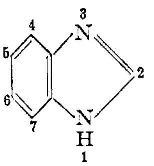


V

under comparable conditions,[3] and these results are summarized in Table II.

TABLE II

RESULTS OF TESTS FOR VITAMIN B_{12}-LIKE ACTIVITY

Substituted benzimidazoles	Amounts fed daily	No. of rats	Wt. increment g.-15 days
Negative Controls	...	57	28
Vitamin B_{12}	0.125 μg.	20	64
Benzimidazole	2.0 mg.	8	37
1-Methyl-	2.0 mg.	9	27
2-Methyl-	2.0 mg.	10	29
4-Methyl-	2.0 mg.	7	31
5-Methyl-	2.0 mg.	10	59
2,5-Dimethyl	2.0 mg.	8	17
4,6-Dimethyl-	2.0 mg.	10	37

Benzimidazole, 1-methyl-, 2-methyl-, 4-methyl- and 4,6-dimethylbenzimidazole did not elicit a significantly high response. 2,5-Dimethylbenzimidazole appeared to act as a growth-depressant and may have inhibitor activity. 5-Methylbenzimidazole showed significant growth activity, a fact which is interesting since 6- and 7-methyl substitutions in the 9-(1'-D-ribityl)-isoalloxazine series show low riboflavin activity.[5]

Both 5,6-dimethylbenzimidazole and the corresponding diamine, 1,2-dimethyl-4,5-diaminobenzene were observed to be inactive in the *Lactobacillus lactis* Dorner assay for vitamin B_{12} activity. They were tested at concentrations up to 0.5 mg./ml. by Miss Muriel C. Caswell of our Microbiology Department.

These benzimidazoles were prepared by the reaction of the diamine with the appropriate acid essentially as described in the literature, and the melting points were identical with the published constants: benzimidazole,[6] 1-methylbenzimidazole,[7] 2-methylbenzimidazole,[8] 4-methylbenzimidazole,[9] 5-methylbenzimidazole,[10] 2,5-dimethylbenzimidazole[11] and 4,6-dimethylbenzimidazole.[12]

Summary

5,6-Dimethylbenzimidazole and 1,2-diamino-4,5-dimethylbenzene, which are degradation products of vitamin B_{12}, have been found to show vitamin B_{12}-like growth activity when fed to rats maintained on a diet devoid of animal protein and containing thyroid powder. These two products are active at milligram-levels in contrast to vitamin B_{12} which is active at the microgram-level.

5-Methylbenzimidazole showed significantly high vitamin B_{12}-like activity also. Benzimidazole and four monomethyl and dimethyl derivatives failed to elicit significantly high activity. 2,5-Dimethylbenzimidazole appeared to show growth-depressant or inhibitor properties.

(5) Karrer, V. Euler, Malmberg and Schopp, *Svensk. Kem. Tids.*, **47**, 153 (1935); Karrer and Strong, *Helv. Chim. Acta*, **18**, 1343 (1935).

(6) Pauly and Gundermann, *Ber.*, **41**, 4012 (1908).

(7) Fischer and Veiel, *ibid.*, **38**, 321 (1905).

(8) Hinsberg and Funcke, *ibid.*, **27**, 2189 (1894).

(9) Gabriel and Thieme, *ibid.*, **52**, 1081 (1919).

(10) Ladenburg, *ibid.*, **10**, 1123 (1877); Fischer, *ibid.*, **22**, 641 (1889).

(11) Ladenburg, *ibid.*, **8**, 677 (1875).

(12) Fischer and Rigaud, *ibid.*, **34**, 4205 (1901).

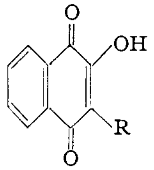
RAHWAY, N. J. RECEIVED JANUARY 13 1950

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Hydroxynaphthoquinones. I. Color and Acidity

BY MARTIN G. ETTLINGER[1]

It is well known[2] that 3-substituted 2-hydroxy-1,4-naphthoquinones (I) are acids comparable in strength to carboxylic acids, and that their salts are deeply colored, from yellow to violet. The influence of the substituent (R) on these two properties is the subject of this paper.



