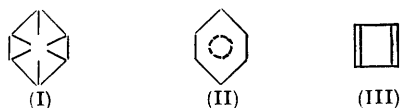


Aromaticity in Seven-membered Ring Systems.

TILDEN LECTURE, DELIVERED BEFORE THE CHEMICAL SOCIETY AT THE IMPERIAL COLLEGE OF SCIENCE, LONDON, ON NOVEMBER 5TH, 1953, AND AT THE UNIVERSITY OF NOTTINGHAM, ON NOVEMBER 26TH, 1953.

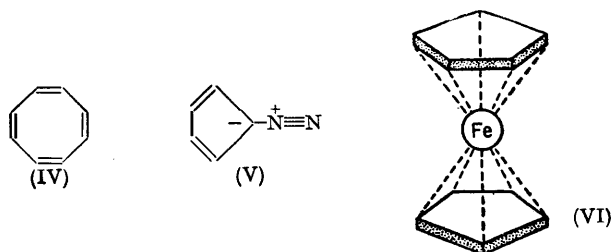
By A. W. JOHNSON, M.A., PH.D., A.R.C.S.

Less than ten years ago a subject closely related to that of the present discourse was treated in another Tilden lecture.¹ The extraordinary change which has occurred in the field of non-benzenoid aromatic ring systems in that short time should in itself be ample justification for reviewing the field once again, but this opinion is strengthened by the firm belief that Sir William Tilden himself would have approved the choice. He was particularly interested² in the structural features which conferred aromatic properties on the benzene molecule and were absent in his terpenes, even though many terpenes contained olefinic double bonds. In his long lifetime he witnessed much of the development of our modern idea of the nature of the benzene nucleus; the Kekulé formula in 1865, the Armstrong and Baeyer centric formula (I) in 1887, the Thiele "partial valency" formula (II) in 1898, Robinson's theory of the "aromatic sextet," and finally in the thirties,³ the molecular-orbital treatment of benzene by Hückel who associated aromatic stability with the presence of six (but not four or eight) π -electrons in a closed ring system.



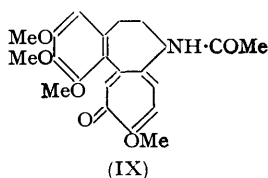
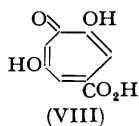
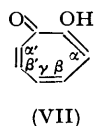
An important consequence of a theoretical approach such as this to a structural problem is the inspiration given to experimental work once the theoretical implications have been appreciated. It is sufficient to recall that ten years ago the tropolone ring system was unknown and that the earlier German reports on *cyclooctatetraene* chemistry were still private documents of the I.G. Farbenindustrie, to emphasise the immense effort which has been put into this branch of experimental organic chemistry in the last decade.

Although *cyclobutadiene* (III) still eludes us, the *cyclooctatetraene* molecule (IV) is known to be puckered and its physical and chemical properties⁴ indicate that the double bonds are largely olefinic in character. *cyclopentadiene* and *cycloheptatriene*, which contain an odd number of carbon atoms in the ring and therefore are not fully conjugated, can, in the form of their ions, fulfil the conditions necessary for achieving the aromatic state. This occurs in the anion of *cyclopentadiene* and in the cation of *cycloheptatriene*. The stability of the *cyclopentadienyl* anion has been recognised for many years and its structural relation to benzene was stressed by Robinson several years ago. The recent preparation of diazo*cyclopentadiene* (V)⁵ which is stable in the presence of copper at 160°, further illustrates the point but the best example is probably the high stability and aromatic character of ferrocene (VI).⁶

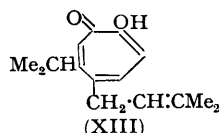
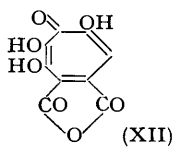
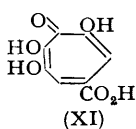
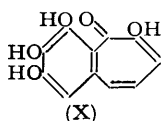


