individual reaction against the reciprocal of the absolute temperature, and checked by the method of least squares.

DISCUSSION

The results as given in Table I show the following facts:

First, the rate constants for the 1,2-esters are somewhat slower than for the 1,3- and 1,4-isomers, thus probably indicating the importance of steric or electrical influences. This is also suggested by the fact that on a purely statistical basis the hydrolysis rates for the diesters should be twice that for the monoesters. This is not found. Actually, the *trans*-1,2-diester is hydrolyzed more rapidly than the *cis*-1,2-diester, while the *trans*-1,2-monoester is hydrolyzed less rapidly than the *cis*-1,2-monoester. This is in line with the rates of acid-catalyzed esterification of the cyclohexanedicarboxylic acids, since the *trans*-1,2-diacid is esterified less rapidly than the *cis*-1,2-diacid, while the *trans*-1,2-monoester is esterified to the diester more rapidly than is the *cis*-1,2-monoester. It should be noted that esterification of a cyclohexanedicarboxylic acid is the reverse of hydrolysis of a monomethyl ester of the acid.

Second, the rate constants for hydrolysis of the dimethyl esters of the 1,3- and 1,4-isomers are approximately twice as great as the rate constants for hydrolysis of the corresponding monomethyl esters. This is predicted on a purely statistical basis, and indicates no change in steric or electrical influences for hydrolysis of the first and second ester groups.

Third, one notes that for the 1,3- and 1,4-isomers, the corresponding *cis*-1,3 and *trans*-1,4 forms behave quite similarly to each other, while the *trans*-1,3 and *cis*-1,4 forms also resemble each other in reaction characteristics. This same result was found for other reactions of cyclohexanedicarboxylic acids and their esters,[2,4,6] and is readily explainable on the basis of the conformations of these compounds.

KNOXVILLE, TENN.

(6) H. A. Smith and P. P. Hunt, *J. Am. Chem. Soc.*, **81**, 590 (1959).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIV OF TENNESSEE]

The Influence of Chelation on the Stabil f Enediols. II.[1] 1,2-Di-2-quinolyl-1,2-ethenediol N Dioxide

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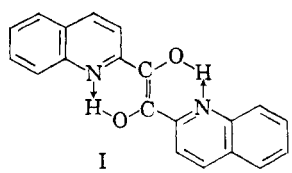
The attachment of an oxygen atom to the nitrogen atom in quinaldehyde does not prevent the formation of the corresponding enediol. At low concentrations of potassium cyanide it is formed as a red solid together with the isomeric quinaldoin. At higher concentrations of potassium cyanide the potassium salt of the enediol is formed either alone or with the quinaldoin. The enediol and quinaldoin are interconvertible and the potassium salt may be converted into the enediol or quinaldoin.

A *trans*-chelated, six- or seven-membered ring structure has been advanced for the enediol. In addition, an explanation has been proposed for the lack of color of its potassium salt.

It has been shown that quinaldehyde, in the benzoin condensation, forms a very stable enediol which has been assigned[3] the *trans*-chelated formula I. In this formula great importance has been



I

attached to the ability of the favorably located quinolyl nitrogen atoms to chelate. In the present investigation the reaction of potassium cyanide on quinaldehyde *N*-oxide has been studied to determine what effect, if any, the added oxygen atom would have on chelation and thus on enediol formation.

Quinaldehyde *N*-oxide was prepared by the selenium dioxide oxidation of quinaldine *N*-oxide. As is often the case in such oxidations, the results were not always reproducible[4] and led to yields from poor to moderate. The solvents used were either 95% ethanol or pyridine. Of the two, pyridine led to the more reproducible results. A portion of the difficulty in this oxidation results because the aldehyde first formed condenses with the starting material to produce the corresponding aldol and stilbazole, results similar to those obtained by Kaplan[5]

(1) Paper I of the series, C. A. Buehler, J. W. Addleburg, and D. M. Glenn, *J. Org. Chem.*, **20**, 1350 (1955).

(2) Present address: Monsanto Chemical Company, Nitro, W. Va.

(3) C. A. Buehler and J. O. Harris, *J. Am. Chem. Soc.*, **72**, 5015 (1950).

(4) H. S. Mosher, *Heterocyclic Compounds*, Vol. 1, Robert C. Elderfield, ed., Wiley, New York, 1950, p. 587.