I

Absorption spectra[2] of both the free hydroxy quinones (I) and their anions contain several bands in the ultraviolet and visible, whereof those at longest wave lengths are most sensitive to structural change, and therefore interesting. For example, the spectra[3,4] of hydrolapachol (I, R = $(CH_2)_2CH(CH_3)_2$) and α-lapachone (II) are identical below 360 mμ, and hence unaltered in that region by substitution of 2-alkoxyl for hydroxyl, but differ in the position of the band extending into the visible. In an un-ionized hydroxy quinone a more intense peak at 330–335 mμ overlaps the interesting one, but in the anion the latter band is shifted on the order of 100 mμ

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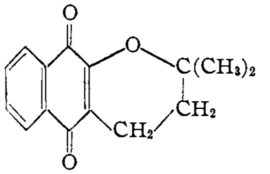
(1) Member of the Society of Fellows, Harvard University.

(2) Fieser, Leffler, *et al.*, THIS JOURNAL, **70**, 3151 (1948).

(3) Cooke, Macbeth and Winzor, *J. Chem. Soc.*, 878 (1939).

(4) Ettlinger, Paper II, THIS JOURNAL, **72**, 3090 (1950).

toward the red, and conveniently separated from the remainder of the spectrum. Although the long wave length maximum of the anion is broad, its center can be located within ±3 mμ.



II

Experimental results are presented in Table I, which contains in each row a side chain R, the position and intensity of the long wave length absorption maximum of the corresponding quinone (I) anion in aqueous solution, the negative logarithm of the acidity constant of I, and, collected from the literature, the pK_a of the identically substituted carboxylic acid. Bands of three anions are illustrated in Fig. 1, and the visible spectra of six free quinones in Fig. 2.

The spectrum in alkali of hydrolapachol (Fig. 1) is, as expected, nearly identical with that of 2-hydroxy-3-γ-cyclohexylpropyl-1,4-naphthoquinone.[2] Spectra of the anions of 2-hydroxy-1,4-naphthoquinone and its 2-alkyl derivatives have also been published[5]; although the reported wave lengths of maxima differ from present results by only 5–6 mμ, the values of log $\epsilon_{\max}$ are 0.4 unit high.

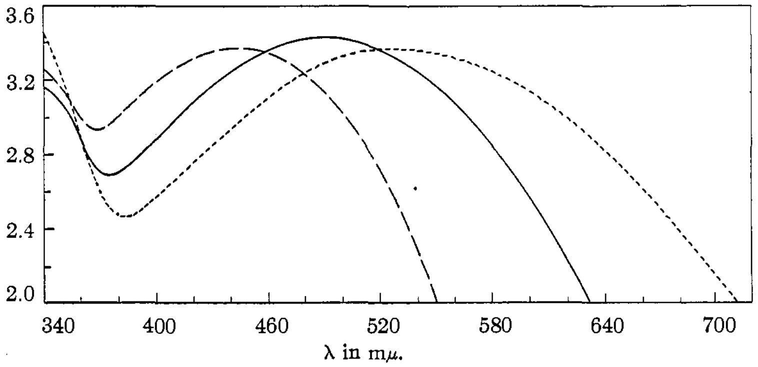


Fig. 1.—Absorption spectra of hydroxynaphthoquinone anions III in water: —, R = $(CH_2)_2CH(CH_3)_2$; ---, R = $CH_2NH^+(CH_3)_2$; ···, R = $CH{=}CH{-}CH_3$.

Acidity constants, except for the benzyl compound, were determined colorimetrically in aqueous solution at constant ionic strengths of 0.05 ($pK_a < 3$) or 0.1 ($pK_a > 3$). The result listed for hydrolapachol was obtained with its more soluble δ-hydroxy derivative, hydrolomatiol[6] (I, R = $(CH_2)_2CH(CH_3)CH_2OH$), in which the side chain oxygen is too remote to cause appreciable difference. The values of pK_a are uncorrected for salt effect,[7] and are roughly 0.1 unit less than the true quantities.

