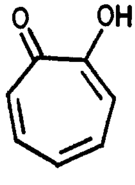
[CONTRIBUTION FROM HICKRILL CHEMICAL RESEARCH LABORATORY]

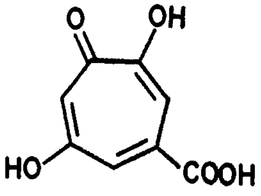
Tropolone

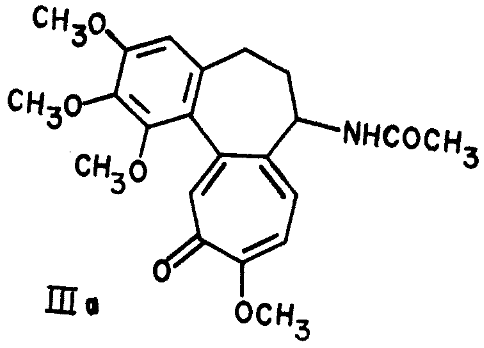
BY W. VON E. DOERING AND LAWRENCE H. KNOX

Tropolone (I) has been synthesized by oxidizing tropilidene with alkaline permanganate. An investigation of the physical and chemical properties has brought the following facts to light. I is an acid of pK_a 6.7 and a base forming a crystalline hydrochloride. I absorbs four moles of hydrogen to give *cis*-cycloheptanediol-1,2. I can be acetylated, benzoylated and methylated. Tropolone methyl ether can be hydrolyzed with acid or alkali and is converted to aminocycloheptatrienone by ammonia. I undergoes substitution reactions with bromine to tribromotropolone, with nitrous acid to nitrosotropolone, with nitric acid to nitrotropolone and with benzenediazonium chloride to phenylazotropolone. I can be aromatized by isomerization to benzoic acid on alkali fusion and by halogenative decarboxylation to halophenols by sodium hypobromite and hypoiodite. Tropolone methyl ether is rearranged with surprising ease to methyl benzoate by sodium methoxide. The hypothetical reaction mechanisms are discussed, the analogy with β-diketones is indicated and the question of aromatic character is considered. The comparable reactions attributable to ring C of colchicine and derivatives are outlined and found to parallel those of tropolone and derivatives very closely. This correspondence of properties constitutes a necessary but insufficient condition that colchicine have a tropolone structure.

The structural hypothesis of tropolone (I) was conceived by Dewar[1] as a unit theoretically capable of accommodating the otherwise perplexing facts of the behavior of stipitatic acid (II). Shortly thereafter, Dewar[2] speculated that ring C of colchicine (III) had the tropolone structure as well (IIIa). To the extent that the convincingly and well reasoned, but still hypothetical, chemical properties of tropolone were identical with those shown by stipitatic acid and ring C of colchicine, these substances were to be assigned structures II and IIIa, respectively.

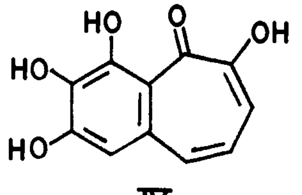

I

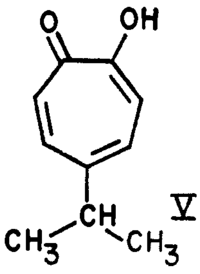

II


IIIa

New experimental efforts to substantiate these structures have been limited. An attempt to synthesize an analog of II has failed.[1] However, it has been shown that hexahydrocolchiceine reacts rapidly with lead tetraacetate[3] and with periodic acid[4] to produce an amorphous material having aldehydic properties and forming an amorphous 2,4-dinitrophenylhydrazone. These observations afford good indication that hexahydrocolchiceine is an α-glycol, a necessary consequence of Dewar's colchicine formulation.

Subsequent, if not consequent to Dewar's announcement, other workers have established the presence of tropolone in two natural products: in purpurogallin (IV) by an investigation[5] culminating in a rational synthesis[6]; and in the thujaplicins (γ-isomer, V) by completely convincing, degradative experiments.[7]


IV


V

The synthesis of tropolone and elucidation of its chemical properties is fundamentally important to provide the experimental basis not only for a valid comparison with products suspected of containing the new grouping (colchicine being a timely example) but also for an intrinsically interesting and potentially extensive area of organic chemistry. There have been reported the syntheses of 3,4-benztropolone[8] and 4,5-benztropolone,[9] derivatives in which the large resonance energy of the fused benzene ring could effect unpredictable changes in the properties of the tropolone ring.

Synthesis of Tropolone.—Tropilidene, C_7H_8 (VI),[10,11] is potentially convertible to tropolone by the oxidation of one ethylenic bond to an α-diketone grouping. Of several apposite reagents, potassium permanganate has been reinvestigated[12] because it is capable of effecting the change in a single step, albeit without any particular speci-

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[1] M. J. S. Dewar, *Nature*, **155**, 50 (1945).

[2] M. J. S. Dewar, *ibid.*, **155**, 141 (1945).

[3] M. J. S. Dewar, *ibid.*, **155**, 431 (1945).

[4] H. R. V. Arnstein, D. S. Tarbell, H. T. Huang and G. P. Scott, THIS JOURNAL, **70**, 1669 (1948); H. R. V. Arnstein, D. S. Tarbell, G. P. Scott and H. T. Huang, *ibid.*, **71**, 2448 (1949).

[5] J. A. Barltrop and J. S. Nicholson, *J. Chem. Soc.*, 116 (1948); R. D. Haworth, B. P. Moore and P. L. Pauson, *ibid.*, 1045 (1948); *ibid.*, 3271 (1949).

[6] D. Caunt, W. D. Crow, R. D. Haworth and C. A. Vodoz, *Chemistry and Industry*, 149 (1950).

[7] H. Erdtman and J. Gripenberg, (a) *Nature*, **161**, 719 (1948); (b) *Acta Chem. Scand.*, **2**, 625 (1948); (c) J. Gripenberg, *ibid.*, **2**, 639 (1948); (d) A. B. Anderson and J. Gripenberg, *ibid.*, **2**, 644 (1948).

[8] J. W. Cook and A. R. Somerville, *Nature*, **163**, 410 (1949).

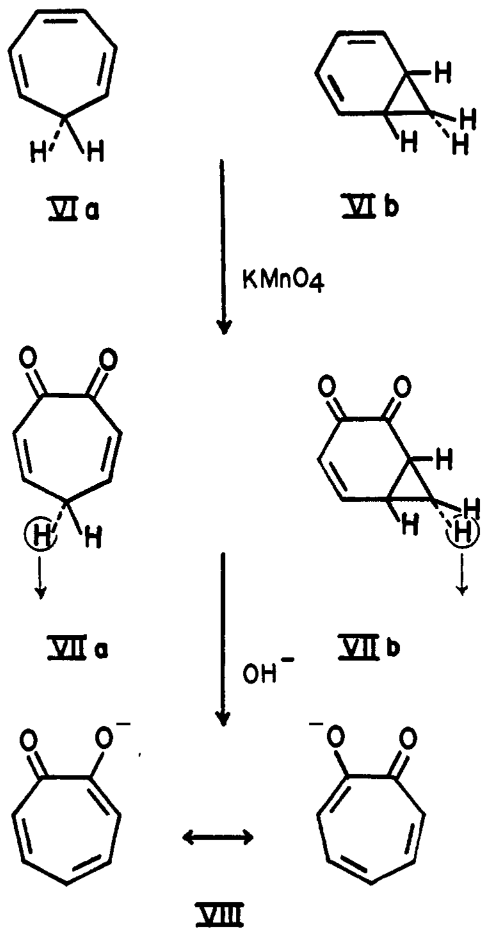
[9] D. S. Tarbell, G. P. Scott and A. D. Kemp, THIS JOURNAL, **72**, 379 (1950).

[10] R. Willstätter, *Ann.*, **317**, 204 (1901).

[11] E. P. Kohler, M. Tishler, H. Potter and H. T. Thompson, THIS JOURNAL, **61**, 1057 (1939).

[12] R. Willstätter, ref. 10, p. 217, mentions the failure to isolate any products from the permanganate oxidation of tropilidene.

ficity. The choice is more or less fortunate depending upon the formulation of tropilidene. If this substance be cycloheptatriene (VIa) as is generally accepted,[10,11,13] the intermediate diketone VIIa could tautomerize to I by the removal of a highly activated hydrogen atom; if it be norcaradiene (VIb), as considered and rejected,[10,13] conversion of the corresponding diketone VIIb to I would require removal of a (substantially) unactivated hydrogen atom. Particularly in the latter event, high concentrations of alkali might become necessary to remove rapidly the sensitive diketone by converting it to the presumably more resistant tropolone anion (VIII).[14]



Tropilidene has been prepared from cycloheptanone by repetition of the work of Kohler, *et al.*,[11] and from benzene and diazomethane by irradiation as already communicated.[15] Both methods give material identical infrared-spectroscopically. Initially, an aqueous suspension of tropilidene was oxidized with aqueous potassium permanganate to give a small amount of material extractable from water with chloroform at *p*H 4.5. Copper acetate precipitated a copper salt which was extractable with chloroform and could be crystallized from the same solvent. Pure tropolone, m.p. 49°, was generated by treating the copper salt with hydrogen sulfide. The yield never amounted to more than 1% of theory. The use of a large excess of potassium hydroxide in 95% ethanol produced the most significant improvement, raising the yield to better than 6% of theory. The structure, insofar as it concerns the arrangement of atoms, is established simply and conclusively by catalytic hydrogenation to an oil which is oxidized to pimelic acid and from which crystalline *cis*-cycloheptanediol-1,2 can be isolated.