TABLE I

EFFECT OF AMOUNTS OF POTASSIUM CYANIDE AND SOLVENTS ON THE PRODUCTS FORMED IN THE BENZOIN CONDENSATION OF QUINALDEHYDE *N*-OXIDE

Trial No.	Weight of Aldehyde, G.	Weight of KCN, G.	Vol. of H_2O as Solvent for KCN, Ml.	Vol. of Pyridine,[a] Ml.	Additional Vol. of H_2O Added, Ml.	Amounts of Products Recovered, %		
						Enediol	Quinaldoin	K Salt
1[b]	1.0	0.05	5	15	5	8	30	0
2[b]	1.0	0.08	2	10	0	0	43	24
3	1.0	0.15	5	15	5	0	0	43
4	1.0	0.20	5	15	5	0	0	30

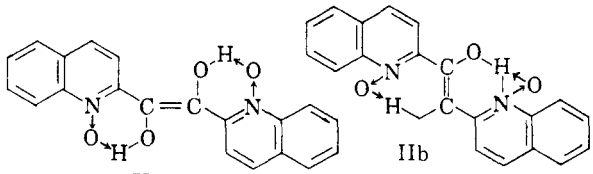
[a] All pyridine used in benzoin condensations was Merck's reagent grade dried over anhydrous barium oxide and redistilled; b.p. 112–114°. [b] Details of Trials 1 (5 × amounts) and 2 are given in the Experimental.

in the oxidation of lepidine. Attempts to produce the aldehyde through the Sommelet reaction or with the use of chromylchloride or chromic anhydride and acetic anhydride were unsuccessful.

The first experiments on the benzoin condensation of quinaldehyde *N*-oxide differed from those previously performed[1,3,6] in that both the enediol and quinaldoin were produced. Later experiments led to the potassium salt of the enediol and the quinaldoin or the potassium salt alone. A study of the experimental conditions, as shown in Table I, was made to determine the variations necessary to produce these results. In these experiments the mixture was stirred for thirty minutes at room temperature and fortunately any enediol which formed separated readily while it was necessary to recover the quinaldoin and potassium salt of the enediol from solution. Thus, the enediol is formed only at the lower concentrations and the potassium salt alone only at the higher concentrations of potassium cyanide. To obtain both the quinaldoin and potassium salt is possible only at a very constricted concentration range.

1,2-Di-2-quinolyl-1,2-ethenediol *N,N'*-dioxide is a red crystalline solid, m.p. 193–194° dec., stable in the dry state, which responds to the usual chemical tests for the enediol grouping. It differs from the enediols in which the amine oxide oxygen is missing in that alcoholic hydrogen chloride converts it into the quinaldoin. It may also be obtained from the potassium salt by treatment with benzoyl chloride. No diacetate or dibenzoate could be obtained from the enediol, perhaps because of the crowding which exists at the normally active hydroxyl groups. The infrared spectrum of a potassium bromide disk of the enediol gave no band indicating free hydroxyl groups.

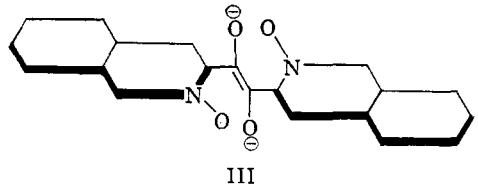
It is not possible at present to assign a definite formula to the enediol. In all probability it possesses the *trans*-configuration, but as such it may be written either with six-membered (IIa) or seven-membered (IIb) chelate rings. The model does not permit a distinction to be made between these two possibilities.



IIa IIb

Quinaldoin *N,N'*-dioxide, an almost white compound, m.p. 158–159°, is the principal product of the reaction except when the higher concentrations of potassium cyanide are employed. Its functional groups do not respond readily to the expected chemical reactions although an osazone identical with that obtained from the quinaldil was prepared. In the presence of pyridine and water it may be converted into the isomeric enediol. The infrared spectrum of a Nujol mull of the quinaldoin shows a medium band at 1690 cm.$^{-1}$, possibly due to the carbonyl group, but the band characteristic of the free hydroxyl group is missing. Thus chelation also appears to be present in the quinaldoin.

The potassium salt is closely related to the enediol and quinaldoin, as it may be produced from either by the addition of potassium cyanide and it may be converted into the quinaldoin by treatment with hydrochloric acid or into the enediol by treatment with benzoyl chloride. It is soluble in water, contains two potassium atoms (ions) per mole, and must be more closely related to the enediol than to the quinaldoin. In contrast to the enediol, it is a white compound. This lack of color is in all probability due to the destruction of coplanarity or near coplanarity of the two ring systems because the negative charges set up on the four oxygen atoms would tend to cause rotation in such a way that the oxygen atoms as shown in III would be as far removed from each other as possible.