TABLE I

VISIBLE SPECTRA OF THE ANIONS AND ACIDITIES OF HYDROXYNAPHTHOQUINONES I

Side chain (R)	$\lambda_{\max}$, log $\epsilon_{\max}$	pK_a	pK_a (RCOOH)
$(CH_2)_2CH(CH_3)_2$[a]	490, 3.42	5.13[g]	4.78[h]
$CH_2CH(OH)CH(CH_3)_2$[a]	482, 3.40	4.96	4.42[i]
$CH_2C_6H_5$[a]	480, 3.43	4.9[g]	4.31[h]
CH_2COCH_3[b]	470, 3.42	4.12	3.58[j]
$CH_2N(CH_3)_2$[c]	468, 3.38	..	..
H[d]	455, 3.45	4.00	3.77[h]
$CH_2NH^+(CH_3)_2$[c]	445, 3.36	2.32[g]	*ca.* 1.95[k]
COC_6H_5[e]	440, 3.38	2.17	*ca.* 1.3[l]
C_6H_5[a]	480, 3.41	4.35	4.20[h]
$CH{=}C(CH_3)_2$[a]	498, 3.40		5.12[h]
$CH{=}CHCH_3$[f]	528, 3.37	4.8	4.69[h] (*trans*)
$CH{=}CHC_6H_5$[f]	548, 3.41		4.44[h] (*trans*)

[a] References to original sources are given by Fieser and Richardson, THIS JOURNAL, **70**, 3156 (1948). [b] Hooker and Steyermark, *ibid.*, **58**, 1202 (1936). [c] Leffler and Hathaway, *ibid.*, **70**, 3222 (1948). [d] Fieser, *ibid.*, **70**, 3165 (1948). [e] Ettlinger, Paper IV; Dischendorfer, Lercher and Marek, *Monatsh.*, **80**, 333 (1949). [f] Hooker, THIS JOURNAL, **58**, 1163 (1936). [g] See text. [h] Dippy, *Chem. Revs.*, **25**, 151 (1939). [i] Of β-hydroxybutyric acid, Kolthoff and Tekelenburg, *Rec. trav. chim.*, **46**, 33 (1927). [j] Pedersen, *J. Phys. Chem.*, **38**, 993 (1934). [k] Johnston, *Proc. Roy. Soc.* (*London*), **A78**, 82 (1906). [l] Böeseken and Felix, *Rec. trav. chim.*, **40**, 568 (1921).

An exception is the value for the dimethylammoniummethyl compound, which is 0.05 high. Hence, the corrected dissociation constants of the dimethylammoniummethyl and benzoyl compounds would not differ significantly. Previous determinations of pK_a of 2-hydroxy-1,4-naphthoquinone,[8] hydrolomatiol,[9] and hydroisolomatiol[9] (I, R = $CH_2CH(OH)CH(CH_3)_2$) from oxidation-reduction potentials vary less than 0.2 from the text.

The acidity constant of the benzyl compound was inferred from data on distribution between ether and aqueous buffers.[10] On a plot of the critical extraction number pE against molecular weight, the point corresponding to the benzyl compound lies approximately 0.25 unit below the straight line of higher ω-phenylalkyl homologs, whereas the cyclohexylmethyl compound is collinear with the ω-cyclohexylalkyl series. Since $pE = pK_a - pK - 2$, wherein K is the distribution constant between ether and water, it is reasonable to suppose that pK is linear with molecular weight throughout the ω-phenylalkyl series, and that pK_a is less by 0.25 ± 0.1 for the benzyl member than for higher homologs or alkyl derivatives.

In the anion III of a hydroxynaphthoquinone I, the negative charge is distributed in the

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(5) Spruit, *Rec. trav. chim.*, **68**, 309 (1949).

(6) Hooker, THIS JOURNAL, **58**, 1181 (1936).

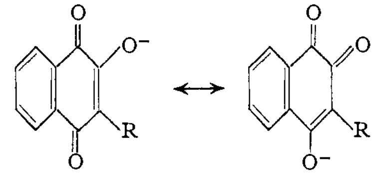
(7) Edsall, in Cohn and Edsall, "Proteins, Amino Acids and Peptides," Reinhold Publ. Corp., New York, N. Y., 1943, Ch. 4.

(8) Fieser and Fieser, THIS JOURNAL, **56**, 1565 (1934).

(9) Ball, *J. Biol. Chem.*, **114**, 649 (1936).

