not far from two of the aromatic types previously reported,[2] namely, diethylamino-ethyl 2-thiophenecarboxylate (with a rating of 1) and diethylamino-ethyl 2-furancarboxylate (with a rating of less than 1).

Summary

A study of the local anesthetic action of some diethylamino-ethyl esters of aliphatic carboxylic acids shows that the chemical correlation of aromatic compounds with some related aliphatic compounds can be extended to include physiological action.

AMES, IOWA

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BRYN MAWR COLLEGE]

THE TAUTOMERISM OF HYDROXY QUINONES

BY LOUIS F. FIESER

RECEIVED SEPTEMBER 16, 1927 PUBLISHED FEBRUARY 4, 1928

It is the purpose of this paper to apply to the problem named in the title certain of the principles governing chemical equilibria, and to present the results of experiments which were carried out with the view of testing and applying this theoretical treatment of the subject.

1. The General Theory

Hydroxynaphthoquinone is typical of the compounds under consideration. While only one form of the substance is known in the solid state,[1] it is necessary to recognize the presence of two tautomeric forms in its solutions in order to account for the course of the hydrolysis of 2-alkoxy-1, 4-naphthoquinones and 4-alkoxy-1,2-naphthoquinones, for a single solid substance results in each case.[2] Among the reactions which demonstrate the presence of hydroxy-α-naphthoquinone in the equilibrium mixture is that with diazomethane,[2] while the ready, reversible reaction of hydroxynaphthoquinone with sodium bisulfite must involve a β-naphthoquinone derivative. Thus these tautomers, which may be referred to as the α and β forms of hydroxynaphthoquinone, must be present in all solutions of the substance and the constant of the tautomeric equilibrium may be defined by the following equation

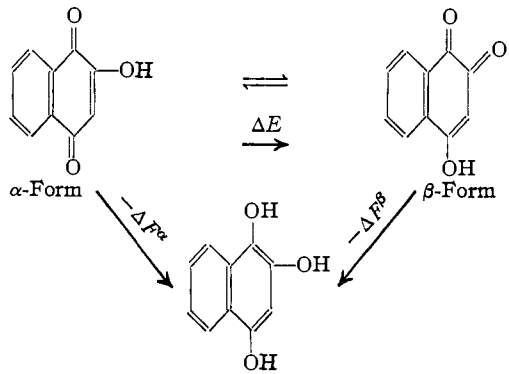
$$K = [\alpha\text{-Form}]/[\beta\text{-Form}] \qquad (1)$$

---

[1] Miller's statement to the contrary, *J. Russ. Phys.-Chem. Soc.*, **43**, 440 (1911), must be discounted. It is possible that the change in his sample on storage and the variation of the point of decomposition of this substance are both due in part to a reaction of the material with glass. Some of the samples which Miller prepared by different methods undoubtedly contained impurities. Dr. Samuel C. Hooker has informed me that, by following with the microscope the crystallization of a red sample of this quinone, he found the red color to be due to the presence of impurities removed only after numerous crystallizations.

[2] Fieser, THIS JOURNAL, **48**, 2922 (1926).

In order to obtain a method of estimating the magnitude of K, use may be made of the fact that the tautomers have a common reduction product.



For the purpose of the following theoretical treatment it is convenient to postulate the free energy changes involved in the conversion of one tautomeric quinone into the other and in the conversion of each quinone into the common hydroquinone. It should be clearly realized that it is not possible at the present time to determine directly any of these quantities. There remains, however, the possibility of developing a method of reasoning by analogy which will serve to give an approximate evaluation of the tautomeric equilibrium constant, and it is with this end in view that a thermodynamic analysis of the problem will be presented. The free energy change in the conversion of the α-form at unit concentration in a given solvent into the β-form at the same concentration, ΔF, is equal to the free energy of reduction of the α-form ($-\Delta F^{\alpha}$) minus the free energy of oxidation of the reductant to the β-form ($-\Delta F^{\beta}$)

$$\begin{aligned} &\alpha\text{-Form} + 2\text{H} = \text{Reductant} - \Delta F^{\alpha} \\ &\text{Reductant} = \beta\text{-Form} + 2\text{H} + \Delta F^{\beta} \\ \text{(Adding)}\quad &\alpha\text{-Form} = \beta\text{-Form} - \Delta F^{\alpha} + \Delta F^{\beta} \\ \text{(Or)}\quad &\Delta F = -\Delta F^{\alpha} + \Delta F^{\beta} \end{aligned} \tag{2}$$

The free energy changes in the reduction of the two quinones are conveniently expressed in terms of the normal reduction potentials of the tautomers in the solvent in question, E_0^{α} and E_0^{β}, since $-\Delta F = nFE_0$. Making these changes, and substituting for ΔF the expression $RT \ln K$, Equation 2 becomes, for 25°

$$\log K = (E_0^{\beta} - E_0^{\alpha})/0.0296 \tag{3}$$

There is thus a simple relationship between the equilibrium constant of the tautomerization and the difference in the normal reduction potentials of the two tautomers. That form which has the lower reduction potential will predominate; thus, if E_0^{α} is less than E_0^{β}, K will be greater than one and [α-Form] > [β-Form]. This principle is novel to the organic

chemist only in its quantitative aspects. Dimroth for example in assigning structures to certain hydroxynaphthoquinone derivatives arbitrarily wrote the α-naphthoquinone formulas because, as he says, "in general, para quinones are more stable than ortho quinones," ("im allgemein Parachinone stabiler sind als Orthochinone.")[3] The first statement of the idea was probably that of Kehrmann,[4] who applied it to a study of the structure of the azines. Beschke[5] presented evidence in support of his conception that, if a given substance can give rise to two different quinones on oxidation, the quinone of lower oxidizing power will result. The presence of a common reduction product is not, however, essential for the interconversion of the tautomers. To be sure, Equation 3 was derived with the use of normal potentials, that is, electrode potentials of mixtures containing equivalent quantities of the oxidant and reductant, but it applies equally well to the "pure solutions" of the quinones.

Before considering extensions of Equation 3, it will be well to demonstrate how this equation can be applied to the solution of practical problems. The isolation of the tautomeric forms of an hydroxy quinone has not yet been accomplished, and it is not likely that potential measurements could be carried out with such substances without the occurrence of a tautomeric change. However, although the terms E_0^β and E_0^α cannot be determined directly, it is possible in many instances to estimate these potentials, or the difference between them, from the known values of compounds of related structure. The soundness of this process of reasoning depends upon the nature of the analogy of which use is made in any particular case. In the following pages, in which an attempt has been made to determine the approximate composition of the equilibrium mixtures of certain hypothetical tautomer pairs, various methods of predicting the potentials of the tautomers have been employed, and each case should be judged on its own merits.

2. Hydroxynaphthoquinone

It will be seen from Equation 3 that all that is required for an evaluation of the equilibrium constant, K, is a knowledge of the difference between the potentials of the tautomers. Although there is at present no way of predicting the potentials of the two possible forms of hydroxynaphthoquinone, it is possible to decide which form would have the higher potential and to estimate the magnitude of the difference between the two values from a knowledge of the potentials of the ethers, I and II. While the potentials of these ethers may not be the same as those of the corresponding hydroxy compounds, it is highly probable that the difference

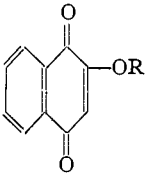
[3] Dimroth and Kerkovius, *Ann.*, **399**, 36 (1913).

[4] Kehrmann, *Ber.*, **31**, 977 (1898).

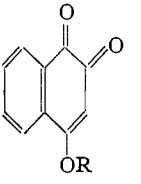
[5] Beschke and Diehm, *Ann.*, **384**, 173 (1911).

between the two values is approximately the same as the difference between the potentials of the two tautomers.

Data which will permit a prediction of the magnitude of this difference are furnished by the results of e. m. f. measurements with a series of ethers of the type of I and II (Table I). In order to prevent the hydrol-



I



II

ysis of the *o*-quinone ethers it was necessary to employ a neutral solution, while the insolubility of some of the ethers in water necessitated the use of an alcoholic solution. The solvent which was consequently employed

TABLE I

REDUCTION POTENTIALS AT 25°

Solvent: 37% alcohol, 0.047 *M* in KH_2PO_4 and 0.047 *M* in Na_2HPO_4

No.	Alkyl group	E_0, v.				ΔE_1, mv.	ΔE_2, mv.	E_0 (av.), v.
		A. 2-Alkoxy-1,4-naphthoquinones						
1	Methyl	0.353	0.354			19.2	19.3	0.353
2	Ethyl	.352	.354			18.0	18.0	.353
3	*n*-Propyl	.353	.353	0.351	0.350	20.1	19.7	.352
4	*n*-Butyl	.351	.352			19.5	19.2	.351
		B. 4-Alkoxy-1,2-naphthoquinones						
5	Methyl	0.433	0.433	0.433		20.1	18.3	.433
6	Ethyl	.430	.430			19.1	18.0	.430
7	*n*-Propyl	.430	.430			18.0	19.9	.430
8	*iso*Propyl	.426	.426			20.4	18.1	.426
9	*n*-Butyl	.422	.423	.421		21.2	18.9	.422

(see table) did not permit the use of the ordinary reducing agents and so the quinones were reduced with hydrogen and a catalyst and the hydroquinones titrated electrometrically with potassium ferricyanide dissolved in the same solvent. The normal reduction potential (E_0) is equal to the e. m. f. of the cell: Pt | Solvent A, Quinone, Hydroquinone | Solvent A | H_2 | Pt, at the point of half-reduction. Under ΔE_1 and ΔE_2 are given the average differences betwen E_0 and the potential at 20% and at 80% oxidation. The theoretical value is 17.8 mv.