III

In III the two central oxygen atoms are probably perpendicular to the two parallel planes containing

(5) H. Kaplan, *J. Am. Chem. Soc.*, **63**, 2654 (1941).
(6) C. A. Buehler and S. P. Edwards, *J. Am. Chem. Soc.*, **74**, 977 (1952).

the two amine oxide ring systems. When chelation occurs between the central and outer oxygen atoms by the intervention of hydrogen atoms, rotation occurs about the single bonds joining the enediol group to the rings and coplanarity is more nearly approached. This rotation would produce a six-membered chelate ring in one direction and a seven-membered one in the opposite direction. As Klevens and Platt[7] have shown, the ion would therefore be expected to be less colored than either chelate since the conjugation existing between the two ring systems is interfered with to an increasing extent as the double bond of the enediol group is forced out of the plane of the two ring systems.

The quinaldoin forms other metallic derivatives with transition elements such as copper, cobalt, etc. These appear to be of the chelate type as they are extremely insoluble in water. The copper chelate possesses the green color associated with copper salts apparently because the larger copper atom forces the two ring systems so far out of a common plane that the contribution of the combined ring systems to color is negligible.

EXPERIMENTAL[8]

Quinaldine N-oxide. The method employed was essentially that of Ochiai.[9] From 60 g. of freshly distilled quinaldine, 150 ml. of glacial acetic acid and 85 ml. of 30% hydrogen peroxide there was obtained 37.8 g. of white quinaldine *N*-oxide hydrate, m.p. 68–69°. Crystallization from a minimum amount of benzene gave a product, m.p. 77–78° (Heller and Sourlis[10] give 77–78°).

Quinaldehyde N-oxide (solvent, pyridine). A mixture of 30 g. of quinaldine *N*-oxide hydrate, 18 g. of freshly sublimed selenium dioxide, and 122 ml. of pyridine was refluxed for 4 hr. The selenium was removed by filtration and the filtrate was concentrated *in vacuo* until almost all the pyridine was removed, after which 80 ml. of water was added. The aqueous solution was extracted with five 80-ml. portions of hot benzene and the combined benzene extracts were concentrated and upon cooling dark green crystals were obtained. Further purification was achieved by extraction twice with ether to give 15.8 g. of green crystals, m.p. 125–126°.

Anal. Calcd. for $C_{10}H_7NO_2$: C, 69.36; H, 4.07. Found: C, 69.21; H, 4.07.

The *phenylhydrazone* melted at 246–247°.

Anal. Calcd. for $C_{16}H_{13}N_3O$: C, 72.98; H, 4.98. Found: C, 72.87; H, 5.01.

1,2-Di-2-quinolylethene N,N'-dioxide. In the preparation of quinaldehyde *N*-oxide from 3 g. of freshly sublimed selenium dioxide, 5 g. of quinaldine *N*-oxide hydrate, and 50 ml. of 95% ethanol, a dark gummy material was obtained on removing the solvent. The aldehyde was removed by extraction with ether and the residue was taken up in dimethylformamide from which the yellow ethene, 0.9 g., was recovered, m.p. 260–261°.

Anal. Calcd. for $C_{20}H_{14}N_2O_2$: C, 76.42; H, 4.49. Found: C, 76.52; H, 4.61.

For identification the ethene was synthesized from quinaldehyde *N*-oxide, quinaldine *N*-oxide, and acetic anhydride. This product also melted at 260–261° and gave no depression in melting point when mixed with the ethene obtained in the oxidation of quinaldine *N*-oxide.

1,2-Di-2-quinolylhydroxyethane N,N'-dioxide. The filtrate from the preparation of the ethene was evaporated to about one-half volume and upon cooling, a pale yellow solid formed. Purification by crystallization from methanol gave 1.3 g. of white aldol, m.p. 217–218°, which turns yellow on exposure to light.

Anal. Calcd. for $C_{20}H_{16}N_2O_3$: C, 72.28; H, 4.85. Found: C, 72.05; H, 4.92.

The aldol was identical with that obtained from the synthetic ethene, described immediately above, by refluxing with concentrated sulfuric acid and water.

1,2-Di-2-quinolyl-1,2-ethenediol N,N'-dioxide. To a mixture of 5.0 g. of quinaldehyde *N*-oxide in 75 ml. of dry pyridine and 25 ml. of water was added, with stirring, 0.25 g. of potassium cyanide in 25 ml. of water. Almost immediately a reddish brown, crystalline precipitate began to form and the solution was stirred at room temperature for 30 min. The red solid, removed by filtration, was washed with 30-ml. portions of water, methanol, and ether in succession. One crystallization from pyridine in an atmosphere of nitrogen gave 0.45 g. (9%) of the brick red enediol, m.p. 193–194° dec. The compound gives a positive test with Tollens' reagent in the cold and decolorizes sodium 2,6-dichlorobenzeneoneindophenol.