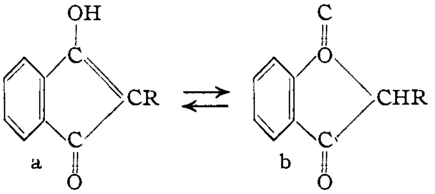
(10) Fieser, Ettlinger and Fawaz, THIS JOURNAL, **70**, 3228 (1948).

ground state chiefly by resonance between the 2- and 4-oxygens as parts of an ionized β-diketonic



III

system, which does not contain the aromatic ring or 1-carbonyl. If the 1-carbonyl is deleted from I, there results a 2-monosubstituted 1,3-indanedione (IV). Although indanediones are



IV

but slightly enolic[11] (1–2%, R = H or CH_3), the enols (IVa, R = CH_3, pK_a 4.2[11]) are as acid as hydroxy quinones. In further parallelism with I, an alkylindanedione[12] in alkali (estimated visible λ_{max} 450 mμ[13]) is more deeply colored than the parent compound[12] or a derivative substituted by a carbonyl group.[13] The simpler model enol of an unconjugated cyclic β-diketone (5,5-dimethyl-1,3-cyclohexanedione, pK_a (enol) 5.23,[11] λ_{max} (anion) 282 mμ[14]) absorbs at shorter wave lengths than I but is of relatively the same acidity. Finally, Table I shows that a carboxylic acid, of which an enolized β-diketone is a vinylog, is 0.1–0.6 logarithmic unit stronger than the corresponding hydroxy quinone I substituted midway between the resonant pair of oxygens, and the variations of acidity in the two series with substitution are similar. It is useful and plausible, though not rigorous,[15] to assume in this paper that increase or decrease of acidity by a substituent is correlated with electron transfer from or to the acidic nucleus.

The spectral data in Table I show the remarkably constant peak intensity of the band examined. Whereas the range of wave length of the maximum is over 100 mμ, the range of extinction is only ±10%, nor are the two functions perceptibly related. Although the band broadens as it is shifted toward the red, it appears that the significant effect of a substituent, conjugated, charged, chelated or not, is a change of wave length.

The first seven side chains in the table contain either hydrogen or a methylene group next to the chromophoric nucleus, and are listed in order of diminishing wave length of the maximum. The acidities of the six extant free quinones increase in identical order, whence their side chains are arranged with increased electron attraction. In this respect also, the dimethylaminomethyl group is properly placed near the middle of the assembly, since its electronegativity is increased over alkyl by the nitrogen, and would be augmented further by a positive charge. Hence, in a series of substituents that do not contain unsaturation or a heteroatom adjacent to the quinone ring, the bathochromic effect in the anion varies in the same order as electron donation to the chromophore.

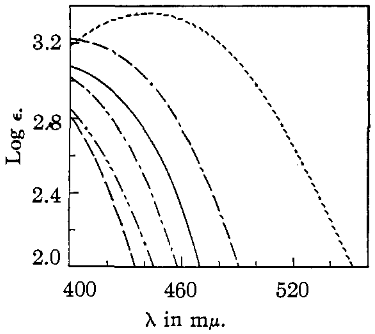


Fig. 2.—Absorption spectra of hydroxynaphthoquinones I in water: —, R = $(CH_2)_2CH(CH_3)CH_2OH$; ·-, R = CH_2COCH_3; ··-, R = H; ---, R = $CH_2NH^+(CH_3)_2$; --·, R = C_6H_5; ···, R = $CH{=}CH{-}CH_3$.

The relation between color and inductive effect in the absence of conjugation of the side chain appears to be independent of the charge on the quinonoid chromophore. The concordance of electron donation and bathochromic effect in the un-ionized quinone is exhibited in Fig. 2. For 2 - hydroxy - 3 - dimethylammoniummethyl - 1,4-naphthoquinone the long wave length band has retired from the visible approximately to the position it occupies for 2-alkoxy-3-alkyl-1,4-naphthoquinones.[3,4] The possibility[5] that the difference between the visible spectra of a hydroxynaphthoquinone I and its alkyl ethers is largely spurious and caused by acidic dissociation of the hydroxy compound is refuted by the present measurements under conditions of known ionization, as well as the remark that the maximum of hydrolapachol near 390 mμ is in the region, from 330 to 410 mμ, where the undissociated quinone absorbs more strongly than its anion. Previous studies[16] have ascribed the spectral differences between *o*-acylphenols and their methyl ethers to chelation. In present terms, the bathochromic effect of hydroxyl compared to alkoxyl may be correlated with the relatively acid weakening, electron releasing property[17] of hydroxyl and the greater

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[11] Schwarzenbach and Felder, *Helv. Chim. Acta*, **27**, 1044, 1701 (1944).

