TROPONES AND TROPOLONES

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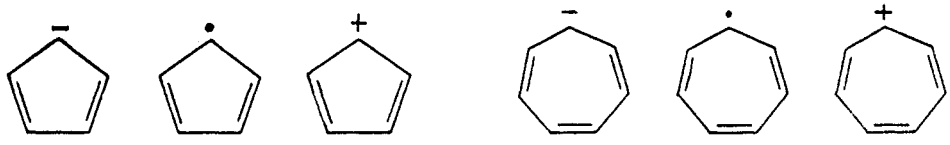
I. Introduction

Undoubtedly one of the most important developments in organic chemistry in recent years has been the attention devoted to what may be described collectively as "non-benzenoid aromatic compounds."[1]

Of the small-ring compounds, cyclobutadiene is still unknown and generally assumed to be too strained to be stable. Cycloöctatetraene exists in a puckered form, the planar form which would be necessary for aromaticity being again too highly strained.

Attention among monocyclic systems may thus be focussed on the five- and seven-membered ring systems. Three possibilities arise in each of these cases which satisfy the condition that it should be possible to write structures in which double and single bonds alternate but cannot be definitely assigned to specific positions. These are the cyclopentadienyl (I) and cycloheptatrienyl (II) anions (a), radicals (b), and cations (c).



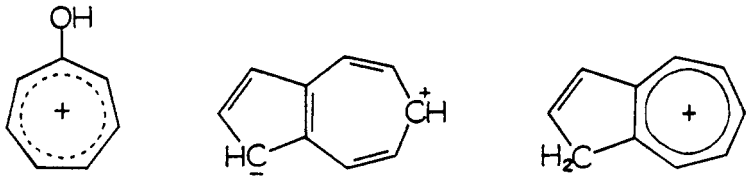
Further limitation is possible according to molecular orbital theory, which has been used by Hückel (151, 152) to predict that aromaticity will be shown only by those rings having $(4n + 2)$ π-electrons. Of the systems mentioned, only the cyclopentadienyl anion and the cycloheptatrienyl cation satisfy this condition. Other workers (366; *cf.* also 140), although stressing the limitations of Hückel's theory, have more recently calculated delocalization (resonance) energies which

[1] This term is taken here to refer to carbocyclic compounds only and is not meant to include heterocycles.

fully support the specific conclusions reached for the cyclopentadienyl and cycloheptatrienyl groups. In fact, they predict triplet ground states for the cyclopentadienyl cation and the cycloheptatrienyl anion.

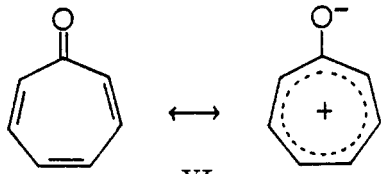
These theoretical predictions are in full accord with the known experimental facts. Thus the acidity of cyclopentadiene is well known and leads to the formation of the cyclopentadienyl anion (e.g., by reaction with alkali metals or Grignard reagents), but this property is absent in cycloheptatriene. On the other hand, the stability of the cycloheptatrienylium ion is now fully recognized and is the reason for the basicity of the tropones, which form the subject of this review. Thus the formation of very stable salts (III) with acids (HX) yields the hydroxycycloheptatrienyl cation, whereas by contrast cyclopentadienones are not only highly unstable, dimerizing rapidly except when heavily substituted, but those which can be obtained in the monomeric form are devoid of basic properties. The isolation of a salt containing the simple cation (IIc) itself has just been announced (98a).

A further interesting example is azulene, which combines the five- and seven-membered ring systems. The view that canonical forms of the type of IV, in which each ring separately attains six π-electrons, play an important part leads to a simple explanation of many properties of azulene; in particular, its salts with strong acids can on this basis be written as shown in formula V (see, e.g., 140 and 419), containing the cycloheptatrienylium ion.



III IV V

The present review is devoted to all derivatives of 2,4,6-cycloheptatrien-1-one (tropone) (VI). The parent member of this class was first described in 1951 (86, 93), and the alternative name "cycloheptatrienylium oxide" was then suggested (93) as corresponding best to its properties. A special place among its

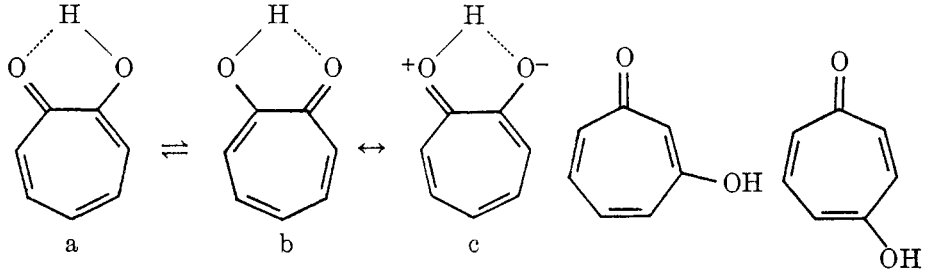


VI
Tropone

derivatives belongs to the 2-hydroxy-2,4,6-cycloheptatrien-1-ones (VII), which have been recognized since 1945 when Dewar (88) predicted that this system would show certain aromatic properties. He suggested that two then known natural products, *viz.*, stipitatic acid (88) and colchicine (89), are representatives of this class, for which he proposed the name "tropolones."

This special position of the 2-hydroxytropones is the result of several factors.

It is now known that Dewar's original formulation (88) overemphasized the importance of internal hydrogen bonding, as indeed he very soon recognized (90). The two forms VIIa and VIIb must be considered not as resonance hybrids but as a highly mobile tautomeric system.



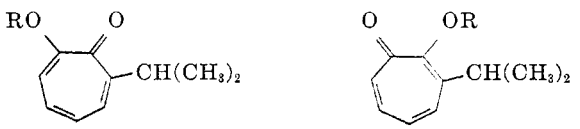
a b c VII Tropolone VIII IX

Yet it is clearly an oversimplification to regard tropolones merely as "hydroxytropones." It must be recognized that both hydrogen bonding and resonance with the ionic form (VIIc) help to increase the stability of tropolone compared not only to tropone but also to the isomeric hydroxytropones VIII (159) and IX, where intramolecular hydrogen bonding must be absent and where the corresponding ionic forms involve greater separation of charge. There is thus no single simple picture of tropolone in purely descriptive terms which will account for all its properties. Indeed, in some connections it will be useful to regard tropolone as a vinylog of a carboxylic acid—another gross oversimplification which disregards completely the aromaticity of the cycloheptatrienylium ion.

Nomenclature

The trivial name "tropolone" has now been sanctioned by such wide usage that it may be considered as generally accepted. It is therefore employed throughout this review in place of the more cumbersome "2-hydroxy-2,4,6-cycloheptatrien-1-one." As the latter name indicates, the carbonyl oxygen is always taken to occupy position 1 and the hydroxyl group position 2. This still leaves the ambiguity arising from the rapid tautomeric equilibrium; thus formulas XIa and XIb are considered to represent a single substance (no two such isomers having ever been definitely distinguished[2]).

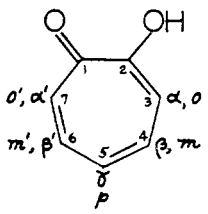
[2] Several tropolones have been obtained in two modifications with different melting points. In no case has it been established conclusively that these are the two tautomeric forms. But suggestive evidence has recently been obtained (410) that the two forms of 3-isopropyltropolone are to be represented as A (R = H) (m.p. 33–34°C.) and B (R = H)



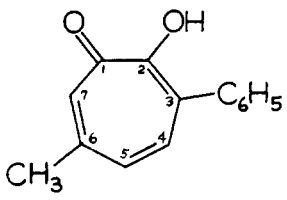
A B

(m.p. 25.5–26°C.), respectively, since they yield different proportions of the two ethers (A: R = CH_3) and (B: R = CH_3) on methylation with diazomethane.

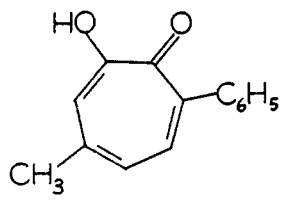
To make possible the assignment of a single unambiguous name, the following rules are proposed: (*1*) That formula is used which leads to the lowest total for



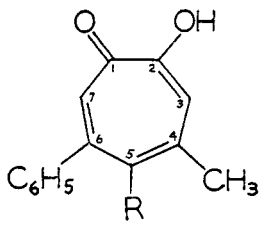
X



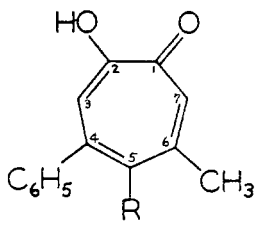
XIa



XIb



XIIa



XIIb

the numbers assigned to the substituents (e.g., compound XI is named as 6-methyl-3-phenyltropolone, corresponding to XIa, and *not* as 4-methyl-7-phenyltropolone (XIb)). (*2*) Where the above rule is indecisive, that substituent which is named first receives the lower of two possible numbers (e.g., compound XII (R = H) is 4-methyl-6-phenyltropolone (XIIa) and *not* 6-methyl-4-phenyltropolone (XIIb); compound XII (R = Br) is 5-bromo-4-methyl-6-phenyltropolone and *not* 5-bromo-6-methyl-4-phenyltropolone). It is implicit in the above rules that all substituents be named in alphabetical order.

Following the recommendation of Patterson (350), numbers are here used exclusively in place of the alternative use of Greek letters or the "ortho," "meta," and "para" designation shown in formula X, both of which are liable to lead to confusion. These two systems have however been widely used in the literature, and the confusion has been heightened by the alternative use of Greek letters to designate isomers of unknown orientation (see, e.g., 284 and 304).

It is considered a logical extension of the above considerations to use the name "tropone" to designate 2,4,6-cycloheptatrien-1-one, but the use of other trivial names has been kept to a minimum.

Most of the material of this review has appeared since the last full review in English (68) was published. Summaries of specific aspects of the field (69, 219, 249, 250, 251), brief reviews (161, 162), and several reviews in other languages (55, 122, 150, 248, 252, 253, 384) have appeared.

II. Natural Tropolones

That tropolone derivatives escaped recognition until 1945 must in large measure be attributed to their relative scarcity in nature. The few natural tropolones known at present can be conveniently divided into three groups:

The simplest are the isopropyltropolones, which have been found to occur in several conifers, all belonging to the family *Cupressaceae*. Four such substances have been isolated, all of which may be regarded as mono- or sesquiterpenes. The second class are hydroxytropolonecarboxylic acids and have hitherto been found only in mould species of the *Penicillium* family. Lastly, colchicine and a few very closely related compounds have been isolated from various *Liliaceae*, particularly from *Colchicum autumnale* (meadow saffron or autumn crocus) and related species.

With the exception of colchicine, all of these substances have been isolated only within the last twenty-five years. Before fuller discussion of the individual compounds, those general properties of tropolones which have been found useful in the elucidation of their structures will be discussed.

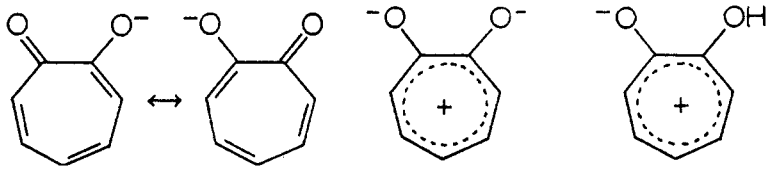
A. RECOGNITION OF THE TROPOLONE NUCLEUS

1. Acidity

The hydroxyl group of tropolone is an enolic hydroxyl; tropolone derivatives invariably possess the properties characteristic of enols and phenols. In particular, they are acidic and the effect of the carbonyl group is to enhance the acidity as it does, for example, in the hydroxyquinones (*cf.* 113) and β-diketones. In common with these, tropolones may be regarded as vinylogs of carboxylic acids. Their dissociation constants are closer to the latter than to those of phenols. The following pK values are illustrative:

Substance	pK	Substance	pK
2-Hydroxy-1,4-naphthoquinone	4.0	Glutaconaldehyde	5.75
Benzoic acid	4.2	Tropolone	7.0
Acetic acid	4.8	Phenol	10.0
Dihydroresorcinol	5.25	Enol form of cyclohexane-1,2-dione	10.3

They show that, on the simple basis of vinylogy, the acidity of tropolone, following in the series acetic acid, dihydroresorcinol, glutaconaldehyde, falls slightly below expectation. As has been pointed out (96), the acidity is certainly not enhanced by aromatic resonance of the ion (XIII). This agrees with expectation, as the resonating ions of the comparison substances are likewise fully equivalent and any additional "aromatic" resonance would have to come from structures (XIV) which must be rather less favored than the corresponding structures (XV) of the free acid.



XIII XIV XV

The recorded dissociation constants of tropolones are collected in table 1. Qualitatively, their acidity may also be gauged from the observation that tropolone

TABLE 1

Acid dissociation constants of tropolones

Compound	pK*	References
Tropolone	6.7	(96)
	6.92	(472)
	6.95	(64)
(at 30°C.)	6.97 ± 0.05	(41)
	7.00 ± 0.04	(158)
(at 20°C.)	7.00 ± 0.02	(65)
3-Methyltropolone	7.92	(472)
4-Methyltropolone	7.26	(472)
5-Methyltropolone	7.12	(472)
3-Isopropyltropolone	7.0 (approx.)	(9)
4-Isopropyltropolone	7.21	(471)
3-Bromotropolone	5.96	(472)
3-Bromo-5-methyltropolone	6.41	(472)
3-Bromo-6-methyltropolone	6.3	(472)
3-Bromo-4-isopropyltropolone	6.68	(471)
3-Bromo-6-isopropyltropolone	6.28	(471)
5-Bromotropolone	6.32	(472)
5-Bromo-4-methyltropolone	6.6	(472)
5-Bromo-4-isopropyltropolone	6.53	(471)
3,5-Dibromotropolone	5.18	(472)
3,5-Dibromo-6-isopropyltropolone	6.28	(471)
3,7-Dibromotropolone	4.68	(472)
3,7-Dibromo-4-methyltropolone	5.59	(472)
3,7-Dibromo-5-methyltropolone	5.35	(472)
3,7-Dibromo-4-isopropyltropolone	6.44	(471)
3,5,7-Tribromotropolone	4.27	(472)
4-Methyl-3,5,7-tribromotropolone	5.17	(472)
4-Isopropyl-3,5,7-tribromotropolone	6.0 (approx.)	(471)
4-Methoxytropolone	7.24	(472)
5-Methoxytropolone	7.75	(472)
3-Hydroxytropolone	6.72; 11.52	(472)
4-Hydroxytropolone	5.76; 9.48	(472)
5-Hydroxytropolone	6.47; 10.10	(472)
Colchiceine	6.74	(423)
Stipitatic acid	3.5 (or less); 5.8; 9.7 (approx.)	(11)
Puberulic acid	4.3 (or less); 5.8; 10.3; 12 (or higher) (approx.)	(11)
3,4-Benzotropolone	9.5 (approx.)	(66)
4,5-Benzotropolone	10	(423)
5-Hydroxy-2,4,7-tribromotropone	3.89	(472)
4-Hydroxy-2,3-benzotropone	6.40	(43)
2-Mercaptotropone	5.90	(316, 317)

* All the values from references 471 and 472 were measured at 25°C.

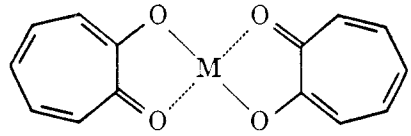
itself will dissolve in aqueous sodium bicarbonate solution with effervescence, but may be at least partially extracted by ether from a solution saturated with carbon dioxide.

Thermodynamic pK values of 4-isopropyltropolone have been measured electrometrically at temperatures from 10° to 40°C. (228).

The alkali metal salts of the simple tropolones and their aqueous solutions are pale yellow in color. The sodium salts are only sparingly soluble in cold water and are readily isolated in crystalline form. The transition metals form highly colored coördination compounds.

Complexes with numerous metals were prepared from hinokitiol (4-isopropyltropolone) before its tropolone nature was recognized (154, 155, 247). The preparation of chelate complexes of tropolone itself and a determination of the forma-

tion constants of eight of these (41, 114) have established the order of stability as: Cu(II) > Be > Pb > (Zn, Ni) > Co(II) > Mg > Ca. This order has been checked for several alkyltropolones (40) and is the same as for many other ligands (*cf.* 156), including β-diketones, salicylaldehydes, etc. The stability is greater than those of complexes of β-diketones of comparable acidity (41); however, in view of the fact that the latter form six-membered chelate rings, whereas the tropolones give five-membered chelate rings, it is difficult to assess the significance of this difference. Zinc, nickel, cobalt, and manganese form complexes of the type $[Mtr_3]^-$, where tr represents the anion derived from the tropolone used. The others listed above form neutral complexes of the type shown in formula XVI. For magnesium both types have been reported (40, 155).



XVI

The green cupric complexes of this type have been investigated extensively. These are insoluble in water but dissolve in and may be crystallized from chloroform, benzene, ethanol, etc. The high melting points limit their usefulness for characterization, but they have repeatedly been utilized for isolation (e.g., 95, 96, 98, 282, 294). The parent tropolone is recovered either by treatment with mineral acids and ether extraction or by treatment with hydrogen sulfide.

The ferric complexes have also been isolated in a few cases. Frequent use has been made of the color reaction with ferric chloride commonly employed also with enols and phenols. With tropolones in alcohol this reagent gives a solution or precipitate of the red ferric compound which, being readily soluble in chloroform and benzene, less soluble in ether, but ordinarily insoluble in water, may be extracted into organic solvents. When excess of the reagent is used, an intense green color is observed. The same color may be obtained in anhydrous ether, but upon addition of water it passes completely into the aqueous phase.

Numerous "complexes" with aniline, *p*-toluidine, ethylenediamine, etc. have been used for characterization of tropolone derivatives, particularly the halogen substitution products. These are presumably salts, although their nature has never been clearly established. Although not all tropolones are capable of yielding such derivatives, no simple correlation with acidity or with structural features has been established.

As phenolic compounds, tropolones undergo coupling with diazonium salts in alkaline solution and are in general readily substituted (Section IV). They form esters under the same general conditions as phenols. These esters are very readily hydrolyzed, frequently by warm water without addition of acid or alkali.

As rather strong acids, tropolones react rapidly with diazomethane in ethereal solution and the resulting ethers resemble esters in their general behavior. Their reactions are discussed in detail in Sections VI and VIII,A. "Esterification" with alcohols and mineral acid is less effective (96, 148).

The analogy to the carboxylic acids is also evident in the inertness of the

carbonyl group towards the usual "carbonyl reagents" such as phenylhydrazine. In this sense, the tropolones and their ethers differ markedly from the tropones, which react normally with these reagents (311). The only known exceptions are some benzo- and dibenzotropolone derivatives (see Section IX) and the 5-nitrosotropolones (see Section VIII,D). Among the sulfur analogs 2-mercaptotropone does not react with ketonic reagents, but a dinitrophenylhydrazone has been obtained from 2-methylmercaptotropones (316).

2. Basicity

Tropolones are not only acidic but also basic, a property they share, if in reduced degree, with the parent tropone system. As has already been mentioned (*cf.* page 10), this property is a direct result of the aromaticity of the cycloheptatrienylium ion. In this sense it contrasts with the acidity of tropolones, which is not aided by that aromaticity.

Whereas tropone itself forms very stable salts with acids (93), most substituted tropones and in particular the tropolones are distinctly less basic. They dissolve in strong acids, but the salts are hydrolyzed by water. Nevertheless, crystalline salts with mineral acids can be frequently isolated and the picrates, in particular, have found repeated use for the separation and identification of tropolones and their derivatives (e.g., 131, 292).

The carbonyl group is thus responsible in large measure for the amphoteric character of tropolones, but its presence as a ketonic function is only revealed after partial or complete saturation of the ring.

3. Reduction

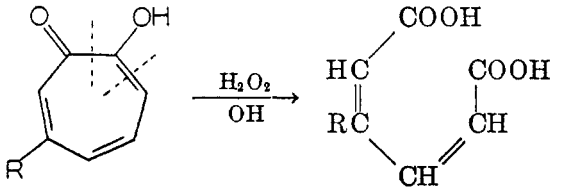
As an "aromatic" system the tropolone nucleus is not reduced by hydrogen in the presence of palladium catalysts. These conditions have, in fact, frequently been used in the preparation of tropolones by hydrogenolysis of their bromo derivatives.

Saturation of the ring can be effected by use of Raney nickel or Adams' platinum oxide as catalysts, the latter having been most commonly employed. Its use leads to a variety of products depending on the precise reaction conditions. As indicated above, ketonic intermediates may be obtained. More complete hydrogenation leads to the cycloheptanediols (7, 8, 182, 401). In a few cases these have been obtained crystalline and compared with synthetic specimens of known structure, thus providing, perhaps, the most direct proof of the orientation of substituents in the tropolone nucleus (96, 98). As the hydrogenation may produce a mixture of *cis* and *trans* diols (and thus with additional substituents a complex mixture of stereoisomers may result), it has more frequently been found preferable to oxidize the crude hydrogenation product (including ketols) to the corresponding substituted pimelic acid, whose identification likewise provides satisfactory evidence for the orientation of substituents in the original tropolone (4, 109, 125, 131).

4. Oxidation

Tropolone is stable under mild oxidizing conditions. Thus persulfate oxidation leads to smooth introduction of a hydroxyl group (see page 53); the hydroxyla-

tion of the double bond in the side chain of nootkatin using performic acid has been described (81, 111); 4-methyltropolone or its ethers can be oxidized to tropolone-4-aldehyde (or its ether) by selenium dioxide (131, 181); strongly alkaline hydrogen peroxide is used in the preparation of tropolone derivatives from purpurogallin and related compounds (130, 131). However, the latter reagent does cause some ring-cleavage and the reaction then involves loss of one carbon atom. Thus tropolone itself, although largely recovered unchanged, yields some *cis,cis*-muconic acid (65)(XVII: R = H), and 4,5-benzotropolone

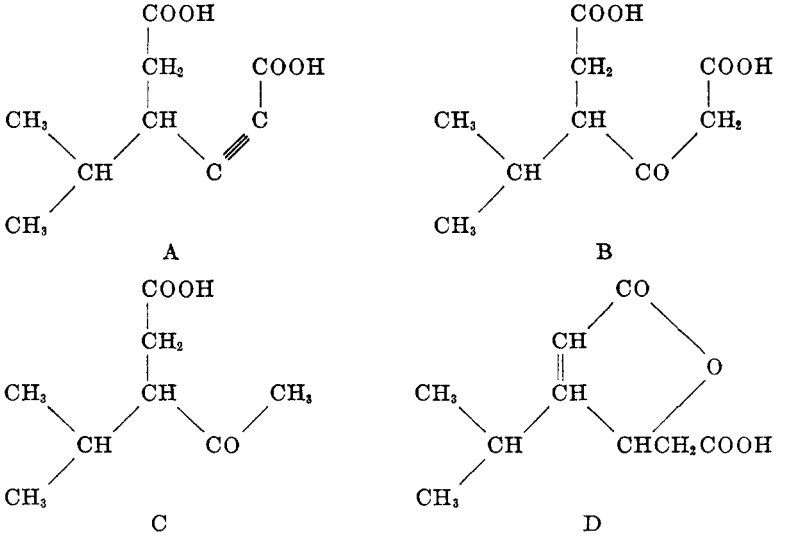


XVII

similarly yields *o*-carboxycinnamic acid (116). The structure of the acid $C_9H_{12}O_4$[3] obtained by peroxide oxidation of hinokitiol has not been fully elucidated. There seems to be little reason to doubt, however, that it is the expected isopropylmuconic acid (XVII: R = $CH(CH_3)_2$).[4]

[3] It has repeatedly been stated (250, 323) that analyses correspond best to this formula. Unfortunately, the only available figures (402) do not agree even approximately with any likely simple formula; they correspond, however, to an approximately equimolecular mixture of the C_9 acid and its monoethyl ester.

[4] The unlikely structure A has been proposed (250) for this acid to explain its facile conversion (402) to β-isopropyllevulinic acid (C) via B. This change can be accommodated easily if XVII (R = *i*-C_3H_7) may be considered to exist in equilibrium with the cyclic form (D).



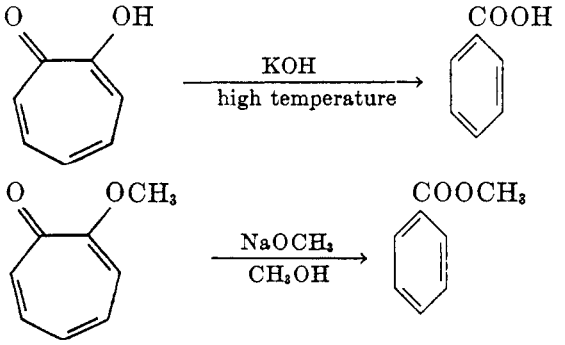
The ease of hydrolysis of unsaturated lactones of this type to levulinic acid derivatives is well known (see, e.g., references 118 and 430).

The rearrangement of colchicine under the same conditions (page 88) has not been observed in any other case, and this difference in behavior remains unexplained.

When applied to stipitatic and puberulic acids, alkaline hydrogen peroxide resulted in smooth formation of aconitic acid, providing important confirmation of the structures assigned to these substances (see page 26).

More extensive oxidations with permanganate or chromic acid, although largely or wholly destroying the tropolone ring, have nevertheless contributed important evidence for the structures of purpurogallin (18) and of colchicine (455), and for the presence of isopropyl groups in α-, β-, and γ-thujaplicin and nootkatin (4, 109, 111, 125, 401) and the 3-methyl-2-butenyl side chain in the latter compound (101, 111).

The most commonly used method of orientation of tropolone derivatives has been the rearrangement to benzoic acid derivatives which is effected by hydroxide or methoxide ion:



The use of this method is justified by the fact that in the numerous cases where independent alternative evidence is available, substituents have invariably retained their relative positions.

Detailed discussion of these rearrangements will be found in Section VI.

5. Physical methods

X-ray crystallography has been used to determine the carbon skeleton of nootkatin (48), to determine the relative positions of the methoxyl and carbonyl groups in and provide general confirmation of the structure of colchicine (185), and to orient the two methyl ethers of 3-bromotropolone (447).

The ultraviolet and infrared spectra have both been utilized in detecting or confirming the presence of a tropolone nucleus (9, 10, 11, 12) and have been extensively studied.

(a) The ultraviolet spectra

An attempt to predict the positions of ultraviolet maxima (91) has been only partially successful. The ultraviolet spectra of tropones and tropolones may be broadly divided into two main regions. The most intense absorption occurs below 270 mμ (log ϵ = 4.0–4.7). In tropone it consists of a maximum near 225 mμ

(log ϵ = 4.33), the exact position and amount of fine structure depending somewhat on the solvent used (86, 93, 311).

It is shifted appreciably to longer wave length by halogen substituents in the 2-position, e.g., in 2-bromotropone which shows the maximum near 245 mμ (94, 408, 413). In tropolone the band is broadened and ranges from 225 to nearly 250 mμ. In the spectrum of tropolone in cyclohexane, three peaks of approximately equal intensity can be clearly distinguished (9, 65, 96, 436) in this region. The absorption of its methyl ether and its acetate are almost indistinguishable from that of the parent compound in this region, while that of the anion is shifted some 10 mμ to a longer wave length. Alkyl substitution has little effect except for a marked lowering in intensity of the higher-wave-length component of this band caused by alkyl groups in the 5-position (9, 292). Halogens again cause a bathochromic shift (436). Additional hydroxyl groups have little effect, but carboxyl substituents cause a strong bathochromic shift, raising the maximum of, for example, stipitatic and (undissociated) puberulic acid to ca. 265 mμ (11, 22, 80). The spectrum of 2-aminotropone is very similar throughout its range to that of tropolone, but the low-wave-length region is somewhat less intense and contains a component (log ϵ = ca. 3.8) extending to 260 mμ (94, 344, 346).

The second region of absorption covers the wide range from 280 to 400 mμ and is slightly less intense (log ϵ = 3.5–4.0). Solvent effects are marked (see, e.g., 311) and both the position (297 mμ) and the intensity (log ϵ = 3.74) of the main maximum of tropone in hydrocarbon solvents are increased in hydroxylic solvents, e.g., water. This may be assumed to result from association with the solvent and resultant increased polarization. In tropone the band is broad and complex, ranging from approximately 280 to 345 mμ. This range is again shifted to longer wave length by halogen substituents (94, 408). In tropolones and aminotropones the region is broader and clearly composed of two groups of bands (9, 65, 94, 96, 346, 436). The section from 300 to 340 mμ corresponds to that of tropone; both its position and its intensity (log ϵ = approx. 3.8) are but little affected by substituents, and only near 325 mμ can a small peak be clearly distinguished above the broad plateau. A much more distinct peak occurs in the anion (at 330 mμ; log ϵ = 4.1). The spectrum of tropolone in water has been shown (96) to be intermediate, indicating partial dissociation.

The second section ranges from 350 to 380 mμ in simple tropolones. In the unsubstituted compound in hydrocarbon solvents, two distinct peaks at ca. 355 and 375 mμ (log ϵ = 3.74) are readily distinguished. These are much less distinct in the alkyltropolones and also tend to merge in hydroxylic solvents. In the corresponding anions these are replaced by a single intense maximum near 390 mμ (log ϵ = 4.0–4.1). This is certainly the most pronounced and characteristic difference observed in the ion (9, 65, 96). It is interesting to note that in the copper chelate (65) this peak is of much lower intensity, although the spectrum otherwise resembles that of the ion. The highest-wave-length peak is absent in tropolone acetate and in the methyl ether (436). It is shifted to 395 mμ (approximately) in 2-aminotropone and to 407 mμ in 2-methylaminotropone (346). It is also susceptible to the influence of substituents in the tropolone nucleus, e.g., the bathochromic effect of halogen. That the presence of this highest maximum

is closely associated with the presence of a free OH (or NH) group adjacent to the carbonyl group and therefore probably with the possibility of hydrogen bonding is further emphasized by the enhanced intensity of the longest-wave-length peak in 3-hydroxytropolone (333, 436) and by the complete absence of this long-wave-length absorption in 3-hydroxytropone (159). This latter substance closely resembles tropone in its high-wave-length spectrum but has a double peak (247 mμ (4.51) and 255 mμ (4.41)) in the lower region; only this shifts markedly in the ion (to 257 mμ (4.60) and 256 mμ (4.55)).

The sulfur analog of tropolone, 2-mercaptotropone, and its methyl derivative show very marked differences throughout the spectral range from the compounds discussed so far. They have two well-spaced low-wave-length peaks at 235 and 267 mμ for the free mercaptan and at 228 and 246 mμ for 2-methylmercaptotropone. The mercaptotroprone has a broad peak at 420 mμ; the methyl derivative has an additional peak at 282 mμ and a broad plateau at 320–395 mμ (317).

(b) The infrared spectra

The infrared spectra have been investigated and discussed extensively (12, 192, 194, 399, 437), with emphasis on the carbonyl and hydroxyl bands. In the tables of compounds in subsequent sections, the papers containing spectra are marked accordingly. Unfortunately, many of the curves have been printed on so small a scale as to be of little value, and the positions of the maxima can only be conjectured.

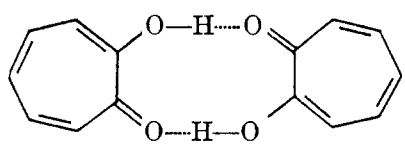
A strong maximum is invariably found between 1600 and 1650 cm.$^{-1}$ This has been regarded as due to the carbonyl group; its exceptionally low wave number (i.e., high wave length) is regarded as the result of the high degree of conjugation, of the high polarity, and of ring strain, all of which should shift the maximum in this direction. The following positions which have been recorded for several tropone derivatives and three other seven-membered ring ketones invite comparison:

Compound	Wave Length of Maximum	Reference
	cm.$^{-1}$	
Cycloheptanone	1699	(399)
2,3-Benzocycloheptanone	1683	(399)
2,6,6-Trimethylcycloheptadien-2,4-one	1661	(399)
3-Hydroxytropone	1647	(159)
4,5-Benzotropone	1641	(399)
Tropone	1638	(93)
Tropolone methyl ether	1625	(96)
Tropolone	1615	(192)
3,7-Di(*p*-methylbenzyl)tropolone	1600	(214)
Copper derivative of tropolone	1595	(192)

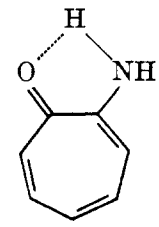
The significant shift of this absorption by ca. 30 cm.$^{-1}$ towards even lower frequency for tropolone as compared to 3-hydroxytropone must be due largely to hydrogen bonding, which is demonstrated much more clearly by the low frequency of the hydroxyl absorption. The latter takes the form of a broad region

of medium intensity at 3100 cm.$^{-1}$ in tropolone compared to a normal hydroxyl frequency of 3600 cm.$^{-1}$

It has been pointed out (192) that this indicates a rather strong intramolecular association of the hydroxyl group, though by no means comparable to that observed in enolized β-diketones. The figures given refer to tropolone in solution. In the solid form, however, the peak is shifted to ca. 3200 cm.$^{-1}$ (194) and this difference, together with other spectral changes, is attributed to a change to an intermolecularly hydrogen-bonded dimeric form (XVIII). The existence of such a form is claimed to be supported by x-ray diffraction studies, but no details of these have appeared. It is noteworthy that there is no corresponding change in the position of the carbonyl frequency in the solid state (194). 2-Aminotropone



XVIII



XIX

has two maxima in the 3300–3600 cm.$^{-1}$ region which have been attributed to the weakly hydrogen-bonded and unbonded N—H groups as shown in formula XIX (194, 344, 346).

The carbon–hydrogen bond-stretching vibration of tropolone occurs near 3000 cm.$^{-1}$, in agreement with its aromatic nature. In tropolone this is partly merged with the hydroxyl band, but it is of course clearly defined in the anion (or copper chelate) and in tropone.

It has been strongly suggested (192) that in addition to the bands discussed above, those at or near 1553 and 1255 cm.$^{-1}$ in tropolone and possibly also those at 1475 and 1440 cm.$^{-1}$ are characteristic of the nucleus and of diagnostic value. Among compounds examined more recently it is notable that all these bands can be found in the spectrum of 3-hydroxytropone (159), whereas tropone lacks the 1440 band but shows absorption at 1582, 1475, and 1225 cm.$^{-1}$ (93) which probably corresponds to the other three bands. The strong band in the 1550–1580 cm.$^{-1}$ region has been attributed to C=C stretching vibrations (194). Tropone has additional maxima at 1524 cm.$^{-1}$ and particularly an interesting one at 3425 cm.$^{-1}$ whose origin has not been explained.

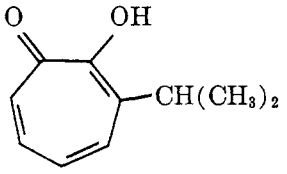
A lowering of the Raman frequency of the carbonyl group in 2,7-dimethyl-4,5-benzotropone compared to other ketones has been noted (442), a doublet being observed at 1617–1628 cm.$^{-1}$

B. SURVEY OF NATURAL TROPOLONES

1. The tropolones of Cupressaceae

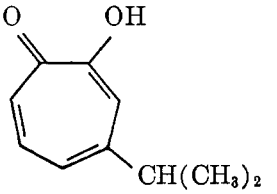
The isolation of various more or less crude samples of hinokitiol (180, 247, 254) and its ferric complex (hinokitin) (247) have been described, and were

followed by the description of the pure product (263) now recognized as 4-isopropyltropolone (XXI). The isomer (XXII) was first obtained from *Thuja*



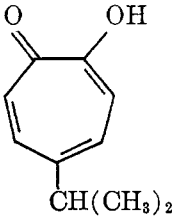
XX

α-Thujaplicin



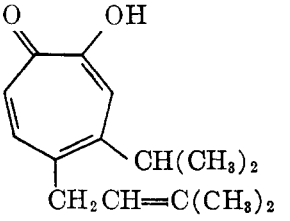
XXI

Hinokitiol or
β-thujaplicin



XXII

γ-Thujaplicin



XXIII

Nootkatin

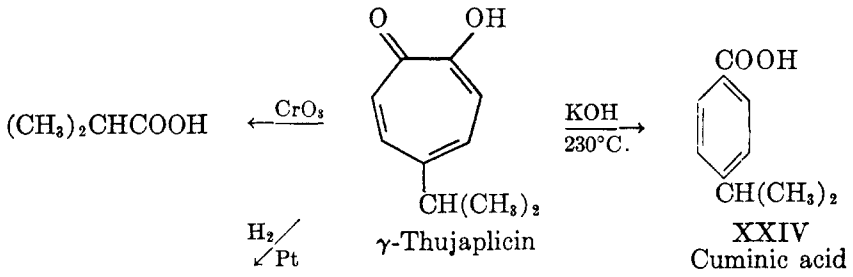
plicata (5). Depending on its source, this species was subsequently found to contain also XXI or the third isomer (XX) (108). The products from this source were termed α-, β-, and γ-thujaplicin (XX, XXI, and XXII, respectively). The identity of β-thujaplicin and hinokitiol was suspected (109) and was confirmed (248, 250) by direct comparison. The last member of this group to be isolated (50) has been termed nootkatin and has structure XXIII. The sources of these products are as follows: *Chamaecyparis obtusa*, Sieb. et Zucc. *f. formosana*, Hayata (= *Ch. taiwanensis*, Masamune et Suzuki) and *Ch. formosensis* contain β-thujaplicin (166, 167, 247). *Thujopsis dolabrata* Sieb. et Zucc. contains α- and β-thujaplicins (348). *Thuja plicata* D. Don contains α-, β-, and γ-thujaplicins (5, 108). *Thuja occidentalis* L. contains α-thujaplicin and either γ-thujaplicin (126) or β-thujaplicin (238). *Chamaecyparis nootkatensis* and *Cupressus macrocarpa* contain nootkatin (50, 81).

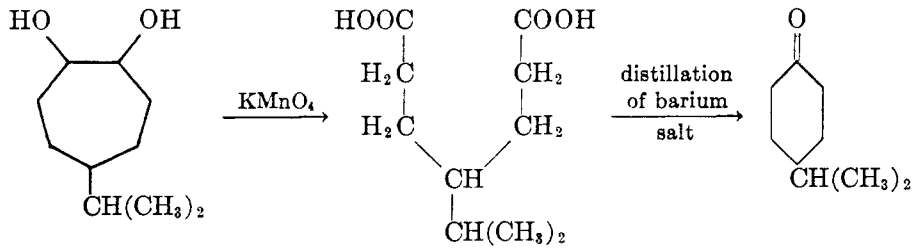
These species owe their strong resistance to wood-destroying fungi largely to the presence of these tropolone derivatives. Both *Ch. obtusa* ("Hinoki") and *Ch. formosensis* ("Benihi") furnish woods important as building materials in Japan and Formosa. The hinokitiol is present in the essential oil of these plants, which is used as a flotation oil in Japan; the acidic waste products from the purification of the oil yield large amounts of hinokitin (254).

In spite of the erroneous formula ($C_{10}H_{14}O_2$ in place of $C_{10}H_{12}O_2$) then accepted on the basis of oxidation experiments (*cf.* footnote 4, page 18), the seven-membered ring, the grouping C=C(OH)—C=O, and the isopropyl group were recognized (249, 263) to be present in hinokitiol on the basis of degradation in-

volving catalytic reduction to the saturated diol, which could be oxidized to a dicarboxylic acid without loss of carbon atoms. The dicarboxylic acid could be cyclized to a ketone, limiting the ring size to a seven-membered ring, since the general properties of the substance excluded a benzenoid system and vigorous oxidation of the acid to acetone demonstrated the nature of the side chain. Parallel work on the thujaplicins (4, 108, 109, 125) followed closely similar lines. Direct chromic acid oxidation yielded isobutyric acid in each case, demonstrating the presence of isopropyl groups.

The three isomeric isopropylpimelic acids obtained by catalytic reduction followed by permanganate oxidation were fully identified in each case by synthesis either of the acids themselves (4, 125) or of the derived cyclohexanone (109). This provided direct proof of the positions of the isopropyl group as illustrated for the case of γ-thujaplicin (5-isopropyltropolone):



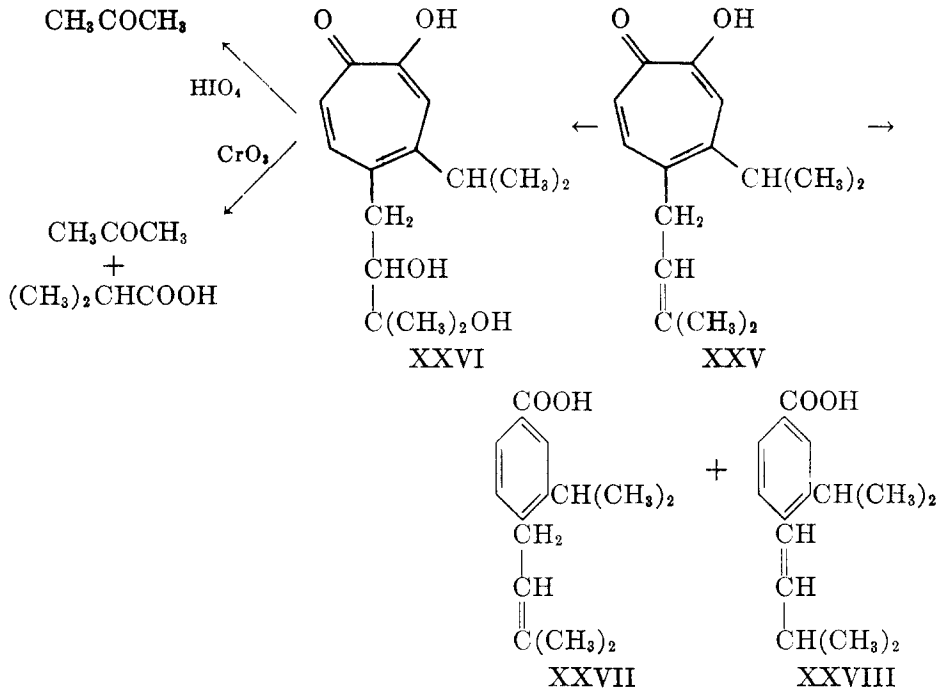


In this case a benzilic acid type of rearrangement to cuminic acid (XXIV) provided additional support.

Synthetic confirmation of the correctness of the structures of the three isopropyltropolones (see following section) has been obtained independently by several methods (table 3).

The tropolone nature of nootkatin was first recognized on the basis of spectroscopic evidence (9, 12). This also indicated that the additional double bond was not conjugated with the ring. Hydroxylation of this double bond yielded a glycol (XXVI) (81, 111) which not only gave acetone on periodate cleavage but also gave both acetone and isobutyric acid on vigorous oxidation. All the carbon atoms were thus accounted for as the ring, an isopropyl group, and a 3-methyl-2-butenyl side chain. The relation of these two groups to each other was deter-

mined by x-ray crystallographic study (48) of the copper chelate of nootkatin. Subsequent chemical confirmation of the resultant structure (XXV) was based



on proof of the structures of the acids (XXVII and XXVIII) obtained by rearrangement of the methyl ether of nootkatin with sodium methoxide (101).

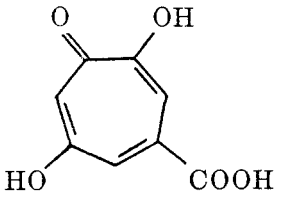
2. The hydroxytropolonecarboxylic acids from Penicillium species

Puberulic and puberulonic acid have been found to occur together in the following species (35, 78, 349): *Penicillium puberulum* Bainier, *P. aurantio-virens* Biourge, *P. cyclopium-viridicatum*, and *P. Johannioli* Zaleski. The ratio of puberulonic to puberulic acid increases approximately in the order given, the last-mentioned species containing nearly only puberulonic acid. Early chemical studies were devoted exclusively to puberulic acid (16, 35) and yielded numerous methyl and acetyl derivatives, but very little structural information.

