[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

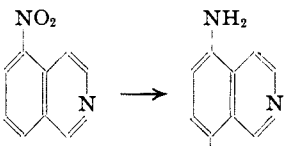
A Comparison of Heterocyclic Systems with Benzene. VI. Quinones of the Quinoline and Isoquinoline Series

BY LOUIS F. FIESER AND ELMORE L. MARTIN

It was desired to obtain for potentiometric study quinones or hydroquinones derived from quinoline and isoquinoline. In the case of the former heterocycle no preparative problem was involved, for 5,8-quinolinequinone is a known compound[1] and Matsumura and Sone[2] have developed a very convenient method for the preparation of the corresponding hydroquinone. In the isoquinoline series, however, compounds of the desired type do not appear to have been described. The three known Bz-hydroxyisoquinolines were first considered as possible starting materials. The only isomer whose structure is fully established, 7-hydroxyisoquinoline, has been prepared by a rather tedious synthesis.[3] The other two compounds have been obtained from the products of high-temperature and low-temperature sulfonation.[4] In analogy with naphthalene, the first of these probably is a β-derivative, and since it differs from the 7-isomer, it probably is 6-hydroxyisoquinoline. The hydroxy compound derived from the other sulfonate has been obtained also from nitroisoquinoline, and since both the sulfonate and the nitro compound are known to be Bz-alpha derivatives[5] the substance is either 5- or 8-hydroxyisoquinoline. The former structure perhaps is the more probable, and we shall refer to the compound as the 5(8)-derivative and formulate it as the 5-isomer, I. Although this compound is not easily obtained, it appeared to be more readily available than the other isomers and a small quantity was prepared and investigated. It was found possible to convert the substance through the benzeneazo derivative into the 5,8 (or 8,5)-hydroxyamino compound II, but the entire process was so unsatisfactory with respect to yields that a better method was sought.

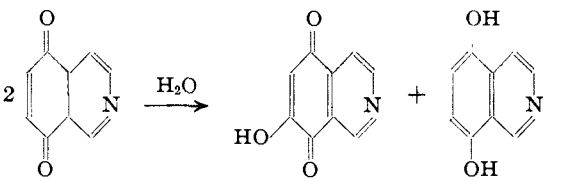
I II

Such a method was found in the electrolytic reduction by Gattermann's method of the readily available 5(8)-nitroisoquinoline, III, for this gave in good yield the isomeric 8,5(5,8)-hydroxyamino compound IV. It was expected that the two *p*-hydroxyamino compounds II and IV would yield on oxidation the same *p*-isoquinolinequinone.



III IV

The same yellow product was indeed obtained in each reaction, but instead of being the expected quinone it had the properties of the corresponding hydroquinone. It was observed that the yield was less than half of the expected amount, that mother liquor was deep red whereas solutions of the pure hydroquinone (salt) are yellow, and that the yield decreased as the amount of oxidizing agent was increased. From these facts it appears very probable that the hydroquinone (VI) results from a disproportionation of the quinone first formed.



V (or isomer) VI

Such a reaction has been well established in the *o*-quinone series.[6] The red mother liquor probably contained a mixture of hydroxyquinones, but no pure product could be isolated. The quinone V could be produced in solution from pure VI, but we were unable to isolate it. The two methods of preparing the hydroquinone establish the structure of 5,8-dihydroxyisoquinoline, VI, and the substance was also obtained by the action of iron and hydrochloric acid on the nitroso

(1) Mathëus, *Ber.*, **21**, 1886 (1888).

(2) Matsumura and Sone, THIS JOURNAL, **53**, 1406 (1931).

(3) Fritsch, *Ann.*, **286**, 12 (1895).

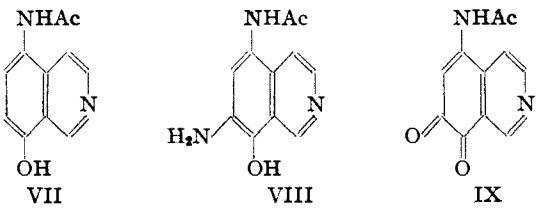
(4) Hoogewerff and van Dorp, *Rec. trav. chim.*, **5**, 308 (1886); Claus and Raps, *J. prakt. Chem.*, **45**, 241 (1892).