[12] Wislicenus, *Ann.*, **246**, 347 (1888); Wislicenus and Koetzle, *ibid.*, **252**, 80 (1889).

[13] Hantzsch, *ibid.*, **392**, 286 (1912); Hantzsch and Gajewski, *ibid.*, **392**, 302 (1912); Hantzsch and Czapp, *Z. physik. Chem.*, **A146**, 131 (1930).

[14] Blout, Eager and Silverman, THIS JOURNAL, **68**, 566 (1946).

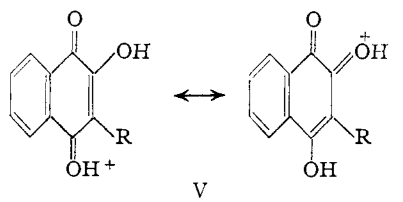
[15] Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Ch. III.

[16] Morton and Stubbs, *J. Chem. Soc.*, 1347 (1940); Morton and Earlam, *ibid.*, 159 (1941).

[17] Table I, ref. *h*.

ionic character[18] of the hydrogen–oxygen bond (39%) compared to carbon–oxygen (22%).

In solution in concentrated sulfuric acid a hydroxynaphthoquinone I, similarly to a carboxylic acid, is converted to the positively charged analog of the anion III, the resonant cation V.[4] Although the interesting absorption maximum of V is overlapped by a more intense peak near 400 mμ, Fig. 3 demonstrates that the displacement of the long wave length band with substitution is directed for V as for the anion and free quinone.



V

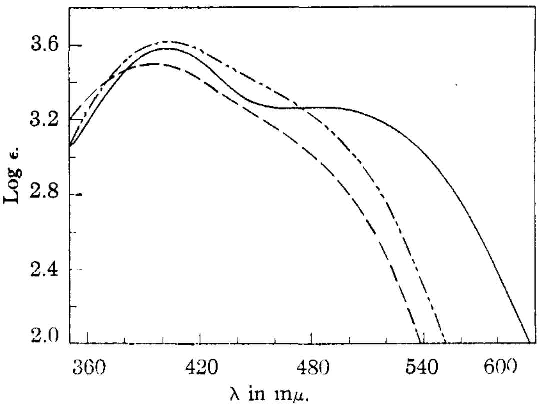
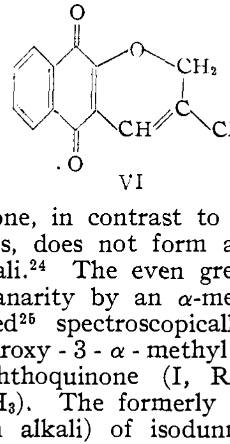


Fig. 3.—Absorption spectra of hydroxynaphthoquinone cations V in 95% sulfuric acid: —, R = $(CH_2)_2CH(CH_3)_2$; ··-, R = H; ---, R = $CH_2NH^+(CH_3)_2$.

The last five side chains in Table I contain unsaturation conjugated with the quinone nucleus. Among the last three quinones and hydrolapachol, the previous relation between acidity and color does not obtain. It is well known[19] that substitution of propenyl for an alkyl side chain and the further extension of the conjugated system in the β-phenylvinyl compound progressively deepen the colors of quinone and anion. In both the unsaturated derivatives mentioned, the side chain double bond is doubtless *trans*, and resonance effective. In the cation of a hydroxy quinone, the spectral influence of conjugation cannot be determined directly because the α,β-unsaturated derivatives are unstable in concentrated sulfuric acid[20] and are partly converted into furanonaphthoquinones.[21] Qualitative observations[22] on unsaturated cyclic quinones indicate, however, that the shift in the cation also is toward the red.