Structures based on the *cycloheptatriene* cation were not recognised until 1945 when Dewar⁷ postulated the tropolone ring system (VII) in order to explain the aromatic properties of the non-benzenoid compound stipitatic acid (VIII), a metabolite of *Penicillium stipitatum*. Shortly afterwards⁸ he incorporated the same ring system into a structure (IX) now known to be substantially correct for the alkaloid colchicine. In the years following, several other natural products containing the tropolone ring system were described. Examples include the α -, β -

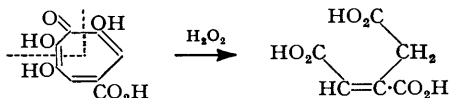
and γ -isopropyltropolones or thujaplicins from the heartwood of western red cedar (*Thuja plicata* D. Don)⁹ and the α - and β -isomers from certain essential oils,¹⁰ e.g., those from *Chama-*



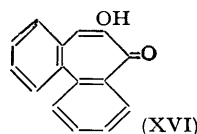
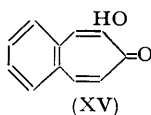
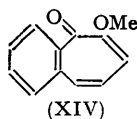
ecyparis taiwanensis and *Thujopsis dolabrata*; purpurogallin (X)¹¹ which is found as its glucosides¹² in certain galls; the mould products puberulic (XI) and puberulonic acid (XII),¹³ and nootkatin (XIII),¹⁴ another wood product, which is a tropolone containing isopropyl and methylbutenyl side-chains.



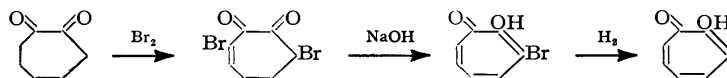
The existence of a tropolone nucleus in a new compound can often be deduced from examination of the ultra-violet¹⁵ and infra-red¹⁶ absorption spectra and also from the display of the now familiar chemical properties such as general aromatic behaviour, rearrangement by alkalis which however are exhibited after hydrogenation of the ring system. Further hydrogenation yields a 1:2-diol which frequently can be oxidised to a dicarboxylic acid.¹⁷ Direct oxidation of a tropolone may also provide useful results as was the case, for example, with benzotropolone,¹⁸ the thujaplicins,¹⁹ and stipitatic²⁰ and puberulic acids,²¹ e.g.:



The carbonyl activity frequently displayed in benzotropolones—e.g., $\alpha\beta$ -benzotropolone methyl ether (XIV) forms a 2:4-dinitrophenylhydrazone,¹⁸ $\beta\gamma$ -benzotropolone (XV) and its methyl ether readily form carbonyl derivatives,²² and the dibenzotropolone (XVI) forms a dioxime and a quinoxaline derivative²³—is attributed to the inhibition of resonance in the tropolone ring by the reluctance of the benzene ring to assume the *o*-quinonoid configuration.



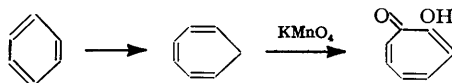
Once the interest in the tropolone series had been established, synthetic routes were rapidly developed and a choice of methods is now available. In the first place Cook²⁴ and independently Nozoe,²⁵ whom many of us were pleased to meet in England this autumn, have used 1:2-cycloheptanediones as starting materials and have effected the necessary dehydrogenation with bromine. The intermediate bromotropolones can be debrominated by hydrogenolysis:



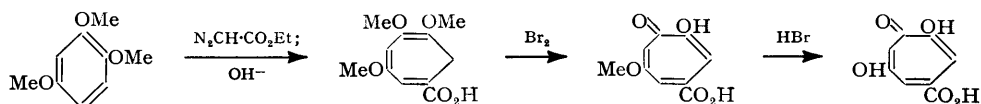
This method has been used for synthesising the three isopropyltropolones or thujaplicins,²⁶ the three methyltropolones,²⁷ β -ethyltropolone,²⁸ β - and γ -*tert.*-butyltropolones,²⁹ $\alpha\beta$ -benzotropolone,¹⁸ indano(5':6'- α : β)tropolone,³⁰ and purpurogallin.³¹ This type of synthesis generally gives good yields at the dehydrogenation step and undoubtedly represents the easiest method