The related stipitatic acid, a metabolite of *Penicillium stipitatum* Thom, was isolated ten years later (34). Its chemistry proved easier to unravel and the following evidence, published by its discoverers (34), enabled Dewar to deduce the correct structure (XXIX) (88) and started the development of the whole tropolone field.

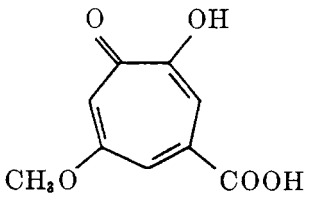
Stipitatic acid yields a monomethyl derivative which is a dibasic acid, a weakly acidic dimethyl derivative, and two isomeric neutral trimethyl derivatives. One of the acidic groupings is a carboxyl group, as shown by decarboxylation with copper in quinoline. Stipitatic acid is substituted by bromine; it is non-ketonic,

but hydrogenation over a platinum catalyst results in absorption of approximately 4.7 moles of hydrogen and yields a ketonic product. Fusion with caustic potash at 300°C. converts it, or better yet its monomethyl ether (XXX), to 5-hydroxyisophthalic acid (XXXI) (34). The probable relationship between stipitatic and puberulic acids was realized (34, 88), but the available evidence permitted no definite conclusion.

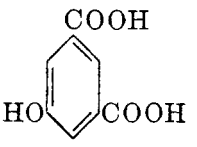


XXIX

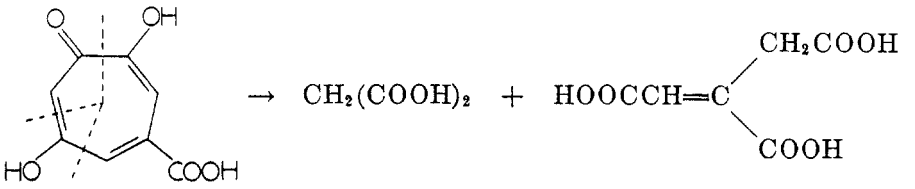
Stipitatic acid



XXX



XXXI

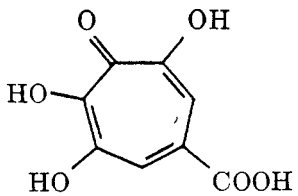


Malonic acid

Aconitic acid

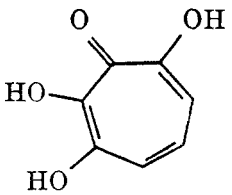
Striking confirmation for the correctness of structure XXIX for stipitatic acid was obtained by its oxidation with hydrogen peroxide to a mixture of aconitic (XXXII) and malonic acids (77, 80).

The analogous oxidation of puberulic acid had already yielded aconitic acid, thus suggesting structure XXXIII (77, 79). The close relationship between the two compounds (and also puberulonic acid) was established at the same time by spectroscopic examination (80, 163). Correction of the formula of puberulonic acid (77, 78) to $C_9H_4O_7$ (rather than $C_8H_4O_6$ as originally assigned) showed that it differed from puberulic acid by the addition of the elements of carbon dioxide and the removal of one molecule of water; this was accompanied by the demonstration that it could be decarboxylated to puberulic acid by heating with aqueous mineral acids (78, 79). The further decarboxylation of puberulic acid

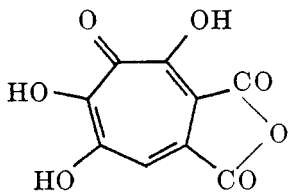


XXXIII

Puberulic acid



XXXIV

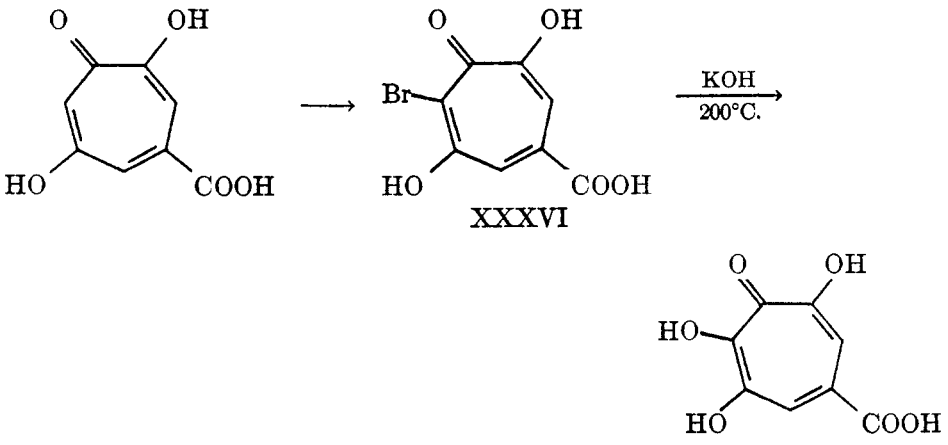


XXXV

Puberulonic acid

to what can now be recognized as the 3,4- (perhaps more correctly called 3,7-) dihydroxytropolone (XXXIV) at its melting point had been demonstrated previously (16). The final assignment of the anhydride structure (XXXV) to puberulonic acid was based chiefly on spectroscopic evidence (10, 11, 163)[5]; it has received valuable confirmation from the study of the anhydride (CXCIII, page 95) obtained by the oxidation of dibromopurpurogallin, which shows properties closely resembling those of puberulonic acid (85).

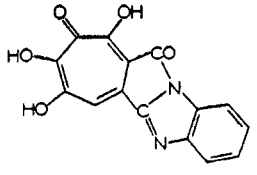
Investigations on this group of compounds have been crowned by the complete synthesis of stipitatic acid by the method described in the following section (see page 38), by which 1,2,4-trimethoxybenzene was converted to the ether (XXX) and hence to stipitatic acid itself (21, 22). Furthermore, this acid was converted through its bromo derivative (thereby identified as XXXVI) to puberulic acid as shown (160):



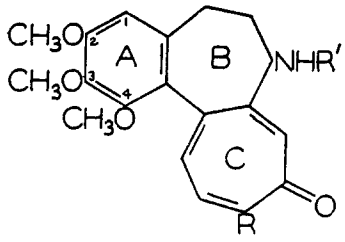
3. The alkaloidal tropolones of Liliaceae

It is considered beyond the scope of the present review to discuss the complex and very detailed investigations which have led to the acceptance of structure XXXVII (R = OCH_3, R′ = OCH_3) for colchicine, particularly as a full review has appeared as recently as 1952 (69). Nor is it proposed to consider the voluminous literature dealing with its biological properties and centered particularly on its effect on mitosis.

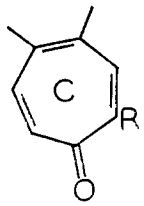
[5] The derivative obtained by treatment with *o*-phenylenediamine, which led to an earlier proposal of an α-diketone formulation (78), was assigned a formula of the following type on this basis (11, 163).



The accepted structure (XXXVII) has not been altered since the last review. Details of the x-ray crystallographic study on which the relative positions of the



XXXVII



XXXVIII

Colchicine

carbonyl and methoxyl groups of the tropolone ring (ring C) are based have now appeared (185). The most recent work on this group of compounds has included a detailed study of the colchicine content (44, 386, 391) and the alkaloid composition of various species (colchicine is normally obtained from *Colchicum autumnale* L., but occurs not only in other colchicum species but also in various other *Liliaceae*, notably several *gloriosa* and *merendera* species (231, 385, 388)); this has led to the isolation of several new compounds (23, 375, 379, 380, 382, 383, 387, 390, 392, 394), all closely related to colchicine. Several of these have been identified, including XXXVII (R = OCH_3, R′ = CHO) (392, 395), XXXVII (R = OCH_3, R′ = CH_3) (188, 189, 395, 438, 441), the three analogs of colchicine in which one of the oxygens in ring A is a free hydroxyl group (25, 27, 359, 393), and the glucoside colchicoside ($OC_6H_{11}O_5$ in place of OCH_3 at position 4) (25).

Numerous transformations have been carried out starting with colchicine and the above naturally occurring derivatives, both with the object of identifying the latter by partial synthesis and in order to prepare numerous analogs for biological testing. They include changes of substituents on the nitrogen (217, 381), numerous ethers in which the alkyl group (R = OAlkyl in formula XXXVII) is changed (148, 360) as well as a large number of derivatives in which this group is replaced by amino (XXXVII: R = NH_2) or various substituted amino (XXXVII: R = NHR″ or NR''_2) groups both in the colchicine series and in the isocolchicine series (partial formula XXXVIII) (28, 129, 148, 360, 362, 381, 439, 440).

Comparison of numerous pairs now enables the correct structural assignment of two substances to the colchicine and isocolchicine series, respectively, to be made on the basis of the higher negative rotatory power and slightly lower main maximum in the ultraviolet always observed for the iso series (148, 441). Optical rotation should be measured in ethanol; aqueous solutions of colchicine and its derivatives show abnormal variations of rotatory power with concentration (see, for example, 26). In chloroform solution isocolchicine forms complexes with the solvent and the specific rotation changes with time (357). C^{14}-labelled colchicine and several derivatives have been described (358).

The irradiation of colchicine by sunlight produces several isomeric substances

(124), at least one of which has been isolated along with colchicine from plant material (e.g. 385), but no information concerning their structure is available.

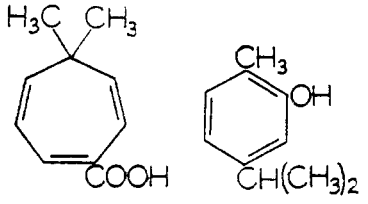
4. The alleged natural occurrence of purpurogallin

Independent reëxamination of several gall species in two laboratories, including careful study of the two species *Diplolepis quercus-folii* L.[6] (107) and *Neuroterus lenticularis* Oliv. (= agamous form of *N. quercus-baccarum* L.) (137), has proved the absence of purpurogallin or any derivative thereof in these species, contrary to the sweeping claims of Nierenstein (243, 245) concerning the isolation of several glucosides of purpurogallin. A specimen of "dryophantin" from the late Professor Nierenstein's collection (obtained through the kindness of Dr. T. Malkin, Bristol) is indistinguishable from synthetic purpurogallin and definitely not a glucoside (137).

C. BIOGENESIS

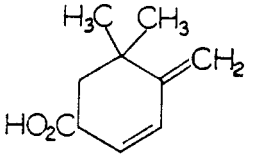
There has been much speculation on the possible origin of the naturally occurring tropolones. Clearly, the three groups of compounds discussed above may be formed by quite different routes.

Todd (433) and Erdtman (105, 106, 108, 109) have emphasized the strong possibility that at least the tropolones of *Cupressaceae* are either directly derived from terpenes or share common precursors with these. The demonstration (110, 127) that thujic acid (dehydroperillic acid), which occurs (5, 203) in close association with the thujaplicins in *Thuja*, has the structure XXXIX is a strong pointer in this direction. Nootkatin occurs associated with carvacrol (XL)

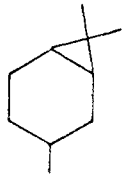


XXXIX
Thujic acid

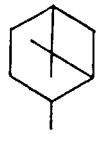
XL
Carvacrol



XLI
Shonanic acid



XLII



XLIII

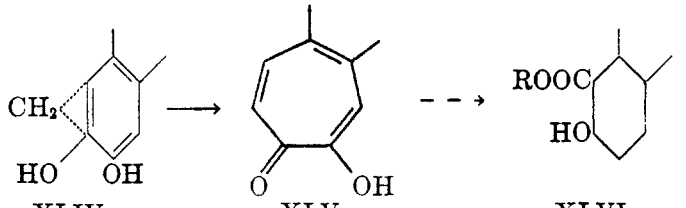
both in *Chamaecyparis nootkatensis* and in *Cupressus macrocarpa* (50, 81); the related *Libocedrus formosana* contains an acid, "shonanic acid" (XLI) (*cf.* 105). Not only does thujic acid share the carbon skeleton of other terpenes (e.g., eucarvone), but it has been pointed out (105, 106) that the three thujaplicins as well as the above three compounds (XXXIX, XL, and XLI) can all theoretically be derived in a simple manner from compounds possessing either the carane (XLII) or the pinane (XLIII) skeleton.

The direct synthesis of tropolones from acyclic components, e.g., 1,6-dialdehydes formed by the oxidation of hexoses condensing with formaldehyde,

[6] Presumably identical with the species referred to by Nierenstein (245) as *Dryophanta Taschenbergi*, although the latter name strictly implies the tiny (3 mm. long) sexual form of *D. quercus-folii*; the much larger agamous form was presumably meant.

has been suggested by Dewar (91), who regards tropolones (e.g., the 5-amino derivative) as possible biological precursors of such biologically important aromatic compounds as *p*-aminobenzoic acid.

The opposite view, that aromatic compounds are precursors of tropolones, has been advanced in several forms. The possibility that the formation of 4-methyltropolone from pyrogallol by way of purpurogallin (*cf.* page 39) has a biological equivalent has been mentioned (135). A more direct ring expansion of, for instance, a catechol derivative reacting with formaldehyde or its biological equivalent to give a tropolone (XLIV → XLV) has been advanced by Robinson (368, 369) in connection with a scheme for the biogenesis of colchicine (368). He considers the tropolones resulting from such a change as possible intermediates in the biogenesis of such alkaloids as yohimbine; these would result from reduction and ring contraction to XLVI. An alternative scheme for the biogenesis



XLIV XLV XLVI

of colchicine involving oxidative coupling of two molecules of 3,4,5-trihydroxyphenylpyruvic acid as the initial step has been advanced by Belleau (24), who points out an interesting possible relationship between colchicine and the morphine group of alkaloids.

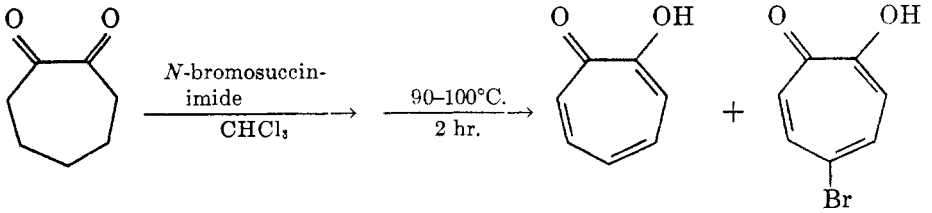
The relationship of stipitatic and puberulic acids to other mould constituents has been discussed by Raistrick (361).

III. Syntheses of Tropones and Tropolones

A. From Cycloheptanone Derivatives

1. From 1,2-cycloheptanediones

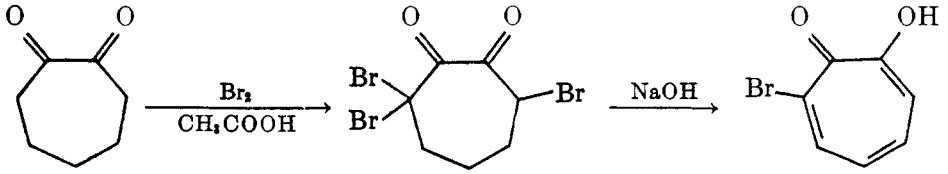
This method has been most widely used and was initially introduced by Cook and collaborators for the synthesis of 3,4-benzotropolone (see page 107). Its extension to the synthesis of tropolone itself was carried out independently by the same group (64, 65) and by Nozoe and collaborators (335). It consists in the bromination of 1,2-cycloheptanedione to yield a mixture of products which lose hydrogen bromide on warming, alone or with base, to give tropolone and its bromo derivatives.



Tropolone XLVII

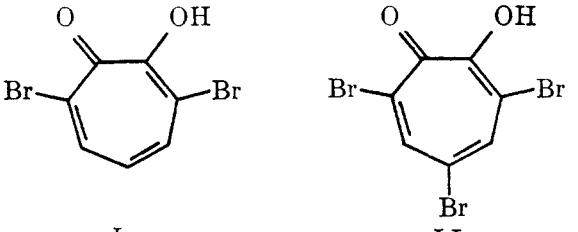
The bromination step may be carried out either by using bromine, in glacial acetic acid or carbon tetrachloride as solvent (64, 65), or by using *N*-bromosuccinimide in chloroform solution (335). In either case the crude product may be subjected to hydrogenolysis over a palladium catalyst to remove the bromine without affecting the tropolone system. In this way both methods afford similar yields (approximately 25 per cent) of the parent tropolone. The bromosuccinimide method, however, appears to be more direct and, with the calculated amount of reagent, the product (without hydrogenolysis) consists chiefly of tropolone accompanied by its 5-bromo derivative (XLVII).

With bromine, the results are highly dependent on the amount used. It has been noted (65) that the amount of bromine appearing in the product always exceeds expectation—undoubtedly owing to side-reactions which destroy the dione with the consumption of relatively little bromine. Thus, with two moles of bromine the chief product is not tropolone but its 3-bromo derivative (XLIX); its formation has been postulated (65) to proceed *via* XLVIII and in any case must require three molecules of bromine. However, when more than two molecular equivalents of bromine are used, the 3,7-dibromo- (L) and 3,5,7-tribromo (LI) derivatives constitute an increasing proportion of the product.



XLVIII XLIX

3-Bromotropolone



L LI

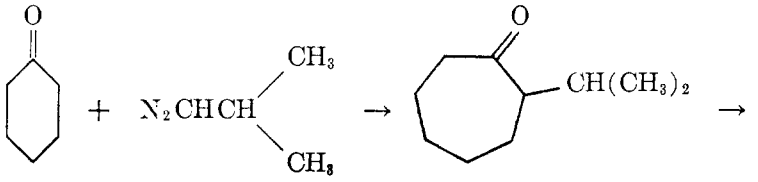
3,7-Dibromotropolone 3,5,7-Tribromotropolone

The bromo derivatives mentioned above are identical with those obtainable by the direct bromination of tropolone. Their orientation is therefore dealt with in the next section.

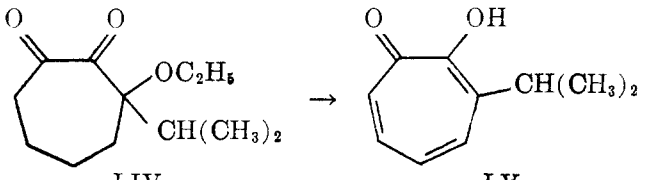
The synthesis of substituted tropolones by this method requires a source of suitably substituted cycloheptanones. Two methods have been widely used for their preparation: (*1*) cyclization of the appropriately substituted suberic acids (294, 336); (*2*) ring enlargement of the corresponding cyclohexanone (itself obtainable from the corresponding phenol) with diazomethane (73, 265, 292, 336). The conversion to the diketone is then nearly always effected with selenium dioxide.

The synthesis of 3-isopropyltropolone (LV) (73, 282) exemplifies the adapta-

tion of the method to a 3-substituted derivative. In this case, the ring expansion of 2-isopropylcyclohexanone with diazomethane fails (282), but the desired ketone (LIII) is obtained from cyclohexanone by reaction with diazoisobutane (LII). Its oxidation by selenium dioxide in ethanol yields LIV rather than the simple dione (73), but this loses ethanol during the remaining stages and affords the desired product (LV).



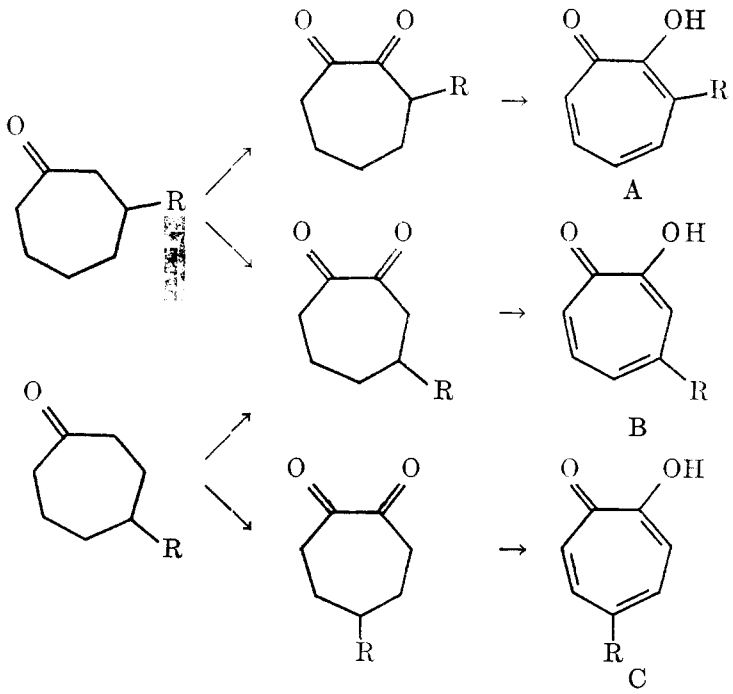
Cyclohexanone LII LIII



LIV LV

3-Isopropyltropolone

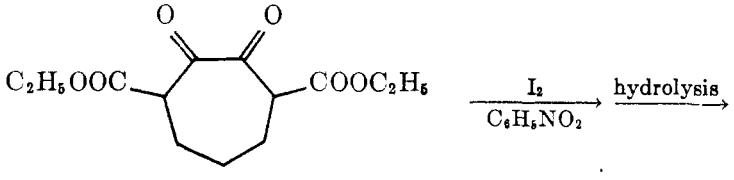
It is clear that a 2-substituted cycloheptanone must lead uniquely to the corresponding 3-substituted tropolone. Ambiguity arises when a 3- or 4-substituted cycloheptanone is used, as shown in the following formulas:



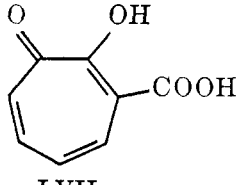
A B C

It is ordinarily impracticable to separate at the dione stage, but any doubt concerning the structure of the product is removed if the products from the two isomeric starting materials are compared, since only B should be produced from both; the identities of A and C follow. In practice it is found that A is produced to a negligible extent if at all (294) even when R is methyl, so that the 3-substituted cycloheptanones are a good source for 4-substituted tropolones. This must be attributed to a very pronounced steric effect in the selenium dioxide oxidation. The 4-substituted ketone yields the expected mixture (73, 265, 334).

Application of the method to the keto ester LVI, obtainable by condensation of pimelic and oxalic esters, led to replacement of both carboxyl groups by bromine (72) yielding only 3,7-dibromotropolone, but dehydrogenation of LVI with iodine in boiling nitrobenzene followed by hydrolysis and sublimation led to tropolone-3-carboxylic acid (LVII).



LVI

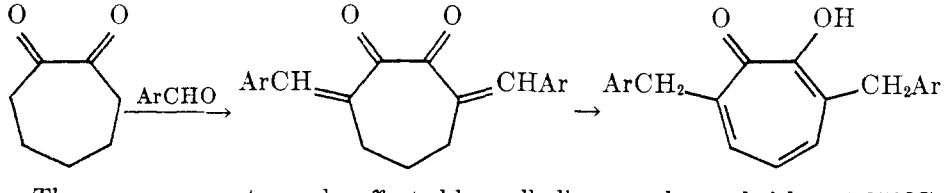


LVII

Tropolone-3-carboxylic acid

It is not clear at which stage the second carboxyl group is lost.

Another method based on cycloheptanedione consists in its condensation with benzaldehyde or other aromatic aldehydes and isomerization of the resultant (substituted) 3,7-dibenzylidene-1,2-cycloheptanediones to (substituted) 3,7-dibenzyltropolones:

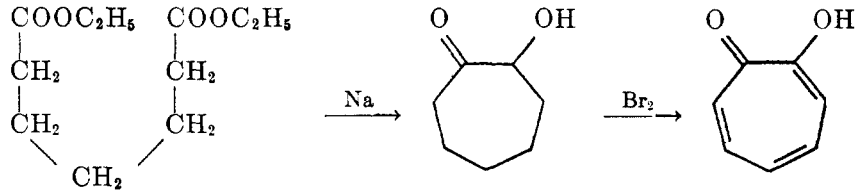


The rearrangement may be effected by palladium on charcoal either at 250°C. or, preferably, in a high-boiling solvent (e.g., triethylene glycol) (214). Alternatively, it may be effected although in less good yield by hydrobromic acid in glacial acetic acid solution (214, 215). Since other acids are ineffective, this rearrangement is believed to involve addition of hydrogen bromide (probably

by a radical mechanism) to the exocyclic double bond(s), followed by its elimination with formation of the endocyclic double bonds (215).

2. From 2-hydroxycycloheptanones

Unsubstituted tropolone has been obtained (191) in two steps from diethyl pimelate by acyloin condensation to the ketol (LVIII), followed by bromination. Unlike the bromination of the diketone (which therefore cannot be an intermediate), this reaction leads smoothly to tropolone free from bromo derivatives.

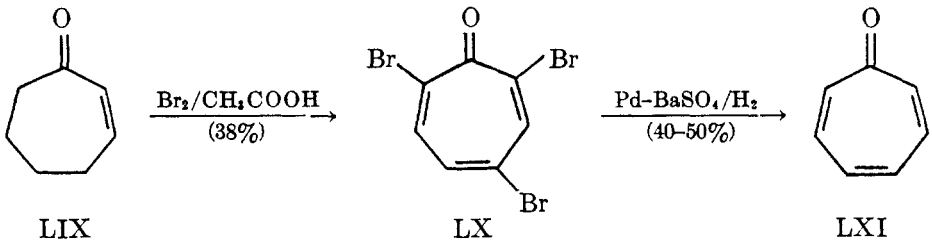


Diethyl pimelate LVIII Tropolone

The method has also been used for an alternative synthesis of 3,7-dibenzyltropolone (215).

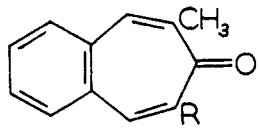
3. From cycloheptanones, cycloheptenones, and cycloheptadienones

The synthesis of tropone (LXI) was first achieved simultaneously by two methods (86, 93). One of these involved the bromination of 2-cyclohepten-1-one (LIX) with four molecules of bromine in acetic acid. This yields 2,4,7-tribromotropone (LX). The further conversion of this to tropone (LXI) is accomplished by hydrogenolysis to remove the bromine atoms (86, 311). This process requires careful control by use of a partially poisoned catalyst (palladium on barium sulfate) and interruption of the reaction after the uptake of three molecules of hydrogen (86, 311). Incomplete hydrogenolysis has yielded 2,7-dibromotropone (311). With a slightly more active catalyst only cycloheptanone can be isolated, showing that tropone is much more readily hydrogenated than tropolone and, at least in this sense, much less aromatic.



LIX LX LXI

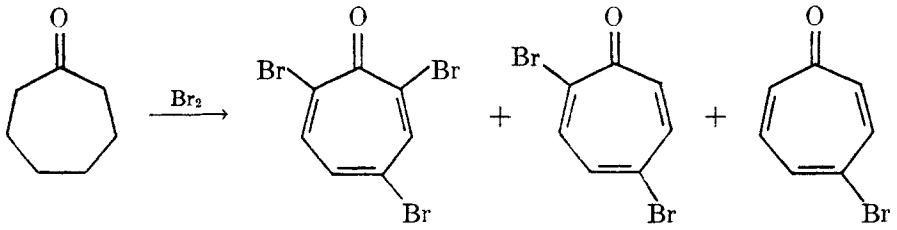
2,4,7-Tribromotropone Tropone



LXII

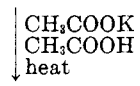
It appears significant, however, that hydrogenation of the first double bond in LXII (R = H or CH_3) is much slower than that of the second (442).

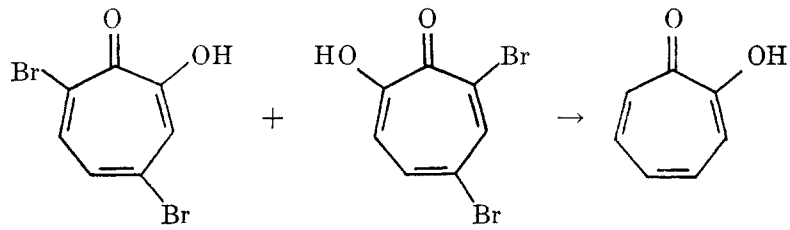
An important improvement in this method resulted from the observation that cycloheptanone can serve as starting material in place of the unsaturated ketone (270, 271). An intermediate tribromocycloheptanone (100) or tetrabromocycloheptanone (270, 272) may be isolated. By its further bromination in acetic acid 2,4,7-tribromotropone (LX) can be obtained in 50 per cent yield. 4-Bromotropone (LXIII) and 2,5-dibromotropone (LXIV) have been identified as byproducts (291). Equally important was the observation (270, 287) that LX may be transformed into a mixture of 3,5- and 3,6-dibromotropolones by refluxing with potassium acetate in acetic acid or butanol:



Cycloheptanone LX LXIV LXIII

2,5-Dibromotropone 4-Bromotropone





With a final hydrogenation stage this process is reported to give tropolone in up to 45 per cent yield from cycloheptanone (270).

Two routes to tropone have been described in which 2,4-cycloheptadienone (LXVI) is the key intermediate. In the first (46), a mixture of cycloheptadienones (including the fully conjugated isomer (LXVI)) was shown to be produced in one step by Hofmann degradation of tropinone methiodide (LXV) and converted into tropone by reaction with bromine in carbon tetrachloride. In the second (422), the *p*-toluenesulfonate (LXVII) of 5-hydroxymethylcyclo-2-hexen-1-one was prepared (in four steps from 3,5-dihydroxybenzoic acid) and converted to the unsaturated ketone (LXVI) by treatment with sodium hydroxide. This reaction is considered to proceed *via* norcaren-3-one (LXVIII). In this case the final step was effected with selenium dioxide. It is interesting to note that this

TABLE 2

Tropones obtained by direct synthesis

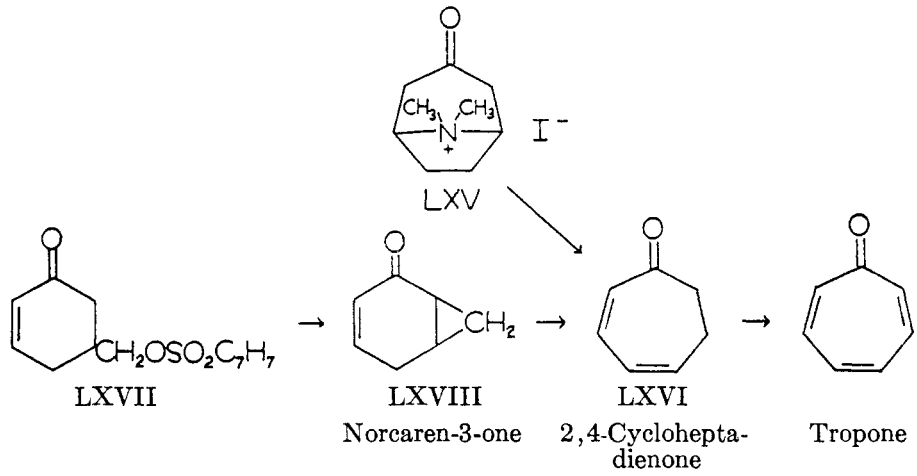
Compound	Melting Point	Melting Point of Picrate	Method‡	References
	°C.	°C.		
Tropone (b.p. 104–105.5°C./10 mm.)		100–101	2	(86*†)
Tropone (b.p. 84–85°C./6 mm.)	−8 to −7	100–101	1	(311*†)
Tropone		99.0–100.3	3	(46, 422)
Tropone (b.p. 113°C./15 mm.)	−8 to −5	99–100	4	(93*†)
4-Bromotropone	100		1	(291)
2,5-Dibromotropone	90		1	(291)
2,4,7-Tribromotropone	184.5–185.5		1	(100, 270, 271*) (*267, *436)
	182–183		2	(86)
2-Phenyltropone	82.5–83.5		2	(103, 262)
4-Bromo-2-phenyltropone	91		2	(262*)
3-Hydroxytropone	179–180 (d.)	165	5	(159*†)
3-Methoxytropone	Oil	128; 145–146	5	(159)
2-Bromo-3-hydroxytropone	222		5	(159)
Tropone-4-carboxylic acid	235–240 (d.)		5	(20*)
2-Bromo-3-methoxytropone-5-carboxylic acid	270–273 (d.)		5	(160)

* An asterisk indicates that the reference contains the ultraviolet absorption curve or maxima of the compound named in the first column.

† A dagger indicates that the reference contains the infrared absorption curve or maxima of the compound named in the first column. When * or † precedes the reference number, the paper is quoted only for the spectrum and does not contain information concerning the preparation of the compound.

‡ Method 1: from cycloheptanone.
Method 2: from the corresponding (substituted) cycloheptenone.
Method 3: from cycloheptadienone.
Method 4: from anisole with diazomethane.
Method 5: from the appropriately substituted anisole with diazoacetic ester.

reagent acts here purely as a dehydrogenating agent, converting LXVI to tropone and not to the more stable tropolone.



B. FROM BENZENE DERIVATIVES

Ring enlargement of benzene derivatives has been accomplished by reaction with diazoalkanes. In particular, two methods have been employed.

TABLE 3

Tropolones obtained by direct synthesis (excluding halogen derivatives)

Substituent in Tropolone	Melting Point	Melting Point of Copper Complex	Method‡	References
	°C.	°C.		
None	50–51	300–303	1	(64, 65*, 335)(*9, *11, *68, *†131, †192, †194, *317, *436)
	49–50		3	(191*)
			4	(270*, 271)
	49	320 (d.)	5	(95*, 96*†)
3-Methyl	50.5–51	>260	1	(292, 293, 307)(†194, *436)
	48–50		1	(40)
4-Methyl	76	237	1	(236, 292, 294)(†194, †399, *436)
	69–70§		1	(40)
	76–77	280–282 (d.)	7	(131*†, 135)
5-Methyl	110	>260	1	(236, 292, 293, 307)(†194, *436)
4-Ethyl	42	156	1	(294)
3-Isopropyl	26–27		1	(73)(*9, *109, †194)
	25.5–26		1	(288)
	33–34	234–235	1	(282, 288)
4-Isopropyl	46–47		1	(73)(*9, †12, *109, †194, *436)
	51.5	177–178	1	(254, 334, 336)
	50–51	92–94	5	(98*†)
5-Isopropyl	79.5		1	(73)(*9, †12, *68, †194, †399)
	78.5–80	252–253	1	(334, 336)
	80–81		5	(98*†)
	82	259–260		(109*)
4-*tert*-Butyl	Oil		1	(265)
5-*tert*-Butyl	99–100		1	(265)
4-Cyclohexyl	88–89		5	(98*†)
5-Cyclohexyl	97–98		5	(98*†)
4,5-Tetramethylene	130	287–288	5	(98*†)
3-Benzyl	51–52	235	9	(300*)
3-Phenyl	116–117	299–300	8	(99)
	118	300	8, 9	(262, 296)
4-Phenyl	97		5	(98*†)
5-Phenyl	125–126	342–345	5	(98*†)
3-*p*-Methoxyphenyl	98–98.5	298 (d.)	9	(330)
3,7-Dibenzyl	118–119		2, 3	(214*†, 215*†)
3,7-Di(*p*-methylbenzyl)	116–118		2	(214*†)
3,7-Di(*p*-methoxybenzyl)	101.5–102.5		2	(214*†)
3,7-Di(*p*-chlorobenzyl)	109–112		2	(214*†)
3,7-Di(*p*-nitrobenzyl)	222.5–223		2	(214*†)
3-Carboxy	202		1	(72)
4-Carbethoxy	90–91		6	(19*, 22*)
4-Carboxy	217–219		6	(22*)
	217		7	(130, 131)
4-Carboxy-6-methyl	223–224		7	(84)
4-Carbethoxy-6-methoxy	154–156		6	(21, 22)
5-Carboxy-3-methoxy	257		6	(160*)
3,4-Dicarboxylic anhydride	251–253		7	(84a, 85)
3-Carboxy-4-carboxymethyl	183–184 (d.)		7	(131, 135)
3,6-Dicarboxy-4-carboxymethyl	230 (d.)		7	(84)

* See footnote to table 2.

† See footnote to table 2.

‡ Method 1: from the appropriately substituted cycloheptanedione by bromination, iodination, or palladium dehydrogenation.

Method 2: by rearrangement of the corresponding substituted dibenzylidene cycloheptanedione.

Method 3: from the corresponding 2-hydroxycycloheptanone.

Method 4: from cycloheptanone.

Method 5: from the corresponding benzene derivative with diazomethane, followed by permanganate oxidation.

Method 6: from the dimethoxybenzene derivative and diazoacetic ester.

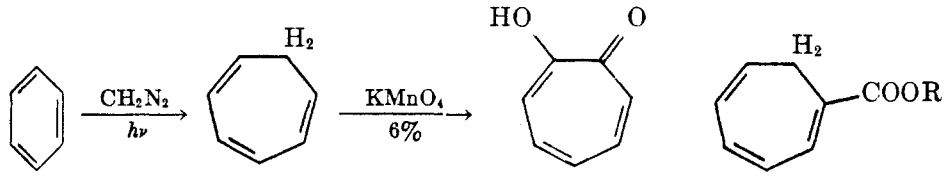
Method 7: from purpurogallin (or its derivatives) by oxidation.

Method 8: by bromination and hydrolysis from the corresponding tropone.

Method 9: by amination and hydrolysis from the corresponding tropone.

§ This product is undoubtedly a mixture of the 4- and 5-methyltropolones.

Reaction with diazomethane takes place under the influence of ultraviolet light and converts benzene to cycloheptatriene (LXIX) (95, 230):



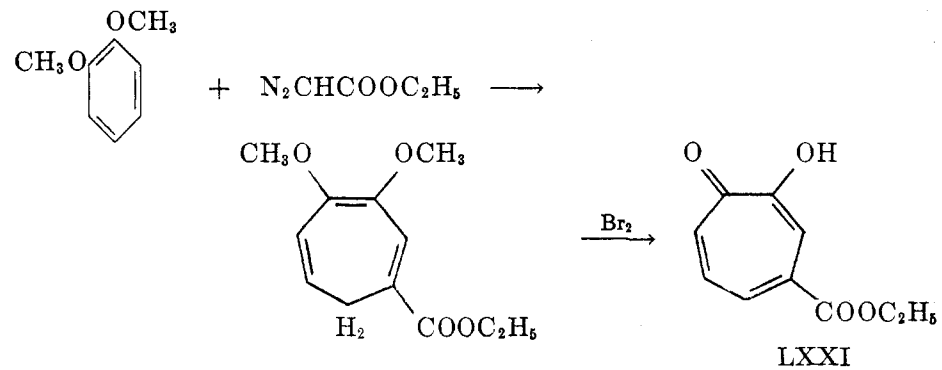
LXIX

Cycloheptatriene

LXX

Reaction with diazoacetic ester yields a cycloheptatrienecarboxylic ester (LXX) (see 22, where earlier references are given). Both types of product have been used in the synthesis of tropone and tropolone derivatives. The first synthesis of tropolone by this method was announced by Doering and Knox (95) simultaneously with the syntheses of this substance (see page 30) by Cook, by Nozoe, and by Haworth (page 95) and their respective collaborators. Doering and Knox showed that the intermediate LXIX can be oxidized to tropolone directly by potassium permanganate; they have subsequently improved (96) and extended (98) this method.

The more direct procedure in which a benzene derivative already carrying the necessary oxygen substituents is used in the ring-expansion step was developed independently and announced in the same year by Johnson and his coworkers (19). They prepared ethyl tropolone-4-carboxylate (LXXI) by the following sequence (19, 21):



LXXI

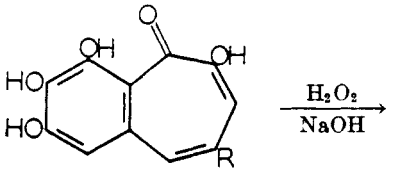
In this version of the method, the ring expansion leads to an alkoxycycloheptatriene, i.e., to the enol ether of a cycloheptadienone derivative; the dehydrogenation of this intermediate with bromine in the final step is analogous to that which has already been discussed above (page 35).

The ready extensions of this method to the preparation of tropone (from anisole and diazomethane) (93), of stipitatic acid (from 1,2,4-trimethoxyben-

zene and ethyl diazoacetate) (21, 22), and of various substituted tropones (20, 159, 160) amply illustrate its versatility.

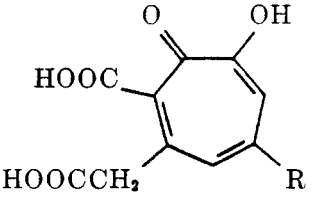
C. FROM PURPUROGALLIN

Purpurogallin (LXXII: R = H) is readily obtained in high yield (113a) from pyrogallol. Its oxidation (131, 135) yields the dicarboxylic acid LXXIII (R = H) in 30–35 per cent yield together with small amounts of LXXIV (85). The product (LXXIII: R = H) loses carbon dioxide at its melting point and is smoothly converted to 4-methyltropolone (LXXV).



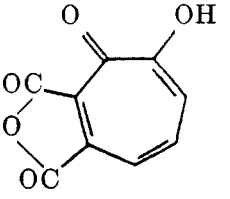
LXXII

$\xrightarrow[NaOH]{H_2O_2}$



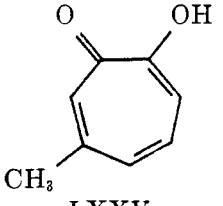
LXXIII

+



LXXIV

This approach not only provided the first preparation of a simple tropolone (135) but is still one of the simplest methods. Both LXXIII (R = H) and LXXV have proved to be versatile intermediates for further synthesis of the tropolone system (see Section VIII,B).

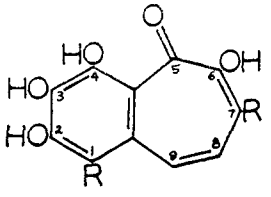


LXXV

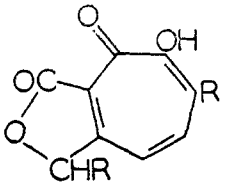
4-Methyltropolone

The extension of the method is, however, severely limited by the availability of purpurogallin derivatives. The oxidation of dibromopurpurogallin (LXXVI: R = Br) (84a) has provided a more convenient preparation of LXXIV, and the oxidation of purpurogallincarboxylic acid (LXXII: R = COOH) (85) yields LXXIII (R = COOH).

The oxidation of 1,7-dialkylpurpurogallins (LXXVI: R = alkyl) takes a different course (138).



LXXVI



LXXVII

Several of these (R = C_2H_5, n-C_3H_7, or n-C_4H_9) do give tropolone derivatives in yields of 5–10 per cent. These products are, however, not dicarboxylic acids of the type of LXXIII and their exact structures are still under investigation. Their analyses and spectra suggest LXXXVII as a possible formulation. Quite anomalous behavior is shown by 1,7-dimethylpurpurogallin (LXXVI: R = CH_3). The only product which can be isolated in this case is not a tropolone derivative; its exact constitution remains to be determined (138).

IV. Substitution Reactions of Tropones and Tropolones

A. General Considerations

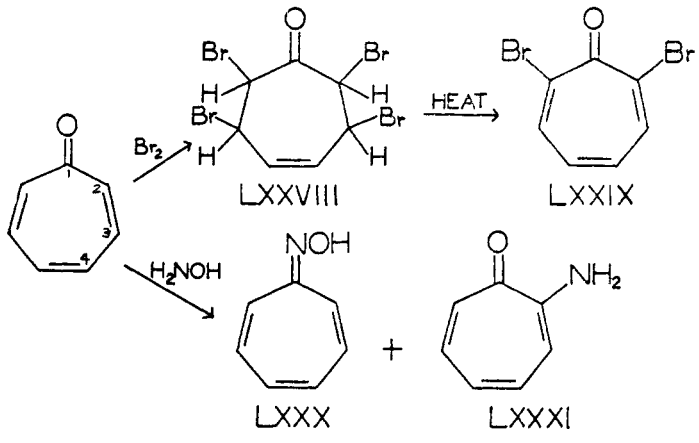
Theoretical calculations (by the molecular orbital method) have been made to predict the positions of substitution both for tropone (39) and for tropolone (91, 195).

