2.[9] The fine structure shown between 2800 and 3400 Å. is markedly similar to that shown by fluorenone. Because of the large bathochromic effect on the carbonyl band in fluorenone, the band is shifted well into the visible region of the spectrum. This, as well as the fine structure, is in agreement with 4,5-diazafluoren-9-one in the 2800–3400 Å. wave length region. Although the carbonyl band was not investigated for 4,5-diazafluoren-9-one in the higher ultraviolet and visible, it has been indicated in the infrared spectrum and also by a 2,4-dinitrophenylhydrazone formation.

TABLE I

Absorption wave length, Å.	Maxima intensity, log E_m	Absorption wave length, Å.	Maxima intensity, log E_m
3160	3.89	3925	2.40
(3090)	3.79	3780	2.43
3035	3.86	(3600)	2.34
(2930)	3.70	(3280)	2.97
2420	4.64	3210	3.07
2360	4.56	3150	3.19
		3060	3.28
		2930	3.54
		(2830)	3.40
		2570	5.00
		2480	4.79

The proof of structure for this new type compound has been substantiated by the use of five separate and distinct chemical and physical observations. These are the preparation of the 2,4-dinitrophenylhydrazone, the picrate, ultraviolet absorption data, as well as infrared studies and sterical considerations Until further structural proof if needed is made available, the structure given may be classified if not proven at least as highly probable.

Acknowledgment.—The authors are indebted to Dr. Reynold C. Fuson for many helpful suggestions and to Miss Elizabeth Peterson and Dr. J. Calvin Brantley for measuring and interpreting the infrared and ultraviolet spectra, respectively. Appreciation is expressed for helpful advice given by Drs. Elliot R. Alexander, Robert L. Frank and Nelson J. Leonard.

Summary

1. 1,10-Phenanthroline-5,6-quinone has been found to lose carbon monoxide under the influence of weak, aqueous solutions of sodium hydroxide to yield 4,5-diazafluoren-9-one, which exemplifies a nitrogen heterocyclic system hitherto unknown.

2. This is the first reaction in which carbon monoxide has been observed to be lost from a 1,2-diketone grouping.

3. An attempt has been made to synthesize 4,5-diazafluoren-9-one by heating binicotinic acid and calcium oxide.

URBANA, ILLINOIS RECEIVED APRIL 25, 1949

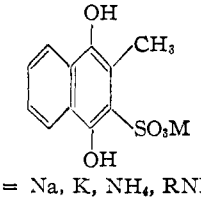
(9) Jones, THIS JOURNAL, **67**, 2127 (1945).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA AND THE ORGANIC RESEARCH DEPARTMENT OF ABBOTT LABORATORIES]

The Structure of the Antihemorrhagic Sodium Bisulfite Addition Product of 2-Methyl-1,4-naphthoquinone (Menadione)[1]

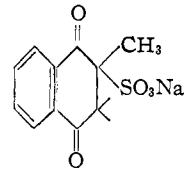
BY MARVIN CARMACK, M. B. MOORE AND M. EARL BALIS

2-Methyl-1,4-naphthoquinone reacts readily in aqueous solution with sodium bisulfite and other bisulfite salts to form two series of isomeric addition compounds, one having high antihemorrhagic activity equivalent to that of the parent quinone, the other having only a small fraction of the activity.[2] The colorless, crystalline sodium salts, $C_{11}H_9O_5SNa$, have been isolated,[2c,d] as have also the salts of potassium, S-benzylisothiuronium, and other cations. On the basis of (1) analogy with the addition of sodium bisulfite to 1,4-naphthoquinone,[3] (2) their easy oxidation to 2-methyl-1,4-naphthoquinonesulfonate salts and (3) by alternative synthesis, Baker, Davies, McElroy and Carlson[2d] showed that the weakly antihemorrhagic series of compounds are salts of 2-methyl-1,4-naphthohydroquinone-3-sulfonic acid (I).



(M = Na, K, NH_4, RNH_3, etc.)