Table I indicates that there is a slight decrease in reduction potential with increasing size of the alkoxyl group. Since of these groups the methoxyl is the most similar in structure to the hydroxyl group, the difference in the potentials of the two methyl ethers may be taken as a measure of the difference in potential of the two tautomeric hydroxy

compounds, though the result is much the same if any other pair of ethers is selected. Substituting the value $E_0^\beta - E_0^\alpha = 0.080$ v. in Equation 3, it is found that for hydroxynaphthoquinone $K = 502$. This means that in the solvent in question only 0.2% of the β-form is present in the equilibrium mixture. From the facts known concerning the variation of quinone reduction potentials with changes in temperature and in solvent (at constant P_H),[6] it can be said that the composition of the equilibrium mixture will be changed to an inappreciable extent by such changes in the conditions. These conclusions are in agreement with all of the known properties of the substance in question and this theoretical treatment finds particular support in the course of the hydrolysis of ethers of the β-form.[2]

3. Naphthopurpurin

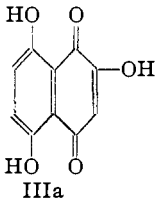
There are two structures, IIIa and IIIb, which represent the possible tautomeric forms of naphthopurpurin.[7] It is not difficult to predict what the reduction potential of a pure substance possessing the structure of IIIa would be, for this differs from naphthazarin, IV, only in having an extra hydroxyl group, and the effect of such a group on the potential of a quinone is easily determined. By the use of certain analogies, a prediction can also be made concerning the potential of IIIb. Thus an idea can be gained of the relative values of E_0 for the two tautomers and, consequently, of the equilibrium constant.

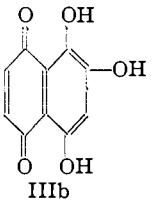
The potential of naphthopurpurin itself can be determined by direct measurement; but this measurement furnishes no indication of the possible existence of two tautomers in the solution. The value found will depend upon the potentials and the concentrations of the tautomers, but there is no way of deducing from this value, taken by itself, the composition of the mixture or the potential of either tautomer. However, if on reasoning by analogy it can be shown, for example, that IIIa would have a much lower potential than IIIb, there is reason to believe that in a solution of naphthopurpurin IIIa predominates to the practical exclusion of IIIb. In this event, the experimentally determined potential of naphthopurpurin would represent the potential of tautomer IIIa in practically pure form, and a comparison of the experimental value with the value predicted for IIIa would furnish a check on the validity of conclusions drawn solely from a consideration of the potentials predicted for the tautomers.

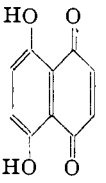
The potential of naphthopurpurin, together with data required for the predictions indicated, is given in Table II. While compound No.

[6] Conant and Fieser, THIS JOURNAL, **44**, 2480 (1922).

[7] In view of the definite chemical and electrochemical evidence pointing to the *p*-quinonoid structure for hydroxynaphthoquinone, it is not necessary to consider an *o*-quinone formula for naphthopurpurin or for the dihydroxyquinone, V, below.


IIIa


IIIb


IV[8]

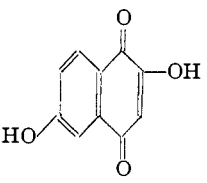

V

TABLE II

REDUCTION POTENTIALS AT 25°

Solvent: 50% alcohol, 0.1 *N* in HCl and 0.2 *N* in LiCl.

No.		E_0, v.				ΔE_1, mv.	ΔE_2, mv.	E_0 (av.), v.
10	Naphthopurpurin (III)	0.243	0.243	0.244	0.243	21.8	20.7	0.243
11	Naphthazarin (IV)	.362	.361	.359	.362	20.2	20.9	.361
12	2,6-Dihydroxy-1,4-naphthoquinone (V)	.303	.304	.302		18.1	18.6	.303

12 was titrated electrometrically with titanous chloride, this reagent could not be employed with the other quinones because highly colored precipitates were formed. In these cases the hydroquinone solutions were prepared by catalytic hydrogenation and titrated with a solution of benzoquinone.

In order to estimate the potential of IIIa, the potentials of 2-hydroxy-1,4-naphthoquinone (E_0 = 0.356 v.),[9] of naphthazarin (IV), and of α-naphthoquinone (E_0 = 0.483 v.)[9] under comparable conditions are rerequired. Thus E_0 (IIIa) = 0.356 − (0.483 − 0.361) = 0.234 v. For a prediction concerning IIIb, it is necessary to know the potential of naphthazarin (IV) and the effect of a hydroxyl group in the β position in the benzoid ring. The latter information is furnished by a comparison of hydroxynaphthoquinone with its 6-hydroxy derivative, V. Then E_0 (IIIb) = 0.361 − (0.356 − 0.303) = 0.308 v. Since the potential predicted for IIIa is 0.074 v. lower than the value estimated for IIIb, it is reasonable to suppose that IIIa is the predominant tautomer. Assuming the accuracy of these predictions, the equilibrium constant for naphthopurpurin calculated from Equation 3 is 157, whence about 0.4% of the less stable tautomer, IIIb, is present at equilibrium.

If this reasoning is correct, the experimentally determined value for naphthopurpurin must be very close to the actual potential of IIIa. The value predicted for IIIa, 0.234 v., agrees just as closely with the value found, 0.243 v., as could be expected. It is not yet possible to calculate potentials with greater accuracy than this. Thus, from the potentials of 4-ethoxy- and 4-(*n*-propoxy)-1,2-naphthoquinone (Table I), one would expect the *n*-butyl derivative to have a potential of 0.430 v.; but the actual value is 0.422 v. The above discrepancy of 0.009 v. is thus of little sig-

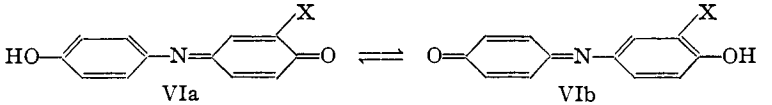
[8] Dimroth and Ruck, *Ann.*, **446**, 123 (1926); Pfeiffer, Oberlin and Segal, *Ber.*, **60**, 111 (1927).

[9] Conant and Fieser, THIS JOURNAL, **46**, 1858 (1924).

nificance. It is significant, on the other hand, that the predicted potential for the other tautomer, IIIb, is 0.065 v. higher than the potential found for naphthopurpurin. It is inconceivable that naphthopurpurin has the structure of IIIb and that the discrepancy in the values is due to the inaccuracy of the calculations.

4. Indophenols

An extensive field for the application of the ideas here presented is that of the indophenols, for in the case of any unsymmetrical indophenol two tautomeric forms such as VIa and VIb are possible. Clark and his



VIa VIb

collaborators, who have carried out a comprehensive study of the electrode potentials of a wide variety of these substances,[10] have recognized throughout the necessity of taking account of the tautomerism of these substances and they have frequently adduced evidence to show that a tautomeric change has taken place during or after the preparation of certain of their compounds. On the other hand, they do not appear to have fully appreciated the fact that the tautomers will have different reduction potentials and that the position of the tautomeric equilibrium depends upon the difference between the two values. While it is not now possible with the aid of this principle to interpret much of the data of these authors in terms of the problem of the effect of substituent groups, a few theoretical considerations may serve to clarify the problem. From the facts known about quinones, it may be said that a substituent group always has a greater effect on the potential when it is attached to the quinonoid nucleus than when situated in an adjacent benzene ring, but that the direction of the effect is the same in each instance. If the substituent, X, is an alkyl or an hydroxyl group, both VIa and VIb will be lower in potential than the parent compound, VIa will be lower in potential than the tautomer and will predominate in the equilibrium mixture. Just the reverse is true when the substituent is a halogen or an acidic group and in this case VIb will predominate; but even if more precise predictions were possible, it would be difficult to tell how they correspond with experimental results because the e.m.f. measurements represent equilibrium values. The relationship between such a value and the potential of a single pure tautomer may be defined in the following way. The equation for the electrode potential of one tautomer (α-Oxid), whether alone or in an equilibrium mixture, at such a P_H that no dissociation takes place, is

[10] (a) Clark and Cohen, *Pub. Health Repts.*, **38**, 933 (1923); (b) Cohen, Gibbs and Clark, *ibid.*, **39**, 381 (1924); (c) *ibid.*, **39**, 804 (1924); Gibbs, Cohen and Cannan, *ibid.*, **40**, 649 (1925).

$$E^{\alpha} = E_0^{\alpha} + 0.059 \log [H^+] + 0.0296 \log [\alpha\text{-Oxid}]/[\text{Red}] \quad (4)$$

If no tautomer is present, [α-Oxid] is equal to the total concentration of the oxidant $[\text{Oxid}]_T$, and the equation applies in the usual way; otherwise the only determinable concentration, the total concentration of the oxidant, is equal to the sum of [α-Oxid] and [β-Oxid]. Expressing the latter quantity in terms of the former and of the equilibrium constant, K, it is seen that

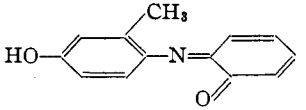
$$[\text{Oxid}]_T = [\alpha\text{-Oxid}] + [\beta\text{-Oxid}]/K$$

whence,

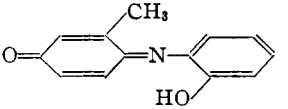
$$E^{\alpha} = E_0^{\alpha} + 0.059 \log [H^+] + 0.0296 \log [\text{Oxid}]_T/[\text{Red}] + 0.0296 \log K/(K+1) \quad (5)$$

If the potential of such a mixture is determined under the usual "normal" conditions ($[H^+ = 1$; $[\text{Oxid}]_T = [\text{Red}]$), the value found, E^{α}, will differ from the normal potential of the α-oxidant by the amount $0.0296 \log K/(K+1)$. Thus if two different tautomers had the same potential ($K = 1$), the apparent normal potential of the mixture would be 8.9 mv. lower than the normal potential of either tautomer. This factor obviously complicates the interpretation of data on the effect of simple substitution where the tautomers may be very close to each other in potential.