Almost simultaneously with this synthesis,[15] Cook, Gibb, Raphael and Somerville[16] communicated an excellent, independent synthesis of tropolone from cycloheptanedione, while Haworth and Hobson[17] achieved a much longer synthesis by way of the degradation of synthetic purpurogallin.

Physical and Chemical Properties of Tropolone.—With acetic anhydride and benzoyl chloride, tropolone forms a crystalline acetate and benzoate, respectively. Both derivatives are insoluble in sodium carbonate solution and reconvertible to tropolone on mild alkaline hydrolysis. The hydroxyl function in tropolone, like enols in general, is therefore quite capable of being esterified. This behavior gives some experimental confirmation for Dewar's negation[3] of his original assertion that intramolecular hydrogen bonding would be responsible for an "aromatic" stability in tropolone.[1] This type of stabilization would have been expected to decrease the reactivity not only of the carbonyl group but of the hydroxyl group as well.

Tropolone is an acid of pK_a 6.7 in equilibrium with a yellow anion. This value may be compared with that of 5.255 and 5.253 for dihydroresorcinol and dimethyldihydroresorcinol, respectively,[18] or the pK_a of 10.30 shown by the enolic form of cyclohexadione-1,2.[19] As in the case of the cyclic β-diketones and carboxylic acids, two structures (VIII) of equal energy in which oxygen bears the negative charge can be written for the tropolone anion. From this point of view it is not surprising that tropolone which can be considered a cyclized vinylog of a β-diketone[20] should show about the same acid strength. Nevertheless, it is worthy of remark that no enhancement of acidity beyond that of a β-diketone appears to be derived from the "aromatic" equivalence of the two resonance structures VIII, in which the three double bonds in a cycle is suggestively reminiscent of Kekulé resonance.

The formation from tropolone of a yellow, crystalline picrate with picric acid and a crystalline hydrochloride with ethereal hydrogen chloride bring to light the remarkable basic character of tropolone. In the conjugate acid of tropolone the positive charge can be borne by the two oxygen atoms (IXa and IXb; R = H), two structures which have counterparts in the conjugate acid of

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[13] J. Thiele, *Ann.*, **319**, 226 (1901).

[14] The subtle structural problem presented by tropilidene is being investigated. It has already been determined that the Diels–Alder reaction product from tropilidene and maleic anhydride[11] has the structure derived from norcaradiene.

[15] W. von E. Doering and L. H. Knox, THIS JOURNAL, **72**, 2305 (1950).

[16] J. W. Cook, A. R. Gibb, R. A. Raphael and A. R. Somerville, *Chemistry and Industry*, **427** (1950).

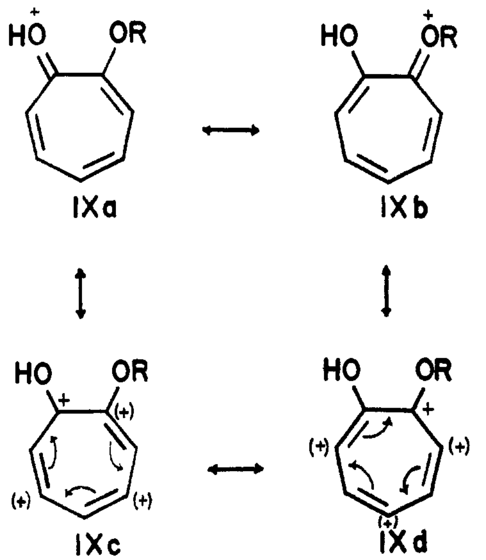
[17] R. D. Haworth and J. D. Hobson, *ibid.*, 441 (1950).

[18] G. Schwarzenbach and K. Lutz, *Helv. Chim. Acta*, **23**, 1162 (1940).

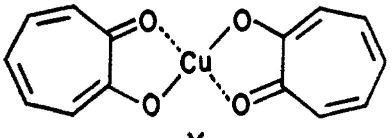
[19] G. Schwarzenbach and C. Wittwer, *ibid.*, **30**, 663 (1947).

[20] One may write $O{=}C{-}(CH{=}CH)_2CH{=}C{-}OH$ and then compare with glutacondialdehyde of pK 5.75.[18]

β-diketones but which do not there suffice to confer a comparable basicity, and most strikingly by all seven carbon atoms (IXc and IXd; R = H). This remarkable resonance possibility is "aromatic" in the sense of requiring a cycle for its existence and involving the stable molecular orbital of six electrons.[21]



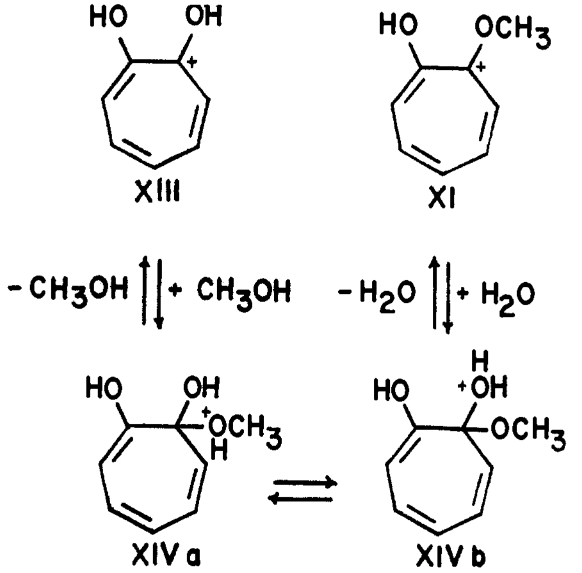
The appearance of a green color with ferric chloride and the formation of a chloroform-soluble copper complex is rather evidently related to the possibility for chelation in the salt (X) and seems commonplace.



X

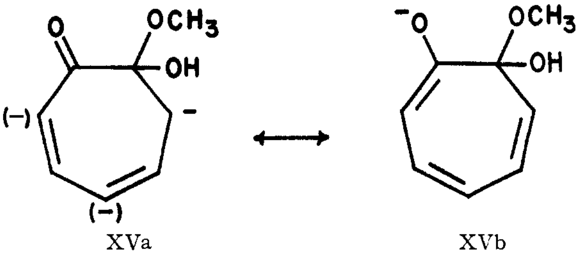
The methylation of tropolone can be accomplished both with diazomethane and with methanolic hydrogen chloride. With the latter reagent the crystalline hydrochloride of tropolone methyl ether (XI) is obtained, whereas the former reagent produces the liquid tropolone methyl ether (XII) which may easily be converted to the hydrochloride XI by dissolving in methanolic hydrogen chloride. Stabilization of this hydrochloride is ascribed to the same possibilities for resonance (IX, R = CH_3) as those described for the conjugate acid of tropolone. Tropolone may be regenerated from its ether either by refluxing with hydrochloric acid or very easily by warming with aqueous sodium hydroxide for a few minutes.

The parallel between the behavior of carboxylic acids and esters, enolizable β-diketones and their related β-methoxy-α,β-unsaturated ketones,[22] and tropolone and its methyl ether is such a striking one that a mechanism analogous to that commonly accepted for the esterification and hydrolysis of acids and esters may be proposed. The conjugate acid of tropolone (XIII) may react reversibly with methanol at any carbon atom (*cf.* IXc and d; R = H) but fruitfully only at the two carbon atoms bearing the hydroxyl function. The resulting adduct XIVa is in equilibrium with XIVb



which by loss of water may produce the conjugate acid of tropolone methyl ether (XI). The demonstration of the existence of XIII and XI lends considerable support to the mechanism.

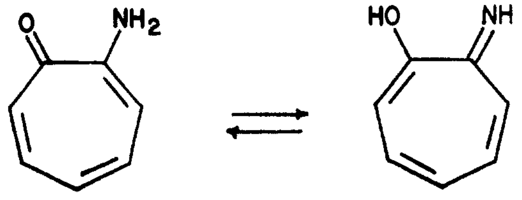
The mechanism of the alkaline hydrolysis is almost certainly analogous to that accepted for the saponification of esters and also applicable to their vinylogs, the β-alkoxy-α,β-unsaturated ketones. Attack of hydroxide ion at the carbon atom bearing the methoxyl group can occur easily because the energy of the resulting intermediate XV (and/or transition state) is markedly lowered mainly through contribution of structure XVb. The



XVa XVb

reaction completes itself by the ejection of methoxide ion and is irreversible because of the acidity of tropolone.

Similarly characteristic of esters is the reaction with ammonia in which tropolone methyl ether (XII) reacts smoothly replacing the methoxyl



XVI XVII

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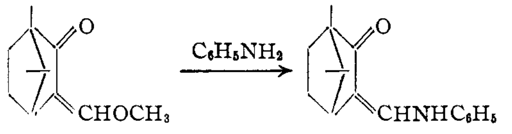
(21) E. Hückel, "Grundzüge der Theorie ungesättigter und aromatischer Verbindungen," Verlag Chemie, Berlin, 1938, pp. 71–75.