Anal Calcd. for $C_{20}H_{14}N_2O_4$: C, 69.36; H, 4.07. Found: C, 69.41; H, 3.98.

Quinaldil N,N'-dioxide. A stream of air was bubbled slowly through a solution of 0.05 g. of the enediol in 20 ml. of pyridine with warming on the steam bath. After 8 hr. the solution turned to a bright yellow color and evaporation to about one-half volume and cooling gave 0.04 g. (80%) of yellow crystals of the quinaldil. Two crystallizations from pyridine produced a m.p. of 258–259°.

Anal. Calcd. for $C_{20}H_{12}N_2O_4$: C, 69.76; H, 3.51. Found: C, 69.59; H, 3.66.

The *p-nitrophenylosazone* was prepared by the usual procedure employed for *p*-nitrophenylhydrazones. The red solid melted at 275–276°.

Anal. Calcd. for $C_{32}H_{22}N_8O_6$: C, 62.54; H, 3.61. Found: C, 62.45; H, 3.76.

Quinaldoin N,N'-dioxide. The filtrate from the separation of the enediol was added to the combined washings and the mixture was evaporated slowly to a volume of about 35 ml. and was then acidified with 25 ml. of 10% hydrochloric acid solution. Evaporation to about 25 ml. and cooling in an ice bath gave greenish brown crystals which were filtered off and dissolved in 600 ml. of boiling benzene. Some insoluble, sticky residue was discarded and the benzene solution, after treatment with Norit A, was evaporated to a volume of 100 ml. Cooling produced a greenish white solid, which on one further crystallization from benzene gave 1.9 g. (38%) of the quinaldoin, m.p. 158–159°.

Anal. Calcd. for $C_{20}H_{14}N_2O_4$: C, 69.36; H, 4.08. Found: C, 69.31; H, 4.31.

The *p*-nitrophenylosazone was prepared by the usual procedure employed for *p*-nitrophenylhydrazones. The red solid melted at 275–276° and gave no depression in melting point when mixed with the osazone obtained from the quinaldil.

Interconversion of quinaldoin N,N'-dioxide and 1,2-di-2-quinolyl-1,2-ethenediol N,N'-dioxide. To 10 ml. of absolute methanol saturated with dry hydrogen chloride was added 0.5 g. of the enediol and the mixture was refluxed under an atmosphere of nitrogen for 45 min. Pouring into 50 ml. of water and heating on a steam bath produced the coagulation of a solid which proved to be starting material. The filtrate upon evaporation to about 15 ml. and cooling gave a white solid, which, when crystallized from benzene, weighed 0.1 g.

(7) H. B. Klevens and J. R. Platt, *J. Am. Chem. Soc.*, 71, 1714 (1949).

(8) All melting points are uncorrected and were determined either on an aluminum block or with a Mel-temp apparatus.

(9) E. Ochiai, *J. Org. Chem.*, 18, 534 (1953).

(10) G. Heller and A. Sourlis, *Ber.*, 41, 2696 (1908).

(20%), m.p. 158–159°. When mixed with the quinaldoin *N,N′*-dioxide obtained in the benzoin condensation, no depression in melting point was obtained.

A mixture of 0.1 g. of the quinaldoin, 20 ml. of pyridine and 5 ml. of water was allowed to stand for 10 days under an atmosphere of nitrogen. At the end of the period the dark solid which had formed was separated and washed with methanol and ether. The dry product, 0.015 g. (15%), when crystallized from pyridine under an atmosphere of nitrogen gave red needles of the enediol, m.p. 192–193° dec.

Potassium salt of 1,2-di-2-quinolyl-1,2-ethenediol N,N′-dioxide. To a mixture of 1.0 g. of quinaldehyde *N*-oxide in 10 ml. of pyridine was added, with stirring, 0.08 g. of potassium cyanide in 2 ml. of water. A white, glistening precipitate, which formed immediately, went into solution after the mixture was stirred for 30 min. at room temperature and refluxed for an equal length of time. Cooling in an ice bath gave a white solid which was crystallized twice from 95% ethanol by adding absolute ether and cooling to give 0.3 g. (24%) of the potassium salt, decomposing at 338–341°. Repeated crystallization from a solution in dimethylformamide by the addition of absolute ether and then from solution in absolute ethanol by the addition of absolute ether failed to give an analytical sample although the percentage of potassium, determined as ash, agreed reasonably well with the theory.

