KN-64-9 QUINOLONOQUINOLONE By: E. E. Jaffe 1/62 - 10/62

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PIGMENT COLOR RESEARCH REPORT

QUINOLONOQUINOLONE

Period Covered January to October, 1962

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PIGMENTS COLOR RESEARCH REPORT

SUBJECT: QUINOLONOQUINOLONE

PERIOD COVERED: January to October, 1962

SUBMITTED BY: E. E. JAFFE DATE SUBMITTED: 4/13/64

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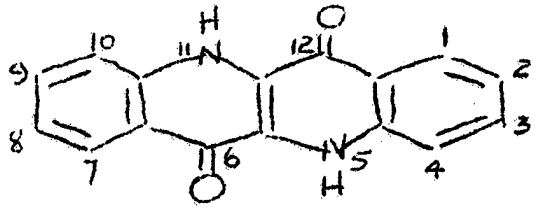
QUINOLONOQUINOLONE

I. NOMENCLATURE

The trivial name of quinolonoquinolone (QQ) was assigned to structure I for the sake of convenience and simplicity. In the chemical literature, the compound is referred to as epindolidione[1]. According to modern nomenclature[2], it should be known as dibenzo (b,g) (1.5) naphthyridine-6,12 (5,11 H) dione.



I

II. OBJECT OF INVESTIGATION

The purpose of this investigation was to find a new synthesis for QQ which would permit the preparation of this compound in good yield and reasonable purity.

III. CONCLUSION

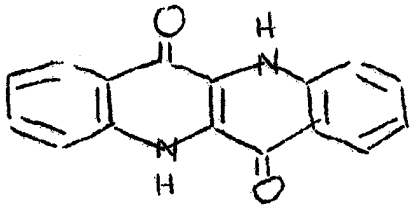
A new synthesis for the preparation of QQ which has the potential for possible commercial scale-up has been developed.

IV. PATENT STATUS

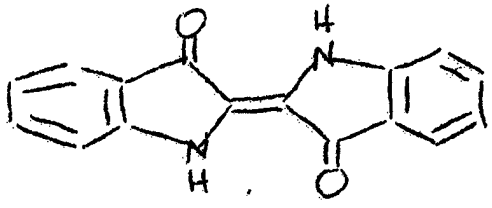
Based on the work described in this report, a patent proposal (CP-37) has been filed with the Legal Department.

V. HISTORICAL BACKGROUND

In 1934, Ainley and Robinson were the first investigators to report the synthesis of 2,8-dimethylquinolonoquinolone, the basic structure of which they called epindolidione. Since QQ is an isomer of indigo, these workers were interested in determining the relationship between their chemical and their physical properties.



