. Ciné substitution via dehydrotropolone.

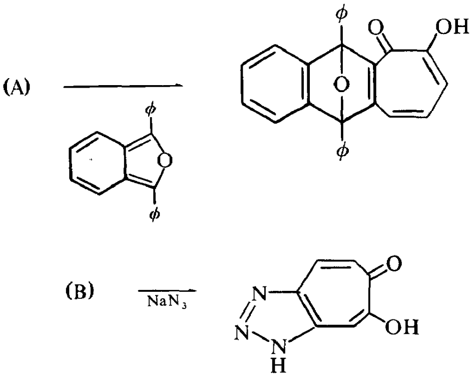


Figure 6. Trapping of dehydrotropolone intermediates.

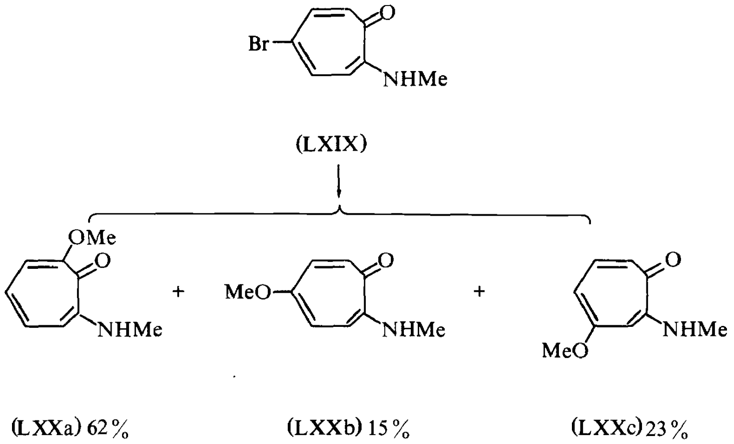
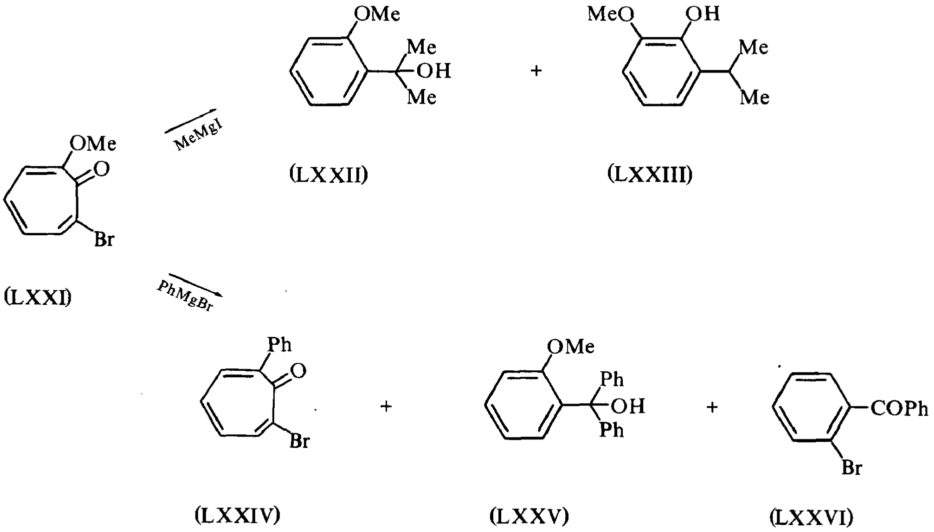


Figure 7. Substitution products from 2-methylamino-5-bromotropone.

Grignard reagents

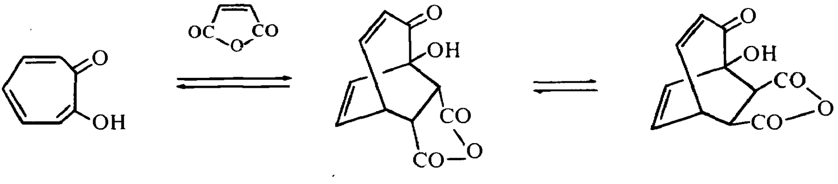
Reactions of troponoids with Grignard reagents are quite complex and very often unexpected products are obtained. For example, in the reaction with methylmagnesium iodide, 2-bromo-7-methoxytropone (LXXI) affords two rearranged products, (LXXII) and (LXXIII), and in addition more than five unidentified products; while with phenylmagnesium bromide the main product was 2-bromo-7-phenyltropone (LXXIV) accompanied by two rearrangement products (LXXV) and (LXXVI) as shown[27].



The nucleophilic substitution reactions of 2-aminotropones have also been studied recently[28].

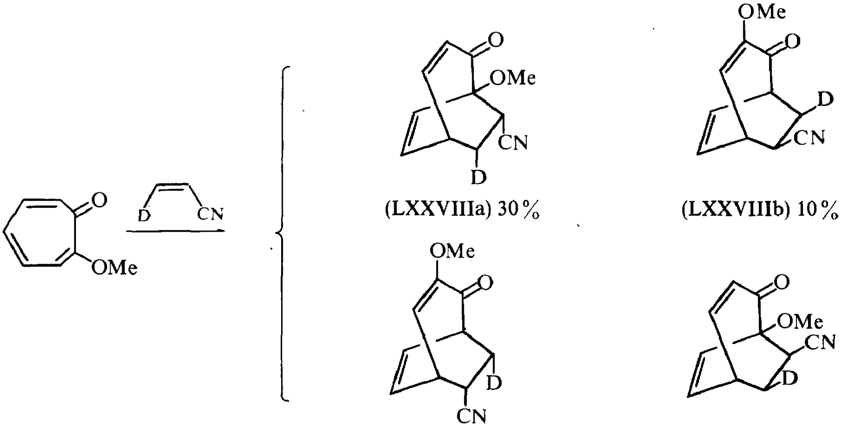
Cycloaddition

Now I would like to turn to the Diels–Alder and other cycloaddition reactions. It is known that tropolone and maleic anhydride can give two isomeric adducts[29a], and a later study has shown that an equimolar mixture



(LXXVIIa) (LXXVIIb)

of the *endo*-(LXXVIIa) and *exo*-adduct (LXXVIIb) are produced in this reaction[29b]. 2-Methoxytropone reacts with acrylonitrile to give four isomers (LXXVIII a–d) as shown in *Figure 8*[30].

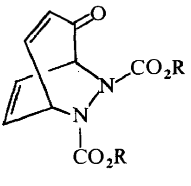


(LXXVIIIa) 30 % (LXXVIIIb) 10 %

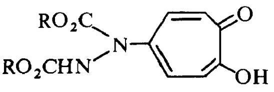
(LXXVIIIc) 19 % (LXXVIIId) 26 %

Figure 8. Reaction of 2-methoxytropone with acrylonitrile.

Azodicarboxylate reacts with tropone to give a [4 + 2] adduct (LXXIX), while reaction of tropolone with this reagent results in the substitution at carbon-5 to give (LXXX)[31]. 4-Phenyl-1,2,4-triazoline-3,5-dione (LXXXI) reacts with tropone and tropolone in a quite similar manner[32].

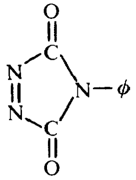


(LXXIX)

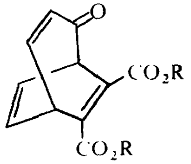


(LXXX)

Acetylenedicarboxylate also reacts with tropone to give an adduct (LXXXII), but the product is very unstable to heat and affords a mixture of various products[33].



(LXXXI)



(LXXXII)

Electron-rich dienophiles such as ethylene, styrene, indene and acenaphthylene also undergo Diels–Alder reactions with tropone on heating (*Figure 9*)[34]. Molecular orbital calculations have been carried out on these reactions. *Figure 10* shows the reaction of tropone and 2-chlorotropone with benzyne. Both [6 + 2] and [4 + 2] adducts are obtained in both cases[35].

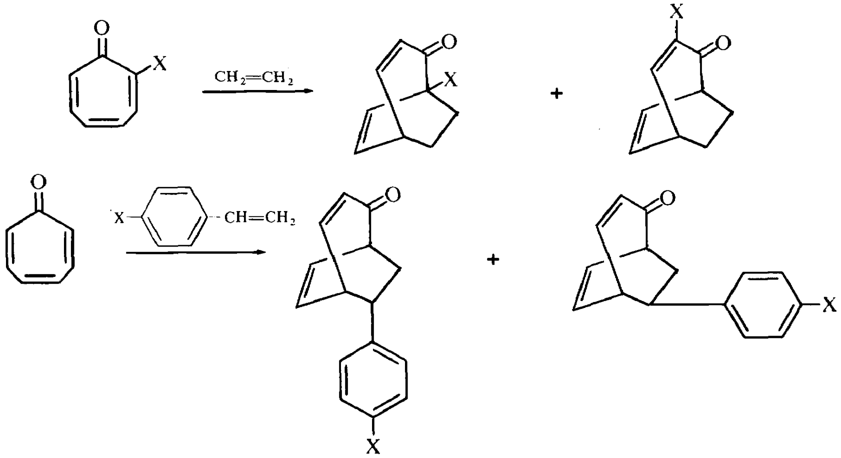


Figure 9. Reaction of tropones with ethylene and styrene.