I



II

The structures of the highly active isomeric salts have not heretofore been adequately explained, although the salts are of clinical importance.[4] They cannot be naphthohydroquinone derivatives, since they resist attack by mild oxidizing agents. The resistance to oxidation also rules out simple types of loose 1,2-addition com-

(1) Presented before the Division of Medicinal Chemistry at the meeting of the American Chemical Society in Chicago, Illinois, April 21, 1948.

(2) (a) M. B. Moore, THIS JOURNAL, **63**, 2049 (1941); (b) Moore and Kirchmeyer, U. S. Patent 2,367,302, *C. A.*, **39**, 2849 (1945); British Patent 547,913, *C. A.*, **38**, 457 (1944); (c) Baker, Davies, McElroy and Carlson, THIS JOURNAL, **64**, 1096 (1942); (d) Ablondi, Price, Baker and Carlson, *ibid.*, **65**, 1776 (1943).

(3) Fieser and Fieser, *ibid.*, **57**, 494 (1935).

(4) The U. S. Pharmacopeia lists the more physiologically active isomer as Menadione Sodium Bisulfite.

plexes, which would be expected to dissociate to some extent and liberate oxidizable bisulfite ion. Bochvar and Shemyakin[5] have proposed structures for the active salts which embody more or less conventional 1,2- and 1,4-addition forms; their suggestion that the stability of the active salts can be accounted for on the basis of resonance interaction does not adequately account for all of the properties of these compounds.

On the basis of new evidence from ultraviolet absorption spectra we wish to suggest that the highly active antihemorrhagic product of sodium bisulfite with Menadione is sodium 2-methyl-1,4-dioxotetralin-2-sulfonate (compound II). The highly active salts of other cations would, by analogy, be similarly represented.

The formation of two series of isomeric salts would thus be explained as the consequence of 1,4-additions occurring in both possible orientations. The rapid but slightly reversible addition involving the 4,3,2-conjugated carbonyl system would provide a basis for explaining the isomerization of the highly active into the weakly active isomeric salts under conditions of prolonged heating. Even though the two isomeric series are formed by analogous processes, the end-products would be expected to possess widely differing properties, inasmuch as the products of series I are readily oxidizable naphthohydroquinone derivatives, whereas the products of series II are derivatives of the thermodynamically unstable 1,4-dioxotetralin series, prevented from undergoing aromatization by the absence of an enolizable hydrogen on carbon atom 2.

The ultraviolet absorption spectrum of carefully purified compound II in water or in 0.01 *M* aqueous sodium bisulfite solution is shown in curve I, Fig. 1. It is quite unlike the spectrum of potassium 2-methyl-1,4-naphthoquinone-3-sulfonate (curve III, Fig. 1) and other typical naphthoquinones,[6] and differs also from the spectrum of a 1,4-naphthohydroquinone.[6e] It does, however, show a close similarity to the spectra of three model *o*-benzenedicarbonyl derivatives: *o*-phthalaldehyde, ninhydrin and 2-methyl-1,4-naphthoquinone-2,3-oxide[7,8] (*cf.* Figs. 1 and 2).

The characteristic yellow color of naphthoquinones is caused by a moderately intense peak or shoulder in the near ultraviolet region extending into the violet region, a band which has been attributed to the conjugated carbonyl groups of the quinonoid system.[6a] The simple *o*-dicarbonyl derivatives of benzene which lack this feature of conjugation are typically colorless (or are only

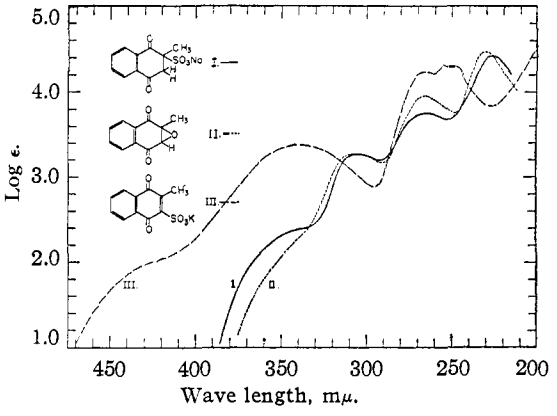


Fig. 1.