When the two tautomers represent widely different structural types, their potentials may be so far apart that one form will predominate almost exclusively and it should be possible to determine its structure. For example, Cohen, Gibbs and Clark[10c] report measurements with *m*-cresol-*o*-indophenol, to which, simply on the basis of the mode of preparation, they assign Formula VIIa. There are, however, two reasons for preferring

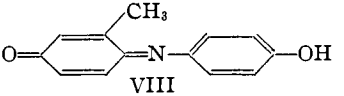


VIIa



VIIb

Formula VIIb, the first being that the methyl group will have a greater effect in lowering the potential of the parent compound when it is attached to the quinonoid nucleus than when situated as in VIIa. But a more fundamental difference in the two structures is that one is *o*-quinonoid, the other *p*-quinonoid. Not only are *o*-quinones always much higher in potential than isomeric *p*-quinones by about 0.07 to 0.10 v., but this also applies to the quinonimines,[11] which are closely related to the indophenols in structure. Thus, both because of its *p*-quinonoid structure and because of the location of the methyl group, VIIb most certainly has the lower potential, and the value of this potential would not be expected to differ greatly from that for *m*-cresol-*p*-indophenol, VIII, while the other tautomer

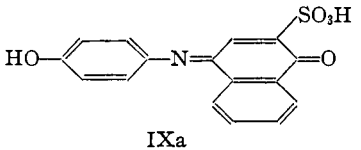


VIII

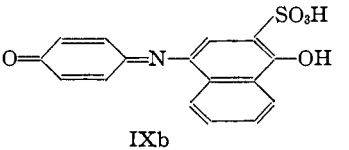
[11] Conant and Pratt, THIS JOURNAL, **48**, 3178 (1926).

must have a potential in the neighborhood of 0.1 v. higher. The experimental results confirm this prediction. The normal potential reported for the "ortho"-indophenol, VII, is 0.647 v.,[10c] while that for the *p*-indophenol, VIII, is 0.632 v.[10b]

Another case to which the same reasoning may be applied is that of 1-naphthol-2-sulfonic acid indophenol,[10a] IX. On considering IXa to be a



IXa

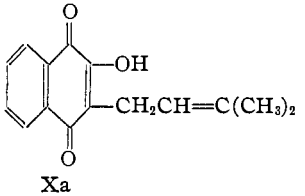


IXb

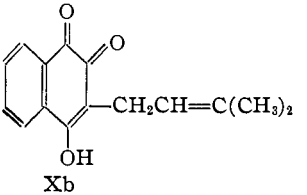
derivative of phenol-indophenol, for which $E_0 = 0.649$ v.,[10b] adding to this value the known effect of attaching a sulfonic acid group to α-naphthoquinone (0.066 v., av.)[9] and subtracting the difference in the potentials of *p*-benzo- and *p*-naphthoquinonimines (0.175 v.,), a value of 0.540 v. for the potential of IXa is obtained. This, of course, is only a rough estimate, and the same is true of any prediction about IXb. However, it is difficult to see how IXb can differ greatly in potential from phenol-indophenol, $E_0 = 0.649$ v., and this is such a decidedly higher figure that there can be little doubt that the substance corresponds essentially to IXa. The experimentally determined value of 0.544 v., since it agrees well with the above estimate for IXa, clearly demonstrates that this is the case.

5. Lapachol and Related Compounds

There is ample evidence in the foregoing facts not only that the factors governing the tautomeric equilibrium have been correctly defined but also that tautomeric quinones in general exist in solution in a condition of equilibrium. While it seems likely that the latter proposition is an entirely general rule, it is of considerable importance to submit the problem to extensive experimental inquiry. A promising series of compounds for this purpose is that of the type of lapachol, X. With highly substituted quinones of this character, addition to the quinone nucleus is retarded,[2] reduction proceeds slowly (see Experimental Part) and it is conceivable that there might be a condition of delayed equilibrium preventing the less stable tautomer, Xb, from rearranging into Xa. Indeed, according to statements in the literature, one such case is known.



Xa



Xb

For the opportunity to study potentiometrically a number of compounds of the lapachol group, I am greatly indebted to Dr. Samuel C. Hooker, who kindly placed at my disposal pure samples of these materials, some of which had been prepared[12] 34 years ago and had been preserved unchanged. Several similar compounds which have recently been prepared synthetically[13] were included in this study, the results of which are summarized in Table III. In every case the quinone was titrated electrometrically with titanous chloride solution, though two of the determinations with Compound No. 23 were made by titration of the hydroquinone.

Since a number of these substances are very reactive in the sense, for example, that lapachol may be converted by various acidic reagents into α- or β-lapachone or chlorohydrolapachol, some fear was entertained that some such changes might occur on dissolving the compound in the alcoholic hydrochloric acid solution or during the course of the measurements. The results of the measurements themselves lead me to believe that this is not the case. Thus, for example, if hydroxyhydrolapachol suffers any reaction, β-lapachone will surely be among the products formed. This quinone has a potential so much higher than that of the original substance or of any other compound likely to be formed (α-lapachone) that its presence would be unmistakably revealed in the titration curve. However, at the suggestion of Dr. Hooker, whose interest has greatly encouraged me in this work, I attempted to prove that some of these very sensitive compounds remain unaltered. At the completion of a titration, in which, as a rule, 0.05 g. of material was dissolved in 200 cc. of solvent, the solution was exposed to the air until oxidation was complete. Water was then added, the solution was extracted thoroughly with ether, the ethereal solution was washed well with water, dried and the ether evaporated. In many cases the original material was obtained directly in crystalline, and very nearly pure, form; but in every instance it was possible to test the residue with such reagents as ammonia or bisulfite solution for the presence of appreciable quantities of by-products and then to obtain the main product in pure form by crystallization. Compounds No. 13, 18, 19, 20, 22, 28, 31, 32, 36 and 37 were so investigated and in every case the material recovered was found by melting point and mixed melting point determinations to be identical with the original material. Since representatives of all of the types of compound most easily affected are included in this list, it is believed that none of the figures in Table III are in error as a result of any change in the quinones, though they do vary in probable accuracy for reasons discussed in the Experimental Part.

[12] (a) Hooker, *J. Chem. Soc.*, **61**, 611 (1892); (b) **69**, 1355 (1896); (c) **69**, 1381 (1896).

[13] (a) Fieser, THIS JOURNAL, **48**, 3201 (1926); (b) **49**, 857 (1927).

TABLE III

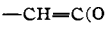
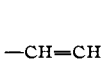
REDUCTION POTENTIALS AT 25°

Solvent: 50% alcohol, 0.1 *N* in HCl and 0.2 *N* in LiCl.

A. Alkyl Hydroxynaphthoquinones

No.	Name	Alkyl group	E_0, v.				ΔE_1, mv.	ΔE_2, mv.	E_0 (Av.), v.
10	2-Allyl-3-hydroxy-1,4-naphthoquinone[13a]	$-CH_2CH=CH_2$	0.299	0.298	0.299		18.1	17.7	0.299
11	2-(α-Methylallyl)-3-hydroxy-1,4-naphthoquinone[13b]	$-CH(CH_3)CH=CH_2$	.286	.288			18.2	15.9	.287
12	2-(γ-Methylallyl)-3-hydroxy-1,4-naphthoquinone[13b]	$-CH_2CH=CHCH_3$	.295	.295	.295		18.1	17.9	.295
13	Lapachol (X)[12a]	$-CH_2CH=C(CH_3)_2$	.285	.289	.286	0.287	17.5	20.0	.287
14	Hydrolapachol[14]	$-CH_2CH_2CH(CH_3)_2$	.286	.285	.285		18.6	18.4	.285
15	Chlorohydrolapachol[12a]	$-CH_2CH_2CCl(CH_3)_2$	.297	.297			23.7	19.5	.297
16	2-(β-chloropropyl)-3-hydroxy-1,4-naphthoquinone[13a]	$-CH_2CHClCH_3$	.305	.304			18.0	21.0	.304
17	Dibromohydrolapachol[12a]	$-CH_2CHBrCBr(CH_3)_2$	.288	.294			27	21	.291
18	Hydroxyhydrolapachol[12a]	$-CH_2CH_2C(OH)(CH_3)_2$	.290	.296	.300	.296	20.8	19.4	.295
19	Lomatiol[15,12c]	$-CH=CHC(OH)(CH_3)_2$	.293	.295			23.2	21.5	.294
20	Hydroxy-*iso*lapachol[12b]	$-CH=C(OH)CH(CH_3)_2$	3.08	.312			21.0	14.9	.310
21	2-(β-Hydroxypropyl)-3-hydroxy-1,4-naphthoquinone[13a]	$-CH_2CH(OH)CH_3$	.307	.309	.307		18.3	17.5	.308
22	*Iso*-β-lapachol[12b]	$-CH=CHCH(CH_3)_2$	.283	.282	.283	.281	23.5	20.8	.282
23	2-Benzyl-3-hydroxy-1,4-naphthoquinone[13a]	$-CH_2C_6H_5$	.294	.296	.297		19.1	18.9	.296

B. β-Naphthoquinone Derivatives

No.	Name	Heterocyclic Ring	E_0, v.				ΔE_1, mv.	ΔE_2, mv.	E_0 (Av.), v.
24	1-Methyl-5,6-benzo-3,4-coumaranquinone[13a,16]		0.406	0.404	0.407		17.4	18.2	.406
25	1,2-Dimethyl-5,6-benzo-3,4-coumaranquinone[13b]		.406	.408	.408		18.8	18.3	.407
26	2-Methyl-7,8-benzo-5,6-chromanequinone[13b]		.399	.398	.400		17.6	18.1	.399

[14] Monti, *Gazz. chim. ital.*, **45**, II, 51 (1915), prepared this substance by hydrogenating the acetyl derivative, or the hydroquinone triacetate, of lapachol and hydrolyzing and oxidizing the products, but she was unable to effect the hydrogenation of lapachol itself with hydrogen and palladium catalyst. It has been found (experiment of Miss Evalyn W. Brodie) that this hydrogenation is easily accomplished with the aid of the platinum-oxide platinum black catalyst of Roger Adams, the reaction being conducted in alcoholic solution at about 40 lbs. pressure. Oxidation of the hydrolapacholhydroquinone formed takes place on exposing the solution to the air; the product, crystallized from petroleum ether, melted at 88–89° (M. 87–89°).