Substitution of phenyl for an alkyl group on the quinone ring is weakly hypsochromic in the anion. In the phenyl derivative, therefore, the two ring systems are non-coplanar and interannular resonance is sterically damped.[23] The inductive electron attraction of the phenyl predominates and causes the shift of absorption to shorter wave lengths. The un-ionized phenyl quinone, however, absorbs (Fig. 2) at longer wave lengths than an alkyl compound and exhibits partial conjugation.

Since steric interference with the side chain does not prevent resonance in the chromophore, the quinonoid ring, and perturbs only a few high energy structures, the effect on light absorption is simple. The large decrease of wave length of the maximum of the anion on passage from the propenyl to the β,β-dimethylvinyl derivative (norlapachol) may be explained on the basis that introduction of the second or *cis* β-methyl group hinders coplanarity of the double bond and ring. The hypothesis is supported by the facts[3] that undissociated norlapachol absorbs in the visible most strongly at 420 mμ, whereas β-methylpyrano-1,4-naphthoquinone (VI), of the same carbon skeleton but planar, absorbs at 463 mμ. Comparably, 2-methyl-3-β,γ,γ-trimethylallyl-1,4-naphthoquinone, in contrast to β-unsubstituted allyl quinones, does not form a blue anion in alcoholic alkali.[24] The even greater steric hindrance of planarity by an α-methyl group has been observed[25] spectroscopically in *cis*- and *trans*-2-hydroxy-3-α-methyl-β-pentadecylvinyl-1,4-naphthoquinone (I, R = $C(CH_3){=}CH(CH_2)_{14}CH_3$). The formerly puzzling yellow color (red in alkali) of isodunniol[26] (I, R = $C(CH_3){=}C(CH_3)_2$) can be comprehended identically.



VI

Coplanarity of the side chain carbonyl and quinone ring of 2-hydroxy-3-benzoyl-1,4-naphthoquinone is dubious. The spectrum in alkali is compatible with operation of the inductive effect alone; the benzoyl group is bulky, and in the anion there presumably is electrostatic repulsion between the side chain and nuclear oxygens. The spectrum[5] of the acetyl quinone (I, R = $COCH_3$) in alkali appears to be shifted even farther toward the ultraviolet. Enforced non-

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[18] Pauling, "The Nature of the Chemical Bond," 2nd ed., Cornell University Press, Ithaca, N. Y., 1940, Ch. II.

[19] Table I, ref. *f*.

[20] Hooker, *J. Chem. Soc.*, **69**, 1355 (1896).

[21] Table I, ref. *b*.

[22] Hooker and Steyermark, THIS JOURNAL, **58**, 1198, 1207 (1936).

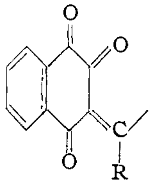
[23] Jones, *ibid.*, **67**, 2127 (1945).

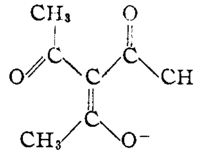
[24] Fieser, Campbell, Fry and Gates, *ibid.*, **61**, 3216 (1939); Karrer, *Helv. Chim. Acta*, **22**, 1146 (1939).

[25] Cram, THIS JOURNAL, **71**, 3953 (1949).

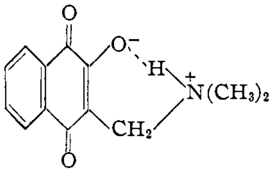
[26] Price and Robinson, *J. Chem. Soc.*, 1493 (1940).

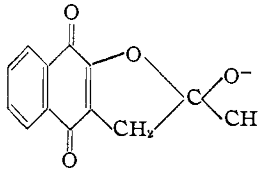
planarity of the side chain carbonyl and quinone system may deepen the color,[27] or, conversely, if resonance between them is effective, the spectral change may not be bathochromic, such as a carbon–carbon double bond produces. The absorption[28] of alkaline 2-formyl-1,3-indanedione, in which the steric hindrance of the side chain is minimal, is a related possible example. If a carbon–carbon double bond is conjugated to the quinone, the additional resonance structures are of high energy and stabilize principally the excited states, but if a carbonyl is substituted, structures such as VII of the anion contribute importantly to the ground state. In a carbonyl-substituted quinone, the increased resonance might stabilize the ground state more than an excited state and displace the corresponding band to shorter wave lengths, if, for example, in the anion the negative charge is less symmetrically distributed in the excited than the ground state. A simple model, the anion of triacetylmethane, in which the absence of a ring may allow a staggered arrangement (VIII) of the oxygens favorable for planarity, is spectrally[29] nearly identical with that of acetylacetone.[30] Another example[31] is furnished by the pair of similarly absorbing anions of nitroform and dinitromethane. The comparison[32] of crystal violet and malachite green is a classic analog.