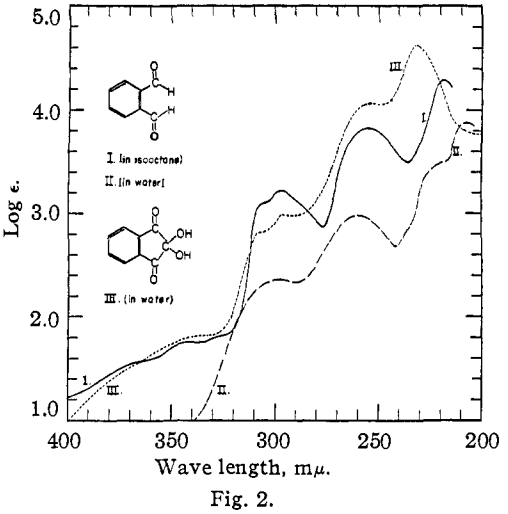


Fig. 2.

faintly colored) and exhibit three well-defined absorption bands in the region between 200 and 400 mμ. There can be little doubt that in compound II and related actively antihemorrhagic salts the 2- and 3-carbon atoms are connected by a single bond. That the active salts do not aromatize to naphthohydroquinone derivatives indicates disubstitution on a beta-carbon atom.[9]

It is interesting to note also that the spectrum of compound II resembles the spectrum of a compound formulated as 2-methyl-2-phytyl-1,4-dioxotetralin by Tishler, Fieser and Wendler.[10] This compound had been isolated as a ketonic by-product of the vitamin K_1 synthesis. Although spectral data are available only over the region 230–320 mμ, the similarities are nevertheless marked among the vitamin K_1 by-product, compound II (curve I, Fig. 1), and 2-methyl-1,4-naphthoquinone-2,3-oxide[7,8] (curve II, Fig. 1).

(5) Bochvar and Shemyakin, *J. Gen. Chem.* (*U. S. S. R.*), **16**, 2033 (1946); *C. A.*, **42**, 895 (1948).

(6) (a) Morton and Earlam, *J. Chem. Soc.*, 159 (1941); (b) MacBeth, Price and Winsor, *ibid.*, 325 (1935); (c) Ewing, Vandenbelt and Kamm, *J. Biol. Chem.*, **131**, 352 (1939); (d) Fieser, Bowen, Campbell, Fry and Gates, THIS JOURNAL, **61**, 1927 (1939); (e) C. J. P. Spruit, *Rec. trav. chim.*, **68**, 309 (1949).

(7) Fieser, Campbell, Fry and Gates, THIS JOURNAL, **61**, 3216 (1939); Fieser, Tishler and Sampson, *ibid.*, **62**, 1628 (1930).

(8) Tishler, Fieser and Wendler, *ibid.*, **62**, 2866 (1940).

(9) A possible alternative formulation of the active salts as alkyl sodium sulfites, R–O–SO_2Na, is considered improbable in view of the extensive literature on additions of bisulfite salts to α,β-unsaturated carbonyl compounds to form keto sulfonic acids; *cf.* Suter, "The Organic Chemistry of Sulfur—Tetracovalent Sulfur Compounds," John Wiley and Sons, Inc., New York, N. Y., 1944, p. 137 ff.

(10) Tishler, Fieser and Wendler, THIS JOURNAL, **62**, 1982 (1940).

Several features of the spectra of the model compounds merit comment. That the sulfonic acid group has only a slight bathochromic effect upon strong chromophoric groups to which it is attached is indicated by the close resemblance of the spectrum of potassium 2-methyl-1,4-naphthoquinone-3-sulfonate (curve III, Fig. 1) to that of its parent quinone,[6hcd] and is further borne out in the recent work of Djerassi[11] with α-sulfonate derivatives of 1-ketotetrahydrophenanthrene.