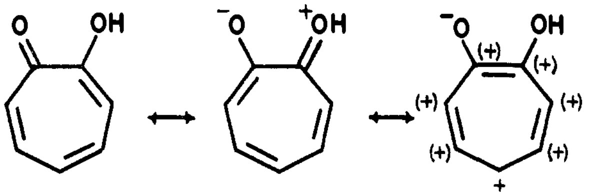
(22) *Cf.* D. Vorländer and M. Kohlmann, *Ann.*, **322**, 239 (1902). They report the etherification of 5,5-dimethyldihydroresorcinol with methanol and sulfuric acid and the saponification of the ether with aqueous carbonate.

group by the amino group. The initial product of the reaction must be formulated as 2-aminocyclohepta-2,4,6-triene-1-one (XVI), although there is no evidence to indicate that the actual product is not the tautomer XVII. This reaction, likewise supporting the ester analogy, may be compared with that of methoxymethylene camphor (XVIII) and aniline to give anilinomethylene camphor (XIX).[23] Like amides, XVI can be hydrolyzed with alkali, tropolone being recovered. Neither a semicarbazone nor a 2,4-dinitrophenylhydrazone could be prepared from tropolone under the customary conditions, but esters also fail to give these derivatives.



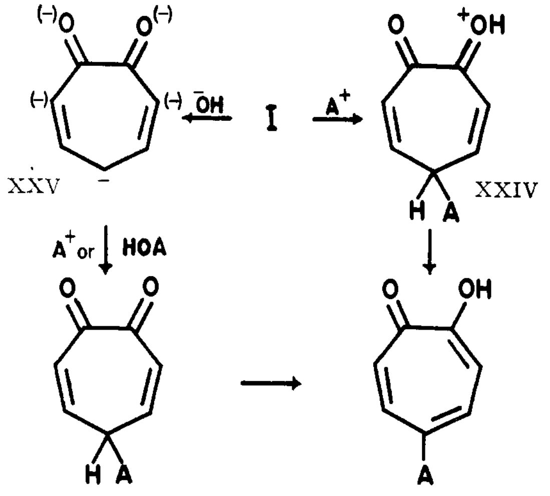
XVIII XIX

The facts so far presented are consistent with the view that tropolone and tropolone methyl ether are closely analogous to carboxylic acids and esters and their vinylogs, the β-dicarbonyl compounds and their ethers. Thus, tropolone and its ether are adequately represented primarily by the typical acid and ester resonance structures (Ia and Ib). The novelty and peculiarity of the tropolone system can be considered to lie in the fact that the otherwise unexceptional type of resonance system (vinylogous with the carboxylic acid type and to be compared with glutacondialdehyde, for example) has its terminal carbonyl and enol groups joined to form a ring. Superficially considered, this situation obscures the analogy with β-diketones and suggests instead an analogy with α-diketones. In assigning to the three double bonds the task of transmitting the resonance interaction of the carbonyl and hydroxyl groups, this theoretical analysis implies that the resonance energy depends on the intactness of the system of three double bonds and to the extent that this energy is large[24] or small disruption of the system will require a more or less high activation energy. The qualitative indication from our experiments that tropolone and its ether react with about the same difficulty as simple carboxylic acids and esters suggests that no large added resonance stabilization is being derived from the unique possibility of distributing the positive charge of the carbonyl group of tropolone to all seven carbon atoms (Ic).



Ia Ib Ic

Tropolone is transformed to a variety of crystalline substitution products by electrophilic reagents. The reagents investigated include bromine in water which produces a crystalline tribromotropolone (XX), aqueous nitrous acid which gives a nitrosotropolone (XXI), dilute nitric acid which gives a nitrotropolone (XXII) and benzenediazonium chloride which produces a colored azo derivative (XXIII). Reasonable structures for these products are formulated on the basis of a probable reaction mechanism which is closely analogous to that accepted for similar reactions with phenols. Like the ortho and para positions in phenol, the 3-, 5- and 7-positions (α and γ) in tropolone are activated to attack by electrophilic reagents because the rate-controlling transition states can be stabilized by resonance of the positive charge with the hydroxyl group (XXIV).



XXVI

XXI, A = NO
XXII, A = NO_2
XXIII, A = —N=N—C_6H_5

The tropolone anion in which a full negative charge is being distributed (XXV) and from which an uncharged intermediate (XXVI) can be formed is much more highly activated. Depending on whether the environment is acidic or basic the substituted tropolone or its anion is generated by appropriate movement of hydrogen. Reaction at the 4- and 6-positions is expected to be strongly inhibited by the inability of a carbonyl group to stabilize a positive charge, the situation being comparable to that in α,β-unsaturated ketones in general. Although the 5-position has the attractiveness of being unhindered by the two oxygen atoms which are adjacent to the 3- and 7-positions, no pressing reason for favoring one position over another is apparent. Indeed, the formation of the tribromo derivative which must rather unequivocally be 3,5,7-tribromotropolone (XX) shows that the three activated positions do not differ markedly in reactivity. Until pertinent experimental evidence is accumulated, the monosubstituted products are being assigned the structures of 5 (or 3) substituted tropolones (XXI, XXII, and XXIII).

In nitrosation, nitration and diazonium salt coupling, substitution is arrested at the monosubstituted stage by the ground-state resonance

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(23) A. W. Bishop, L. Claisen and W. Sinclair, *Ann.*, **281**, 314 (1898).

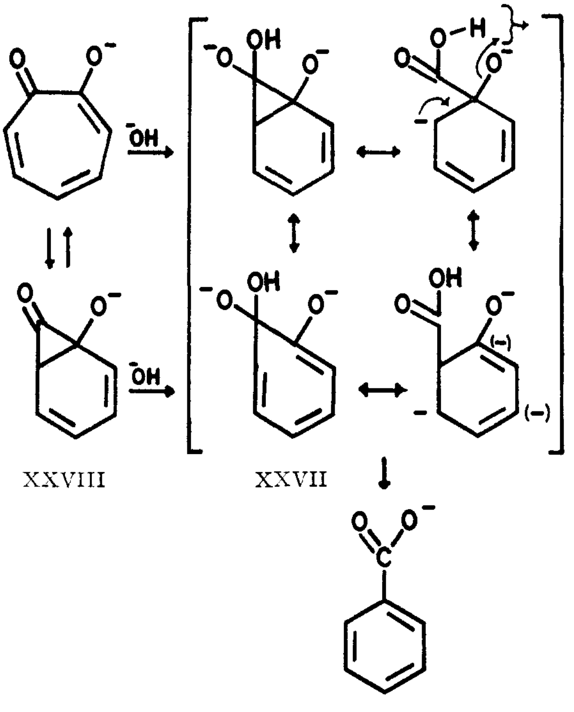
(24) L. Pauling, "The Nature of the Chemical Bond," 2nd ed., Cornell Univ. Press, Ithaca, N. Y., 1942, p. 138, assigns resonance energies of 28 and 24 kcal. to carboxylic acids and esters, respectively.

interaction between the enolic hydroxyl and substituent which is not accompanied by simultaneous lowering of the energy of the transition state for the second substitution. In bromination, substitution by the first bromine atom does not change the resonance picture appreciably so that di- and tribromination proceeds with unimpaired facility.

Reaction of an olefinic system by substitution rather than by addition is indicative of resonance stabilization in the intact system of double bonds. In tropolone, where addition to one of the double bonds could result in loss of the carboxylic acid type of resonance, the favored reaction is substitution in which there is no permanent loss of resonance energy. As an example of reaction by substitution explainable by carboxylic acid type resonance, the familiar 5,5-dimethyldihydroresorcinol is pertinent. The molecule can be chlorinated,[22] nitrosated,[25] nitrated,[25] sulfonated[26] and coupled[27] at the 2-position.

The observation of reaction by substitution is so often considered to be synonymous with aromatic character, that one might ascribe aromatic character to tropolone on the basis of the observed substitution reactions. As a matter of definition, however, substitution is a necessary but insufficient condition for aromatic character. The further condition must be satisfied that the resonance stabilization which is responsible for reaction by substitution must originate from the presence of double bonds in a cycle and must not exist in the corresponding acyclic system. One recalls the classical comparison of benzene and hexatriene as illustration. In order unequivocally to interpret reaction by substitution as indicative of the aromatic character of tropolone, it must be demonstrated that the responsible resonance energy arises specifically from the arrangement of the three double bonds in the seven-membered cycle. Although some resonance may in fact be associated with the presence of the three double bonds in a cycle that would not exist were tropolone acyclic (Ic), there is nothing in the substitution reactions investigated here which supports this contention. The origin of the resonance energy in tropolone much more probably lies in an interaction of the carbonyl and hydroxyl which would still exist if the three double bonds were no longer in a cycle. Accordingly, one would not appear to be justified in ascribing aromatic character to tropolone on this basis.