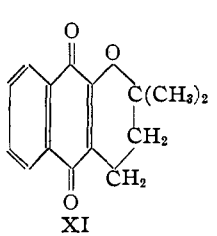
[15] Rennie, *J. Chem. Soc.*, **68**, 784 (1895).

[16] Through an oversight, this compound was incorrectly called 1-methyl-3,4-benzo-5,6-coumaranquinone in the paper in which it is described.

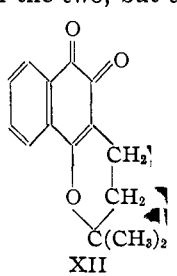
TABLE III (*Concluded*)

No.	Name	Heterocyclic Ring	E_0, v.				ΔE_1, mv.	ΔE_2, mv.	E_0 (Av.), v.
27	2-Phenyl-7,8-benzo-5,6-chromane-quinone[13a]	—C—O—CHC$_6$H$_5$ ‖ | —C—CH$_2$—CH$_2$	.412	.412	.415	.414	18.7	19.8	.413
28	β-Lapachone (XII)[12a]	—C—O—C(CH$_3$)$_2$ ‖ | —C—CH$_2$—CH$_2$	.403	.403	.402		17.7	18.3	.403
29	Bromo-β-lapachone[12a]	—C—O—C(CH$_3$)$_2$ ‖ | —C—CH$_2$—CHBr	.427	.427			18.0	18.0	.427
30	Hydroxy-β-lapachone[12a]	—C—O—C(CH$_3$)$_2$ ‖ | —C—CH$_2$—CHOH	.411	.411			18.5	18.0	.411
31	*Iso*propylfuran-β-naphthoquinone[12b]	—C—O—CCH(CH$_3$)$_2$ ‖ ‖ —C———CH	.460	.460			17.9	17.4	.460
		C. α-Naphthoquinone Derivatives							
32	1-Methyl-4,5-benzo-3,6-coumaran-quinone[13a]	—C—O—CHCH$_3$ ‖ | —C———CH$_2$	.376	.374	.375		18.9	18.2	.375
33	2-Methyl-6,7-benzo-5,8-chromane-quinone[13b]	—C—O—CHCH$_3$ ‖ | —C—CH$_2$—CH$_2$	.307	.307	.308		19.3	18.9	.307
34	α-Lapachone (XI)[12a]	—C—O—C(CH$_3$)$_2$ ‖ | —C—CH$_2$—CH$_2$	.305	.303	.305		18.0	18.3	.304
35	Hydroxy-α-lapachone[12b]	—C—O—C(CH$_3$)$_2$ ‖ | —C—CH$_2$—CHOH	.321	.319			20.9	20.3	.320
36	*iso*Propylfuran-α-naphthoquinone[12b]	—C—O—CCH(CH$_3$)$_2$ ‖ ‖ —C———CH	.283	.284			19.9	19.3	.283
		D. *Compound of Unknown Structure*							
37	Paternò's "Isolapachone"	C$_{15}$H$_{12}$O$_3$[17],[12a]	.366	.365			20.6	23.8	.365

The bearing of these results on the problem of tautomerism may be stated in the following way. In order to determine, in light of the present theory, whether lapachol has the structure of Xa or Xb or is an equilibrium mixture of the two, it is necessary to have some information regarding the relative potentials of the two forms. Of course, judging from the facts known about the simple naphthoquinones, it is probable that the *p*-quinone form has the lower potential of the two, but this conclusion



XI



XII

[17] Paternò, *Gazz. chim. ital.*, **19**, 622 (1889).

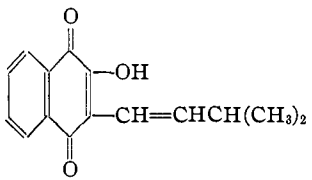
is placed upon a more secure basis by the observation that of the isomers of lapachol, α and β-lapachone (XI and XII), the *p*-quinone is lower in potential than the isomer by 0.099 v. Lapachol, then, should correspond to Xa. The potential of lapachol has been determined, but there is no altogether sound basis for deciding whether or not the value is consistent with Xa. However, it will be recalled that the potential of hydroxy-naphthoquinone is very close to that of a series of its *p*-quinone ethers and, if the *p*-quinonoid structure for the hydroxy compound is granted, it is safe to say that lapachol should correspond with some degree of approximation to α-lapachone, since the latter is similar, in structure and properties, to an alkyl-alkoxy-naphthoquinone. It may be objected that the two substances differ in their degree of saturation and are therefore not comparable, but the figures for lapachol and its hydrogenation product (No. 14) are so close together as to indicate that a double bond situated as it is in lapachol has no appreciable influence upon the potential. At least there is ample justification for stating that lapachol, if it has the structure of Xa, should have a potential closer to that of α-lapachone than to that of β-lapachone. This is in fact the case: the value is 0.017 v. lower than that of α-lapachone and 0.116 v. lower than that of the β-isomer. Thus both the electrochemical theory and the electrochemical results favor Formula Xa. Hooker[12a] was led to regard lapachol as a *p*-quinone because of its resemblance to hydroxynaphthoquinone, because of its yellow color (α-lapachone is yellow, β-lapachone is red) and because it volatilizes with steam. A further fact which affords strong support of this view is that lapachol reacts only to a very slight extent with sodium bisulfite,[13b] thus differing from almost all *o*-quinones.

What has been said of lapachol is true of almost all of the hydroxy compounds in the table (Group A). In those cases where the heterocyclic ortho and para quinone isomers are listed under B and C, it is seen that the *o*-isomer always has the higher potential and that the hydroxy quinone always corresponds much more closely in potential to the *p*-quinone heterocyclic derivative. This statement is true even though a surprising value appears for one of the heterocyclic compounds, namely, No. 32. The potential of this *p*-coumaranquinone is much higher than those of the *p*-chromanequinones, Nos. 33 and 34, while the isomeric *o*-coumaranquinone, No. 24, as well as the coumaran, No. 25, are close in potential to the *o*-chromanequinones, Nos. 26 and 28. That No. 32 has the same heterocyclic ring as No. 24 is clearly demonstrated by a series of interconversions described in the Experimental Part; but an interpretation of the potential of the substance is still to be sought.

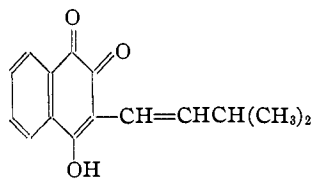
The potential of *iso*propylfuran-β-naphthoquinone (No. 31) is higher in relation to the *o*-coumaran and *o*-chromanequinones than is the isomer, No. 36, in relation to the corresponding *p*-quinones but, when it is observed

that the furan derivatives alone possess unsaturated heterocyclic rings, this is not altogether surprising. A similar situation is found in the relationship between anthraquinone and phenanthrenequinone and with other unsaturated heterocyclic analogs of these compounds.[18]

But even though we are still far from a complete understanding of the relationship between reduction potentials and structure, the peculiarities here noted do not affect the question at issue. The two furan derivatives, Nos. 31 and 36, surely differ very decidedly in potential and the hydroxylic substance, *iso*-β-lapachol (No. 22), agrees closely with the α-isomer in potential and not at all with the β-isomer. Therefore, it is believed that this compound has the structure of XIIIa. This conclusion



XIIIa



XIIIb

is supported by the fact that the potential of the compound is just about what would be expected from a consideration of the values for the unsaturated alcohols, Nos. 19 and 20, and from the fact that an alcoholic hydroxyl group produces a slight increase in the potential (compare Nos. 14 and 18), provided that the substance in question is regarded as a *p*-quinone. On the other hand, this conclusion is contrary to the views of Hooker,[12b] who discovered the compound and assigned to it Formula XIIIb. Hooker's reason for adopting the *o*-quinone formula was largely because the substance is red in color, and to anyone who has had occasion to observe the sharp distinction between the red or orange *o*-quinones of Group B and the yellow *p*-quinones of Group C, the argument does not lack plausibility. Indeed, in an earlier paper[13b] I made use of this property, in the absence of other evidence, in assigning a tentative structure to the phenyl chromanequinone, No. 27, and the results of the present experiments indicate the correctness of the choice of the *o*-quinonoid formula in this case. But I do not consider the color of a quinone, even in a group of fairly closely related substances, to be an infallible guide to its structure. There are, in fact, cases in which the rule that *p*-quinones are yellow in color does not hold. Among *p*-naphthoquinones which are decidedly red in color, mention may be made of naphthazarin, whose structure is not equivocal, and of naphthopurpurin; while a wide variety of halogen substituted 2,5- and 2,6-dialkoxy-*p*-benzoquinones is described in the literature as being red.[19] On the other hand, there is no exception to the

[18] Fieser and Ames, THIS JOURNAL, **49**, 2604 (1927).