That the three-membered oxide ring in 2-methyl-1,4-naphthoquinone-2,3-oxide essentially removes the conjugation between the carbonyl groups is indicated by the absence of the band in the visible region typical of the naphthoquinones and by the close resemblance of its spectrum with those of compound II and Tishler, Fieser and Wennler's 2-methyl-2-phytyl-1,4-dioxotetralin. This is interesting in view of recent indications that epoxide rings may have some tendency to show conjugative effects with other unsaturated groups.[12]

The similar form but much lower intensity of the spectrum of *o*-phthalaldehyde in water or alcohol as compared with its spectrum in isoöctane is probably a significant indication of extensive solvation of this compound in hydroxylic solvents.[13]

The structure proposed for compound II provides a satisfactory basis for explaining the stability in neutral or acidic media, the ready regeneration of 2-methyl-1,4-naphthoquinone in alkaline medium, the equivalence in physiological activity of the salt and the parent Menadione, and the isomerization under prolonged heating. In mildly basic solutions (and probably under physiological conditions) the elements of sodium bisulfite can be eliminated by the well-known "beta-cleavage mechanism"[14] involving the following sequence of steps: removal of a proton at carbon-3, formation of the resonating enolate anion, and spontaneous detachment of the sulfonate group as a sulfite ion.

Acknowledgment.—We are greatly indebted to Mr. R. T. Rapala for the preparation and purification of some of the compounds used for the spectrometric studies.

Experimental

Sodium 2-Methyl-1,4-dioxotetralin-2-sulfonate (Compound II).—The addition of sodium bisulfite to 2-methyl-1,4-naphthoquinone was carried out according to the procedure previously described.[2] The purified colorless, crystalline salt obtained from aqueous solution gave analyses indicating approximately four molecules of water of crystallization. The spectrum determined for this material agreed fairly well with the spectrum determined on another specimen which was purified by washing with 95% ethyl alcohol, followed by several recrystallizations from the same solvent; the colorless, nicely crystalline product from 95% alcohol showed the composition of a dihydrate.

Anal. Calcd. for $C_{11}H_9O_5SNa \cdot 2H_2O$: C, 42.30; H, 4.19. Found[15]: C, 42.06, 42.13; H, 4.12, 4.09.

The spectrum of the best specimen of compound II dihydrate from 95% alcohol was determined in the Beckman Model DU quartz spectrophotometer in 0.91 *M* aqueous sodium bisulfite solution prepared from pure sodium metabisulfite; a stock solution of 0.01 *M* sodium bisulfite was used in the comparison cell. The spectrum thus determined, as shown in curve I, Fig. 1, conformed fairly closely to Beer's law in the various dilutions required for the determination of the entire spectrum (log ε 1–2 measured at 10^{-2} *M*, log ε 2–3 at 10^{-3} *M*, log ε 3–4 at 10^{-4} *M*, etc.). The spectrum of the tetrahydrate as determined in pure water was practically identical except that some deviation from Beer's law was observed in passing from one dilution to another.

Potassium 2-Methyl-1,4-naphthoquinone-3-sulfonate.—The weakly antihemorrhagic potassium bisulfite addition salt of Menadione was prepared according to published procedures.[2c] The solution of the whole reaction product was oxidized with acid dichromate[2a,c,3]; when potassium chloride was added to the resulting solution, bright yellow plates of the potassium salt of the methylnaphthoquinonesulfonic acid separated; analysis indicated that some potassium chloride had coprecipitated, but since the inorganic salt should not modify the spectrum no attempt was made to remove the impurity. Allowance was made in the calculations for the actual content of naphthoquinone.

Anal. Calcd. for $C_{11}H_7O_5SK$: C, 45.50; H, 2.43. Calcd. for $C_{11}H_7O_5SK$ + 7.6% KCl by weight: C, 42.0; H, 2.24; chloride, 3.61. Found[16]: C, 42.10; H, 2.24; chloride, 3.14.

The spectrum of the potassium naphthoquinonesulfonate was determined in distilled water, dilutions being made as described for compound II.

2-Methyl-1,4-naphthoquinone-2,3-oxide.—A specimen of the oxide was prepared from 2-methyl-1,4-naphthoquinone and alkaline hydrogen peroxide by the procedure of Fieser, Campbell, Fry and Gates.[7,17] The compound was recrystallized from methanol–water, m. p. 93.5–94.5° cor., and its spectrum was determined in absolute ethyl alcohol (*cf.* curve II, Fig. 1). Data on the absorption peaks of vitamin K_1 oxide have been reported[8]; maxima for the latter oxide were found at 305 mμ (log ε 3.31) and 259 mμ (log ε 3.79).