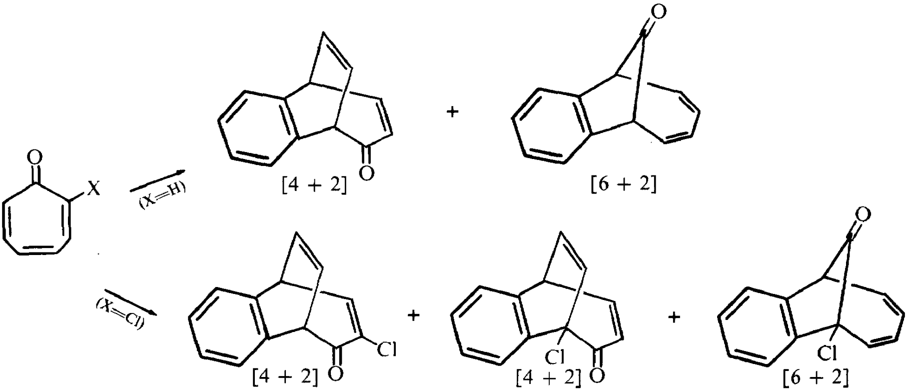
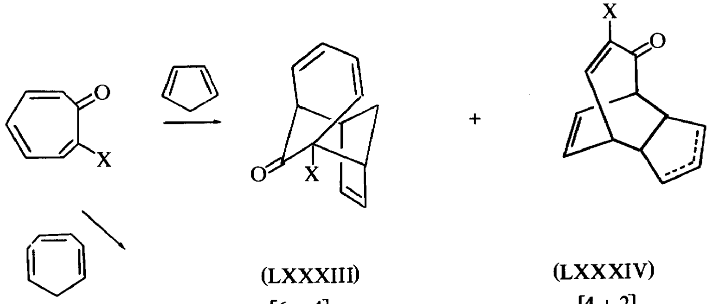


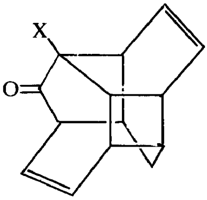
Figure 10. Reaction of tropones with benzyne.

Tropones react with cyclopentadiene on heating to give [6 + 4] and [4 + 2] adducts (LXXXIII and LXXXIV)[36], while tropone and its chloro derivative react with cycloheptatriene to afford cage molecules (LXXXV)[37]. 2-Methoxytropone, however, affords another type of product (LXXXVI)[38] besides (LXXXV : X = OMe).

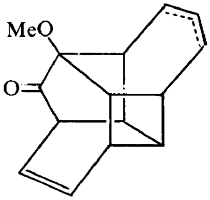


(LXXXIII)
[6 + 4]

(LXXXIV)
[4 + 2]



(LXXXV)
[6 + 4, 4 + 2]

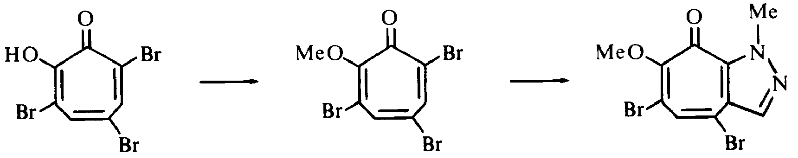


(LXXXVI)
[6 + 4, 4 + 2]

Reaction with diazomethane, carbene, enamines and ylides

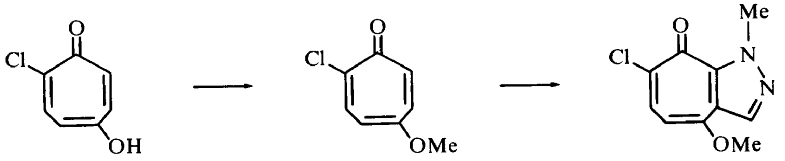
Diazomethane

Next I will describe reactions of troponoids with several other reagents. Diazomethane easily adds to some troponoids to give pyrazolotropone derivatives, presumably through a sequence of reactions: cycloaddition,



(LXXXVII)

(LXXXVIII)



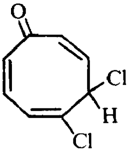
(LXXXIX)

(XC)

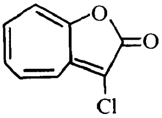
dehydrogenation (or dehydrohalogenation) and finally *N*-methylation. For example, 3,5,7-tribromotropolone (LXXXVII)[39a] and 2-chloro-5-hydroxytropone (LXXXIX)[19] afford (LXXXVIII) and (XC) respectively via their methyl ethers by the reaction with diazomethane.

Dichlorocarbene

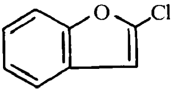
By the reaction of dichlorocarbene which is generated from sodium trichloroacetate or trichloromethylphenyl-mercury, a cyclooctatrienone (XCI) is produced, minor products being chloroazulanone (XCII) or chlorobenzofuran (XCIII)[40]. Similar ring-enlargement of the troponoid nucleus was also observed by Franck-Neumann[41] through reaction with diazoalkanes.



(XCI)



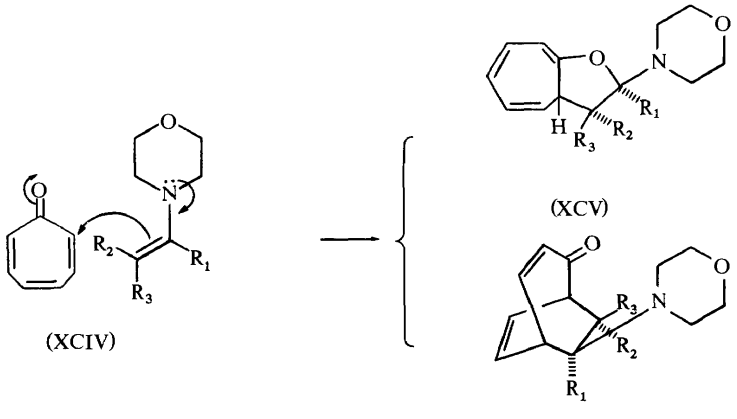
(XCII)



(XCIII)

Enamine

Enamines (XCIV) also react with tropone to provide compounds (XCV) and (XCVI)[42].

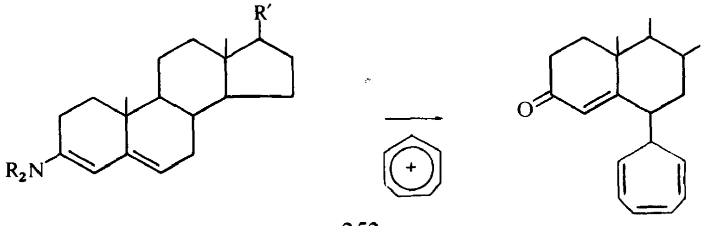


(XCIV)

(XCV)

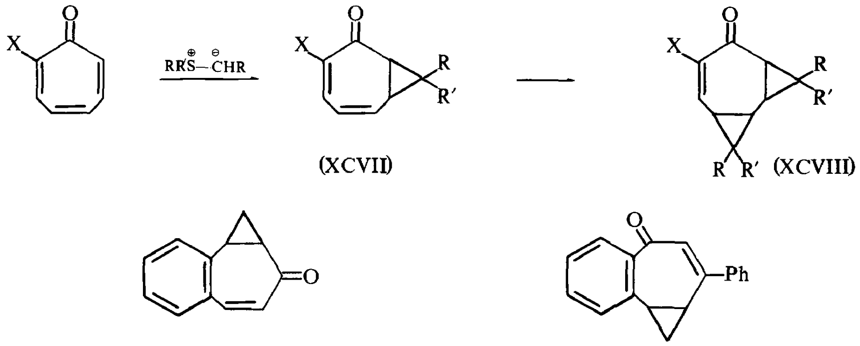
(XCVI)

An example of the reaction of the tropylium ion with an enamine is shown below[43].



Ylides

Monohomo- (XCVII) and bishomotropone (XCVIII) are obtained by reaction of a S-ylide ($RR'\overset{+}{S}-\overset{-}{C}HR$)[44], and this reaction is also applied to benzotropones to give (XCIX) and (C)[45] (*Figure 11*).



(XCVII)

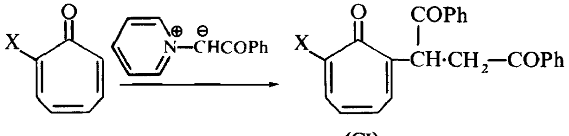
(XCVIII)

(XCIX)

(C)

Figure 11. Preparation of homotropones.

In the case of an *N*-pyridinium ylide, compound (CI) was produced by the attack of two moles of the reagent[45].

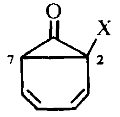


(CI)

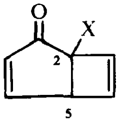
Reaction of tropone with phosphonium ylide ($Ph_3P{=}CHR$) provides a 2-substituted tropone (CII) and a rearranged product (CIII)[46]. 2-Halo- and 2-methoxy-tropone afford phosphorus-containing oxa-azulanone-type compounds (CIV). The latter compounds undergo ring cleavage and recyclization with acid and alkali, and (CIV) affords azulene derivatives (CVI) with acetylenedicarboxylate (*Figure 12*).

