QUARTERLY REVIEWS

THE TROPOLONES

By J. W. Cook, D.Sc., F.R.S.
(Regius Professor of Chemistry, University of Glasgow)
and J. D. Loudon, D.Sc., Ph.D.
(Lecturer in Chemistry, University of Glasgow)

Until recently, very few natural products had been shown to be derived from *cyclo*heptane. Occasionally such structures have been proposed and later discarded as, for example, in the case of irone. The rarity of *cyclo*heptane derivatives in Nature and the errors which have been made in assigning such structures have inevitably led to a somewhat cautious attitude towards new suggestions of their presence. It is true that there have been a number of well-authenticated examples: these include tropine and the alkaloids derived from it, and the sesquiterpene ketone β-vetivone and some related naturally occurring azulenes. But the tropane alkaloids are bridged-ring compounds and might equally well be regarded as substituted piperidines. Even in the azulenes the seven-membered ring is subordinated to the essential unit of structure in which it occurs fused with another ring of five carbon atoms.

The present Review gives an account of a new class of natural product, in which a seven-membered carbon ring is the common structural feature. Several of these natural products have been synthesised and the class has been expanded, and knowledge of its physical and chemical properties enriched, by the inclusion of new members of purely synthetic origin. Among the latter is the parent compound, the hydroxy*cyclo*heptatrienone (I), for which the more convenient name, tropolone, has come into general acceptance and use.

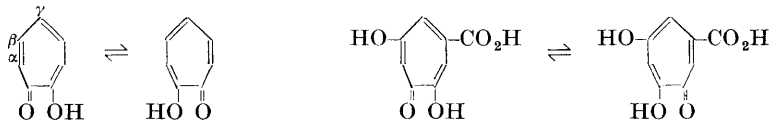
The Mould Tropolones.—Like the name itself, the tropolone concept was first suggested by Dewar [1] who advanced it in 1945 to interpret the recorded chemical behaviour of stipitatic acid. This acid is produced by the mould *Penicillium stipitatum* Thom and was isolated from the culture media by Birkinshaw, Chambers, and Raistrick.[2] These investigators gave an extensive and accurate account of the chemistry of the acid but did not propose a structural formula. They pointed out a general resemblance to another mould acid, puberulic acid, which had been isolated by Birkinshaw and Raistrick [3] from cultures of *P. puberulum* Baines and from *P. aurantio-virens* Biourgs, and they regarded the two acids as probably representing a new

[1] *Nature*, 1945, **155**, 50.
[2] *Biochem. J.*, 1942, **36**, 242.
[3] *Ibid.*, 1932, **26**, 441.

type of mould product. A third acid, puberulonic acid,[3] which was isolated together with puberulic acid, was considered by Barger and Dorrer [4] to be structurally related to the latter acid but the evidence for this view was never disclosed. Oxford, Raistrick, and Smith [5] also obtained puberulic and puberulonic acids from *P. Johannioli* Zaleski and *P. cyclopium-viridicatum* series.

Despite the simplicity of its molecular formula, $C_8H_6O_5$, stipitatic acid confronted its investigators with a chemical problem which was as complex as it was novel. It could be shown [2] that of the five oxygen atoms in the molecule two were accounted for in a carboxyl group and two were in the form of enolic hydroxyl groups, one of which had more strongly developed acidic properties than the other. The fifth oxygen atom resisted direct identification but, since hydrogenation products of stipitatic acid showed ketonic properties, it appeared to be present as a masked ketonic group which became unmasked in course of reduction. The oxygen atoms were again implicated in the formation of *two* isomeric neutral trimethyl derivatives, $C_7H_3O(OMe)_2{\cdot}CO_2Me$, when the acid reacted with diazomethane. Moreover, the relationship between these oxygen atoms had to be conceived within a carbon framework which could account for a striking experimental fact, namely, that stipitatic acid was isomerised when fused with alkali affording 5-hydroxy*iso*phthalic acid in high yield. In face of these requirements and in view of the molecular formula perhaps the most perplexing feature of all was the absence of ethylenic reactivity. Stipitatic acid readily dissolved in cold concentrated hydrochloric or nitric acid and was recovered on dilution with water. It appeared to form a loose addition complex with bromine in water, was unchanged by bromine in glacial acetic acid, and was monosubstituted by bromine in aqueous acetic acid.

It was the inspiration of genius which led Dewar [1] to conclude that the properties of stipitatic acid are accommodated in the formula (II) and, as corollary to this conclusion, that tropolone (I) represents a new type of aromatic structure. At that time tropolone was unknown but its subsequent synthesis, and the later work on stipitatic acid, have amply confirmed both of these deductions.

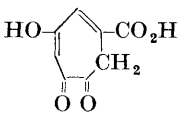


(I.) (I*a*.) (II.) (II*a*.)

The aromatic nature of tropolone is more fully discussed on p. 124 but it may be noted here that the carbonyl and the hydroxyl group of (I) are linked to each other through a chain of conjugated ethylenic groups and will therefore affect each other, in some measure, as they do in a carboxyl group. This is certainly not a complete analogy but it assists in correlating the pronounced acidity and lack of ketonic character associated with the

[4] *Biochem. J.*, 1934, **28**, 11. [5] *Chem. and Ind.*, 1942, **61**, 485.

tropolone system. Moreover, it shows how partial reduction—by destroying conjugation—may evoke ketonic reactivity as instanced in reduced stipitatic acid. At this stage also reference must be made to the tautomeric potentialities of tropolones. The identity of the two possible enolic forms (I) and (I*a*) confers on the parent compound a symmetry which would also obtain in γ-monosubstituted derivatives. Such symmetry is not maintained in α- or β-substituted tropolones where the corresponding enolones are distinct as exemplified by (II) and (II*a*). In practice, however, this has not led to isolable tautomers, presumably because the mobility of the system is high. The single compound isolated in such cases is usually but arbitrarily formulated as one or other of the alternative structures. These structures, on the other hand, become fixed in the derived methyl ethers and the two trimethyl derivatives of stipitatic acid undoubtedly correspond to the two enolone forms (II and II*a*). Tautomeric α-diketo-forms, of which two are theoretically possible in tropolone, cannot be present to any appreciable extent in view of the inertness displayed towards carbonyl reagents and to *o*-phenylenediamine. It is noteworthy, however, that α-diketones in general, and the related diosphenols (hydroxy*cyclo*hexenones) in particular, share the capacity to undergo benzilic acid rearrangement, the process involving ring contraction in the case of the cyclic compounds. This provides a basis for interpreting the isomerisation of stipitatic acid when fused with alkali: thus, applied to (II) or to the diketo-form (II*b*), benzilic change gives a product (III) which would be expected to undergo ready dehydration, thereby affording 5-hydroxy*iso*phthalic acid (IV) in accordance with the experimental result.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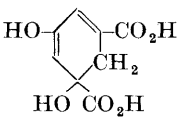
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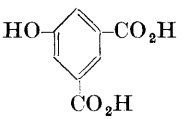
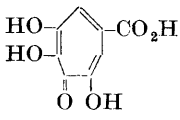

(IV.)

The structural chemistry of the mould tropolones has been developed by Johnson and Todd and their collaborators. They showed [6] that stipitatic acid may be oxidised by alkaline hydrogen peroxide to a mixture of aconitic and malonic acids and have supplemented this confirmatory degradative evidence by a synthesis [7] of stipitatic acid (p. 116) which provides the final proof of the structure (II ⇌ II*a*). In agreement with a suggestion made by Dewar,[8] they concluded [6] that puberulic acid, $C_8H_6O_6$, is a hydroxystipitatic acid and they adopted the formula (V)—or one of its tautomers—since only this vicinal arrangement of the oxygen atoms is consistent with the formation of aconitic acid (VI), observed when puberulic acid was oxidised with alkaline hydrogen peroxide. Their investigations also extended to puberulonic acid [9] for which they established the molecular

[6] Corbett, Johnson, and Todd, *J.*, 1950, 6, 147; cf. *Chem. and Ind.*, 1949, 626.
[7] Johnson, Taylor, and Todd, personal communication; see Bartels-Keith, Johnson, and Taylor, *Chem. and Ind.*, 1951, 337. [8] *Nature*, 1945, **155**, 479.
[9] Corbett, Hassall, Johnson, and Todd, *J.*, 1950, 1.

formula $C_9H_4O_7$ and a simple relationship with puberulic acid, *viz.*, $C_9H_4O_7 + H_2O \longrightarrow CO_2 + C_8H_6O_6$ (V), representing conversion of the former into the latter in hot aqueous solution. Because of the resistance to acetylation shown by puberulonic acid—and not shared by puberulic acid—Corbett, Johnson, and Todd [6] suggested for the former acid a structure of type (VII), but this has now been abandoned, mainly on spectroscopic evidence, in favour of the tropolone structure (VIII). The latter was first proposed by Aulin-Erdtman [10] from the ultra-violet absorption behaviour of puberulonic acid at various pH values and has subsequently been confirmed by the infra-red absorption spectrum of the acid determined independently both by the Swedish [11] and the Cambridge [12] investigators.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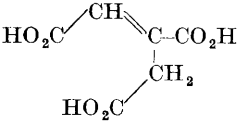
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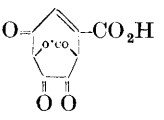
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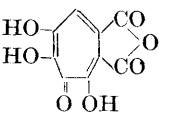
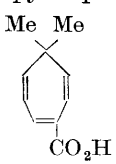

(VIII.)

The repercussions of Dewar's ideas on tropolone and on stipitatic acid were by no means confined to the chemistry of mould products. They had a stimulating and almost immediate effect on investigations which were proceeding at different centres, relating to a variety of natural products and embracing problems partly of long standing, partly new. Dewar himself suggested [13] that a tropolone methyl ether structure best interpreted the chemical behaviour associated with ring C of colchicine, the alkaloid of *Colchicum autumnale* Linn. Barltrop and Nicholson [14] obtained experimental evidence leading to their re-formulating purpurogallin as a benzotropolone derivative and this was promptly confirmed by the work of Haworth, Moore, and Pauson.[15] Meanwhile Erdtman and Gripenberg,[16] in association with Anderson,[17] isolated and identified three new tropolones, the thujaplicins, from the heartwood of *Thuja plicata* D. Don. Added to this degradative work, which preceded the developments in mould tropolones, there was unceasing effort to synthesise the tropolone ring system. This, which began with an abortive experiment by Dewar,[1] first achieved success in the synthesis of $\alpha\beta$-benzotropolone by Cook and Somerville,[18] followed by that of $\beta\gamma$-benzotropolone by Tarbell, Scott, and Kemp,[19] and of purpurogallin by Caunt, Crow, Haworth, and Vodoz,[20] and culminated in three almost simultaneous but distinct syntheses of tropolone itself—by Doering and Knox [21] in America, by Cook, Gibb, Raphael, and Somerville,[22] and by

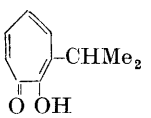
[10] Chemical Society Symposium on Tropolones, London, November 2nd, 1950; cf. *Chem. and Ind.*, 1951, 12, 28.
[11] Aulin-Erdtman and Theorell, *Acta Chem. Scand.*, 1950, **4**, 1490.
[12] Johnson, Sheppard, and Todd, *J.*, 1951, 1139.
[13] Dewar, *Nature*, 1945, **155**, 141.
[14] *J.*, 1948, 116.
[15] *J.*, 1948, 1045.
[16] *Nature*, 1948, **161**, 719.
[17] Anderson and Sherrard, *J. Amer. Chem. Soc.*, 1933, **55**, 3813.
[18] *Nature*, 1949, **163**, 410.
[19] *J. Amer. Chem. Soc.*, 1950, **72**, 379.
[20] *J.*, 1950, 1631.
[21] *J. Amer. Chem. Soc.*, 1950, **72**, 2305.
[22] Cook, Gibb, Raphael, and Somerville, *Chem. and Ind.*, 1950, 427.