QQ



INDIGO

[1] D. A. Ainley and R. Robinson, J. Chem. Soc. 1934, 1508

[2] A. M. Paterson et al, Ring Index, 2nd Edition, No. 5062

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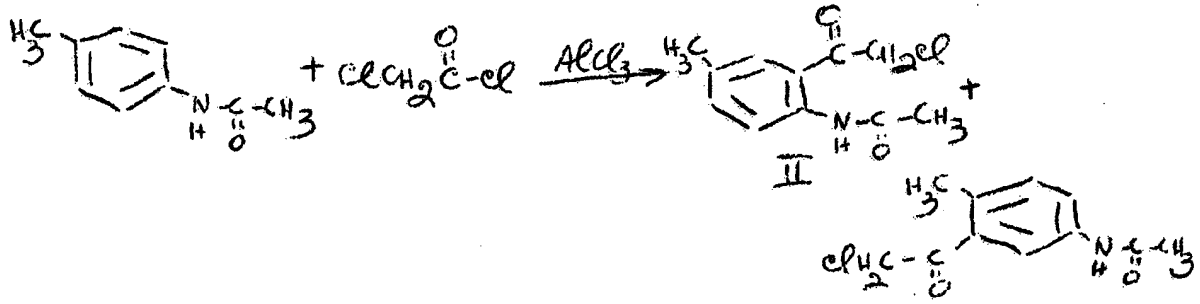
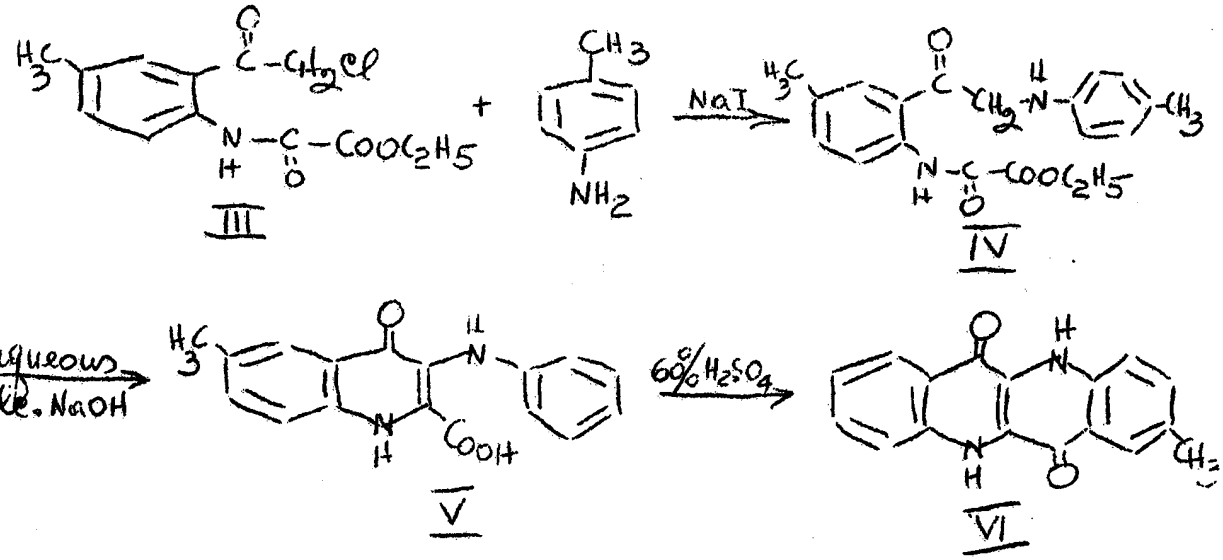
Although many methods for the synthesis of indigo were well known, the synthesis of its isomer QQ posed considerable difficulties. After exploring several possibilities without apparent success, the above investigators finally succeeded in synthesizing the dimethyl derivative of QQ. The synthesis of 2,8-dimethylQQ rather than the parent compound was undertaken because the envisioned starting material for this particular synthetic approach was known in the literature as a methyl derivative. The compound in question was ω-chloro-2-amino-5-methylacetophenone which could be prepared as the minor component of a mixture of isomers according to Kunckell[1] as follows:



II

Hydrolysis of II with aqueous HCl gave the amine which on ethoxalylation yielded ω-chloro-2-ethoxalylamino-5-methylacetophenone, III. Reaction of III with p-toluidine yielded IV which was cyclized and hydrolyzed to 3-p-toluidino-2-carboxy-6-methyl-4-quinolone, V, which was in turn cyclized to 2,8-dimethyl QQ, VI. The product was purified by repeated sublimations. The overall yield based on ω-chloro-2-amino-5-methyl-acetophenone was 20.3%.



III IV V VI

[1]Kunckell, F., Ber. 33, 2644 (1900)