of preparing tropolone itself. Nozoe and his colleagues ³² have obtained small yields of tropolone by bromination of *cycloheptanone* with subsequent hydrogenolysis, and Knight and Cram ³³ have used 2-hydroxycycloheptanone, from the acyloin condensation of pimelic ester, as the starting material. The main drawback to this type of approach is that a lengthy synthesis of the requisite *cycloheptane-1:2-dione* starting material may be involved in the preparation of substituted tropolones. The isomerisation of 3:7-dibenzylidene*cycloheptane-1:2-dione* to 3:7-dibenzyltropolone ³⁴ is an interesting but not very flexible modification of this type of approach.

A second general method involves the ring expansion of benzenoid derivatives by use of aliphatic diazo-compounds. Thus Doering and Knox ³⁵ have oxidised *cycloheptatriene*, from benzene and diazomethane, with permanganate to give tropolone; and, by use of substituted benzenes, β - and γ -isopropyl-, β - and γ -phenyl-, ³⁶ β - and γ -chloro-, ³⁷ and β' : γ -tetramethylene ³⁶ derivatives of tropolone have been prepared, the last from tetralin.

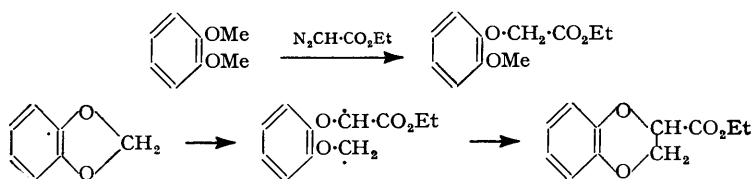


Independently we have employed diazoacetic ester and by having the oxygen atoms of the tropolone already present in the benzene ring as methoxy-groups before the reaction we have exercised more control over the course of the oxidation, *e.g.*, in the synthesis of tropolone- β -carboxylic acid from veratrole and of stipitatic acid from 1:2:4-trimethoxybenzene: ³⁸

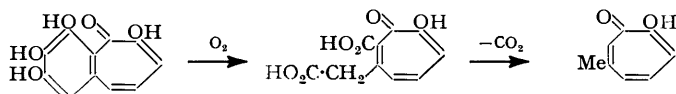


The ready availability of substituted benzenes is a factor which is greatly in favour of these methods for preparing substituted tropolones but the yields obtained are never very high although much of the unchanged benzenoid component can be recovered and used again. The use of diazoacetic ester rather than diazomethane permits the isolation of the pure crystalline intermediate *cycloheptatriene* acids.

An interesting side reaction which is brought about when alkoxybenzenes are heated with diazoacetic ester involves the replacement of one of the *O*-alkyl groups by an ethoxycarbonyl-alkyl group, leading to the formation of phenoxyacetic acids. ³⁹ This free-radical displacement reaction was further exemplified by the conversion of methylenedioxybenzene into benzodioxan-2-carboxylic ester:

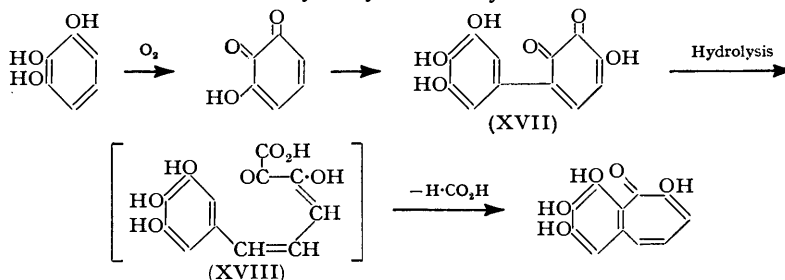


Apart from the general methods of synthesis, Haworth ⁴⁰ (see also Nozoe ⁴¹) has degraded purpurogallin to β -methyltropolone on a relatively large scale by oxidation of the benzene ring and decarboxylation of the resulting dicarboxylic acid:

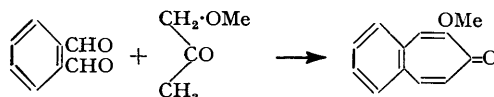


The mechanism of the formation of purpurogallin from pyrogallol has also been discussed, ⁴² and it is postulated that pyrogallol undergoes self-condensation, possibly *via* 3-hydroxy-*o*-benzoquinone to the hydroxylated phenyl-*o*-benzoquinone derivative (XVII). As the formation of purpurogallin from pyrogallol operates in neutral or weakly acid solution it was proposed that (XVII) on acid hydrolysis might give (XVIII) which on cyclisation and loss of formic acid should yield purpurogallin. The theory, admittedly speculative, would explain the formation of purpurogallin monoethyl ether from pyrogallol and its ethyl ether and of

purpurogallin- β -carboxylic acid from pyrogallol and gallic acid,⁴³ and the non-formation of a purpurogallin derivative from 1 : 2-dihydroxy-3-methoxybenzene.

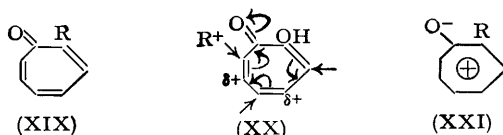


It is remarkable that no syntheses of simple tropolones exist which comprise the formation of the ring by the condensation of aliphatic compounds. Tarbell⁴⁴ and independently Fernholz⁴⁵ have prepared $\beta\gamma$ -benzotropolone by the condensation of acetol or its ethers with phthalaldehyde but attempts to apply this synthesis to maleic dialdehyde failed, *m*-hydroxybenzaldehyde being the only condensation product isolated.⁴⁶ Similarly the reaction of nitromalondialdehyde and diacetyl gave no tropolone derivatives, and a number of other negative condensations of this general type have been reported.



Many physical measurements have been carried out on tropolone and related compounds and provide a clear picture of the fine structure of the ring system. *X*-Ray measurements on the copper derivative of tropolone⁴⁷ show that the carbocyclic ring system is an almost regular heptagon with a C-C distance of 1.4 Å, suggesting quite strong aromatic character. The heat of combustion has been determined by several workers, and from this the resonance energy can be calculated, the latest value⁴⁸ being 33–36 kcal./mole, which is of the same order as calculated values^{49, 50} and compares with the value of 36 kcal./mole for benzene. The *X*-ray measurements also show that the copper atom is not symmetrically placed with regard to the two oxygen atoms which can therefore be differentiated at any particular moment. This agrees with the results of a theoretical analysis of the infra-red spectrum of tropolone⁵⁰ as well as the electron-diffraction pattern.⁵¹ In tropolone itself or in a symmetrically substituted tropolone it is impossible to differentiate between the oxygen atoms on a time-average basis and a state of rapid dynamic equilibrium between the two tautomeric forms is assumed. This is facilitated by the strong hydrogen bonding between the hydrogen and the carbonyl-oxygen atom, as is apparent from many of the physical and chemical properties of the molecule, *e.g.*, the "displaced" carbonyl band at 1615 cm.⁻¹ and the reduced intensity of the hydroxyl band in the infra-red spectrum, the volatility, the formation of metallic derivatives,⁵² the non-formation of carbonyl derivatives, and so on.

The acidic hydroxyl group (pK_a 7.0 \pm 0.2 at 20°⁵³) of tropolone can be acylated and alkylated and tropolone can be re-formed from its esters or ethers by acid or alkaline hydrolysis. With thionyl chloride, tropolone is converted into 2-chlorotropolone (XIX; R = Cl)⁵⁴ and this compound with ammonia or amines yields the 2-aminotropolones (XIX; R = NR'R'), as does tropolone methyl ether (XIX; R = OMe).⁵⁵