Haworth and Hobson [23] in Britain. While this brief survey is in no sense complete, it puts into perspective the main sequence of events by which the tropolone concept was developed and brought into general recognition. Each of these events had its own particular setting and significance which call for fuller description.

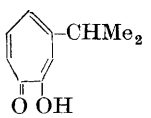
The Thujaplicins.—It has been known for nearly thirty years that it is possible to extract from the heartwood of western red cedar substances which are antibiotic to wood-destroying fungi and are clearly responsible for the great durability of the wood. In 1933 two of these substances were described by Anderson and Sherrard; [17] they were isomeric, having the molecular formula $C_{10}H_{12}O_2$, but while one was identified as a carboxylic acid the other (m.p. 82°) was regarded as a phenol. Later, from Swedish-grown *Thuja plicata* D. Don, Erdtman and Gripenberg [24] isolated in addition to these two compounds a new " phenolic " isomeride of m.p. 32° and they obtained a further isomeride of m.p. 52° from a liquid " phenolic " fraction which had been preserved by Anderson and which in the meantime had partly crystallised. The carboxylic acid, originally named " dehydroperillic acid " because of a mistaken relationship to perillic acid, was re-named thujic acid and has the *cyclo*heptatriene structure shown in (IX): [25] its fragrant methyl ester has also been isolated from western red cedar.[26] The three remaining isomers were named in the order of increasing m.p. α-, β-, and γ-thujaplicin and were identified as the corresponding α-, β-, and γ-*iso*propyltropolones (X), (XI), and (XII).



(IX.)



(X.)



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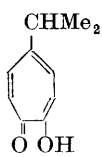


(XII.)

Erdtman and his colleagues established the structures of the three thujaplicins by a series of parallel investigations.[25] All three compounds yielded *iso*butyric acid on oxidation and afforded octahydrides on catalytic hydrogenation. Only octahydro-γ-thujaplicin was thereby obtained in crystalline form and it was shown to be an αβ-diol by its cleavage with periodic acid to a di-aldehyde. When oxidised with potassium permanganate each of the octahydrides yielded an *iso*propylpimelic acid and by the synthesis of α-, β-, and γ-*iso*propylpimelic acids it was shown that, respectively, these were identical with the acids obtained, through the hydrides, from α-, β-, and γ-thujaplicin, thus proving the respective structures (X), (XI), and (XII). Cook, Raphael, and Scott [27] subsequently synthesised the three thujaplicins by the methods described on p. 115.

[23] Haworth and Hobson, *Chem. and Ind.*, 1950, 441.

[24] Erdtman and Gripenberg, *Acta Chem. Scand.*, 1948, **2**, 625; Gripenberg, *ibid.*, p. 639; Anderson and Gripenberg, *ibid.*, p. 644.

[25] Erdtman and Gripenberg, *Nature*, 1949, **164**, 316; Gripenberg, *Acta Chem. Scand.*, 1949, **3**, 1137.

[26] Kurth, *J. Amer. Chem. Soc.*, 1950, **72**, 5778.

[27] *J.*, 1951, 695.

None of the thujaplicins reacts with the usual ketonic reagents. On one occasion, presumably because the platinic oxide catalyst was of inferior quality, α-thujaplicin was hydrogenated to an oily, ketonic hexahydride. This probably contained the ketol grouping, –CH(OH)·CO–, since it reacted readily with periodic acid and, when oxidised with potassium permanganate, afforded α-*iso*propylpimelic acid.

The *Thujas* are botanically related to *Chamaecyparis* and to *Thujopsis*. From the heartwood of the Japanese " hinoki " tree (*Chamaecyparis obtusa* Sieb. et Zucc.) * Nozoe [28] isolated an oil which he named " hinokitiol ", and Nozoe and Katsura [29] later obtained it as a pure, crystalline solid which proved to be identical with β-thujaplicin.[30] α- and β-Thujaplicin were also found in *Thujopsis* species, and Erdtman [30] and his colleagues have isolated a new tropolone, nootkatin, $C_{15}H_{20}O_2$, from *Chamaecyparis nootkatensis*: the detailed chemistry of nootkatin has not yet been published (cf. p. 129).

Nozoe and his colleagues appear to have carried out an extensive investigation of hinokitiol and to have come at least close to appreciating its structure and chemical nature. Reference is later made to some of their results (p. 124), but unfortunately neither the original papers nor abstracts of these are available to the Reviewers who owe much of their information to the kindness of Professor H. Erdtman.† Under the title " Co-ordination compounds of hinokitiol, *o*-diketone with seven-membered carbon ring " there is one abstract of a paper by Iinuma,[31] where it is stated that the salts with numerous metals have been prepared, and this abstract is followed by another in which co-ordination complexes with a number of bivalent metals are listed.

Colchicine.—In contrast to the relatively simple monocyclic tropolones of the mould products and of the thujaplicin group the alkaloid colchicine, $C_{22}H_{25}O_6N$, is tricyclic. Fortunately, however, knowledge of its structure is sufficiently advanced in other respects to enable the question of its relationship to tropolone to be sharply defined. Attention here is directed mainly to this relationship, a fairly complete discussion of the general structure of colchicine being available elsewhere.[32]

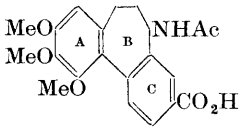
One of the three rings present in colchicine, ring A, is already benzenoid and is identified in the oxidation products as 3 : 4 : 5-trimethoxyphthalic

[28] Nozoe, *Bull. Chem. Soc. Japan*, 1936, **11**, 295; *Chem. Abs.*, 1936, **30**, 5793.
[29] *J. Pharm. Soc. Japan*, 1944, **64**, 181.
[30] Erdtman, unpublished work; cf. ref. 10.
[31] *J. Chem. Soc. Japan*, 1943, **64**, 91, 742; *Chem. Abs.*, 1947, **41**, 4731.
[32] Loudon, *Ann. Reports*, 1948, **45**, 190.

* There is some uncertainty about the source which is alternatively reported (Erdtman) as *Ch. taiwanensis*, which is probably identical with *Ch. formosensis* Matsum., Beniki.

† [*Added in proof.*] The Reviewers have recently received reprints of publications by Nozoe *et al.* describing the synthesis of tropolone (*Proc. Japan, Acad.*, 1950, **26**, No. 7, 38), of hinokitiol (β-thujaplicin) (*ibid.*, p. 43) and of α-thujaplicin (*ibid.*, p. 47), together with work on the substitution products of hinokitiol (*ibid.*, No. 8, pp. 14, 19, 24; No. 9, pp. 30, 38, 45, 50; No. 10, pp. 25 and 32). Notes on γ- and α-aminotropolone have recently appeared (Nozoe *et al.*, *J. Amer. Chem. Soc.*, 1951, **73**, 1895) and a general survey of Nozoe's work will shortly be published by him in *Nature*.

acid. A second ring, ring C, readily becomes benzenoid and does so in course of certain reactions which will be discussed below. The products of these reactions are found to conform to one or other of two key structures, namely (XIII) and (XIV ; R = H). These structures are firmly established for the compounds to which they have been assigned. Thus *allo*-colchiceine (XIII) has been converted by Fernholtz [33] into *N*-acetylcolchinol (XIV ; R = H) by the standard procedure, *viz.*, $R{\cdot}CO_2H \longrightarrow R{\cdot}NH_2 \longrightarrow R{\cdot}OH$. The structure of *N*-acetylcolchinol, which accordingly becomes determinative, was first proposed from degradative evidence by Cook, Barton, and Loudon,[34] and has recently been confirmed by two independent syntheses of its methyl ether—in the natural, optically active form by Cook, Jack, and Loudon,[35] and in the racemised form by Rapoport, Williams, and Cisney.[36]



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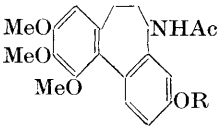

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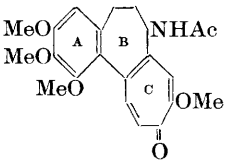

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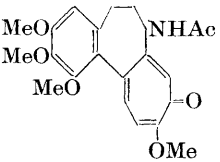

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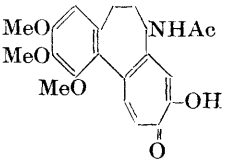


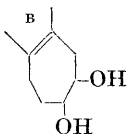
(XVII.)

With these key structures established, discussion can now be centred on the nature of ring C before this ring becomes benzenoid and on the manner in which the change is accomplished.

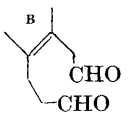
Incorporating Dewar's suggestion [13] that ring C has the structure of a tropolone methyl ether and limiting the possibilities in the light of facts as subsequently ascertained show the most plausible structure for colchicine to be given in formula (XV) or in the alternative (XVI). There is at present no satisfactory differentiation between these alternatives. The tropolone arrangement of ring C reflects the ester-like properties of the alkaloid, revealed in the ease with which the methoxyl substituent of this ring undergoes hydrolysis—the product being colchiceine (XVII)—or, in reaction with amines, suffers replacement by an amino-residue.[37] It accommodates the enolic properties of colchiceine and the formation from the latter of two *O*-methyl ethers, namely colchicine and *iso*colchicine (XV/XVI), by reaction with diazomethane.[38]

[33] *Annalen*, 1950, **568**, 63. [34] *J.*, 1945, 176.
[35] *Chem. and Ind.*, 1950, 650 ; *J.*, 1951, 1397.
[36] *J. Amer. Chem. Soc.*, 1950, **72**, 3324 ; 1951, **73**, 1414.
[37] B.P. 577,606 ; cf. *Chem. Abs.*, 1947, **41**, 1716.
[38] Meyer and Reichstein, *Pharm. Acta Helv.*, 1944, **19**, 127 ; Sorkin, *Helv. Chim. Acta*, 1946, **29**, 246.

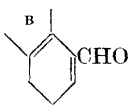
Hydrogenation of both colchicine and colchiceine stops short of complete saturation of ring C. It gives rise to hexahydrides in each of which the survival of one ethylenic linkage is shown by the formation of an oxide when the compound is caused to react with perbenzoic or monoperphthalic acid.[39, 40] Hexahydrocolchicine is a monoalcohol, whereas hexahydrocolchiceine is a diol and there is evidence that the latter, in conformity with its derivation from a structure such as (XVII), is an $\alpha\beta$-diol, *e.g.*, (XVIII). It reacts with lead tetra-acetate [13] or with periodic acid, and from the gum obtained by use of the latter reagent Tarbell *et al.*[41] were able to prepare an amorphous 2 : 4-dinitrophenylhydrazone. This, however, did not correspond to the dialdehyde (XIX) to be expected from simple cleavage, but appeared to be derived from a monoaldehyde such as (XX) which could well arise from (XIX) through cyclisation. Neither colchicine nor colchiceine reacts with the usual carbonyl reagents, but here again it is significant that, by hydrogenating colchiceine with palladised charcoal as catalyst, Tarbell *et al.*[40] obtained a product which afforded a 2 : 4-dinitrophenylhydrazone apparently derived from a tetrahydrocolchiceine. It is unfortunate that these hydrazones and their immediate precursors have not been obtained crystalline but although individually the results from reduction may not be wholly convincing yet collectively they provide strong support for the tropolone formula. Moreover, Šantavý and Brdička, on the basis of their independent polarographic measurements,[42] and Scott and Tarbell [43] from studies on infra-red absorption, find close similarities between colchiceine and γ-thujaplicin.