For tropone, it is found that both electrophilic and free-radical substitution should occur at the 2-position. For nucleophilic substitution such prediction proved impossible (39), owing to the opposing effects of the atom localization energies (lowest again at C_2 and highest at C_3) and of the electron densities (highest at C_2 and lowest at C_3). This is unfortunate, since a glance at the "cycloheptatrienylium oxide" formulation of tropone (see page 11) will show that it must undergo nucleophilic substitution much more readily than electrophilic substitution.

It is not surprising, therefore, that the validity of the above predictions remains unknown. Bromination of tropone and its derivatives does go in the 2-position as predicted, but the reaction proceeds through a complex (296, 311). This, as in the case of tropolone (see below), may affect the position of substitution. Nozoe (297, 308) indeed regards this as an addition reaction involving, e.g., the intermediate LXXVIII for dibromination—although on this basis the absence of 3-substitution requires explanation. It would therefore be premature to conclude that the 2-position is generally preferred. It may be significant, however, that further bromination stops at the stage of 2,7-dibromotropone (LXXIX) (308) and only in the case of 2-phenyltropone has bromination to a 5-substituted derivative, 5,7-dibromo-2-phenyltropone, been observed (297).

The reaction of tropone with hydroxylamine may safely be assumed to be of the nucleophilic type. It yields a mixture of the oxime (LXXX) and 2-amino-

tropone (LXXXI) in proportions depending on the reaction conditions. Only in one case has the simultaneous formation of a second isomeric (3 or 4?)-amino-



tropone been reported (296). From the analogous reaction with hydrazine, only 2-aminotropone derivatives have been isolated (262, 298, 300). It thus appears that in nucleophilic substitution other than at the carbonyl group the 2-position is preferred.

The nature of the reaction by which 2,4,7-tribromotropone is hydroxylated in the 5-position (267) on heating with strong acids deserves further study.

The conclusions reached in two theoretical treatments of substitution in tropolone differ considerably. Dewar (91), from calculation of the relative π-electron energies of various possible quinonoid transition states, concluded that both electrophilic and radical substitution should occur in the 5-position and nucleophilic substitution in the 4-position. The energies calculated (91) for electrophilic substitution at other positions indicate that it should be much more difficult at the 3(or 7)-position than at the 5-position and again (but only slightly) more difficult at the 4-position than at the 3-position.

These predictions are not in agreement with experimental fact. As shown below, 3-substitution cannot be much more difficult than 5-substitution, but 4-substitution is so far unknown.

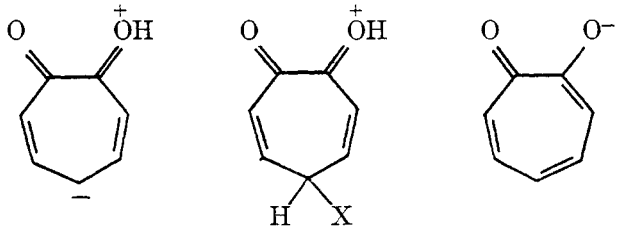
Kurita and Kubo (195) have reached theoretical conclusions in better agreement with these facts by considering the π-electron distribution in conjunction with the free valence indices. However, they conclude that 3-substitution should be easier than 5-substitution, whereas the reverse seems to be actually the case; their figures suggest that 4-substitution, while more difficult, should certainly not be impossible.

Experimentally, a general preference for 5-substitution is well established for a large number of electrophilic reactions, as illustrated in chart I (page 46).

The one major exception to this rule is halogenation. Here the 3-position is preferred to such a degree that even in dibromination the product is almost exclusively the 3,7-dibromo derivative and only the third halogen atom enters

the 5-position. The reason for this apparent anomaly must almost certainly be sought in the nature of the intermediate complex. It has been observed (63, 131, 341) that when bromine is added to a tropolone dissolved in an inert solvent such as chloroform, an orange-red complex precipitates. A number of these complexes have been isolated and various formulations suggested (63, 341). However, analyses vary between one and one and one-half atoms of bromine per tropolone molecule and the exact nature of the complexes remains open to question. The bromine is loosely held, but on treatment of the complex with water, rapid bromination occurs and a mixture of bromotropolones and tropolone hydrobromide results.

The degree of reactivity of tropolones towards electrophilic reagents parallels that of phenols; it has been argued that this implies a significant contribution of canonical structures of the type of LXXXII. However, it is clear (both from theoretical considerations and from the measured dipole moments) that such structures are heavily outweighed by those of opposite polarity, so that all the carbon atoms must be considered to bear a partial positive charge in the ground state. It appears not only adequate, but more correct, therefore, to explain the ease of substitution by X^+ as due simply to the stabilization of the transition state by resonance with structures of the type of LXXXIII.



LXXXII LXXXIII LXXXIV

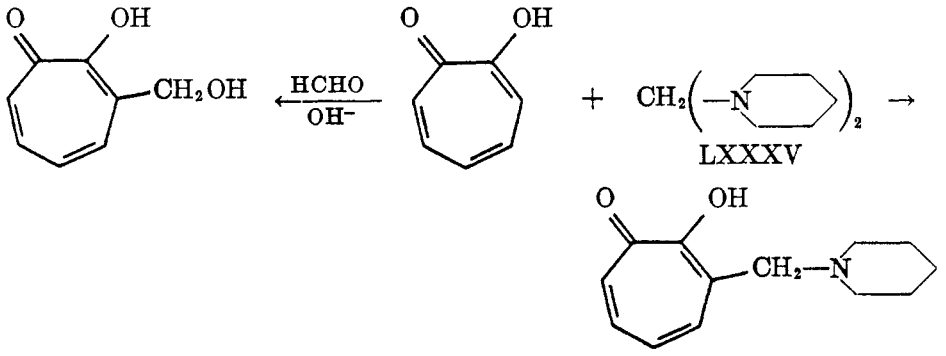
Illustrative of the high degree of reactivity are the nitrosation reaction, the coupling of tropolones with diazonium salts in alkaline solution (here reaction is of course with the anion LXXXIV), and the facile condensation with alkaline formaldehyde.

Both in the last-mentioned reaction and in the closely related aminomethylation reaction, the 3-substituted derivatives are formed as the main products. This further exception to the general rule of 5-substitution parallels the preference for ortho-substitution (over para-substitution) in the same reactions of phenols.

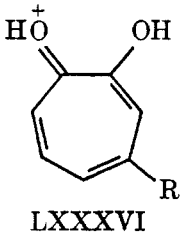
The aminomethylation reaction can be realized very smoothly by refluxing the tropolone with the methylenebis derivative of a secondary amine (e.g., LXXXV) in alcoholic solution (181), but fails completely when attempted under the usual conditions of the Mannich reaction.

This is one of numerous examples of the failure of tropolones to undergo substitution reactions in the presence of strong acids (in the Lewis sense), a failure which severely limits the number of possible reactions of this type. Attempts to

carry out Friedel–Crafts reactions (74, 132), chloromethylations (74, 134a), Gattermann reactions (74, 134a), or sulfonations with concentrated or fuming



sulfuric acid (248, 327) have invariably met with complete failure[7] and nitration is retarded by sulfuric acid (249, 284). This is undoubtedly due to the formation of the protonated ion (LXXXVI) (with hydrogen acids or its equivalent with other acids); in this ion, the charge is shared by all ring carbon atoms. Moreover, resonance with structures of the type (LXXXIII) discussed above is no longer possible in the transition state.



LXXXVI

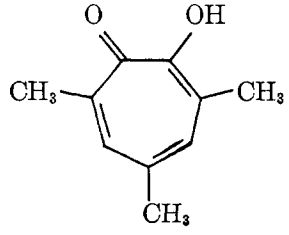
In the case of sulfuric acid, this view received confirmation from measurements of the depression of the freezing point of 99.9 per cent sulfuric acid by 4-methyltropolone (209a). These show no measurable variation during several days at 25°C. or even after heating for several hours at 100°C. The observed van't Hoff *i* factor is 2 (within the limits of accuracy of the determination), as expected for complete ionization to LXXXVI (R = CH_3) and HSO_4^-. The constancy of this value proves complete absence of sulfonation under these conditions.

Sulfonation has, however, been accomplished with sulfamic acid at 150°C. and in the case of unsubstituted tropolone yields the 5-sulfonic acid (327, 328).

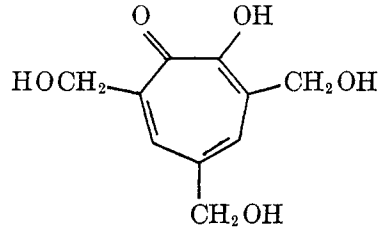
Separate study of different substitution reactions reveals marked differences in specificity. At one extreme, substitution may be restricted completely to the 5-position and fail when this position is blocked, and, at the other extreme, secondary effects of other substituents (e.g., steric hindrance) may completely change the course from exclusive 5- to exclusive 3-substitution.

[7] The suggestion (88) that the dibasic diacetyl derivative obtained from stipitatic acid with acetic anhydride and sulfuric acid (34) is the result of nuclear acylation has remained without experimental confirmation.

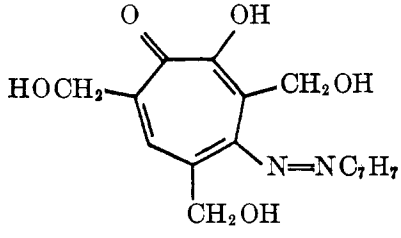
Perhaps the most remarkable fact in this connection is that no single case of substitution in the 4-position has ever been observed, although careful separations have been carried out in order to isolate all minor products in addition to the main substitution product. It is therefore of interest to test whether substitution reactions are possible with tropolones in which the 3-, 5-, and 7-posi-



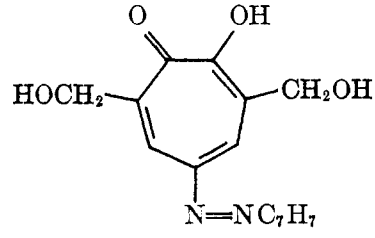
LXXXVII



LXXXVIII



LXXXIX



XC

tions are blocked. Two such cases have been examined briefly. Trimethyltropolone (LXXXVII) fails to decolorize bromine in alcoholic solution, but only a small proportion of the starting material was recovered after 2 hr. with an excess of this reagent (307). Trihydroxymethyltropolone (LXXXVIII) undergoes smooth azo-coupling and the product has been regarded as LXXXIX, resulting from substitution in the 4-position (307). In view of the established specificity of azo-coupling of tropolones (see below), this conclusion is likely to be erroneous and requires reëxamination. It is known that both *o*- and *p*-hydroxymethyl derivatives of phenols couple with displacement of formaldehyde, sometimes even when one *o*-position remains vacant (473–477). It is therefore suggested that the product from LXXXVIII is not LXXXIX, but most probably 3,7-dihydroxymethyl-5-(*p*-tolylazo)tropolone (XC).

The only available results are therefore inconclusive and the question of 4-substitution requires reinvestigation with reagents less likely to substitute in or displace the side chain.

B. METHODS OF ORIENTATION

Orientation of substitution products must depend ultimately on the orientation of a number of key compounds by the methods of structure determination described in Section II for the natural tropolones, *viz.*, systematic oxidative or reductive degradations and the rearrangement reactions leading to benzenoid compounds of known orientation. For the latter both the methoxide-catalyzed

rearrangement of the tropolone methyl ethers and the fusion of tropolones with caustic alkali has been used. The former is generally preferable, as it proceeds under mild conditions, but the latter is also useful. The nitrotropolones are of special importance in this connection, as their extremely facile rearrangement with dilute aqueous alkalis provides a key to the many substitution products which may be derived from them.

The majority of tropolone derivatives have been oriented by relating them to a few key compounds, either by changing the substituent or by further substitution. Several examples are included in chart I, which summarizes the relationships of 5-substituted tropolones. Thus the orientation of the 5-nitro derivative by rearrangement leads to the structure assignment of the azo and nitroso compounds, as all three can be reduced to the same amine. The latter in turn can be diazotized, and the diazonium salt undergoes Sandmeyer and related reactions leading to the orientation of numerous other derivatives. In the case of the 5-bromo compound a double check is obtained by direct rearrangement. The "further substitution" method is illustrated by the bromination of the 5-sulfonic acid to 3,7-dibromotropolone-5-sulfonic acid, also obtained by the sulfonation of 3,7-dibromotropolone of independently established constitution; this case again is cross-checked by direct rearrangement of the sulfonic acid to *p*-hydroxybenzoic acids. Such double checking fully substantiates the assumption that substitution reactions of tropolone are restricted to the 3-, 5-, and 7-positions. Exactly similar methods apply of course not only to the 5-, but also to the 3-, and 4-substituted derivatives. The 4-amino derivatives, however, are converted directly to 4-hydroxytropolones by nitrous acid; the diazonium salts cannot be obtained in this case (85), thus eliminating the use of the Sandmeyer reaction.

A number of derivatives have been successfully oriented by comparison of their dipole moments with values calculated for the likely isomers (193, 196, 198, 200).

C. INDIVIDUAL REACTIONS

1. Azo-coupling (see table 4)

A large number of tropolone derivatives in which there is known to be a free 5-position have been successfully coupled in alkaline solution with diazotized *p*-toluidine and several other diazonium salts. With the exception only of 4-*tert*-butyltropolone (265), where steric hindrance may be too great, all of these substances give coupling products. Frequently it has been possible to establish unambiguously that the group has entered the 5-position, and in no case have two isomeric coupling products been reported. Even more significantly, it has never been found possible to isolate the coupling product from any tropolone in which the 5-position is blocked, even though all other positions may be vacant (see, e.g., 293, 305, 334).

It may be concluded that azo-coupling in the tropolone series is restricted to the 5-position. Substituents in the 3-position, including NO_2, SO_3H, etc., do not

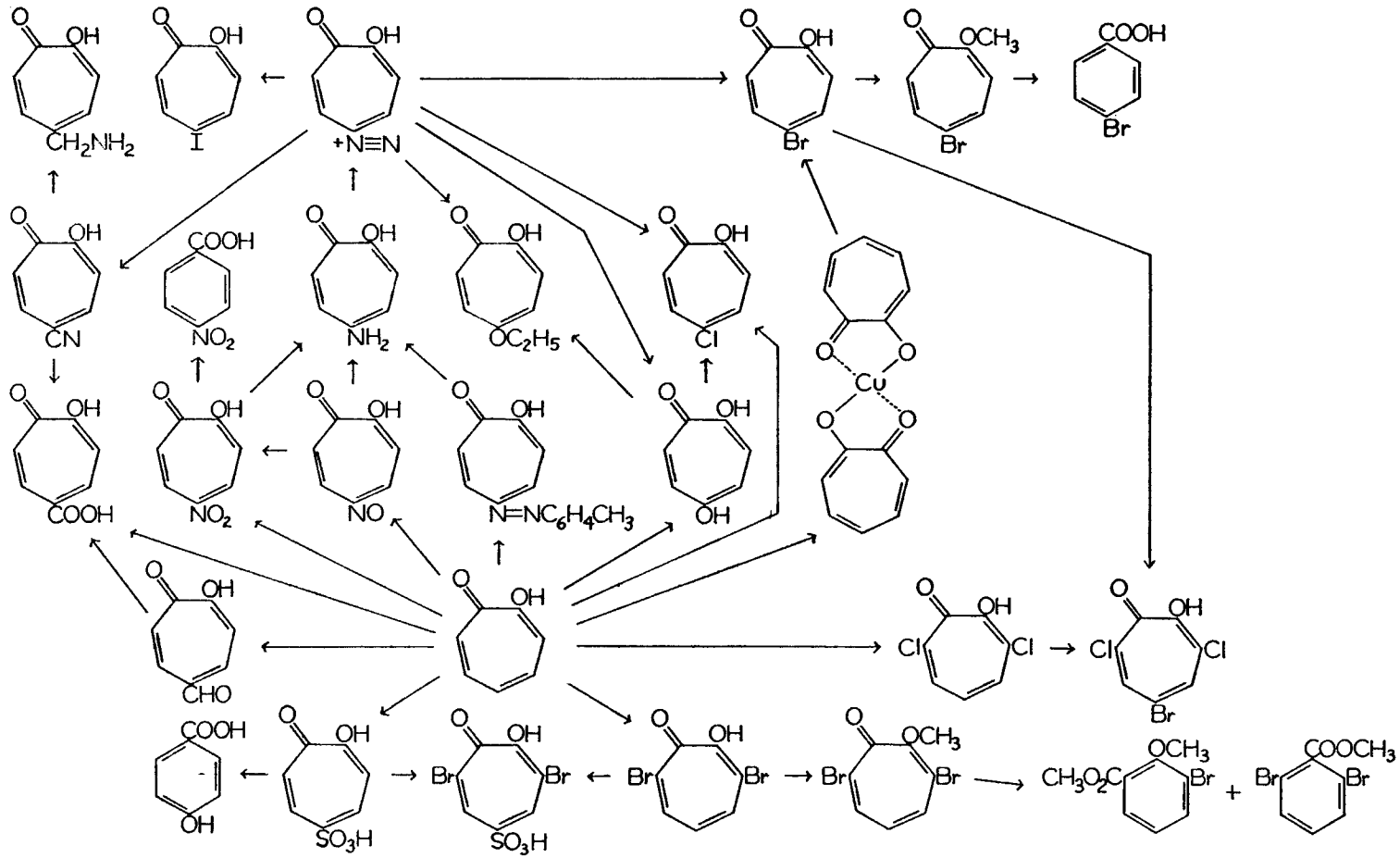


Chart I. Interrelation and orientation of 5-substituted tropolones

appear to influence this reaction (283, 327). It has therefore been utilized as a test for the presence of a free 5-position in tropolones of unknown orientation (e.g., 190, 293, 327, 405).

2-Aminotropone likewise undergoes coupling in the 5-position, as has been shown by hydrolysis of its phenylazo derivative to 5-phenylazotropolone (344, 346).

2. Nitrosation (see table 4)

Nitrous acid, usually in glacial or aqueous acetic acid solution, converts tropolones to the 5-nitroso derivatives. In the absence of interference from other substituents, the reaction proceeds in high yield and reduction of the nitroso compound thus obtained provides the best route to the corresponding 5-aminotropolone. When the 5-position is blocked, substitution at the 3-position may be possible, but 5-methyl-3-nitrosotropolone, the only product of this type reported so far (292, 293), has not been adequately characterized.

A profound influence on nitrosation is exerted by alkyl groups in the 4-position. Not only the bulky isopropyl group (337) but even a methyl group (236, 337) in this position results in a much lower yield of 5-nitroso compound, accompanied by a rearrangement product (see page 90) which may result from attack at the 7(or 3)-position.

3. Nitration (see table 4)

Nitration has usually been carried out with nitric acid in glacial acetic acid. The use of cupric nitrate in acetic acid is sometimes advantageous (461). The main product, 5-nitrotropolone, is accompanied by a smaller amount of the 3-isomer (70, 72, 347). The nitration of 4-methyltropolone similarly produces 5-, 7-, and 3-nitro derivatives in yields decreasing in that order. With the bulkier isopropyl group in the 4-position, the reaction occurs predominantly in the least hindered 7-position, although both the 5- and the 3-nitro isomers are also formed (274, 284, 337). Dinitration (236, 269, 284, 289, 337) has been reported, but a case of possible trinitration (250, 284) has not been confirmed. Nitro groups facilitate the rearrangement to the corresponding benzoic acids (*cf.* page 84). The orientations of the nitro compounds are thus ascertained with particular ease.

4. Sulfonation

The sulfonation of tropolone with sulfamic acid leads to the 5-sulfonic acid, possibly accompanied by the 3,5-disulfonic acid (290, 328). The orientation of the main product is securely established (*cf.* chart I). However, the reaction takes place equally readily in the 3-position, not only when the 5-position is blocked by an alkyl group (334) or by halogens (264, 327, 328) but also when it is hindered by alkyl substituents in the 4-position. Thus, 4-methyltropolone yields a product which couples with *p*-tolyldiazonium chloride and is therefore regarded as 6-methyltropolone-3-sulfonic acid (236). In the case of hinokitiol,

TABLE 4

Products obtained by coupling tropolones with p-tolyldiazonium salts and by the nitrosation and nitration of tropolones; amines derived from these

A. Products of substitution in the 5-position

Substituents in Starting Material (Tropolone)	Melting Point of *p*-Tolylazo Derivative	Melting Point of Nitroso Derivative	Melting Point of Nitro Derivative	Melting Point of Amine	References
	°C.	°C.	°C.	°C.	
None	201		194	173–175	(65, 72)
	202–203.5			177–177.5	(325, 335)
				(225–226 (d.))‡	
		175–180	191 (d.)		(96)(*†312)
		180		176–177	(324)
			197 (d.)		(269, 283)
		180	195–197	177–177.5	(347)
3-Methyl	168–169	185			(292, 293)
4-Methyl	177–178 (d.)			224 (d.)	(131)
		178 (d.)	176–177	224 (d.)	(133, 134)
	186	165–175	175.5–176	223–224	(236, 292, 294)
4-Ethyl	141–142				(294)
3-Isopropyl	130–131	180		173–174	(288, 348)
				(155–156)‡	
			112–113	172–173	(461*)
4-Isopropyl	138–139				(320, 322)
			147–148§	131–132	(256, 257, 274, 284, 309)
			158	(144–145)‡	
3-Phenyl	178	195	195	118	(296, 298*)
3-*p*-Methoxyphenyl	178	162–163		152–153	(330)
3-Benzyl	149–150	200	146	112–113	(300)
3,6-Dimethyl	185–186				(307)
3,7-Dimethyl	158–159				(307)
6-Isopropyl-3-methyl	150			122	(307)
				(71)‡	
3-Hydroxymethyl	162–163			202 (d.)	(306, 307)
				(173–174)‡	
3,7-Dihydroxymethyl	173				(307)
3-Hydroxymethyl-6-methyl	173				(307)
3-Hydroxymethyl-6-isopropyl	154			189	(306, 307)
				(137–139)‡	
3-Bromo	187–188	170	112	197.5–198	(269, 283, 290, 331, 335, 347)
			138–139		(72)
3-Iodo	188–189				(190)
3-Bromo-6-methyl	238–239 (d.)			200	(236, 292)
3-Bromo-7-methyl	189–190.5				(292, 293)
3-Chloro-4-isopropyl	119–120.5				(305)
3-Chloro-6-isopropyl	160–161				(264, 305)
3-Bromo-4-isopropyl	117–117.5		149–150 (?)		(256, 257, 304, 305, 309)
3-Bromo-6-isopropyl	162 (170)		112; 136; 157§		(284, 305, 320)
3-Allyl-7-bromo	126–127				(405)
3,7-Dichloro	187–188				(341)
3,7-Dichloro-4-isopropyl	161				(305)
3,7-Dibromo-4-isopropyl	159				(305)
7-Bromo-3-chloro-4-isopropyl	156–157				(305)
3-Nitro-6-isopropyl			155		(274, 289, 337)
6-Methyl-3-sulfonic acid (NH_4 salt)	272–273				(236)

* The ultraviolet spectra of one or more of the products listed are contained in this reference.

† This reference contains the infrared spectrum of nitrosotropolone.

‡ Melting point of the picrate of the amine.

§ Two (tautomeric ?) forms isolated.

TABLE 4—*Concluded*

B. Products of substitution in other positions

Substituents in Starting Material	Nitro Derivative		Melting Point of Corresponding Amine	References
	Position of NO_2 group	Melting point		
		°C.	°C.	
None	3	153	86	(72, 347)
4-Methyl	3	206	151	(134)
	7	146–147	136–137	(134)
5-Methyl	3	193		(292, 293)
4-Isopropyl	3	125; 155§	121	(274, 284, 309, 400)
	7	56	99	(284, 309)(*436)
5-Isopropyl	3	143.5–145		(318, 334)
3-Phenyl	7	146–148		(330)
C. Dinitration products				
None	3,5 or 3,7 (?)	138 (d.)		(269)
4-Methyl	5,7 (?)	132.8–133.5		(236, 292)
3-Isopropyl	5,7	92.5–93		(461*)
4-Isopropyl	5,7	155		(256, 274, 289, 337)
3-Bromo	5,7	162.5–163.5		(283)

the structure of the product is firmly established (327) as 6-isopropyltropolone-3-sulfonic acid (XCI) as shown:

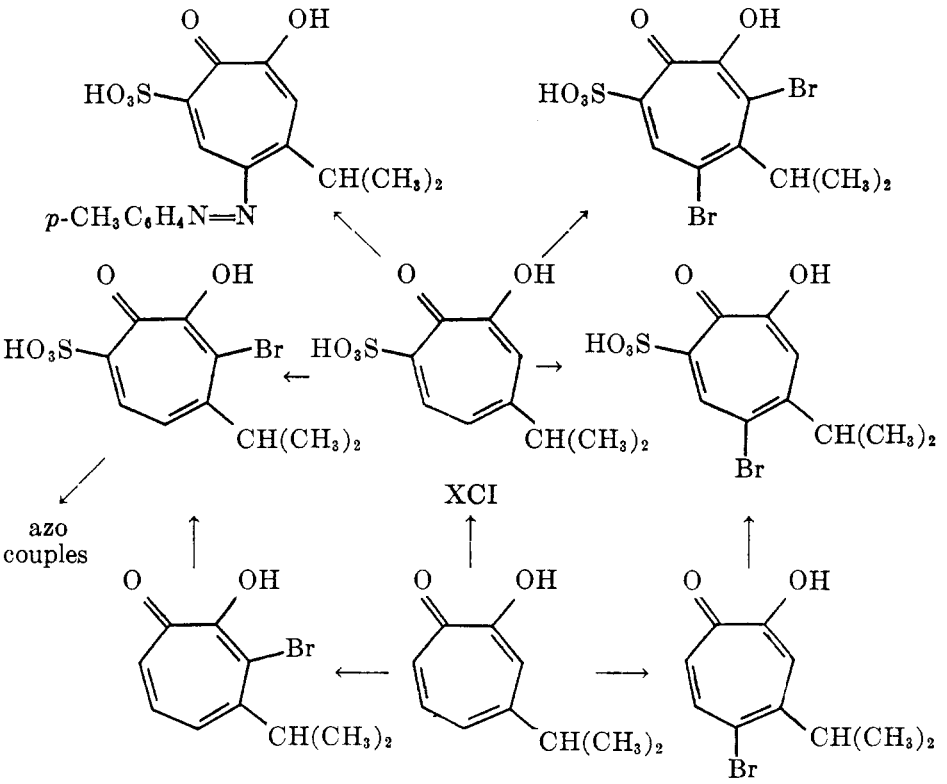


TABLE 5

Halogen-substituted tropolones obtained by direct synthesis (method A), by halogenation (method B), or by the Sandmeyer reaction (method C)

A. Chloro and bromo derivatives

Other Substituents	Chlorine Derivative		Bromine Derivative		Method	References
	Position of Cl	Melting point	Position of Br	Melting point		
		°C.		°C.		
None			3	107–108 (82–83)‡	A	(64, 65, 290, 335)(†194, *436)
			5	190–191	A	(335)(†194, *436)
			3,5	152–153.5 (121.5–126)‡	A	(270, 271, 287)(*436)
			3,6	122 (151–151.5)‡	A	(270, 271, 272, 287)
			3,7	159–160 (140–141)‡	A	(65, 335)(†194, *436)
			3,5,7	126–127	A	(65)(†194)
			3	107–108	B	(63)
	5	181.5–183	5	190–191	B	(63, 190)
	3,7	171	3,7	159–160	B	(63, 290, 341)
	3,5,7	125–125.5 (165)‡	3,5,7	126–127 (166–167)‡	B	(63, 96, 116, 290, 335, 341)(*197)
	5	181.5–182	5	190–191	C	(72, 325, 331)
3-Bromo	7	163.5 (128–129)‡			B	(341)
	5,7	116–117.5 (165–165.5)‡			B	(341)
	5	126–128	5	152–153.3	C	(290)
5-Bromo	3,7	119–119.5 (171–172)‡			B	(341)
3,7-Dichloro			5	119–119.5	B	(341)
3-Methyl			7	123–124	A	(40, 236, 292, 293)
			5,7	143–144	A	(292, 293)
4-Methyl			5	172.5	A	(236, 292)
			7	86 (70)‡	A	(236, 292)
			3,7	140 (112)‡	A	(236, 292)
			3,5	151 (114–115)‡	A	(236, 292)
	5	177.5–178	7	85–86	B	(131, 236, 292)
			3,7	139–140	B	(131, 294)
	3,5,7	100–101 (157–158)‡	3,5,7	99.5–100.5	B	(236, 292)
	5	177.5–178	5	172.5	C	(236, 292)
5-Methyl			3	115	A	(236, 292, 293)
			3,7	140 (103–104)‡	A	(236, 292)
			3,7	140	B	(292, 293, 307)
4-Ethyl			7	65–66	B	(294)
			3,7(?)	94–95	B	(294)
3-Isopropyl			7	21.5–22.5	A	(282)
			7	21.5–22.5	B	(288)
	5,7	79–80	5,7	80–81	B	(282, 288, 348)
	5	68.2–68.6	5	49.5–51	C	(288)
4-Isopropyl	3	48.5 (85–85.5)‡	3	41.5 (74–74.5)‡	B	(264, 304, 406)

*† See footnote to table 2.

‡ Melting points of the corresponding p-toluidine salts are given in parentheses below those of the parent compound.

TABLE 5—*Continued*

A. Chloro and bromo derivatives—*Continued*

Other Substituents	Chlorine Derivative		Bromine Derivative		Method	References
	Position of Cl	Melting point	Position of Br	Melting point		
		°C.		°C.		
4-Isopropyl	5	119.5			B	(264)
	7	47.5 (88.5–89.5)‡	7	56 (96–98)‡	B	(264, 304, 309, 321, 323, 400, 406)
			(?)	97–98	B	(319)
	3,7	127–128 (107.5–108.5)‡	3,7	134	B	(264, 304, 309, 321, 323, 336, 400, 406)
	5,7	103–105	5,7	96	B	(264, 304, 309, 323, 406)
	(?)	81–82			B	(264)
	3,5,7	63–64	3,5,7	90–91.5(?) (125–126)‡	B	(304, 309, 323, 406)
	3	48.5	3	41.5	C	(275)
	5	119.5	5	102–103	C	(264, 304, 319)
	7	47.5	7	56	C	(275)
3-Bromo-4-isopropyl	7	117.5			B	(304, 309)
	(?)	Oil (128–129)‡			B	(309)
7-Bromo-4-isopropyl	3	142–143 (95–98)‡			B	(309, 406)
	5	88			B, C	(309, 406)
	(?)	67–68			B	(406)
3-Chloro-4-isopropyl			7	142–143	B	(309)
5-Chloro-4-isopropyl			7	88	B	(309)
7-Chloro-4-isopropyl			3	117.5	B	(309)
			(?)	84 (92)‡	B	(309)
7-Iodo-4-isopropyl			3	125.5–126	B	(321)
5-Isopropyl			3	59.5	A	(334)
			3,7	143.5 (132–133)‡	A	(334)
			3	59.5	B	(336)
	3,7	112–113 (137)‡	3,7	143.5	B	(318)
4-*tert*-Butyl (?)			3(?)	90–91	B	(265)
			7(?)	150–151	B	(265)
5-*tert*-Butyl (?)			3,7	(?)	B	(265)
3-Phenyl			7	124–125	A	(262*)
			5,7	128–129	B	(262*)
5-Bromo-3-phenyl	7	125–125.5			B	(262)
3-Benzyl			5,7	126	B	(300)
3,6-Dimethyl			5,7	123–124	B	(307)
3-Methyl-6-isopropyl			5,7	101.5–102	B	(307)
3-Hydroxymethyl-6-methyl			5,7	123–124	B	(307)
3-Hydroxymethyl-6-isopropyl			(?)	132	B	(307)
5-Nitro			3	112 (182)‡	B	(283)
4-Isopropyl-5-nitro	7	123–124	7	135–136	C	(256)
5-Sulfonic acid			3,7		B	(328)
6-Methyl-3(?)-sulfonic acid			7(?)		B	(236)
			5,7		B	(236)
6-Isopropyl-3-sulfonic acid			5	211–212§	B	(327)
			7	204–205§	B	(327)
			5,7		B	(327)
4-Isopropyl-5-*p*-tolylazo			7	162	B	(320)
5-Acetamido			3	201–204	B	(331)
5-Acetamido-4-isopropyl			3 or 6(?)	180.5–181	B	(257)

§ Aniline salt.

TABLE 5—*Concluded*

A. Chloro and bromo derivatives—*Concluded*

Other Substituents	Chlorine Derivative		Bromine Derivative		Method	References
	Position of Cl	Melting point	Position of Br	Melting point		
		°C.		°C.		
5-Methoxy			3	174.5–175	B	(332)
3-Carbomethoxy-4-acetic acid			7	173 (d.)	B	(286)
4-Hydroxy-6-carboxylic acid			3	275	B	(34, 160)
4-Methyl-6-carboxylic acid			5,7(?)	214–215 (d.)	B	(85)
4-(2-Hydroxy-3-phenylpropyl)			3,5,7	125	B¶	(278)
4-Methyl-6-carboxylic acid			3,5,7	222–223 (d.)	B¶	(85)
4-Acetic acid			3,7	195 (d.)	B¶	(286)
			3,5,7	215 (d.)	B¶	(286)

B. Iodo derivatives

Other substituents	Iodine Derivative		Method	References
	Position of I	Melting point		
		°C.		
None	3	104	B	(190)
	3,7(?)	180–181	B	(190)
	5	185–186	C	(325, 331)
3-Bromo	5	163.5–164	C	(290)
3-Isopropyl	5	65–66	C	(288)
4-Isopropyl	7	48.5–49 (86.5)‡	B	(321)
	5	87–88	C	(319)

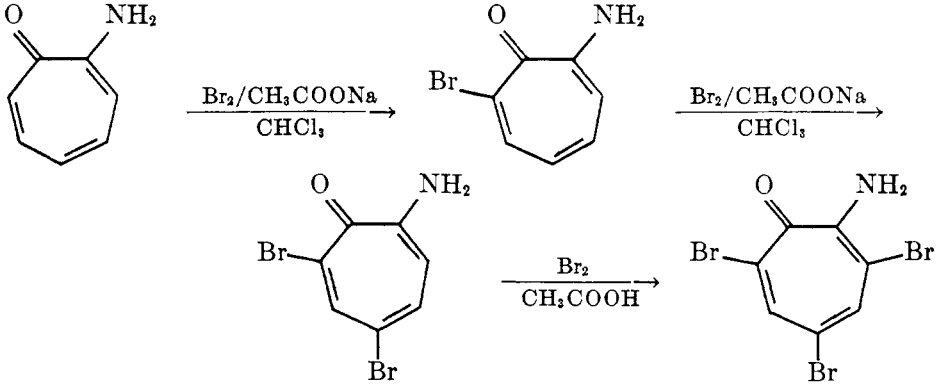
¶ Decarboxylative bromination of the corresponding 3-carboxylic acid.

The orientation of the two monobromo derivatives of hinokitiol is fully established from independent evidence. The position of sulfonation in 3-isopropyltropolone (288) and 3-phenyltropolone (262) is unknown.

5. *Halogenation (see table 5)*

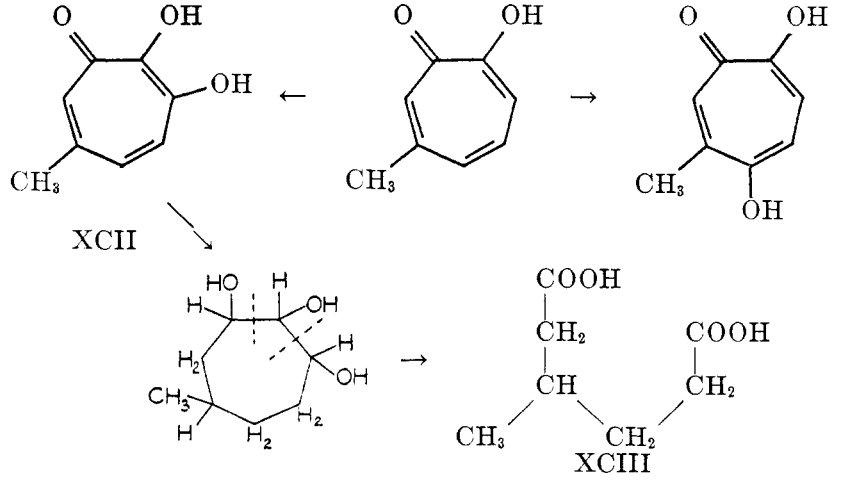
The mono-, di-, and trisubstitution of tropolones with halogen has been studied extensively. Various solvents have been used. In the case of unsubstituted tropolone, only 3-mono- and 3,7-disubstitution has been observed (the only doubtful case being the diiodotropolone (190), in which the position of the second iodine atom is unknown). Two reactions have been reported, however, which yield predominantly the 5-halogen derivative: (*a*) The reaction of the cupric complex of tropolone with bromine (63) yields 5-bromotropolone. (*b*) The sodium salt of tropolone reacts with iodine monochloride giving a mixture of 5-chlorotropolone and a complex from which 3-iodotropolone is obtained by the action of water (190). The halogenation of alkyl-substituted tropolones likewise affords predominantly the 3- and 7-substituted derivatives, but a small amount of simultaneous 5-substitution is evident from the isolation of 5-chloro-4-methyltropolone together with the trichloro derivative in the chlorination of

4-methyltropolone (236, 292), from the isolation of 5-chloro-4-isopropyltropolone (264, 406), and from the formation of both 3,7- and 5,7-dibromo derivatives in the bromination of 4-isopropyltropolone or its ethers (304, 309, 323). When both the 3- and the 7-positions are blocked, 5-substitution occurs readily and 3,5,7-trihalogen derivatives are readily obtained. The 3- and 7-positions are of course equivalent in tropolone, and the halogenation of tropolone ethers (*cf.* 309, 329) has not yet been studied under conditions which avoid hydrolysis of the ether grouping so as to reveal any difference in reactivity between these two positions. It is of interest in this connection that bromine has been shown (346) to enter 2-aminotropone first in the 7-position, then in the 5-position, and only when both these are blocked in the 3-position, indicating a definite decrease in reactivity of the positions in that order:



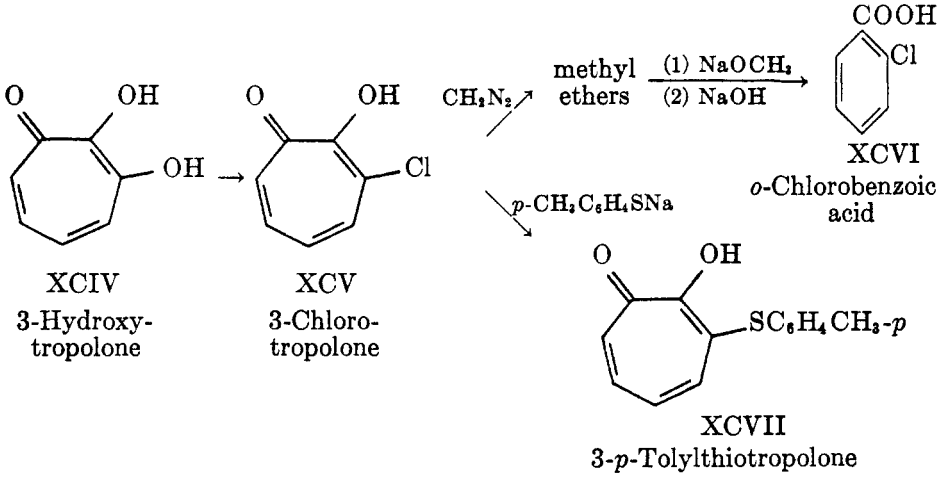
6. Hydroxylation

Oxidation of tropolones with alkaline persulfate yields a mixture of the 3- and 5-hydroxy derivatives in which the latter predominates (3, 332, 333). Since



β-Methyladipic acid

the 5-hydroxytropolones and their ethers are also obtainable by diazotization and hydrolysis or alcoholysis of the corresponding 5-aminotropolones, their orientation presents little problem. Two methods have been used to orient the 3-isomer. In the case of 3-hydroxy-5-methyltropolone (XCII) (the product resulting from substitution at position 7 in 4-methyltropolone), the method employed involved catalytic reduction followed by oxidation of the product to β-methyladipic acid (XCIII) (3). In the case of 3-hydroxytropolone (XCIV) thionyl chloride was employed to convert it to 3-chlorotropolone (XCV), which in turn was identified both by rearrangement of its methyl ether to *o*-chloro-



benzoic acid (XCVI) and by conversion to 3-*p*-tolylthiotropolone (XCVII), previously obtained from 3-bromotropolone of known orientation (333).

7. Hydroxymethylation

In this reaction, carried out with alkaline formaldehyde solution at 60–65°C., 3-substitution predominates, but not to the complete exclusion of 5-substitution. Disubstitution (3,7 and 3,5) and trisubstitution (3,5,7) products have been shown to be formed (306, 307). Identification of the products has been carried out by reduction of the hydroxymethyl compounds with hydriodic acid to the corresponding methyltropolones (307), and rearrangement of the latter to methylbenzoic acids.

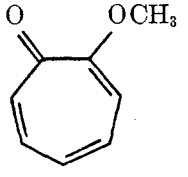
8. Reimer–Tiemann reaction

This has been accomplished only in very low yield (74), but it is at least of theoretical interest that chloroform and carbon tetrachloride react with tropolone in alkaline solution as they do with phenols, introducing an aldehyde or carboxyl group, respectively, in the 5-position.

V. Substitution (Nucleophilic) of Elements and Groups Other than Hydrogen (See Table 6)

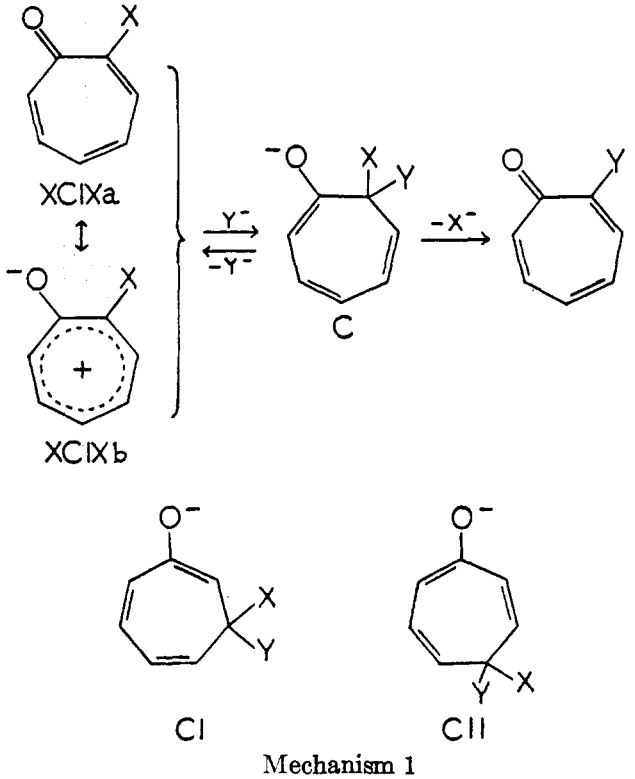
The view (*cf.* page 12) that tropolone may be regarded as a vinolog of a carboxylic acid may be illustrated by numerous reactions paralleling those of

the carboxyl group. Thus the ether (XCVIII) of tropolone (its ester on this basis) may be obtained not only by reaction with diazomethane, but also—if in less good yield—by "esterification" with methyl alcohol and hydrogen chloride (96). Like an ester, XCVIII reacts with ammonia (or an amine) to give 2-amino(or substituted amino)-tropone (the amide of tropolone); these products may also be formed from tropolone *via* 2-chlorotropone (the vinolog of an acid chloride) obtained by the action of thionyl chloride.