(5) Jeiteles, *Monatsh.*, **15**, 814 (1894); Fortner, *ibid.*, **14**, 155 (1893).

(6) Fieser and Fieser, THIS JOURNAL, **57**, 492 (1935).

derivative of the 5(8)-hydroxy compound (method of Matsumura and Sone[2]).

An ortho quinone of the series was obtained starting with the readily available IV, which was converted through the monoacetate VII and its *p*-sulfobenzeneazo compound into the amine VIII. Oxidation yielded an ortho quinone which



may have either of the alternate structures: 5-acetylamino-7,8-isoquinolinequinone (IX) or 8-acetylamino-5,6-isoquinolinequinone.

Potential Measurements

Titrations of the reductants were carried out as indicated in the fifth paper.[7] Both the quinoline- and isoquinoline-quinone were too sparingly soluble in solutions more alkaline than about *p*H 7 to permit an extension of the data of Tables I and II. The normal potentials for the two systems under such conditions that there is no ionization (E_0) are very nearly identical. The difference in the basic dissociation constants of the oxidant and of the reductant is in each case about four *pK* units, the quinone being the weaker base. Quinolinequinone is so weakly basic that the value

TABLE I

POTENTIALS OF THE SYSTEM FROM 5,8-QUINOLINEQUINONE (25°)[8]

Titrations of the reductant with $K_3Mo(CN)_8$. E_0 = 0.5570 v. $K_r^b = 1.76 \times 10^{-5}$. $K_0^b = 1.10 \times 10^{-1}$. $E_n = E_0 + E_h + 0.0295 \log [1 + [H^+]/K_r^b] - 0.0295 \log [1 + [H^+]/K_0^b]$.

*p*H	Hydrogen elec. potential, E_h, v.	Potential when [Ox.] = [Red.], E_n, v.	E_n (found − calcd.), mv.	
0.10	−0.0059	0.6631	+1.3	
1.05	.0621	.5979	−0.7	
1.24	.0733	.5802	−2.0	
1.64	.0970	.5460	−3.7	0.09 slope
3.49	.2064	.3942	+5.4	
3.71	.2193	.3697	+0.3	
3.89	.2300	.3532	−1.0	
4.45	.2631	.3101	+1.8	
4.80	.2838	.2877	+6.3	
5.70	.3370	.2233	+2.9	
6.32	.3736	.1833	−0.1	0.06 slope
6.80	.4020	.1542	− .8	

(7) Fieser and Martin, THIS JOURNAL, **57**, 1835 (1935).

(8) Results of W. H. Thalheimer, who prepared 5,8-quinolinehydroquinone by the method of Ref. 2.

TABLE II

POTENTIALS OF THE SYSTEM FROM 5,8-ISOQUINOLINEQUINONE (25°)

Titrations of the reductant with bromine water or (above *p*H 7) $K_3Mo(CN)_8$. For equation see Table I. E_0 = 0.5642 v. $K_r^b = 1.93 \times 10^{-6}$. $K_0^b = 7.01 \times 10^{-3}$.

*p*H	Hydrogen elec. potential E_h, v.	Potential when [Ox.] = [Red.], E_n, v.	E_n (found − calcd.), mv.	
0.50	−0.0296	0.6397	+0.2	0.06 slope
1.15	.0680	.6015	+1.3	
1.27	.0751	.5941	+1.3	
1.80	.1064	.5592	+0.8	
2.18	.1289	.5298	−1.5	
3.27	.1933	.4445	+2.0	0.09 slope
4.31	.2548	.3500	−1.3	
4.95	.2926	.2934	−1.9	
5.34	.3157	.2639	−0.2	
6.13	.3624	.2018	.0	
6.99	.4132	.1504	− .6	0.06 slope
7.62	.4505	.1137	.0	

reported for K_0^b is in this case only a rough approximation. The isoquinoline compounds are distinctly more basic (one *pK* unit) than the corresponding quinoline derivatives.