(XVIII.)



(XIX.)



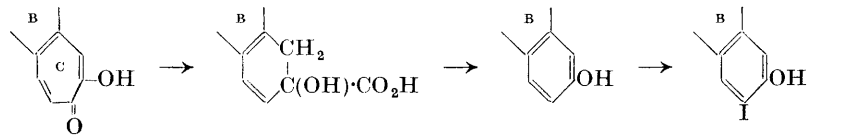
(XX.)

Accordingly there remains to consider the changes by which colchicine is converted into compounds of the colchinol or *allo*colchiceine type. If these transformations are confined to ring C and are capable of being interpreted in terms of the tropolone structure of ring C, then the formula for the alkaloid is virtually settled. Incidentally it is through these changes, or rather through the interpretation placed on them, that ring C of colchicine is restricted to the orientation shown in (XV/XVI).

Windaus [44] first brought about a change of the type in question by treating colchiceine with cold hypoiodite in alkali, thereby obtaining *N*-acetyl-

[39] Bursian, *Ber.*, 1938, **71**, 245.
[40] Arnstein, Tarbell, Scott, and Huang, *J. Amer. Chem. Soc.*, 1949, **71**, 2448.
[41] *Idem, ibid.*, 1948, **70**, 1669.
[42] Šantavý, *Coll. Czech. Chem. Comm.*, 1949, **14**, 145; Brdička, *Arkiv Kemi, Min., Geol.*, 1948, **26**, *B*, No. 19.
[43] *J. Amer. Chem. Soc.*, 1950, **72**, 240.
[44] *Sitzungsber. Heidelberg Akad. Wiss., Math.-Nat. Kl., A*, 1914, 18 Abh.; 1919, 16 Abh.

iodocolchinol (XXIII) which he reduced to *N*-acetylcolchinol (XXII). Later, Čech and Šantavý obtained *N*-acetylcolchinol directly by oxidising colchiceine with hydrogen peroxide in alkali.[45] These changes could occur through benzilic rearrangement and oxidation of the intermediate (XXI), with or without an iodination step. But, if they do so, it is remarkable that in absence of the oxidising agent colchiceine shows little tendency to undergo benzilic change, although this might be expected to lead through the same intermediate, by dehydration, to *allo*colchiceine (XIII). On the other hand, *allo*colchiceine, as its methyl ester, *allo*colchicine (XXVI), is rapidly formed when colchicine—but not colchiceine—is heated with sodium methoxide in methanol.[46, 33] Here again molecular rearrangement with intermediates such as (XXIV) and (XXV) could be postulated. The tropolone structure, therefore, does provide within the confines of ring C a plausible enough interpretation of the structural changes which are encountered and, accordingly, the alternative formulæ (XV/XVI) adequately express the known chemical properties of colchicine. It should be noted, however, that the changes in question are not only novel but have not so far been reproduced in any tropolone of rigidly proved structure (cf. p. 121).*



(XVII.) (XXI.) (XXII.) (XXIII.)

(XV.) (XXIV.) (XXV.) (XXVI.)

In addition to colchicine, Šantavý and Reichstein [47] have recently isolated no less than seven new crystalline alkaloids which were found distributed in groups in the seeds, flowers, and corms of *Colchicum autumnale* Linn. At least four of these are closely allied to colchicine. One, identified

[45] *Coll. Czech. Chem. Comm.*, 1949, **14**, 532.

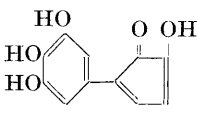
[46] Šantavý, *Helv. Chim. Acta*, 1948, **31**, 821.

[47] *Ibid.*, 1950, **33**, 1606; Šantavý, *Pharm. Acta Helv.*, 1950, **25**, 248.

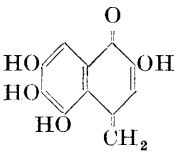
* [*Added in proof.*] A notable contribution to the chemistry of the parent tropolone has recently been made by Doering and Knox (*J. Amer. Chem. Soc.*, 1951, **73**, 828). The compound, of which the acetate, benzoate, picrate, and hydrochloride (indicating the basic character of tropolone) are described, is shown to afford *cis-cyclo*heptane-1 : 2-diol on hydrogenation and nitroso-, nitro-, phenylazo-, and tribromo-tropolone on substitution by the appropriate electrophilic reagents. In addition, close analogies to the behaviour of colchicine and colchiceine are found in (*a*) the rearrangements of tropolone and its methyl ether to benzoic acid and its methyl ester respectively in alkaline media, (*b*) the ultimate formation of tri-iodophenol by the action of sodium hypoiodite on tropolone, and (*c*) the conversion of tropolone methyl ether into the corresponding 2-amino*cyclo*heptatrienone by reaction with ammonia.

by partial synthesis from colchicine, has an *N*-formyl group in place of the *N*-acetyl group. Two others have a hydroxyl group in place of a methoxyl group in ring A and yield colchicine on methylation. A fourth, probably a homologue of colchicine, yields colchiceine on hydrolysis and *allo*colchiceine when heated with sodium methoxide in methanol. A fifth compound closely resembles colchicine in absorption spectrum, while the two remaining compounds—mutually linked by a hydroxy–methoxy-relationship—appear to portend some departure from the strict colchicine pattern. There are indications that the number of these alkaloids will be increased still further and developments in the structural chemistry of the series will be awaited with interest.

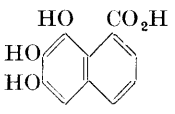
Purpurogallin.—Purpurogallin is a red colouring matter formed by oxidation of pyrogallol with a variety of oxidising agents of which the most convenient and satisfactory is sodium iodate.[48] It is also found in Nature, being present in the form of diglucosides in various galls.[49] Originally prepared by Girard in 1869,[50] it attracted the attention of A. G. Perkin [51] who established its molecular formula, $C_{11}H_8O_5$, and described some of its more notable features. The problem of its molecular structure, however, for long proved to be intractable. The earlier work on the subject was reviewed by Willstätter and Heiss [52] who proposed formula (XXVII). Formula (XXVIII) had been earlier suggested and was subsequently adhered to by Nierenstein,[53] but as several of the more significant claims made in its support were never substantiated,[54, 14] Willstätter's formula became the more generally accepted.



(XXVII.)



(XXVIII.)



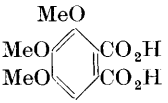
(XXIX.)

In essentials the structural problem was to find a formula portraying purpurogallin's four phenolic or enolic hydroxyl groups, its masked ketonic group and a not too distant relationship to naphthalene. This last requirement had been imposed by Perkin's observation [55] that purpurogallin was isomerised when heated with strong alkali affording purpurogallone, an acid which gave naphthalene by distillation with zinc. He correctly formulated this acid as (XXIX).

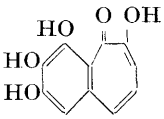
Neither of the formulæ (XXVII) or (XXVIII) need be discussed here, for it is inconceivable that a compound of the latter structure would be unaffected by hydrogen chloride in ethanol at 150°, whereas purpurogallin, as Barltrop and Nicholson showed,[14] is stable under these conditions.

[48] Evans and Dehn, *J. Amer. Chem. Soc.*, 1930, **52**, 3647.
[49] Nierenstein and Swanton, *Biochem. J.*, 1944, **38**, 373.
[50] *Ber.*, 1869, **2**, 562.
[51] Perkin and Steven, *J.*, 1903, **83**, 192.
[52] *Annalen*, 1923, **433**, 17.
[53] Dean and Nierenstein, *Ber.*, 1913, **46**, 3868.
[54] Herzig, *Annalen*, 1923, **432**, 99.
[55] *J.*, 1912, **101**, 808.

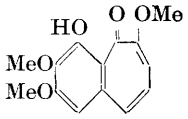
Moreover, the same authors found that purpurogallin tetramethyl ether is oxidised by cold potassium permanganate to 3 : 4 : 5-trimethoxyphthalic acid (XXX) and this fact effectively disposes of formula (XXVII). To replace these discarded formulæ Barltrop and Nicholson proposed the benzotropolone structure (XXXI) and this is now completely established. As will be appreciated it accounts for isomerisation to (XXIX) by the benzilic type of rearrangement, which is so frequently met with tropolones.



(XXX.)



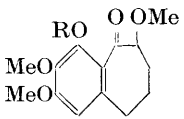
(XXXI.)



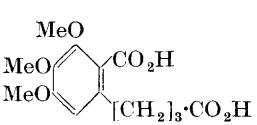
(XXXII.)

In view of the straightforward oxidation which yields (XXX) it may seem strange that the penta-substituted benzenoid ring of purpurogallin was not clearly identified at an early date : this was very largely owing to the nature of the methylation products. Purpurogallin is readily methylated to a trimethyl and less readily to a tetramethyl ether. The latter affords the same trimethyl ether on hydrolysis but, contrary to what might be supposed, the trimethyl ether does not contain all three methoxyl groups in the benzenoid ring. On oxidation it does not yield trimethoxyphthalic acid (XXX)—which could hardly escape detection—and it is best formulated as (XXXII). This provides a relation between carbonyl and hydroxyl groups such as is found in derivatives of 1-hydroxyanthraquinone wherein the hydroxyl group is not easily methylated and the methyl ether, once formed, is rather easily hydrolysed.

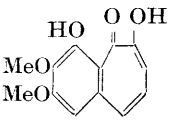
Other properties of the trimethyl ether are in good accord with formula (XXXII). When hydrogenated with Raney nickel as catalyst it affords a hexahydride which is a phenol and not an $\alpha\beta$-diol.[14] It is not easily hydrogenated in presence of palladium catalysts, but Haworth, Moore, and Pauson [15] found that use of Adams's catalyst led to a mixture of products from which, with the aid of Girard's reagent-T, they isolated a tetrahydride. This was a phenolic ketone (XXXIII ; R = H). On methylation it afforded a methyl ether (XXXIII ; R = Me) identical with a specimen obtained by hydrogenating purpurogallin tetramethyl ether and showing ketonic properties. The same authors proved the nature of the ring structure in (XXXIII ; R = Me) by oxidising the compound with alkaline hydrogen peroxide to the dibasic acid (XXXIV) which they identified by synthesis.



(XXXIII.)



(XXXIV.)

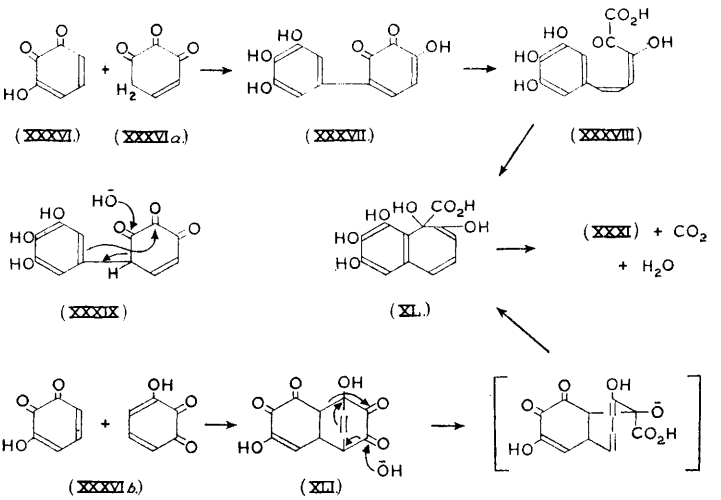


(XXXV.)