XCVIII

Replacements of this type are by no means restricted to atoms or groups in the 2-position, but can be effected at any position of a tropone or tropolone derivative as far as present evidence has shown. In all cases the formulation as a vinylog of a carboxylic acid, ester, acid chloride, amide, etc. is possible. It is perhaps better, however, to write the replacement as occurring by the sequence of steps illustrated for a 2-substituted tropone:



Mechanism 1

TABLE 6

Nucleophilic substitution reactions

Starting Material	Reagent and Conditions	Product	Melting Point	Yield	References
		A. Replacement of OH			
			°C.	*per cent*	
Tropolone	$SOCl_2$ or PCl_3	2-Chlorotropone	63–64	90	(1, 97*)
4-Isopropyltropolone	$SOCl_2$ in benzene‡	2-Chloro-4(and 6)-isopropyltropone	Oil	50	(98)
5-Isopropyltropolone	$SOCl_2$ in benzene‡	2-Chloro-5-isopropyltropone	Oil	40	(98)
4-Phenyltropolone	$SOCl_2$ in benzene‡	2-Chloro-4(and 6)-phenyltropone	Oil		(98)
5-Phenyltropolone	$SOCl_2$ in benzene‡	2-Chloro-5-phenyltropone	158		(98)
3-Hydroxytropolone	$SOCl_2$	3-Chlorotropolone	102–103		(333)
4-Hydroxytropolone	$SOCl_2$	2,4(or 2,6)-Dichlorotropone	67.5–68		(266*)
5-Nitrosotropolone	NH_3 (aqueous)	2-Amino-5-nitrosotropone	210 (d.)		(312*, 346)
5-Nitrotropolone	NH_3	2-Amino-5-nitro-tropone	243–244		(345, 346)
3,5-Dinitro-6-isopropyltropolone	NH_3	2-Amino-5,7-dinitro-4-isopropyltropone	234–235		(344)
	$C_6H_5NH_2$	2-Anilino-5,7-dinitro-4-isopropyltropone	148–149 159–160		(344)
	p-$CH_3C_6H_4NH_2$	2-*p*-Toluidino-5,7-dinitro-4-isopropyltropone	202–203		(344)
	p-$ClC_6H_4NH_2$	2-*p*-Chloroanilino-5,7-dinitro-4-isopropyltropone	194–196		(344)
Tropolone	*n*-C_4H_9Li	2-*n*-Butyltropone	Oil	83	(94*)
	C_6H_5Li	2-Phenyltropone	84.5–85.5	70	(94*)
Cupric tropolone	C_6H_5Li	2-Phenyltropone	84.5–85.5	89	(99)
	o-$CH_3OC_6H_4Li$	2-*o*-Methoxyphenyltropone	93.5–94.5	63	(99)
		B. Replacement of halogen			
2-Chlorotropone	HBr/CH_3COOH‡; 2 hr.	2-Bromotropone	60–60.5	75	(94*†)
	KI/CH_3COOH‡; 5 hr.	2-Iodotropone	71–71.5	54	(94*†)
	$(C_2H_5)_4NI/CH_3COOH$	2-Iodotropone	71–71.5		(94)
2-Bromo-7-chlorotropone	HCl/CH_3COOH; 100°C.; 7 hr.	2,7-Dichlorotropone	131–132		(408*)
3-Bromo-2-chlorotropone	HCl/CH_3COOH	2,3-Dichlorotropone	72–74		(408*)
3,5,7-Tribromotropolone	HCl; 150°C.	3,5,7-Trichlorotropolone	128–128.5	77	(97*)
3-Iodo-6-isopropyltropolone	Cl_2/CH_3COOH	3,7-Dichloro-4-isopropyltropolone	124–126		(321)
	$Br_2/CHCl_3$	3-Bromo-6-isopropyltropolone	56		(321)
	Br_2/CH_3COOH	3,7-Dibromo-4-isopropyltropolone	134		(321)
2-Chlorotropone	NH_4Cl (aqueous)	Tropolone	50	Low	(1)
	2.4 *N* HCl; 150°C.; 9 hr.	Tropolone	50	58	(94)
	H_2O; 150°C.; 9 hr.	Tropolone	50	8	(94)

2,7-Dichlorotropone	$NaOH/C_2H_5OH$	3-Chlorotropolone	104–105	40	(413*)
		2-Chloro-7-ethoxytropone	85–87	8	
3-Bromo-2-chlorotropone	$NaOH/C_2H_5OH$	2-Chloro-3-hydroxytropone	210–215	5	(413*)
		2-Chloro-3-ethoxytropone		5	
3-Bromotropolone	$Cu(OCOCH_3)_2$/pyridine; 125–130°C.	3-Hydroxytropolone	138.5–139.5		(266)
	CH_3ONa/CH_3OH	3-Hydroxytropolone	138.5–139.5		(266)
		3-Methoxytropolone	79–80	Trace	
2-Bromo-7-chlorotropone	$NaOH/C_2H_5OH$; cold	3-Bromotropolone	107–108	10	(338, 413)
	HCl/CH_3COOH; 100°C.; 7 hr.	3-Chlorotropolone	104		(408)
3-Bromo-2-chlorotropone	HCl/CH_3COOH	2-Chloro-3-hydroxytropone	210–215		(408*)
3-Bromo-2-chloro-4-isopropyltropone	H_2SO_4	Mixture of 3-bromo-6-isopropyl- and 3-chloro-4-isopropyltropolones			(411)
2-Bromo-7-phenyltropone	$NaOH/C_2H_5OH$	3-Phenyltropolone	111–113	10	(296*)
	HBr/CH_3COOH (aq.); 160°C.; 6 hr.	3-Phenyltropolone	116–116.5	77	(99*†)
Bromostipitatic acid	KOH; 200°C.; 15 min.	Puberulic acid	317	58	(160*†) (*11, †12 *68, *78, *80, *163)
2-Bromo-5-carboxy-3-methoxytropone	KOH/CH_3OH‡; 2 hr.	5-Carboxy-3-methoxytropolone	257		(160*†)
2,3,5,7-Tetrachlorotropone	$NaOH/C_2H_5OH$	3,5,7-Trichlorotropolone	128–128.5	10	(97*)
2,4,7-Tribromotropone	CH_3COOK/CH_3COOH‡; 20 hr.	3,5-Dibromotropolone	152–153.5		(270, 271, 287)
		3,6-Dibromotropolone	118–120		
2-Chlorotropone	$NaOCH_3$; 80°C.; 4 hr.	2-Methoxytropone	Oil		(1)
	NH_3/CH_3OH; 100°C.; 4 hr.	2-Aminotropone	100–101		(1, 408) (†194, *436)
			104–105		
	NH_3/CH_3OH; 130°C.; 3 hr.	2-Aminotropone	100–101		(94*)
			104–105		
2-Chlorotropone or 2-bromotropone	p-$CH_3C_6H_4NH_2$ in cyclohexane‡	2-p-Toluidinotropone	108.5–109.5		(338, 408)
2,7-Dichlorotropone	$(C_2H_5)_2NH$ in benzene‡; 2 hr.	2-Chloro-7-diethylaminotropone	56		(1)
	p-$CH_3C_6H_4NH_2$ in xylene‡; ½ hr.	2-Chloro-7-p-toluidinotropone	121		(1)
2-Chloro-6-methyltropone	$C_6H_5NH_2$; 140°C.	2-Anilino-6-methyltropone	121–122		(3)
2,4,7-Tribromotropone	$C_6H_5NH_2$ in benzene‡	2-Anilino-4,7-dibromotropone	197	80	(271, 272)
	p-$CH_3C_6H_4NH_2$ in benzene‡	2,4(and 2,5)-Dibromo-7-p-toluidinotropone	178–184		(271)
	N_2H_4 in benzene‡	2,4(or 2,5)-Dibromo-7-hydrazinotropone	151 (d.)		(271)
		2,5(or 2,4)-Dibromo-7-hydrazinotropone	175 (d.)		
Cupric 3-bromotropolone	$C_6H_5SO_2NHK$ in pyridine; 135–140°C.	3-Phenylsulfonamidotropolone	181–182	70	(266*)
2,4,7-Tribromotropone	Pyridine in benzene‡; 2 hr.	2,4(and 2,5)-Dibromo-7-troponylpyridinium bromide			(271)
2-Bromotropone	CuCN; 130°C.	2-Cyanotropone	138–139		(338)
3-Bromotropolone	CuCN in pyridine‡; 15 min.	3-Cyanotropolone	165		(1)
	CuCN; 230–240°C.; 18 hr.	3-Cyanotropolone	174–175		(286)
2-Chlorotropone or 2-bromotropone	$NaSH/C_2H_5OH$	2-Mercaptotropone	55	Good	(316*†, 317*†)
	CH_3SNa	2-Methylthiotropone	42.5–44		(314, 317*†) (*†316)

TABLE 6—*Continued*

Starting Material	Reagent and Conditions	Product	Melting Point	Yield	References
		B. Replacement of halogen—*Continued*			
			°C.	*per cent*	
2-Chlorotropone	CH_3COSNa	2-Acetylmercaptotropone	170		(316)
	C_6H_5COSNa	2-Benzoylmercaptotropone	106		(316)
	Na_2S_2	Di(2-troponyl) disulfide	206		(316, 317*)
	Na_2S	Di(2-troponyl) sulfide	171		(316, 317*)
	Sodium salt of 2-mercaptotropone	Di(2-troponyl) sulfide	171		(316, 317)
	$HSCH_2COONa$	2-Troponylthioacetic acid	193		(316, 317)
2-Chlorotropone or 2-bromotropone	p-$CH_3C_6H_4SNa$	2-p-Tolylthiotropone	148		(1, 314, 317*, 338)
2-Chlorotropone	p-$O_2NC_6H_4SNa$	2-p-Nitrophenylthiotropone	198–199		(317)
	Sodium salt of 2-mercapto-4-methylthiazole	2-(2-Troponylthio)-4-methylthiazole	124		(317)
2,7-Dichloro- or 2-bromo-7-chlorotropone	NaSH	2-Chloro-7-mercaptotropone	92–93		(316, 317*)
	CH_3SNa	2,7-Dimethylthiotropone	130		(314, 317*)
	p-$CH_3C_6H_4SNa$ in C_2H_5OH	2-Chloro-7-p-tolylthiotropone	165		(1, 314)
2,7-Dichlorotropone	p-$CH_3C_6H_4SNa$ in C_2H_5OH‡	2,7-Di-p-tolylthiotropone	259–260; 266		(1, 314, 317)
2-Bromo-7-methoxytropone	NaSH	Sodium salt of 2-methoxy-7-mercaptotropone			(317)
	Na_2S_2	Di(2-methoxy-7-troponyl) disulfide	220–221		(317)
	CH_3SNa	2-Methoxy-7-methylthiotropone	Oil		(315, 317)
	CH_3SNa	2,7-Dimethylthiotropone	129–130		(315, 317)
2,4,7-Tribromotropone	CH_3SNa	4-Bromo-2,7-dimethylthiotropone	135		(314, 317)
	p-$CH_3C_6H_4SNa$	4-Bromo-2,7-di-p-tolylthiotropone	181		(314, 317)
	p-$CH_3C_6H_4SNa$ in C_2H_5OH‡; 5 hr.	2,4,7-Tri-p-tolylthiotropone	185		(314, 317)
3-Bromotropolone (sodium salt)	NaSH	Disodium salt of 3-mercaptotropolone			(317)
3-Bromotropolone (sodium salt)	Na_2S_2	Di(3-tropolonyl) disulfide	236		(317)
	CH_3SNa	3-Methylthiotropolone	110–111		(317)
3-Bromotropolone (sodium salt or methyl ether)	C_6H_4SNa	3-Phenylthiotropolone	140		(315, 317*)
3-Bromo- or 3-chlorotropolone	p-$CH_3C_6H_4SNa$ in pyridine‡; 1 hr.	3-p-Tolylthiotropolone	175–176		(1, 315, 317, 333)
3,7-Dibromotropolone	p-$CH_3C_6H_4SNa$	3,7-Di-p-tolylthiotropolone	158–159		(72, 315, 317)
3,7-Dibromo-2-methoxytropone	p-$CH_3C_6H_4SNa$	3,7-Di-p-tolylthio-2-methoxytropone	167.5–168.5		(315, 317)
3,5,7-Tribromotropolone	p-$CH_3C_6H_4SNa$	5-Bromo-3,7-di-p-tolylthiotropolone	216		(72, 315, 317)
	p-$CH_3C_6H_4SNa$	3,5-Dibromo-7-p-tolylthiotropolone	165		(315, 317)
5-Bromo-3,7-di-p-tolylthiotropolone	p-$CH_3C_6H_4SNa$; 150°C.; 12 hr.	3,5,7-Tri-p-tolylthiotropolone	182		(72)
2-Chlorotropone	C_6H_5MgBr or C_6H_5Li	2-Phenyltropone	84–85.5	59	(94)
2-Bromotropone	$C_6H_5CH_2MgCl$	2-Benzyltropone	Oil	50	(300)

C. Replacement of alkoxyl

2-Methoxytropone	3 *N* HCl†; 3 hr.	Tropolone	50	52	(96)
	2 *N* NaOH‡; 5 min.	Tropolone	50	73	(96)
3-Methoxytropone	50% HBr	3-Hydroxytropone	179–180		(159)
Colchicine	Aqueous NaOH	Colchiceine			(115, 148)
	C_2H_5OH/p-$CH_3C_6H_4SO_3H$	Colchiceine ethyl ether	134–138		(148)
Isocolchicine	C_2H_5OH/p-$CH_3C_6H_4SO_3H$	Colchiceine ethyl ether	222–223		(148)
2-Methoxy-6-methyltropone	$(CH_3)_2CHCH_2ONa$	2-Isobutoxy-6-methyltropone	Liquid		(3)
2-Bromo-7-methoxytropone	NaOH	3-Bromotropolone	108	40	(285)
3-Bromo-2-methoxytropone	2 *N* NaOH; 100°C.; 15 min.	3-Bromotropolone	108	7	(285)
5-Bromo-2-methoxytropone	2 *N* NaOH; 100°C.; 15 min.	5-Bromotropolone	191	70	(285)
3,7-Dibromo-2-methoxytropone	2 *N* NaOH; 100°C.; 15 min.	3,7-Dibromotropolone	160	10	(285)
2-Methoxy-7-methylthiotropone	5 *N* NaOH	3-Methylthiotropolone	110		(315)
3-Methoxy-5-carboxytropolone	HBr/CH_3COOH; 100–110°C.; 6 hr.	3-Hydroxytropolone-5-carboxylic acid	293–294		(160*†)
4-Methoxy-6-carbethoxytropolone	HBr (48%); 110°C.; 12 hr.	Stipitatic acid	282		(21, 22) (*11, †12, *68, *80, *163)
2-Methoxytropone	NH_3/C_2H_5OH; 110°C.; 6 hr.	2-Aminotropone	100–101	47	(96)
	Liquid NH_3 at room temperature	2-Aminotropone	106–107	90	(344*†, 346)
	CH_3NH_2	2-Methylaminotropone	79–80		(345, 346)
	$(CH_3)_2NH$	2-Dimethylaminotropone	19.5–21.5		(345, 346)
	p-$CH_3C_6H_4NH_2$	2-p-Toluidinotropone	108.5–109.5		(345, 346) (*278)
	N_2H_4	2-Hydrazinotropone	95–96		(345, 346)
2-Methoxy-4-methyltropone	NH_3/CH_3OH; 80°C.; 65 hr.	2-Amino-4-methyltropone	123		(2, 3)
	$(CH_3)_2NH$; room temperature	2-Dimethylamino-4-methyltropone	Liquid	90	(3)
	$C_6H_5NH_2/CH_3OH$; 90°C.	2-Anilino-4-methyltropone	98–99		(2, 3)
2-Methoxy-6-methyltropone	NH_3/CH_3OH; 80°C.; 65 hr.	2-Amino-6-methyltropone	111–112	65	(2, 3)
	Liquid NH_3; room temperature; 5 days	2-Amino-6-methyltropone	111–112	89	(3)
	$(CH_3)_2NH$; 20°C.; 7 days.	2-Dimethylamino-6-methyltropone	−2 to +2		(3)
	$C_6H_5NH_2/CH_3OH$; 90°C.	2-Anilino-6-methyltropone	121–122		(2)
	N_2H_4/H_2O; 100°C.; 5 min.	2-Hydrazino-6-methyltropone	124		(2, 3)
2-Methoxy-4-methyltropone	N_2H_4/H_2O; 100°C.; 5 min.	2-Hydrazino-4-methyltropone	134–135		(2)
2-Methoxy-6-methyltropone	Morpholine‡; 50 hr.	2-Morpholino-4-methyltropone	89–90		(3)
2-Isobutoxy-6-methyltropone	$C_6H_5NH_2$; 150°C.; 11 hr.	2-Anilino-6-methyltropone	121–122		(3)
4-Isopropyltropolone methyl ether (mixture of the two isomers)	NH_3 (gas)	2-Amino-4-isopropyltropone	105		(345, 346, 409)
		2-Amino-6-isopropyltropone	82–83		
	N_2H_4-H_2O/CH_3OH; room temperature; 3 days	2-Hydrazino-4-isopropyltropone	105–106		(409)
		2-Hydrazino-6-isopropyltropone	111–112		
2-Methoxy-3-isopropyltropone	N_2H_4	2-Hydrazino-3-isopropyltropone	Resin		(410)
2-Methoxy-7-isopropyltropone	N_2H_4	2-Hydrazino-7-isopropyltropone	72–72.5		(410)
3-Bromotropolone methyl ether	NH_3/CH_3OH; 110°C.; 8 hr.	Impure aminobromotropone	140		(1)
2-Bromo-7-methoxytropone	NH_3 (liquid)	2-Amino-7-bromotropone	134.5–135		(344, 345, 346)
	p-$CH_3C_6H_4NH_2$	2-Bromo-7-p-toluidinotropone	124.5–125		(345, 346)
	N_2H_4	2-Bromo-7-hydrazinotropone	157–158		(345, 346)

TABLE 6—*Continued*

Starting Material	Reagent and Conditions	Product	Melting Point	Yield	References
		C. Replacement of alkoxyl—*Continued*			
			°C.	*per cent*	
3-Bromo-2-methoxytropone	NH_3 (liquid)	2-Amino-3-bromotropone	100–100.5		(344, 345, 346)
	N_2H_4/ether; room temperature; 10 min.	3-Bromo-2-hydrazinotropone	114–116		(408)
5-Bromo-2-methoxytropone	NH_3	2-Amino-5-bromotropone	170–171		(291, 345, 346)
3,7-Dibromo-2-methoxytropone	NH_3 (liquid)	2-Amino-3,7-dibromotropone	133.5–134.5		(345, 346)
3,5,7-Tribromo-2-methoxytropone	NH_3 (liquid)	2-Amino-3,5,7-tribromotropone	202.5–203		(345, 346)
	NH_3 (gas)	2-Amino-3,5,7-tribromotropone	202.5–203	70	(346)
3-Bromo-2-methoxy-6-isopropyltropone	N_2H_4	3-Bromo-2-hydrazino-6-isopropyltropone	103–104		(411)
7-Bromo-2-methoxy-4-isopropyltropone	N_2H_4	7-Bromo-2-hydrazino-4-isopropyltropone	112–114		(411)
2-Methoxy-3-phenyltropone	NH_3	2-Amino-3-phenyltropone	127.5–128.5		(298)
2-Methoxy-7-phenyltropone	NH_3	2-Amino-7-phenyltropone	211		(296*, 298)
	N_2H_4	2-Hydrazino-7-phenyltropone	192 (d.)		(298)
4-Bromo-7-methoxy-2-phenyltropone	NH_3 (liquid)	7-Amino-4-bromo-2-phenyltropone	211.5 (d.)		(262*)
3,5-Dibromo-2-methoxy-7-phenyltropone	NH_3	2-Amino-3,5-dibromo-7-phenyltropone	138		(262*)
2-Methoxy-5-acetamidotropone	NH_3 (liquid)	2-Amino-5-acetamidotropone	192.5–193.5		(346)
2-Methoxy-5-nitrotropone	NH_3 (liquid)	2-Amino-5-nitrotropone	243–244 (d.)		(346)
Colchicine or colchiceine ethyl ether	NH_3 (aqueous); room temperature; 18 hr.	"Colchiceine amide"	258.5–259.5	95	(148*†)§
Isocolchicine or isocolchiceine ethyl ether	NH_3 (aqueous); room temperature; 48 hr.	"Isocolchiceine amide"	159–162	90	(148*†)§
2-Methoxytropone	CH_3SNa/C_2H_5OH‡; 30 min.	2-Methylthiotropone	42.5–44	Poor	(317)
2-Bromo-7-methoxytropone	CH_3SNa	2,7-Dimethylthiotropone	129–130		(315)
Colchicine	NaSH	Thiocolchiceine	190 (d.)		(259)
2-Methoxytropone	C_6H_5MgBr	2-Phenyltropone	84.5–85.5		(94, 295*, 298) (*436, †194)
	p-$CH_3OC_6H_4MgBr$	2-p-Methoxyphenyltropone	58–58.5		(330)
	$C_6H_5CH_2MgCl$	2-Benzyltropone	Oil	Trace	(300*)
2-Methoxy-4-methyltropone	C_6H_5MgBr	5-Methyl-2-phenyltropone	99		(3, 138)
2-Methoxy-6-methyltropone	C_6H_5MgBr	3-Methyl-2-phenyltropone	93		(3, 138)
4-Isopropyltropolone methyl ether (mixture of isomers)	C_6H_5MgBr	(?)-Isopropyl-(?)-phenyltropone (?)-Isopropyl-(?)-phenyltropone	93–94 Oil		(295*, 298) (*436)
3-Bromo-2-methoxytropone	C_6H_5MgBr	(?)-Bromo-(?)-phenyltropone	115–115.5		(299)
2-Bromo-7-methoxytropone	C_6H_5MgBr	(?)-Phenyltropolone¶ (?)-Bromo-(?)-phenyltropolone	96–97 162–163		(290)
3,7-Dibromo-2-methoxytropone	C_6H_5MgBr	3,7-Dibromo-2-phenyltropone	118.5–119		(299)

D. Replacement of toluenesulfonyloxy

Tropolone *p*-toluenesulfonate	3 *N* HCl/CH_3OH	Tropolone	50		(94)
	10% KOH/C_2H_5OH; 5 min.	Tropolone	50	76	(94)
	$(C_2H_5)_4NI$ in CH_3COOH; 5 hr.	2-Iodotropone	71		(94)
	5% NH_3/CH_3OH; 110–120°C.; 6 hr.	2-Aminotropone	100–101	53	(94)
	p-$CH_3C_6H_4SNa$	2-*p*-Tolylthiotropone	147–148		(72)

E. Replacement of NR_2

2-Aminotropone	2 *N* KOH	Tropolone	50		(346)
2-Amino-7-methyltropone	NaOH	3-Methyltropolone	50		(412)
2-Amino-6-methyltropone	6 *N* NaOH‡; 20 hr.	4-Methyltropolone	77		(2)
2-Amino-7-phenyltropone	6 *N* KOH/C_2H_5OH‡; long time	3-Phenyltropolone	117–118		(296, 298*)
2-Amino-7-benzyltropone	KOH/C_2H_5OH	3-Benzyltropolone	51–52	75	(300)
2-Amino-7-*p*-methoxyphenyltropone	2 *N* NaOH/C_2H_5OH‡; 30–35 hr.	3-*p*-Methoxyphenyltropolone	98–98.5		(330)
2-Amino-3-bromotropone	2 *N* KOH	3-Bromotropolone	107–108		(346)
2-Amino-7-bromotropone	2 *N* KOH	3-Bromotropolone	107–108		(346)
2-Amino-5-bromotropone	KOH/C_2H_5OH‡	5-Bromotropolone	190–191		(346)
2-Amino-3,7-dibromotropone	KOH/C_2H_5OH‡	3,7-Dibromotropolone	159–160		(346)
7-Amino-2,4-dibromotropone	KOH/C_2H_5OH‡	3,5-Dibromotropolone	153		(346)
2-Amino-3,5,7-tribromotropone	KOH/C_2H_5OH; room temperature	3,5,7-Tribromotropolone	126–127		(346)
7-Amino-4-bromo-2-phenyltropone	KOH/C_2H_5OH	5-Bromo-3-phenyltropolone	136–137		(262*)
2-Amino-5-phenylazotropone	KOH/C_2H_5OH	5-Phenylazotropolone	160.5–161.5		(346)
2-Amino-4-methyltropone	$C_6H_5NH_2$‡	2-Anilino-4-methyltropone	98–99		(2)
2-Amino-6-methyltropone	$C_6H_5NH_2$‡	2-Anilino-6-methyltropone	121–122		(2, 3)
2-Amino-6-isopropyltropone	N_2H_4	2-Hydrazino-6-isopropyltropone	82		(409)
2-Amino-7-phenyltropone	N_2H_4	2-Hydrazino-7-phenyltropone	192 (d.)		(298)
2-Dimethylamino-4-methyltropone	C_6H_5MgBr	5-Methyl-2-phenyltropone	99		(3, 138)
2-Dimethylamino-6-methyltropone	C_6H_5MgBr	3-Methyl-2-phenyltropone	93		(3, 138)

F. Cu^{++}- or Fe^{+++}-catalyzed replacement of $NHNH_2$

2-Hydrazinotropone	HCl/$CuSO_4$	2-Chlorotropone	66–67		(408*)
	HBr/$CuSO_4$	2-Bromotropone	61–62		(338) (*408)
	HI/$Fe_2(SO_4)$	2-Iodotropone Tropone	71–72		(338, 408*)
2-Hydrazino-6-methyltropone	HCl/$CuSO_4$	2-Chloro-6-methyltropone	58–59		(3)
2-Hydrazino-3-isopropyltropone	HCl/$CuSO_4$	2-Chloro-3-isopropyltropone	Oil		(410)
2-Hydrazino-4-isopropyltropone	HCl/$CuSO_4$	2-Chloro-4-isopropyltropone	Oil		(409*)
2-Hydrazino-6-isopropyltropone	HCl/$CuSO_4$	2-Chloro-6-isopropyltropone	Oil		(409*)

TABLE 6—*Concluded*

Starting Material	Reagent and Conditions	Product	Melting Point	Yield	References
		F. Cu^{++}- or Fe^{+++}-catalyzed replacement of $NHNH_2$—*Continued*			
			°C.	*per cent*	
2-Hydrazino-7-isopropyltropone	$HCl/CuSO_4$	2-Chloro-7-isopropyltropone	Oil		(410)
2-Bromo-7-hydrazinotropone	$HCl/CuSO_4$	2-Bromo-7-chlorotropone	147–149		(346, 408*)
	$HBr/CuSO_4$	2,7-Dibromotropone	170–171		(338, 408*)
	$CH_3COOH/Cu(OCOCH_3)_2$	3-Bromotropolone	107–108	Trace	(408)
		2-Bromotropone	61–62	Trace	
	$H_2SO_4/Fe_2(SO_4)_3$	2-Bromotropone	61–62	Trace	(408)
		2,7-Dibromotropone	170–171	Trace	
3-Bromo-2-hydrazinotropone	$HCl/CuSO_4$	3-Bromo-2-chlorotropone	111–112		(408*)
	$HBr/CuSO_4$	2,3-Dibromotropone	123–124		(408*)
3-Bromo-2-hydrazino-6-isopropyltropone	$HCl/CuSO_4$	3-Bromo-2-chloro-6-isopropyltropone	80–81		(411*)
7-Bromo-2-hydrazino-4-isopropyltropone	$HCl/CuSO_4$	7-Bromo-2-chloro-4-isopropyltropone	84		(411*)
		G. Replacement of SR			
2,7-Dimethylthiotropone	$NaOH/C_2H_5OH$	3-Methylthiotropolone	110–111		(314, 317)
		H. Simultaneous replacement of OH and Br			
3-Bromotropolone	$SOCl_2$	2,7-Dichlorotropone	129–130		(1, 311, 317) (*408)
3,5,7-Tribromotropolone	$SOCl_2$	2,3,5,7-Tetrachlorotropone	115–116		(97†)

* Reference contains ultraviolet absorption data for the product named in column 3 (*cf.* footnotes to table 2).

† Reference contains infrared absorption data for the product named in column 3 (*cf.* footnotes to table 2).

‡ At reflux temperature of solvent or reagent named.

§ For other references and reactions of colchicine and isocolchicine with other amines see page 28.

¶ *Cf.* footnote 8 on page 67.

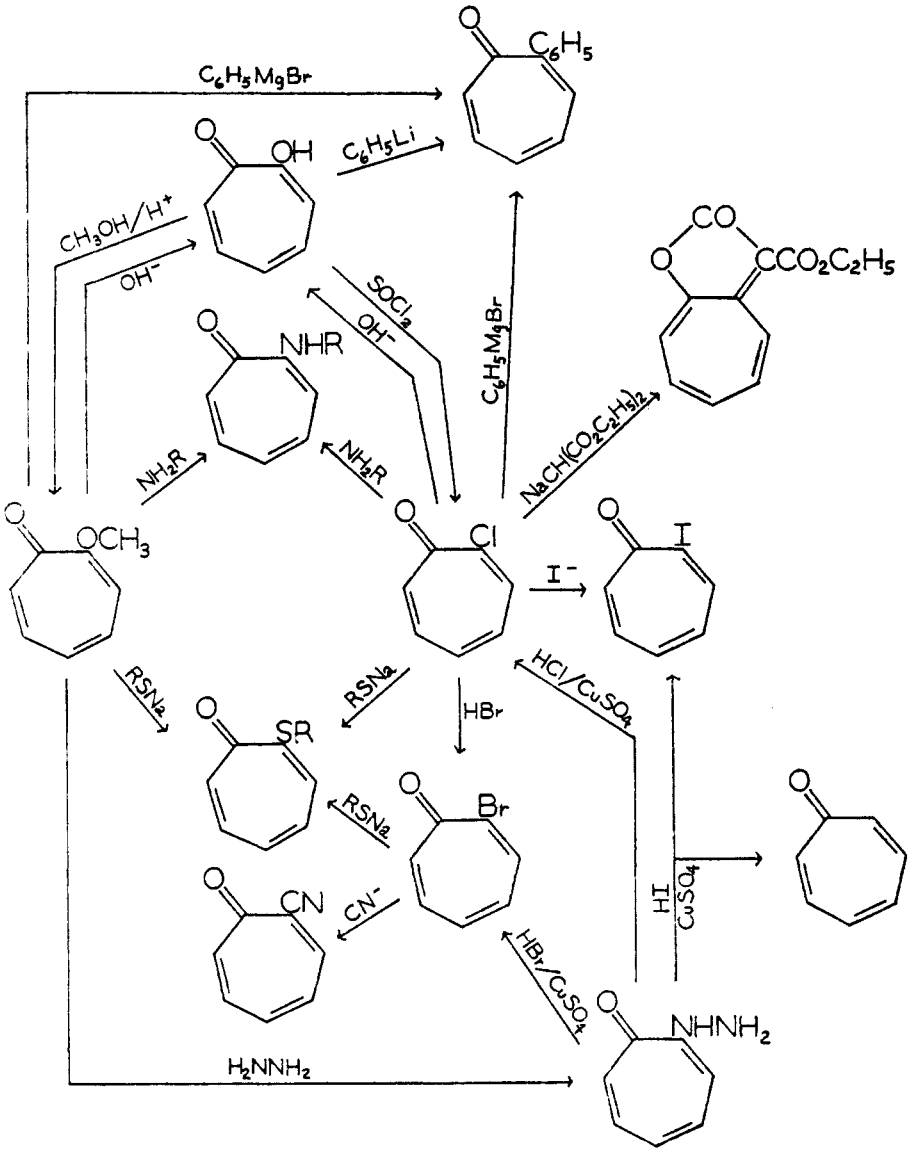
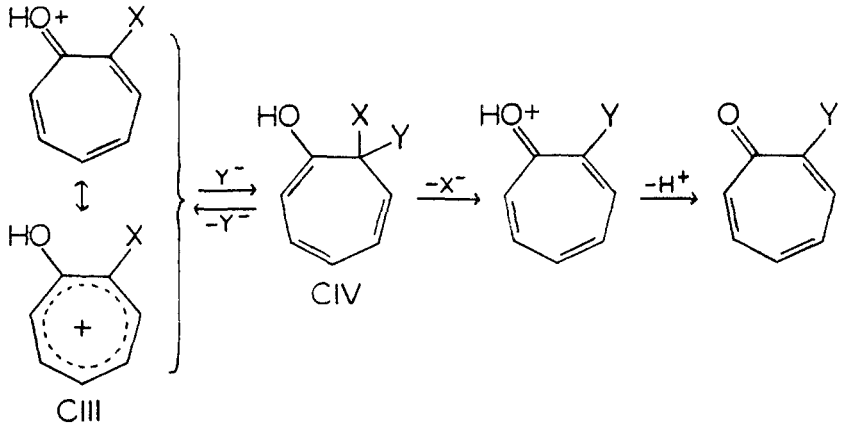


Chart II. Interconversion of 2-substituted tropones

Here the intermediate can take the stable resonance form (C) and the corresponding intermediates for the 3- and 4-positions are shown in CI and CII, respectively. On this view, the process is seen as a characteristic result of the nature of the tropone nucleus, particularly when written in the form shown in formula XCIXb. A number of illustrative examples of such reactions are collected in chart II.

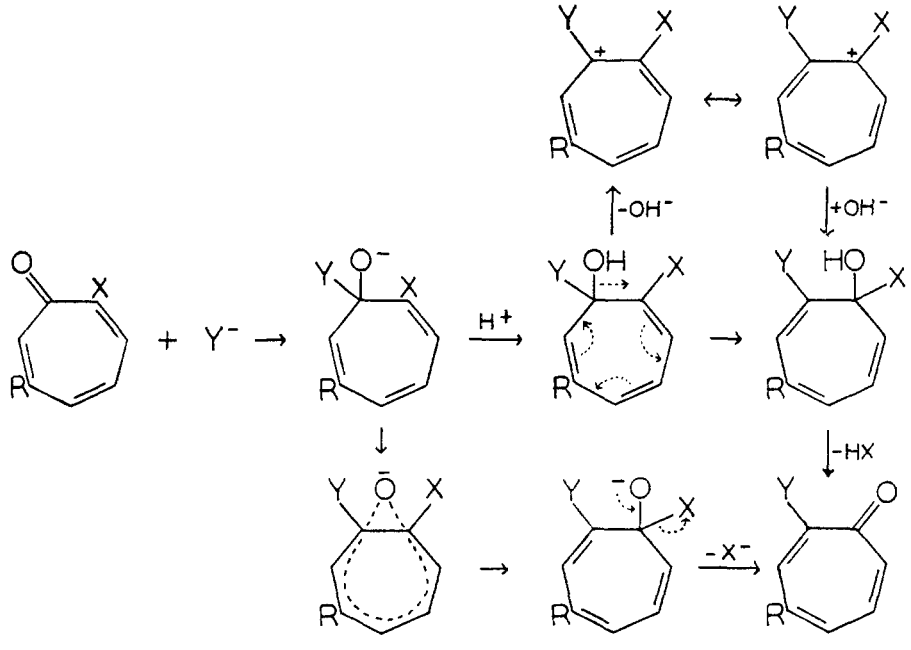
Those reactions taking place in acidic medium may be represented by the modified version of the above mechanism in which the starting material is the protonated tropone derivative, e.g., CIII:



Here the intermediate (CIV) is even more stable relative to the starting material.

In all cases where basic conditions are involved, the reactions compete to a greater or lesser extent with processes involving rearrangement to benzenoid compounds; these are described in the following section.

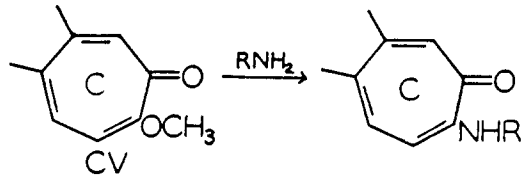
The simplest view of these two competitive processes is undoubtedly that simple substitution results from direct displacement as formulated above, whereas rearrangement results from nucleophilic attack at C_1 (i.e., the carbonyl group). It has been pointed out, however (e.g., 3) that attack at C_1 may alternatively lead to substitution (without rearrangement) as indicated, for example, by the following mechanism:



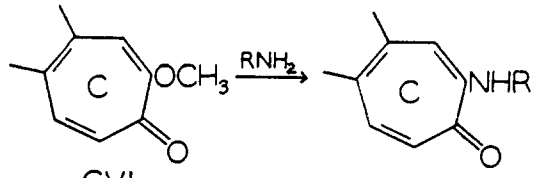
Mechanism 2

This mechanism is written for an unsymmetrical tropolone derivative to show that the final product which would result differs in that case from the product of direct displacement of the group X. In no case have two isomeric products of this type been observed, so that both mechanisms cannot be operative simultaneously.

Evidence in favor of the direct displacement mechanism has been available (148) from the reactions of colchicine and isocolchicine (partial formulas CV

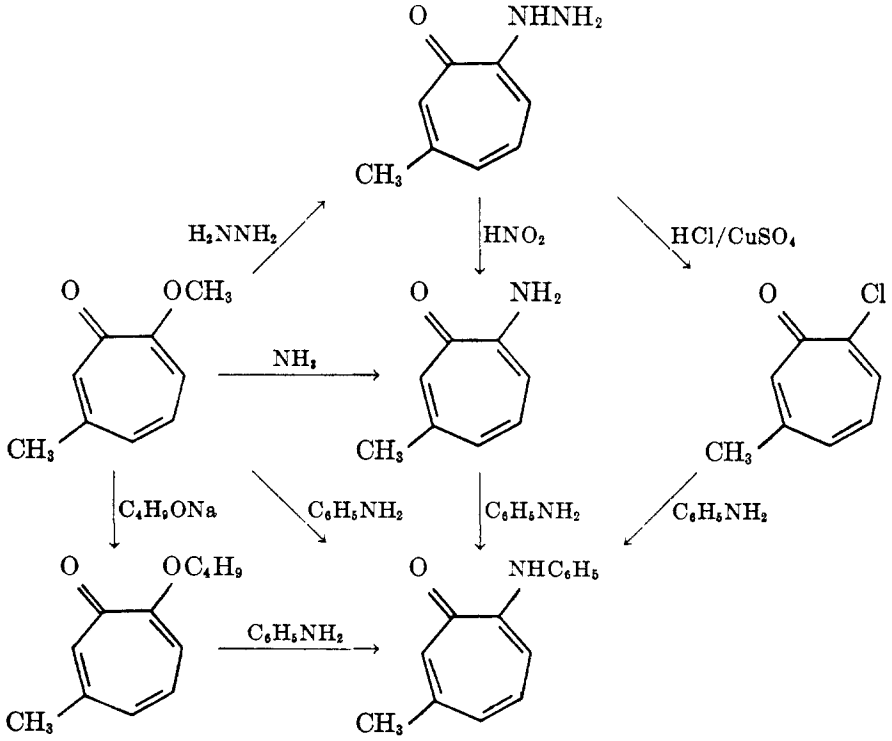


CV



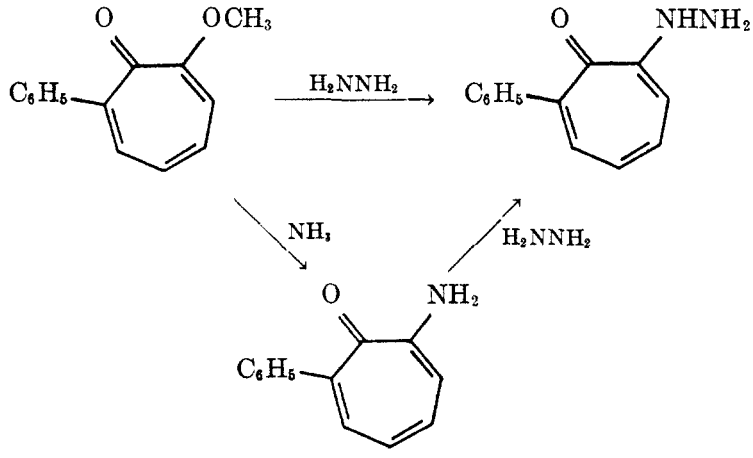
CVI

and CVI, respectively). The products from their reactions, e.g., with amines, fall into two groups; all those obtained from colchicine have, like the parent

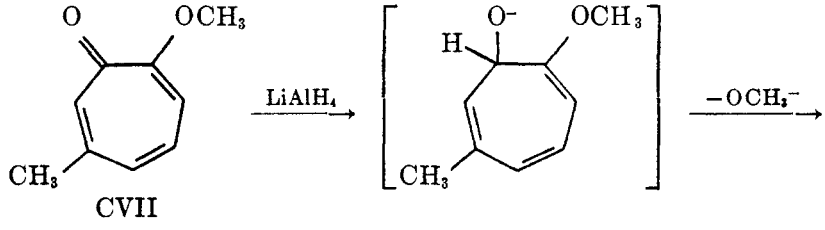


compound, lower negative specific rotation, slightly higher main maxima in the ultraviolet, and higher potency in biological tests than isocolchicine and its derivatives, a regularity suggestive of the configurational correspondence expected from the direct replacement mechanism. More rigorous proof has been obtained (3) by the demonstration that when the same compound can be obtained by one, two, or three successive replacements, the same product results in every case, as shown in the following reaction scheme. This result cannot be explained if the substituent (X or Y in mechanism 1) changes place with the carbonyl oxygen in any of the steps.

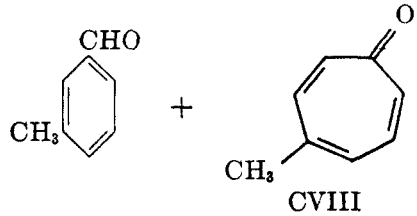
A second example illustrating the same point in the case of derivatives of 3-phenyltropone (298) is shown below:



At least one case is known, however, in which a mechanism of the second type must be followed. This involves the reduction of the 4-methyltropolone methyl ether (CVII) with lithium aluminum hydride to yield mainly *m*-tolualdehyde



CVII

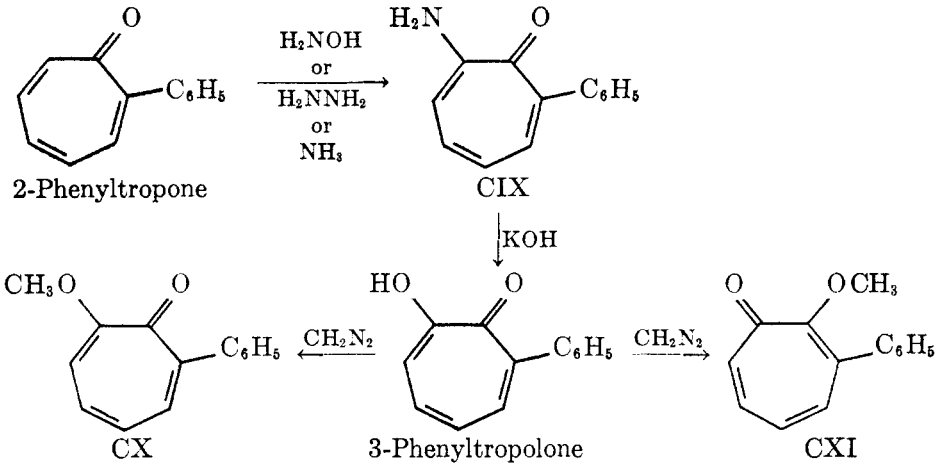


CVIII

m-Tolualdehyde 4-Methyltropone

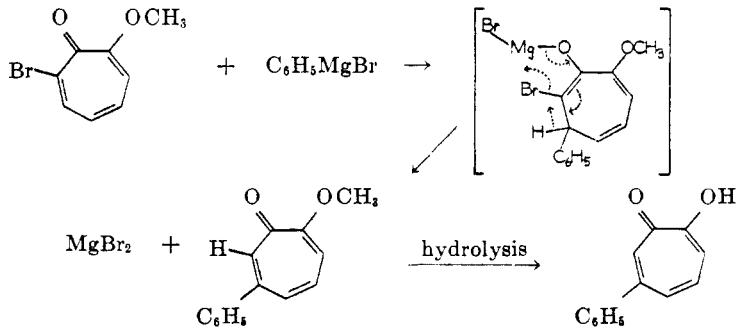
(by rearrangement) but also some 4-methyltropone (CVIII) (3). For simplicity this reaction may be regarded as replacement of methoxyl (X = OCH_3) by hydride ion (Y = H) occurring according to mechanism 2. It has been suggested (3) that Grignard reactions may, by analogy with this, take the same course. Whether they in fact do so, or follow the simpler direct replacement mechanism,[8] is still under investigation (138).