Photochemical and reverse reactions

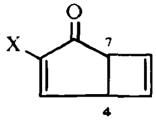
Now I would like to direct your attention to the photochemical behaviour of troponoid compounds. Three types (A, B and C) of photo-induced bond isomerizations are possible for this ring system and also dimerization



(A)



(B)



(C)

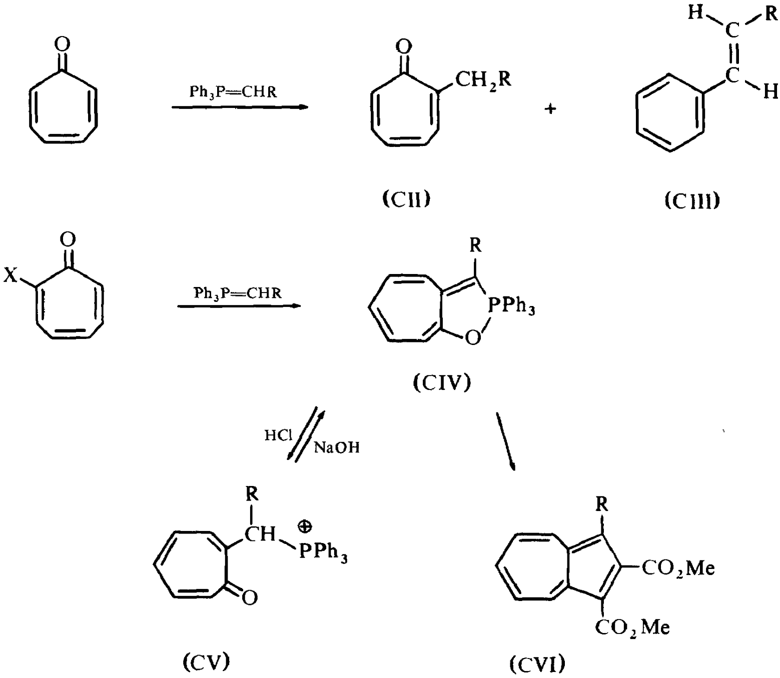
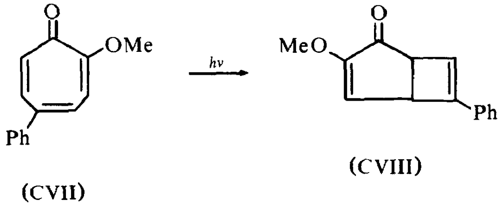


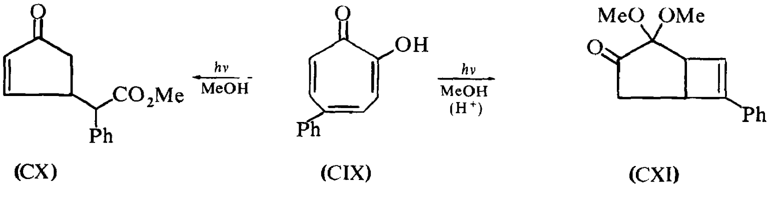
Figure 12. Reaction with phosphonium ylide.

reactions are expected[47]. Mukai and others have extensively studied substituent effects on the photochemical reactions of troponoids.

The methyl ether of 5-phenyltropolone (CVII) gives a type-C isomer (CVIII), while 5-phenyltropolone (CIX) itself in methanol affords compound (CX), which is assumed to be produced from a B-type isomer. In contrast,



in the presence of acid (CIX) affords a ketal (CXI) of a C-type valence tautomer[48].



Photochemistry of 5-chlorotropolone (CXII) and its methyl ether (CXIII) is also recorded (*Figure 13*)[49].

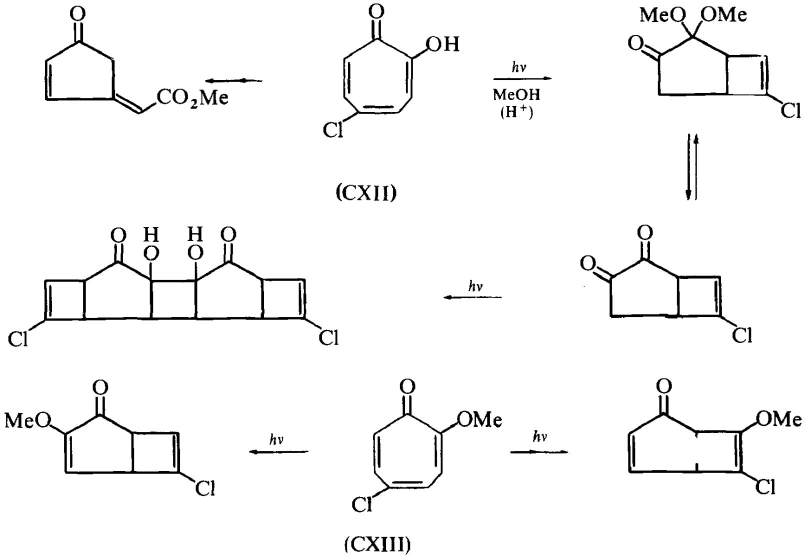
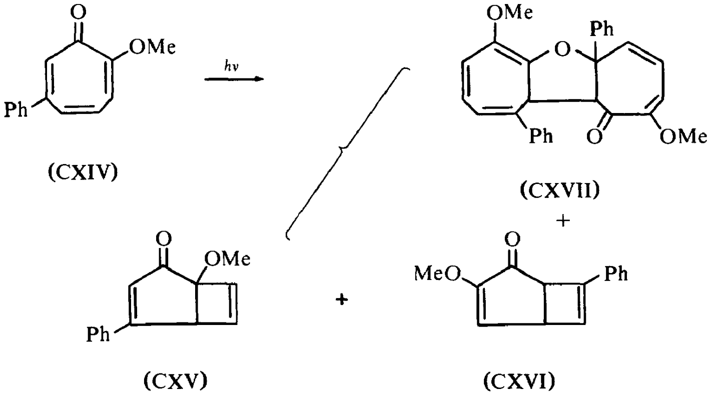


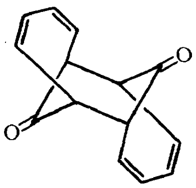
Figure 13. Photochemistry of 5-chlorotropolone.

2-Methoxy-6-phenyltropolone (CXIV) affords on irradiation valence tautomers of type B (CXV) and C (CXVI) in addition to a dimer (CXVII)[50].

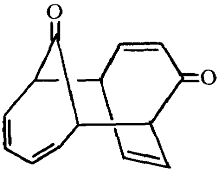


It is interesting that tropone affords three kinds of photodimers, [6 + 6], [6 + 4] and [4 + 2] types (CXVIII, CXIX and CXX), and benzene[51]. Benzene is very likely formed through type A cyclization.

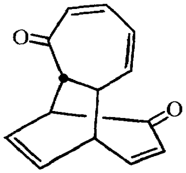
It has been known that bicyclic valence tautomers of type B and C and photodimers usually undergo ring-opening at high temperatures around 400°. Recently we have found that a valence tautomer of structure (CXXII) having an electron withdrawing group such as cyano, formyl, carboxyl,



(CXVIII)

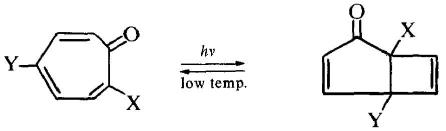


(CXIX)



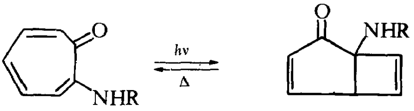
(CXX)

methoxycarbonyl or phenyl at the 5-position, very easily reverts to the starting material (CXXI) below room temperature[52]. For example, photoproduct (CXXII) from 2-methylamino-5-cyanotropone thermally isomerizes to the original compound (CXXI) very rapidly even at −70°. Therefore we must perform the photoreaction at very low temperatures in order to observe this type of rearrangement.



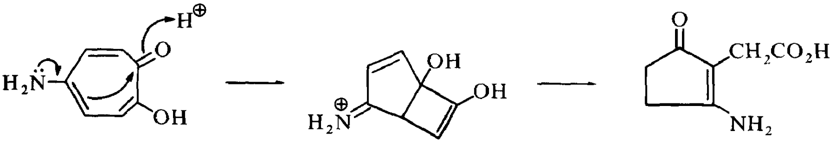
(CXXI) (CXXII)

The course of photo-isomerization and thermal ring opening of 2-substituted aminotropones (CXXIII ⇄ CXXIV) are also under investigation by Mukai and his group[53].



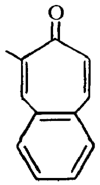
(CXXIII) (CXXIV)

5-Aminotropolone (CXXV) is easily transformed into a 3-aminocyclopentenone derivative (CXXVII) in acid medium, probably through the intermediate (CXXVI)[54].

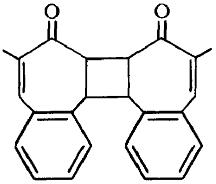


(CXXV) (CXXVI) (CXXVII)

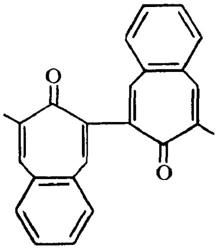
Irradiation of a 4,5-benzotropone (CXXVIII) affords a dimer (CXXIX), and a ditroponyl derivative (CXXX)[55].