Although hydrogenation of purpurogallin itself is reported to give erratic results,[15] the unveiling of ketonic reactivity in these hydrogenated methyl

ethers is clearly the counterpart of the behaviour found in other partially hydrogenated tropolones. Haworth, Moore, and Pauson [56] placed the structure of purpurogallone (XXIX) beyond dispute by an unequivocal synthesis of its trimethyl ether. Finally Caunt, Crow, Haworth, and Vodoz,[20] by the method described on p. 114, synthesised purpurogallin 2′ : 3′-dimethyl ether (XXXV), a compound which is also obtainable by partial methylation of purpurogallin. This dimethyl ether was converted by diazomethane into the trimethyl ether (XXXIII ; R = H) and demethylation of the latter with hydrogen bromide completed the synthesis of purpurogallin.

The intriguing question of how pyrogallol becomes converted into purpurogallin on oxidation has probably still to be given a final answer although it has been the subject of considerable speculation and experiment. Willstätter and Heiss [52] originally proposed a mechanism involving oxidation of pyrogallol to the unknown *o*-diphenoquinone (XXXVII) through the corresponding hexahydroxydiphenyl. Critchlow and Haworth,[57] however, have shown that the hexahydroxydiphenyl cannot be oxidised to purpurogallin, but nevertheless they retain (XXXVII) as a plausible intermediate and regard it as being formed directly by condensation between two molecules (XXXVI) and (XXXVI*a*) of 3-hydroxy-1 : 2-benzoquinone. The

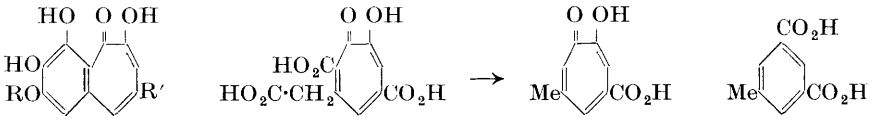


subsequent stages of their scheme are conceived as hydrolysis of (XXXVII) to (XXXVIII), cyclisation to (XL) and thence oxidation to purpurogallin. An alternative mode of formation for the intermediate (XL) from (XXXVII),[15] *viz.*, benzilic change as indicated in (XXXIX), is now considered less likely since purpurogallin can be prepared under neutral or acid conditions. A similar criticism may also be applicable to the mechanism (XXXVI*b*) → (XLI) → (XL), which was proposed by Dewar [10] and

[56] *J.*, 1949, 3271. [57] Personal communication.

is based on a Diels–Alder type of condensation between two molecules of 3-hydroxy-1 : 2-benzoquinone.

Willstätter and Heiss [52] found that neither 3-methoxycatechol nor 3-methoxy-1 : 2-benzoquinone can be oxidised to a purpurogallin derivative, but that oxidation of either in presence of pyrogallol gives a monomethyl ether of purpurogallin. By similar means Critchlow and Haworth [57] prepared a purpurogallin monoethyl ether and showed by its properties and by its methylation and subsequent oxidation to 5-ethoxy-3 : 4-dimethoxyphthalic acid that in all probability it has the structure (XLII ; R = Et, R′ = H). Under suitable oxidation conditions [58, 59] gallic acid, alone or preferably in admixture with pyrogallol, affords a purpurogallin-monocarboxylic acid. Crow and Haworth [59] have shown that this is the acid (XLII ; R = H, R′ = CO_2H) since it may be degraded to (XLIII) (cf. below), the structure of which is proved by partial decarboxylation, yielding (XLIV), and isomerisation of this β-methyltropolone-β′-carboxylic acid to uvitic acid (XLV).

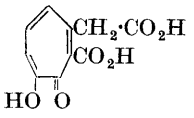


(XLII.) (XLIII.) (XLIV.) (XLV.)

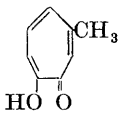
The mechanisms outlined above accommodate the formation and orientation of these derivatives of purpurogallin, decarboxylation of one gallic acid residue being involved where this compound is oxidised in absence of pyrogallol. The failure of pure 3-methoxy-1 : 2-benzoquinone to undergo this type of oxidation is explicable on the one hand by the absence of a component of type (XXXVI*a*) ; while, on the other hand, Dewar points out that the greater resonance energy in this methyl ether and the absence of hydrogen bonding across the *peri*-positions at stage (XLI) will both be unfavourable factors.

Biogenesis of Tropolones.—Pyrogallol derivatives are widely distributed in Nature where it seems likely that purpurogallin is formed, as in the laboratory, by oxidation of pyrogallol. Except for the diglucosides already mentioned, however, there is as yet no direct indication that derivatives or homologues of purpurogallin are obtainable from natural sources. In this connection, Haworth, Moore, and Pauson [15] drew attention to an interesting possibility for the biogenesis of monocyclic tropolones, which is based on their study of the oxidation of purpurogallin. The latter compound in alkaline solution is oxidised by air with degradation of the benzenoid ring and formation of the tropolone-carboxylic acid (XLVI). This acid, when heated above its melting point, is decarboxylated affording β-methyltropolone (XLVII). The suggestion was made that on these lines the thujaplicins may arise from the corresponding pyrogallols by oxidation to, and degradation of, purpurogallin analogues.

[58] Perkin and Perkin, *J.*, 1904, **85,** 243 ; 1908, **93,** 1188.
[59] Crow and Haworth, personal communication.

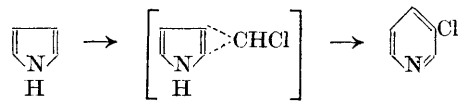


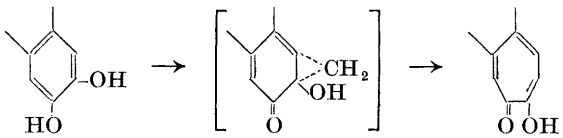
(XLVI.)



(XLVII.)

Sir Robert Robinson [60] also regards phenols as a potential source of tropolones in Nature. In his view one mode of formation, not necessarily the unique method, is the condensation of polyhydric phenols with formaldehyde or its biological equivalent. The process is conceived as analogous to the production of β-chloropyridine from pyrrole and requires reactive vicinal positions in the nucleus :

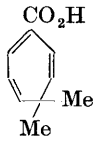




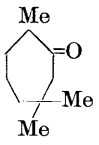
Erdtman [24, 10] has pointed out that the chemical constituents of *Pinaceae* and *Cupressaceae*, two families of conifers, are markedly different in character. While phenols are common in the former group, the constituents of *Cupressaceae* are mainly terpenoid and the phenol derivatives found, such as carvacrol, thymoquinone, and hydrothymoquinone, are usually elaborated on a terpene basis. Since it is not with the first group but with this second group that tropolones of the thujaplicin type are associated in Nature, Erdtman considers that these tropolones have a terpene origin and that nootkatin, $C_{15}H_{20}O_2$ (p. 104), is the tropolone analogue of a sesquiterpene. The carbon system of the thujaplicins cannot, of course, be constructed directly by the formal linking of *iso*prene units, but it may be recalled (cf. p. 103) that the compounds are found in association with thujic acid (X). The latter is structurally related to eucarvone (XLVIII) which is usually regarded as terpenoid and, formally, the carbon system here may be derived from that of the carane type (XLIX) by breaking the appropriate bond of the smaller ring. An additional, or a different, mechanism must, however, underlie a genetic relation between terpenes and thujaplicins. This requires some process whereby the single-carbon side-chain of the menthane (L), carane (XLIX), or pinane (LI) type becomes incorporated into the expanded ring (LII). On the simplest view such ring expansion might be concomitant with an oxidation process but at present a sound experimental basis is lacking.

Other biogenetic schemes are possible (cf. Dewar [61]) and it is indeed probable that tropolones are formed in natural processes by a number of

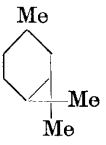
[60] *Proc. Roy. Soc.*, 1951, *A*, **205**, 1 ; see also ref. 10.
[61] *Nature*, 1950, **166**, 790.



(IX.)

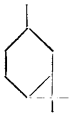


(XLVIII.)

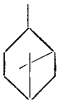


(XLIX.)

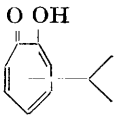
(L.)



(XLIX.)



(LI.)



(LII.)

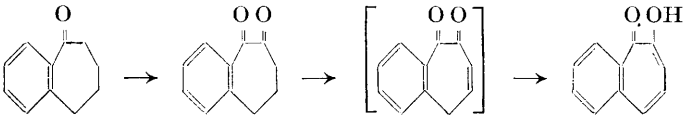
quite distinct routes. Robinson [60] considers that tropolones are possible intermediates in the biogenesis of alkaloids. Thus, expansion of the benzene ring in dihydroxyphenylalanine to a tropolone intermediate is a conceivable model for a step leading either to ring-disruption, as in the biogenesis of strychnine and its congeners, or to ring-modification in accordance with the structural pattern found in yohimbine.

Syntheses of Tropolones.—In view of the stability and low energy content of aromatic systems it might be expected that the synthesis of tropolones would prove to be a relatively simple matter. On the other hand, the stability of a molecule, once it is formed, affords no guarantee that the reaction route leading to that molecule will be the only one followed by a highly reactive precursor. Undoubtedly a number of the fruitless attempts to synthesise the tropolone ring system owe their failure to an unfortunate choice of reaction conditions. In the successful syntheses to be described here the conditions used in the final stages are often of paramount importance, yet it will also be apparent that tropolones can be formed and can survive in most remarkable circumstances.

Perhaps the most obvious and at the same time the most general route for the synthesis of tropolones is dehydrogenation of *cyclo*heptane-1 : 2-diones which may be regarded as members of the hydroaromatic series corresponding to aromatic tropolones. These diones may be prepared by a number of methods and in particular by oxidising a reactive methylene group in appropriate *cyclo*heptanones by means of selenium dioxide. Of the variety of dehydrogenating agents available, so far only two have proved to be of value in practice, but it can scarcely be doubted that as experience in this field grows other reagents will be brought into service.

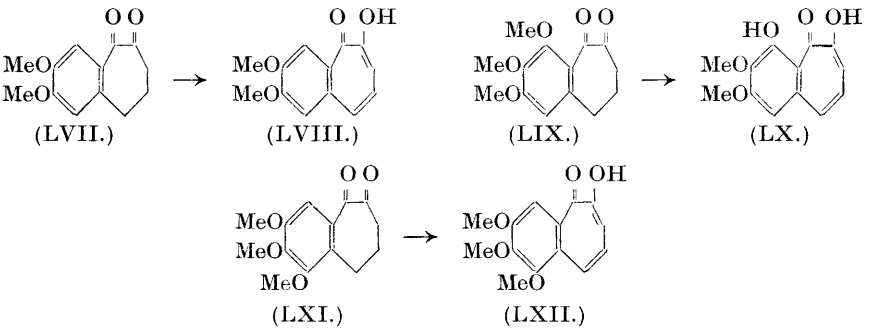
Both the successful applications of dehydrogenation technique were described by Cook and Somerville [18] in respect of their synthesis of $\alpha\beta$-benzotropolone (LVI). This was the first synthesis of the tropolone ring system and became the prototype of several others. It was initially achieved by the action of bromine on 3 : 4-benzosuberane-1 : 2-dione (LIV) which in turn was prepared by oxidising 2 : 3-benzosuberone (LIII) with selenium dioxide. Dehydrogenation by means of bromine may be regarded as combined bromination–dehydrobromination, leading in the present case

from (LIV) to (LV), a diketo-form of (LVI). A monobromo-derivative of benzotropolone was also encountered and afforded benzotropolone when hydrogenated with palladium–charcoal as catalyst. The second method, which gave a somewhat better yield, consisted in heating a solution of (LIV) in boiling trichlorobenzene with 10% palladised charcoal under nitrogen. This second method, however, was to prove ineffective when applied to the synthesis of tropolone itself, whereas the first in a modified form was successful (cf. below).