[19] (a) Kehrmann, *J. prakt. Chem.*, [2] **40**, 365 (1889); (b) Jackson and Bolton, THIS JOURNAL, **36**, 1473 (1914); (c) Levine, *ibid.*, **48**, 797 (1926); (d) Hunter and

rule that the stable form of a quinone is the form possessing the lowest oxidizing power, unless the present case constitutes an exception and the reduction potential of a quinone, in contrast to the color, is a well defined and well understood physico-chemical constant.

A further fact which supports the contention that *iso*-β-lapachol is a *p*-quinone is that the substance does not react with sodium bisulfite. The bisulfite reaction, like color, is not an absolutely safe criterion of structure, for a few *o*-quinones, such as Compound No. 27 and 4-phenyl-methoxy-1,2-naphthoquinone,[13a] react only to a slight extent with sodium bisulfite; but, considered together with other properties, it is not without value.

The results given in Table III permit of several interesting observations concerning the relationship between reduction potential and structure, the more important of which will be briefly mentioned. While an hydroxyl group attached to a quinonoid nucleus lowers the potential by about 120 mv.,[9] an hydroxyl group in a saturated or unsaturated side chain or in a saturated heterocyclic ring raises the potential by from 8 mv. to 28 mv., the effect being greater the closer the group is to the quinonoid ring. The quinonoid substitution of chlorine or bromine causes an average increase in potential of 18 mv.,[9] and side chain substitution of these elements produces about the same effect. An increase in the size of an alkyl group, or an increase in the number and character of the alkyl or aryl groups attached to a saturated heterocyclic ring, produces no appreciable alteration in the potential. The presence of a double bond in a side chain has little influence on the potential, regardless of its position.

6. Certain Alkoxy Naphthoquinones

Reference has been made to the fact that hydroxynaphthoquinone and its *p*-quinone ethers have about the same reduction potentials and that this fact, granting the assumption of the *p*-quinonoid structure of the hydroxy compound, indicates that the hydroxyl and alkoxyl groups have approximately the same potential-lowering effect. In an attempt to establish the correctness of this conclusion by independent evidence and thus further establish the correctness of the reasoning of Section 2, several 2-methoxy-3-alkyl-1,4-naphthoquinones, such as the methyl ether of lapachol, were prepared and examined potentiometrically, the idea being that, since lapachol exhibits little tendency to exist in an *o*-quinonoid form,[20] a comparison of it with its ether is of somewhat greater significance than

Levine, *ibid.*, **48**, 1608 (1926). It is of significance that certain diaryl-*p*-benzoquinones [(e) Pummerer and Prell, *Ber.*, **55**, 3111 (1922); (f) Pummerer and Fiedler, *Ber.*, **60**, 1439 (1927)], as well as 2,5-dihydroxy-*p*-benzoquinone [(g) Scholl and Dahll, *Ber.*, **57**, 81 (1924)], have been obtained in both a yellow form and an orange or red form.

[20] The failure of lapachol to react readily with sodium bisulfite is evidence of this point.

in the case of hydroxynaphthoquinone. But no satisfactory potential measurements could be obtained with any of these compounds, the difficulty apparently being that equilibrium between the quinone and its reduction product was never attained, or was reached extremely slowly.

Isonaphthazarin and its mono- and dimethyl ethers were next examined (see Table IV), but the results are inconclusive. A consideration of the

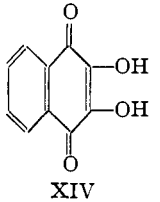
TABLE IV

REDUCTION POTENTIALS AT 25°[21]

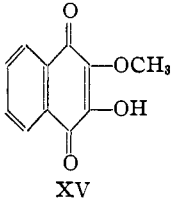
Solvent: 50% alcohol, 0.1 *N* in HCl and 0.2 *N* in LiCl.

No.		E_0, v.				ΔE_1, mv.	ΔE_2, mv.	E_0 (av.)
38	Isonaphthazarin	0.282	0.281	0.282	0.282	17.9	18.1	0.282
39	Isonaphthazarin monomethyl ether	.330	.328	.329	.330	18.7	19.7	.329
40	Isonaphthazarin dimethyl ether	.385	.387	.388		20.2	18.9	.387

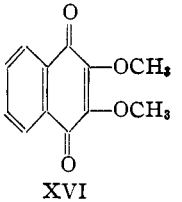
reduction potentials of α-naphthoquinone (E_0 = 0.483 v.) and of hydroxynaphthoquinone (E_0 = 0.356 v.) shows that one quinonoid hydroxyl group produces a potential lowering of 0.127 v. If isonaphthazarin is regarded as a *p*-quinone (XIV), it appears that a second hydroxyl group has an effect of only 0.074 v., or that the effect of each of the two groups is only 0.100 v. While such a result is not without parallel,[9] it is equally permissible to consider isonaphthazarin to be a β-naphthoquinone derivative, when the effect of each of the two hydroxyl groups is represented by a quantity, 0.147



XIV



XV



XVI

v., which is somewhat more comparable with the value for one such group.

The red color of isonaphthazarin is hardly indicative of an *o*-quinonoid structure in view of the fact that naphthazarin is likewise red. Negative evidence in favor of the *p*-quinone formula is furnished by the fact that sodium bisulfite is without action on the substance, while the conversion of the compound into XVI (yellow, insoluble in bisulfite solution) by the action of diazomethane affords some support of this view. However, the evidence is not sufficiently conclusive to warrant a final decision, and consequently the relationship of isonaphthazarin to its ethers, XV and XVI, which are probably *p*-quinones, cannot be adequately defined, though the fairly regular increase in potential from XIV to XV to XVI is suggestive. I am inclined to consider that isonaphthazarin is a *p*-quinone, that in the dihydroxy series an ether has a considerably higher potential than

[21] Determined by titration of the hydroquinones with benzoquinone solution.

the corresponding hydroxy compound, that in the series of the alkyl-hydroxy-naphthoquinones an ether is only slightly higher in potential than the hydroxy compound (compare α-lapachone and hydrolapachol), and that there is no difference between the two in the case of hydroxy-naphthoquinone. But these conclusions, even if they were adequately established, would not serve to answer the question stated at the beginning of this section.

7. The Influence of the Hydrogen-Ion Concentration on the Position of the Tautomeric Equilibrium

The equations given above apply only to solutions which are of such acidity or of such a character that no ionization of either the oxidant or the reductant takes place. In view of the striking color changes which frequently accompany the dissolution of hydroxy quinones in alkali, and particularly because it has often been assumed that such a color change is the result of a process of tautomerization, it is of considerable interest to extend the simple equations to include solutions of any hydrogen-ion concentration.

The case of a quinone containing a single dissociable hydroxyl group, whose hydroquinone has three hydroxyl groups, will be considered (e. g., hydroxynaphthoquinone). A general expression for the electrode potential of a solution of one pure tautomer (α-Oxid) of any acidity is as follows[22]

$$E^{\alpha} = E_0^{\alpha} + 0.0296 \log [\alpha\text{-Oxid}]_T + 0.0296 \log \underbrace{(k_1k_2k_3 + k_1k_2[H^+] + k_1[H^+]^2 + [H^+]^3)}_{\text{Term (a)}}/[\text{Red}]_T - 0.0296 \log (k_\alpha + [H^+]) \quad (6)$$

in which $[\alpha\text{-Oxid}]_T$ and $[\text{Red}]_T$ are the total concentrations of the oxidant and reductant and thus account for both the dissociated and undissociated material, k_1, k_2 and k_3 are the three dissociation constants of the reductant, and k_α is the dissociation constant of the quinone, or oxidant. This equation applies equally well to the potential of the tautomer in an equilibrium mixture, provided that a means can be found for evaluating $[\alpha\text{-Oxid}]_T$. A similar equation applies to the second tautomer (β-Oxid) and, since the two tautomers have a common reduction product, Term (a) is identical in each case and we may write

$$E^{\beta} = E_0^{\beta} + 0.0296 \log [\beta\text{-Oxid}]_T + \text{Term (a)} - 0.0296 \log (k_\beta + [H^+]) \quad (7)$$

It is obvious that in an equilibrium mixture the potentials of the two systems must be identical ($E^{\alpha} = E^{\beta}$). On equating (6) and (7) the following expression results:

$$0.0296 \log [\alpha\text{-Oxid}]_T/[\beta\text{-Oxid}]_T = (E_0^{\beta} - E_0^{\alpha}) + 0.0296 \log (k_\alpha + [H^+])/(k_\beta + [H^+]) \quad (8)$$

Defining a general tautomeric equilibrium constant, or the ratio of the

[22] Compare Clark and Cohen, *Pub. Health Repts.*, **38**, 666 (1923).

concentrations of the two reactants in any solution, thus: $K' = [\alpha\text{-Oxid}]_T/[\beta\text{-Oxid}]_T$, Equation 8 becomes

$$\log K' = (E_0^\beta - E_0^\alpha)/0.0296 + \log (k_\alpha + [H^+])/(k_\beta + [H^+]) \qquad (9)$$

Equation 9 shows that in acid solutions where $[H^+]$ is considerably greater than k_α or k_β, the equilibrium constant is a function only of the difference in the normal potentials of the tautomers, that is, the equation reduces to Equation 4, which was derived in a different way. In alkaline solutions where $[H^+]$ is inappreciable with respect to k_α and k_β, the equilibrium constant is again independent of $[H^+]$ but its logarithm differs from that of the value in acid solution by the term $\log (k_\alpha/k_\beta)$. These relationships for the extremes of acidity and alkalinity where the quinones exist as undissociated molecules or as ions, respectively, may be expressed as follows

$$\log K(\text{un-ionized}) = (E_0^\beta - E_0^\alpha)/0.0296 \qquad (10)$$

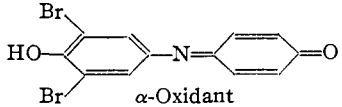
$$\log K(\text{ionized}) = (E_0^\beta - E_0^\alpha)/0.0296 + \log (k_\alpha/k_\beta) \qquad (11)$$

On combining these expressions

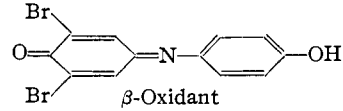
$$K \text{ (ionized)} = K \text{ (un-ionized)} (k_\alpha/k_\beta) \qquad (12)$$

The extent of the change in the equilibrium constant on passing from an acid to an alkaline solution is thus dependent upon the ratio of the dissociation constants of the two tautomers. If these constants are the same, as is probably approximately true in the case of hydroxynaphthoquinone, no change in the equilibrium constant will result.