(CXXVIII)

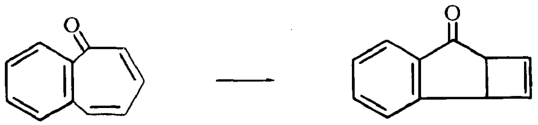


(CXXIX)



(CXXX)

Very recently Ebine[56] has found that 3,4-benzotropone (CXXXI) affords



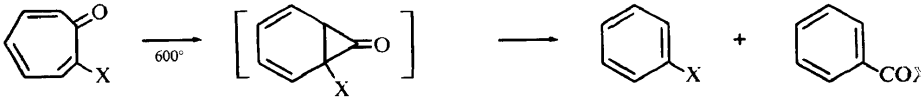
(CXXXI) (CXXXII)

a normal valence bond isomer (CXXXII), while 3,4-benzotropolone (CXXXIII) gives an unusual isomer of structure (CXXXIV).

(CXXXIII) (CXXXIV)

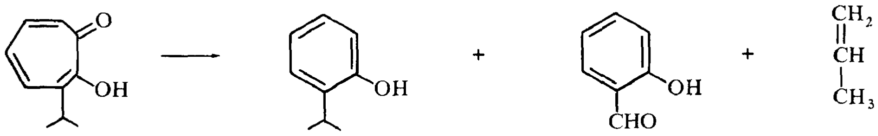
Thermal decomposition and rearrangement

Mukai and others have investigated some pyrolytic reactions of troponoids, and found that most troponoids afforded a benzene derivative (CXXXVI), presumably through a norcaradienone intermediate (CXXXV) by decarbonylation, and in addition a non-decarbonylated product (CXXXVII)[57]. Another example is the thermolysis of α-thujaplicin



(CXXXV) (CXXXVI) (CXXXVII)

(CXXXVIII), which on heating at 600° gave *o*-isopropylphenol (CXXXIX) and salicylaldehyde, together with propene[58].



(CXXXVIII) (CXXXIX)

Thermal reactions of tropone tosylhydrazone[59], tropone ketal[60] and bicyclo[3,2,0]heptadienones[61] have also been studied.

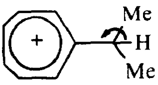
HEPTAFULVENE AND ITS RELATED COMPOUNDS

Heptafulvenes

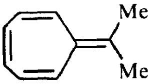
It is known that heptafulvene itself is too unstable to be isolated[62], but 8,8-disubstituted compounds (CXL) with electron-withdrawing groups, such as cyano or ethoxycarbonyl are stable, due to the resonance contributions of a dipolar structure (CXLa)[63].

(CXL) (CXLa)

However, 8,8-dimethylheptafulvene (CXLII) easily polymerized when we tried to isolate it from its conjugate acid (CXLI)[64].



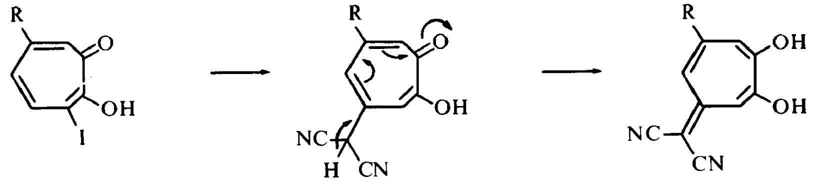
(CXLI)



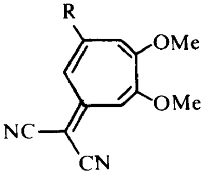
(CXLII)

Interestingly 3-iodotropolone (CXLIII) reacts with the malononitrile carbanion in liquid ammonia, to afford 2,3-dihydroxy-8,8-dicyanoheptafulvenes (CXLIVb) which are more stable than the tropolone form (CXLIVa)[65]. The former (CXLIV) can be converted to various troponimines (CXLVI) or heterocyclic compounds (CXLVII) via the dimethyl ether (CXLV).

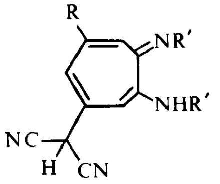
Dicyanoheptafulvene provides halogeno-substituted compounds by an addition–elimination reaction, and undergoes easily reversible cycloaddition with enamines[66a]. The properties of 1,6-dimethyl-8,8-dicyanoheptafulvene have been noted[66b].



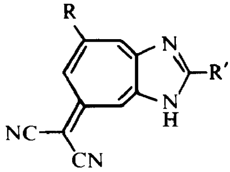
(CXLIII) (CXLIVa) (CXLIVb)



(CXLV)

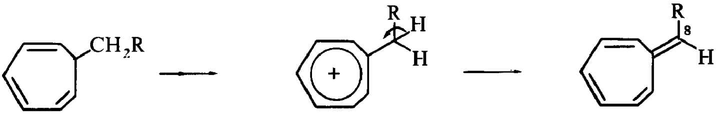


(CXLVI)



(CXLVII)

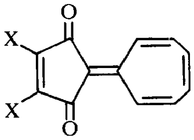
8-Mono-substituted heptafulvenes (CL) have been synthesized by Kitahara and others[67] starting from substituted cycloheptatrienes (CXLVIII: R = CN, CHO, CO_2Et) via tropylium ions (CXLIX). The hydrogen at C-8 of the cyano derivative (CLa) is substituted by electrophilic reagents to give 8,8-disubstituted derivatives (CLI: X = NO_2, CHO, CF_3CO). It (CLa) gives azulene derivatives (CLII or CLIII) with sodiomalononitrile or acetylenedicarboxylate, and a dimer (CLIV) on heating at 170°[68] (*Figure 14*).



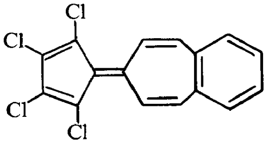
(CXLVIII) (CXLIX) (CL)

Sesquifulvalene, heptafulvalene

Sesquifulvalenedione[69] (CLV) and tetrachlorobenzosesquifulvalene (CLVI)[70] are far more stable than sesquifulvalene (IV) itself[71].



(CLV)



(CLVI)

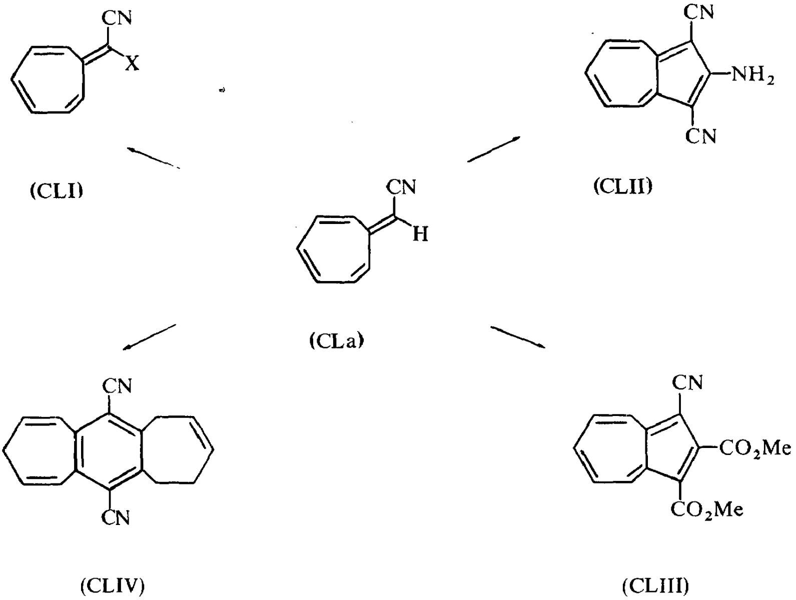
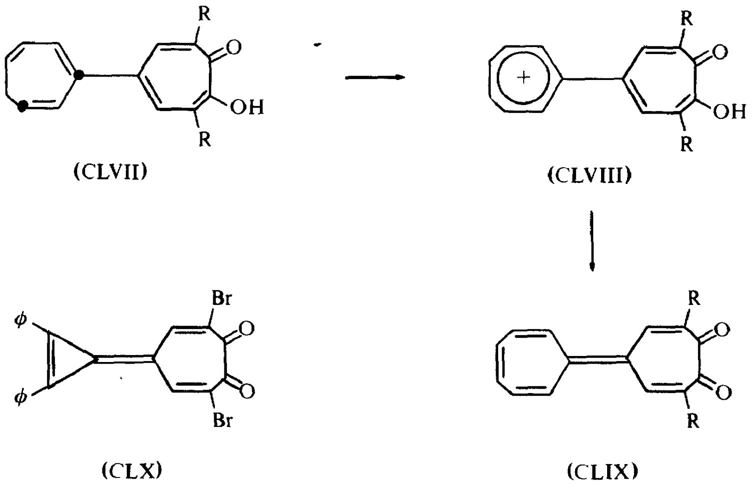


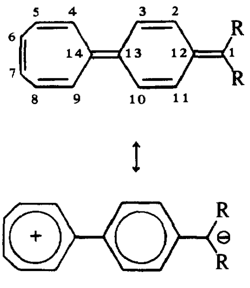
Figure 14. Reactions of 8-cyanoheptafulvene.

Very recently heptafulvalenediones (CLIX) were synthesized from 5-tropyltropolones[72b] (CLVII) by Takase and others[72a] via their respective tropylium ions (CLVIII). Heptatriafulvalenedione (CLX) was also obtained by a similar method[72].