VII


VIII

The most novel part of the survey concerns the spectral effects of groups separated by a saturated carbon atom from a chromophore, which have not been studied extensively hitherto.[33,34] In quinones only the direction of electron displacement by the unconjugated substituent is important, and it is unnecessary to attempt a distinction, on the basis of intensity or wave length, whether the interaction occurs by electrostatic induction, direct or through the side chain, hyperconjugation, possible chelation as in IX (III, R = $CH_2NH^+(CH_3)_2$) or ring formation as in X (III, R = CH_2COCH_3). A positively charged nitrogen substituted in the β-position of an alkyl side chain causes a greater shift (45 mμ) than a conjugated double bond (38 mμ). It is noteworthy that the positively charged side chain is hypsochromic whether the quinonoid system is positively or negatively charged, although the displacements of absolute charge on the chromophore must be opposite. If mere increase of absolute quantity of resonant charge on a chromophore increased the wave length, the dimethylammoniummethyl group would be bathochromic in a quinone in sulfuric acid. The observed similarity of cation and anion might suggest a sort of conjugation in an alkyl side chain. However, in malachite green a *p*-dimethylammonium group, which does not resonate with the chromophore, is bathochromic, a *p*-methyl hypsochromic,[35] in reverse of the effects presently examined. The subject merits further investigation.


IX


X

Experimental

Absorption Spectra.—Determinations were made with a Beckman Ultraviolet Spectrophotometer, Model DU, used through the kindness of Dr. I. H. Scheinberg. Spectra of un-ionized quinones were measured in hydrochloric acid (0.01–1 *N*) solutions, commonly prepared by treatment of the quinone with alkali and acidification, and were corrected for dissociation if necessary. The quinone anions were observed in 0.1 *N* sodium hydroxide, except that the one containing the dimethylammoniummethyl side chain was examined in a phosphate buffer of *p*H 6.2.

Acidity Constants.—For determination of the acidity of a hydroxy quinone at a fixed ionic strength (0.1 or 0.05), a stock solution of approximately known concentration, 3.5–13 mg./100 cc., according to the solubility in water, was prepared in 0.2 or 0.1 *N* sodium hydroxide. A 5-cc. aliquot was diluted with water to 10 cc. and its optical density measured with the spectrophotometer at three wave lengths, spaced 10 mμ apart, the shortest of which was chosen 20–30 mμ greater than that of the visible maximum of the anion to lessen absorption by un-ionized quinone. Another 5-cc. aliquot was treated with sufficient acetic or citric acid to bring its *p*H to a useful region, diluted to 10 cc., its absorption at the three prescribed wave lengths measured, and its *p*H determined with a glass electrode and Beckman *p*H meter, Model G, at an ambient temperature of 26–33°. The optical densities of the buffer were corrected roughly for effect of free quinone if necessary, and from these values and the densities in alkali the ratio of anion to free quinone in the buffer was calculated and combined with the *p*H to furnish pK_a. The scatter of three

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(27) Brooker, White, Sprague, Dent and van Zandt, *Chem. Revs.*, **41**, 325 (1947).

(28) Lifschitz, *Ber.*, **47**, 1401 (1914).

(29) Birckenbach, Kellermann and Stein, *Ber.*, **65**, 1071 (1932); Schwarzenbach and Lutz, *Helv. Chim. Acta*, **23**, 1147 (1940).

(30) Grossmann, *Z. physik. Chem.*, **109**, 305 (1924).

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values of pK_a, obtained for each quinone in different buffers, was at most 0.06 and averaged 0.02 unit.