The above equations apply equally well to the indophenols. In a number of the substances of this type which were examined by Clark and his collaborators,[10] the hydroxyl group of one tautomer is surrounded by halogen atoms and will consequently have a dissociation constant greater than that of the second tautomer in which this group is situated in a benzene ring. As a result, the composition of the equilibrium mixture will vary with the P_H of the solution in a manner defined by Equation 9. Clark, observing that the apparent dissociation constant of 2,6-dibromophenol-indophenol is considerably greater than the dissociation constant of phenol-indophenol, concluded, with reason, that the predominant tautomer was that in which the hydroxyl group is in the halogen substituted ring[10b,c] (XVIIa) but it must be noted that such statements apply only



α-Oxidant
XVIIa



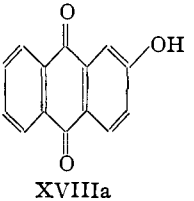
β-Oxidant
XVIIb

in the P_H range at and beyond which dissociation of the oxidant becomes appreciable. It is reasonable to suppose that the ratio of the dissociation constants of the two tautomeric forms of XVII is approximately

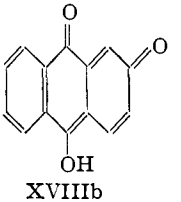
equal to the ratio of the apparent dissociation constant of this substance to the dissociation constant of phenol-indophenol, whence: $k_\alpha/k_\beta = 250$. Then, by Equation 12, the tautomeric equilibrium constant of the ionized quinones is two hundred and fifty times as great as that of the quinones in the un-ionized condition. The process of dissociation greatly increases the proportion of the α-oxidant in the equilibrium mixture. Obviously the fact that this tautomer predominates when the quinones are dissociated furnishes no basis for considering that this is true under any other conditions.

The case of naphthopurpurin, III, is also illustrative. The fact that this substance, like hydroxynaphthoquinone, is a stronger acid than naphthoquinones with hydroxyl groups only in the benzenoid nucleus (see Experimental Part) might be taken as evidence that the one hydroxyl group of doubtful position is attached to the quinone nucleus as in IIIa, which may be termed the α-form. But the argument only applies to the ionized substance. The product of the three dissociation constants of this α-form will surely be greater than the corresponding product for the β-form, IIIb, which means that K(ionized) is greater than K(un-ionized), and again ionization favors the α-form.

Finally, it is of interest to consider the possibility of tautomeric change in the hydroxyanthraquinone series. The properties of the β-derivative, XVIII, for example, leave little doubt that under all ordinary conditions the substance corresponds to XVIIIa (α-form), and yet, largely in order to account for certain color phenomena, the assumption has often been made that a rearrangement to XVIIIb (β-form) takes place on the formation of



XVIIIa



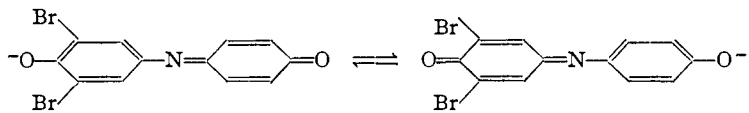
XVIIIb

salts of this substance.[23] Now the normal reduction potential of XVIIIb, which has an extended quinonoid structure similar to that of amphinaphthoquinone, would surely be much the higher of the two; consequently the constant for the un-ionized quinones must be a large number, indicating that XVIIIa predominates. A change to XVIIIb on ionization can only take place if the dissociation constant of this substance is considerably less than that of XVIIIa. But from what is known regarding the acidic strength of hydroxy quinones, it appears highly probable that the

[23] Scholl and Zincke, *Ber.*, **51**, 1419 (1918); this paper contains references to the earlier literature; Barnett, "Anthracene and Anthraquinone," D. Van Nostrand Co., New York, **1921**, p. 252; Goodall and Perkin, *J. Chem. Soc.*, **125**, 470 (1924); Moir, *ibid.*, **1927**, 1809.

dissociation constant of XVIIIb is not less, but greater, than that of the more stable tautomer, and this reasoning leads to the conclusion that under no conditions can a tautomeric change in the manner indicated occur.

Before concluding this discussion it seems advisable to call attention to the question of the validity of postulating the existence of a tautomeric equilibrium between ions. While it is hardly appropriate to consider in any detail the subject of the mechanism of reactions in connection with a problem which is concerned solely with equilibria, some statement of the possibilities in this direction is necessary. A conception which has been of service in developing the present theory is that each tautomer preserves its structure on ionization but that a rearrangement of its linkages and a shift of the charge from one center to another is possible. Thus the ions of XVIIa and XVIIb would have the following structures and they would be in equilibrium with each other



IXa IXb

An alternate view is that the change from one ion to the other takes place only by the combination of the ion with a hydrogen ion, tautomeric change, and dissociation. The resultant equilibrium would be the same in either event.

On the other hand, one may question the existence of tautomers in the ionic state and prefer to consider that the dissociation of the two tautomers produces a single ion, an ion to which it is impossible to assign a formula such as IXa or IXb. It then would be necessary to suppose that one oxygen atom of this ion has a different tendency than the other oxygen to combine with a hydrogen ion, for the two un-ionized molecules have, or can have, different dissociation constants. Thus the conception of a single ion with two tendencies to combine with hydrogen ion is contrasted with the view that there are two ions, each of which has a definite affinity for hydrogen ion. If the former view were adopted it would be necessary to consider the whole question of tautomerism from a point of view different from that given above and with the use of a new terminology. In this paper preference has been given to the latter idea, which permits the use of ordinary organic formulas and which introduces no novel conceptions, but I do not wish to indicate that this view is considered to be the only one by means of which it is possible to arrive at the conclusions here presented.

I expect to consider the problem of the tautomerism of the amino quinones in a future communication.

Experimental Part

Alkoxy-naphthoquinones.—The quinones listed in Table I have been described previously,[2] with the exception of the two *n*-propoxy derivatives. The latter substances were prepared in the usual manner by the action of *n*-propyl iodide on the silver salt of hydroxynaphthoquinone in benzene suspension, 10% of the salt being converted into hydroxynaphthoquinone, while of the remainder 74% was converted into the *o*-quinone ether and 13% into the *p*-quinone ether. The *p*-quinone ether was also prepared by esterification of the hydroxy compound with *n*-propyl alcohol and hydrogen chloride.

4-(*n*-Propoxy)-1,2-naphthoquinone crystallizes from ligroin-benzene in the form of very long, thick, orange-yellow needles, m. p. 116°.

Anal. Calcd. for $C_{13}H_{12}O_3$: C, 72.19; H, 5.60. Found: C, 71.97; H, 5.66.

2-(*n*-Propoxy)-1,4-naphthoquinone crystallizes from ligroin or from water, forming long, pale yellow needles melting at 91°.

Anal. Calcd. for $C_{13}H_{12}O_3$: C, 72.19; H, 5.60. Found: C, 72.17; H, 5.74.

The remarkable ease with which hydrolysis of the *o*-quinone ethers of this series takes place has been noted.[2] On examining samples which had been prepared one year previously and stored in cork-stoppered specimen tubes, it was observed that specimens of the ethyl and allyl[13a] ethers had lost their luster; they were yellow and not orange-yellow; they were partially soluble in cold ammonia solution and a marked odor of allyl alcohol was apparent in the tube containing the allyl derivative. Analysis of the latter (dried) material, which was originally an analyzed sample of alloxy-β-naphthoquinone, indicated that it was a mixture of 46.5% of the ether and 53.5% of hydroxynaphthoquinone (calcd.: C, 70.34; H, 4.03. Found: C, 70.34; H, 4.04).

Alkyl Methoxynaphthoquinones.—Since compounds of the type of lapachol are strongly acidic substances, it was to be expected that diazomethane would attack the hydroxyl group before adding to the double bond. This was the case, for compounds were obtained which, from the results of analysis and of hydrolysis experiments, were found to be ethers; their melting points and analyses are listed in the accompanying table.

TABLE V

2-ALKYL-3-METHOXY-1,4-NAPHTHOQUINONES

Alkyl group	M. p., °C.	Calcd., % C	Calcd., % H	Found, % C	Found, % H
$-CH_2CH{=}C(CH_3)_2$	53	74.97	6.30	74.99	6.28
$-CH_2CH{=}CHC_6H_5$	90.5	78.92	5.30	78.92	5.36
$-CH_2C_6H_5$	83.5	77.67	5.07	77.56	5.10
$-CH(C_6H_5)_2$	112.5	81.33	5.12	81.26	5.12

In each case the compound was obtained, on evaporating the ethereal solution, in the form of an oil which solidified on rubbing. Crystallized from ligroin or petroleum ether, the substances, with exception of the last one, formed short, well-formed, yellow needles. The diphenylmethyl derivative formed hard lumps of crystal aggregates. The substances are all very readily soluble in the usual organic solvents and very sparingly soluble in water. Unlike the alkoxy-α-naphthoquinones, they are hydrolyzed with considerable difficulty by sodium hydroxide or alcoholic alkali. Triphenylmethylhydroxynaphthoquinone did not react with diazomethane under conditions suitable for the preparation of the above compounds.