As a potential α-diketone[28] tropolone was heated with concentrated alkali in the hopes of effecting a rearrangement of the benzilic acid type. Whereas at 170° tropolone was recovered unchanged, at 220° it was mainly converted to benzoic acid. In contrast to the usual benzilic acid rearrangement, this unique transformation is an isomerization and is noteworthy in that the transition state which appears most reasonable (XXVII) arises by the reaction of hydroxide ion with the anion of tropolone, a situation of high energy which is also encountered in describing a mechanism for the Wallach rearrangement of α-diketones.[29] It may well be a significant correlation that the more weakly acidic α-diketones normally rearrange with alkali at temperatures of 100–140°, whereas the more strongly acidic tropolone requires a considerably higher temperature. It seems improbable that the reaction is strictly analogous to the benzilic acid rearrangement in being initiated from the neutral α-diketone tautomer of tropolone. Nevertheless, it is clear that the rearrangement would be more attractively formulated by a singly charged transition state in which case a proton could be added to the oxide ion in the transition state XXVII, although in an alkali fusion this too seems improbable. The recent establishment of a cyclopropanone intermediate in the Faworskii rearrangement by Loftfield[30] suggests consideration of the hypothetical cyclopropanone tautomer of tropolone, hydroxynorcaradienone (XXVIII), from which the protonated transition state XXVII could be more easily derived.



XXVIII XXVII

When tropolone is treated with sodium hypobromite or hypoiodite, a mixture of bromo- or iodophenols is obtained which is identified by conversion to 2,4,6-tribromophenol or 2,4,6-triiodophenol, respectively. In the bromination some tribromotropolone is also obtained. Ring contraction, aromatization and loss of a carbon atom have occurred. The facility of this aromatization, in contrast to that brought about by alkali alone, is analogous to the much greater ease of rearrangement shown by non-enolizable α-diketones than by their enolizable relatives. A pertinent illustration is the chlorinative conversion of catechol ultimately to perchloro-

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(25) P. Haas, *J. Chem. Soc.*, **91**, 1433 (1907).

(26) W. von E. Doering and F. M. Beringer, This Journal, **71**, 2221 (1949).

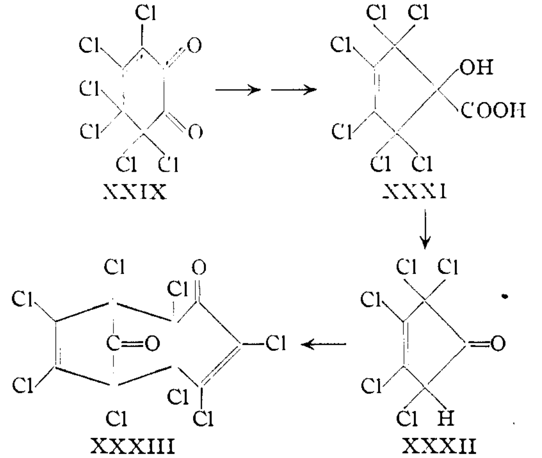
(27) B. H. Iyer, *J. Indian Inst. Sci.*, **21A**, Pt. 6, 65 (1938).

(28) A preliminary experiment in which tropolone was treated with deuterium oxide was not very satisfactory but gave a value of 0.75 atom of hydrogen exchanged. This result indicates that the carbon–hydrogen bonds do not exchange rapidly in water and that the α-diketone tautomer is not in rapidly established equilibrium with tropolone.

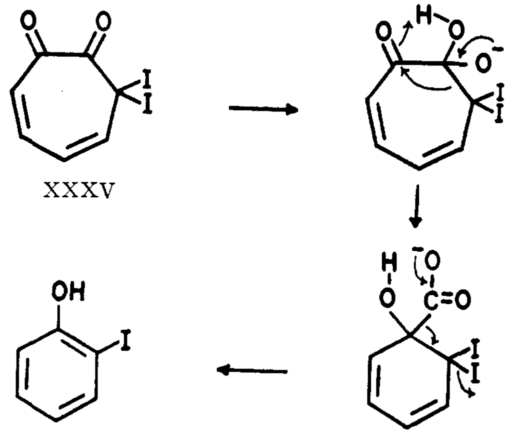
(29) O. Wallach, *Ann.*, **414**, 296 (1918); **437**, 148 (1924).

(30) R. B. Loftfield, This Journal, **72**, 632 (1950).

indanone (XXXIV). In this change,[31] hexachlorocatechol (XXIX) rearranges very readily to the α-hydroxy acid XXX in sodium carbonate solution in which the enolized tetrachlorocatechol is of course stable. XXX may be converted to XXXIV directly or it may be isomerized thermally to its double bond isomer XXXI which on cautious warming in water loses chloride ion and carbon dioxide in a commonplace β-elimination to give XXXIII *via* the intermediate XXXII. A similar series of steps satisfactorily accommodates the halogenative aromatization of tropolone.

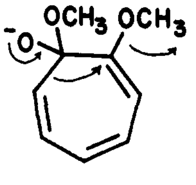


When tropolone has been halogenated (*cf.* XXVI for mechanism) to one of the several possible, nonenolizable, *gem*-dihalo α-diketones (*e.g.*, XXXV), facile rearrangement to the α-hydroxy acid XXXVI may occur. Like XXXI this α-halo acid may easily lose halide ion and carbon dioxide to give the halophenol.

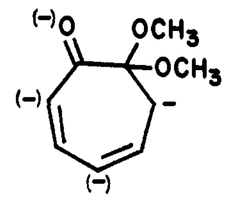


The mechanism shown is one of several satisfactory variations which gives a necessary role to the halogen.[32]

Another aromatization is encountered in the reaction of tropolone methyl ether with refluxing methanolic sodium methoxide to produce methyl benzoate. This novel and facile rearrangement cannot conceivably involve an α-diketone and is, therefore, not strictly of the benzilic acid type. Rather a mechanism comparable to that written above for the formation of benzoate ion (*cf.* XXVII) in the alkali fusion and concerted in the sense that the methoxyl begins to move away as the rearrangement proceeds seems reasonable (*cf.* XXXVII). The much greater ease of the rearrangement in which a singly negatively charged transition state is involved is in contrast to the difficulty of the rearrangement of tropolone anion and affords considerable confirmation for the essential correctness of the doubly negatively charged transition state hypothesized in the latter rearrangement. It is noteworthy that of the two fruitful positions for attack of a base in tropolone methyl ether, position 2 which leads to replacement (*e.g.* by hydroxyl and amino) is the more reactive but becomes a fruitless position when methoxide is the base (*cf.* XXXVIII) and only in this event can rearrangement which necessitates attack at position 1 predominate.



XXXVII



XXXVIII

The ultraviolet spectra of tropolone in aqueous acid, aqueous alkali and water are shown in Fig. 1 The dominant feature is the large shift to longer wave lengths in the spectrum of the anion. The curve in water appears to be a combination of that of tropolone and its anion, a result not unexpected in view of the marked acidity of tropolone and the intensity of the anion absorption.[33]

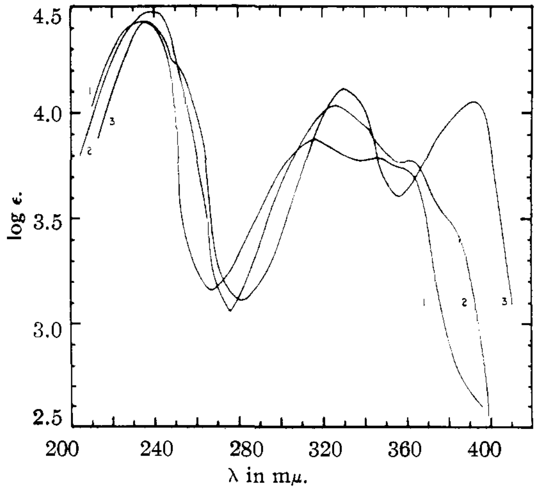


Fig. 1.—Absorption spectra of tropolone in 0.01 *N* hydrochloric acid (curve 1), in water (curve 2) and in 0.01 *N* sodium hydroxide (curve 3).

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(31) T. Zincke and F. Küster, *Ber.*, **21**, 2719 (1888); **22**, 486 (1889); **23**, 812, 2200 (1890); **26**, 2104 (1893). T. Zincke and H. Günther, *Ann.*, **272**, 243 (1893); T. Zincke, *ibid.*, **296**, 135 (1897); T. Zincke and A. Rohde, *ibid.*, **299**, 367 (1898); T. Zincke and K. H. Meyer, *ibid.*, **367**, 1 (1909).

(32) J. Čech and F. Šantavý, *Coll. Czech. Chem. Comm.*, **14**, 532 (1949), propose an alternative mechanism for the related reaction of colchiceine which has disadvantages obvious in terms of the discussion above.

(33) The spectrum reported previously[15] for tropolone in ethanol is also a combination of the two spectra. The same difficulty is apparent in the spectra reported for β- and γ-thujaplicin in ethanol.[7b]

In Fig. 2 are the spectra of tropolone methyl ether and tropolone in isoöctane, the latter showing considerably more fine structure than the spectrum in the hydrogen bonding solvents, water and ethanol.