The absence of group migration in the substitutions with ammonia, hydrazine, etc. has been valuable in making possible the assignment of structure to pairs of methyl ethers obtained from unsymmetrical tropolones. The simplest cases arise when the structure of one product is known from an independent mode of preparation. 3-Phenyltropolone has been prepared (262, 298) from 2-phenyltropone by the sequence shown:



In this sequence, the structure of the intermediate 2-amino-7-phenyltropone (CIX) is unambiguous. As expected, 3-phenyltropolone gives two methyl ethers.

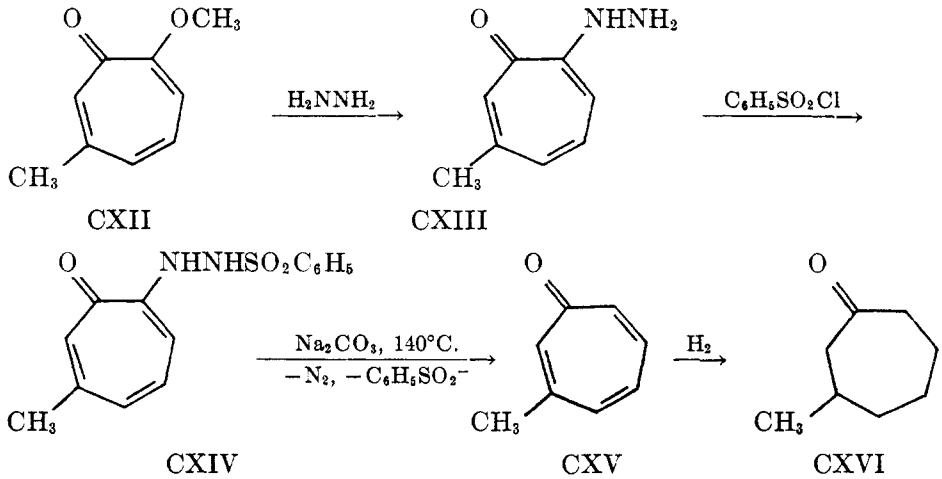
[8] The further possibility of attack by the Grignard reagent at C_3 must also be considered. This would represent 1,4-addition of the Grignard reagent to the unsaturated ketone system. The formation of "a phenyltropolone, m.p. 96–97°C." (299), almost certainly identical with 4-phenyltropolone, m.p. 97°C. (98), by the action of phenylmagnesium bromide on 3-bromo-7-methoxytropone may be a case in point. On this interpretation it may be formulated as follows:



One of these gives with ammonia the same aminotropone (CIX) and must therefore possess the corresponding structure (CX). The alternative structure (CXI) belongs to the second isomer; the latter as expected reacts with ammonia to give a new aminophenyltropone, undoubtedly 2-amino-3-phenyltropone (298).

When such a simple comparison substance is unavailable, two methods have been found useful. Both of these involve initial conversion of the ether to the hydrazinotropone and are thus dependent on the above proof that no change in position of the substituent is involved in this step.

The first is illustrated for the case of one of the ethers of 4-methyltropolone for which it was first used (2):

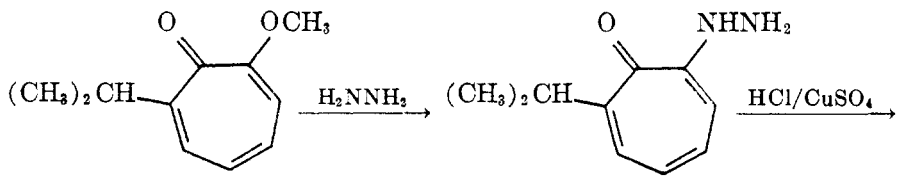


CXII CXIII CXIV CXV CXVI

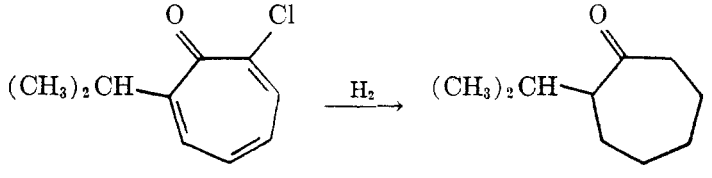
It consists in converting the ether (CXII) *via* the hydrazino derivative (CXIII) to the benzenesulfonylhydrazino derivative (CXIV). This, analogously to the sulfonylhydrazides of carboxylic acids, loses nitrogen and the elements of benzenesulfinic acid and yields the tropone (CXV). (The analogous reaction of the carboxylic acid analog is the McFadyen–Stevens aldehyde synthesis.)

The tropone (CXV) is then identified by reduction to the corresponding cycloheptanone (CXVI). In the above case one ether yields 3-methylcycloheptanone. It must therefore be 2-methoxy-6-methyltropone; in agreement with this, the isomeric ether (2-methoxy-4-methyltropone) gives rise to 4-methylcycloheptanone.

The second method is illustrated for 7-isopropyl-2-methoxytropone (CXVII), one of the two isomeric ethers derived from α-thujaplicin. In this case, the hydrazino derivative (CXVIII) is converted to the corresponding chlorotropone (CXIX) by treatment with cupric sulfate and hydrochloric acid. The chlorotropone is then reduced directly to the cycloheptanone derivative (CXX) (410). It has been demonstrated that the two methods agree and yield the same cycloheptanones (409, 410).



CXVII CXVIII



CXIX CXX

When two different functional groups are available for nucleophilic substitution in a tropone derivative both may be replaced; if only one is attacked, the nature of the group replaced may depend on the nature of the attacking agent. This is exemplified in chart IIIA by the reactions of 3-bromo-7-methoxytropone (CXXI). It is seen that although replacement of halogen by hydroxyl ions can occur, both this reagent and ammonia or its derivatives replace alkoxyl groups in preference to halogen. The same preference is shown in the corresponding rearrangement reactions caused by these reagents (*cf.* table 7). The opposite is true of mercaptide ions, which replace either exclusively the halide or, when excess reagent is used, both groups. Similar dependence on the nature of the attacking group has been noted in aromatic nucleophilic substitution reactions (for a summary see reference 45, pp. 335–8). These generalizations apply equally when the relationship of the alkoxyl group and halogen atom to each other is changed. This is illustrated in chart IIIB, where the corresponding reactions of the isomeric ether of 3-bromotropolone (3-bromo-2-methoxytropone) (CXXII) are summarized. The only significant differences arise from the greater tendency of this substance to undergo rearrangement. The 2,3-dihalotropones which may be derived from this compound *via* the corresponding hydrazino derivative also provide the information that halogen in the 3-position of tropone may be replaced with at least the same ease as in the 2-position (413).

A remarkable specificity has been observed in the reaction of 2,4,7-tribromotropone (CXXIII) with aniline (272; *cf.* 287), 2-anilino-4,7-dibromotropone (CXXIV) being isolated in 80 per cent yield. Thus the 2-position appears to be attacked to the virtual exclusion of the almost equivalent 7-position!

The possibility of nucleophilic replacements at the 4-position is evident from examination of the behavior of CXXIII with *p*-tolylmercaptide ion. When excess of the reagent is used, all bromine atoms are replaced, yielding 2,4,7-tri(*p*-tolylmercapto)tropone (CXXIV: R = *p*-$CH_3C_6H_4S$—). However, smaller

amounts of reagent lead smoothly to the 4-bromo-2,7-di(*p*-tolylmercapto)-tropone (CXXV: R = Br) (or the corresponding methylthio derivative with sodium methylmercaptide) (317). The 4-position is thus markedly less reactive than the 2-position; that this difference applies under acidic conditions is revealed by the smooth hydrolysis of 2,4,7-tribromotropone (CXXIII) to a mixture of 3,5- and 3,6-dibromotropolones (see page 35).

A similar difference in the reactivity of the corresponding 3- and 5-positions in tropolone is indicated by examination of the behavior of 3,5,7-tribromotropolone (CXXVI). This reacts rapidly with the sodium salt of thiocresol in boil-

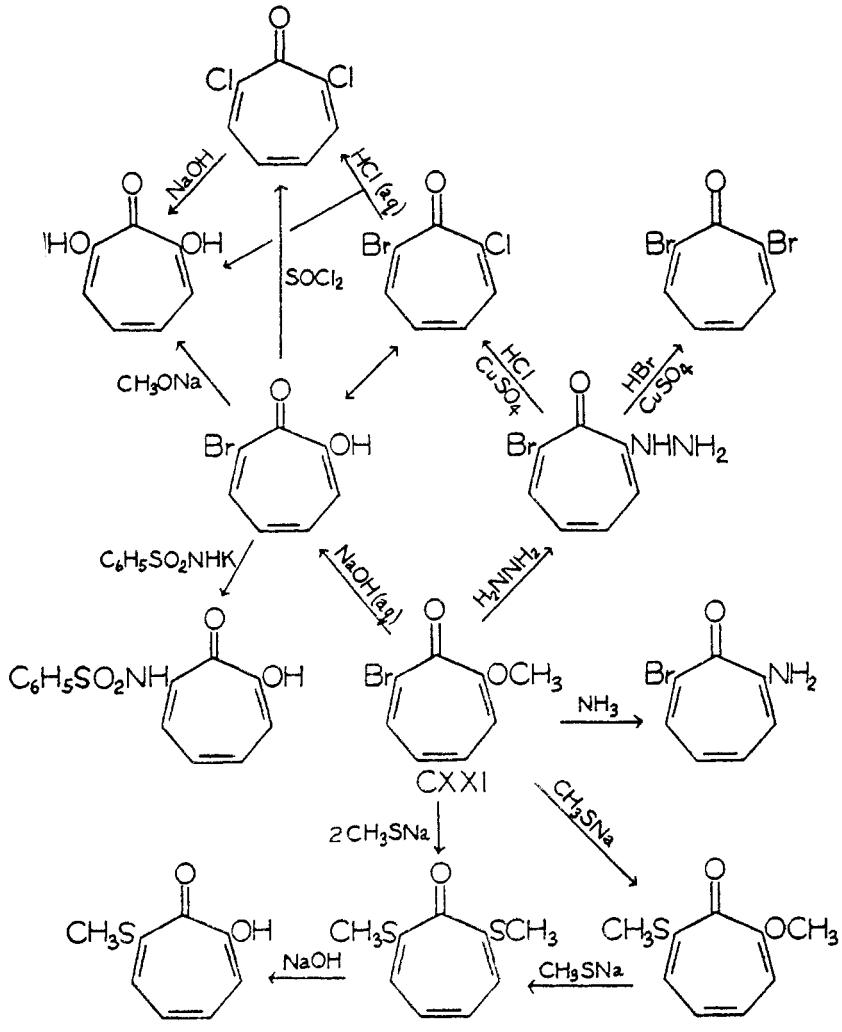


Chart IIIA. Reactions of 2-bromo-7-methoxytropone

ing alcohol, yielding the 3-monosubstitution (CXXVII) and 3,7-disubstitution (CXXVIII) products (72, 315). However, the third bromine is replaced only at a much higher temperature (72). The reported isolation (315) of 3-bromo-5,7-di(*p*-tolylmercapto)tropolone in one experiment in place of CXXVIII is in-

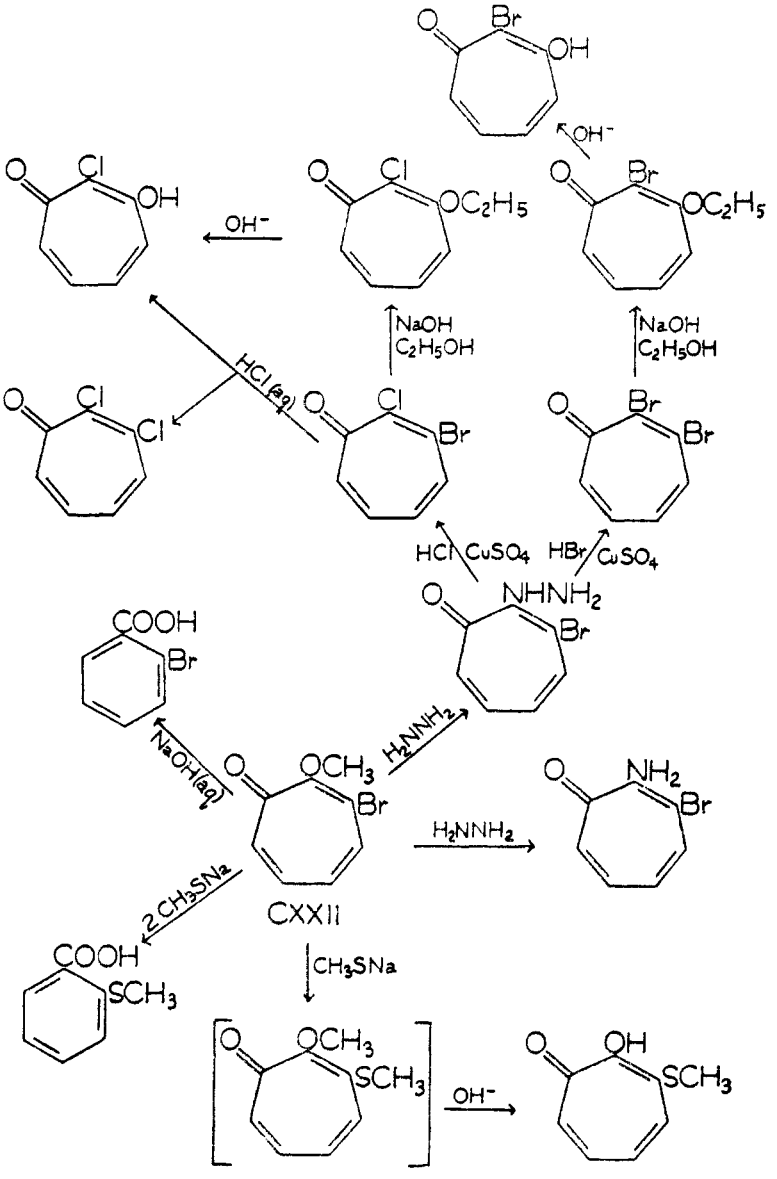
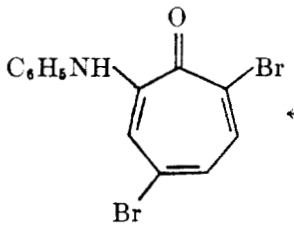


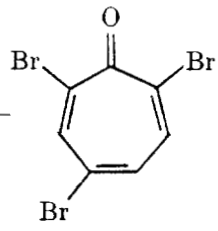
Chart IIIB. Reactions of 3-bromo-2-methoxytropone



CXXIV

2-Anilino-4,7-dibromotropone

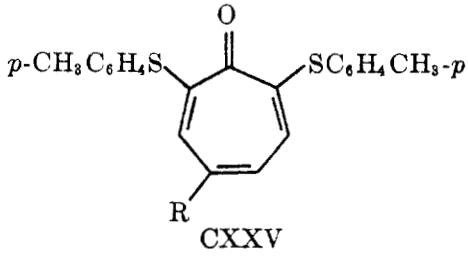
$C_6H_5NH_2$



CXXIII

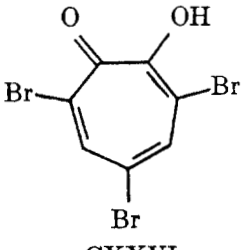
2,4,7-Tribromotropone

p-$CH_3C_6H_4SNa$



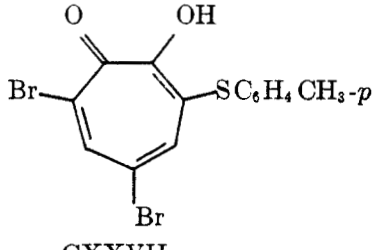
CXXV

teresting in this connection, but confirmation of its structure is lacking and reproducible conditions for its production have not been described.

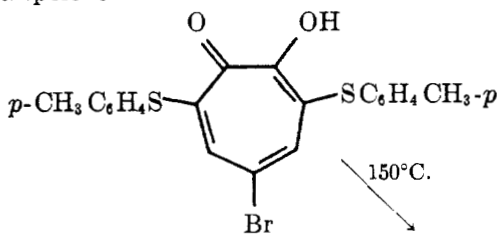


CXXVI

3,5,7-Tribromotropolone

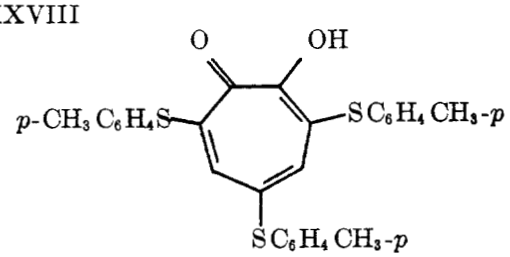


CXXVII



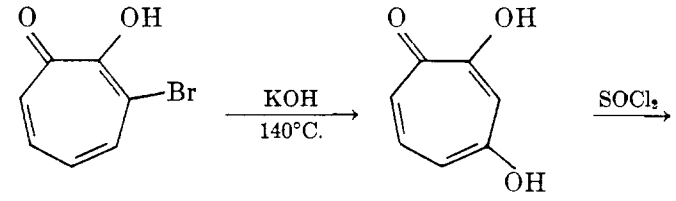
CXXVIII

150°C.



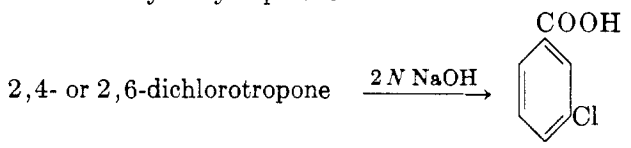
The existence of tropolone as an anion in basic medium makes nucleophilic substitution under these conditions much more difficult than in the corresponding tropone derivatives. Except with the powerfully nucleophilic mercaptides, rather vigorous conditions become necessary. The direct replacement of halogen by unsubstituted amide ion has not been reported, but the potassium salt of benzenesulfonamide reacts in pyridine solution at 135–140°C., converting 3-bromotropolone (as its cupric complex) to the 3-benzenesulfonamidotropolone (see chart IIIA), which is smoothly hydrolyzed to 3-aminotropolone by strong acid.

Simple replacement of the bromine in 3-bromotropolone (CXXIX) by hydroxyl has been effected (266) by treatment with methanolic sodium methoxide at 140–150°C., but its reaction with potassium hydroxide (at 130–140°C.) has been shown (266) to proceed in an unexpected fashion, yielding not 3- but 4-hydroxytropolone (CXXX):



CXXIX — 3-Bromotropolone

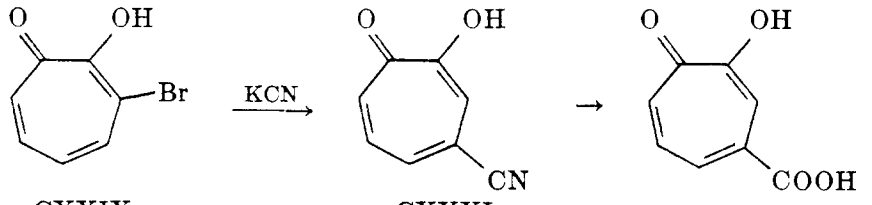
CXXX — 4-Hydroxytropolone



m-Chlorobenzoic acid

Its structure follows from conversion to *m*-chlorobenzoic acid as shown. The reaction is reminiscent of what has been termed "cine-substitution" and observed in a number of aromatic nucleophilic substitution reactions (45, pp. 382–8). The mechanism of such replacements in benzene derivatives has been discussed (365), but in the present case other possibilities exist and further experimental evidence must be awaited.

The reaction of 3-bromotropolone with potassium cyanide takes a parallel course, yielding the nitrile (CXXXI), although with cuprous cyanide (1, 286) simple substitution takes place. Both isomers are identified after hydrolysis to the carboxylic acids, by comparison with products of established structure (266).



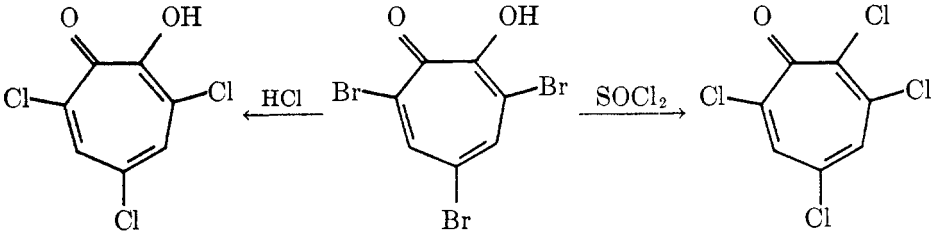
CXXIX — 3-Bromotropolone

CXXXI — 4-Cyanotropolone

Tropolone-4-carboxylic acid

The reaction of bromostipitatic acid with potassium hydroxide at 200°C. to yield puberulic acid (see page 27) represents an example of the reaction where the substituent does not change position, but in this case the adjacent positions are blocked.

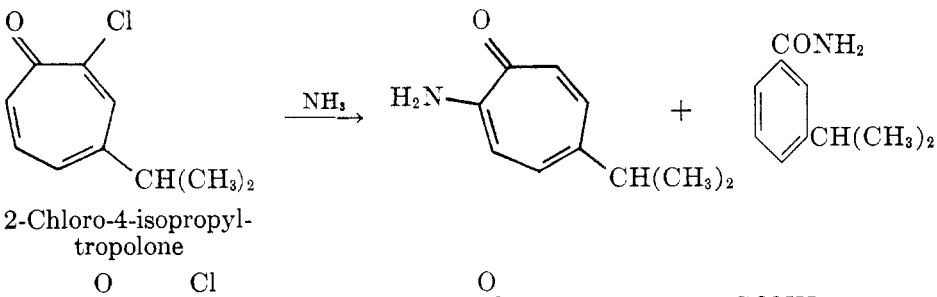
Under acidic conditions tropolone exists as the conjugate acid and nucleophilic substitution is thereby greatly facilitated. This is reflected in the complete replacement of bromine by chlorine when 3,5,7-tribromotropolone is heated with hydrochloric acid at 150°C. (97). Replacement may also be caused by thionyl chloride, but in this case it is accompanied and possibly preceded by replacement of the hydroxyl group:



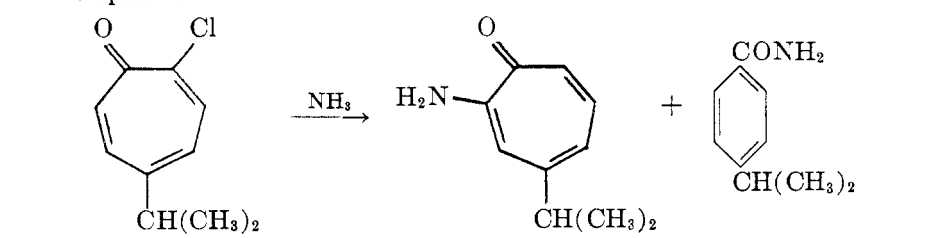
3,5,7-Trichlorotropolone — 3,5,7-Tribromotropolone — 2,3,5,7-Tetrachlorotropone

Direct replacement of the hydroxyl group by amino becomes possible in nitro- and nitrosotropolones (312, 344, 345, 346). The latter have also been shown to react similarly with phenylhydrazine, semicarbazide, and hydroxylamine (312) and thus appear to constitute an exception to the rule that tropolones fail to react with ketonic reagents (*cf.*, however, page 101).

A most remarkable change in the position of the substituent has been observed in the ammonolysis of 2-chloro-4-isopropyltropolone and 2-chloro-5-isopropyltropolone as shown:



2-Chloro-4-isopropyltropolone

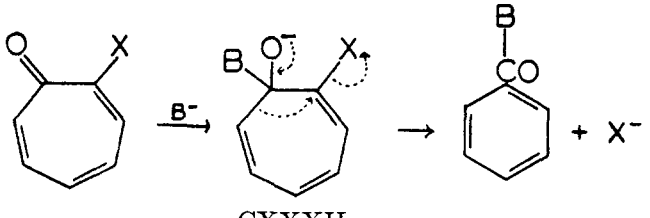


2-Chloro-5-isopropyltropolone

This reaction occurs with methanolic ammonia at room temperature under conditions under which unsubstituted 2-chlorotropone remains unattacked. It is accompanied by extensive aromatization, which becomes the exclusive reaction in the case of 2-chloro-6-isopropyltropone (342).

VI. Rearrangement Reactions of Tropones and Tropolones (See Table 7)

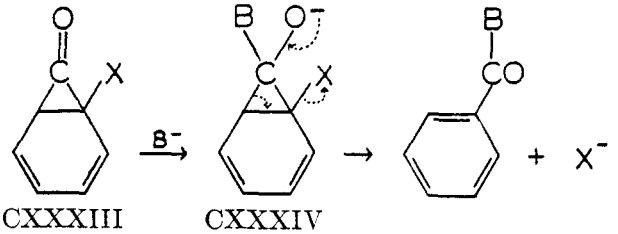
This section deals with all reactions in which tropolones and tropones undergo ring contraction to benzene derivatives. The importance of this type of reaction as a means of determining the detailed structure of tropolone derivatives has been referred to (page 45). Many of the reactions here discussed occur simultaneously with the nucleophilic displacements at the 2-position discussed in the preceding section. The proportions of the two reactions may in such cases vary considerably with relatively small changes in reaction conditions, and may depend on the presence of substituents not directly involved in the change. It has been pointed out (page 65) in this connection that the substitutions (without rearrangement) can be shown to occur in most cases by direct attack of the base at the carbon carrying the group which is being displaced. It was also stated that the simplest view, to account for the competing rearrangement reactions, assumes that rearrangement involves attack at the carbonyl carbon. This may be represented in the general case by the simple expression:



CXXXII

Mechanism I

Another way in which this may be represented is shown below:



CXXXIII CXXXIV

Although it may now be regarded as established that tropolones and tropones do not normally exist in the norcaradienone form (CXXXIII), the possibility that bicyclic intermediates of the type of CXXXIV (*cf.* 96) may be important in rearrangement reactions cannot be neglected. In the absence of direct evidence and to avoid unnecessary complication, this point is not further considered in

TABLE 7

Rearrangement reactions of tropones and tropolones

Compound	Reagent and Conditions	Product	Yield	References
A. Rearrangements of tropolones with caustic alkalis				
			per cent	
Tropolone	KOH; 230–235°C.	Benzoic acid	7	(96)
4-Methyltropolone	KOH; 300°C.	*m*-Toluic acid		(131)
5-Isopropyltropolone	KOH; 230°C.	*p*-Isopropylbenzoic acid	10	(109)
Colchiceine	CH_3ONa	Allocolchiceine		(377)
4-Methyltropolone-3-carboxylic acid	KOH; 320–340°C.	3-Methylphthalic acid	40	(85)
3-Methoxytropolone-5-carboxylic acid	KOH; 240°C.; 15 min.	5-Hydroxyisophthalic acid	30	(160)
Stipitatic acid	KOH; 300°C.; 10 min.	5-Hydroxyisophthalic acid	35	(34)
Stipitatic acid methyl ether	KOH; 300–320°C., 15 min.	5-Hydroxyisophthalic acid	100	(34)
Tropolone-3,4-dicarboxylic anhydride	NaOH; 170–180°C.; 3 min.	Hemimellitic acid		(85)
Tropolone-5-sulfonic acid	KOH; 180°C.	*p*-Hydroxybenzoic acid		(328)
4-Methyl-3-nitrotropolone	30% NaOH‡; 10 min.	2-Nitro-*m*-toluic acid	70	(134)
4-Methyl-5-nitrotropolone	2 *N* NaOH‡; 1 hr.	4-Nitro-*m*-toluic acid	25	(133, 134)
5-Methyl-3-nitrotropolone	2 *N* NaOH‡; a few minutes	2-Nitro-*p*-toluic acid		(293)
6-Methyl-3-nitrotropolone	2 *N* NaOH‡; 30 min.	6-Nitro-*m*-toluic acid	20	(134)
4-Isopropyl-3-nitrotropolone	KOH; 160°C.	3-Isopropyl-2-nitrobenzoic acid		(274, 284)
4-Isopropyl-5-nitrotropolone	KOH; 160°C.	3-Isopropyl-4-nitrobenzoic acid		(274, 284)
3,5-Dinitro-6-isopropylbenzoic acid	Recrystallize from C_2H_5OH	2,4-Dinitro-5-isopropylbenzoic acid		(289)
3-Bromo-5,7-dinitrotropolone	5 *N* KOH; 100°C.; 5 min.	(?) 2-Bromo-4,6-dinitrobenzoic acid		(283)
3,4-Benzotropolone	KOH; 180–185°C.	1-Naphthoic acid	Good	(66)
Purpurogallin	KOH; 170°C.	6,7,8-Trihydroxy-1-naphthoic acid		(136, 353, 355)
Purpurogallin trimethyl ether	KOH; 160–170°C.	6,7-Dimethoxy-8-hydroxy-1-naphthoic acid (lactone)		(136, 353)
3-Nitro-4,5-benzotropolone	10% NaOH; 21°C.	1-Nitro-2-naphthoic acid		(116, 423)
B. Rearrangements of 2-halotropones with alkali				
2-Chlorotropone	H_2O‡	Benzoic acid		(1)
	3% NaOH; 50–60°C.; 30 min.	Benzoic acid		(1)
	3 *N* NaOH; 100°C.; 3 hr.	Benzoic acid	70	(97)
2-Bromotropone	1 *N* NaOH; 100°C.; 1 hr.	Benzoic acid	42	(94)
2-Iodotropone	1 *N* NaOH; 100°C.; 1 hr.	Benzoic acid	52	(94)
2,4(or 2,6)-Dichlorotropone	2 *N* NaOH	*m*-Chlorobenzoic acid		(266)
2,7-Dichlorotropone	3% NaOH; 60°C.; 1 hr.	*o*-Chlorobenzoic acid	20	(1, 413)

2,7-Dibromotropone	NaOH or KOH/C_2H_5OH	*o*-Bromobenzoic acid	35	(311, 413)
		3-Bromosalicylaldehyde	5	(413)
2,3-Dibromotropone	NaOH/C_2H_5OH	*o*-Bromobenzoic acid	20	(413)
		Ethyl *o*-bromobenzoate	15	
2,5-Dibromotropone	NaOH	*p*-Bromobenzoic acid		(291)
2-Bromo-7-chlorotropone	NaOH/C_2H_5OH; room temperature	*o*-Chlorobenzoic acid	40	(338, 413)
		3-Chlorosalicylaldehyde	15	
3-Bromo-2-chlorotropone	NaOH/C_2H_5OH	*o*-Bromobenzoic acid	35	(413)
		Ethyl *o*-bromobenzoate	10	
2,4,7-Tribromotropone	KOH/CH_3OH or CH_3ONa/CH_3OH	2,4-Dibromobenzoic acid		(271)
		2,5-Dibromobenzoic acid		
2,3,5,7-Tetrachlorotropone	NaOH/C_2H_5OH	2,3,5-Trichlorobenzoic acid	53	(97)
2-Chloro-5-isopropyltropone	10% KOH/C_2H_5OH	*p*-Isopropylbenzoic acid	17	(98)
2-Chloro-4(and/or 6)-isopropyltropone	10% KOH/C_2H_5OH	*m*-Isopropylbenzoic acid	38	(98)
2-Chloro-5-phenyltropone	10% KOH/C_2H_5OH	Biphenyl-4-carboxylic acid		(98)
2-Chloro-4(and/or 6)-phenyltropone	10% KOH/C_2H_5OH	Biphenyl-3-carboxylic acid		(98)
2-Bromo-7-phenyltropone	10% KOH/C_2H_5OH	Biphenyl-2-carboxylic acid	30	(99)
2,4-Dibromo-7-phenyltropone	KOH/C_2H_5OH‡	4-Bromobiphenyl-2-carboxylic acid		(297)
3,7-Dibromo-2-phenyltropone	KOH/C_2H_5OH‡	6-Bromobiphenyl-2-carboxylic acid		(299)
2-Chloro-3-methoxytropone	CH_3ONa/CH_3OH‡; 30 min.	*o*-Anisic acid		(413)
2,4,7-Tribromo-5-methoxytropone	CH_3ONa/CH_3OH	4,6-Dibromo-*m*-anisic acid		(267)
2-Bromo-3-methoxytropone-5-carboxylic acid	KOH; 140°C.; 170°C., 5 min.; 200°C., 10 min.	5-Hydroxyisophthalic acid		(160)

C. Rearrangements of methyl ethers of tropolones with alkali

2-Methoxytropone	CH_3ONa/CH_3OH	Methyl benzoate	46	(96)
2-Methoxy-6-methyltropone	CH_3ONa/CH_3OH; then NaOH	*m*-Toluic acid	Poor	(3)
2-Methoxy-5-cyclohexyltropone	CH_3ONa/CH_3OH; then NaOH	*p*-Cyclohexyll enzoic acid		(98)
4-Cyclohexyltropolone methyl ether	CH_3ONa/CH_3OH; then NaOH	*m*-Cyclohexyl enzoic acid		(98)
4,5-Tetramethylenetropolone methyl ether	CH_3ONa/CH_3OH; then NaOH	5,6,7,8-Tetrahydro-2-naphthoic acid		(98)
3-Benzyltropolone methyl ether	CH_3ONa/CH_3OH; then NaOH	2-Benzylbenzoic acid		(300)
3,5-Dimethyltropolone methyl ether	CH_3ONa/CH_3OH; then NaOH	2,4-Dimethylbenzoic acid		(307)
3,6-Dimethyltropolone methyl ether	CH_3ONa/CH_3OH; then NaOH	2,5-Dimethylbenzoic acid		(307)
3-Methyl-6-isopropyltropolone methyl ether	CH_3ONa/CH_3OH; then NaOH	5-Isopropyl-2-methylbenzoic acid		(307)
2-Methoxy-3,5,7-trimethyltropone	CH_3ONa/C_4H_9OH‡; 15 hr.	2,4,6-Trimethylbenzoic acid		(307)
3-Chlorotropolone methyl ether	CH_3ONa/CH_3OH; then NaOH	*o*-Chlorobenzoic acid		(333)
2-Bromo-7-methoxytropone	CH_3ONa/CH_3OH‡; 15 hr.	Methyl *o*-bromobenzoate	22	(285)
3-Bromo-2-methoxytropone	CH_3ONa/CH_3OH‡; 10 hr.	Methyl *o*-bromobenzoate	60	(285)
	NaOH/CH_3OH; 0°C.; 1 hr.	Methyl *o*-bromobenzoate	60	(285)
	2 *N* NaOH; 15 min.	*o*-Bromobenzoic acid	50	(285)
	CH_3SNa	2-Methylthiobenzoic acid		(315, 317)
5-Bromo-2-methoxytropone	CH_3ONa/CH_3OH; then NaOH	*p*-Bromobenzoic acid	35	(63, 285)

‡ Reflux.

TABLE 7—*Concluded*

Compound	Reagent and Conditions	Product	Yield	References
C. Rearrangements of methyl ethers of tropolones with alkali				
			per cent	
3,6-Dibromo-2-methoxytropone	CH_3ONa/CH_3OH; room temperature	Methyl 2,5-dibromobenzoate	30	(287)
3,7-Dibromo-2-methoxytropone	CH_3ONa/CH_3OH‡; 5 hr.	Methyl 2,6-dibromobenzoate	65	(63, 285)
		3-Bromo-*o*-anisic acid		
	NaOH/CH_3OH; 0°C.; 3 hr.	Methyl 2,6-dibromobenzoate	80	(285)
		2,6-Dibromobenzoic acid	5	
		3-Bromo-*o*-anisic acid	5	
	2 *N* NaOH; 100°C.	Methyl 2,6-dibromobenzoate	18	(285)
		3-Bromo-*o*-anisic acid	20	
4,7-Dibromo-2-methoxytropone	CH_3ONa/CH_3OH; 100°C.; 5 hr.	Methyl 2,5-dibromobenzoate	80	(287)
2-Methoxy-3,5,7-tribromotropone	CH_3ONa/CH_3OH‡; 3 hr.	Methyl 2,4,6-tribromobenzoate	55	(63, 97, 285)
			74	
		3,5-Dibromo-*o*-anisic acid	10	
			20	
	NaOH/CH_3OH; 0°C.	Methyl 2,4,6-tribromobenzoate	82	(285)
		2,4,6-Tribromobenzoic acid	3	
		3,5-Dibromo-*o*-anisic acid	9	
	2 *N* NaOH; 100°C., 20 min.	Methyl 2,4,6-tribromobenzoate	6	(285)
		2,4,6-Tribromobenzoic acid	7	
		3,5-Dibromo-*o*-anisic acid	35	
2-Methoxy-3,5,7-trichlorotropone	CH_3ONa/CH_3OH	Methyl 2,4,6-trichlorobenzoate	79	(97)
		3,5-Dichloro-*o*-anisic acid	19	
4-Bromo-7-methoxy-2-phenyltropone	CH_3ONa/CH_3OH; then NaOH	5-Bromobiphenyl-2-carboxylic acid		(262)
3-Nitrotropolone methyl ether	CH_3ONa/CH_3OH; then NaOH	*o*-Nitrobenzoic acid		(70, 72)
2-Methoxy-5-nitrotropone	CH_3ONa/CH_3OH; then NaOH	*p*-Nitrobenzoic acid	40	(70, 72, 269)
3-Isopropyl-5-nitrotropolone methyl ether	CH_3ONa/CH_3OH; then NaOH	2-Isopropyl-5-nitrobenzoic acid		(461)
3-Isopropyl-5,7-dinitrotropolone methyl ether	CH_3ONa/CH_3OH; then NaOH	2-Isopropyl-4,6-dinitrobenzoic acid (?)		(461)
3-Bromo-5-nitrotropolone methyl ether	CH_3ONa/CH_3OH; then NaOH	2-Bromo-4-nitrobenzoic acid		(72)
3-Phenylthiotropolone methyl ether	CH_3ONa/CH_3OH; then NaOH	2-Phenylthiobenzoic acid		(315, 317)
3,7-Di-*p*-tolylthio-2-methoxytropone	KOH/C_2H_5OH	2,6-Di-*p*-tolylthiobenzoic acid		(315, 317)
3-Carbomethoxy-4-styryltropolone methyl ether	CH_3ONa/CH_3OH; then NaOH	3-Styrylphthalic acid		(281)
Nootkatin methyl ether	CH_3ONa/CH_3OH; then NaOH	3-Isopropyl-4-(3-methyl-2-butenyl)benzoic acid		(101, 111)
		3-Isopropyl-4-(3-methyl-1-butenyl)benzoic acid		
Colchicine	CH_3ONa/CH_3OH	Allocolchicine		(115, 148)
	C_2H_5ONa	Allocolchiceine ethyl ester		(115)
	C_3H_7ONa	Allocolchiceine propyl ester		(115)
D. Rearrangements of 2-methoxy- or 2-halotropones with ammonia				
2-Chloro-6-isopropyltropone	NH_3/C_2H_5OH; cold	*m*-Isopropylbenzamide		(409)
2,4,7-Tribromotropone	NH_3/CH_3OH or NH_3 (liquid)	2,4-Dibromobenzamide		(100, 270, 271, 279, 287)
		2,5-Dibromobenzamide		

3,7-Dibromo-2-methoxytropone	NH_3 (liquid)	2,6-Dibromobenzamide		(345, 346)
2-Methoxy-3,5,7-tribromotropone	NH_3 (liquid)	2,4,6-Tribromobenzamide 3,5-Dibromo-2-methoxybenzamide 2-Amino-3,5-dibromobenzamide (?)		(345, 346)
	NH_3 (gas)	3,5-Dibromo-2-methoxybenzamide	21	(346)
2-Amino-5,7-dinitro-4-isopropyltropone	Heat in C_2H_5OH	2,4-Dinitro-5-isopropylbenzamide		(344)

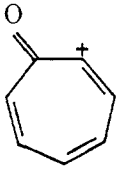
E. Miscellaneous other rearrangements

2,7-Dimethylthiotropone	$NaOH/C_2H_5OH$	2-Methylthiobenzoic acid		(314, 317)
2-Methylthiotropone	CH_3ONa	2-Methylthiobenzoic acid		(317)
2-Phenyltropone	KOH/C_2H_5OH‡; 10 min.	Biphenyl-2-carboxylic acid	10	(298)
2-*p*-Methoxyphenyltropone	$NaOH/C_2H_5OH$‡	4′-Methoxybiphenyl-2-carboxylic acid		(330)
Tropone-4-carboxylic acid	KOH	Terephthalic acid	20	(20)
Tropolone	$SOCl_2$	2-Chlorobenzaldehyde		(1)
	NaOBr	2,4,6-Tribromophenol		(96, 116)
	NaOI	2,4,6-Triiodophenol	20	(96)
Tropolone or 3-bromotropolone	(1) Br_2/CH_3COOH; (2) KOH/CH_3OH	3,5-Dibromosalicylic acid		(116)
Sodium tropolonate	I_2/CH_3OH	2,4-Diiodobenzoic acid	Low	(190)
3-Iodotropolone	I_2/CH_3OH	2,4-Diiodobenzoic acid 2,4,6-Triiodobenzoic acid	15 25	(190)
Colchiceine	NaOBr	Tribromo-*N*-acetylcolchinol		(216)
	NaOI	*N*-Acetyliodocolchinol		(458)
4-Methyltropolone	HNO_2	4-Methylsalicylic acid		(236)
4-Isopropyltropolone	HNO_2	4-Isopropylsalicylic acid		(337)
2-Amino-4-methyltropone	HNO_2	6-Methylsalicylaldehyde		(3)
2-Amino-6-methyltropone	HNO_2	4-Methylsalicylaldehyde		(3)
3-Aminotropolone	HNO_2	Salicylic acid		(72)
3-Amino-4-methyltropolone	HNO_2	6-Methylsalicylic acid	80	(134)
3-Amino-6-methyltropolone	HNO_2	4-Methylsalicylic acid	80	(134)
3-Amino-4-isopropyltropolone	HNO_2	6-Isopropylsalicylic acid		(275, 276, 277)
3-Amino-6-isopropyltropolone	HNO_2	4-Isopropylsalicylic acid		(275, 276, 277, 279)
3-Amino-6-isopropyl-5-nitrotropolone	HNO_2	4-Isopropyl-5-nitrosalicylic acid		(256)
(?)-Aminocolchiccine	HNO_2	Corresponding salicylic acid derivative		(241)
2,3,5,7-Tetrachlorotropone	*p*-$CH_3C_6H_4SNa$	2,4,6-Trichlorobenzoic acid		(72)
2-Benzenesulfonylhydrazino-7-bromo-4-isopropyltropone	Na_2CO_3/glycol; 140°C.	*p*-Isopropylbenzoic acid		(411)
2-Methoxytropone	C_6H_5MgBr	Triphenylcarbinol		(295, 298, 299)
7-Bromo-2-methoxytropone	C_6H_5MgBr	*o*-Methoxyphenyldiphenylcarbinol		(299)
3,7-Dibromo-2-methoxytropone	C_6H_5MgBr	(?)-Bromobiphenylyldiphenylcarbinol		(299)
2-Methoxy-4-methyltropone	C_6H_5MgBr	*m*-Tolyldiphenylcarbinol		(3)
2-Methoxy-6-methyltropone	C_6H_5MgBr or C_6H_5Li	*m*-Tolyldiphenylcarbinol		(3)
2-Methoxy-4-methyltropone	$LiAlH_4$	*m*-Tolualdehyde		(3)
2-Methoxy-6-methyltropone	$LiAlH_4$	*m*-Tolualdehyde		(3)
2-Methoxytropone	$LiAlH_4$	Benzaldehyde		(74)

the following discussion. It may indeed be held that the above two schemes are only extreme forms of the same mechanism.