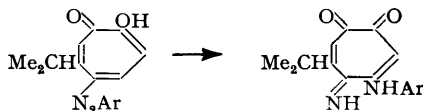


These replacements as well as similar reactions with hydrazine, thiols, alkoxides, and cyanides, and halide exchange give support to the view^{54, 55} that tropolone, its ethers, 2-chlorotropolone, and 2-aminotropolone are cyclic vinylogues of a carboxylic acid, esters, acid chloride, and amide, respectively. Accordingly the observed α - and γ -orientation of the electrophilic substitution products of tropolone may be ascribed to the directive influence of the "cyclic" carboxyl group (XX). However not all of the observed reactions of tropolone and its derivatives

are interpreted satisfactorily by this formulation and Doering and Knox⁵⁶ have preferred to regard tropolone as (XXI; R = OH) in which the presence of the *cycloheptatrienylium* cation is emphasised. On this basis *cycloheptatrienone* or tropone (XXI; R = H) is the parent compound, and tropolone the *o*-phenol of the series and the hydroxyl group of tropolone plays an important rôle in the orientation and ease of substitution.

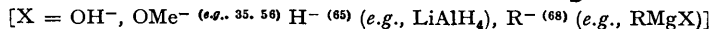
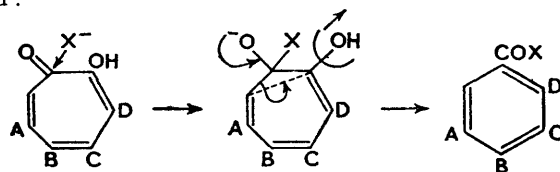
The reactions of tropolone and its homologues have been studied in great detail by Cook and by Haworth in this country and especially by Nozoe in Japan who has published, since 1949, some hundred papers on the whole field of tropolone chemistry. One of the most important of Nozoe's starting materials, β -isopropyltropolone or hinokitiol⁵⁷ is discarded in kilogram quantities in the form of its red ferric derivative during the purification of the essential oil of *Chamaecyparis taiwanensis*, which is used as a flotation oil in Japanese mines.

The substitution reactions of the tropolones have followed the trends already well established with benzene. The orientation was determined by linking up the various reactions by compounds such as the amino- and halogeno-tropolones formed by more than one method and then checking the orientation of these key compounds by alkaline ring-contraction to benzenoid derivatives. Of the various electrophilic substitutions, nitration,⁵⁸ halogenation,^{35, 45, 59} sulphonation,⁶⁰ and hydroxymethylation⁶¹ all cause reaction at the α - and the γ -position, as had been predicted from theoretical considerations.⁴⁹ Nitrosation^{35, 62} and diazo-coupling,^{24, 35, 63} however, are difficult to effect in any position other than γ and consequently the presence of a bulky group in the β -position, *e.g.*, the isopropyl group of hinokitiol, may affect both the ease of these reactions and the properties of the product, as in the unusual rearrangement of the azo-compounds derived from hinokitiol to the so-called hinopurpurins⁶⁴ brought about by crystallisation from ethanol :

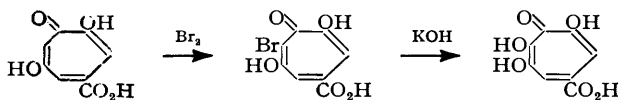


However not all of the standard aromatic reactions can be applied to the tropolone ring system, and several authors^{61, 65} have reported failure to effect Friedel-Crafts substitutions, Gattermann and Kolbe reactions, and chloromethylation, undoubtedly in some of these cases because of the formation of stable intermediate tropolone complexes. Small yields of tropolone- γ -aldehyde and γ -carboxylic acid have been obtained⁶⁵ by the action of chloroform (Reimer-Tiemann) and carbon tetrachloride respectively on tropolone in the presence of alkali, and α -allyltropolone can be prepared by the intramolecular Claisen rearrangement of tropolone *O*-allyl ether.⁶⁶