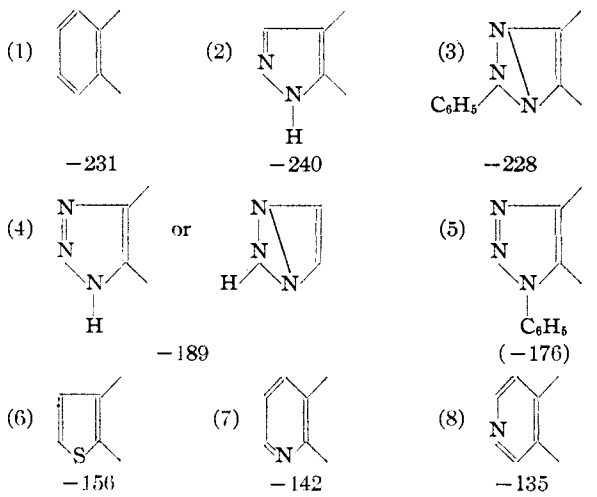
5-Acetylaminoisoquinoline-7,8-quinone, IX (or 8,6,5), is so sparingly soluble in water that satisfactory results were obtained only in the strongly acid region. In titrations of the hydroquinone with potassium dichromate at *p*H 0.40–0.50, the difference between the oxido–reduction electrode at half-oxidation and a hydrogen electrode in the same buffer was found to be 0.7573 v. (av.). As nearly as can be judged from available data, this substituted ortho quinone bears the normal relationship in potential to the para quinone of the isoquinoline series.

Discussion

A sufficient number of heterocyclic systems have been studied in this series of investigations to warrant a brief analysis of the main results. In initiating the work it was pointed out[9] that the lowering in the potential of a benzoquinone resulting from the fusing on of a benzene ring to produce a naphthoquinone probably gives a measure of the inertness or aromaticity of the benzene nucleus. The reactivity of one of the quinonoid ethylenic linkages is dampened when it becomes at the same time an integral part of an aromatic ring. If this premise is correct, the lowering in potential produced by a heterocycle, in comparison with the effect of a benzene ring, might give a measure of the relative degree of aromaticity of the heterocyclic ring. The ring systems for

(9) Fieser, THIS JOURNAL, **48**, 1097 (1926).

which reliable data are now available are indicated in the accompanying chart.



EFFECT OF AROMATIC RINGS ON THE POTENTIAL OF A QUINONE (IN MV.).

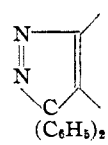
The question of prime importance is whether or not the diminished degree of unsaturation characteristic of the aromatic state is the only factor involved in determining the effect of the different heterocyclic rings. Were this the case the results would indicate that the pyrazole ring (2) is strongly aromatic, that the pyridine ring in the condition of either (7) or (8) is weakly so, and that the thiophene ring occupies a somewhat intermediate position. It is not easy to decide on the basis of other data if this is a reasonable relationship. The ease of substitution is hardly a valid criterion, because it is so likely to be determined, in part at least, by the character of the hetero atom. The ease of substitution of thiophene and furan may be connected with the presence in the ring of a key atom which when joined to a benzene ring facilitates substitution. The reluctance of the pyridine ring to react with many substituting reagents may be because the reaction is conducted in an acidic medium where the hetero atom forms an ionic, positive pole, so that it functions as a meta-directing group and retards substitution. The fact that Py-hydroxyquinolines and isoquinolines, unlike the naphthols, exist to a large extent in the ketonized forms points to a weakened condition of aromaticity of the pyridine ring, for the tendency to retain the completely aromatic type is an important characteristic of the benzene ring. On the other hand, the pyridine ring is remarkably resistant to attack by oxidizing agents, even under conditions such that there is no stabilization of the ring by salt-formation, and indeed it surpasses benzene in this respect. The thiophene ring is much more susceptible to oxidation. Although the different lines of evidence are conflicting, the relative positions of thiophene and pyridine indicated by the electrochemical results appear dubious. On the whole pyridine seems to possess more of the attributes of the truly aromatic type.

That some factor other than the aromaticity may be of influence in determining the potentials of the heterocyclic quinones has been recognized from the outset,[9] and it has been suggested[9,10] that the hetero atom may function as a part of a substituent group, independently of the stability of the ring. A group containing bivalent sulfur would shift the potential of a quinone to a more negative level, while a substituent containing the —N=C or the —C=N linkage of quinoline or isoquinoline probably would have the opposite effect. If the figures given above could be corrected for these possible effects, the value representing the aromaticity of the thiophene ring would become less negative and that for the pyridine rings would become more negative. These changes would be such as to bring the results into better accord with the general inferences from chemical observations, and we are inclined to believe that until such corrections can be made, or until they can be proved to be negligible, the results of the electrochemical comparisons should be viewed with caution.