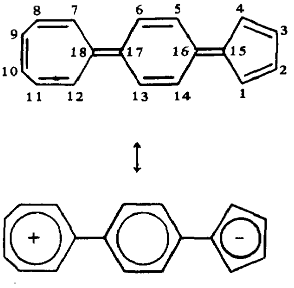


Quinarene

Recently much interest has been directed to the synthesis of compounds of type (A) and (B), which have an inserted six-membered quinonoid ring



(A)

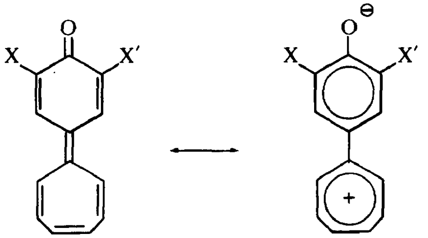


(B)

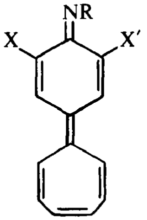
in the cross-conjugated hydrocarbon system, such as heptafulvene (III) and sesquifulvalene (IV). The oxygen analogue (CLXI) of this compound (A), which may be considered an extended tropone, was synthesized abroad[73] as well as in Japan[74], and the names 'quinotropilidene'[73] or 'benzoquinonetropide'[74] have been assigned to such systems. Recently we have proposed the common name 'quinarene' for these compounds; (A) was named [1,6,7]quinarene, and (B), [5,6,7]quinarene. The numbering system is shown on the structure.

1-*Oxa*[1,6,7]*quinarenes*

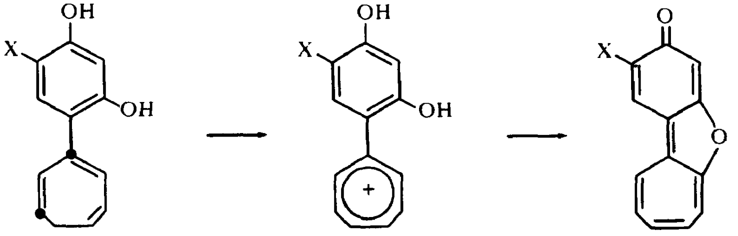
We have achieved the synthesis of various 1-oxa[1,6,7]quinarenes (CLXI) and their nitrogen analogues (CLXII). 1-Oxa[1,6,7]quinarene derivatives having a condensed furan ring system (CLXIV) are also derived from 4-tropylresorcinol (CLXIII)[75]. All such compounds (CLXI, CLXII and CLXIV) show a large solvent effect in their electronic spectra[74].



(CLXI)



(CLXII)

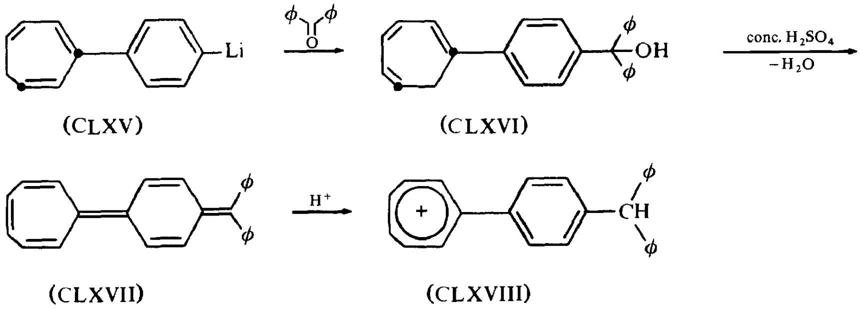


(CLXIII)

(CLXIV)

[1,6,7]*Quinarenes*

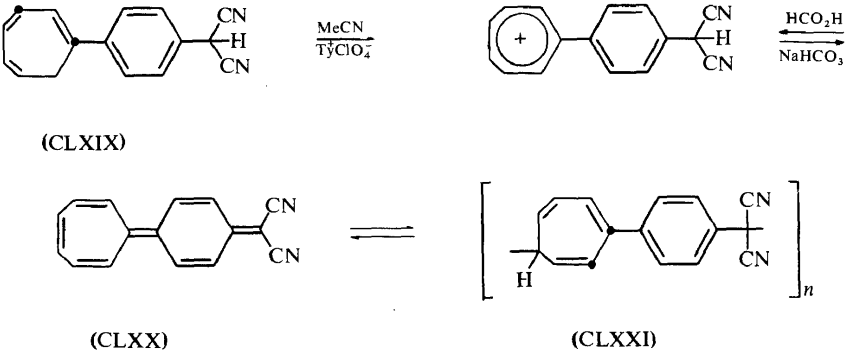
The carbinol (CLXVI), which is prepared from tropylphenyl-lithium (CLXV) and benzophenone, initially exhibits a deep blue colour in concentrated sulphuric acid which gradually forms a colourless solution of a cation (CLXVIII)[76]. It is highly probable the blue colour appears due to the formation of 1,1-diphenyl[1,6.7]quinarene (CLXVII)[74].



(CLXV) (CLXVI)

(CLXVII) (CLXVIII)

1,1-Dicyano[1,6,7]quinarene (CLXX) has also been synthesized as shown in *Figure 15*[77]. This compound (CLXX) is quite stable in a dilute solution, but it is noteworthy that a deep blue solution of this compound soon becomes colourless and upon evaporation of the solvent colourless polymer (CLXXI) is obtained. However, the blue colour of the monomer (CLXX) reappears on heating in a polar solvent.



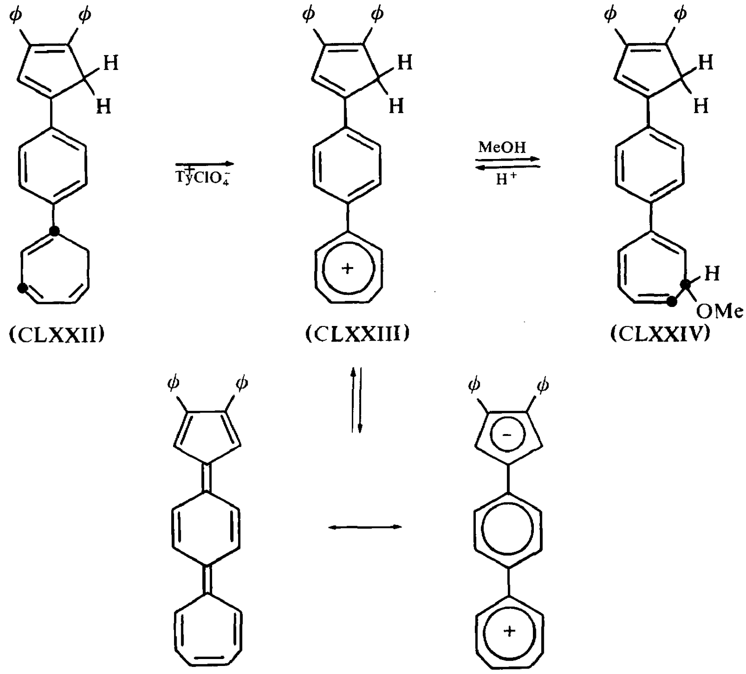
(CLXIX)

(CLXX) (CLXXI)

Figure 15. Synthesis of 1,1-dicyano[1,6,7]quinarene.

[5,6,7]*Quinarene*

When cyclopentadienylphenyltropilidene (CLXXII), which is obtained by the reaction of (CLXV) and 3,4-diphenylcyclopentenone, was treated with trityl perchlorate, bluish-black needles of the cation (CLXXIII) were obtained, and its electronic spectra were markedly solvent-dependent. This compound gave a colourless methoxy derivative (CLXXIV) with methanol, and reverted to the original cation (CLXXIII) on acidification. We could not isolate the desired quinarene hydrocarbon (CLXXV), but only one broad singlet at around τ 2.82 in its n.m.r. spectrum indicated that quinarene (CLXXV) might exist in solution in equilibrium with the cation (CLXXIII)[78]. Quantum mechanical calculations could not differentiate between the two species (CLXXIII) and (CLXXV)[79].



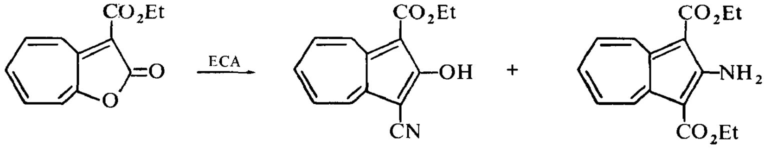
(CLXXII) (CLXXIII) (CLXXIV)

(CLXXV)

Azulenes

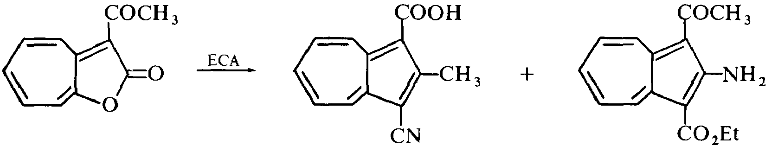
Nozoe–Seto–Matsumura's azulene synthesis

The well known Ziegler–Hafner azulene synthesis[80] does not involve dehydrogenation, and it is ideal for the preparation of azulenic hydrocarbons. Almost at the same time we also developed a new method for the synthesis of 1,2,3-trisubstituted azulenes directly in one step, starting with reactive troponoids with two moles of active methylene compounds in the presence of a base, and we proposed a tentative mechanism involving three principal intermediates[81a]. This method complements the method of Ziegler–Hafner, and our method is particularly useful for the synthesis of azulene carrying various, versatile functional groups which cannot be prepared otherwise[81b].