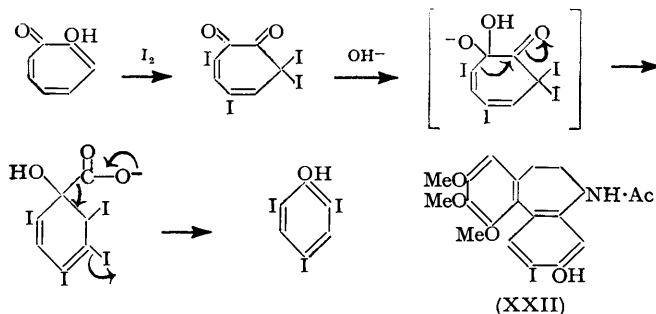
The widespread use of the alkaline rearrangement of tropolones to derivatives of benzoic acid^{35, 67} which is the basis of the interpretation of the course of the substitution reactions depends upon the observation that substituent groups, even in the α -positions, retain their relative positions in the ring during the rearrangement which is of the benzenic type and is generally represented :



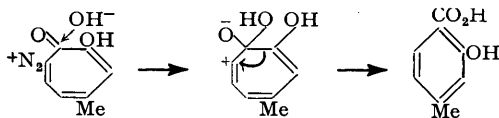
The presence of electron-attracting groups in the α - and the γ -position accentuates the electron deficiency at C₍₁₎ and therefore facilitates the rearrangement, *e.g.*, $\alpha\gamma$ -dinitrohinokitiol forms 2 : 4-dinitro-5-isopropylbenzoic acid with warm aqueous alcohol.⁶⁹ On the other hand puberulic acid can be largely recovered after fusion with potassium hydroxide at 300°.⁷⁰ Such vigorous alkaline conditions may of course cause side reactions such as the conversion of halogen⁷¹ or sulphonic acid⁷² substituents into hydroxyl, but this may not be always undesirable, as in a recent synthesis⁷³ of puberulic acid from stipitatic acid :



Although tropolone is a monoenolic form of a cyclic α -diketone it does not readily assume the diketo-structure and consequently the analogy of the alkaline rearrangement with the benzil-benzilic acid change is by no means complete. The formal resemblance to the benzilic rearrangement is more evident in the ring-contractions of tropolones brought about by alkalis in the presence of halogens where cyclic non-enolisable α -diketone intermediates are involved. Thus tropolone can be degraded to *sym*-tri-iodo-^{85, 74} or -tribromo-phenol,⁴⁵ and colchicine to *N*-acetyliodocolchicinol (XXII) : ⁷⁵

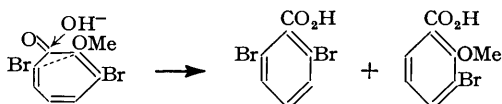


Concerning the direction of ring closure in the alkaline rearrangement of tropolones, the displacement of the hydride ion at $C_{(7)}$ with consequent $C_{(1-2)}$ fission is always more difficult than displacement of the $C_{(2)}$ -hydroxyl or -methoxyl anion with consequent $C_{(1-7)}$ fission and the rearrangement occurs as shown above. However, if the $C_{(7)}$ -hydride ion can be displaced indirectly so that a carbonium ion is formed momentarily at $C_{(7)}$, the ring closure occurs in the alternative manner with retention of the $C_{(2)}$ -hydroxyl group. Such a situation occurs for example in the decomposition of diazonium salts of α -aminotropolones which gives derivatives of salicylic acid : ⁷⁶



The nitrosation of tropolones containing bulky β -substituents also leads to salicylic acids ⁷⁷ and probably involves a similar type of intermediate.

$C_{(7)}$ -Carboxy-, ⁷⁸ -nitro-, ⁷⁹ -methyl, ⁶¹ and -phenyl ⁸⁰ groups are all retained in preference to the $C_{(2)}$ -hydroxyl or -methoxyl groups in the alkaline rearrangements, but with α -halogeno-substituents cases have been reported ^{56, 71} where both reactions occur :

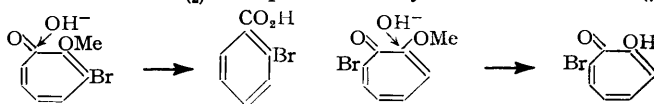


Under the influence of Grignard reagents the displacement of the bromine may be the main reaction : ⁶⁸