While a revision may be required along the lines indicated, it is also possible that the results are essentially valid as they stand. It may be noted that the results of different comparisons of the same heterocycle have been remarkably concordant, and that the influence of a pyridine ring is practically the same whether the nitrogen atom is in the α- or the β-position with respect to the quinonoid nucleus. One other observation may be made which strongly indicates that the potential-lowering effects defined above reflect in some measure a property fundamentally connected with the aromatic character of the heterocycles. As judged by the general criteria of stability and lack of chemical reactivity, the 1-phenyltriazole ring system (5) certainly is to be classed as aromatic, and, like the benzene ring, it produces a decided lowering in the potential of a quinonoid nucleus to which it is joined. While formally

(10) Fieser and Kennelly, THIS JOURNAL, **57**, 1611 (1935).

similar to (5), the diphenyl pseudopyrazole ring (9) has entirely different properties.[11] The azo linkage is very reactive, the ring can be cleaved with great ease, and the system is distinctly unstable and in no sense aromatic. The difference is adequately reflected in the potentials, for the effect of fusing this truly unsaturated ring to *p*-benzoquinone is to raise the potential by the substantial amount of 110 mv. From the potentials above it would be concluded that (5) and (9) are fundamentally different, and that the azo group of (5), if indeed it exists as such, has a modified or dampened character quite distinct from an ordinary center of unsaturation, for in the latter case the effect upon the potential would be in the positive direction.

(9) 

Experimental Part

5(8)-Hydroxyisoquinoline.—Isoquinoline sulfate (0.2 mole) was sulfonated essentially according to Weissgerber[12] (with 110 g. of fuming acid, 50% sulfur trioxide, at 20–25° for forty-eight hours), the solution was poured onto 500 g. of a mixture of ice and water and the solution was allowed to stand undisturbed. Long, colorless needles soon separated, and the pure α-sulfonic acid was easily obtained by recrystallization of this material from water; yield, 30 g. (72%). We consider the tedious separation through the barium salt unnecessary. No improvement could be made in the alkali fusion and the best yield was 17% (m. p. 228–230°).

5(8)-Hydroxy-8(5)-aminoisoquinoline (II).—The hydroxy compound (1.45 g.) was coupled with diazotized aniline in alkaline solution and the azo compound was reduced with sodium hydrosulfite. The yellow amine which separated was dissolved with a trace of stannous chloride in 3 cc. of concentrated hydrochloric acid and 5 cc. of water. After clarification, 20 cc. of concentrated acid was added to the hot, yellow filtrate. On cooling, the product separated as stout, bright yellow needles of the dihydrochloride; yield, 1 g. (43%).

Anal. Calcd. for $C_9H_{10}ON_2Cl_2$: C, 46.35; H, 4.33. Found: C, 46.07; H, 4.47.

5(8)-Amino-8(5)-hydroxyisoquinoline (IV).—5(8)-Nitroisoquinoline was prepared as described by Claus and Hoffmann,[13] the yield of crude material, m. p. 104–108°, being 74%. The electrolytic reduction of the nitro compound (12 g.) in sulfuric acid solution (120 cc.) was carried out as described in the fifth paper.[7] After twenty-four hours the yellow solution was filtered from calcium sulfate through asbestos, diluted with an equal volume of water, and allowed to stand for several days in the ice box. Fine yellow needles of the amine sulfate separated and were collected on an asbestos filter; yield, 20 g. This salt probably contains two molecules of sulfuric acid; it dissolves readily in water and presently the solution deposits fine yellow needles of the **monosulfate**, which is very sparingly soluble in water.

Anal. Calcd. for $C_9H_8ON_2 \cdot H_2SO_4$: C, 41.83; H, 3.90; S, 12.42. Found: C, 41.89; H, 4.30; S, 12.57.