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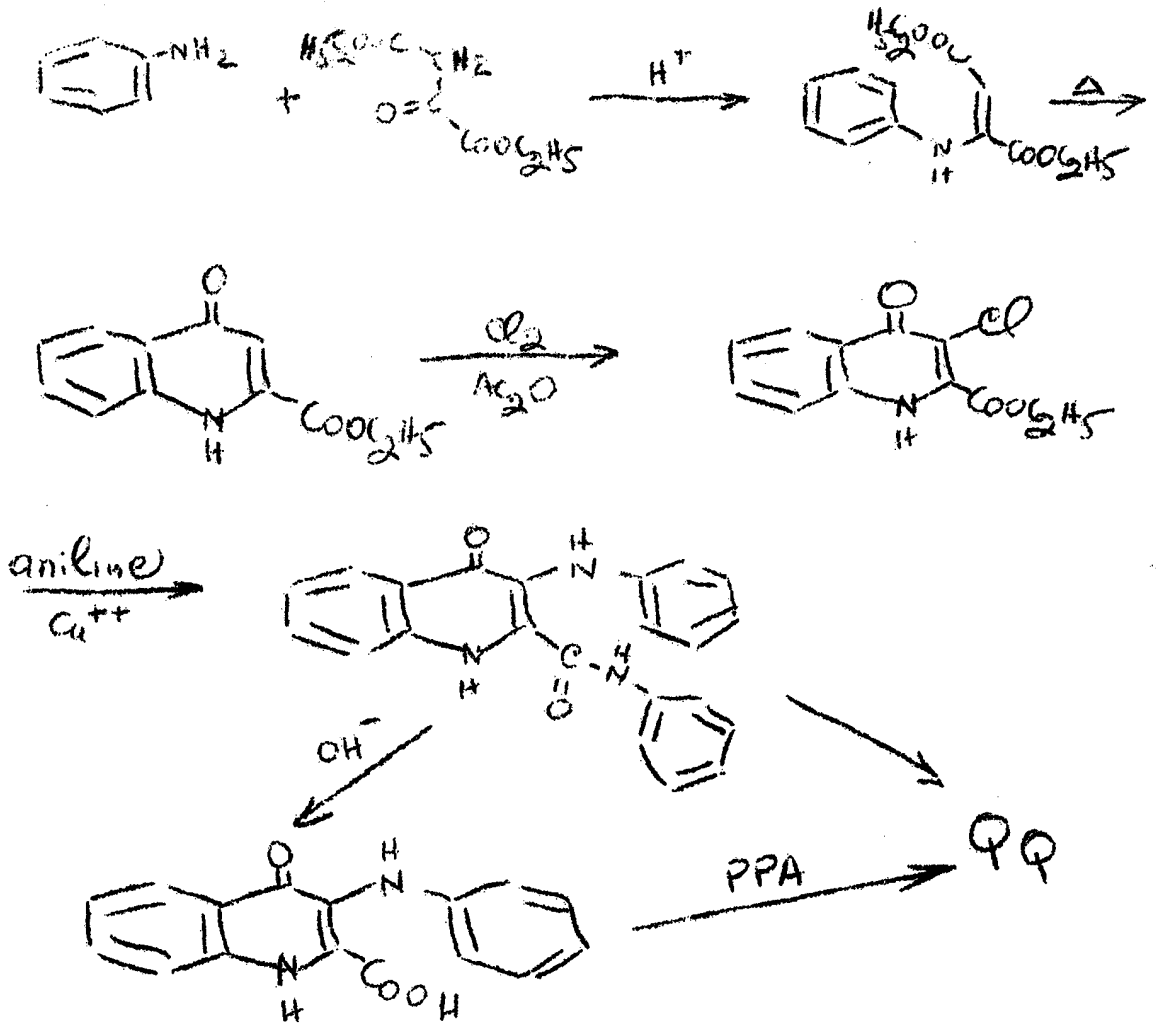
In 1948, a Swiss team of investigators succeeded in synthesizing the parent compound QQ by a slight modification of the Ainley-Robinson approach.

deDiesbach et al[1] introduced the required ω-halogen in o-ethoxyalylaminoacetophenone by photochemical bromination. Following the displacement of bromine with aniline, the other required reactions were carried out according to known methods to yield unsubstituted QQ.

More recently in the Newark Pigments Laboratory, G.R.Aldridge[2] synthesized QQ by the following sequence of reactions.



[1]H.deDiesbach, A.Schürch and G.Calvin, Helv.Chim.Acta, **31**, 716 (1949)