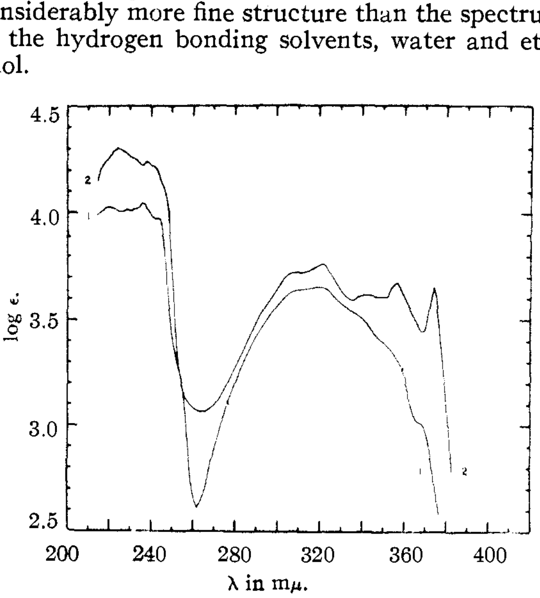


Fig. 2.—Absorption spectra of tropolone methyl ether in isoöctane (curve 1) and tropolone in isoöctane (curve 2).

The curves in Fig. 3 provide independent spectroscopic evidence for the existence of the conjugate acid of tropolone in aqueous hydrochloric acid solution.

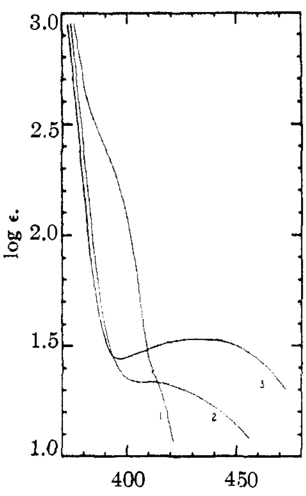
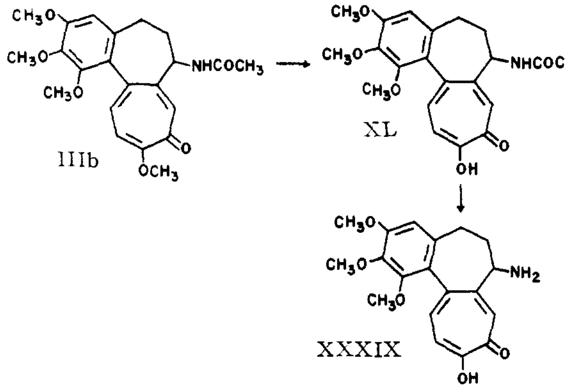


Fig. 3.—Absorption spectra of tropolone in water (curve 1), 0.01 N hydrochloric acid (curve 2) and 1.0 N hydrochloric acid (curve 3).

The infrared absorption spectra of tropolone and tropolone methyl ether are reproduced in Fig. 4. The absence of a band in the typical carbonyl absorption region is noticeable and is in complete accord with the results obtained with substituted tropolones.[34] The shift of the carbonyl band is at least 100 cm.$^{-1}$ and must correspond to a profound change in the group. Any contribution of the aromatic resonance Ic would decrease the force constant of the carbon–oxygen bond, increase the bond distance and, therefore, cause a shift to longer wave lengths. The wide band centered at 3200 cm.$^{-1}$ suggests moderate but not strong hydrogen bonding. It affords some confirmation for Dewar's revised prognostication[1,3] that intramolecular hydrogen bonding could not be expected to play a significant role in determining the resonance energy of tropolone.

The Structure of Ring C of Colchicine.—The proposal of Dewar[2] that colchiceine contains the tropolone ring system has appeared very attractive from a theoretical point of view and has received some support from the oxidative experiments[3,4] but has awaited for more adequate confirmation the experimental demonstration of parallelism between the chemical and physical properties of tropolone and its methyl ether and those ascribable to ring C of colchiceine and colchicine. Tarbell and Bill[35] in their recent comparison of the properties of 4,5-benztropolone with those of colchiceine have found poor correspondence, which they quite plausibly ascribed to the altered resonance situation in 4,5-benztropolone. With the present synthesis and preliminary examination of tropolone it becomes possible to make this comparison. The appropriate reactions in the colchicine series are mentioned briefly without comment where the positive correlation is obvious.

Trimethylcolchicinic acid (XXXIX) gives a dibenzoate with benzoyl chloride in pyridine and two *isomeric* dibenzene sulfonates with benzene sulfonyl chloride.[36] This observation of isomeric esters, clearly impossible with the symmetrical tropolone, is in complete accord with the asymmetric situation of the tropolone ring in colchicine.



IIIb XL XXXIX

Colchiceine (XL) is an acid of pK_a 6.75.[35] Colchicine and many derivatives become yellow on treating with strong mineral acid and have been suspected of containing a basic function in addition to the acetamido group.[36] At least in the case of XXXIX a crystalline dihydrochloride has been isolated.[36] Colchiceine (XL) gives a green coloration with excess ferric chloride and forms a green, crystalline copper complex.[37]

Colchicine is hydrolyzed to colchiceine and methanol by dilute hydrochloric acid[38] and also by boiling with alkali.[39] The methylation of colchiceine can be effected either with methanolic hydrogen chloride[40] or by diazomethane[41] in which case there is obtained a mixture of colchicine and isocolchicine, consistent with the presence of an unsymmetrical tropolone ring.[42] Colchicine reacts with ammonia

(34) G. P. Scott and D. S. Tarbell, This Journal, **72**, 240 (1950).

(35) D. S. Tarbell and J. C. Bill, Abstracts of Papers, 118th Meeting, American Chemical Society, Chicago, September 3, 1950, p. 95 N.

(36) A. Windaus, *Sitzber. Heidelberg. Akad. Wiss., Math.-naturw. Klasse*, 2 Abh., (1911); *Chem. Zentr.*, **82**, I, 1638 (1911).

(37) S. Zeisel, *Monatsh.*, **7**, 557 (1886).

(38) S. Zeisel, *ibid.*, **4**, 162 (1883).

(39) S. Zeisel, *ibid.*, **9**, 1 (1888).

(40) G. Johanny and S. Zeisel, *ibid.*, **9**, 865 (1888).

(41) N. Lettré and H. Fernholz, *Z. physiol. Chem.*, **278**, 175 (1943).

(42) M. Sorkin, *Helv. Chim. Acta*, **29**, 246 (1946).

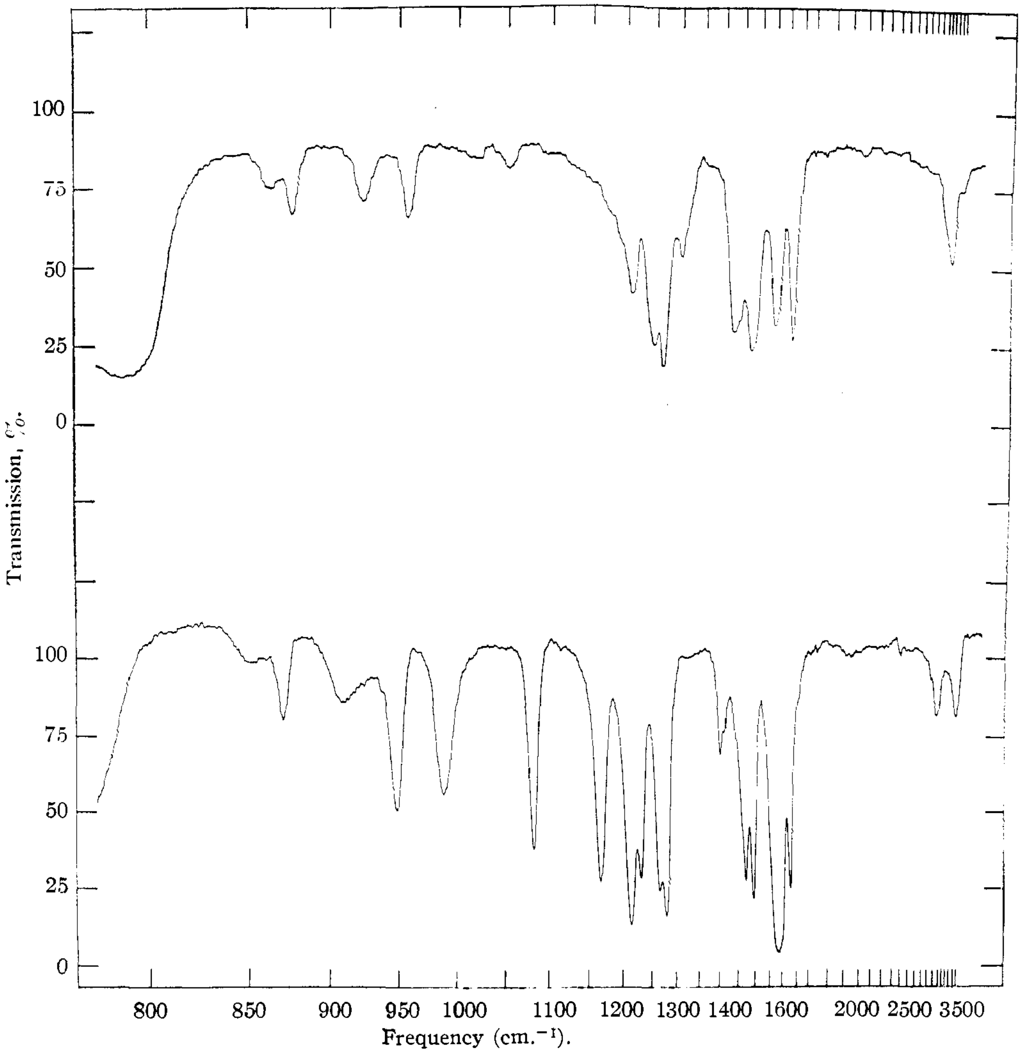


Fig. 4.—Infrared spectra of tropolone in carbon tetrachloride (upper curve) and tropolone methyl ether, undiluted (lower curve).

to give N-acetyltrimethylcolchicinamide in which the methoxyl group has been replaced by amino and from which colchiceine is obtained on hydrolysis with sodium carbonate solution.[39]

The only clearly characterized substitution products of colchicine are the little investigated mono-, di- and tribromo derivatives.[43] Their formation is not inconsistent with a tropolone system in colchicine, which would present two activated positions for substitution in addition to the free position in ring A.