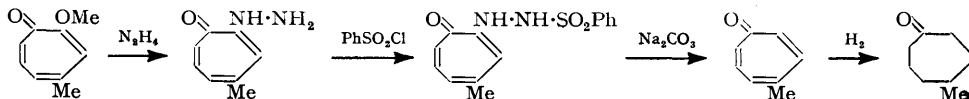
Besides attack at $C_{(1)}$, leading to ring-contraction, a nucleophilic reagent can also cause substitution at $C_{(2)}$ (or at any other position in the ring) and the relative extent of these alternative reactions at $C_{(1)}$ or $C_{(2)}$ is profoundly affected by steric factors, *i.e.*, by the nature of the α -substituents. In an ether of an unsymmetrically (α - or β -)substituted tropolone, the labile tautomerism between $C_{(1)}$ and $C_{(2)}$ is destroyed and in consequence there are two isomeric forms, *e.g.*, in the α -series (substituents at $C_{(3)}$ or $C_{(7)}$). The orientation of these ethers is conveniently accomplished by physical methods, *e.g.*, determination of dipole moments ⁸¹ or *X*-ray measurements, but chemical methods along the lines already indicated can be used. For example, in the case of the isomeric ethers of α -bromotropolone, *i.e.*, 3- and 7-bromotropolone methyl

ethers, nucleophilic displacement of the methoxy-group is more difficult in the case of the 3-isomer because of steric hindrance, and consequently the anionic attack occurs at C₍₁₎ (causing rearrangement), rather than at C₍₂₎ as is predominately the case with the C₍₇₎-isomer : ⁷¹

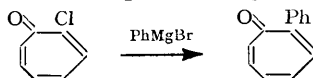


A similar situation obtains in the reaction with phenylmagnesium bromide. ⁶⁸

In the β (4 and 6)-substituted tropolone series, steric hindrance is of minor importance but Haworth and his collaborators ⁸² have devised a degradation of the two β -methyltropolone methyl ethers which yields the 3- and 4-methylcycloheptanones, *e.g.* :

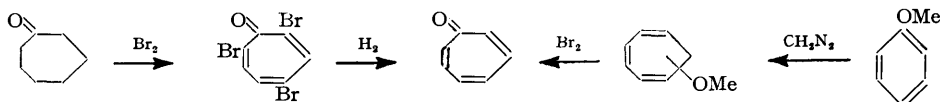


This method is one of several available for obtaining tropones (*i.e.*, hydrogen, alkyl, or aryl substituents at C₍₂₎) from tropolones; another is through the 2-halogenotropolones by hydrogenolysis or by reaction with organometallic compounds, ⁸³ *e.g.* :

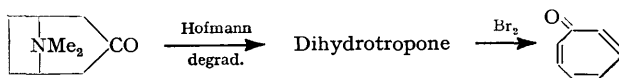


The 2-halogenotropolones required for this synthesis may be obtained from tropolones by the action of thionyl chloride ⁸⁴ or more conveniently by the decomposition of the hydrochlorides of the 2-hydrazinotropolones with cupric salts. ⁸⁴ 2-Alkyl- and 2-aryl-tropolones have also been obtained from the tropolone ethers, ^{83, 85} copper derivatives, ^{83, 86} or even tropolone itself ⁸³ with organometallic compounds.

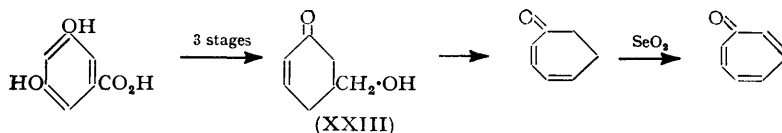
The parent tropone, or *cycloheptatrienone*, has been synthesised either from *cycloheptenone* ⁸⁷ or better *cycloheptanone* ⁸⁸ by oxidative bromination to 2 : 4 : 7-tribromotropone and subsequent hydrogenolysis, or alternatively, from anisole by ring expansion with diazomethane and subsequent oxidation by bromine of the methoxycycloheptatriene, ⁸⁹ a method closely resembling the Cambridge tropolone synthesis :