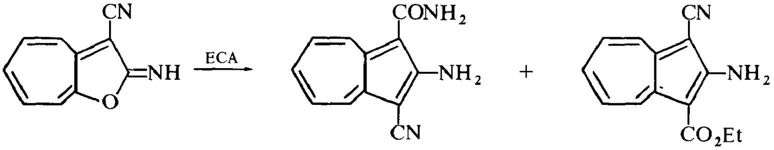


(CLXXVI) (CLXXVII) (CLXXVIII)

Later we were able to isolate the 1-oxaazulanone-type intermediates[82], such as (CLXXVI), (CLXXIX) and (CLXXXII), to which a second carbanion was condensed. For example, reaction of 2-chlorotropone with diethyl malonate provided (CLXXVI) which was further condensed with ethyl cyanoacetate (ECA) to give a cyano ester (CLXXVII) and a small amount of diester (CLXXVIII). Compound (CLXXIX) which was obtained from a reactive troponoid and ethyl acetoacetate, was condensed with cyanoacetate to give 3-cyano-2-methylazulenecarboxylic acid (CLXXX) accompanied by a 2-aminoazulene derivative (CLXXXI). 1-Oxaazulanonimine (CLXXXII), which was obtained from 2-chlorotropone with malononitrile, afforded 2-amino-1,3-dicyanoazulene (CLII) with further mole of malononitrile, while (CLXXXIII) and a small amount of (CLXXXIV) were obtained by the reaction of the same imine (CLXXXII) with ethyl cyanoacetate.



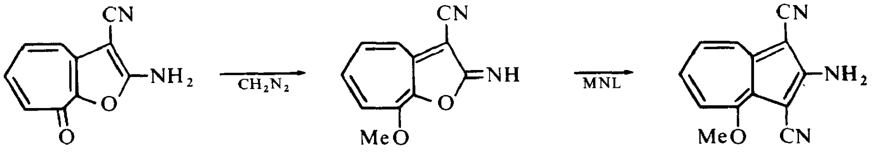
(CLXXIX) (CLXXX) (CLXXXI)



(CLXXXII) (CLXXXIII) (CLXXXIV)

It is noteworthy that a free carboxyl group of (CLXXX) and a carbamoyl group of (CLXXXIII) were produced by the ring opening of intermediates (CLXXIX) and (CLXXXII). Considering several pieces of evidence, we have proposed the revised mechanism (*Figure 16*) involving three principal intermediates (A, B and C) in our azulene synthesis[82]; the first path is formation of *oxaazulanone* (A) by the attack of one mole of carbanion on the troponoid (I) at position-2 or -7, the second step is formation of a *heptafulvene* intermediate (B), by the attack of a second carbanion at position-9 of intermediate (A), followed by ring opening. This second intermediate (B) has four functional groups and the third *azulanone* intermediate (C) was formed by ring closure either at C-a or b. The final step is an elimination process by the attack of a base, completing aromatization to afford azulenes (D).

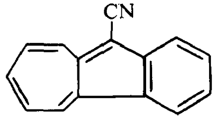
The furanotropone derivative (CLXXXV), which was obtained from tropolone tosylate and malononitrile (MNL), could be used for the synthesis of 4-methoxyazulenes (CLXXXVII), via the methyl ether (CLXXXVI)[83].



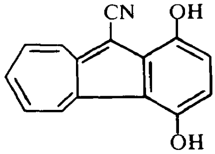
(CLXXXV) (CLXXXVI) (CLXXXVII)

Benzazulenes

Benzazulene derivatives (CLXXXVIII and CLXXXIX) were synthesized from 8-cyanoheptafulvene (CLa) by condensation with benzyne or benzoquinone[84].



(CLXXXVIII)



(CLXXXIX)

Benzazulene (CXCI) itself was also obtained by ring closure of *o*-tropylbenzaldehyde ethyleneketal (CXC)[85].

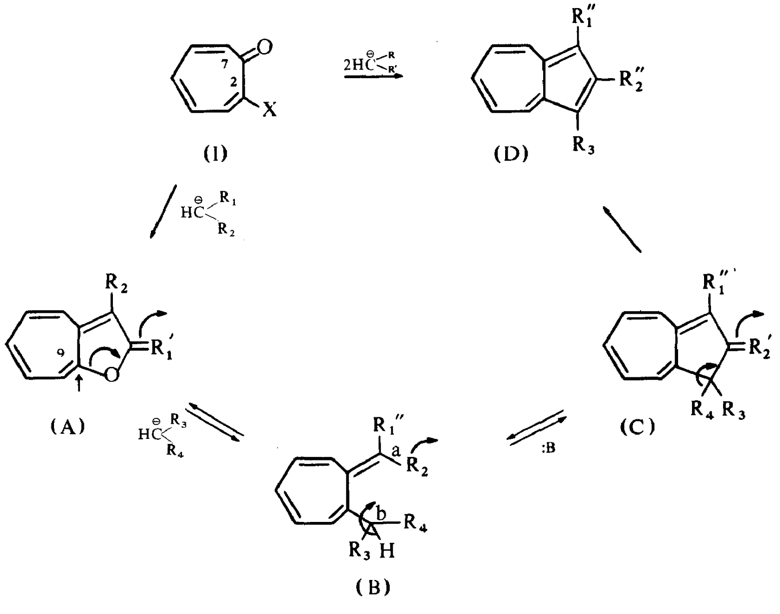
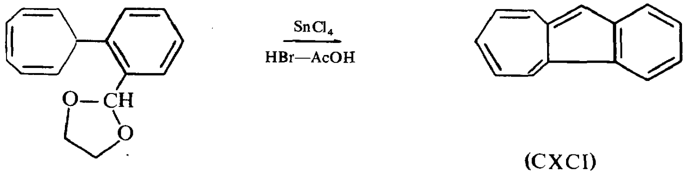


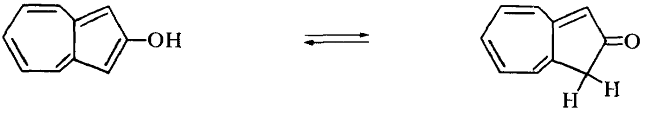
Figure 16. General outline of the mechanism of azulene synthesis by Nozoe *et al.*



(CXC) (CXCI)

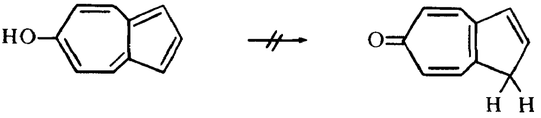
Tautomerism of hydroxyazulenes

Recently it has been shown that 2-hydroxyazulene (CXCII) exists in enolic form (CXCIIa) in methanol, and in azulanone-form (CXCIIIb) in chloroform



(CXCIIa) (CXCIIb)

or in water[86]. This behaviour is quite similar to that of 2-hydroxyguaiazulene[87]. However, 6-hydroxyazulene (CXCIII) exists exclusively in enolic form (CXCIIIa)[86].

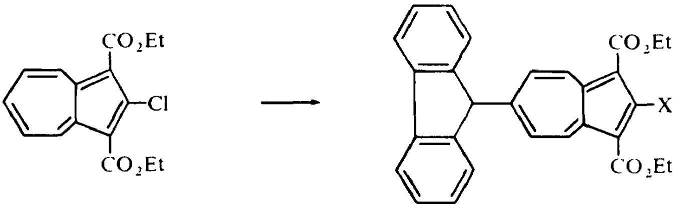


(CXCIIIa) (CXCIIIb)

Reactions of azulenes

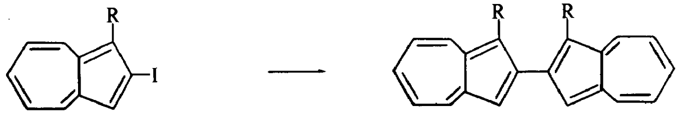
Nitrosation[88] and tropylation[89] of azulene derivatives as well as nucleophilic substitution[90] of haloazulenes were studied in our laboratory. With nucleophilic reagents, the 2-chloroazulene derivative (CXCIV) is substituted either at position-2 or at -6, depending on the nature of the reagent. For example, 6-fluorenylazulene (CXCV: X = Cl or H) is obtained from (CXCIV) by the reaction of fluorenylide anion[91a].

Iodoazulenes (CXCVI), especially those having electron-withdrawing groups at position-1 are readily coupled by activated copper to give various



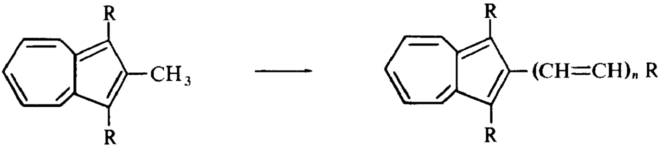
(CXCIV) (CXCV)

biazulenyl derivatives (CXCVII). 2-Methylazulenes (CXCVIII) can be converted to styrylazulene or diazulylbutadiene (CXCIX) with a suitable aldehyde.



(CXCVI) (CXCVII)

Alternatively, the methylazulene (CXCVIII) is first oxidized to a 2-formylazulenes, which in turn is condensed with active methyl containing reagents[91b].