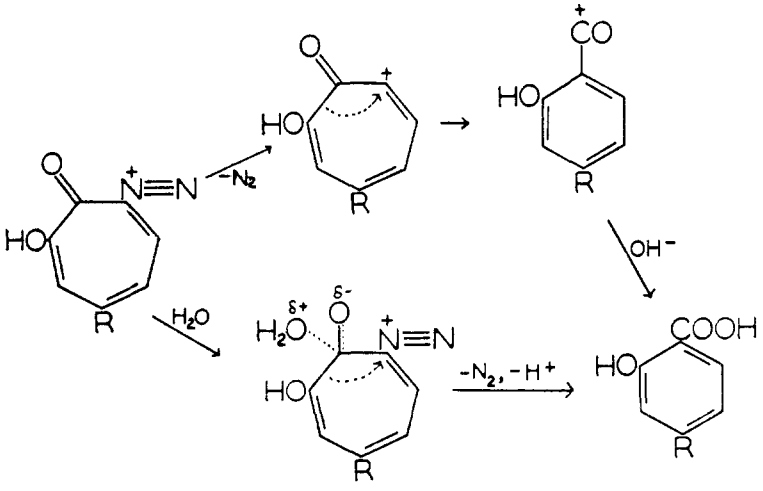
Kinetically, it may be assumed that the reaction (and also the corresponding substitution without rearrangement) is strictly bimolecular in the sense that the attack by the base (B^-) may either precede or perhaps be simultaneous with the elimination of the substituent X, but that a prior (and therefore rate-controlling) dissociation of X cannot be involved, except with the most strongly electronegative substituents (X). This is evident from the general behavior of the halotropones. The absence of primary dissociation of chlorine in 2-chlorotropones is clearly shown by its inertness towards silver nitrate even under vigorous conditions (3, 94, 408). 2-Bromotropone, however, reacts with silver nitrate on warming (408).

It follows that the ion CXXXV cannot be an intermediate in most of the rearrangements. It may be formed indirectly in the rearrangements observed



CXXXV

(72, 134, 276, 277) during the decomposition of tropolone-3(or 7)-diazonium salts. Even in these cases, however, there is no evidence to rule out prior attack by, e.g., hydroxyl ion or solvent molecules, as suggested in formula CXXXVI (*cf.* 134, 162).

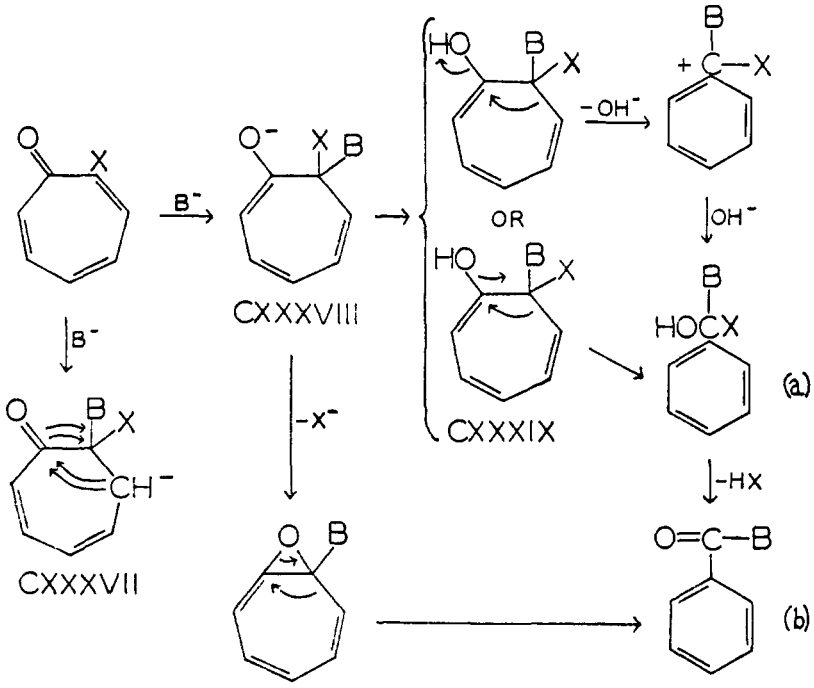


CXXXVI

It was pointed out above (page 66) that, although the most direct path of substitution is normally followed, an alternative path involving initial attack at the carbonyl carbon is not only possible but for certain reactions more probable.

Similarly, although the most direct path of rearrangement involves attack at

the 1-position, several other paths have been suggested (3, 74, 97) which lead to the same end-product. The various schemes which have been proposed differ in some details, but all involve the attack by a base (B^-) at the 2-position followed by rearrangement in which the original carbonyl oxygen is displaced. The most concise way in which this has been written (97) is shown in formula CXXXVII; but, although not different in principle, it may be convenient for fuller consideration to write down the expanded schemes (mechanism II, a and b); this is not intended to imply that the various steps shown are necessarily consecutive rather than simultaneous.



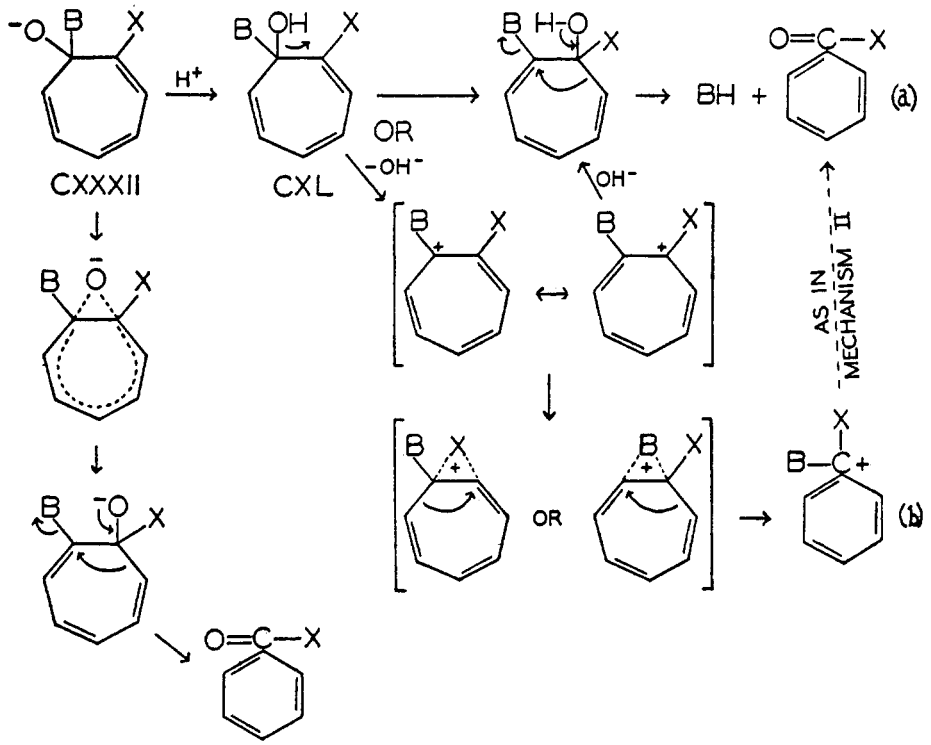
Mechanism II

In mechanism IIa attack by the base (B^-) is followed by acceptance of a proton; the resultant neutral product (CXXXIX) is considered to rearrange with elimination of a hydroxyl ion, followed by addition of hydroxide to the rearranged ion (3). A direct 1,2-shift of the hydroxyl group simultaneous with the rearrangement is of course equally if not more probable. It may further be thought that addition of a proton is unlikely in the highly alkaline medium used for most of the rearrangements and the alternative scheme (mechanism IIb) (more closely corresponding to CXXXVII) is written to show that this may indeed be quite unnecessary.

To these two principal schemes (mechanisms I and II) must be added variants involving intermediate migrations, which, while minor in principle, may yet be distinguishable by the results obtained.

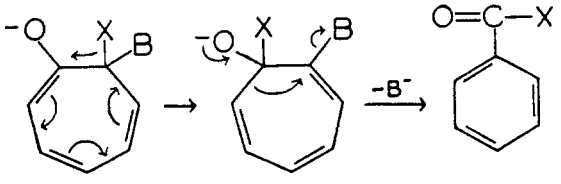
If the attacking radical B migrated, e.g., in intermediate CXXXII (mechanism I), the further changes of the resultant intermediate (CXXXIX) yield results indistinguishable from those of mechanism II; similarly the migration of B in CXXXVIII (mechanism II) to CXXXII gives results indistinguishable from those of mechanism I.

However, CXXXII (mechanism I) may also undergo migration of the oxygen, or of the hydroxyl group of the corresponding conjugate acid (CXL), as shown in mechanism III (*cf.* 74), in which variants similar to those of mechanism II are indicated:



Mechanism III

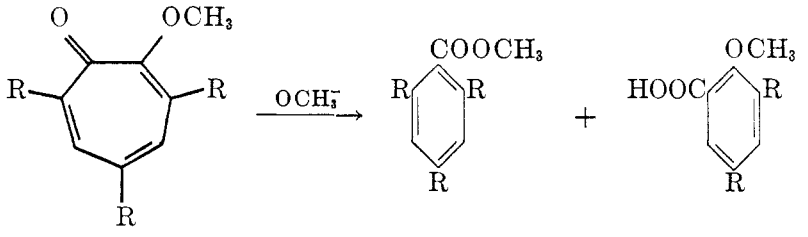
Lastly, intermediate CXXXVIII (mechanism II) may suffer migration of X as shown in mechanism IV, where it is seen that the subsequent rearrangement, although quite analogous to that of mechanism I, leads to retention of X and elimination of B:



CXXXVIII

Mechanism IV

The relative merits of the two main mechanisms have been discussed (97) on the basis of the following evidence: Rearrangement of 3,5,7-trichloro- or 3,5,7-tribromotropolone methyl ether (CXLI: R = Cl or Br) with sodium methoxide (97) yields in each case approximately 75 per cent methyl 2,4,6-trichloro(or tribromo)benzoate (CXLII) and 20 per cent 3,5-dichloro(or dibromo)-2-methoxybenzoic acid (CXLIII):

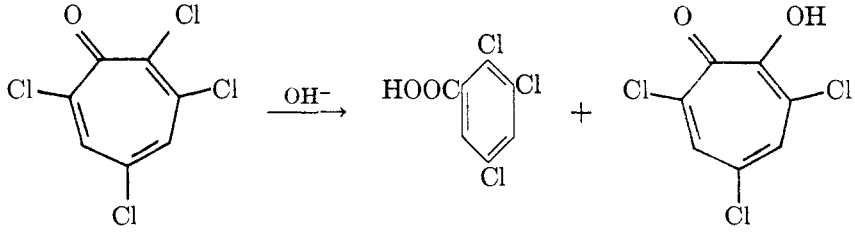


CXLI CXLII CXLIII

It is pointed out (97) that the predominant elimination of the stronger base methoxide ion (rather than halogen) here observed is inconsistent with mechanism I. A rate-determining nucleophilic attack at C_2 as in CXXXVII is therefore preferred.

It is necessary to point out that this example merely emphasizes the complexity of the rearrangements by proving that mechanism I is not alone adequate to explain the products observed. The various mechanisms outlined above are, however, by no means mutually exclusive. There is no evidence to suggest that two mechanisms may not be followed simultaneously. Indeed, the dependence of the proportions of rearranged and unrearranged products, and of different rearranged products, both on the nature of the nucleophilic reagent and on the reaction conditions, strongly suggests that a multiplicity of mechanisms are involved.

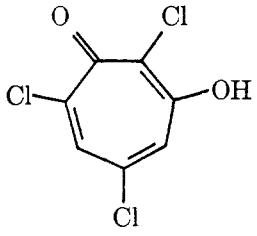
Thus, the action of hydroxide on 2,3,5,7-tetrachlorotropone (CXLIV) reported in the same paper with the above rearrangements (97) yields 53 per cent 2,3,5-trichlorobenzoic acid (CXLV) and ca. 10 per cent 3,5,7-trichlorotropolone (CXLVI).



CXLIV CXLV CXLVI

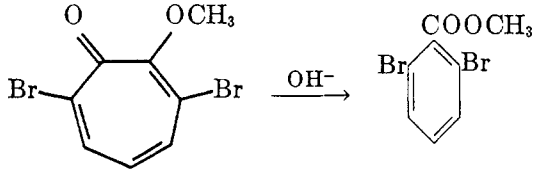
2,3,5,7-Tetrachlorotropone 2,3,5-Trichlorobenzoic acid 3,5,7-Trichlorotropolone

The suggested mechanism (CXXXVII) for both processes provides no suggestion why attack at C_7 should lead to exclusive rearrangement and attack at C_2 to substitution with no rearrangement. (The method of isolation used would not lead to the detection of the product of attack at C_3 (i.e., CXLVII), which may also be expected to be formed (*cf.* page 69)).



CXLVII

Likewise unexplained is the formation of CXLIII (R = Cl or Br) as the sodium salt of the free acid rather than as the methyl ester under the conditions used (sodium dissolved in anhydrous methanol). The opposite effect is noted (285) in the rearrangement of 3,7-dibromotropolone methyl ether (CXLVIII) with sodium hydroxide in methanol. Although the attacking ion in this case is undoubtedly the hydroxyl and not the methoxyl ion, the product is the ester (CXLIX) rather than the free acid. Such a result would be anticipated on the basis of mechanisms IIIa and IV, but is equally possible on the basis of mechanism IIa or IIIb if HB is eliminated in place of HX.



CXLVIII CXLIX

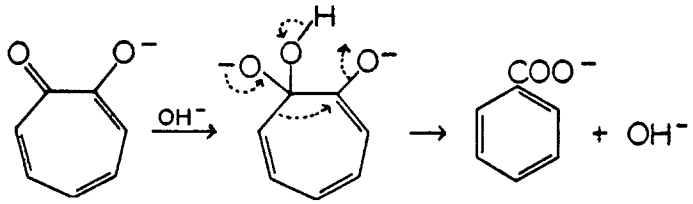
Methyl 2,6-dibromobenzoate

The most important of the rearrangements to which the above mechanisms apply and which have been widely used for determining positions of substituents are the rearrangements of tropolone methyl ethers (i.e., 2-methoxytropones) and of 2-halotropones with methoxide, hydroxide, or ammonia. These normally proceed under very mild conditions (room temperature or more rapidly in boiling methanol). Only in the case of 3,5,7-trimethyltropolone methyl ether is it reported (307) that no change took place with sodium methoxide in methanol, and that the higher temperature of boiling butanol was necessary to effect the reaction. The analogous rearrangement with sodium methylmercaptide has also been observed (*cf.* chart IIIB).

Frequent use has also been made of the direct rearrangements of tropolones by the action of caustic alkalis. The conditions necessary for this reaction vary widely. It has been demonstrated that nitro substituents greatly facilitate the reaction—so much so that dinitrotropolones may rearrange in hot aqueous or

alcoholic solution even without the addition of base (134, 289). More commonly, however, high-temperature fusion with potash is required and such groups as hydroxyl definitely inhibit the reaction. Thus, stipitatic acid rearranges in good yield to 5-hydroxyisophthalic acid (*cf.* page 26) but only with potassium hydroxide at 300°C. (34). Puberulic acid is unattacked even under these vigorous conditions; even higher temperatures cause complete decomposition, so that the rearrangement could not be observed in this case (79).

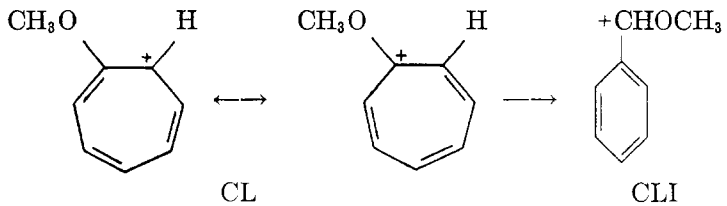
The reason (96) for the strenuous conditions of this reaction is to be seen in the fact that attack of a nucleophilic reagent upon the anion of a tropolone is required under the strongly alkaline conditions used, so that much electrostatic repulsion has to be overcome. In principle, the mechanism does not otherwise differ significantly from the schemes already proposed and may be written, e.g., corresponding to mechanism I, as follows (96):



The conditions of the reaction are such that both sulfonic acid groups (328) and halogens may simultaneously be replaced by hydroxyl. In the former case, this probably does not affect the interpretation of the results concerning the position of substitution. But in view of the shift of position reported for the substitution of halogen by hydroxyl (*cf.* page 73), special caution is necessary in interpreting the results in that case.

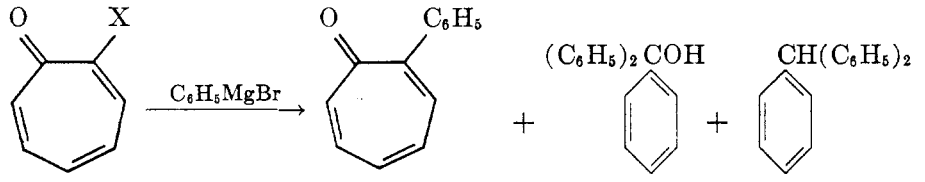
Other rearrangements which can be adequately explained on the basis of one or all of the above mechanisms include, apart from the rearrangement of the tropolone-3-diazonium ion which occurs as a side reaction in the Sandmeyer reaction and has already been discussed (*cf.* page 80), the rearrangements which accompany lithium aluminum hydride reduction and Grignard reactions.

The reduction by lithium aluminum hydride (*cf.* page 66) of tropolone methyl ether yields benzaldehyde as the main product (74). If this reaction is regarded as involving attack by a hydride ion (or its equivalent), several of the above mechanisms appear possible. Two of these have actually been proposed specifically for this reaction (3, 74). The first of these proposals (74) involves mechanism III in the form which would lead *via* CL and CLI. It might be assumed, however, that the further conversion of CLI to benzaldehyde, which involves addition of hydroxyl ion and loss of methanol, would only occur on treatment of



the reaction mixture with water and that, consequently, any further reduction (of CLI) would lead to benzyl methyl ether. This, however, has not been observed, whereas in another case (3) prolonged treatment has been shown to yield the corresponding free benzyl alcohol; this may be interpreted as an indication that one of the other modes of reaction is more probable and that the free aldehyde may be present in the reaction mixture.

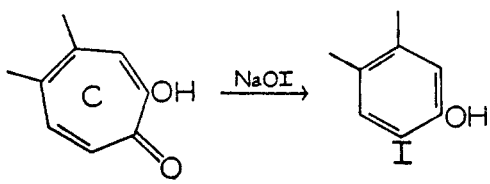
The Grignard reaction has been carried out in several ways, and it has been observed that in addition to the simple substitution product (*cf.* page 67) triphenylcarbinol (or a derivative thereof) is frequently (and perhaps always) formed as a byproduct resulting from rearrangement. This is a minor side reaction when tropolone methyl ether or a 2-halotropone or 2-dialkylaminotropone is treated with, for example, phenylmagnesium bromide,



2-Halotropone — Triphenylcarbinol — Triphenylmethane

but becomes the main reaction when the ether is treated with phenyllithium (3). On the other hand, phenyllithium reacts with free tropolone or its copper chelate with little or no rearrangement (94, 99). The additional production of triphenylmethane (298) may be attributed to reductive action by the Grignard reagent on the carbinol initially formed. The further action of the Grignard reagent on 2-phenyltropone has been mentioned (298), but the nature of the product is at present unknown. However, the fact that a new product is formed may indicate that free phenyltropone is not present in the reaction mixtures of the other Grignard reactions mentioned, but is only liberated after treatment with water.

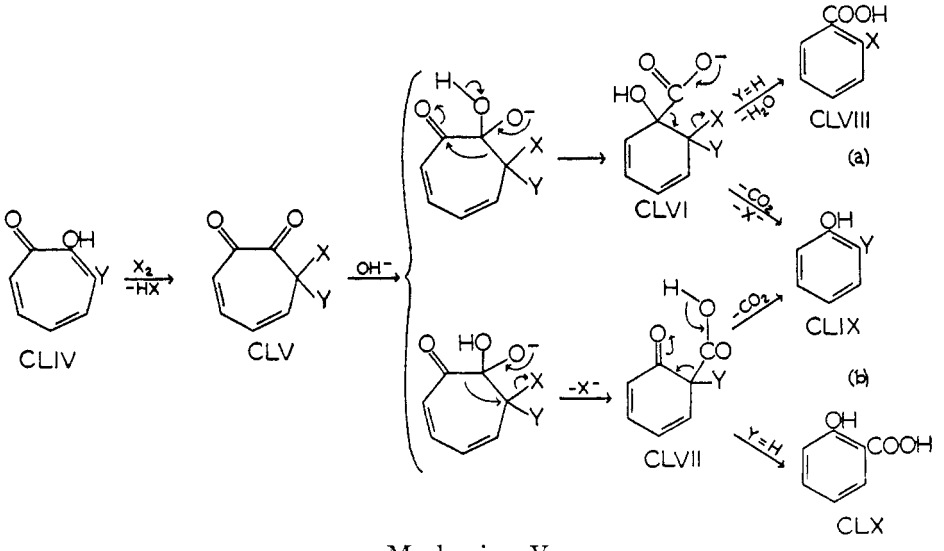
A different rearrangement mechanism has generally been assumed (54, 96, 116, 162) for the rearrangements caused by hypohalite and first observed (458) in the case of colchiceine (458), which with hypoiodite yields *N*-acetyliodocolchinol (partial formulas CLII and CLIII):



CLII — CLIII

It is thought that this and related changes involve a typical benzilic acid type of rearrangement proceeding through an α-diketone intermediate. Even this,

however, can lead to rearrangement in two different directions (54, 116, 190, 216) and evidence is available to suggest that both are followed. The initial attack of halogen on the tropolone (CLIV) leads to an intermediate (CLV) which may either rearrange directly or, if Y = H, may tautomerize to the 3-halotropolone (CLIV: Y = halogen), which may then react with more halogen to yield CLV (X = Y = halogen), which then rearranges rapidly. In the latter case the two mechanisms as shown lead to the same product, an *o*-halophenol

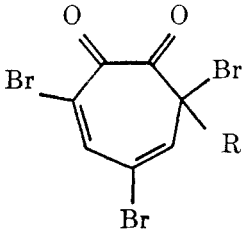


Mechanism V

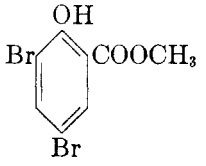
(CLIX). Thus with excess hypoiodite, tropolone yields 2,4,6-triiodophenol (63, 96). However, the rearrangement of CLV (Y = H), occurring directly without further halogenation, can yield several products. The halophenol (CLVIII) is still a possibility by either mechanism, being formed *via* CLIX (Y = H) by subsequent further halogenation. However, an alternative path is also available; CLVI (X = halogen, Y = H) may lose water to give the *o*-halobenzoic acid (116, 216). This mode of rearrangement may be observed when tropolone or 3-iodotropolone is treated with a limited amount of hypoiodite (190), in which case 2,4-diiodobenzoic acid and 2,4,6-triiodobenzoic acid are formed.

If the second mechanism (Vb) is followed, the intermediate CLVII (Y = H) may in place of losing carbon dioxide simply tautomerize to the salicylic acid. This mode of rearrangement has been realized in an indirect way. The bromination of tropolone or 3-bromotropolone has been found (116) to yield a small amount of the intermediate CLXI (R = H). Like the analog CLXI (R = Br), obtained from 3,5,7-tribromotropolone (116), this has not been obtained pure; more convincing evidence for the formation of intermediates of this type is obtained in the 4,5-benzotropolone series from the isolation of both CLXIII

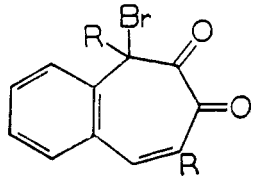
(R = H) and CLXIII (R = Br). When the intermediate CLXI (R = H) is treated with cold alkali, it rearranges in good yield to CLXII.



CLXI

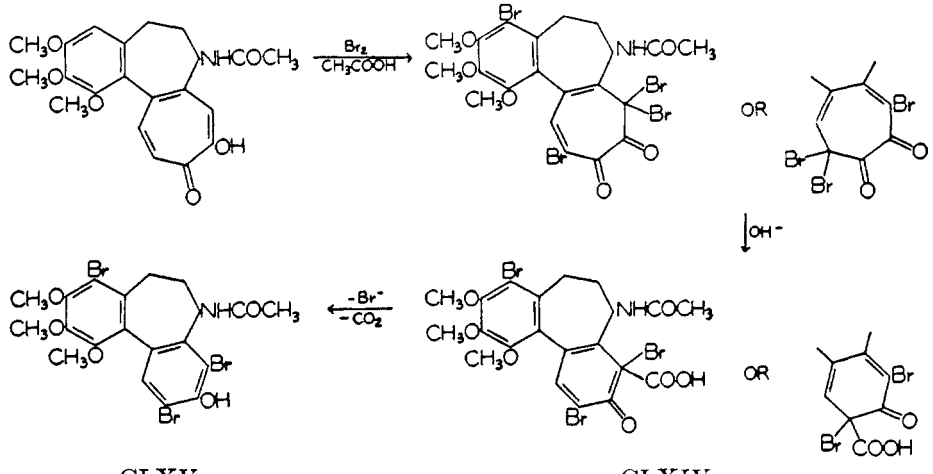


CLXII



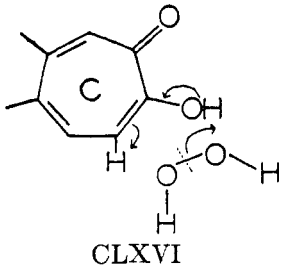
CLXIII

Evidence for the formation of intermediates of the type of CLVII has been obtained by the bromination of colchiceine in acetic acid (216, 457, 458a). The product has properties shown (216) to be in good agreement with the formulation CLXIV and is rearranged by aqueous sodium carbonate to *N*-acetyltribromocolchinol (CLXV).

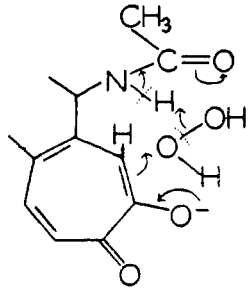


CLXV
N-Acetyltribromocolchinol

CLXIV



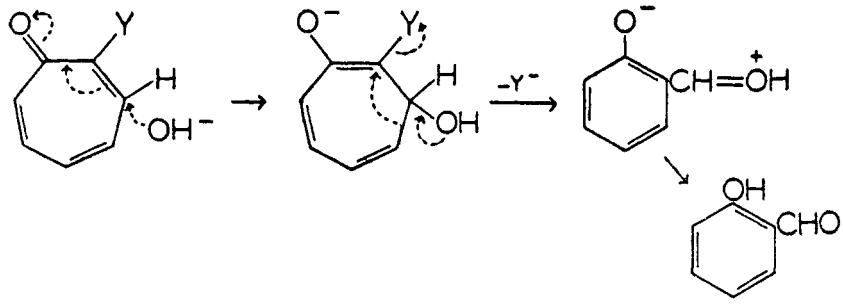
CLXVI



CLXVII

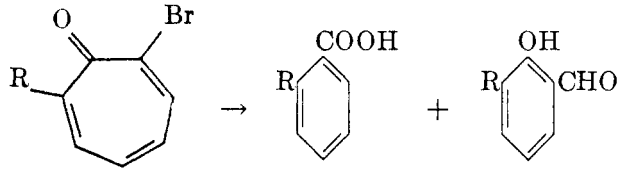
The unique rearrangement of colchiceine with alkaline peroxide (54) (*cf.* page 19) to *N*-acetylcolchinol must also follow one of the above mechanisms (V: X = OH). The initial attack may be represented as in partial structures CLXVI or CLXVII.

In all the rearrangements discussed, the initial attack by the base is assumed to occur at the 1- or 2-position of the tropone nucleus. Consideration must now be given to the possible results of attack at the 3-position, e.g., by hydroxyl ions:



Mechanism VI

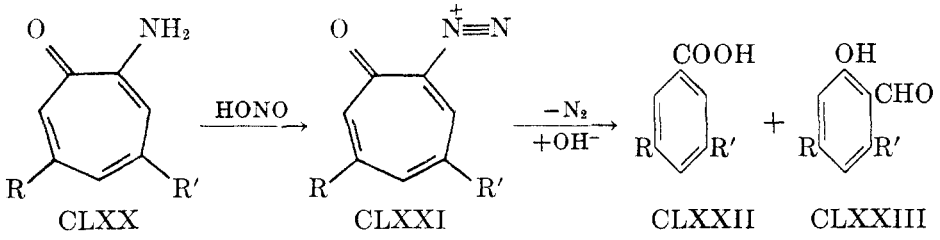
The reaction sequence shown indicates that such attack may also lead to rearrangement. Examples of rearrangements leading to derivatives of salicylaldehyde are known and may be examples of the operation of this mechanism. Thus the reaction (338, 413) of 2,7-dibromotropone (CLXVIII: R = Br) with sodium hydroxide yields 3-bromo-2-hydroxybenzaldehyde (CLXIX: R = Br) as well as *o*-bromobenzoic acid formed by one of the more usual mechanisms (I to IV). 2-Bromo-7-chlorotropone (CLXVIII: R = Cl) yields the analogous chloroaldehyde (CLXIX: R = Cl).



CLXVIII CLXIX

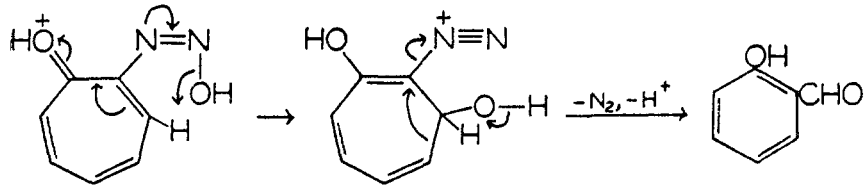
Another example is the reaction of 2-amino-4(or 6)-methyltropone (CLXX) with nitrous acid (3). This may be assumed to proceed through a diazonium salt (CLXXI) and thus yield a toluic acid (CLXXII), by analogy with the behavior of the tropolone-3-diazonium salts (see page 80). In addition to this the methylsalicylaldehydes (CLXXIII: R = CH_3, R′ = H, and R = H, R′ = CH_3, respectively) are also formed. The mechanism which has been suggested (3) for this reaction differs from the above only in the sequence of the steps. In this case, it can also be written in the cyclic form CLXXIV, if the diazonium hydroxide is admitted as a possible intermediate.

Strongly reminiscent of these rearrangements is the observation that the conversion of tropolone to 2-chlorotropone by thionyl chloride is accompanied by some rearrangement to *o*-chlorobenzaldehyde (1).



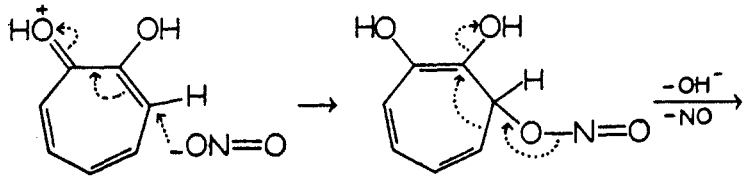
CLXX CLXXI CLXXII CLXXIII

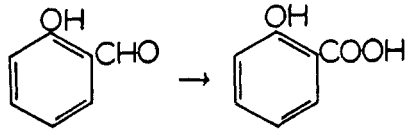
R = H, R′ = CH_3 or R = CH_3, R′ = H.



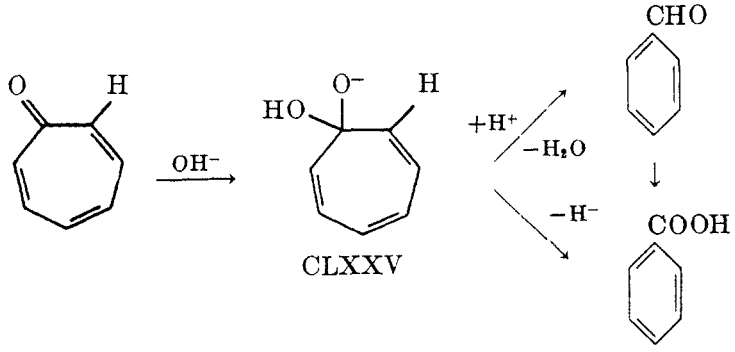
CLXXIV

The formation of salicyclic acid derivatives has been noted in the nitrosation of several alkyltropolones (236, 337). This must involve an oxidative step and the possibility may be entertained that this oxidation follows rearrangement. In that case the corresponding salicylaldehydes should be intermediates, and reëxamination of these reactions might reveal their presence. If this should prove to be so, the rearrangement may take the above form, as indicated below:





Oxidation must also be involved in the rearrangement of simple tropones by alkali to benzoic acid derivatives. It has been suggested that the first stage in



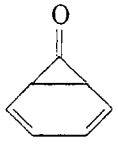
CLXXV

this reaction is attack at position 1 to give CLXXV (20). However, whether the oxidation takes the form of simple hydride elimination (resulting in rearrangement by the above mechanism (I: X = H)) is not clear. Again the possibility of a hydride shift during the rearrangement to give a benzaldehyde derivative and subsequent oxidation (or Cannizzaro reaction) cannot be excluded on the available evidence.

A surprising case of this rearrangement is the interaction of 2-methylmercaptotropolone with methoxide ion to give 2-methylmercaptobenzoic acid rather than unsubstituted benzoic acid (317). The latter would be expected to result from elimination of the methylmercaptide ion in accordance with mechanisms I to IV, as occurs in the reaction of 2,7-dimethylmercaptotropone to give the same product.

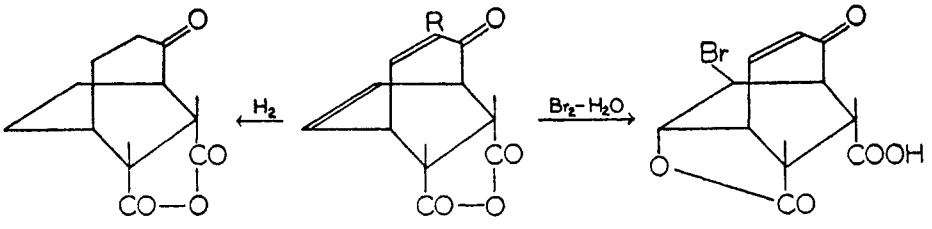
VII. Addition Reactions of Tropones and Tropolones

Contrary to theoretical prediction (39), tropone can act as a diene in a reaction of the Diels–Alder type with maleic anhydride (303, 311). This reaction has also been realized with 2-bromotropone (303), 2-phenyltropone (298), and with a number of tropolones (326, 403, 404, 407). In formulating the products, the assumption has apparently been made that the theory (39) correctly predicts the 2- and 5-positions (*viz.* in tropolone the 3- and 6-positions) as the most likely for such addition. Other possibilities, including that of reaction in the norcaradiene form (CLXXVI) (*cf.* cycloöctatetraene!), have not received considera-



CLXXVI

tion. In the case of the adduct from tropone and maleic anhydride however, the ultraviolet spectrum has been found to be in agreement with the structure CLXXVII (R = H) postulated for this product and to show the expected changes on reduction to the tetrahydro derivative (CLXXVIII) (303). The same reduced compound (CLXXVIII) is obtained from the bromotropone adduct (CLXXVII:

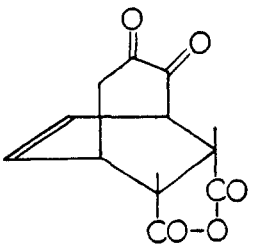


CLXXVIII CLXXVII CLXXIX

R = Br). The stereochemical assignment (CLXXVII) is based on the conversion with bromine water to a bromolactone which is assumed to be of the type shown in formula CLXXIX, and the product is described as "endo-*cis*." An accurate

definition of the term "endo" in this connection is required if much confusion is to be avoided.

An analogous formulation (CLXXX) has been used for the adduct obtained from tropolone. As expected, unsymmetrically substituted tropolones, e.g., *hinokitiol* and *3-bromotropolone*, yield at least two isomeric adducts (404, 407). The stereochemical formulation (CLXXX) is again based on the formation



CLXXX

of a bromolactone, despite the fact that bromination of CLXXX in acetic acid yields a product identical with one of the adducts obtained (326, 404) from 3-bromotropolone; the results show that bromination has taken place at the reactive methylene group adjacent to the C=O group, as might be expected, and not at the double bond. This assignment must therefore be regarded as purely speculative, particularly as two impossible structures, violating Bredt's rule, have been employed (403, 407) in accounting for further transformation products.

Indeed, even the presence of the 1,2-diketone system in these products has not been demonstrated (only a monophenylhydrazone has been obtained (326, 407) in a reasonable state of purity), and this grouping (if present) may be expected to undergo very facile benzilic acid rearrangement. Thus, much further work is required to establish the correct structures of these adducts and their transformation products.

The ability of tropone derivatives to act as dienophiles rather than dienes in Diels–Alder reactions (39) has apparently not been tested.

The only other addition reactions which have been described are hydrogenation (see page 17) and possibly (*cf.* page 40) halogenation.

VIII. Miscellaneous Reactions and Properties of Tropolones

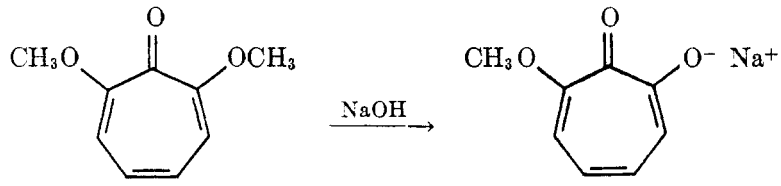
A. Ethers and Esters of Tropolone

These compounds and their extremely facile hydrolysis by alkali (and acids) have been referred to earlier (page 16), and the reaction of the methyl ethers has been discussed in some detail in Sections V and VI. Some special features, however, remain to be pointed out.

Perhaps as a result of the absence of hydrogen bonding, the methyl ethers possess larger dipoles than the parent compounds (*cf.* table 8). Closely connected with this are the greater solubility of the ethers in water (*cf.* 68, 131) and their higher boiling points (329), which indicate stronger intermolecular association.

That the ease of hydrolysis is general for the ethers is evident from the fact

that not only the methyl but also the *p*-nitrobenzyl ethers are rapidly saponified by warm alkali (131). That, on the other hand, only one ether group in 2,7-dimethoxytropone (CLXXXI) is thus hydrolyzed and that the second then behaves as a normal phenolic ether type may simply be attributed to the fact that the 3-methoxytropolone resulting from the first hydrolysis step will exist as the ion CLXXXII in basic medium. However, a 2-methoxy group is always hydrolyzed preferentially. Methoxy groups in other positions of the tropone nucleus are certainly less susceptible to alkaline hydrolysis.



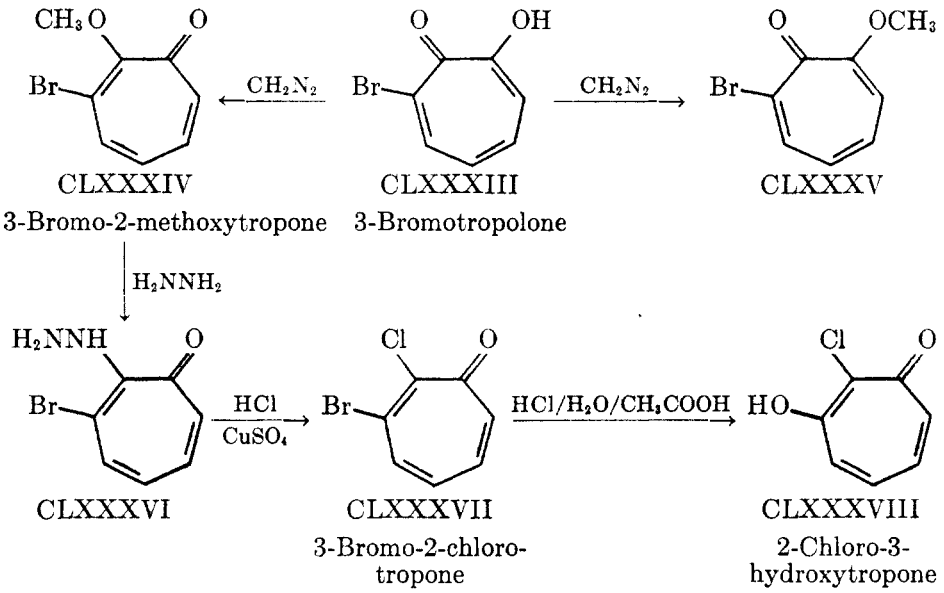
CLXXXI
2,7-Dimethoxytropone

CLXXXII

The equally facile hydrolysis of the esters is no doubt responsible for reported failures (e.g., 65) to obtain acetates, etc. Tropolones do in fact react quite readily and smoothly with acid anhydrides or acid chlorides. From tropolone itself, an acetate (96), a benzoate (96), a 3,5-dinitrobenzoate (65), and a *p*-toluenesulfonate (94) have been prepared. The latter undergoes the expected replacements of the toluenesulfonate group by iodide, NH_2, etc. (94). In the case of 5-amino-4-isopropyltropolone it has been demonstrated that the hydroxyl group may be esterified by acetic anhydride under conditions which leave the amino group free (257). The diacetate obtained by more vigorous acetylation is, however, readily hydrolyzed by hot water to yield the simple *N*-acetyl derivative.

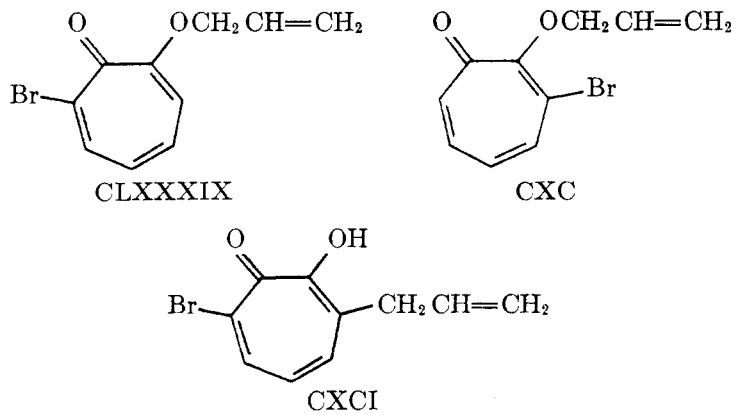
Unsymmetrically substituted tropolones will, of course, give rise to two isomeric series of ethers or esters. Such isomers have frequently been observed; indeed, isomeric benzenesulfonates of colchiceine (455, 456) and isomeric methyl ethers of stipitatic acid (34) were known before their tropolone structures were suggested (88, 89) and constituted arguments in favor of these structures. The very dissymmetry necessary to make such isomerism possible will also frequently make one of the isomers easier to form. It is not surprising that in certain cases a single product has been isolated in high yield (e.g., 461).

In the case of the ethers, this isomerism has been studied in some detail. Separation of the isomers has been achieved by fractional crystallizations of the ethers (285, 332) or their picrates (130, 131) and in some cases by chromatography (410, 411). Three methods for the determination of their orientations have already been discussed (page 67). In addition, x-ray crystallography (447) and dipole measurements have been used. Moreover, the structures of the isomeric methyl ethers of 3-bromotropolone (CLXXXIII) were originally deduced from the greater tendency of one isomer to undergo rearrangement rather than simple displacement reactions (*cf.* chart III on pages 70–71); this isomer was therefore regarded as 3-bromo-2-methoxytropone (CLXXXIV) (285).



This assignment rests on the assumption that this difference between the two ethers (CLXXXIV and CLXXXV) is the result of steric factors and that, furthermore, the displacement reaction involves attack at C_2 but the rearrangement attack at C_1. It is therefore of theoretical interest that this assignment was correct, as shown both by the x-ray data (447) and by the conversion of CLXXXIV *via* CLXXXVI and CLXXXVII to 2-chloro-3-hydroxytropone (CLXXXVIII), while the isomeric ether (CLXXXV) yields only 3-chlorotropolone by the same sequence of reactions (408).