The result of the alkali fusion of colchicine is not known directly but from the fact that oxidation of the crude fusion product affords trimellitic acid, it can be inferred that ring C was converted to a substituted benzoic acid derivative.[44]

Colchiceine reacts smoothly with sodium hypoiodite to give N-acetyliodocolchinol (XLI)[44] the structure of which follows from the oxidation of the corresponding methyl ether, N-acetyliodocolchinol methyl ether, to 4-methoxy-5-iodophthalic acid,[45,46] from the degradation to 2,3,4,7-tetramethoxyphenanthrenequinone,[47] and from the total synthesis of *dl*-colchinol methyl ether.[48]

Colchicine but not colchiceine reacts readily with methanolic sodium methoxide to give methyl colchicicate[49] (*allo*colchicine),[50] which has been related unequivocally to N-acetylcolchinol[50] and, therefore, has the structure XLII.

The occurrence of these specific and unusual rearrangements in both the tropolone and colchicine series constitutes particularly convincing indication that colchicine contains the tropolone system as its ring C. The assignment of the position of the oxygens relative to ring B at present depends on mechanistic interpretation. To the extent that the rearrangements occur by the mechanisms considered in the discussion of tropolone, colchicine has the structure IIIb, the relative position of the carbonyl and methoxyl being indeterminate. This formulation is the same as that deduced by Čech and

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[43] S. Zeisel and K. Stockert, *Monatsh.*, **34**, 1339 (1913).

[44] A. Windaus, *Sitzber. Heidelberg. Akad. Wiss., Math.-naturw. Klasse*, 18 Abh. (1914); *Chem. Zentr.*, **85**, II, 1455 (1914).

[45] A. Windaus, *Ann.*, **439**, 59 (1924).

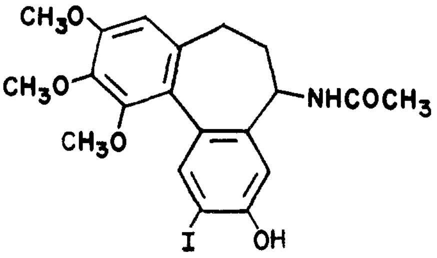
[46] R. Grewe, *Ber.*, **71**, 907 (1938).

[47] N. Barton, J. W. Cook and J. D. Loudon, *J. Chem. Soc.*, 176 (1945).

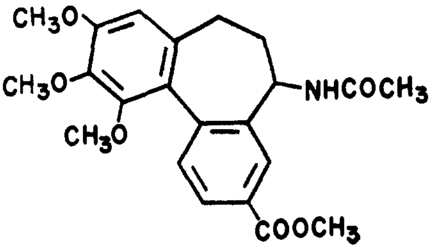
[48] H. Rapoport, A. R. Williams and M. E. Cisney, THIS JOURNAL, **72**, 3324 (1950).

[49] F. Šantavý, *Helv. Chim. Acta*, **31**, 821 (1948).

[50] H. Fernholz, *Ann.*, **568**, 63 (1950).



XLI



XLII

Šantavý[32] on different mechanistic grounds and corrects the formulation IIIa of Dewar who presumably had no knowledge of the paper of Barton, Cook and Loudon[47] in which the position of the fourth methoxyl in deaminocolchinol methyl ether is proved.

This investigation was supported in part by a research grant from the National Institutes of Health, Public Health Service, and in part by a research grant from the American Cancer Society. We wish to thank Mr. Alfred P. Wolf for determining the infrared spectra.

Experimental[51]

Permanganate Oxidation of Tropilidene, C_7H_8 (VI).—The starting material, tropilidene, was prepared both by repeating the method of Kohler, *et al.*,[11] and by the new photochemical reaction of benzene and diazomethane.[15] A large number of oxidations were carried out, but only the optimum procedure is reported in detail.

To a mixture of 1400 ml. of 95% ethanol and 240 ml. of 45% potassium hydroxide cooled to −10° and 9.2 g. (0.1 m.) of VI (b.p. 114°), there was added 52 g. (10 molar equiv.) of potassium permanganate in 2400 ml. of water with vigorous stirring at such a rate that the temperature could be maintained at −5° by means of an ice-salt-bath. Following the addition which required 3.5 hours, the mixture was filtered and freed of the bulk of the ethanol by distillation on the steam-bath at 50–60° under reduced pressure. After extraction with chloroform (6 100-ml. portions), the alkaline solution was acidified to *p*H 2–3 with 6 *N* sulfuric acid and extracted with 100-ml. portions of chloroform until a test sample failed to give a green coloration with alcoholic ferric chloride. The total chloroform extract of the acidified solution (600–800 ml.) was concentrated to about 100 ml. and shaken vigorously with 100 ml. of saturated aqueous cupric acetate. The chloroform layer was withdrawn and further extraction with warm chloroform (100-ml. portions) was continued until a colorless extract resulted. Concentration of the combined, dark colored extracts until crystals appeared, followed by cooling gave 0.811 g. of the **copper salt of tropolone (X)**. Concentration of the mother liquor and cooling gave an additional 0.141 g. raising the yield to 0.952 g. (6.3% of theory).

The copper salt was recrystallized from chloroform practically quantitatively as light green needles, m.p. 320° (dec.). It is insoluble in water and sparingly soluble in most organic solvents.

Anal. Calcd. for $C_{14}H_{10}O_4Cu$: Cu, 20.65. Found: Cu, 20.79.

When more concentrated permanganate was used without added alkali and with either water, aqueous acetone or ethanol as solvent, the yields ranged from 0.3 to 0.9%. The addition of alkali effects the major increase in yield (3 to 4%), although high dilution of the permanganate causes further improvement (see optimum preparation above).

Tropolone (I).—Hydrogen sulfide, passed into a solution of 1.48 g. of the copper salt (X) in 100 ml. of warm chloroform, precipitated copper sulfide which was removed by filtration through Super-Cel. Distillation of the solvent left a residue which crystallized on cooling. Recrystallization from hexane gave slightly discolored needles, 1.05 g., m.p. 47–48°. Concentration of the mother liquor gave an additional 0.10 g. making the total recovery 98% of theory. A second recrystallization followed by sublimation at 100° (150 mm.) gave colorless needles of pure tropolone, m.p. 49°.

Anal.[52] Calcd. for $C_7H_6O_2$: C, 68.85; H, 4.95; neut. equiv., 122.1. Found: C, 68.86; H, 4.94; neut. equiv., 122.8.

Tropolone is appreciably soluble in water and separates in colorless needles from a saturated solution in warm water on cooling. It is very soluble in most organic solvents with the exception of the hydrocarbons. From the *p*H at half neutralization obtained by potentiometric titration a pK_a of 6.7 was found. In dilute sodium carbonate, sodium hydroxide or potassium hydroxide I forms a yellow anion and on addition of concentrated alkali, the yellow salt is precipitated almost quantitatively. Tropolone dissolves in warm concentrated hydrochloric acid and separates unchanged in colorless needles on cooling. Its solutions in water and organic solvents are colored green by alcoholic ferric chloride.

Hydrogenation of Tropolone.—Tropolone, 0.061 g. (0.0005 m.), was hydrogenated in 95% ethanol over platinum oxide, four molar equivalents of hydrogen being absorbed rapidly. After the catalyst was filtered, the solvent was distilled on the steam-bath, the last traces being removed *in vacuo* at room temperature. The pale yellow, glassy residue crystallized on scratching. Recrystallization from cyclohexane gave colorless needles, 0.018 g. (28%), m.p. 40–41°, which was raised to 47–48° by a second recrystallization from cyclohexane. On admixture with authentic *cis*-**cycloheptanediol-1,2**, m.p. 49°, it melted at 47–49°.

Authentic *cis*-cycloheptanediol-1,2 was prepared by the permanganate oxidation of 4.8 g. (0.05 m.) of cycloheptene according to the procedure described by Böeseken and Derx[53] in 22.6% yield. The fraction, b.p. 120–125° (11 mm.) (1.47 g.), solidified and after recrystallization from cyclohexane melted at 49° (1.01 g.) (reported,[53] m.p. 46°).

The mixed, oily glycols obtained by hydrogenation of 0.061 g. of tropolone were dissolved in 2 ml. of water, warmed on the steam-bath, and treated dropwise with 0.160 g. (6 molar equiv.) of potassium permanganate in 7 ml. of water. After centrifugation, acidification, extraction with ether and evaporation of the extracts, 0.047 g. of crystalline residue was obtained. Recrystallization from benzene gave 0.028 g. (35% based on tropolone) of colorless prisms of pimelic acid, m.p. 103° (m.p. 102–103° in admixture with authentic pimelic acid, m.p. 101–102°).