Polyhydroxynaphthoquinones.—The most convenient method of preparing naphthazarin is that patented by Baeyer and Co.[24] and more fully described by Charrier and

[24] Ger. Pat. 71,386.

Tocco.[25] Fuming sulfuric acid of the concentration called for not being available, it was found that satisfactory results were obtained by adding a solution of 25 g. of sulfur in 375 cc. of 18% fuming sulfuric acid to a well-stirred suspension of 50 g. of 1,5-dinitronaphthalene in 230 cc. of concd. sulfuric acid. The temperature was not allowed to rise above 60°, though it is sometimes necessary to maintain this temperature by external heating for a short time in order to complete the reaction. The product was worked up in the usual way; average yield, 26 g. A sample for the potential measurements was purified by sublimation.

The preparation of naphthopurpurin at first presented some difficulties because neither this substance nor naphthazarin is easily identified. Alkaline solutions of mixtures of the two quinones can be prepared which are indistinguishable in color from an alkaline solution of naphthopurpurin. Finally, recourse was had to potentiometric analysis. Since the two quinones differ decidedly in reduction potential (Table II) a titration curve (of the catalytically prepared hydroquinone solution) serves to reveal the presence of one of these substances in a mixture consisting largely of the other, and it furnishes a fairly accurate idea of the relative concentrations. The titration curve consists of two distinct logarithmic curves and it is easily interpreted. Only traces of naphthopurpurin were detected in samples prepared according to Jaubert[26] by grinding together 4 g. of naphthazarin, 8 g. of finely powdered manganese dioxide and 8 cc. of concd. sulfuric acid. On dissolving the same quantity of the quinone in 30 cc. of concd. sulfuric acid, slowly sprinkling in 8 g. of manganese dioxide, with very vigorous stirring, and heating the mixture for twenty minutes at 125°, a product containing equal parts of naphthazarin and naphthopurpurin resulted. At 160° the material was largely destroyed.

The manganese dioxide method was soon abandoned for a modification of a method described in the patent literature,[27] in which the oxidation of naphthazarin is accomplished by the action of air in an alkaline solution. In order to separate the product from traces of unchanged material, advantage was taken of the fact that naphthopurpurin is much the stronger acid of the two. It is also of advantage to purify the monosodium salt, for naphthopurpurin itself does not crystallize at all well from any of the available solvents.

A solution of 5 g. of naphthazarin in 1.2 liters of water containing 35 cc. of 6 *N* sodium hydroxide solution was heated on the water-bath, with a rather rapid stream of air passing through the solution, for four and one-half hours. The solution was rendered just acid with acetic acid, when the color changed from fuchsin-red to a dull red, cooled and a slight amount of precipitated material was removed by filtration. In order to obtain the sodium salt, the solution is best concentrated to a volume of about 500 cc. and treated with an equal volume of saturated sodium chloride solution. The dark red salt then separates in the form of a fine powder. It dissolves rather readily in water but does not crystallize without the use of sodium chloride and it was not obtained in a form entirely free from this reagent. The barium salt, obtained by adding barium chloride solution to a hot solution of the sodium salt, is only moderately soluble in water and it can thus be washed free of inorganic material.

Anal. Calcd. for $(C_{10}H_5O_5)_2Ba$: Ba, 25.08. Found: 24.90.

Naphthopurpurin prepared from the reprecipitated sodium salt corresponded in properties with Jaubert's material. In its strongly acidic character, this quinone closely

[25] Charrier and Tocco, *Gazz. chim. ital.*, **53**, 431 (1923). This paper is incorrectly quoted in *Chemical Abstracts*, **18**, 254 (1924).

[26] Jaubert, *Compt. rend.*, **129**, 684 (1899).

[27] Ger. pat. 167,641.

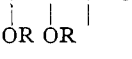
resembles 2-hydroxy- and 2,6-dihydroxy-1,4-naphthoquinone. All of these substances dissolve readily in sodium acetate solution and are precipitated from an alkaline solution only by a large excess of acetic acid. This property is not shared by naphthoquinones containing hydroxyl groups only in the benzenoid ring, such as juglone or naphthazarin, while the presence of a second hydroxyl group or of an alkyl group in the quinonoid nucleus somewhat decreases the acidic strength of hydroxynaphthoquinone.

2,6-Dihydroxy-1,4-naphthoquinone was obtained from 6-hydroxy-1,2-naphthoquinone[28] in the manner described by Dimroth and Kerkovius.[29] Some improvement was effected in the preparation of the starting material, 2,6-dihydroxynaphthalene. Schaeffer's salt (150 g.) was fused with potassium hydroxide according to the directions of Willstätter and Parnas[30] but, since it appears that 2,6-dihydroxynaphthalene readily undergoes decomposition in alkaline solution, the product was not cooled and dissolved in water, but the melt, while still hot, was ladled out into a mixture of 700 cc. of concd. hydrochloric acid and enough ice to give a final volume of about 5 liters. The crude product was crystallized with the use of animal charcoal from 2 liters of water, when it was observed that some decomposition occurs during the process of dissolution unless the suspension is vigorously stirred. The yield of light brown material melting at 209° (uncorr.) was 50 g., and the substance dissolved in alkali with the color and the fluorescence of the product obtained by the above-named authors after a lengthy process of purification.

Isonaphthazarin-dimethyl Ether.—Isonaphthazarin[31] was crystallized from glacial acetic acid and the sample melted at 282°. On adding 1.1 g. of this substance to an ethereal solution of diazomethane prepared from 5 cc. of nitrosomethylurethan, a rapid evolution of nitrogen took place, the red crystals soon dissolved and long, yellow needles were deposited. Recrystallized from ether, the substance melted at 115°. It is readily soluble in alcohol or ligroin, very readily soluble in ether or benzene and insoluble in water or in bisulfite solution.

Anal. Calcd. for $C_{12}H_{10}O_4$: C, 66.04; H, 4.62. Found: C, 65.86; H, 4.65.

Isonaphthazarin Monomethyl Ether.—The action of alkali on the above substance is very interesting because a single ether group is attacked and the resulting substance is resistant to hydrolysis to a marked degree. In this behavior, 2,3-dimethoxy-1,4-naphthoquinone closely resembles 2,3-dichloro-1,4-naphthoquinone, only one of whose chlorine atoms is replaced by the action of alkali or of amines. The latter reactions have been enumerated and discussed by Fries and Ochwat,[32] who regard the substitution reactions as involving either a "mobile" atom or 1,4-addition. While I am inclined to consider the hypothesis of 1,4-addition as the more attractive, particularly as applied to the hydrolysis of alkoxy naphthoquinones,[2] it seems odd that the 1,4-addition of alkali to the system, —C=C—C=O, takes place readily, while a similar



addition to the systems —C=C—C=O and —C=C—C=O (lapachol methyl ether)

occurs only very slowly.

The dimethyl ether was warmed on the water-bath for a short time with 1% sodium hydroxide solution. It soon dissolved with the production of a deep red solution from

[28] Kehrmann, *Ber.*, **40**, 1962 (1907).

[29] Dimroth and Kerkovius, *Ann.*, **399**, 36 (1913).

[30] Willstätter and Parnas, *Ber.*, **40**, 1410 (1907).

[31] Zincke and Ossenbeck, *Ann.*, **307**, 11 (1899).

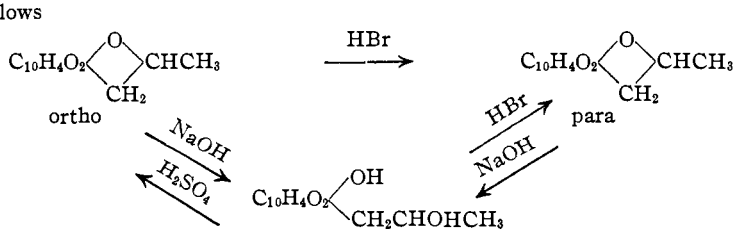
[32] Fries and Ochwat, *Ber.*, **56**, 1291 (1923).

which, on acidification, a yellow product separated in quantitative yield. The compound crystallized from water, in which it dissolves readily at the boiling point, in the form of fluffy clusters of small needles; from ligroin-benzene solution stout yellow needles were deposited, m. p. 152°. Like hydroxynaphthoquinone, the substance forms a soluble bisulfite addition product. Prolonged boiling of the alkaline solution of the ether failed to bring about further hydrolysis.

Anal. Calcd. for $C_{11}H_8O_4$: C, 64.70; H, 3.95. Found: C, 64.43; H, 4.14.

1-Methyl-4,5-benzo-3,6-coumaranquinone (No. 32).—The peculiar position of the potential of this compound suggested the possibility that the structure ascribed to it[13a] might be incorrect. The compound had been previously obtained only as a by-product in the conversion of 2-allyl-3-hydroxy-1,4-naphthoquinone into its hydrochloride and, in very small yield, directly from the latter substance, and it had not been adequately studied. It has now been found that a better yield can be obtained as follows. Two g. of allyl-hydroxy-naphthoquinone was dissolved in 20 cc. of glacial acetic acid, 10 cc. of constant-boiling hydrobromic acid was added and the solution was heated on the water-bath for one and one-fourth hours. On pouring the solution into a large volume of water, a brown oil separated and soon solidified. The collected material was treated with ammonia solution until the extract was no longer red and it was then dissolved in glacial acetic acid, a small quantity of chromic acid was added to destroy oily impurities, the solution was diluted and allowed to cool. A further crystallization from ligroin gave a pure product, m. p. 166–167°; yield, 0.5 g.