The dihydrochloride, which is considerably more soluble in water, was prepared as follows. The crude sulfate from 12 g. of the nitro compound was suspended in 100 cc. of water, covered with a layer of ether to prevent oxidation, and the acid was neutralized with solid sodium bicarbonate. The solid became bright red and then yellow, as the neutral point was reached. The yellow amine was collected, washed with water and quickly dissolved with a trace of stannous chloride in 18 cc. of concentrated hydrochloric acid and 50 cc. of water. After heating the solution and filtering it through charcoal, 200 cc. of concentrated hydrochloric acid was added. The stout yellow needles which separated on cooling were washed with dilute acid, alcohol and ether; yield, 13.3 g. (83%). The salt is readily soluble in water and it dissolves in alkali with a green coloration.

Anal. Calcd. for $C_9H_8ON_2 \cdot 2HCl$: C, 46.35; H, 4.33; Cl, 30.44. Found: C, 46.25; H, 4.34; Cl, 30.61.

The dibenzoyl derivative was prepared by shaking an aqueous suspension of the sulfate with benzoyl chloride and alkali. An oil formed and soon solidified. The substance crystallized from alcohol as fine, colorless needles, m. p. 223–224°.

Anal. Calcd. for $C_{23}H_{16}O_3N_2$: C, 74.98; H, 4.38. Found: C, 74.96; H, 4.42.

Isoquinoline-5,8-hydroquinone Hydrochloride (VI).—(a) A suspension of 5.16 g. of crude 5(8)-amino-8(5)-hydroxyisoquinoline sulfate in 25 cc. of water was treated at 5° with 24 cc. of cold 20% ferric chloride solution. The solid material soon dissolved to give a deep red solution and after standing for a time a fine, yellow precipitate began to separate. After cooling in ice for one hour, this was collected and washed free of red mother liquor with ice water. The crude product was dissolved in 40 cc. of hot water and 10 cc. of concentrated hydrochloric acid and brought down with 75 cc. of concentrated acid, when it gave no test for sulfate ion. After a further crystallization from dilute acid the hydrochloride was obtained as fine, yellow leaflets; yield, 0.73 g. It darkens at about 260° and has no melting point. The substance gives no coloration with ferric chloride, it rapidly darkens in alkali and it gives a very sparingly soluble sulfate.

Anal. Calcd. for $C_9H_7O_2N \cdot HCl$: C, 54.71; H, 4.09; Cl, 17.95; N, 7.18. Found: C, 54.76; H, 4.20; Cl, 18.05; N, 7.16.

(b) The preparation from 5(8)-hydroxy-8(5)-aminoisoquinoline was similar and gave an identical product.

(c) 5(8)-Hydroxyisoquinoline (1.45 g.) was converted into the nitroso derivative by slowly acidifying an alkaline solution of the substance containing sodium nitrite. The crude, moist nitroso compound was dissolved quickly in 400 cc. of hot water containing 12 cc. of concentrated hydrochloric acid and the filtered solution was treated at 95° with 3 g. of iron powder, added in one hour with stirring. The solution was filtered, concentrated in vacuum, and treated with 10 cc. of concentrated hydrochloric acid.

(11) Fieser and Peters, THIS JOURNAL, **53**, 4080 (1931).
(12) Weissgerber, *Ber.*, **47**, 3179 (1914).
(13) Claus and Hoffmann, *J. prakt. Chem.*, **47**, 253 (1893).

Yellow crystals of the hydroquinone hydrochloride separated on cooling; yield, 0.2 g. (10%).

Dibenzoyl isoquinoline-5,8-hydroquinone formed colorless needles from alcohol, m. p. 162–163°.

Anal. Calcd. for $C_{23}H_{15}O_4N$: C, 74.78; H, 4.10. Found: C, 74.80; H, 4.28.

Diacetyl 5(8)-amino-8(5)-hydroxyisoquinoline.—This derivative was obtained from the dihydrochloride of the aminohydroxy compound with acetic anhydride and sodium acetate either in an aqueous solution (60% yield) or without a solvent (69% yield). It crystallizes from dilute alcohol as long, colorless needles, m. p. 208–209°.

Anal. Calcd. for $C_{13}H_{12}O_3N_2$: C, 63.91; H, 4.96. Found: C, 64.02; H, 5.13.