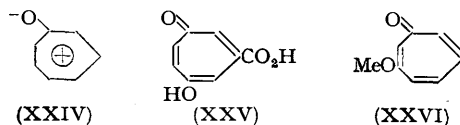
Quite recently, ⁹⁰ tropinone has been degraded to tropone by elimination of the amine bridge by the Hofmann reaction, and oxidation of the dihydrotropone(s) so obtained :



In another synthetic approach to tropone, ^{90a} 3 : 5-dihydroxybenzoic acid has been converted into 5-hydroxymethylcyclohex-2-enone (XXIII) which yields dihydrotropone on treatment of the toluene-*p*-sulphonate with alkali.



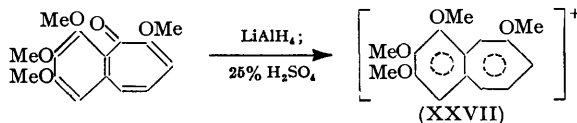
Several authors have preferred to regard tropone as *cycloheptatrienylium oxide* (XXIV), both on theoretical grounds ⁹¹ and on the basis of its physical and chemical properties, *e.g.*, the high dipole moment ^{81, 92} and boiling point (113°/15 mm.), the water miscibility, and the nuclear bromination and amination (by hydroxylamine). ⁸⁸



Substitution in the 2-position of the tropone nucleus occurs easily and thus the transition from the tropone to the tropolone series, involving the replacement of $-\text{NH}_2$ or $-\text{Br}$ by $-\text{OH}$, presents no great difficulty.^{83, 86, 93} Tropone however also shows some of the properties of an unsaturated ketone: it is unstable towards alkalis, it forms Diels-Alder adducts with maleic anhydride⁸⁸ as do several of the simple tropolones,⁹⁴ and, in spite of a preliminary report to the contrary,⁸⁷ it forms an oxime, a semicarbazone, and a variety of substituted phenylhydrazones all of which are coloured crystalline solids.⁸⁸

Very few substituted tropones lacking a 2-substituent have been described. However, the diazoacetic ester reaction with anisole gave a product which yielded tropone-4-carboxylic acid after oxidation with bromine.⁹⁵ The properties of this substance suggest a zwitterion type structure: it sublimes only with the greatest difficulty and so far it has resisted decarboxylation. In alkali it rearranges very easily to terephthalic acid. The properties of the 5-hydroxytropone-3-carboxylic acid (XXV)⁹⁶ are very similar and the syntheses of these acids led us to explore the possibility of preparing 3- and 4-hydroxytropones themselves to compare their properties with those of tropolone.* Unfortunately our work is still incomplete although we have obtained the methyl ether (XXVI), picrate, and hydrochloride of 3-hydroxytropone and there is little doubt that, like tropone itself, the other isomers of hydroxytropone will prove to be less stable and much less volatile than tropolone.

Our efforts to prepare compounds containing the *cycloheptatrienylium* cation with no oxygen to bear the compensating negative charge, including the attractive combination of a *cycloheptatrienylium* cation with a *cyclopentadienylium* anion, have so far been unsuccessful and at present the only representative of this type of structure is a substituted benzocycloheptatrienylium salt (XXVII) obtained by reduction of tetramethylpurpurogallin with lithium aluminium hydride and decomposition of the product with strong acid.⁹⁷



From what is known of the properties of these *cycloheptatrienylium* and tropone derivatives it seems that the contribution of the five-membered hydrogen-bonded ring system, with its two oxygen atoms, to the stability of tropolone is of great importance and that simplifications of the tropolone ring, while still retaining the basic *cycloheptatrienylium* cation structure, result in a marked decrease in the aromatic character.

It gives me great pleasure to thank my Cambridge collaborators, past and present, for their loyal support, and especially Professor A. R. Todd, whose guidance and wise counsel have been a source of inspiration to all of us throughout our work.

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* Since these lectures were given, 3-hydroxytropone, m. p. 179—180°, has been isolated in the Cambridge laboratories.

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