On boiling this substance with diluted sodium hydroxide solution, a deep red solution results and on acidification there is precipitated a compound which has the appearance of 2-(β-hydroxypropyl)-3-hydroxy-1,4-naphthoquinone. The latter substance was previously obtained from the isomeric *o*-coumaranquinone and the relationship of the two isomers to each other would be adequately established by proving the identity of the two samples of the alcohol. Such a comparison, however, was not convincing because the melting point of the material depends to some extent upon the rate of heating, the state of subdivision and probably upon the condition of the glass surface of the capillary. On the other hand, each specimen was converted into the *p*-coumaranquinone (No. 32), a substance easily identified, by following the above directions for the allyl derivative. The *o*-coumaranquinone, No. 24, was likewise transformed into its isomer by a similar treatment, and it could be obtained from the hydroxypropyl derivative by the action of concd. sulfuric acid. This series of conversions, summarized as follows



proves that the heterocyclic ring is the same in the two isomers.

E.m.f. Measurements.—The procedure for carrying out a titration with a hydroquinone solution was as follows. Sufficient of the quinone for two determinations was dissolved in a suitable solvent and the solution was placed, together with some 5% platinized asbestos, in a 500cc. bottle. The rubber stopper of this bottle carried tubes for the admission and outlet of hydrogen and a tube extending to the bottom and ending in a wide, flared tube fitted with a filter plate covered with filter paper and secured in position with gauze and thread. To the upper end of this tube was attached a short

section of pressure tubing into which a glass tube could later be fitted for the purpose of removing the hydroquinone solution. This filter tube was freed of solution and of air with a stream of hydrogen and then closed. The air in the bottle was displaced by hydrogen, the bottle was closed to the atmosphere and the whole was shaken mechanically, the bottle being connected to a hydrogen reservoir under a slight pressure. At the same time the oxidation-reduction half-cell vessel was freed of oxygen with a stream of nitrogen and, when reduction of the quinone was complete, connection between this vessel and the bottle was made through a nitrogen-filled tube and half of the solution was transferred under hydrogen pressure. The solution was then swept with nitrogen while acquiring the temperature of the thermostat and a titration with a solution of a suitable oxidizing agent was carried out. The remainder of the solution in the bottle was shaken for an additional period of time before the second titration; consequently, if reduction were incomplete in the first instance, this fact would be revealed by a lack of agreement in the two determinations. While the shape of the titration curve usually affords sufficient evidence of incomplete reduction or of air leakage, it is of value to have this additional check on the method, particularly because in a few instances the quinone solution does not lose its color on hydrogenation. This was generally true in the case of certain anthraquinones to be described in a future paper. In some instances hydrogenation was so slow in the presence of platinized asbestos that the platinum-oxide platinum black catalyst of Adams[33] was employed.

The alcoholic phosphate buffer solution mentioned in Table I was prepared by diluting 1.9 liters of a solution 0.087 *M* in potassium dihydrogen phosphate and 0.087 *M* in disodium hydrogen phosphate to a volume of 3.5 liters with 95% alcohol. It was estimated that the resulting solution contains approximately 37% of alcohol.

Reference has been made to the failure to obtain satisfactory measurements with any of the compounds listed in Table V. To this list may be added 2-cinnamyl-, 2-diphenylmethyl- and 2-triphenylmethyl-3-hydroxy-1,4-naphthoquinone. With all of these compounds the potentials were not constant, the end-point was uncertain and the approximately determined normal potentials differed in duplicate titrations by as much as 20 mv. It will be noted that all of these substances are *p*-quinones completely substituted with large groups.

In the lapachol series (Table III) considerable difference in the behavior of the various compounds was noted. Since the determinations were all carried out in very nearly the same manner, the time required for the actual titration is of some significance in indicating, it is believed, the relative velocities of reduction. With the hydroxy-*p*-quinones of Group A, from one and one-half to three hours was required; with the heterocyclic *p*-quinones (Group C), the titrations occupied from one to two hours, while with the heterocyclic *o*-quinones (Group B), a titration was completed in about twenty minutes, even in the case of the phenylated derivative, No. 27. In Groups A and C, reduction was the slowest with the most highly substituted compounds such as dibromohydrolapachol and hydroxy-α-lapachone. These facts may be interpreted in the following manner. Regardless of their character, substituents attached to an *o*-naphthoquinone cannot hinder the 1,4-addition of hydrogen because

[33] Voorhees with Adams, THIS JOURNAL, **44**, 1397 (1922).

they are not directly connected to the 1,4-system: O=C—C=O, and because they are joined to a double bond which retains the same position in the hydroquinone. In a *p*-naphthoquinone, on the other hand, the substituents are attached to the 1,6-conjugated system to the ends of which hydrogen adds.[34] The substituents, to a degree depending upon their size and character, retard the velocity of the addition of hydrogen because the 1,6-system suffers rearrangement as a result of the process of reduction and the double bond between the substituted carbon atoms becomes a single bond. Ring formation between the substituent groups decreases somewhat the hindrance of these groups.

In conclusion, I wish to express my thanks to Dr. Samuel C. Hooker for generously supplying me with a number of compounds for this investigation, and to acknowledge my indebtedness to the Cyrus M. Warren Fund of the American Academy of Arts and Sciences for a grant which has aided this work.

Summary

The constant of the equilibrium between the tautomers, hydroxy-α-naphthoquinone and hydroxy-β-naphthoquinone, depends upon the reduction potentials of these two forms, according to the equation

$$\log K = (E_0^{\beta} - E_0^{\alpha})/0.0296$$

where K = [α-Form]/[β-Form]. In order to estimate the value of K, the reduction potentials of a number of ethers of the α and β forms have been determined, with the result that, as an approximation, K = 502.

In order to test the principle that that tautomer will predominate which has the lower reduction potential, the potentials of the two tautomeric forms of naphthopurpurin have been estimated from the values for certain related compounds, and it has been found that the actual potential of naphthopurpurin corresponds closely with the value estimated for the tautomer of lower potential. Similar analysis of the results of Clark for two indophenols furnishes additional support of the point at issue.

The reduction potentials of a number of compounds of the type represented by lapachol are consistent with this principle and, with one exception, the electrochemical results are consistent with all other known properties of these substances. It is considered that, contrary to the views of the discoverer of the compound, *iso*-β-lapachol is a *p*-quinone.

The variation of the tautomeric equilibrium constant with the hydrogen-ion concentration has been formulated, and it has been shown that the

[34] Kohler and Butler, THIS JOURNAL, **48**, 1036 (1926). The 1,6-addition to *p*-quinones of the magnesium subiodide of Gomberg and Bachmann, *ibid.*, **49**, 236 (1927), as well as the 1,4-addition of this reagent to *o*-quinones, has been established by boiling the dark green suspension which results with acetyl chloride, when the hydroquinone diacetate is formed in good yield.

ratio of the equilibrium constant of the undissociated tautomers to the constant for the completely ionized substances is equal to the ratio of the dissociation constants of the two hydroxy quinones.

BRYN MAWR, PENNSYLVANIA

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BRYN MAWR COLLEGE]

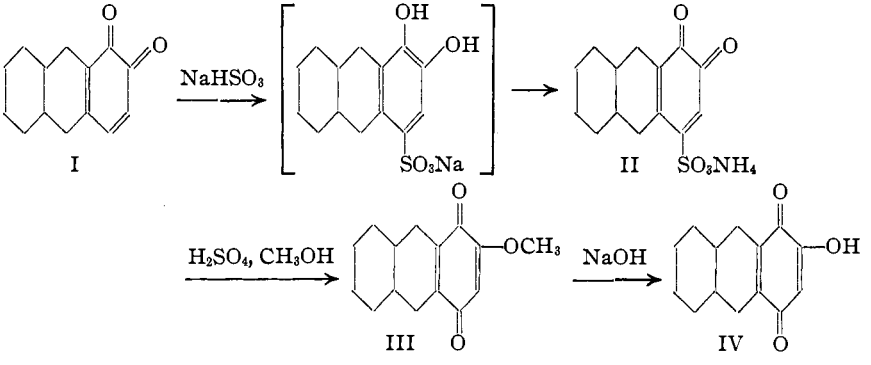
2-HYDROXY-1,4-ANTHRAQUINONE

BY LOUIS F. FIESER

RECEIVED SEPTEMBER 16, 1927 PUBLISHED FEBRUARY 4, 1928

The interest attaching to the properties of hydroxynaphthoquinone, in particular with regard to the abnormal course of its alkylation reactions[1] and the position of the equilibrium between its tautomeric forms,[2] renders it a matter of some importance to examine the hitherto unknown compound named in the title. The chemistry of anthracene is so different from that of naphthalene that it should be possible to determine, in this way, if the phenomena referred to are at all general.

The most satisfactory method found for the preparation of 2-hydroxy-1,4-anthraquinone is indicated as follows



The conversion of II into III involves hydrolysis of the sulfonate group, tautomeric change to IV, and esterification. Good yields were obtained in all of the reactions when pure materials were employed, but it was found most convenient to use crude 1,2-anthraquinone,[3] when the over-all yield from β-anthrol was only 23% of the theoretical. The sulfonate, II, was also obtained from 1-nitroso-2-anthrol.[3] This was converted, by acidifying its solution in sodium bisulfite solution, into 1-amino-2-anthrol-4-sulfonic acid, and the latter was easily oxidized to the quinone, II, by nitric acid. The yield, however, was very poor.

[1] (a) Fieser, THIS JOURNAL, **48**, 2922 (1926); (b) **48**, 3201 (1926); (c) **49**, 857 (1927).

[2] Fieser, *ibid.*, **50**, 439 (1928).

[3] Lagodzinski, *Ann.*, **342**, 59 (1905).