(LIII.) (LIV.) (LV.) (LVI.)

The second of these methods provided the key to the synthesis of purpurogallin by Caunt, Crow, Haworth, and Vodoz.[20] In view of the inaccessibility of the dione (LIX) these authors first experimented with the analogous dione (LVII) and showed that it afforded the benzotropolone (LVIII) when dehydrogenated with palladium–charcoal in boiling trichlorobenzene, although other attempted methods failed. Applied to (LIX), dehydrogenation was accompanied by demethylation of the methoxyl group in the *peri*-position, but the product (LX) was immediately identifiable as a dimethyl ether of purpurogallin and was readily converted into purpurogallin itself (p. 110). Caunt, Crow, and Haworth [62] improved the yields obtained in these cases and extended the method to a synthesis of (LXII) from the dione (LXI).



(LVII.) (LVIII.) (LIX.) (LX.)

(LXI.) (LXII.)

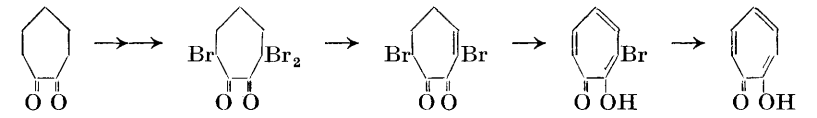
During their earlier efforts to synthesise the tropolone ring system Cook and Somerville [18] had attempted to prepare the parent compound by bromination of *cyclo*heptane-1 : 2-dione (LXIII), but this proved troublesome under the conditions then used. Later, after the successful issue to their work on benzotropolone, they returned to the quest of tropolone itself and Cook, Gibb, Raphael, and Somerville [63] showed that it is possible, under

[62] Caunt, Crow, and Haworth, *J.*, 1951, in the press; cf. Barltrop, Johnson, and Meakins, *J.*, 1951, 181.

[63] *J.*, 1951, 503; cf. ref. 22.

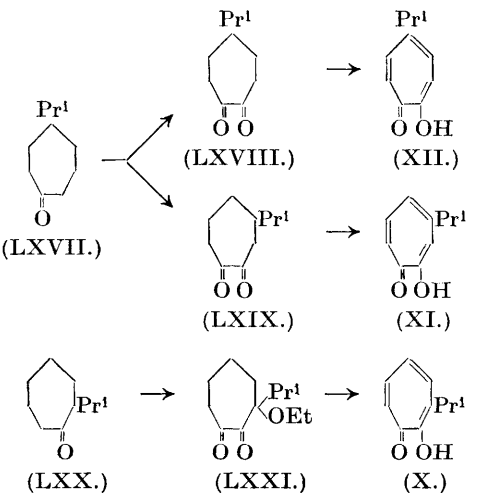
carefully regulated conditions, to prepare this compound in very satisfactory yield.

The reaction of bromine with the dione (LXIII) was found to be complex and sensitive to reaction conditions. As was to be expected the nature of the products varied with the proportions of bromine used and, in addition to tropolone itself, mono-, di-, and tri-bromotropolones were ultimately isolated. Bromination, however, was by no means uniform and, for a practical preparation of tropolone, advantage was taken of a sparingly soluble intermediate formed from the dione and two moles of bromine in acetic acid. This compound had properties compatible with the structure (LXV) and presumably arose from the tribromo-dione (LXIV). On treatment with sodium hydroxide solution it was quantitatively converted into the sparingly soluble and highly crystalline sodium salt of a bromotropolone (LXVI). Hydrogenolysis of this salt with palladised charcoal as catalyst afforded the parent tropolone and sodium bromide.



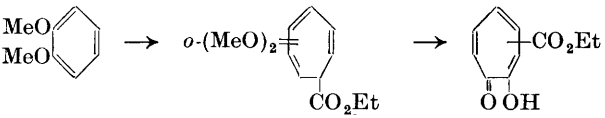
(LXIII.) (LXIV.) (LXV.) (LXVI.)

By the same process Cook, Raphael, and Scott [27] synthesised the three thujaplicins. The mixed diones (LXVIII) and (LXIX), obtained by oxidation of 4-*iso*propyl*cyclo*heptanone (LXVII), afforded on bromination and treatment with sodium hydroxide a mixture of the sodium salts of bromo-β- and -γ-thujaplicin. Hydrogenolysis led to the mixed β- and γ-thujaplicins (XI) and (XII) which were separated by fractional crystallisation. In similar stages the ethoxylated dione (LXXI), which was the product of oxidising 2-*iso*propyl*cyclo*heptanone (LXX) with selenium dioxide, was converted into α-thujaplicin.

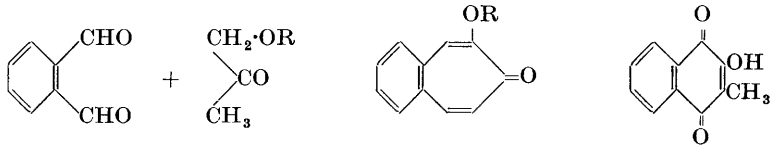


(LXVII.) (LXVIII.) (XII.) (LXIX.) (XI.) (LXX.) (LXXI.) (X.)

Bartels-Keith and Johnson [64] have briefly reported the synthesis of a tropolone-carboxylic ester, in which again the final stage is dehydrogenation by means of bromine. Condensation of veratrole with diazoacetic ester afforded 1 : 2-dimethoxy*cyclo*heptatriene-*x*-carboxylic ester and this, by the action of bromine in chloroform, was simultaneously hydrolysed and dehydrogenated affording a tropolone-carboxylic ester. The location of the carbethoxy-group has still to be settled but the tropolone character of the compound was established by its chemical and physical properties. By a similar process, starting from 1 : 2 : 4-trimethoxybenzene, stipitatic acid has been synthesised.[7]

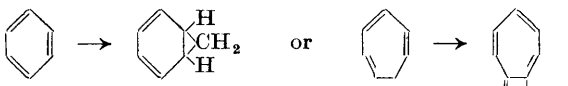


While these successes were attending the use of dehydrogenation methods other lines of approach had also reached their goal. Shortly after Cook and Somerville described their synthesis of $\alpha\beta$-benzotropolone, Tarbell, Scott, and Kemp [19] reported an elegant synthesis of $\beta\gamma$-benzotropolone and of its aryl ethers (LXXIV ; R = H or aryl). These compounds were formed by condensation of phthalaldehyde (LXXII) with hydroxy- and aryloxy-acetones (LXXIII ; R = H or aryl) in presence of alkali at ordinary temperatures. In the case of the parent compound a quantity of phthiocol (LXXV) was simultaneously produced in course of the reaction.



(LXXII.) (LXXIII.) (LXXIV.) (LXXV.)

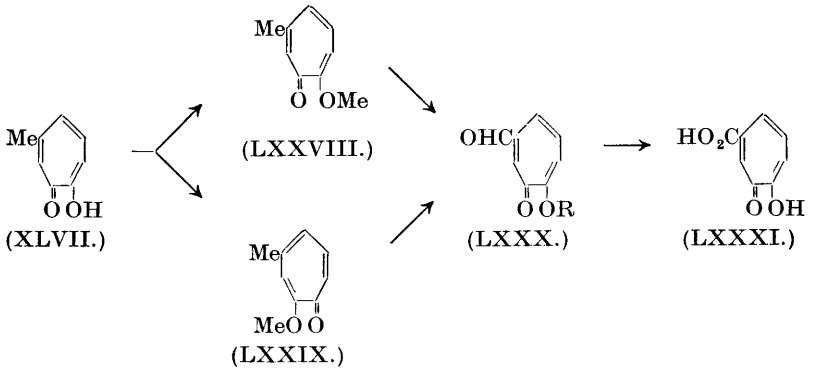
A remarkable synthesis of tropolone was described by Doering and Knox.[21] By irradiating a solution of diazomethane in benzene they obtained a compound which was probably *cyclo*heptatriene (LXXVII) although the norcaradiene structure (LXXVI) was not definitely excluded. When this compound was oxidised with aqueous potassium permanganate tropolone was formed and was isolated and purified through its copper complex. While this method appears to have little preparative value because of the low yield obtained (*ca.* 1%), the individual steps are of considerable interest and, in particular, the second offers striking testimony of the readiness with which the tropolone system is formed and of its resistance to further oxidation.



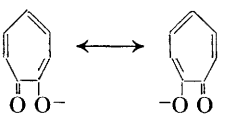
(LXXVI.) (LXXVII.)

[64] *Chem. and Ind.*, 1950, 677.

By the synthesis of purpurogallin the monocyclic oxidation products (XLVI) and (XLVII) (p. 111) are automatically brought within the class of synthetic tropolones. Haworth and Hobson [65] have improved this method of approach and have developed it into a synthesis of tropolone. β-Methyltropolone (XLVII) on methylation afforded two methyl ethers (LXXVIII) and (LXXIX). In each of these the *C*-methyl group was oxidised by means of selenium dioxide but whereas one of the isomers yielded a formyltropolone methyl ether (*e.g.*, LXXX ; R = Me) the other, through incidental demethylation of the methoxyl group, yielded a formyltropolone (*e.g.*, LXXX ; R = H). Both of these aldehydes were further oxidised by alkaline silver oxide affording tropolone-β-carboxylic acid (LXXXI) from which, by decarboxylation, tropolone itself was obtained.



General Properties of Tropolones.—The tropolones are crystalline solids, the monocyclic members and colchiceine being almost colourless, puberulonic acid and the unsubstituted benzotropolones yellow, and purpurogallin red. As a class they dissolve more readily in hydroxylic solvents than in ether or hydrocarbons and may frequently be isolated or purified by reason of the ease with which they undergo sublimation. As enols they readily form salts with alkali but it is noteworthy that in many cases, *e.g.*, bromotropolone and the two benzotropolones, the sodium salt is comparatively insoluble in the alkaline mother-liquor. These alkali salts are all more coloured than the parent tropolones and this fact is attributable to increased resonance in the anions, as illustrated in (LXXXII).



(LXXXII.)

[65] *J.*, 1951, 561; cf. ref. 23.

	$FeCl_3$	Cu salt in $CHCl_3$	Aq. $NaHCO_3$	KOH-fusion	Hydrogenation products	Electrophilic reagents
Tropolone . .	green	sol.	sol.	isomerised	octahydride (ii)	Brominates Nitrates Couples
β-Methyl-tropolone	green	sol.	sol.	isomerised	hexahydride (i)	Brominates Nitrates Couples
α-Thujaplicin .	green	sol.	insol.	?	hexahydride (i) octahydride (ii)	—
β-Thujaplicin .	green	sol.	insol.	?	octahydride (ii)	Brominates Nitrates Couples
γ-Thujaplicin .	green	sol.	insol.	isomerised	octahydride (ii)	—
Stipitatic acid .	deep red	?	sol.*	isomerised	tetrahydride (i)	Brominates
Puberulic acid .	deep red	?	—	unchanged	—	—
Colchiceine .	olive-green	sol.	—	decomp.	tetrahydride (i) hexahydride (ii)	Brominates Does not couple
αβ-Benzo-tropolone	brown-red	sol.	insol.	isomerised	tetrahydride (i) hexahydride (ii)	—
βγ-Benzo-tropolone	"positive"	?	insol.	?	hexahydride (ii)	—
Purpurogallin .	brown-red	?	—	isomerised	tetrahydride	Brominates
Tropolone-carboxylic ester	green	?	sol.	?	—	—

* Contains CO_2H: with MeOH–HCl affords a dimethyl derivative which is sol. in NaOH, but insol. in $NaHCO_3$.