The authentic pimelic acid, m.p. 101–102°, was obtained in 38.0% yield by permanganate oxidation of synthetic *cis*-cycloheptanediol-1,2 followed by recrystallization of the crude product from benzene.

Tropolone Acetate (a).—Acetyl chloride, 0.03 ml., was added to a cold mixture of 0.061 g. (0.0005 m.) of tropolone and 0.15 ml. of dry pyridine. After being warmed briefly and cooled, the mixture was acidified with cold dilute hydrochloric acid and extracted with chloroform. The chloroform extract was washed with cold 2 *N* sodium carbonate and water, and concentrated to give an oil which crystallized. Recrystallization from cyclohexane gave almost colorless crystals, 0.031 g. (38% of theory), m.p. 69–70°. Sublimation at 60–70° (5 mm.) gave colorless tropolone acetate, m.p. 70°, which gave no coloration with alcoholic ferric chloride.

Anal.[54] Calcd. for $C_9H_8O_3$: C, 65.85; H, 4.91. Found: C, 65.95; H, 5.05.

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(51) All melting points are corrected.

(52) Microanalysis by Elek Microanalytical Laboratories, Los Angeles, California.

(53) J. Böeseken and H. G. Derx, *Rec. trav. chim.*, **40**, 529 (1921).

(54) Microanalysis by Schwarzkopf Microanalytical Laboratory, Middle Village, Long Island, New York.

Acidification of the alkaline and aqueous wash liquors, followed by extraction with chloroform, and treatment of the chloroform extract with saturated aqueous cupric acetate as already described, gave 0.009 g. of tropolone copper salt. The yield of ester, based on tropolone consumed, amounted to 43% of theory.

(b).—A mixture of 0.061 g. of tropolone, 0.15 ml. of dry pyridine and 0.05 ml. of acetic anhydride, after standing 24 hours at room temperature, was warmed briefly, cooled and treated as described above. Recrystallization from cyclohexane gave 0.047 g. (57% of theory) of product, m.p. 69–70°. From the alkaline and aqueous wash liquors, 0.002 g. of tropolone copper salt was recovered, raising the yield to 59% of theory (based on tropolone consumed).

A mixture of 0.009 g. of the acetate and 0.5 ml. of 6 *N* sodium hydroxide was heated for 30 minutes on the steam-bath. The yellow, alkali-insoluble sodium salt of tropolone separated rapidly. Acidification, followed by extraction with chloroform, and treatment of the chloroform extract with aqueous cupric acetate, gave 0.008 g. (95% of theory) of tropolone copper salt, m.p. 320° (dec.) after recrystallization from chloroform.

Tropolone Benzoate.—A mixture of 0.050 g. (0.0004 m.) of tropolone, 0.15 ml. of dry pyridine and 0.04 ml. of benzoyl chloride was warmed briefly on the steam-bath, cooled and centrifuged. The crystalline product was washed with dilute sodium carbonate, dried (0.051 g.) and recrystallized twice from ethanol giving colorless crystals, 0.028 g. (31% of theory), of tropolone benzoate, m.p. 129–130°, which showed no coloration with alcoholic ferric chloride.

Anal.[52] Calcd. for $C_{14}H_{10}O_3$: C, 74.33; H, 4.45. Found: C, 73.83; H, 4.61.

A mixture of 0.008 g. of the benzoate and 0.5 ml. of 6 *N* sodium hydroxide was heated for 2 hours on the steam-bath. From this hydrolysis mixture, 0.005 g. (80% of theory) of tropolone copper salt was obtained, m.p. 320° (dec.) after recrystallization from chloroform.

Tropolone Picrate.—A solution of 0.038 g. of tropolone in 2 ml. of saturated alcoholic picric acid was heated to boiling, diluted with 1 ml. of warm water and allowed to cool. The picrate separated in yellow needles (0.076 g.), m.p. 82–83° which was raised to 83.5–84° after two recrystallizations from ethanol.

Anal.[54] Calcd. for $C_{13}H_9O_9N_3$: C, 44.46; H, 2.58; N, 11.97. Found: C, 43.96; H, 3.09; N, 12.08.

Tropolone Hydrochloride.—Dry hydrogen chloride, passed into a solution of 0.050 g. of tropolone in 3 ml. of dry ether, precipitated a colorless product which softened at 114–115°, partially melted at 125–127° and evolved gas at 131–132°. No change in melting point behavior was observed after recrystallization from absolute methanolic hydrogen chloride (10%)–dry ether mixture from which the salt separated in star-like clusters of needles. Potentiometric titration of a freshly prepared sample gave a neut. equiv. of 159.8 (calcd., 158.6). The salt decomposed slowly at room temperature with evolution of hydrogen chloride and progressive lowering of the melting point range.

Anal.[54] Calcd. for $C_7H_7O_2Cl$: C, 53.01; H, 4.45; Cl, 22.36; OCH_3, 0.0. Found: C, 55.11; H, 5.06; Cl, 19.96; OCH_3, 0.55.

Tropolone Methyl Ether (XII).—A solution of 0.100 g. (0.0008 mole) of tropolone in 5 ml. of dry ether containing a few drops of methanol was treated with a dry ethereal solution of diazomethane until a drop of the solution gave no coloration with alcoholic ferric chloride. After removal of the solvent, evaporative distillation of the residual oil gave 0.075 g. (68%) of tropolone methyl ether, a pale yellow liquid which has not been obtained crystalline.

Anal.[52] Calcd. for $C_8H_8O_2$: C, 70.59; H, 5.92; OCH_3, 22.90. Found: C, 71.17; H, 5.88; OCH_3, 23.05.

Tropolone Methyl Ether Hydrochloride (XI).—Tropolone methyl ether, 0.035 g. (0.00025 m.) was treated with 1.5 ml. of 10% absolute methanolic hydrogen chloride giving a precipitate which was brought into solution by warming. On cooling, 0.041 g. (95%) of slightly discolored needles was obtained. Recrystallization from 10% absolute methanolic hydrogen chloride gave colorless needles, m.p. 130° (dec.).

Anal.[54] Calcd. for $C_8H_9O_2Cl$: C, 55.67; H, 5.25; Cl, 20.54; OCH_3, 17.98. Found: C, 55.42; H, 5.49; Cl, 20.42; OCH_3, 17.52.

The pure salt was also obtained by passing dry hydrogen chloride gas into a dry ethereal solution of tropolone methyl ether. The colorless precipitate, after centrifugation and drying, melted at 130° (dec.).

Reaction of Tropolone with Methanolic Hydrogen Chloride.—A solution of 0.061 g. (0.0005 m.) of tropolone in 1 ml. of 10% absolute methanolic hydrogen chloride was heated for 3 hours on the steam-bath under reflux. The solvent was removed under reduced pressure and the residual oil, which crystallized, was dissolved in 2 ml. of cold water, brought to *p*H 8 with 1 *N* sodium bicarbonate solution, and extracted with chloroform. The reddish oil obtained by evaporation of the solvent, 0.053 g., was dissolved in dry ether and treated with dry hydrogen chloride to give 0.043 g. of salt, m.p. 104–105°. Recrystallization from 5% absolute methanolic hydrogen chloride–ether mixture gave colorless needles, 0.033 g. (38%), m.p. 125–126° (dec.). A second recrystallization from methanolic hydrogen chloride–ether mixture raised the melting point to 130° (dec.), which was not depressed in admixture with the hydrochloride salt, m.p. 130° (dec.), obtained from tropolone methyl ether prepared by methylating tropolone with diazomethane. In admixture with tropolone hydrochloride, it melted at 90–100° (dec.).

From the alkaline solution, 0.023 g. of tropolone copper salt was recovered, raising the yield of tropolone methyl ether hydrochloride to 55.0% (based on tropolone consumed).

Hydrolysis of Tropolone Methyl Ether (a).—Tropolone methyl ether, 0.030 g. (0.00022 m.), was heated on the steam-bath with 1 ml. of 3 *N* hydrochloric acid for 3 hours. On working the hydrolysis mixture, 0.017 g. (52%) of tropolone copper salt was obtained, m.p. 320° (dec.).

(b).—Tropolone methyl ether, 0.080 g. (0.00058 m.), was heated for 5 minutes on the steam-bath with one ml. of 2 *N* sodium hydroxide. On working the saponification mixture, 0.065 g. (73%) of tropolone copper salt was obtained, m.p. 320° (dec.).

2-Aminocycloheptatrienone (XVI).—A solution of 0.108 g. (0.0008 m.) of tropolone methyl ether in 8 ml. of 5% absolute methanolic ammonia was heated in a sealed tube at 110° for 6 hours. Distillation of the solvent gave a reddish oil which crystallized on scratching. Recrystallization from water afforded 0.046 g. (47%) of 2-aminocycloheptatrienone (XVI), m.p. 90–93°. Sublimation at 100° and 4 mm., followed by two recrystallizations from acetonitrile, gave stout yellow needles, m.p. 100–101°.

Anal.[54] Calcd. for C_7H_7ON: C, 69.42; H, 5.83; N, 11.57. Found: C, 69.11; H, 5.89; N, 11.83.

The 2-aminocycloheptatrienone is insoluble in the usual hydrocarbon solvents, sparingly soluble in cold water, moderately soluble in acetonitrile and extremely soluble in hydroxylic solvents. Its solutions in water and ethanol are colored an intense green by alcoholic ferric chloride.