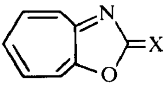


(CXCVIII) (CXCIX)

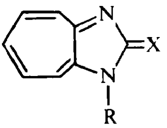
Troponoids with heterocyclic ring system

Various heterocyclic compounds are well known to be derived from reactive troponoids by the reaction with nucleophilic reagents or by the application of known method of ring-closure[1].

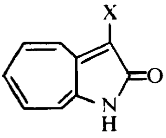
The Sankyo group has been continuously active in this area, and various heterocyclic troponoids having condensed oxazole[92], pyrazole[93] or pyrrole ring systems[94]—e.g. (CC), (CCI) and (CCII)—were synthesized and the properties of these compounds were studied. Takase obtained heterocyclic derivatives (CCIII and CCIV) from 3-acetonyltropolone[95], and Seto and



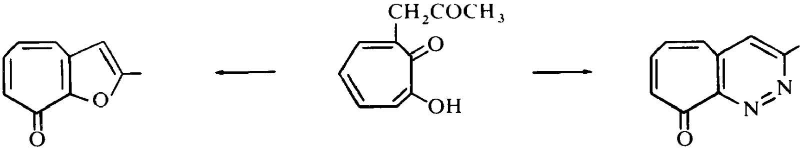
(CC)



(CCI)

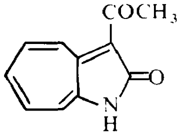


(CCII)

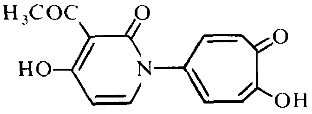


(CCIII) (CCIV)

others[96] obtained condensed hetero systems (CCV and CCVI) by the reaction of diketene on 2-aminotropone and 5-aminotropolone respectively.

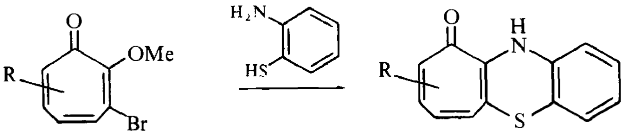


(CCV)



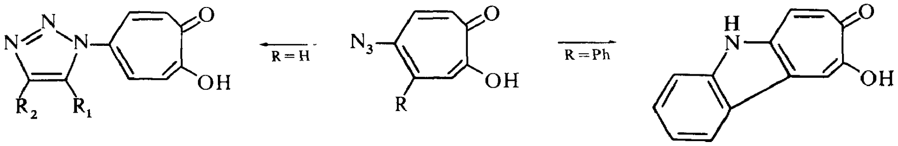
(CCVI)

In our laboratory, thiazinotropone derivatives (CCVII) and their oxides and dioxides were obtained from 3-bromo-2-methoxytropones[97].



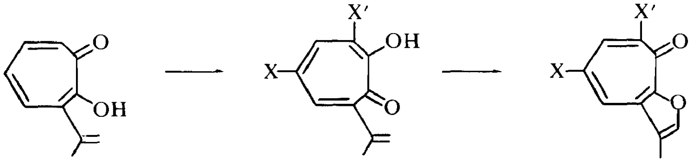
(CCVII)

5-Azidotropolones (CCVIII) were converted to triazolotropolones (CCIX) on one hand, and to indolotropolone (CCX) on the other, presumably



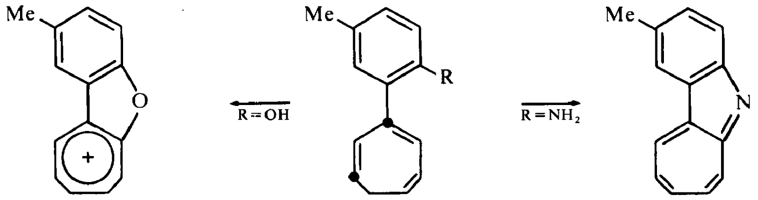
(CCIX) (CCVIII) (CCX)

through a nitrene intermediate in the latter case[98]. α-Dolabrin (CCXI) could be first substituted by electrophilic reagents to afford substituted derivatives (CCXII) which could be converted to furotropone derivatives (CCXIII) by bromine or by per acid[99].



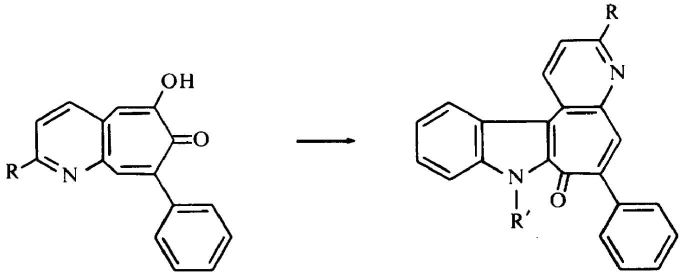
(CCXI) (CCXII) (CCXIII)

Benzofurotropylium ion (CCXIV) was obtained from *o*-tropylphenol (CCXV: R = OH)[100], while benzazaazulene (CCXVI) was derived from *o*-tropylaniline (CCXV: R = NH_2)[101].



(CCXIV) (CCXV) (CCXVI)

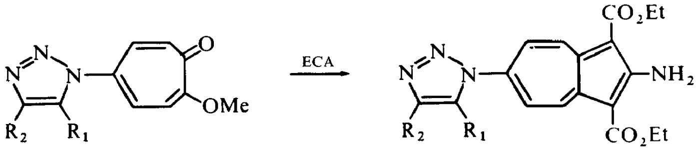
Pyridotropolones (CCXVII) and their derivatives (CCXVIII) were synthesized by Yamane and his co-workers[102a].



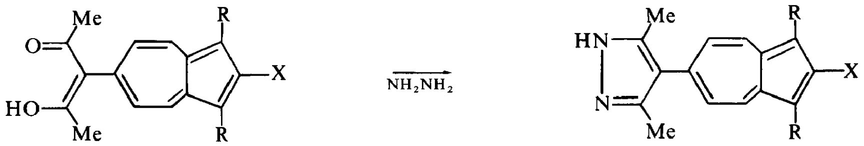
(CCXVII) (CCXVIII)

Azulenes with heterocyclic ring system

Troponoids having a heterocyclic ring as a sidechain, e.g. (CCXIX), can be converted to azulenes (CCXX) by our method[98], or azulenes having an appropriate side chain, e.g. (CCXXI), also can be used in ring closures to heterocyclic compounds (CCXXII)[102b].

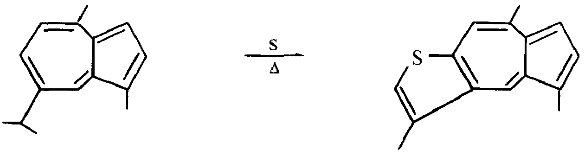


(CCXIX) (CCXX)



(CCXXI) (CCXXII)

The azulenothiophene derivative (CCXXIV) was obtained from guaiazulene (CCXXIII) on heating with sulphur[103].

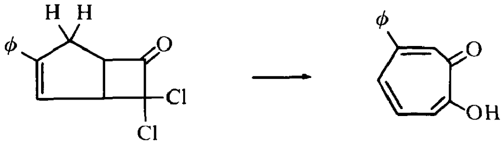


(CCXXIII) (CCXXIV)

MISCELLANEOUS

Synthesis of tropolones and some reactive troponoids

Now I would like to turn to the synthesis of tropolone and its simple derivatives which are useful for the synthesis of various troponoid compounds. Stevens and Bartlett's tropolone synthesis[104] is elegant and practical and several attempts to synthesize substituted tropolones by this method were also carried out in our country. In the case of lauryl- and stearyl-tropolone a mixture of β- and γ-isomers was obtained in 5:1 ratio[105a], while only 4-phenyltropolone (CCXXVI) was obtained through a crystalline intermediate of structure (CCXXV)[105b].



(CCXXV) (CCXXVI)

When this method was applied to dimethylfulvene instead of cyclopentadiene, we obtained α-dolabrin (CCXXVIII) instead of the expected β-dolabrin probably through chloroacetate intermediates (mixture of two isomers) from the adduct (CCXXVII)[106]. Kitahara and his co-workers[107] carried out extensive studies on this reaction and proposed the mechanism shown in *Figure 17.* They thought that the adduct (CCXXVII) from dimethyl-fulvene is transformed first to norcaradienone intermediate (A), and then to dihydrotropone intermediate (B) by the attack of a base at position-1, and finally gives rise to α-dolabrin by elimination of hydrogen chloride. Moreover, they carried out a ^{14}C labelling experiment and arrived at the conclusion that tropolone itself is very likely produced by the same mechanism through norcaradienone (C) from the adduct (CCXXIX). Professor Bartlett has very recently informed me that an alternative mechanism is more likely to be operative for the same reaction[108].

Tropolone was also derived from tropone by air oxidation in the presence of cupric salt[21b], as well as from a cyclic peroxide (CCXXX), which was obtained by the photo-oxidation of tropone, by reduction with thiourea[109].