(i) Shows ketonic properties.
(ii) Is an αβ-diol.

The Table above summarises some of the more typical reactions given by tropolones with various reagents. Although the majority of enols give a positive colour test with ferric chloride, two points relevant to the behaviour of tropolones deserve comment. In the first place, the colour pro-

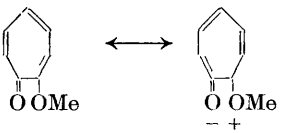
duced is intense and provides a useful and delicate test for the compounds : secondly, tropolones form co-ordination complexes with the ferric ion. Gradual addition of ferric chloride solution to an aqueous solution of tropolone in water first produces a red precipitate which, on continued addition, redissolves with development of the characteristic deep-green solution. The red precipitate consists of ferric tropolone which crystallises from its intensely coloured solutions in chloroform as reddish-black needles and contains the metal in co-ordinated form.[63] Co-ordination complexes of tropolones with other metals are also known (cf. p. 104) and the formation of a green, chloroform-soluble complex from cupric or cuprammonium salts in a water–chloroform mixture affords another test for tropolones. In their ability to form these chelate compounds, tropolones appear to be exceptional among enols derived from $\alpha\beta$-diketones, although the property is commonly shared by enolic forms of $\alpha\gamma$-diketones.

The acidic strength of tropolones appears to vary from case to case. By electrometric titration Speakman [66] found the value pK 7·00 $\pm$ 0·2 at 20° for tropolone and pK 7·30 $\pm$ 0·2 at 20° for β-methyltropolone, and Aulin-Erdtman [67] records pK 7 for β-thujaplicin. These values are intermediate between those of phenol (pK 10·0) and acetic acid (pK 4·8). In most cases, however, precise measurement is not available, but, whereas β-methyltropolone and colchiceine react with sodium hydrogen carbonate to form the respective sodium salts, they are not extracted from solution in chloroform and are only partly extracted from ether by this reagent. Furthermore, all three thujaplicins, and preferentially α-thujaplicin, are precipitated from solution in alkali by means of carbon dioxide. Neither of the isomeric benzotropolones reacts with bicarbonates but the bromo- and nitro-derivatives of tropolone dissolve with effervescence. Molecular-weight determinations of tropolone,[63] β-methyltropolone,[65] and β-thujaplicin [67] in organic solvents show that the compounds are monomeric. Accordingly, hydrogen bonding of the intermolecular type common to carboxylic acids is excluded and, although a rather high value is found [68] for the latent heat of sublimation of tropolone ($\Delta H_s = +20{\cdot}0 \pm 0{\cdot}2$ kcals. per mole at 20°), some degree of internal hydrogen bonding is adumbrated (cf. p. 129).

Attention has already been drawn (p. 101) to the tautomeric potentialities which give rise to the formation of two isomeric ethers when an unsymmetrically substituted tropolone is methylated. Stipitatic acid (p. 101), colchiceine (p. 105), β-methyltropolone,[65] and the dibasic acid (XLVI) from which it is derived (cf. p. 111) all yield such pairs of methyl derivatives. So far as is known O-methylation in tropolones is not accompanied by the C-methylation occasionally found in the case of $\alpha\beta$-diketones. Among the alkylating agents used are diazo-methane, -ethane, and -diphenylmethane ; methyl sulphate, methyl iodide, and p-nitrobenzyl bromide in presence of alkali ; and the " esterifying " combination methanol–hydrochloric acid. As a rule the ethers, like esters, are readily hydrolysed but an interesting

[66] Cf. ref. 63 ; and personal communication.
[67] Aulin-Erdtman, *Acta Chem. Scand.*, 1950, **4**, 1031.
[68] Nicholson, cf. ref. 63.

departure is provided by the hydrolysis of purpurogallin tetramethyl ether to the trimethyl ether (p. 109) in which the formal structure of a tropolone methyl ether survives. The remarkable fact that colchiceine has a lower solubility in water than has its methyl ether, colchicine, is duplicated by the lower solubility of tropolone than of tropolone methyl ether. The possibility that this is the result of hydration is not excluded by the observation that each of these ethers yields a hydrate which is less soluble than the anhydrous form.[63, 69] Dewar,[8] on the other hand, regards the ionic resonance exemplified by (LXXXIII) as best interpreting the high solubility of the ethers. Tropolone methyl ether [63] and the two methyl ethers of β-methyltropolone [65] form picrates whose feeble colour (yellow) suggests that they are salts rather than molecular compounds.



(LXXXIII.)

In contrast to the ease with which it is alkylated, the hydroxyl group in tropolones is much less readily acylated and comparatively few acyl derivatives are known. Tropolone forms a crystalline 3 : 5-dinitrobenzoate.[63] $\beta\gamma$-Benzotropolone yields a crystalline acetate,[19] and purpurogallin a tetra-acetate.[54] Puberulonic acid, which resists acetylation, is separated from puberulic acid by treatment of the mixture with acetic anhydride and sodium acetate : thereby, puberulic acid affords a diacetate while puberulonic acid yields a sparingly soluble, acid sodium salt.[3] But puberulic acid is a dihydroxy-tropolone-carboxylic acid and in the diacetate the α-enolone group is probably not acetylated if the positive ferric colour test—red-brown changing to green—described by Barger and Dorrer [4] (but contrast Birkinshaw and Raistrick [3]) can be taken as significant. On the other hand, from trimethylcolchicinic acid (deacetylcolchiceine) one *ON*-dibenzoyl derivative and a pair of *ON*-dibenzenesulphonyl derivatives have been obtained.[70] In each of these the enol group is acylated and the duplication of dibenzenesulphonyl derivatives corresponds to the two possible tautomeric enolones. This appears to be the only example of the fixation of tropolone tautomers through acylation. Two isomeric diacetates of stipitatic acid—a monohydroxytropolone-carboxylic acid—are indeed known, but only one of them titrates as a monobasic acid, the second titrating as a dibasic acid.[2] While, therefore, the former is certainly an acetoxy-enolone acetate, the latter, which is prepared by the action of acetic anhydride and sulphuric acid, must contain a *C*-acetyl group formed by acetylation at a carbon atom of the ring.[1]

Considered as a means of elucidating structure, perhaps the most im-

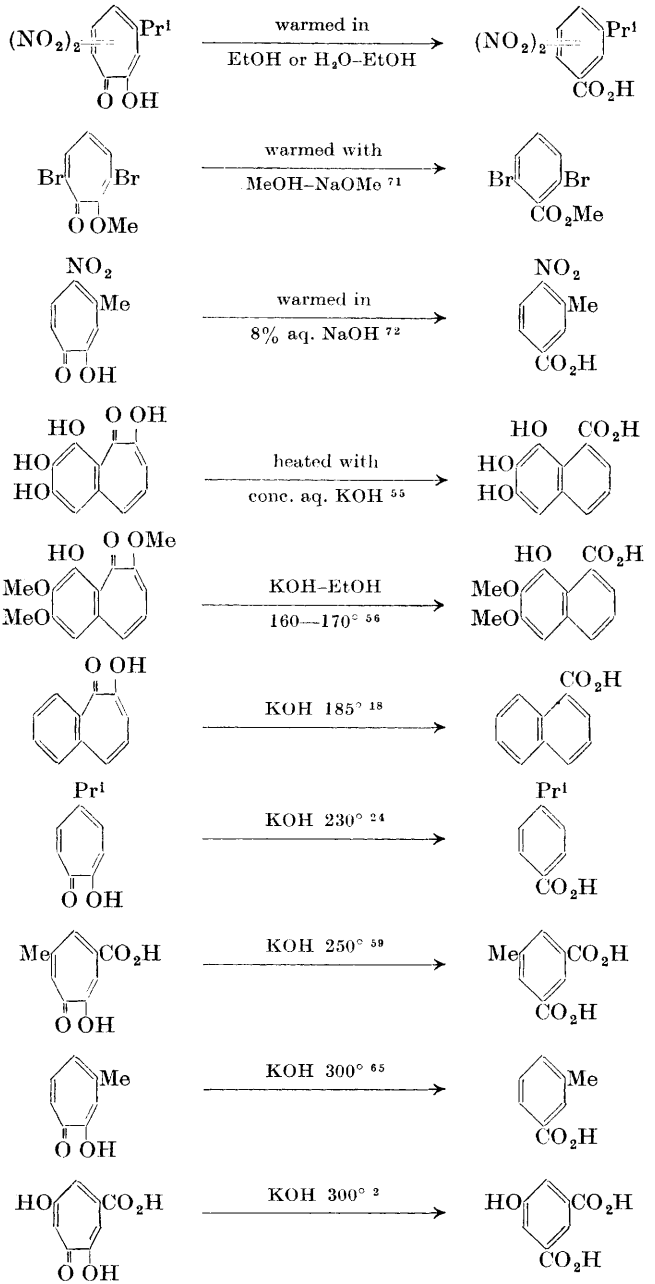
[69] Loudon and Speakman, *Research*, 1950, **3**, 583.
[70] Windaus, *Sitzungsber. Heidelberg Akad. Wiss., Math.-Nat. Kl., A*, 1911, 2 Abh.

portant reaction of tropolones is the type of benzilic rearrangement whereby the tropolone ring is changed to a benzenoid form. Examples of this change in stipitatic acid (p. 101) and in purpurogallin (p. 109), and the modifications in colchicine and colchiceine (p. 107), have already been encountered. The ability to rearrange is by no means equally held among tropolones, as may be seen from the notes of reaction conditions which are attached to the changes formulated on following page. These, moreover, are the cases in which rearrangement has been realized: in others failure to effect analogous change has been recorded, *viz.*, with tropolone,[63] puberulic acid,[6] and brominated β-methyltropolones:[65] in others again there is no record of the change having been investigated.

It is in the light of this varied response by different tropolones towards benzilic change that the rearrangements described in connection with colchicine must be judged. Although the second example given overleaf is analogous to the rearrangement of colchicine to *allo*colchicine, the type of rearrangement which produces a phenol from a tropolone appears to be peculiar to the colchicine series. Stipitatic acid is known to give a positive iodoform reaction.[2] The action of iodine and alkali on puberulic acid was examined by Barger and Dorrer [4] but without definite result. Cook, Gibb, Raphael, and Somerville [63] found that tropolone methyl ether, unlike colchicine, was unaffected when heated with sodium methoxide in methanol, while treatment of tropolone with cold sodium hypoiodite afforded a compound * which was not an iodophenol as would have been expected by analogy with the behaviour of colchiceine. These results are, of course, inconclusive: they do not show that the tropolone structures in colchicine and colchiceine are incapable of undergoing the changes which are attributed to them and which they appear to interpret satisfactorily.