***o*-Phthalaldehyde.**—*o*-Xylene[18] was brominated to crystalline tetrabromo-*o*-xylene and the latter was hydrolyzed to *o*-phthalaldehyde as described by Thiele and Günther.[19] The product was separated from the reaction mixture by steam distillation, extracted from the aqueous distillate with ethyl acetate, and recrystallized from hexane–pentane; thin, faintly yellow plates, m. p. 55° sharply, cor. (reported m. p. 56–56.5°[19]).

The spectrum of *o*-phthalaldehyde was determined in isoöctane (Spectro-Grade, Phillips Petroleum Company), in absolute alcohol, and in distilled water. The spectrum in isoöctane conformed well to Beer's law in all of the 1:10

(11) Djerassi, *J. Org. Chem.*, **13**, 848 (1948).

(12) (a) Heilbron, Johnson, Jones and Spinks, *J. Chem. Soc.*, 727 (1942); (b) Campbell, Linden, Godshalk and Young, THIS JOURNAL, **69**, 880 (1947); (c) Rogers, *ibid.*, **69**, 2544 (1947).

(13) In water, for example, hydration of the aldehyde functions would destroy their power to conjugate with the benzene ring. Hydration of one of the two functional groups would produce a molecule approximately equivalent spectroscopically to *o*-tolualdehyde, while hydration of both functional groups would give a derivative roughly equivalent to *o*-xylene. In either case the intensity of absorption would be diminished without the appearance of any new peaks which would distort the absorption due to unhydrated molecules; *cf.* Lauder, *Trans. Faraday Soc.*, **44**, 729 (1948).

(14) Examples of such cleavages have been presented by Arnold, Bortnick and McMullen, THIS JOURNAL, **64**, 1410 (1942), and by R. Connor, private communication.

(15) Analyses by Mrs. Sarah M. Woods, University of Pennsylvania.

(16) Analyses by Mr. E. F. Shelberg, Abbott Laboratories.

(17) We wish to thank Reynold E. Holmén for preparing this sample.

(18) We wish to thank Mr. H. W. May, Chemical Department of the Barrett Division, Allied Chemical and Dye Corporation, Philadelphia, for a gift of specially purified *o*-xylene.

(19) Thiele and Günther, *Ann.*, **347**, 106 (1906).

dilutions necessary to cover the entire spectrum (one dilution for each log ϵ unit). The spectra in each of the two hydroxylated solvents showed appreciable deviations from Beer's law and uniformly much lower absorption than in isoöctane. Only the curves in water and in isoöctane are shown in Fig. 2; the curve in alcohol was similar in form to, and intermediate in intensity between, the spectra in water and isoöctane.

As a model compound to demonstrate the magnitude of contributions from hydrated forms, the tetraacetate of *o*-phthalaldehyde was prepared according to the directions of Thiele and Winter.[20] As anticipated, its spectrum had the appearance characteristic of benzene, toluene, xylenes, etc., and its intensity of absorption was much weaker than that of the aldehyde. In dilute aqueous hydrochloric acid its solutions readily hydrolyzed, whereupon the spectra of the resulting solutions assumed the appearance of aqueous solutions of *o*-phthalaldehyde.[21]

Ninhydrin (Triketohydrindene Hydrate).—Commercial ninhydrin (Paragon Testing Laboratories) was recrystallized from water giving almost colorless needles. The spectrum in water is very similar to that of *o*-phthalaldehyde in isoöctane, except for the peak in the far ultraviolet region, which occurs nearer the visible with ninhydrin than with the aldehyde.

(20) Thiele and Winter, *Ann.*, **311**, 360 (1900).

(21) The spectra of *o*-phthalaldehyde in various solvents have been reported previously: (a) Valyashko and Boltina, *J. Russ. Phys. Chem. Soc.*, **46**, 1741 (1914), *C. A.*, **9**, 2070 (1915); (b) Purvis, *J. Chem. Soc.*, **105**, 2482 (1914). Since it is difficult to translate these older data into modern terminology, it seemed desirable to repeat the spectrometric measurements under conditions comparable with those used for the naphthoquinone derivatives.