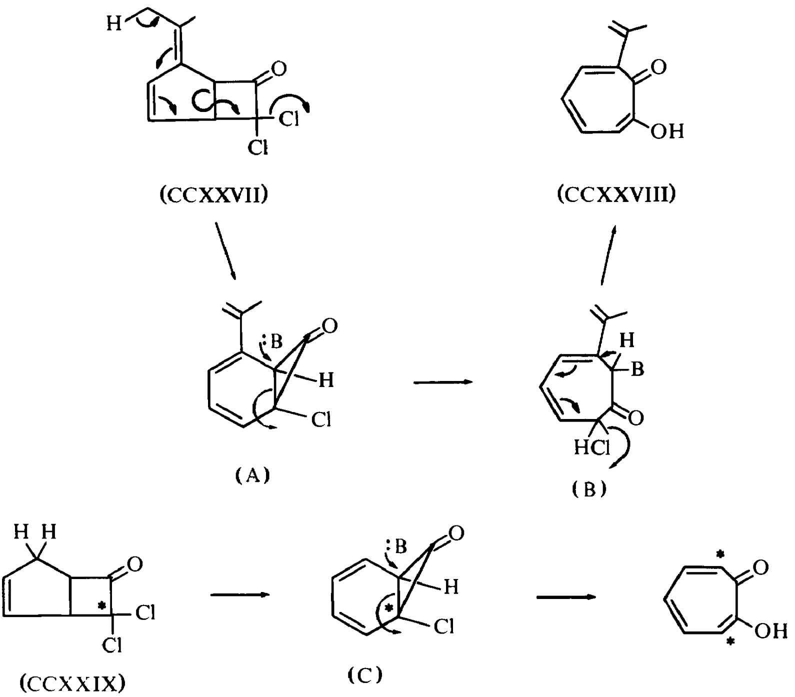
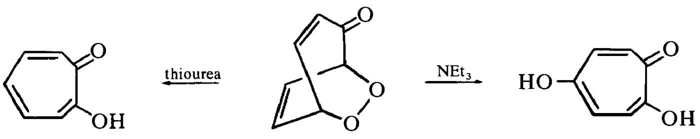


Figure 17. Mechanism of Stevens and Bartlett for tropolone synthesis used by Kitahara and others.

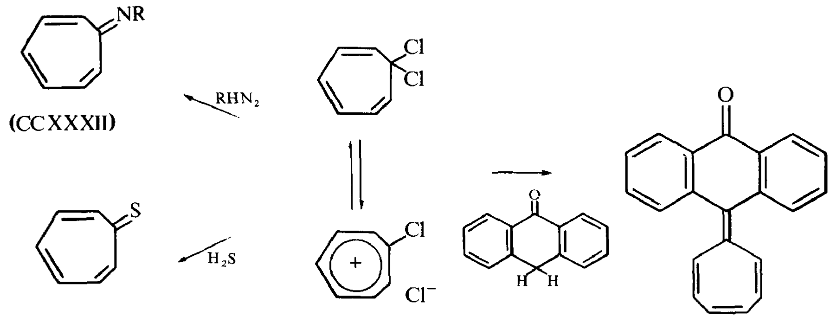
5-Hydroxytropolone is now easily available from this peroxide by treatment with triethylamine.



(CCXXX)

Reactive troponoids

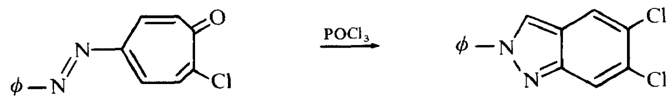
Kitahara and others[110] obtained 7,7-dichlorotropilidene (CCXXXI) from tropone and thionyl chloride and conveniently utilized this compound for the preparations of troponeimine (CCXXXII), troponethione (CCXXXIII), azulene (CLII) and the ketone (CCXXXIV) (*Figure 18*). Kikuchi [111] derived 2-chlorotropones having functional groups such as nitro, cyano and arylazo groups (e.g. CCXXXVa) from corresponding tropolones. In some cases, rearrangement products, such as (CCXXXVI), were obtained as byproducts.



(CCXXXII)

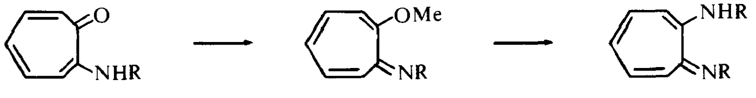
(CCXXXIII) (CCXXXI) (CCXXXIV)

Figure 18. Reaction of 7,7-dichlorotropone.



(CCXXXVa) (CCXXXVI)

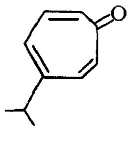
2-Aminotropones (CCXXXVII) are easily methylated by heating them with excess dimethylsulphate to give the methyl ether such as (CCXXXVIII), and then converted to the 2-aminotroponeimines (CCXXXIX)[112]. These reactive troponoids could be used for the synthesis of various troponoids and heterocyclic compounds[92–94].



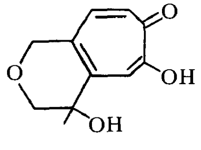
(CCXXXVII) (CCXXXVIII) (CCXXXIX)

Natural troponoids

Next I will describe some recent studies of naturally occurring troponoids. Nezukone (CCXL) is the first tropone found in nature, from the heartwood of *Thuja standishii* Carr and *Thuja plicata* Donn[113]. Ito and Kitadani[114] described three more diterpenoid tropolones[1d] (β- and γ-asunarin and γ-hibanin), but it is not clear whether these compounds are true natural



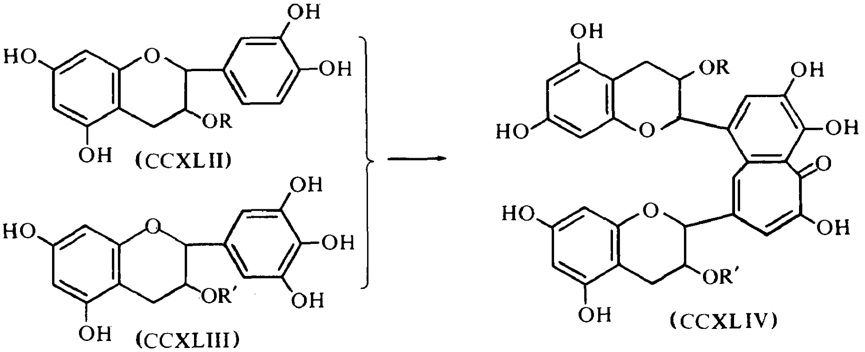
(CCXL)



(CCXLI)

products or artefacts produced from β-dolabrin by condensation. Biosynthetic studies of metabolite 'sepedonin' (CCXLI) are being carried out[115].

Roberts[116] found an orange-red pigment 'theaflavin' in black tea and supposed its structure might be a derivative of benzotropolone. Later, Takino and others[117] obtained the same pigment and its gallates from black tea, as well as by the enzymatic oxidation of the mixture of tea catechin, (namely epicatechin (CCXLII) and epigallocatechin (CCXLIII) or their gallates (CCXLIVb: R = H, R′ = galloyl; CCXLVc: R = R′ = galloyl), and established the structure for theaflavin (CCXLIVa: R = R′ = H)[117, 118]. Black tea of good quality contains much more gallate and digallate than free theaflavin.



(CCXLII)

(CCXLIII)

(CCXLIV)

The total synthesis of colchicin was reported independently by Eschenmoser, van Tamelen, and the Sankyo group[119], and also other groups in Europe and the USA. Recently two more approaches have appeared in Japan, which simulated supposed biogenetical pathways[120].

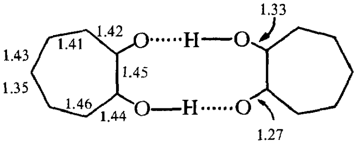
Physiochemical and theoretical studies

Physicochemical studies and theoretical treatment of troponoid compounds were extensively investigated in Japan. The n.m.r. spectra[121] and mass spectra[122] of troponoids, dipole moments of sesquifulvenes[123], e.s.r. spectra of anion radicals of troponoids[124] and azulenes[125], as well as the x-ray determination of the structure of benzotropones[126], heptafulvenes[127], furotropone derivative[128] and studies on some metal chelates of troponoids[129] have been reported. Molecular orbital treatments on electronic spectra and acidity of troponoids[130] and other nonbenzenoid aromatic compounds[131] are also published.

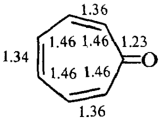
CONCLUSION

As I have already demonstrated, troponoids clearly show polyolefinic properties, in addition to some aromatic character. Very recently Bertelli and others[132], on the basis of n.m.r. spectra and dipole moments, and molecular orbital calculations, concluded that the dipolar character of troponoids had been thus greatly overestimated and that tropone very closely resembles a polyenone. From the organic chemical standpoint, however, we have to conclude that troponoid behaviour can be considered to be olefinic or aromatic depending upon the structure of troponoids, reagents and reaction conditions.

In this respect, it is interesting that x-ray crystallography[133] shows that all the C—C bonds in the tropolone ring (CCXLV) are very similar to those of aromatic bonds, while recent electron diffraction measurements of tropone[134] (CCXLVI) show clearly double bond alternation.



(CCXLV)



(CCXLVI)

Troponoids are undoubtedly very intriguing compounds, in spite of their rather simple structures. Thus, although much of their chemistry has been studied in foreign countries as well as in Japan in the last two decades, I feel that the more we study the more new problems appear, and at present many problems still await further investigation in every respect. To me it is not an exaggeration to state that the precise nature of virtually all reactions is still subject to investigation in the future. I hope this Symposium (ISNA) becomes a spring board for inspiring further study in this field of chemistry.

In concluding my talk I would like to thank my colleages for providing some unpublished results utilized in this lecture.

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