Quinaldoin N,N′-dioxide. Evaporation of the filtrate, from which the potassium salt was separated, to about 4 ml. and cooling gave brown crystals which, when crystallized from benzene using Norit A, yielded 0.43 g. (43%) of almost white needles, m.p. 157–158°.

Conversion of potassium salt to quinaldoin N,N′-dioxide. The salt, 2.0 g., in aqueous solution was acidified with hydrochloric acid and the mixture was extracted with ether in a continuous liquid-liquid extraction apparatus. The almost white solid, recovered from the ether and crystallized from benzene, weighed 1.8 g. (100%), m.p. 158–159°. There was no depression in melting point when mixed with an authentic sample.

Conversion of potassium salt to enediol. A mixture of 0.6 g. of the salt and 1.4 g. of benzoyl chloride (Eastman, white label) was boiled for 5 min. and, upon cooling, 80 ml. of ether and then 40 ml. of water were added. The red solid, which separated, was removed by filtration, washed with water, and dried. It weighed 0.37 g. (75%), melted at 190–191° dec. and gave the expected color tests. No depression in melting point was obtained when mixed with an authentic sample.

Copper derivative of quinaldoin N,N′-dioxide. The copper derivative was obtained in attempting to oxidize the quinaldoin to the quinaldil as follows: To a solution of 1 g. of copper sulfate in 50 ml. of water and 50 ml. of pyridine was added 1 g. of quinaldoin *N,N′*-dioxide. Heating overnight on a steam bath with air passing through the mixture gave 1.1 g. of a green solid, m.p. 306–307°, insoluble in water and most organic solvents. Final purification was accomplished by crystallization four times from a solution in dimethylformamide by the addition of absolute ether. The presence of water of crystallization in the chelate was indicated by strong infrared absorption at 3300 cm.$^{-1}$

Anal. Calcd. for $C_{40}H_{24}N_4O_8Cu_2.2H_2O$: C, 56.40; H, 3.31; N, 6.58; Cu, 14.9. Found: C, 56.16, 56.26; H, 3.89, 3.48; N, 6.57; Cu (ash) 15.2, 15.5.

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KNOXVILLE, TENN.

[CONTRIBUTION FROM THE WARNER-LAMBERT RESEARCH INSTITUTE]

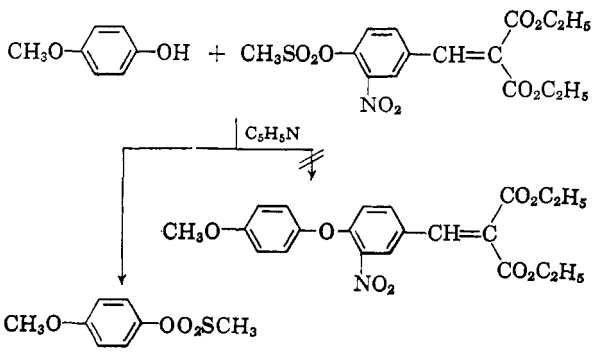
β-[3-Iodo-4-(4′-hydroxyphenoxy)phenyl]propionic Acid and Iodinated Derivatives[1]

ROBERT I. MELTZER, SHELDON FARBER, EDWARD MERRILL, AND AL CARO

Received July 18, 1960

A number of alternate preparations of β-[3-iodo-4-(4′-hydroxyphenoxy)phenyl]propionic acid are presented. The iodination of this compound and the resulting products are described.

In pursuance of an interest in analogs of thyroxine, β-[3-iodo-4-(3′-iodo-4′-hydroxyphenoxy)-phenyl]propionic acid and its 3,3′,5′-triiodo analog were required. The method of synthesis employed in the preparation of 3,5-diiodo analogs[2] was not applicable because the syntheses depend on the activation of a methanesulfonyloxy group by two nitro groups. It was hoped that the methanesulfonyloxy group in the position *para* to a bis(carbethoxy)vinyl group might prove to be sufficiently activated by even one *ortho* nitro group. This proved not to be the case. Transesterification took place to the exclusion of etherification.[3]



(1) Presented before the Division of Medicinal Chemistry at the 132nd meeting of the American Chemical Society, New York, N. Y., September 1957.

(2) R. I. Meltzer, D. L. Lustgarten, and A. Fischman, *J. Org. Chem.*, 22, 1577 (1957) and references therein.