A mixture of 0.010 g. of XVI and 0.5 ml. of 6 *N* sodium hydroxide was heated for 3 hours on the steam-bath. Ammonia was slowly evolved and the oil gradually dissolved with separation of the yellow sodium salt of tropolone. On working the saponification mixture in the usual way, 0.006 g. (48%) of tropolone copper salt was obtained, m.p. 320° (dec.) after recrystallization from chloroform.

Tribromotropolone (XX).—A solution of 0.049 g. (0.0004 m.) of tropolone in 2 ml. of water treated with 1.79 ml. (3 molar equiv.) of a solution prepared by dissolving 5.36 g. of bromine and 7.5 g. of potassium bromide in water and bringing to 50 ml. gave an immediate yellow precipitate. The crude product, 0.123 g. (86%), m.p. 115–116° after two recrystallizations from ethanol, gave yellow needles of tribromotropolone (XX), m.p. 123°.

Anal.[52] Calcd. for $C_7H_3O_2Br_3$: C, 23.43; H, 0.84; Br, 66.82. Found: C, 23.72; H, 0.97; Br, 66.60.

An alcoholic solution of tribromotropolone is colored an intense green by alcoholic ferric chloride.

Nitrosation of Tropolone.—A solution of 0.049 g. (0.0004 m.) of tropolone in 2 ml. of water was treated with 2 ml. of aqueous nitrous acid prepared by dissolving 0.050 g. of barium nitrite in 2 ml. of water, adding dilute sulfuric acid just sufficient to precipitate the barium, and centrifuging. After 30 minutes, the nitroso compound, which had precipitated as yellow needles, was centrifuged, washed twice with water and dried. The combined product from two runs weighed 0.050 g. (42%). From the mother liquors tropolone was recovered as the copper salt (0.041 g.). The yield based on tropolone consumed amounted to 62%. **Nitrosotropolone** (XXI) crystallized from acetonitrile in yellow needles which darkened at 145° and decomposed at 175–180°. In alcohol solution, nitrosotropolone gave a green coloration with alcoholic ferric chloride.

Anal.[54] Calcd. for $C_7H_5O_3N$: C, 55.64; H, 3.33; N, 9.27. Found: C, 55.69; H, 3.56; N, 9.40.

Nitration of Tropolone.—A solution of 0.050 g. (0.0004 m.) of tropolone in 2 ml. of water was treated with 2 ml. of cold 1:1 nitric acid. Crystallization occurred within 10 to 15 minutes. The product was immediately centrifuged, washed twice with cold water and dried. From the crude material, 0.030 g. (45%), m.p. 185–188°, two recrystallizations from acetonitrile gave **nitrotropolone** (XXII), m.p. 191° (dec.).

Anal.[54] Calcd. for $C_7H_5O_4N$: C, 50.31; H, 3.01; N, 8.38. Found: C, 50.41; H, 3.15; N, 8.45.

An alcoholic solution of nitropolone is colored an intense green by alcoholic ferric chloride.

Coupling Reactions of Tropolone (a).—α-Naphthylamine, 0.0716 g. (0.0005 m.), was diazotized in 0.5 ml. of 6 *N* hydrochloric acid with 0.060 g. of sodium nitrite in 2 ml. of water. Addition of the diazonium salt solution to 0.060 g. (0.0005 m.) of tropolone in 3 ml. of 2 *N* sodium hydroxide solution produced an immediate precipitation of a deep red sodium salt. After filtration, washing with water and finally alcohol, the product weighed 0.121 g. Its insolubility discouraged further work.

(b).—Freshly distilled aniline, 0.047 g. (0.0005 m.), was diazotized in a mixture of 0.1 ml. of concentrated hydrochloric acid and 0.25 ml. of water with 0.040 g. (0.00058 m.) of sodium nitrite in 0.1 ml. of water. The diazonium salt solution was added with stirring to a solution of 0.061 g. (0.0005 m.) of tropolone in 3 ml. of 1.5 *N* sodium hydroxide solution. The orange-red sodium salt separated rapidly. On acidification with 3 *N* hydrochloric acid and filtration, the crude dye was obtained as a yellowish-brown solid, 0.097 g. (86%), m.p. 148–150°. After three recrystallizations from acetonitrile, **phenylazotropolone** (XXIII) was obtained as orange-red needles, m.p. 160–161°.

Anal.[54] Calcd. for $C_{13}H_{10}O_2N_2$: C, 69.02; H, 4.45; N, 12.39. Found: C, 68.93; H, 4.59; N, 12.55.

Fusion of Tropolone with Potassium Hydroxide.—Tropolone, 0.1 g., was heated at 230–235° in a nickel crucible with 0.2 ml. of water and 1.5–2.0 g. of potassium hydroxide for 20 minutes. After being cooled, the light brown melt was dissolved in water, acidified and extracted with ether. Evaporation of the ether gave a dark red oil which partially crystallized. After being centrifuged, the crude acid, 0.017 g., was sublimed, giving 0.007 g. of benzoic acid which was recrystallized twice from cyclohexane, m.p. 117–118° (m.p. 118–121° on admixture with benzoic acid, m.p. 122°).

When the fusion was carried out at 160–170°, tropolone, 0.062 g. (62.0% recovery), was the only product that could be isolated.

From a solution of 0.048 g. (0.0004 m.) of tropolone in a mixture of 8 ml. of ethylene glycol and 1 ml. of 45% potassium hydroxide which had been refluxed for 48 hours at 170°, tropolone was recovered as the copper salt (0.044 g.) in 72% of theory.

Reaction of Tropolone with Sodium Hypobromite (a).—To a solution of 0.049 g. (0.0004 m.) of tropolone in 3 ml. of 2 *N* sodium hydroxide, 2 ml. of a 2 *N* sodium hydroxide solution containing 0.260 g. (4 molar equiv.) of bromine was added. The mixture was heated on the steam-bath for 3 hours, cooled, acidified and extracted with ether. The residue obtained after evaporation of the ether was sublimed giving 0.087 g. of light yellow material. Crystallization from hot 50% aqueous ethanol gave 0.029 g. of yellow needles, m.p. 110–114°. A second recrystallization from ethanol afforded pure tribromotropolone, m.p. 122–123°, alone and in admixture with tribromotropolone prepared above. Concentration of the mother liquor and cooling gave 0.031 g. of an almost colorless product, m.p. 80–85°, which dissolved in 2 *N* sodium hydroxide leaving a small residue. Acidification of the alkaline solution gave 0.029 g. of 2,4,6-tribromophenol which, after sublimation, melted at 92° (m.p. 91–93° on admixture with authentic 2,4,6-tribromophenol, m.p. 94°).

(b).—To a solution of 0.048 g. (0.0004 m.) of tropolone in 4 ml. of 2 *N* sodium hydroxide, 2 ml. of a solution of 0.13 g. (2 molar equiv.) of bromine in 2 *N* sodium hydroxide was added. After 15 hours at room temperature, the mixture was acidified, and extracted with chloroform. Evaporation of the extracts gave a brown viscous oil which was dissolved in 3 ml. of ethanol and treated with a slight excess of aqueous bromine. Dilution with 25 ml. of water and filtration gave 0.037 g. of 2,4,6-tribromophenol, m.p. 89–91° after two recrystallizations from 50% aqueous ethanol (m.p. 90–92° in admixture with a sample of 2,4,6-tribromophenol, m.p. 91–92°).

Reaction of Tropolone with Sodium Hypoiodite.—Iodine, 0.25 g. (2 molar equiv.), was dissolved in 2 ml. of cold 2 *N* sodium hydroxide and added to a solution of 0.061 g. (0.0005 m.) of tropolone in 3 ml. of 2 *N* sodium hydroxide. After 3 hours at room temperature, the mixture was heated for 1 hour on the steam-bath, cooled and treated with an additional 0.25 g. of iodine in 2 ml. of 2 *N* sodium hydroxide. After being heated an additional hour and a half on the steam-bath, the mixture was cooled, acidified, treated with 2 ml. of 0.1 *N* sodium thiosulfate and filtered. The dark colored product was dissolved in 3 ml. of 2 *N* sodium hydroxide, centrifuged from a small quantity of yellow insoluble material and reprecipitated with acid. The crude material, 0.047 g. (20%), was sublimed and recrystallized from ethanol to give 2,4,6-triiodophenol, m.p. 158° (m.p. 158–159° on admixture with 2,4,6-triiodophenol, m.p. 158–159°).

Rearrangement of Tropolone Methyl Ether with Sodium Methoxide.—A solution of 0.108 g. (0.0008 m.) of tropolone methyl ether (XII) in 4 ml. of absolute methanol containing 0.02 g. of dissolved sodium was refluxed on the steam-bath for 12 hours. Distillation of the solvent gave a mixture of oil and salt (sodium methoxide) possessing the odor of methyl benzoate. This residue was heated for 3 hours on the steam-bath with 2 ml. of 6 *N* sodium hydroxide. Acidification, ether extraction and evaporation of the ether gave 0.072 g. of crystalline residue. Recrystallization from cyclohexane followed by sublimation at 100° gave 0.045 g. (46%) of benzoic acid, m.p. 120–121° (m.p. 120–121° on admixture with an authentic sample, m.p. 120–121°).

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