Attempts to Resolve Compound II.—Since the structure proposed for the active antihemorrhagic salt contains one asymmetric carbon atom, it should exist in enantiomorphic forms and should form two diastereoisomeric salts with an optically active cation. Several attempts were made to prove the existence of such stereoisomerism by formation of crystalline salts with *l*(+)-arginine hydrochloride[22] and with quinine methiodide. These salts did not appear to be suitable for resolution, and no conclusive results were obtained.

Summary

1. On the basis of spectrometric comparison with several simple *o*-benzenedicarbonyl compounds, the actively antihemorrhagic sodium bisulfite addition product of 2-methyl-1,4-naphthoquinone is assigned the structure sodium 2-methyl-1,4-dioxotetralin-2-sulfonate.

2. The formation of the active salt, "Menadione Sodium Bisulfite," its reconversion into Menadione under certain conditions, and other properties are accounted for on the basis of reasonable reactions.

3. *o*-Phthalaldehyde exists largely in solvated forms in water and alcohol solutions.

(22) Harris, Mozingo, Wolf, Wilson and Folkers, THIS JOURNAL, **67**, 2100 (1945).

PHILADELPHIA 4, PENNSYLVANIA
NORTH CHICAGO, ILLINOIS RECEIVED AUGUST 8, 1949

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, DUKE UNIVERSITY]

Boron Fluoride Catalyzed Addition of Aliphatic Anhydrides to Aldehydes[1]

BY EUGENE H. MAN, JAMES J. SANDERSON[2] AND CHARLES R. HAUSER

In an attempt to acetylate propionaldehyde with acetic anhydride by the boron fluoride method for the acetylation of ketones to form β-diketones,[3] we were unable to isolate any of the expected β-ketoaldehyde. Instead, there was obtained propylidene diacetate which was formed presumably by the addition of the anhydride to the carbonyl group of the aldehyde in accordance with the equation

$$CH_3CH_2CHO + (CH_3CO)_2O \xrightarrow{BF_3} CH_3CH_2CH(OCOCH_3)_2$$

Whereas the acylation of ketones with anhydrides requires an equivalent amount of boron fluoride,[3] the addition of acetic anhydride to the carbonyl group of the aldehyde requires only a catalytic amount of this reagent.

The addition reaction has been realized with various aldehydes and anhydrides. The results are summarized in Table I. On the basis of preliminary experiments, the procedure (Method A) adopted in the reactions with acetic anhydride consists in adding the aldehyde to excess of the anhydride accompanied by the addition, from time to time, of a few drops of boron fluoride etherate.[4] In no case were there more than twenty drops of the etherate required in order to produce the maximum yield, although the yield appeared not to be lowered by the presence of slightly more than an equivalent amount of the catalyst. This method, employing only a catalytic amount of boron fluoride, was found most satisfactory also with *n*-butyric anhydride and benzaldehyde, but it produced mixtures of products with *n*-butyric or propionic anhydride and other aldehydes. The procedure (Method B) adopted in these other cases consists in adding a mixture of the anhydride and aldehyde to 10% more than an equivalent of the boron fluoride etherate catalyst. Both Methods A and B gave mixtures of products with acetic anhydride and formaldehyde. The reaction appeared to fail with succinic anhydride and propionaldehyde.

Wegscheider and Späth[5] have effected the addi-

(1) Part of this work was carried out under Contract N7onr-455 with the Office of Naval Research.

(2) Carbide and Carbon Chemicals Corporation Fellow, 1946–1948.

(3) See Hauser and Adams, THIS JOURNAL, **66**, 345 (1944); Adams and Hauser, *ibid.*, **67**, 284 (1945).

(4) Eastman Kodak Co. reagent containing 45% by weight of boron fluoride was employed.

(5) Wegscheider and Späth, *Monatsh.*, **30**, 825–869 (1909); see also Kirrmann, *Bull. soc. chim.*, **53**, 295 (1933).