5-Acetylamino-7-(*p*-sulfobenzeneazo)-8-hydroxyisoquinoline (or 8,6,5).—The above diacetyl compound (2.41 g.) was dissolved in a cold solution of 1 g. of sodium hydroxide in 25 cc. of water (hydrolysis of the O-acetyl group) and the solution was treated at 0° with a suspension of the diazo compound from 2.09 g. of sulfanilic acid. A portion of the deep purple-red solution after being diluted yielded a brown, crystalline precipitate of the azo compound on acidification.

Anal. Calcd. for $C_{17}H_{14}O_5N_4S$: C, 52.82; H, 3.65. Found: C, 52.40; H, 3.99.

5-Acetylamino-7-amino-8-hydroxyisoquinoline Dihydrochloride, VIII (or 8,6,5).—The remainder of the solution of the azo compound was treated with sodium hydrosulfite and warmed gently until the color was discharged. The crystalline, yellow precipitate was dissolved in 20 cc. of water and 4 cc. of concentrated hydrochloric acid, and the clarified solution was saturated with hydrogen chloride at 0°, when fine yellow needles of the dihydrochloride soon separated; yield, 1.3 g. (43%). The salt is only moderately soluble in water but it is slow to crystallize.

Anal. Calcd. for $C_{11}H_{11}O_2N_3 \cdot 2HCl$: C, 45.52; H, 4.52. Found: C, 45.12; H, 4.70.

5-Acetylaminoisoquinoline-7,8-quinone Hydrochloride, IX (or 8,6,5).—A solution of 0.29 g. of VIII in 4 cc. of water and 0.5 cc. of concentrated hydrochloric acid was treated at 10° with 2 cc. of 20% ferric chloride solution added in one portion. The solution became red and fine, yellow needles soon separated. The product was washed free of dark mother liquor with concentrated acid, dissolved in 10 cc. of water, and 1 cc. of concentrated acid was added to the clarified solution. Golden yellow needles soon separated in 51% yield. Without isolating any of the intermediates, the yield from diacetyl aminohydroxyisoquinoline was 38%.

Anal. Calcd. for $C_{11}H_8O_3N_2 \cdot HCl$: Cl, 14.03. Found: 13.93, 13.94.

Summary

Isoquinoline-5,8-hydroquinone has been prepared by three methods, and the oxido–reduction systems from this reductant and from the known quinoline-5,8-hydroquinone have been studied potentiometrically. An analysis is presented of the results obtained in this series of investigations of the degree of aromaticity of various heterocyclic rings.

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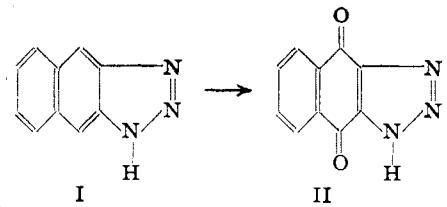
A Comparison of Heterocyclic Systems with Benzene. VII. Isologs of Anthraquinone Containing One and Two Triazole Rings

BY LOUIS F. FIESER AND ELMORE L. MARTIN

When this work was undertaken no unsubstituted quinones of the type indicated in the title were known, but in a paper published in March of this year Fries, Walter and Schilling[1] described the preparation of *lin*-naphthotriazole-8,9-quinone (II) by the oxidation of *lin*-naphthotriazole (I) with chromic anhydride. We had at the time performed a similar experiment, but the succession of steps leading to II was so generally unsatisfactory that a better method was developed.



I II

Ullmann and Ettisch[2] worked out an excellent method of preparing 2,3-dichloro-1,4-naphthoquinone from α-naphthol and found that one of the two chlorine atoms is easily replaced by reaction with ammonia. The halogen atom of the amino compound (III) is resistant to attack by amines under comparable conditions, but Fries and Ochwat[3] found that the acetyl derivative IV reacts normally with aromatic amines to give arylamino derivatives. On treating the acetyl compound IV with dry ammonia in nitrobenzene solution, we found that the substance is converted

(1) Fries, Walter and Schilling, *Ann.*, **516**, 248 (1935).

(2) Ullmann and Ettisch, *Ber.*, **54**, 270 (1921).

(3) Fries and Ochwat, *ibid.*, **56**, 1295 (1923).