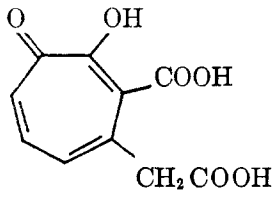
The allyl ethers (CLXXXIX and CXC) of the same 3-bromotropolone (CLXXXIII) have been shown (405) to undergo the Claisen rearrangement, the only example of this reaction so far recorded in the tropolone series. The same product is reported to be formed from both ethers and is assigned the structure CXCI on the basis of the normal mechanism of the reaction and the



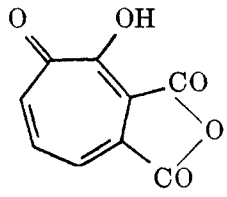
ability of the product to couple with diazonium salts. The formation of this product from CXC is perhaps surprising but cannot be regarded as established, since one of the ethers (assumed to be CXC) was only obtained as an oil and may be a mixture; alternatively, the ethers might be interconvertible under the conditions of the reaction.

B. 4-SUBSTITUTED TROPOLONES

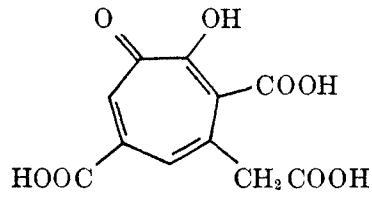
Whereas numerous 3- and 5-substituted tropolones are accessible by direct substitution reactions, tropolones with functional substituents in the 4-position can only be obtained by indirect routes. Apart from the tropolone-4-carboxylic acid obtained from veratrole by ring expansion with diazoacetic ester (19, 20) and the analogous synthesis of stipitatic acid (21, 22), all the derivatives of this type which have been obtained so far are derived from purpurogallin and its derivatives. The key starting materials are the dicarboxylic acid (CXCII) obtained by oxidation of purpurogallin itself (131, 135), the anhydride (CXCIII) of the lower homolog obtained as a byproduct in the same process (85) or more efficiently by oxidation of dibromopurpurogallin (84a), and the tricarboxylic acid (CXCIV) obtained from purpurogallincarboxylic acid (84, 85).



CXCII



CXCIII

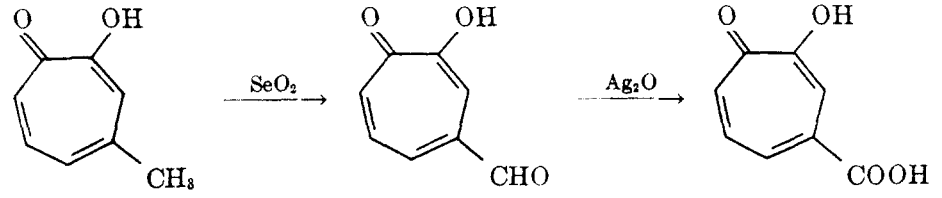


CXCIV

In these acids, the side-chain carboxyl group and carboxyl groups in the 3-position are readily lost, but not those in the 4-position. Thus both CXCII and CXCIV lose two molecules of carbon dioxide at the melting point to yield 4-methyltropolone (CXCV) and 4-methyltropolone-6-carboxylic acid (CXCVIII), respectively (84, 85, 135). The anhydride (CXCIII) similarly loses one molecule of carbon dioxide when heated with water at 170–180°C. (85), giving tropolone-4-carboxylic acid (CXCVII), which has also been made from 4-methyltropolone (CXCV) (130, 131); the latter may be converted by oxidation either of its methyl ethers (130, 131) or (in similar overall yield) of the free tropolone (181) with selenium dioxide to the aldehyde (CXCVI), which is further oxidized to CXCVII by silver oxide (130, 131). Decarboxylation of CXCVII obtained in this way provided one of the first syntheses of unsubstituted tropolone.

Partial decarboxylation of CXCII has also been carried out. On heating in nitrobenzene (85), warming with pyridine to 50°C. (286), or refluxing with hydrochloric acid (181), the side-chain carboxyl group is removed preferentially, yielding CXCIX (R = H). Both partial hydrolysis of its diester and methanolysis of its anhydride (CCV) convert CXCII to the same monomethyl ester (CC), which undergoes decarboxylation to the methyl ester of the same acid (CXCIX:

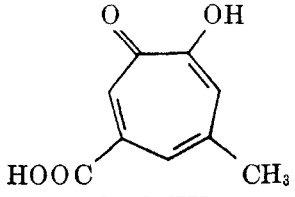
R = H). However, when the anhydride (CCV) is opened with ammonia, the amide (CCI) is obtained, which may be decarboxylated to CCII (R = NH_2) and hydrolyzed to tropolone-4-acetic acid (CCII: R = OH) (85). This acid



CXCV
4-Methyltropolone

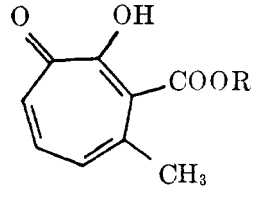
CXCVI
Tropolone-4-aldehyde

CXCVII
Tropolone-4-carboxylic acid

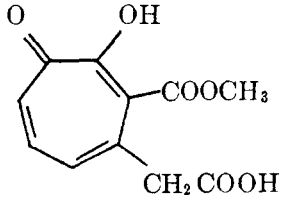


CXCVIII
4-Methyltropolone-6-carboxylic acid

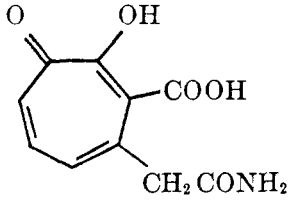
can also be obtained (286) as a result of the observation that bromination of the dicarboxylic acid (CXCII) proceeds with elimination of carbon dioxide to give CCIII (R = H) or with excess bromine to give CCIII (R = Br). The acid (CXCIV) behaves analogously (85). Hydrogenolysis of the tribromo compound (CCIII: R = Br) leads to the bromine-free acid (CCII: R = OH), which has been further converted to 4-aminomethyltropolone (CCIV) by the Schmidt reaction (286). This last product is of interest because in it the nitrogen bears the same relation to the tropolone nucleus as in colchicine.



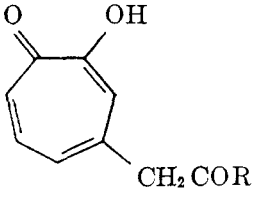
CXCIX



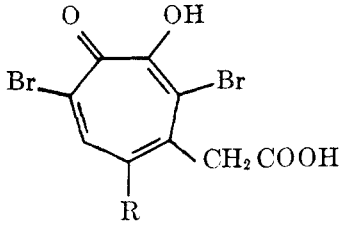
CC



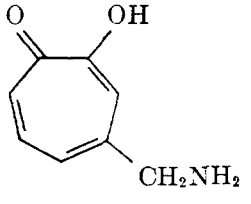
CCI



CCII

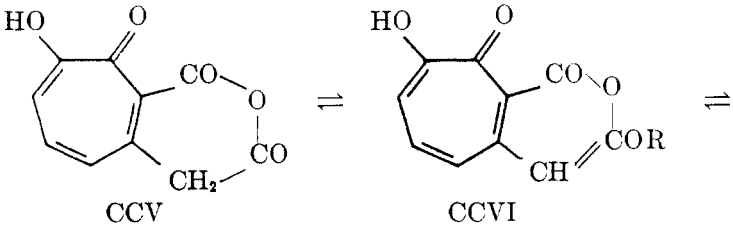


CCIII

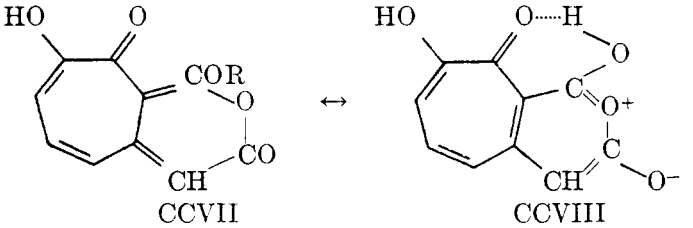


CCIV

On treatment with concentrated sulfuric acid, the anhydride CCV is obtained from CXCII (85, 281). It is a red compound (in contrast to the colorless acid (CXCII)), and its behavior suggests that it exists largely as the enol form CCVI

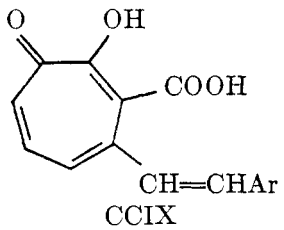


CCV CCVI

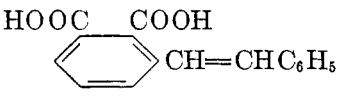


CCVII CCVIII

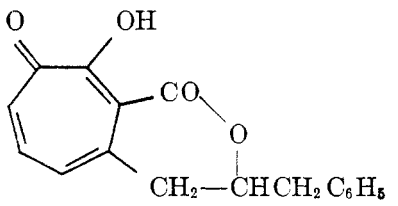
(R = H) (85) or perhaps as CCVII (R = H); in connection with the high color of this substance, it may be interesting to note that the enol CCVII (R = H) may be written in the resonance form CCVIII, which bears a striking resemblance to the structure of purpurogallin. Acetic anhydride converts CCV or the free acid (CXCII) to an enol acetate (CCVI or CCVII: R = $COCH_3$) of the anhydride (85, 280, 281).



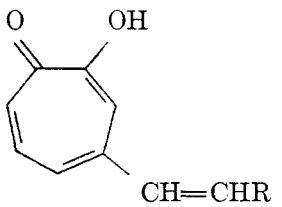
CCIX



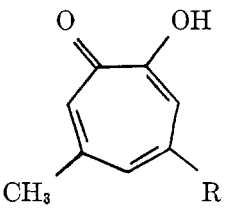
CCX



CCXI



CCXII



CCXIII

It has been shown (85, 280, 281, 425) that either the acid (CXCII) or its anhydride (CCV) readily undergoes a Perkin condensation with aromatic aldehydes. The side-chain carboxyl group is eliminated in the process, and the products have the structure shown in formula CCIX. Definite proof that the carboxyl group which is retained in this reaction is the one directly attached to the tropolone nucleus has been obtained by treating the dimethyl derivative of

CCIX (Ar = C_6H_5) with sodium methoxide. This effects rearrangement to stilbene-2,3-dicarboxylic acid (CCX), which forms an anhydride and which was also obtained for comparison by an unambiguous synthesis (281). It is also evident from the result of the analogous condensation of the anhydride (CCV) with phenylacetaldehyde (278, 281), in which case the product is obtained as the lactone (CCXI) (278).

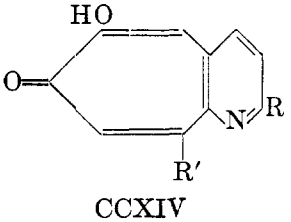
These products (CCIX and CCXI) have been decarboxylated by heating in basic solvents to yield CCXII (85, 281). An attempt to use such styryltropolones, particularly CCIX (Ar = *o*-$NH_2C_6H_4$), in a Pschorr type of cyclization met with failure. This is attributed to their *trans* configuration, suggested by infrared spectroscopic evidence (425).

The methyl ester (CCXIII: R = $COOCH_3$) of 4-methyltropolone-6-carboxylic acid (prepared as above) has been converted (85) by a Curtius degradation by way of the hydrazide (CCXIII: R = $CONHNH_2$) and azide (CCXIII: R = CON_3) to the ethylurethan (CCXIII: R = $NHCOOC_2H_5$) and benzylurethan (CCXIII: R = $NHCOOCH_2C_6H_5$). The ethylurethan could not be hydrolyzed, but the benzylurethan afforded the desired 4-amino-6-methyltropolone (CCXIII: R = NH_2) in low yield on hydrogenolysis. The same product was obtained more efficiently in one step from the azide (CCXIII: R = CON_3) by refluxing with hydrochloric acid in acetic acid (85). No intermediate diazonium salt was detectable when this amine (CCXIII: R = NH_2) was converted with nitrous acid to 4-hydroxy-6-methyltropolone (CCXIII: R = OH) (85).

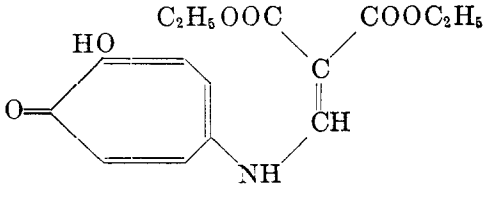
This important result indicates that 4-substituted tropolones differ fundamentally from the 3- and 5-substituted isomers. Whereas 3- and 5-diazonium salts can readily be obtained (*cf.* page 45), the 4-amino derivative is hereby shown to behave much more like an acid amide, of which it is of course a vinylog.

C. PYRIDOTROPOLONES

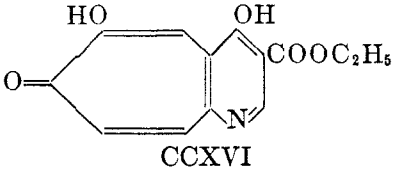
The behavior of 5-aminotropolones as typical aromatic amines, evident from their ability to yield diazonium salts, is further illustrated by their ability to undergo reactions analogous to the typical quinoline syntheses. Thus both 5-aminotropolone and its 4-methyl derivative have been shown to react with



CCXIV



CCXV



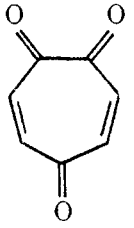
CCXVI

acetaldehyde (or crotonaldehyde) in the presence of hydrochloric acid in a Doebner–Miller reaction to yield the pyridotropolones CCXIV (R = CH_3, R′ = H) (417) and CCXIV (R = R′ = CH_3) (3), respectively, in high yield. The parent pyridotropolone (CCXIV: R = R′ = H) has been obtained by the Skraup method (71). A fourth product of this type has been obtained by the condensation of 5-aminotropolone with ethoxymethylenemalonate to CCXV, which was smoothly cyclized on further heating to CCXVI (417), but the analogous cyclization of the condensation product of 5-amino-4-methyltropolone and ethyl acetoacetate failed (3).

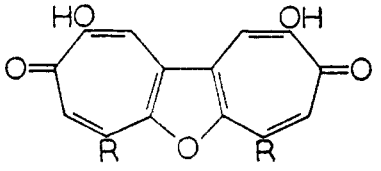
D. TROPOLOQUINONOID SYSTEMS

The possible existence of systems of the type shown in formula CCXVII has been mentioned (90), and such substances have been referred to as tropoloquinones (90) or tropoquinones (257, 258, 333). No clear demonstration of the stable existence of such compounds has ever been given, although structures of this type have been suggested for various products.

The most direct route to such compounds would be the oxidation of 5-hydroxytropolones. This has been attempted, but in the case of 5-hydroxytropolone



CCXVII

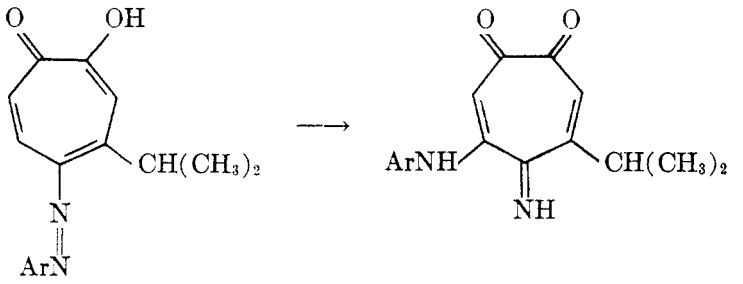


CCXVIII

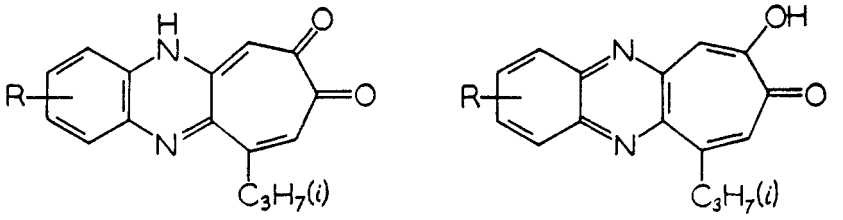
itself has yielded only products of ring cleavage (332, 333), while a product from the oxidation of 4-methyltropolone is a yellow compound of the formula $C_{16}H_{12}O_5$ (3). This product still behaves as a tropolone and yields a diacetate. Structure CCXVIII in which R equals CH_3 has been suggested as the most probable formulation (3). The analogous formulation CCXVIII in which R equals $CH(CH_3)_2$ is now favored (255) for a similar product obtained by oxidation of 5-amino-4-isopropyltropolone and originally regarded as of the type shown in formula CCXVII (257).

"Tropoloquinonoid" structures have been strongly advanced for the so-called hinopurpurins (250, 258, 320, 322). These products are obtained by heating 5-arylazo-4-isopropyltropolones (CCXIX) (azohinokitiols), usually in acetic acid but also in inert solvents. A variety of products of this type containing different aryl groups and also some containing additional substituents in the tropolone nucleus have been obtained (258, 305, 320, 322). They are highly colored products (usually purple) and are isomeric with the azo derivatives from which they are obtained. On the basis of the failure of these hinopurpurins to yield the aromatic amines ($ArNH_2$) on reduction (320, 322), the N—N bond is believed to have been broken during their formation; by analogy with the formation

(117) of 2-anilino-1,4-naphthoquinone from 4-phenylazo-1-naphthol under similar conditions, they are therefore formulated as 4-arylamino-5-imino-6-isopropyltropoloquinones (CCXX). This structure is not, however, considered established beyond doubt (255); structure CCXXI is under consideration as a



CCXIX CCXX



CCXXI CCXXII

possible alternative (255). The latter, however, must be considered as tautomeric with CCXXII, and in this sense it is not strictly a quinone.

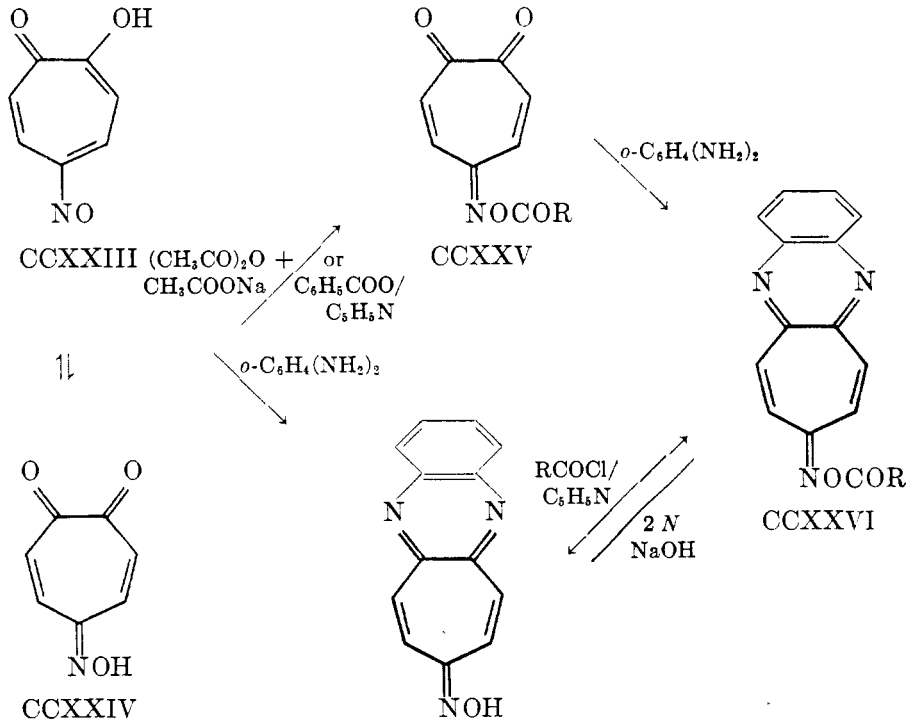
The rearrangement involved in the formation of these products has only been observed when an isopropyl group is present in the 4-position, i.e., adjacent to the azo group. It is therefore believed (320) that steric hindrance provides the driving force for the change; unfortunately, the arylazo group could not be introduced into tropolones carrying the even bulkier *tert*-butyl group in the 4-position (265).

In support of structure CCXX, these products yield dioximes (255, 258) and, contrary to an earlier report (258), also condense with *o*-phenylenediamine (255). Against this must be set the inertness of the supposed imine group in the 5-position whose presence could not be confirmed (258). Such a group might be expected to undergo hydrolysis under the conditions of formation of the compounds. Determinations of the molecular weights of the hinopurpurins are also lacking.

In contrast to the dark color of the hinopurpurins—a color perhaps to be expected from a system such as shown in formula CCXVII—certain derivatives of 5-nitrosotropolone, which are also believed to have tropoloquinonoid structures, are only yellow.

Like *p*-nitrosophenol, 5-nitrosotropolones are at least theoretically capable of exhibiting tautomerism. That they normally exist in the tropolone form (CCXXIII) is indicated by the formation of chelate complexes with transition metals (312). The ultraviolet spectrum of 5-nitrosotropolone (CCXXIII) shows

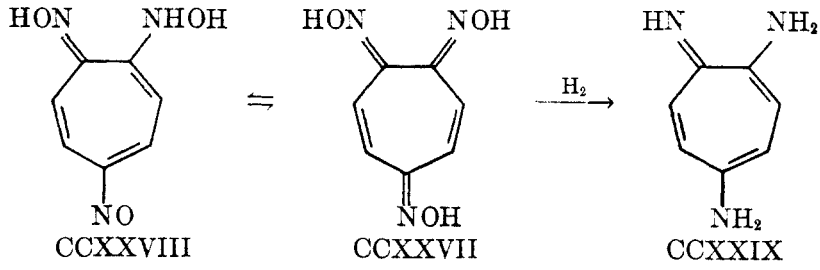
it to be partially ionized in methanolic solution as indicated by a strong band in the 460 mμ region, which is also found in the anion but is absent in acidic medium (312). A much less intense band in the same region is found in the spectrum of its acetate. The spectrum of this derivative indicates clearly that it must differ structurally from its parent compound. More direct evidence for its structure (CCXXV: R = CH_3) is obtained from its reaction with *o*-phenylenediamine (312). There is formed the acetate (CCXXVI: R = CH_3) of the condensation product similarly obtained with 5-nitrosotropolone itself. The benzoate behaves similarly.



This behavior is best explained on the basis of the quinonoid structure (CCXXV) for the acetate and benzoate, as shown above. This implies that the free nitroso compound is itself capable of reacting in the tautomeric quinonoid form (CCXXIV), a fact which explains why, in contrast to all other tropolones, it can react with ketonic reagents.

Whereas only a monophenylhydrazone and monosemicarbazone have been obtained (312), hydroxylamine affords both the monoxime (CCXXX) of 5-nitrosotropolone and the dioxime (CCXXVII) (312, 313, 347) of its quinonoid form (i.e., the trioxime of tropoloquinone). Both these substances may be regarded as tautomeric and as having, at least theoretically, both "tropolone" and "tropoloquinone" forms. This is illustrated by the alternative formulation

CCXXVIII for CCXXVII; catalytic reduction of this product yields 2,5-diaminotroponeimine (CCXXIX) as an oil which has been characterized by the



CCXXVIII CCXXVII CCXXIX

2,5-Diaminotroponeimine

formation of several crystalline salts and by its reaction with formic acid (see p. 103). The ultraviolet spectrum of its hydrochloride has been shown (313)

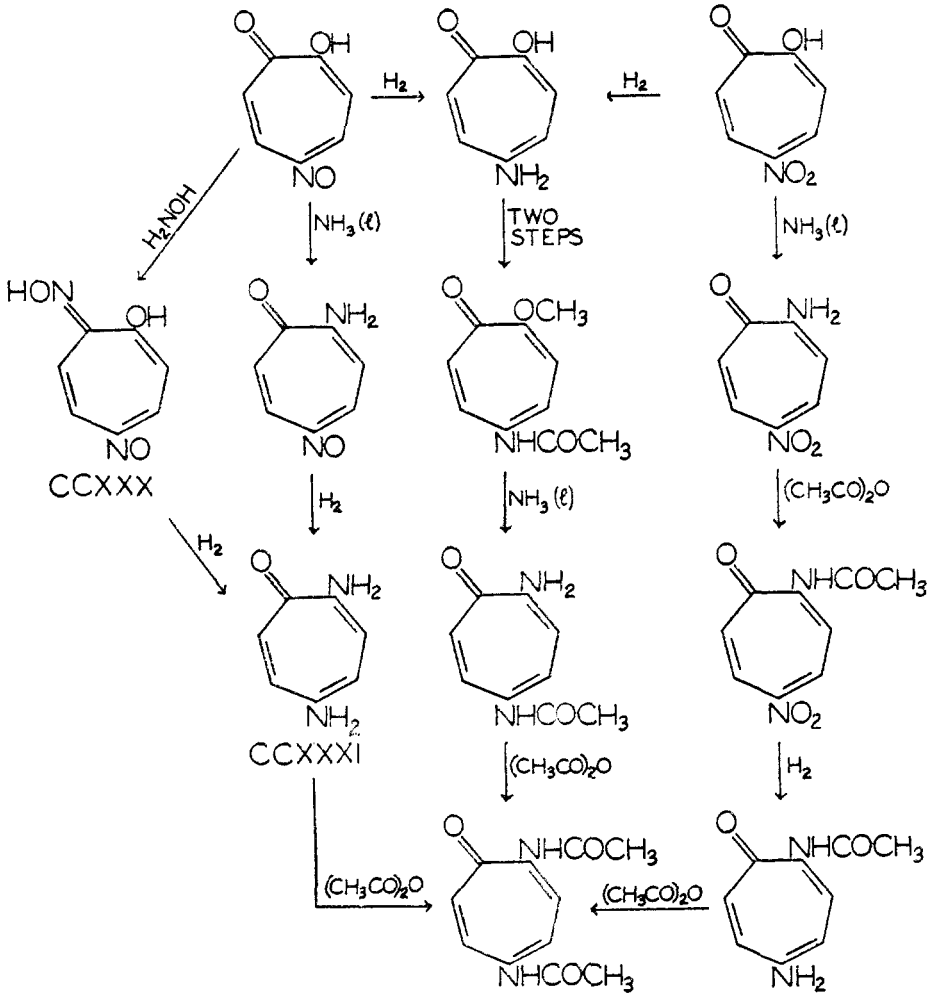


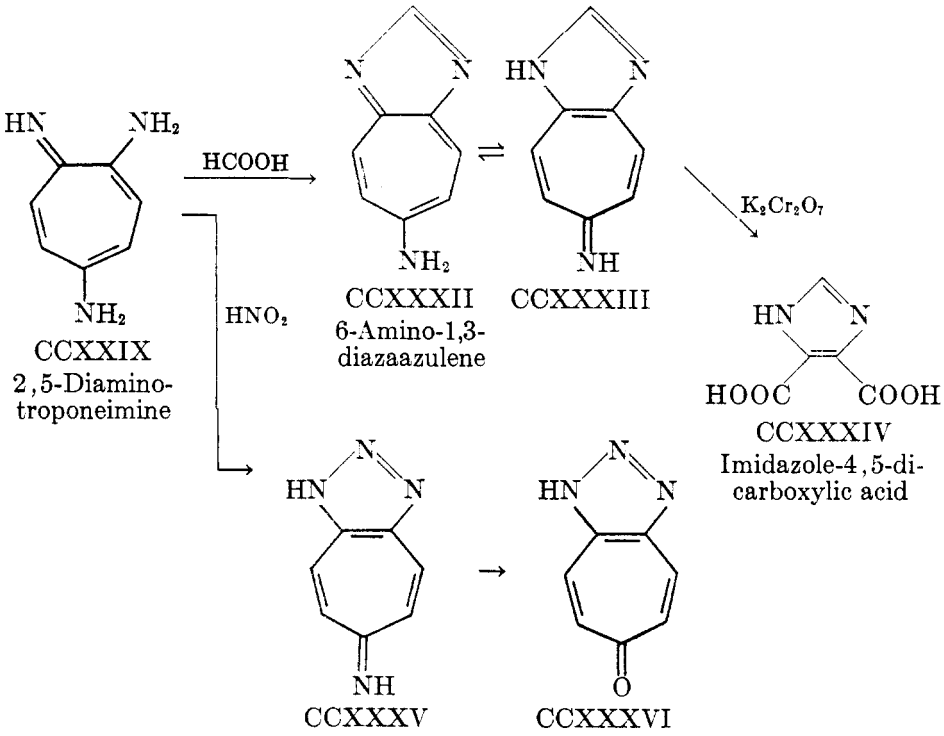
Chart IV. Reactions relating 2,5-diaminotropone to 5-substituted tropolones

to be similar to that of the hydrochloride of 2,5-diaminotropone (CCXXXI) obtainable similarly from CCXXX. The relation of CCXXXI to other tropolone derivatives is shown in chart IV.

The condensation of 5-nitrosotropolones with primary aromatic amines yields crystalline products whose structures remain unknown (312, 347).

E. AZA-, OXA-, AND THIAAZULENES FROM TROPOLONES

When 2,5-diaminotroponeimine (CCXXIX) is treated with formic acid, the product is 6-amino-1,3-diazaazulene (CCXXXII) (313). It is considered to exist normally in the tautomeric form (CCXXXIII), since it fails to behave as a primary amine. Its structure is proved by dichromate oxidation to imidazole-4,5-dicarboxylic acid (CCXXXIV). The action of nitrous acid is considered to



convert CCXXIX to the 2-aza analog (CCXXXV) of CCXXXIII, which is hydrolyzed by dilute alkali to the triazolotropone (CCXXXVI), but the structures of these products have not yet been confirmed (260).

As shown in chart V the unsubstituted 1,3-diazaazulene (CCXXXVIII) can be obtained from tropolone methyl ether by reaction with thiourea in the presence of sodium ethoxide and oxidative desulfurization of the 2-mercapto-1,3-diazaazulene (CCXXXVII) so formed (301, 302). The imidazole nucleus is again demonstrated in the product (CCXXXVIII) by oxidation.

An analogous condensation occurs with guanidine (310), and the relation of the product to CCXXXVII has been demonstrated (see chart V). Both con-

densations have been applied to colchicine (259), and the guanidine condensation has also been applied to the methyl ethers of 4-methyl- (310), 4- and 5-isopropyl- (310, 343), and 3-bromo- and 5-nitrotropolones (294a). It has been found (310) that the same condensation product is obtained from both 4- and 6-methyl-2-methoxytropone, indicating that the 1- and 2-positions become equivalent in this reaction. This may be regarded as further evidence for the structures assigned to these products.

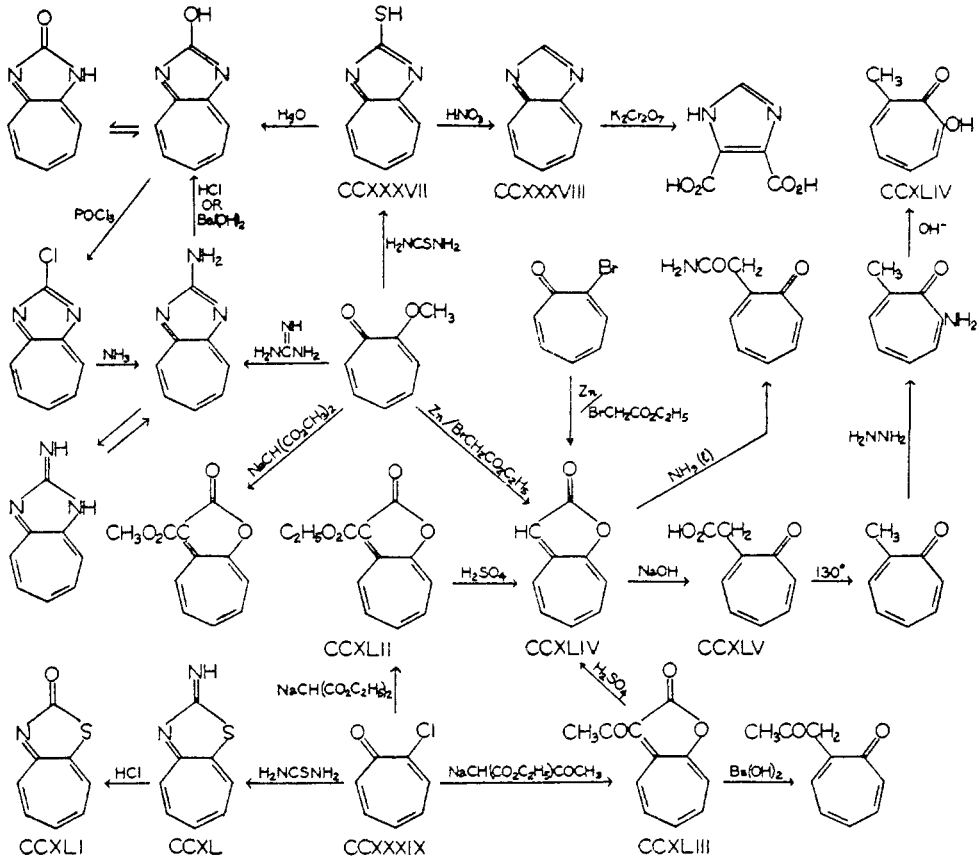


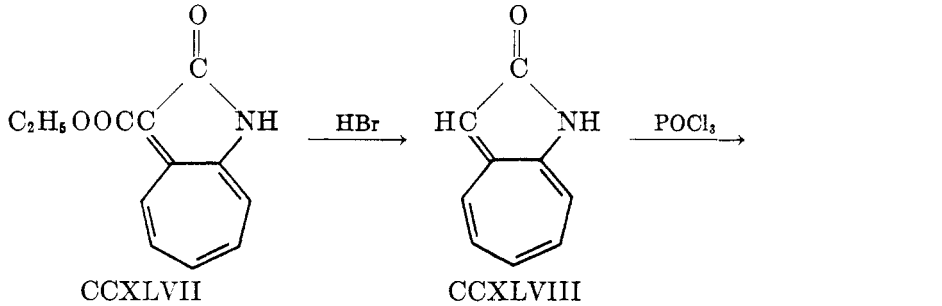
Chart V. Azulene analogs obtainable from tropones and their reactions

When thiourea is condensed with 2-chlorotropone (CCXXXIX), the imine (CCXL) of 2-keto-1,2-dihydro-3-aza-1-thiaazulene (CCXLI) is produced (261).

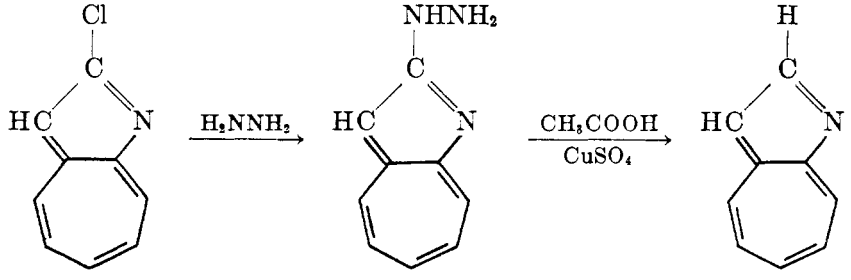
2-Chlorotropone (CCXXXIX) (338, 412) and its 4-, 5-, and 6-isopropyl derivatives (343) have been shown to react with both ethyl sodiomalonate and ethyl sodioacetoacetate. An analogous reaction of tropolone methyl ether has also been observed (94; *cf.* also 412). The structures (CCXLII and CCXLIII) of the products from 2-chlorotropone follow from their hydrolysis with strong acid to 2-keto-1,2-dihydro-1-oxaazulene (CCXLIV) and further degradation of the latter. CCXLIV is also obtained from tropolone methyl ether or 2-bromotropone by the Reformatsky reaction (339). Hydrolysis converts CCXLIV to

tropone-2-acetic acid (CCXLV), which has been further converted in several stages to the known 3-methyltropolone (CCXLVI) (412).

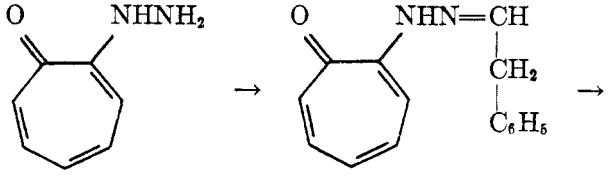
Ethyl sodiomalonate condenses similarly with 2-aminotropone to yield CCXLVII, which is hydrolyzed by hydrobromic acid to 2-keto-1,2-dihydro-1-azaazulene (CCXLVIII) (340). 2-Amino-5-isopropyltropone reacts similarly (343). By successive treatment with phosphorus oxychloride, hydrazine, and finally cupric sulfate CCXLVIII has been converted to 1-azaazulene (CCXLIX) itself, as shown:



CCXLVII CCXLVIII

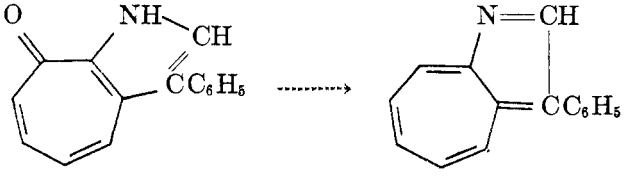


CCXLIX
1-Azaazulene



CCL
2-Hydrazino-tropone

CCLI



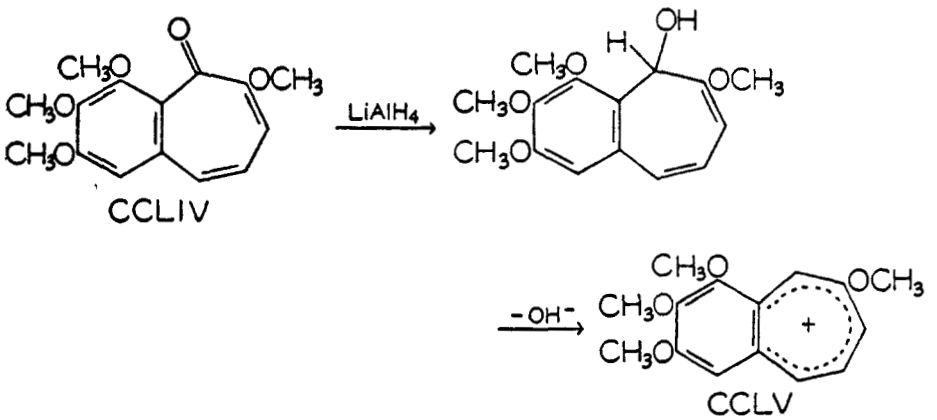
CCLII
8-Keto-3-phenyl-1,8-dihydro-1-azaazulene

CCLIII
3-Phenyl-1-azaazulene

This interesting product (CCXLIX) has been obtained as a red oil, characterized by a picrate and styphnate (340). 3-Phenyl-1-azaazulene (CCLIII) has been prepared (273) by a closely similar route from 8-keto-3-phenyl-1,8-dihydro-1-azaazulene (CCLII). The latter is itself obtained from the condensation product (CCLI) of 2-hydrazinotropone (CCL) and phenylacetaldehyde by the equivalent of a Fischer indole synthesis.

IX. Benzotropones and Benzotropolones

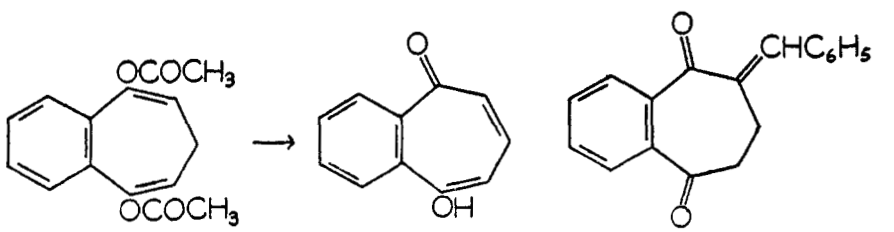
Fusion of a benzene ring to the tropone or tropolone systems causes a marked diminution of their characteristic properties. Many similarities remain however, at least in the 3,4-benzotropolones. A substituted benzocycloheptatrienylium salt (CCLV) has been obtained (112) by reduction of purpurogallin tetramethyl ether (CCLIV) with lithium aluminum hydride, followed by treatment with



CCLIV CCLV

acid. A theoretical study of the benzocycloheptatrienylium cation and the corresponding radical and anion has been published (140).

2,3-Benzotropone is unknown, but its 4-hydroxy derivative (CCLVII) has been obtained by bromination of the enol-acetate (CCLVI) of 2,3-benzocycloheptane-1,4-dione (43). Unlike monocyclic tropones this substance is unaffected by caustic potash even at 220°C. Its acidity and ketonic behavior agree with ex-



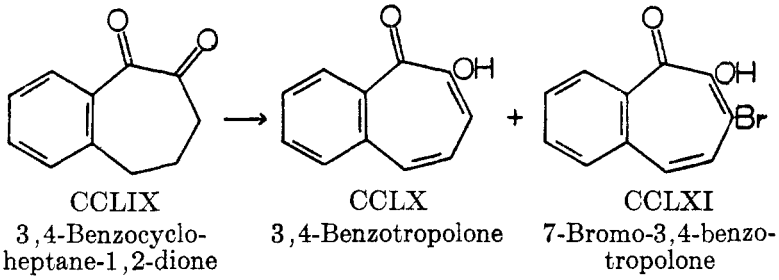
CCLVI CCLVII CCLVIII

pectation; only its marked basicity, as shown by the formation of an unstable hydrochloride, reveals its relation to monocyclic analogs. In view of the successful synthesis of CCLVII and the smooth isomerization of 2,7-dibenzylidenecycloheptane-1,2-dione (*cf.* page 33), the reported failure of the attempted isomerization

of CCLVIII to 5-benzyl-4-hydroxy-2,3-benzotropone must be attributed to the choice of unsuitable reaction conditions (17).

A. 3,4-BENZOTROPOLONE AND ITS DERIVATIVES

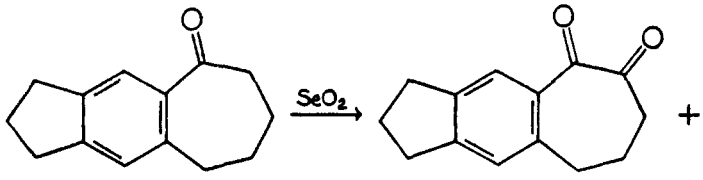
The synthesis (66, 75, 268) of 3,4-benzotropolone (CCLX) by the bromination and dehydrobromination of 3,4-benzocycloheptane-1,2-dione (CCLIX) to a mixture of CCLX and 7-bromo-3,4-benzotropolone (CCLXI), followed by hydrogenolysis of the latter, formed the model for the subsequent synthesis of tropolone by the same method (*cf.* page 30). It was originally carried out by using bromine in acetic acid as the brominating agent and was subsequently improved by the use of *N*-bromosuccinimide (234). Benzotropolone is also



CCLIX
3,4-Benzocyclo-heptane-1,2-dione

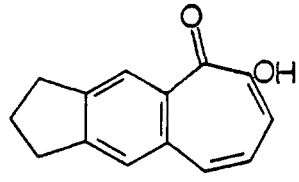
CCLX
3,4-Benzotropolone

CCLXI
7-Bromo-3,4-benzo-tropolone



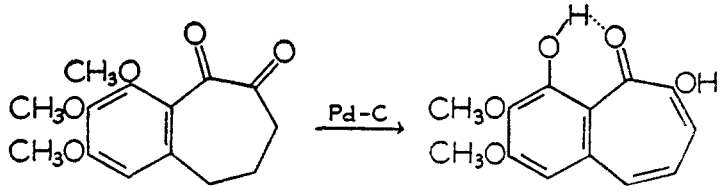
CCLXII

CCLXIII



CCLXIV

formed by direct dehydrogenation of the dione (CCLIX) with palladium on charcoal (66, 75). In the case of its 2′, 3′-trimethylene derivative, a small amount of the tropolone (CCLXIV) was isolated in the preparation of the intermediate dione (CCLXIII) by selenium dioxide oxidation of CCLXII followed by distillation (47).

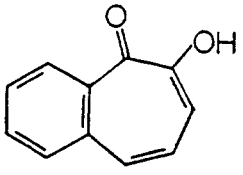


CCLXV

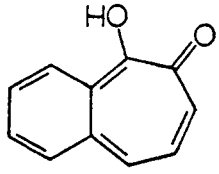
CCLXVI

The same method, using palladium dehydrogenation of the corresponding dione, has also been applied to the syntheses of the 2′, 3′-dimethoxy- (17, 52, 53) and 2′,3′,4′-trimethoxybenzotropolones and of purpurogallin (51, 52, 53). In the latter case, dehydrogenation of 1′,2′,3′-trimethoxy-3,4-benzocycloheptane-1,2-dione (CCLXV) is accompanied by demethylation and yields purpurogallin dimethyl ether (CCLXVI) (53).