Tropolones are fairly resistant to the action of reducing agents, nevertheless the ring system can be hydrogenated both by means of nascent hydrogen and by the use of catalysts. The process is seldom simple since, apart from complications introduced by stereoisomerism in the products, hydrogenation may be only partial (cf. Table, p. 118) or may be attended by elimination of an oxygen atom.[15, 39] In practice, therefore, hydrogenated material is frequently obtained as an oily mixture in which the constituents vary with the method and with the type and quality of the catalyst used. Hydrogenation with platinum as catalyst is the commonest procedure but Raney nickel is said to be advantageous for the reduction of colchiceine to hexahydrocolchiceine.[40] Palladium catalysts such as palladised charcoal are sometimes capable of effecting partial hydrogenation, as in the cases of colchiceine and αβ-benzotropolone, but they do not lead to hydrogenation of tropolone itself and have been extensively used in reducing bromotropolones to tropolones. Reduction of stipitatic acid by means of zinc and acetic acid affords a ketonic product which has not been identified,[2] while

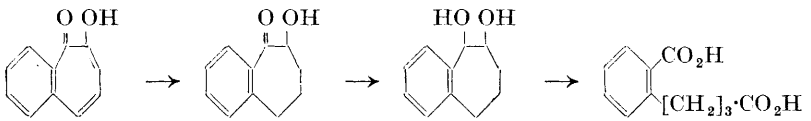
* [*Added in proof.*] This compound has since been identified as iodoform. Doering and Knox (footnote, p. 107) have shown that tri-iodophenol may also be isolated. They also found that tropolone methyl ether is isomerised by prolonged treatment with sodium methoxide.



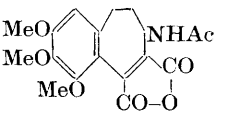
[71] Cook, Gibb, and Raphael, unpublished work.
[72] Haworth and Jeffries, *Chem. and Ind.*, 1950, 841.

purpurogallin trimethyl ether when reduced by amalgamated zinc and acids yields phenolic ketones.[15]

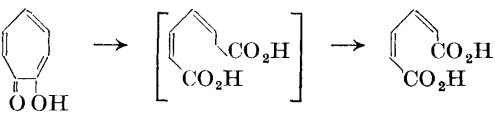
It is a characteristic, albeit negative, property of tropolones that they do not react with the usual carbonyl reagents, although an interesting exception to this rule is found in the aryl ethers of $\beta\gamma$-benzotropolone, which display ketonic reactivity.[19] The presence of the ketonic group, however, is frequently revealed—either explicitly or by implication—through the products of reduction. Fully hydrogenated tropolones, octahydrotropolones, are $\alpha\beta$-diols and as such may be titrated with periodic acid yielding open-chain dialdehydes, or may be oxidised with potassium permanganate or hypobromite to the open-chain dicarboxylic acids. In the benzotropolones, and presumably also in colchiceine, where one double bond is either common to two rings or can become so in course of hydrogenation, this double bond survives reduction and the hexahydrotropolones are again $\alpha\beta$-diols. On the other hand, partial hydrogenation commonly leads to ketols which exhibit ketonic properties and afford the same oxidation products as the corresponding $\alpha\beta$-diols. This behaviour is illustrated for the case of $\alpha\beta$-benzotropolone:[18]



It is consistent with the aromatic character of the tropolone ring that some resistance towards oxidation is shown and this is clearly implicit in two of the methods by which tropolone itself has been prepared (pp. 116 and 117). In one of these the methyl side-chain of β-methyltropolone is selectively oxidised first to an aldehyde and then to a carboxylic group, but it is unlikely that oxidation of side-chains, characteristic of benzenoid compounds, will be applicable to tropolones apart from the use of selective oxidising agents. Indeed it is probable that vigorous oxidation will afford a means of identifying alkyl groups which are attached to the ring. This is instanced in the oxidation of the thujaplicins to *iso*butyric acid by means of chromic acid (p. 103) and also in the case of colchiceine which is oxidised by potassium permanganate to compounds of type (LXXXIV).[73] Tropolone itself when oxidised by hydrogen peroxide in alkali yields a small amount of *cis-cis*-muconic acid (LXXXV),[63] and similar oxidations of the more vulnerable stipitatic and puberulic acids have already been mentioned (p. 101).



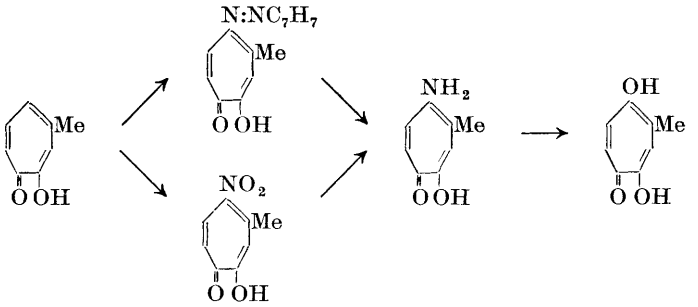
(LXXXIV.)



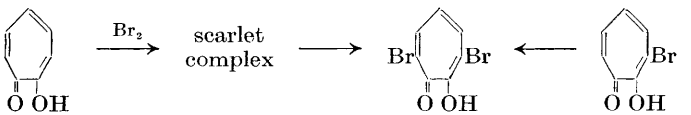
(LXXXV.)

[73] Cook, Johnstone, and Loudon, *J.*, 1950, 537; Horning, Ullyott, *et al.*, *J. Amer. Chem. Soc.*, 1950, **72**, 4840.

Tropolones are substituted by electrophilic reagents (Table, p. 118). According to quantum-mechanical calculations made by Dewar,[61] monosubstitution in tropolone should occur almost exclusively in the γ-position. Some support for this prediction is found by Haworth and his collaborators [65, 72] in the behaviour of β-methyltropolone, although here the influence of the β-methyl substituent should be taken into account. This compound couples with diazotised *p*-toluidine and on nitration forms a mononitro-derivative. In each case the product may be reduced to the same amino-β-methyltropolone, which may be diazotised and converted into hydroxy-β-methyltropolone. Since the nitro-compound is oriented through its conversion into 4-nitro-*m*-toluic acid (p. 122), the reactions are represented by the following scheme:



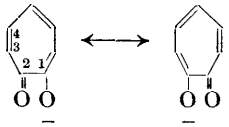
Tropolone itself is known to undergo nitration and coupling with diazotates, and its bromo-derivatives were encountered in the process by which it was prepared by Cook, Gibb, Raphael, and Somerville (p. 115). These authors note that by direct action of bromine on tropolone there is first produced a scarlet complex which disproportionates into tropolone and a dibromotropolone. The same dibromotropolone is formed by brominating the monobromotropolone (LXVI; p. 115) obtained in the course of synthesis, and the relationships are represented as follows:



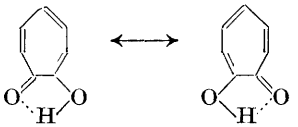
The formation of intermediate complexes has been noted for stipitatic acid (p. 100) and for β-methyltropolone.[65] In the latter case the complex is decomposed by water to a mixture of mono- and di-bromo-methyltropolones. Nozoe is said to have prepared numerous halogeno-, nitro-, and halogeno-nitro-derivatives of hinokitiol (p. 104) as well as products of diazo-coupling, but detailed information is scanty and there appears to be some doubt whether in some cases substitution is accompanied by conversion into the benzenoid form (see footnote, p. 107).

The Fine-structure of Tropolones.—It was stated earlier (p. 100) that the analogy between the carboxyl group and a conjugated hydroxycarbonyl system provided a helpful but incomplete basis for interpreting the

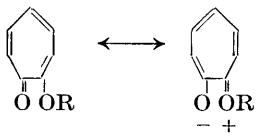
aromatic nature of tropolone. Undoubtedly this conjugation, as instanced in the resonance forms of the tropolone anion (LXXXII), is an important factor but neither here, nor in the hydrogen-bonded (LXXXV) or zwitterion (LXXXVI) structures, nor yet when tropolone is written as a tautomeric system of high mobility (I ; I*a*), do the formulæ convey, without further explanation or assumption, a convincing picture of aromaticity. This is in part due to the inadequacies of chemical symbolism and to this extent is common to other cases, but also in part to the unusual position which tropolone shares with azulene among aromatic compounds.



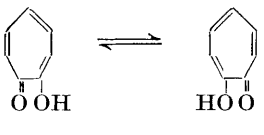
(LXXXII.)



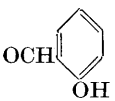
(LXXXV.)



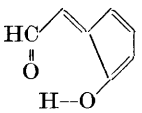
(LXXXVI.)



(I ; I*a*.)



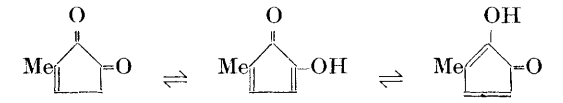
(LXXXVII.)



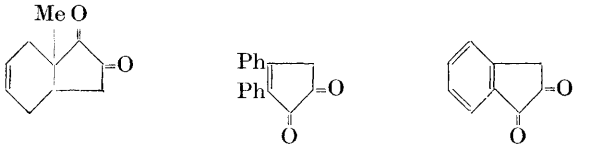
(LXXXVIII.)

Inspection of these tropolone formulæ will show that the bond between the oxygen-bearing carbon atoms—the 1 : 2-bond—of tropolone is not essential to the conjugation : it is always represented as a single bond. If it is truly represented in this non-essential subordinate role then formulæ such as (LXXXVII) or (LXXXVIII), obtained by transferring this 1 : 2-bond to the 1 : 3- or 1 : 4-position, should represent compounds of tropolone-like properties. Formula (LXXXVII) is, of course, that of salicylaldehyde which, although aromatic, displays in common with *o*-phenolic ketones full carbonyl reactivity. It would be interesting to ascertain whether formula (LXXXVIII) —especially as it may be written with a hydrogen bond, thereby introducing at least a superficial resemblance to azulene—represents a compound of aromatic stability or of the typical fulvene tendencies to polymerisation and auto-oxidation : unfortunately the compound is unknown. A parallel line of inquiry—again valid in the absence of any particular significance to be associated with the 1 : 2-bond—emerges from considering tropolone as the cyclic vinylogue of a carboxylic group. This leads to comparison of tropolone with the known compound (LXXXIX) which, as the lower vinylogue of a methyltropolone, appears to have comparable potentialities for tautomerism and resonance. Yet this compound has ketonic properties :

it is reported [74] to condense with *o*-phenylenediamine forming a quinoxaline derivative and to react as a dienophile with butadiene affording the adduct (XC). Furthermore, phenylated *cyclo*pentenediones such as (XCI), and indane-1 : 2-diones, including the parent compound (XCII), are all known to display ketonic properties combined with varying degrees of enol character.[75] These facts suffice to show that, contrary to a suggestion made by Dewar,[1] hydroxy*cyclo*pentadienones do not closely resemble tropolones and that the aromatic character of the latter is uniquely determined.



(LXXXIX.)



(XC.) (XCI.) (XCII.)

From the point of view of the fine structure of tropolones an *X*-ray investigation of copper tropolone carried out by Robertson [76] has yielded results of importance. This derivative was chosen for study because the copper atom is phase-determining for certain even-index reflections and this permits elaboration of the molecular structure quite independently of structural chemistry. The ring system is thereby revealed as a flat *regular* heptagon, with two attached oxygen atoms of which one is more closely implicated than the other in binding the copper atom. The 1 : 2-bond is therefore not a " long " bond, devoid of double-bond character, as is implied in the chemical formulæ for tropolone, but appears indeed to be indistinguishable from the other bonds in the ring. Moreover, on the basis that annular strain is a disruptive influence which opposes resonance, then, since the natural angle (125°) between a double and single bond for tetrahedral carbon suffers greater distortion in hydroxy*cyclo*pentadienone (pentagonal angle = 108°) than in tropolone (heptagonal angle = 128·6°), it is clear that resonance will be less in the 5-membered than in the 7-membered ring system. The resonance energy of tropolone computed from thermochemical measurements by Nicholson [68] is 28·6 kcals. per mole, which is considerably lower than the value, *viz.*, about 47 kcals. for tropolone or 57 kcals. for the tropolone anion, theoretically derived by Dewar [61] using the standard molecular-orbital method.