Summary

The acidities and visible spectra of certain 3-substituted 2-hydroxy-1,4-naphthoquinones were measured and correlated. Particular attention was given to the influence of groups separated from the chromophore by a saturated carbon atom.

CAMBRIDGE 38, MASSACHUSETTS

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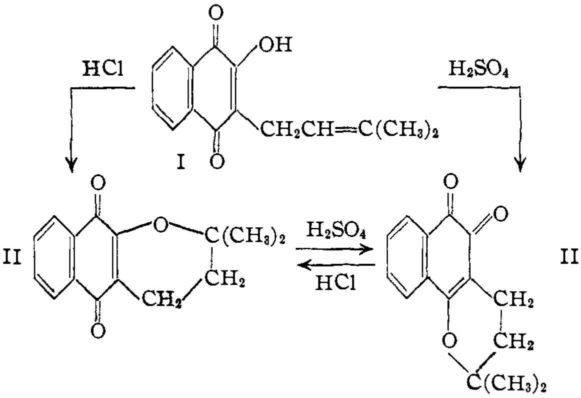
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Hydroxynaphthoquinones. II. Cyclization and the Basicity and Interconversion of *Ortho* and *Para* Quinones

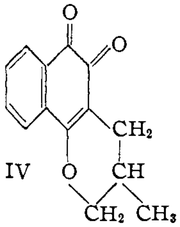
BY MARTIN G. ETTLINGER[1]

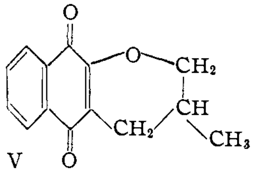
At the commencement of brilliant investigations of the natural pigment lapachol (I), Hooker discovered[2] that the course of reaction of lapachol and strong acids apparently depended on the specific acid employed. In concentrated hydrochloric acid lapachol was cyclized to the *para* quinone α-lapachone (II), but in concentrated sulfuric acid to the isomeric *ortho* quinone β-lapachone (III). Hooker also established a quantitative isomerization of α-lapachone to β-lapachone in sulfuric acid and the reverse in hydrochloric acid, and hence a probable inversion of equilibrium. These observations, termed by Hooker "very remarkable," were confirmed after controversy,[3,4] and extended to the corresponding quinones derived from bromolapachol[5] and norlapachol[6] and to the isodunniones.[7] The lack of theoretical consideration of the problem[8] evoked the present paper.

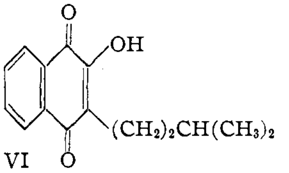


Largely from the work of Hammett[9] and collaborators, knowledge of solutions in sulfuric acid is now extensive. A useful acidity scale spanning all sulfuric acid–water mixtures has been devised and many oxygenated organic compounds proved to behave as simple neutral bases in these solvents. 2,5-Dihydroxybenzoquinone with pK_a -7.0[10] is nearly half ionized in 80% sulfuric acid, whereas anthraquinone (pK_a -8.15)[9] is over tenfold weaker. More strongly basic hydroxynaphthoquinone analogs are benzalacetophenone (pK_a -5.61)[9] and acetylacetone enol (pK_a -5.0).[11]

The ionization of hydroxynaphthoquinone ethers in sulfuric acid can be established spectroscopically. Since α-lapachone is unstable in concentrated sulfuric acid, the *ortho–para* isomeric pair of β-methyldihydropyranonaphthoquinones[12] (IV and V) was used. The absorption spectra of IV and V and hydrolapachol (VI) appear in Fig. 1 for ethanol solutions, and in Fig. 2 for 95% sulfuric acid. Whereas in ethanol the *o*-quinone differs from the *p*-quinones in intensity of the 280 and 330 mμ bands and at long wave lengths,[13] the spectra in concentrated sulfuric acid, except for small differences in the inflection near 480 mμ which relatively deepen[14] the color of the *p*-isomers, are identical. The inference is that IV and V each add a proton in sulfuric acid to furnish, respectively, the ions VII and VIII, which, together with the cation (IX, R = $(CH_2)_2CH(CH_3)_2$, R′ = R″ = H) of VI are examples


IV


V


VI

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[1] Member of the Society of Fellows, Harvard University.

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