Although the name 3,4-benzotropolone has been used, it would be more correct to refer to this substance as either 6,7-benzotropolone or 7-hydroxy-2,3-benzotropone, since it is certain that it exists normally only in one form (CCLXVII) and not as the tautomer (CCLXVIII), which would lack Kekulé resonance of the benzene ring.



CCLXVII



CCLXVIII

In agreement with this view, only one methyl ether can be obtained from 3,4-benzotropolone or any of its derivatives. The same considerations apply to 4,5-benzotropolone (see below).

In general properties 3,4-benzotropolone resembles tropolone. It is amphoteric, forms a chloroform-soluble copper chelate, and readily undergoes electrophilic substitution. By analogy with tropolone, the bromo, chloro, and sulfonic acid derivatives thus obtained have been assumed (66, 268) to be substituted in the 7-position. A tolylazo derivative has been described (268) as have also two disubstitution products, dibromo- (66) and dinitro- (268) 3,4-benzotropolones, both presumably 5,7-disubstituted.

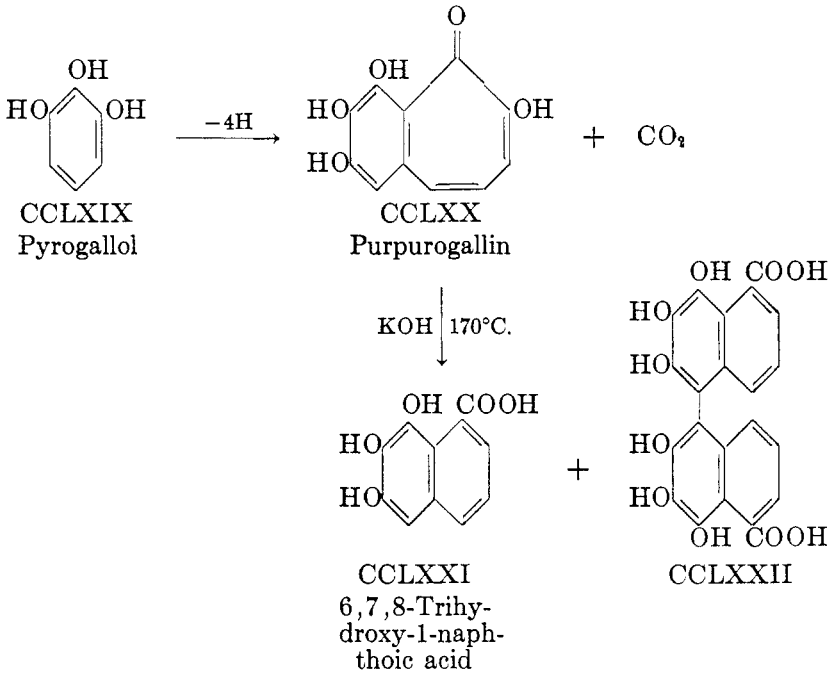
Although a methyl ether of the bromo derivative has been obtained with diazomethane (268), the formation of the ether of the parent compound by this method (268) has been disputed (66). The oily ether obtained (66) by the action of methyl *p*-toluenesulfonate yields a 2,4-dinitrophenylhydrazone (66), as do the ethers of 4,5-benzotropolone (240, 423, 424), in marked contrast to the ethers of tropolone and its monocyclic derivatives.

The rearrangement of 3,4-benzotropolone (and its derivatives) to 1-naphthoic acid (derivatives) by potash fusion proceeds at a lower temperature than that of the monocyclic analogs.

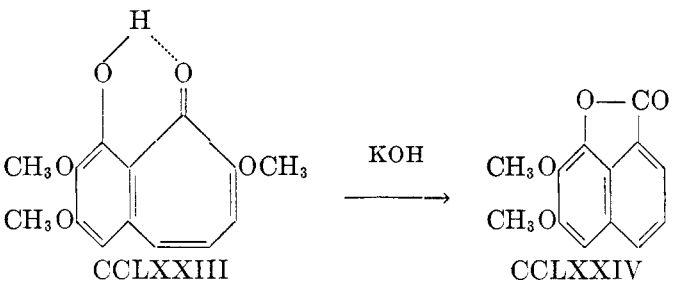
The best-known benzotropolone derivative is purpurogallin (CCLXX), obtained by the oxidation of pyrogallol (CCLXIX) with a wide variety of oxidizing agents under neutral or weakly acidic conditions (32, 33, 56, 57, 58, 59, 104, 121, 123, 147, 218, 244, 245a, 354, 356, 420, 448, 459). The preferred reagent is potassium iodate (113a).

Earlier work on the constitution of purpurogallin (87, 143, 144, 451) included its conversion to naphthalene by zinc dust distillation (245a, 355) and its rear-

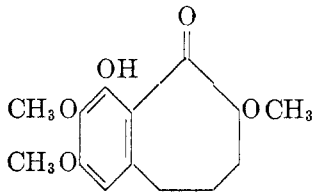
rangement to 6,7,8-trihydroxy-1-naphthoic acid (CCLXXI) on potash fusion. This change is accompanied by oxidation, resulting in the formation of CCLXXII as the major product along with CCLXXI (353, 355). This complication may be



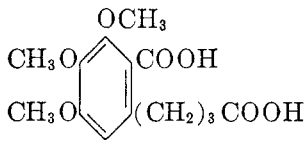
avoided by rearrangement of the trimethyl ether (CCLXXIII) of purpurogallin, which yields the lactone (CCLXXIV). The structures of CCLXXI and CCLXXII have been confirmed by synthesis (136).



The structure CCLXX was proposed for purpurogallin on the basis of the oxidation of its tetramethyl ether to 3,4,5-trimethoxyphthalic acid (18). This was confirmed by hydrogenation of the trimethyl ether (CCLXXIII) to CCLXXV, followed by methylation and oxidation to the dicarboxylic acid (CCLXXVI), which was identified by synthesis (135). Final proof was obtained by complete synthesis as mentioned above. X-ray crystal diffraction studies (102, 426) have added further confirmation.



CCLXXV

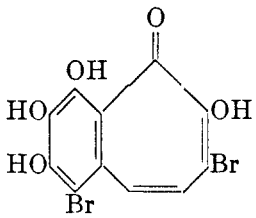


CCLXXVI

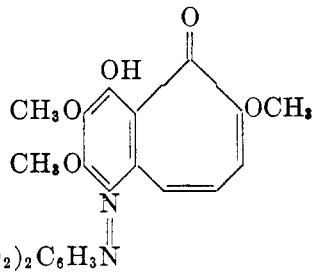
Numerous ethers and esters of purpurogallin have been described (58, 135, 142, 144, 353, 355, 432). Strong hydrogen bonding makes methylation beyond the trimethyl derivative (CCLXXIII) difficult (353, 451); conversely, hydrolysis of the tetramethyl ether to CCLXXIII is extremely easy (135, 144, 353).

The bright red color of purpurogallin appears enhanced in the 3′-monoalkyl derivatives. However, further etherification of the hydroxyl groups on the six-membered ring causes a marked diminution of color, and the tetraalkyl or tetraacyl derivatives are white. These changes affect only the (relatively weak) absorption in the visible range, the corresponding changes in the ultraviolet (135, 352, 432) being relatively small. The infrared spectrum of purpurogallin has also received attention (209).

Bromine converts purpurogallin to a dibromo derivative (58, 87, 355), whose structure (CCLXXVII) follows from its alternative formation from 4-bromopyrogallol (82). Brief warming with dilute sodium hydroxide effects a remarkable debromination of CCLXXVII to CCLXX (138).



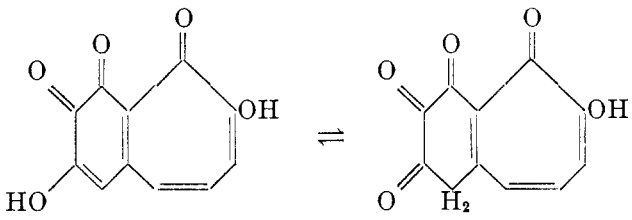
CCLXXVII



CCLXXVIII

Azo-coupling yields amorphous polysubstitution products, but from the tetramethyl ether and diazotized 2,4-dinitroaniline a product believed to be CCLXXVIII has been obtained with simultaneous loss of a methyl group (352).

The stability of the tropolone ring to oxidation enables the benzene ring of



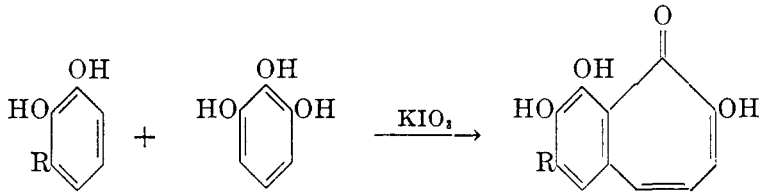
CCLXXIX

purpurogallin to be oxidized preferentially, presumably *via* the quinone (CCLXXIX), to products discussed in Section VIII,B. The intense blue color observed (121, 448) initially when purpurogallin is dissolved in alkalis in the presence of air represents the first stage of this oxidation and provides a sensitive color test.

Much interest attaches to the mechanism by which purpurogallin is formed from pyrogallol. Any proposal must take into account the following facts:

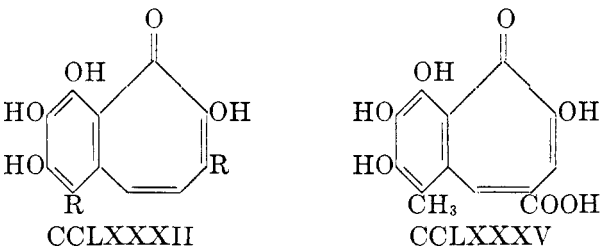
The reaction proceeds under very mild conditions. It is normally carried out at ice temperature. It is readily effected under physiological conditions by the enzyme peroxidase (13, 14, 420, 450, 452, 453, 454), a reaction which is used for the estimation of that enzyme (204, 205). It can even be brought about by palladium-catalyzed abstraction of hydrogen without air or other oxidizing agents (449).

The reaction fails when any of the hydroxyl groups of pyrogallol are etherified, but a mixture of the monomethyl (or ethyl) ether (CCLXXX: R = OCH_3 or OC_2H_5) and pyrogallol can be oxidized to a monoalkyl ether of purpurogallin. The structure CCLXXXI (R = OCH_3 or OC_2H_5) has been established (83) for the ether thus obtained. Similarly, a mixture of catechol (CCLXXX: R = H) and pyrogallol can be oxidized to CCLXXXI (R = H) (351, 451).

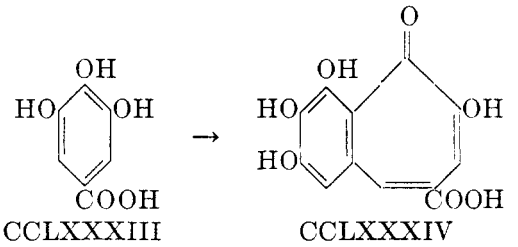


CCLXXX CCLXXXI

4-*n*-Alkyl- and 4-bromopyrogallol (but not the 4-COOH, 4-NO_2, or 4-OCH_3 derivatives) can be oxidized to the corresponding 1,7-disubstituted purpurogal-



CCLXXXII CCLXXXV

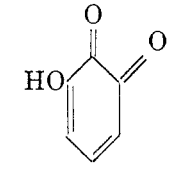


CCLXXXIII CCLXXXIV

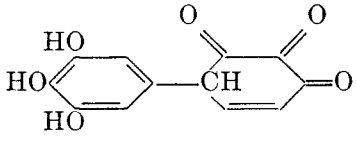
Gallic acid

lins (CCLXXXII) (82, 83, 138). 5-Substituted pyrogallols do not yield purpurogallin derivatives with the exception of gallic acid (CCLXXXIII), which reacts (84, 354, 451) with elimination of carbon dioxide to yield purpurogallincarboxylic acid (CCLXXXIV), whose structure has been established unambiguously (84). Its formation is improved by oxidizing a mixture of pyrogallol and gallic acid. A mixture of 4-methylpyrogallol and gallic acid yields a similar product, presumably CCLXXXV (82).

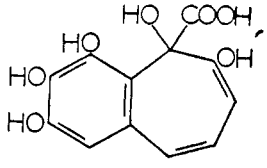
Two mechanisms have been proposed for the formation of purpurogallin; both assume initial oxidation of pyrogallol to the corresponding *o*-quinone (CCLXXXVI). The view that this dimerizes to the diphenyl derivative (CCLXXXVII) (83, 135) is an adaptation of an earlier mechanism (451). Several paths have been envisaged by which CCLXXXVII might rearrange to



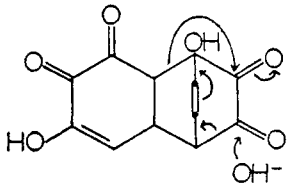
CCLXXXVI



CCLXXXVII



CCLXXXVIII



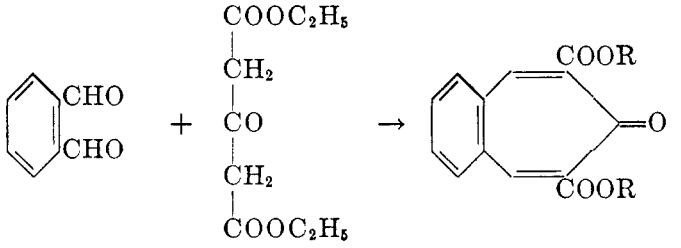
CCLXXXIX

CCLXXXVIII, which is then further oxidized to purpurogallin. The alternative view (92) that dimerization of CCLXXXVI takes the form of a Diels–Alder reaction yielding CCLXXXIX, which likewise rearranges to CCLXXXVIII, makes it more difficult to account for the failure of pyrogallol 1-methyl ether (CCLXXX: R = OCH_3) to undergo the reaction.

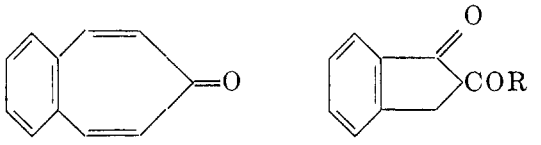
B. 4,5-BENZOTROPONE AND 4,5-BENZOTROPOLONE

The condensation of phthalaldehyde (CCXC) with acetonedicarboxylic ester (CCXCI) yields CCXCII (R = C_2H_5) (429). This product has been hydrolyzed both to the corresponding half-ester and to the free acid (CCXCII: R = H). The latter loses one molecule of carbon dioxide at its melting point and the second is lost on heating with acid, leading to 4,5-benzotropone (CCXCIII) itself (431). This substance and its homologs are reported to be inert towards ketonic reagents (phenylhydrazine and hydroxylamine) (431), an observation which deserves reinvestigation in view of more recent observations on the monocyclic analog. The homologs of CCXCIII (the 2-methyl, 2-ethyl, 2-*n*-propyl, 2,7-dimethyl, and 2,7-diphenyl derivatives) can be prepared directly by condensation of phthalaldehyde with the appropriate ketone, but acetone, methyl

isopropyl ketone, and methyl isobutyl ketone yield only (428, 431) the indanone derivatives (CCXCIV: R = CH_3, $CH(CH_3)_2$, and $CH_2CH(CH_3)_2$, respectively), which are observed as minor byproducts in some of the other cases (431). Recent reinvestigation of these 4,5-benzotropone derivatives has been confined to dipole moment (29, 442) and spectroscopic studies (399, 442).

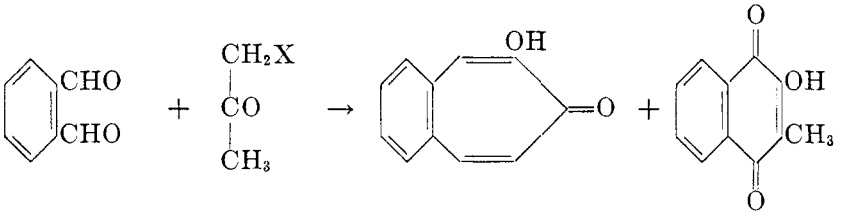


CCXC Phthalaldehyde CCXCI CCXCII



CCXCIII 4,5-Benzotropone CCXCIV

The use of bromoacetone (116) or hydroxyacetone (424) in the condensation with phthalaldehyde leads to 4,5-benzotropolone (CCXCV). When hydroxyacetone is used, phthiocol (CCXCVI) is also obtained. The same reaction has been



CCXCV 4,5-Benzotropolone CCXCVI Phthiocol

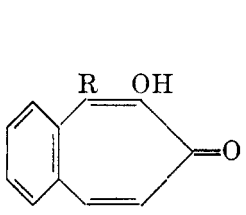
X = Br or OH.

applied to methoxyacetone (240, 423), phenoxy- and *p*-nitrophenoxyacetones (424), and methoxymethyl ethyl ketone (116). The resulting ethers, but not the free tropolones, yield 2,4-dinitrophenylhydrazones and other carbonyl derivatives (240, 423, 424).

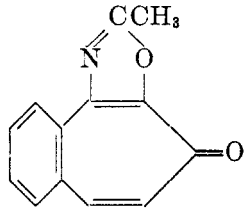
Other important differences between the 4,5-benzotropolone derivatives and their monocyclic analogs are seen in the low acidity (see table 1) of 4,5-benzotropolone and the corresponding behavior of its methyl ether like a phenolic

ether rather than like an ester. On the other hand, the methyl ether is sufficiently basic to form a crystalline hydrobromide; the infrared spectra show the typically low carbonyl frequencies (*cf.* page 21).

Aromatization of the tropolone ring in 4,5-benzotropolone is difficult (contrast 3,4-benzotropolone!) and only its 3-nitro derivative (CCXCVII: R = NO_2) has been rearranged to 1-nitro-2-naphthoic acid (116, 423). The 3-nitro derivative and also the 3-bromo and 3-*p*-nitrophenylazo derivatives are readily obtained from 4,5-benzotropolone by direct substitution (116, 240, 423). On the other



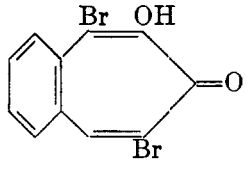
CCXCVII



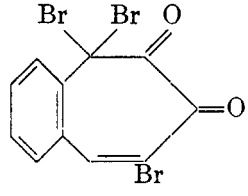
CCXCVIII

hand, salt formation with nitric acid complicates the nitration of the methyl ether of 4,5-benzotropolone and results in the formation of the 3-nitro derivative and nitration products substituted in the benzene ring (240). Reduction of the 3-nitro-4,5-benzotropolone (CCXCVII: R = NO_2) yields the corresponding amino derivative (CCXCVII: R = NH_2), which on acetylation gives the oxazole derivative (CCXCVIII) (240).

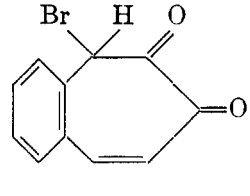
When CCXCV is brominated in acetic acid, CCXCVII (R = Br) and a dibromo derivative, presumably CCXCIX, can be obtained (116, 423). Further bromination yields CCC, which reverts to CCXCIX on reduction with sulfur dioxide.



CCXCIX



CCC



CCCI

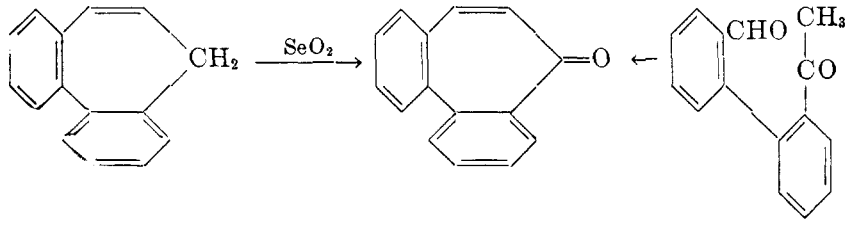
In carbon tetrachloride solution the intermediate bromination product (CCCI) can be isolated, and this is readily hydrolyzed to CCXCVII (R = OH) (116).

C. DIBENZOTROPONES AND DIBENZOTROPOLONES

These substances appear to be devoid of the typical properties of tropones and tropolones.

2,3,4,5-Dibenzotropone (CCCIII) has been obtained by oxidation of 1,2,3,-4-dibenzocycloheptatriene (CCCII) with selenium dioxide (62). It has also been obtained (67) by internal condensation of CCCIV, itself prepared by a two-step oxidation of 9-methylphenanthrene. Several substituted derivatives have been obtained by similar condensations (36, 67).

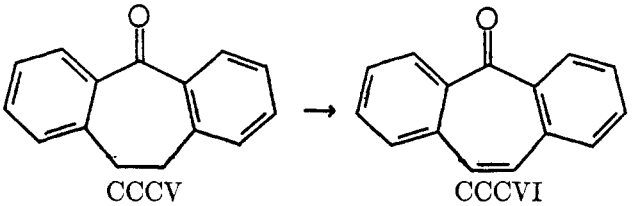
A dinitrophenylhydrazone can be obtained from CCCIII and also from its isomer (CCCVI) (30, 31, 42). The latter is obtained by bromination and dehydrobromination of CCCV (30, 42, 76, 435). Mono- and dinitro derivatives of CCCVI have been obtained similarly (49).



CCCII
1,2,3,4-Dibenzocycloheptatriene

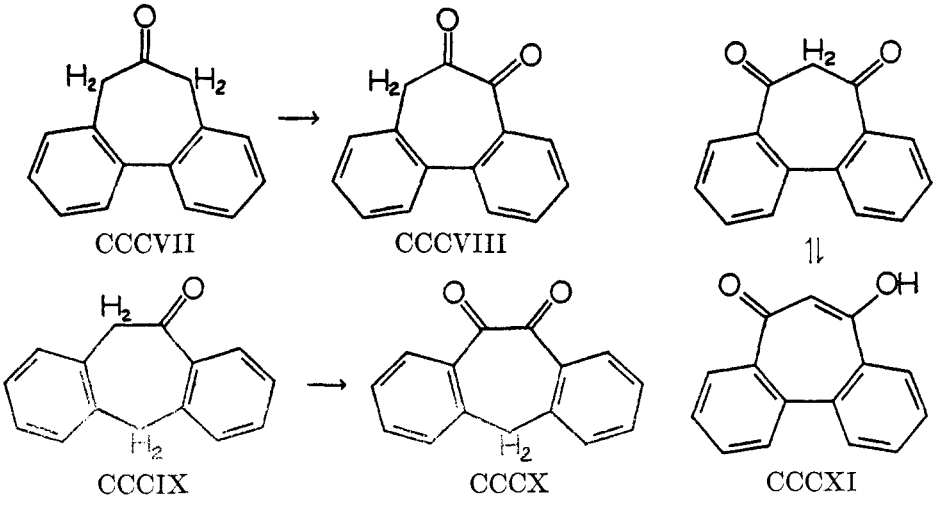
CCCIII
2,3,4,5-Dibenzotropone

CCCIV



CCCV CCCVI

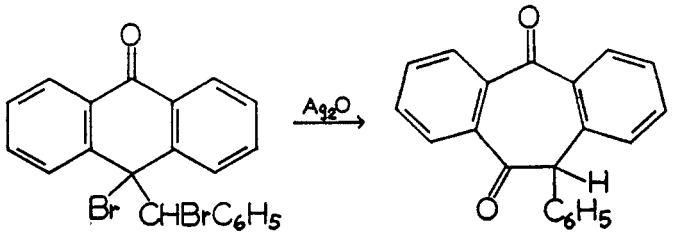
Both CCCVIII (370) and CCCX (364), obtained from CCCVII and CCCIX, respectively, by selenium dioxide oxidation, behave as typical α-diketones; this



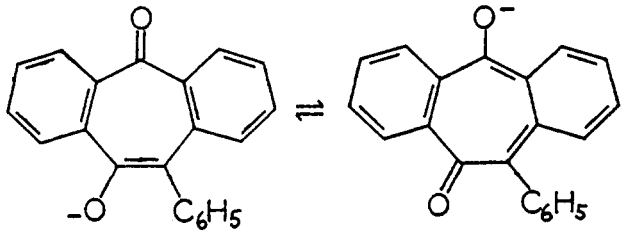
CCCVII CCCVIII CCCIX CCCX CCCXI

is shown by the formation of quinoxalines and by their facile benzilic acid rearrangements to phenanthrene- and anthracene-9-carboxylic acid, respectively. As a β-diketone, CCCXI, synthesized from diphenic acid (220), is largely enolized; it has the acidity and undergoes the facile electrophilic substitutions expected

of such a system. The same acidity is shown by CCCXIII (42), which is a vinylog of a β-diketone, and forms a red sodium salt which must contain the resonating



CCCXII CCCXIII



CCCXIV

anion CCCXIV. CCCXIII is obtained by a semipinacoline-type rearrangement of CCCXII on treatment with silver oxide (60, 61).

X. Physical Properties and Structure of Tropolones and Tropones

A wide variety of physical measurements have been made on tropolone and to a lesser degree on tropone, chiefly with a view to throwing light on their fine structure. The theoretical discussions have been mentioned in earlier sections, as have the spectroscopic studies, the measurements of acid dissociation constants (basicities have not been studied quantitatively), and the measurements of stability constants of the coördination compounds of tropolone. All other measurements are summarized in this section.

A. SOLUBILITIES

Two papers have been devoted specifically to the solubilities of various tropolone derivatives in water, determined by potentiometric titration (471, 472).

B. POLAROGRAPHIC REDUCTION

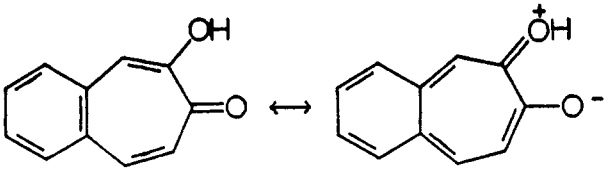
Polarographic measurements have been carried out on colchicine and several of its derivatives (37, 38, 38a, 377, 378), tropolone (158, 239), 4-methyltropolone and its methyl ether (2-methoxy-6-methyltropone) (239), 5-isopropyltropolone (38, 38a, 378), and 4,5-benzotropolone (239). In all these cases essentially similar behavior is observed. At low pH values a single reduction wave is observed, which in all cases represents a single electron reduction involving a hydrogen ion as shown by its dependence on pH.

In alkaline solutions a further reduction step appears, also involving a single electron, but no hydrogen ion (239; but *cf.* also 38a).

Discrepancies between the results of different workers have been attributed largely to the use of different buffer systems (239). Bearing in mind such variations, there is no significant difference in the behavior of the different tropolones except benzotropolone.

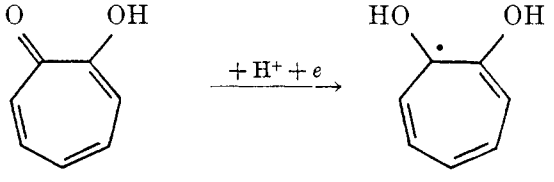
For the first wave, the half-wave potential has a value of approximately −1.35 v. at pH 7. Reduction of the tropolone ethers is markedly easier; the lowering of the potentials of the first wave varies somewhat with pH (particularly in the case of colchicine), but in the case of the ether of 4-methyltropolone it is ca. 100 mv., corresponding to an energy difference of approximately 2.3 kcal. The second wave has a half-wave potential of ca. −1.5 v. throughout the pH range in which it can be observed, both for the tropolones and for their ethers.

For 4,5-benzotropolone, the corresponding potentials are ca. −1.1 v. at pH 7 for the first wave and ca. −1.33 v. for the second wave. Both stages of the reduction are seen to be much easier in this case. This has been attributed (239) to the reduced resonance of the tropolone ring in this system, owing to the fact that the canonical form (CCCXV) involves a quinonoid six-membered ring.



CCCXV

The first reduction step in the case of tropolone has been pictured as shown (CCCXVI → CCCXVII). Since it is apparently irreversible, the resultant



CCCXVI CCCXVII

radical may be assumed to undergo rapid secondary changes, whose nature can only be conjectured, since no products have been isolated. If this picture of the first reduction step is correct, the greater ease of reduction of the ethers may perhaps be due to their increased basicity. Moreover the potential should become independent of pH when all the tropolone is present as the conjugate acid; but in the absence of dissociation constants of the conjugate acid, it cannot be determined whether this should have been observed within the pH range studied.

A polarographic method for the estimation of colchicine has been described (376).

C. MAGNETIC SUSCEPTIBILITIES

The diamagnetic susceptibilities of the following tropone derivatives have been measured by the Gouy method (139, 229, 311) (values of $\chi_M \times 10^6$ are given

in parentheses): Tropone (54); tropolone (−74); anhydrous tropolone methyl ether (−71 ± 2); tropolone methyl ether hemihydrate, $(C_8H_8O_2)_2 \cdot H_2O$ (−160 ± 7); hinokitiol (−102 ± 1); 3-isopropyltropolone (−100 ± 3; −97 ± 2); 2-methoxy-7-isopropyltropone (−105); 2-methoxy-7-bromotropone (−88).

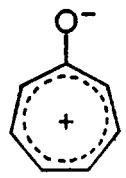
The errors given appear to represent the variations between several measurements. Judging by the small quantities of the substances employed and the description of the method used, the actual limits of error are likely to be appreciably greater.

The authors have drawn conclusions concerning the fine structure of the substances examined from a comparison of the experimental data with values calculated by the Pascal method from atomic parameters. Some of these conclusions are in direct conflict with other evidence. In view of the assumptions and approximations made in arriving at these conclusions, their value appears extremely doubtful.

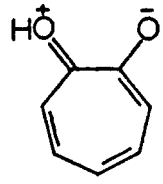
D. DIPOLE MOMENTS

The known dipole moments of tropone and tropolone derivatives are collected in table 8. They have been demonstrated to be in good agreement with the assumption that the moment results chiefly from contributions of structures of the type shown in formula CCCXVIII for tropone, with additional contributions from forms of the type shown in formula CCCXIX for tropolone derivatives. In tropolone itself, the direction of the dipole can be defined as being along a line through the center of the ring and midway between the two oxygen atoms.

On this basis, and using for substituents the moments they have in corresponding benzene derivatives, it has been possible to calculate theoretical values in



CCCXVIII



CCCXIX

fair agreement with the observed data. Such calculations have been successfully used to assign structures to a number of halogen derivatives of previously unknown orientation and to confirm the orientation of others (193, 196, 198, 199, 200, 201). The assignments have subsequently been verified by chemical methods (see, e.g., 275). It has even been possible to assign correctly the structures of isomeric ethers of 4-methyltropolone (2, 131), but it must be admitted that the success in this case may have been partly fortuitous.

The main interest in the dipole moments arises, however, in the light that they can throw on the extent to which tropolones and particularly tropones are polarized, i.e., the relative importance of CCCXVIII and the uncharged structure.

Comparison of the value for tropone with that for cycloheptanone (3.04 D)

TABLE 8

Dipole moments

Compound	μ in Benzene	Temperature	References
	D	°C.	
Tropolone	3.71	25	(193, 198)
	3.64	35	(193, 198)
	3.53	25	(201)
Tropolone derivative:			
3-Methyl	3.27	25	(196, 292, 293)
4-Methyl	3.88	30	(196, 292, 293)
	3.9		(437a)
5-Methyl	3.94	25	(196, 292, 293)
3-Isopropyl	3.37	25	(200)
4-Isopropyl	4.04	25	(193, 197, 198)
3-Bromo	3.91	25	(200)
5-Bromo	2.07	25	(200)
3-Bromo-7-methyl	4.05	25	(196, 292, 293)
3-Bromo-6-methyl	4.42	25	(196, 292)
5-Bromo-4-methyl	2.68	25	(196, 292)
3-Bromo-5-methyl	4.51	30	(196, 292, 293)
3-Bromo-4-isopropyl	4.4	25	(199)
3-Bromo-6-isopropyl	4.32	33	(196, 292)
3-Chloro-4-isopropyl	4.38	25	(199)
3-Chloro-6-isopropyl	4.74	25	(199)
5-Chloro-4-isopropyl	2.7	25	(199)
3,7-Dibromo	3.57	25	(200)
3,7-Dibromo-4-methyl	4.19	30	(196, 292)
3,7-Dibromo-5-methyl	4.27	30	(196, 292, 293)
3,7-Dibromo-4-isopropyl	4.27	33	(193, 197, 198)
3,5-Dibromo-7-isopropyl	2.82	25	(200)
3,5-Dibromo-6-isopropyl	3.14	20	(193, 198)
3,7-Dichloro-6-isopropyl	4.46	25	(199)
3,5,7-Tribromo	1.84	25	(193, 198)
4-Methyl-3,5,7-tribromo	3.02	25	(196, 292)
4-Isopropyl-3,5,7-tribromo	3.05	25	(200)
3-Nitro-6-isopropyl	6.19	25	(193, 198)
3,5-Dinitro-6-isopropyl	4.63	20	(193, 198)
2-Methoxytropone	4.72	25	(201)
2-Methoxytropone hemihydrate	6.81	20	(201)
	6.78	30	(201)
	6.80	40	(201)
2-Methoxytropone derivative:			
6-Methyl	4.9		(437a)
	5.06	25	(201)
7-Isopropyl	4.11	25	(201)
3-Bromo	3.31	25	(201)
7-Bromo	5.51	25	(201)
Tropone	4.17	25	(201, 311)
	4.30		(120)
Tropone derivative:			
2-Phenyl	3.82	25	(201)
2-*p*-Methoxyphenyl	3.63	25	(201)
4-Bromo-2-phenyl	2.73	25	(201)
3,7-Dibromo-2-phenyl	3.67	25	(201)
2-Methyl-4,5-benzo	4.25		(442)
2,7-Dimethyl-4,5-benzo	3.7		(442)
	3.66		(29)
2,7-Diphenyl-4,5-benzo	3.69		(29)

(128) has been made (201). It has been pointed out (162, footnote 92) that this neglects the effect of conjugation, and the value (4.00 D) (29) for 3,5-dimethylcyclo-2-hexen-1-one has been quoted in this connection. In the latter substance the methyl groups must make a considerable contribution. (By analogy with the moments of acraldehyde and crotonaldehyde (29), which have the appropriate *s-trans*-configuration, the 3-methyl group alone is responsible for approximately 0.6 D of the above value.) Hence the value for unsubstituted cyclohexenone is probably only some 0.3–0.4 D higher than that of cyclohexanone (3.01 D (29)).

Clearly no satisfactory quantitative comparison can be made until the values of the dipole moments of cycloheptenone, of the recently described 2,4-cycloheptadien-1-one (46, 422), and the still unknown 2,6-cycloheptadien-1-one become available. However, the qualitative conclusion that the aromaticity of CCCXVIII enhances the polarity appears justified.

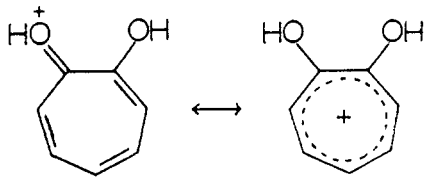
Comparison of the moments of 2-methyl- and 2,7-dimethyl-4,5-benzotropones with the observed value for dibenzylideneacetone (442) neglects the *s-cis-s-cis* configuration of the latter (29), and calculations of the value for the corresponding *s-trans-s-trans* form are too uncertain (29) to lead even to a qualitative conclusion.

E. X-RAY DIFFRACTION

X-ray studies of the crystal structure of colchicine (185), colchiceine (235), nootkatin (48), purpurogallin (102, 426), and 3-bromotropolone methyl ether (447) have been aimed chiefly at the determination or confirmation of the structures of these substances.

Much useful information has, however, been gained from a two-dimensional crystal analysis of cupric tropolone (367). It shows that the tropolone nucleus is a planar, almost regular heptagon with an average carbon–carbon distance of 1.40 Å. These conclusions are confirmed by more recent studies of tropolone hydrochloride (397) and sodium tropolonate (396) of which full details are not yet available.

Observed variations of the carbon–carbon bond lengths are within the limits of possible error, and it is therefore not yet known whether real differences exist. The two carbon–oxygen bonds in the copper chelate are, however, clearly different. The carbonyl carbon–oxygen bond is 1.25 Å. long and the other carbon–oxygen



CCCXX CCCXXI

bond is 1.34 Å. The corresponding oxygen–copper distances are 1.98 and 1.83 Å., respectively.

By contrast, the carbon–oxygen distances in the hydrochloride are approximately equal; their lengths (1.40–1.42 Å.) correspond to very little double-bond character, emphasizing the importance of structure CCCXXI relative to CCCXX.

F. ELECTRON DIFFRACTION

Two electron diffraction studies of tropolone (141, 184) have yielded results which can be satisfactorily explained on the basis of the model suggested by the x-ray data. The most likely carbon–carbon and carbon–oxygen bond distances deduced from the electron diffraction studies (184) agree well with the values given above for cupric tropolone.

G. HEAT OF COMBUSTION AND RESONANCE ENERGY

Two independent measurements of the heat of combustion of tropolone (149, 242) lead in good agreement to the values -37.1 and -37.2 ± 0.3 kcal./mole for the heat of formation of gaseous tropolone at 25°C. From these, by the use of different standard bond energies, the different authors deduce values of 36 (149) and 29 (242) kcal./mole for the resonance energy of tropolone.

In the absence of agreed standards, not only for the calculation of the resonance energies themselves but also for comparison of the values so obtained with suitable reference substances, the significance of these results is debatable.

XI. Biological Properties of Tropolones

Considerable attention has been devoted to the physiological properties of tropolones. Unfortunately much of the Japanese literature on this subject, devoted chiefly to the effects of hinokitiol (4-isopropyltropolone), is unavailable to the reviewer.

A. ANTIMITOTIC EFFECT

In view of the outstanding effect of colchicine on mitosis, the action of other tropolones is of considerable interest. A substantial number of such compounds have been tested (175, 176, 177, 211, 374, 398). Most are completely inactive or show activity of a very low order. The highest activity so far encountered in a simple tropolone derivative in tests against sarcoma is that of 5-amino-3-bromotropolone (175). Some basic tropolone derivatives have shown mitotic activity when tested on plant cells (443, 444, 445).

Numerous colchicine derivatives have been tested (see, e.g., 210, 212, 213, 232, and 389) and although no compound more active than colchicine has been found, numerous modifications of the structure have been shown to result in little or only partial loss of activity. At the same time, toxicity is sometimes greatly reduced, so that the ratio of the minimum effective dose to the maximum tolerated dose is in some cases much more favorable. Both the retention of activity and the decrease in toxicity are observed in several compounds in which the tropolone ring has been rearranged to a benzenoid system. Thus the conclusion seems inescapable that the tropolone ring system has little significance for antimitotic activity.

B. BACTERIOSTATIC AND BACTERICIDAL ACTIVITY

The mould metabolites puberulic and puberulonic acids, which are active (349) against Gram-positive bacteria, first directed attention to the potentialities of tropolones in this field. *Thuja* extracts possess activity, unrelated to Gram staining, *in vitro* but not *in vivo* (418). More recently the activity of hinokitiol (6, 169, 171, 178, 221, 223, 227, 233, 237, 418, 446, 463, 466) and of various other tropolones (6, 15, 179, 221, 222, 225, 446, 463, 464, 465) against a variety of bacteria has received extensive study. The activity of hinokitiol on spirochetes has received attention (467); it has been reported to show activity against both sulfathiazole-susceptible and sulfathiazole-resistant dysentery bacteria (183). An enhancement of streptomycin sensitivity has also been reported (446).

Greatest attention has been devoted to the action of hinokitiol (145, 146, 168, 169, 170, 172, 173, 174, 202, 221, 233, 415, 416, 434, 460, 466) and more recently a few other tropolones (202, 221, 222, 466) on tubercle bacilli. Therapeutic application of hinokitiol against tuberculous fistulae (186, 187, 462), tuberculous pyothorax (246), and tuberculous conjunctivitis (157) has been reported.

Hinokitiol has also been applied against Koch–Weeks conjunctivitis (164), pulmonary abscesses (470), gangrene of the lung (373), decubitus (187, 421), and blepharitis (153, 165).

The observation (119) that certain tropolones inhibit the oxidation of inositol by bacterial enzymes may throw light on their mode of action.

C. ANTIFUNGAL ACTIVITY

The notable resistance to fungi shown by the wood of trees containing tropolones has led to the demonstration of fungistatic and fungicidal properties of significant degree in the isopropyltropolones (15, 363, 418) and in 3,4-benzotropolone (15).

D. GENERAL

Studies of the toxicity and local action of hinokitiol (206) and of its action on the respiratory and circulatory system (207) and on muscles and peripheral nerves (208) have been made. The fate of hinokitiol in the organism (226, 371, 372), its best mode of administration (469), and its estimation (224, 225, 427) and that of tropolone (225, 468) have received attention.

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XIII. Addendum

(November 15, 1954)

The oxidation of hydroxymethyltropolones with manganese dioxide in benzene has provided a convenient route to the corresponding aldehydes, and a variety of condensation reactions of these aldehydes have been studied (488). Further oxidation yields the corresponding acids, also obtained directly from the hydroxymethyl derivatives with Tollens reagent. The same authors describe numerous mono- and dicarboxylic acids obtained *via* the corresponding nitriles from bromotropolone derivatives.

Several tropolones have been found (488) to undergo an interesting reaction with selenium dioxide. The products are shown to be di-3(or 7)-tropolonyl diselenides.

The action of phenyllithium on the copper complex of 4-methyltropolone has been found to yield a third isomeric phenylmethyltropone differing from those obtained from the two methyl ethers. The mechanisms previously advanced can account for only two isomeric products; indeed they are now found to be applicable only to the product obtained from the copper chelate, which is identified as 6-methyl-2-phenyltropone. The other two products are identified as 5-methyl-2-phenyl- and 3-methyl-2-phenyltropone, formed from 2-methoxy-4-methyl- and 2-methoxy-6-methyltropone, respectively. This result is attributed to a 1,8-addition of the Grignard reagent to the unsaturated carbonyl system (482). The same mechanism presumably applies to other cases of this reaction, and an analogous scheme will account for the "anomalous" replacement of halogen by ammonia already reported (342).

The observation (491) that isocolchicine on treatment with methylmercaptan gives (though in low yield) thiocolchicine identical with that similarly obtained from colchicine shows that this replacement can likewise take place by at least two mechanisms. This is also the first report concerning replacement with mercaptans under acidic conditions in place of the reaction with mercaptide ion used by other investigators. Several derivatives of thiocolchicine are also reported (491, 492), including the sulfoxide, which is obtained in two stereoisomeric modifications resulting from the asymmetry of the sulfur atom. Some new observations on the effects of irradiation on colchicine and several derivatives have been reported (487). The oxidation product obtained from colchicine with periodic acid has been shown to be a diunsaturated lactonic acid and is the first example of oxidative cleavage of the tropolone ring system without loss of carbon atoms (480).

Both Nozoe (486) and Sebe (488) now recognize the initial products of oxidation of hinokitiol with alkaline peroxide as muconic acids (*cf.* footnote 4). The main oxidation product is identified as α-isopropylmuconic acid, its previously reported transformation to β-isopropyllevulinic acid being now denied (486). However, although β-isopropylmuconic acid has not been found, its formation may be inferred from the presence of β-isopropyllevulinic acid in the oxidation product. Thus, as expected, either C_1 or C_2 may be eliminated in the reaction.

Similar oxidation of 3-isopropyl-, 5-isopropyl-, and 4-methyltropolones has led to the isolation of α-isopropyl-, β-isopropyl-, and α-methylmuconic acids, respectively (483).

Other recent publications include reports on a synthesis of 5-hydroxy-3,4-furotropolone (490), further work on the formation constants of metal chelates of tropolones (479) and benzotropolones (478), more detailed accounts of work previously reported on nootkatin (481) and on the maleic anhydride addition reaction (489), and patents on the preparation of tropone (484) and its aryl derivatives (485).

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