The ultra-violet absorption properties of tropolones are, in several respects, similar to those of benzenoid compounds. Thus the resemblance,

[74] Dane, Schmitt, and Rautenstrauch, *Annalen*, 1937, **532**, 29.

[75] Geissman and Koelsch, *J. Org. Chem.*, 1938, **3**, 480, 489 ; Koelsch and Hochman, *ibid.*, p. 503 ; Perkin, Roberts, and Robinson, *J.*, 1912, **101**, 232 ; 1914, **105**, 2405.

[76] Robertson, *J.*, 1951, 1222 ; cf. ref. 10.

in regard to both the wave-lengths of maximal absorption and the corresponding extinction coefficients, is greater between tropolone itself [21, 22, 63, 67] and salicylaldehyde than between tropolone and a comparable aliphatic compound like octatrienal (Fig. 1). The high intensity of absorption in the near ultra-violet is indicative of one large extended chromophore, a structure which necessitates that the ring system has a planar configuration (cf. the non-planar *cyclo*octatetraene, Fig. 1), and the vibrational fine structure of the bands shows that the system possesses considerable rigidity.

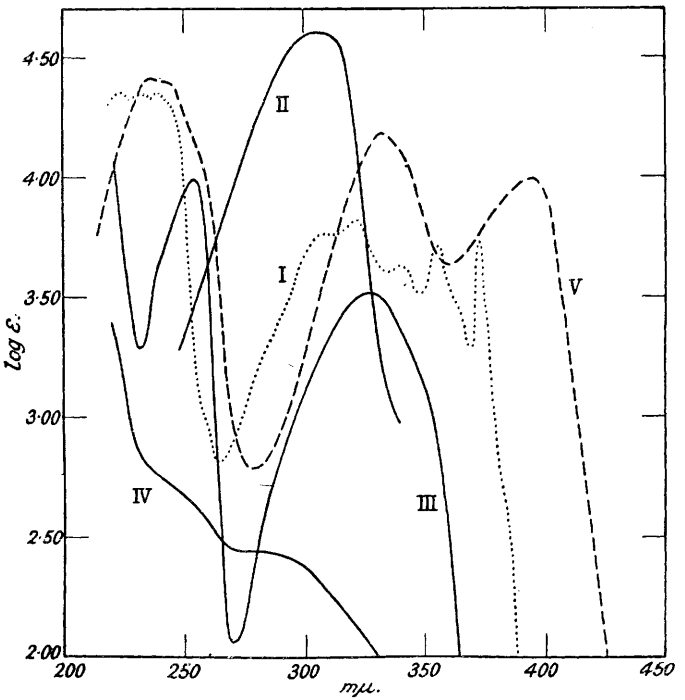


FIG. 1

Extinction curves for tropolone in cyclo*hexane (according to Cook, Gibb, and Raphael)* (I),[67] *octatrienal in hexane* (II), *salicylaldehyde in hexane* (III), cyclo*octatetraene in* cyclo*hexane* (IV), *and γ-thujaplicin in aqueous solution of* pH 12.[67]

The ultra-violet absorption of tropolone occurs in two distinct wave-length ranges : one (A) below 250 mμ., and the other, which is most conveniently considered in two portions (a shorter wave-length portion B up to 340 mμ., and a longer wave-length portion C about 340 mμ.), in the region 290—375 mμ.

The position of the band A is almost unaffected by the presence of alkyl substituents in the ring [24] (Fig. 2, γ-thujaplicin), but the introduction of an ester group [64] or of hydroxyl and carboxyl or acid anhydride groupings [11] causes its displacement to longer wave-lengths (Fig. 2, stipitatic, puberulic, and puberulonic acids). Dissociation of an attached carboxyl

group causes a slight hypsochromic shift,[11] and dissociation of a hydroxyl group results in a bathochromic displacement [67, 11] as is the case with benzenoid compounds.

The group of maxima B is similarly independent of alkyl substituents [24] (Fig. 2, γ-thujaplicin) but is weakened in stipitatic acid and disappears in puberulic acid [11] (Fig. 2). In solutions sufficiently alkaline to cause dissociation of the " olone " hydroxyl group, the same effect is observed, the absorption being intense in the case of tropolone and the thujaplicins,[67]

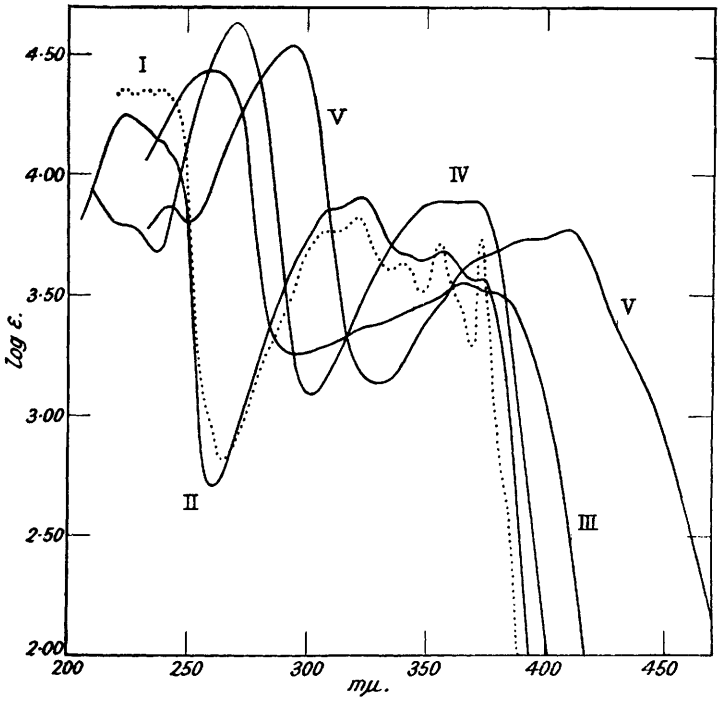


FIG. 2

Extinction curves for tropolone in cyclo*hexane* (I),[67] *γ-thujaplicin in heptane* (II),[67] *stipitatic acid in dioxan* (III),[11] *puberulic acid in ethanol* (IV),[11] *and puberulonic acid in dioxan* (V).[11]

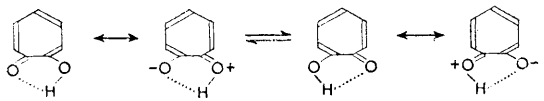
much weaker in the case of stipitatic acid,[11] and questionable with puberulic acid.[11] In all cases the group of maxima coalesce to form a single peak which is displaced towards the red.

The band C at *ca.* 340—375 mμ. is also largely unaffected by the presence of alkyl substituents [24] (Fig. 2, γ-thujaplicin), but, unlike A and B, it is also comparatively unchanged by the introduction of hydroxyl or carboxyl groups [11] (Fig. 2, stipitatic and puberulic acids). However, an acid anhydride grouping (puberulonic acid,[11] Fig. 2) causes a marked shift to longer wave-lengths, and ionisation of the " olone " hydroxyl group causes a bathochromic displacement with simultaneous intensification and

contraction of the band [cf. thujaplicins [67] (Fig. 1), and stipitatic acid [11]].

The band A may contain a double maximum as predicted by Dewar [61] from a consideration of resonance energies, and the other double maximum predicted by the same author to occur somewhat below 390 mμ. may correspond to the long-wave portion C of the broad band of tropolone which extends from 290 to 375 mμ. The short-wave portion of this band (B) was not predicted, however, and it is evident that more experimental and theoretical studies are necessary before all the ultra-violet absorption phenomena are understood. Nevertheless the characteristic extinction properties have been utilised recently to establish the tropolone nature of the substances nootkatin [67] and puberulonic acid [11] whose constitutions have not been completely elucidated by purely chemical methods.

The infra-red absorption spectra [11, 19, 43, 64, 77, 78] for tropolone and several of its derivatives show bands at about 3100 and 1620 cm.$^{-1}$, which are considered to have their origins in the hydroxyl and carbonyl groups respectively. They are accordingly considerably lower in frequency than the bands normally characteristic of these groups. In the case of the hydroxyl band the shift is attributed to intramolecular hydrogen bonding but is much less than is found in the enol form of a typical β-diketone, such as acetylacetone,[79] where the frequency position is significantly lower at 2700 cm.$^{-1}$. Koch [77] therefore decides against the possibility of resonance degeneracy in tropolone involving two equivalent bonds between the proton and the two oxygen atoms. He supports the view that symmetry is achieved on a time-average basis by proton oscillation (XCIII*a* and XCIII*b*), with important resonance contributions from ionic structures such as (XCIV). His calculation of the resonance energy of such a system agrees with the experimental value as found by Nicholson for tropolone (p. 126). Hydrogen bonding and conjugation are both regarded as contributing to the low frequency of the carbonyl bond, but it is noteworthy [78] that the band at 1610 cm.$^{-1}$ for β-methyltropolone is replaced in the case of the corresponding methyl ethers by a strong band at 1600 cm.$^{-1}$ and a weaker one at 1630 cm.$^{-1}$. Koch has pointed out [77] that the strong bands at, or near, 1615, 1553, and 1255 cm.$^{-1}$ and possibly two others at 1475 and 1440 cm.$^{-1}$ appear to be characteristic of tropolones and may serve for their identification in complex molecules.

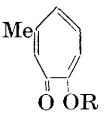


(XCIII*a*) (XCIV) (XCIII*b*)

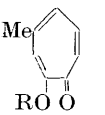
Tyrell and Mills [10] measured the dipole moments of β-methyltropolone and its higher-melting methyl ether in benzene and compared the values found with those calculated for the four non-polar structures (XCV and

[77] Koch, *J.*, 1951, 512. [78] Broomfield, cf. refs. 10 and 65.
[79] Rasmussen, Tunnicliff, and Brattain, *J. Amer. Chem. Soc.*, 1949, **71**, 1068.

XCVI ; R = H or Me).[80] Their preliminary results are shown in the table, the calculated moment being maximal where the group R is in the *trans*-position with respect to the carbonyl group. In general, the observed values are higher than expected and, while reserving their conclusions regarding β-methyltropolone, these investigators conclude in respect of the methyl ether that ionic structures must contribute to the resonance. Among the ionic structures possible, there are some in which the oxygen-bearing carbon atoms are linked by a double bond and such ionic structures may provide a basis for interpreting Robertson's findings (p. 126) in the case of copper tropolone.



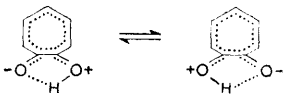
(XCV.)



(XCVI.)

	R = H			R = H		
	Max., D.	Min., D.	Obsd., D.	Max., D.	Min., D.	Obsd., D.
Structure (XCV)	4·1	1·8	3·9	3·8	2·1	4·9
Structure (XCVI)	3·7	1·9		3·5	2·1	

While, therefore, at the present stage the picture of the fine-structure of tropolone is only beginning to emerge and although it is certainly premature to generalise on particular results yet, in the absence of a better means, the aromatic structure of tropolone may be formulated tentatively as (XCVII). This represents in composite form most of the features which have been discussed.



(XCVII)

The Reviewers gratefully acknowledge the assistance of Mrs. G. Aulin-Erdtman who kindly contributed the description and diagrams of ultra-violet absorption spectra given on pp. 127–128. They are also indebted to Professor R. D. Haworth, F.R.S., and to Professor A. R. Todd, F.R.S., for information which was still in course of publication at the time when this Review was written.

[80] Cf. Kubo, Nozoe, and Kurita, *Nature*, 1951, **167**, 688.