[2]Report KN-63-2

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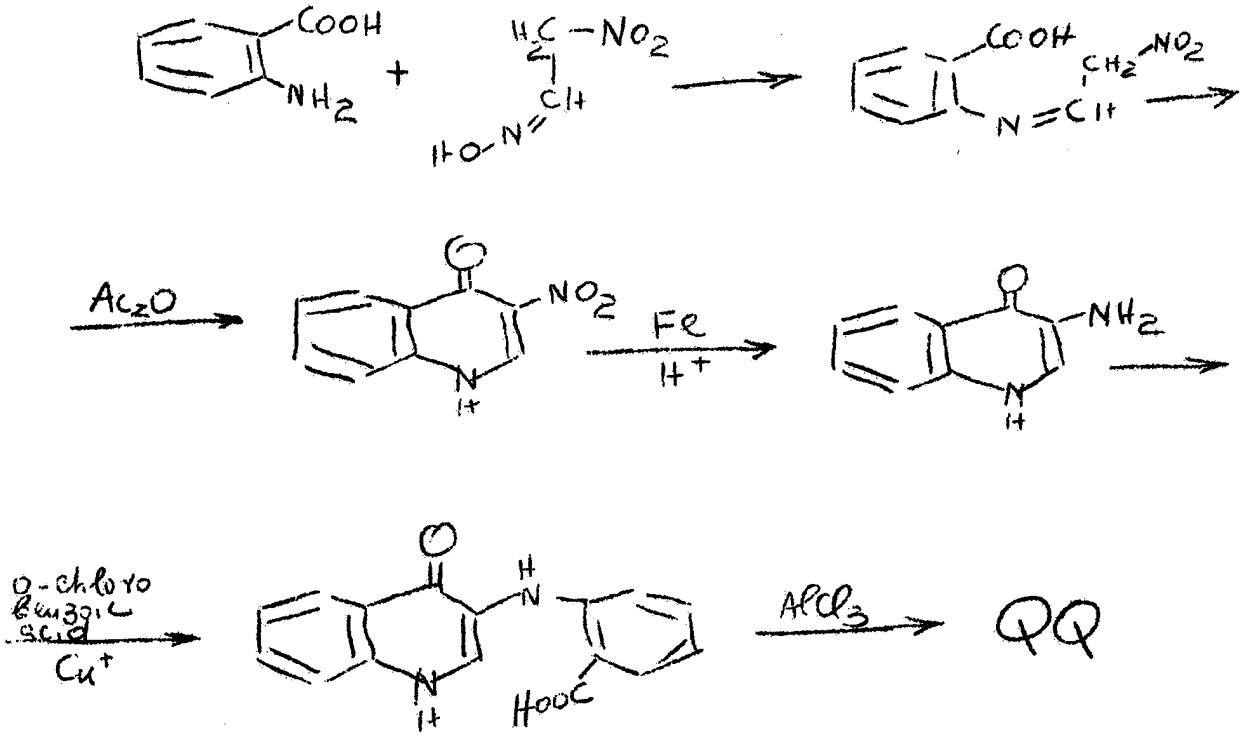
This synthesis has also given a low overall yield of QQ which required extensive purification to achieve op'mum pigment properties. In addition, the process required the e of several organic solvents.

Still another synthesis of QQ described by H. Patrick[1] gave a product of low purity and low yield according to e following sequence of reactions.



VI. DISCUSSION

The synthesis of QQ which was developed in the present investigation delivers a product of high purity and good yield. The individual reactions are summarized below.

[1]Report KN-62-18.

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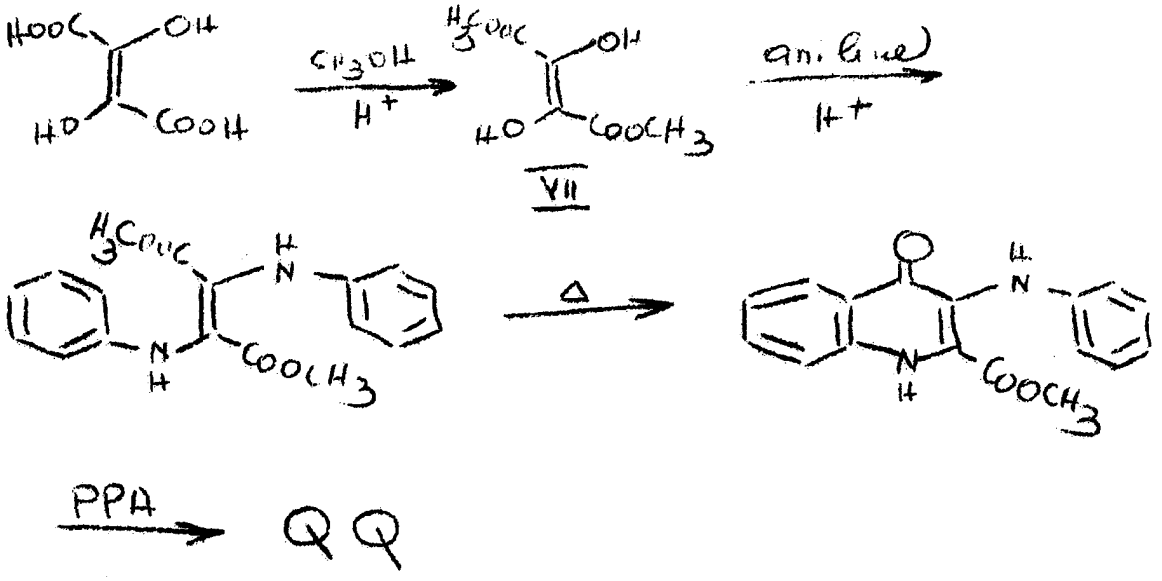
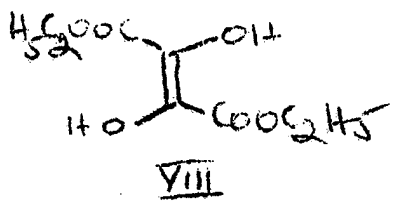


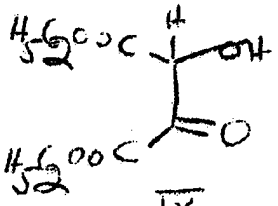
It has been demonstrated that starting with dimethyl dihydroxyfumarate (VII), the synthesis can be integrated into a potentially useful commercial process.

1. Esterification of Dihydroxyfumaric Acid

Esterification of dihydroxyfumaric acid is a well-known reaction[1,2]. Depending on the alcohol used in the esterification, a single compound or a mixture of isomers may be obtained. When methanol was used, a yield of 45.1% of the dimethyl ester (VII) was reported[1]. On the other hand, the use of ethanol[2] gave a mixture of diethyl dihydroxyfumarate VIII, m.p. 61-62°C., and its isomer diethyl hydroxyoxalacetate IX, m.p. 128-133°C.



VIII



IX

From a practical point of view, the dimethyl ester of dihydroxyfumaric acid is more desirable since methanol is less expensive and the esterification reaction gives rise to a single compound. However, the use of other esters is not objectionable since a mixture of isomers, as will be shown later, should not affect the final outcome of the synthesis.

[1]E.F.Hartree, J.Am.Chem.Soc., 75, 6244 (1953)
[2]S.Goodwin and B.Witkop, J.Am.Chem.Soc., 76, 5599 (1954)

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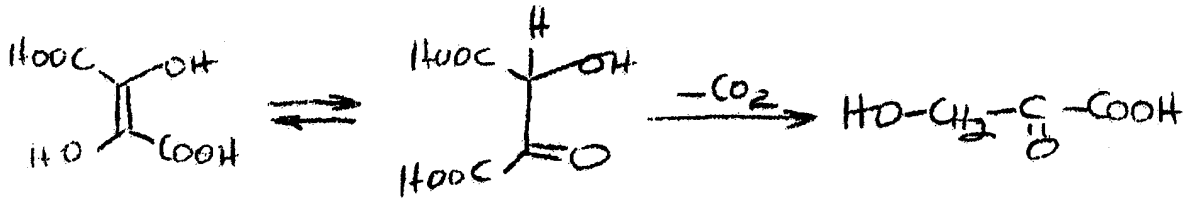
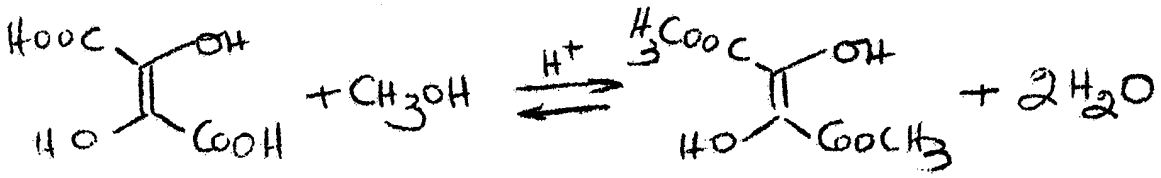
Using infrared spectroscopy, Goodwin and Witkop[1] have shown that dihydroxyfumaric acid exists in the form suggested by its name and not in its isomeric or geometrically isomeric form suggested by others. In addition, it was shown that the dimethyl ester is derived from the acid without undergoing any isomeric changes.

Dihydroxyfumaric acid is fairly unstable with respect to heat since any isomerization would give rise to a β-keto acid which can be expected to undergo decarboxylation easily.



As a consequence of this instability, it is impossible to resort to the distillation of product water in order to increase the yield in the esterification reaction.



To eliminate this difficulty, water was removed from the above equilibrium by introducing anhydrous magnesium sulfate into the reaction mixture which was kept at about 5°C. In this way, a yield as high as 93% of dimethyl dihydroxyfumarate was obtained. The acid catalyst in this reaction was gaseous hydrogen chloride which was bubbled into a solution of dihydroxyfumaric acid in methanol at about 5°C. The use of concentrated sulfuric acid as a catalyst was unsuccessful.

[1]S. Goodwin and B. Witkop, J. Am. Chem. Soc., 76, 5599 (1954)

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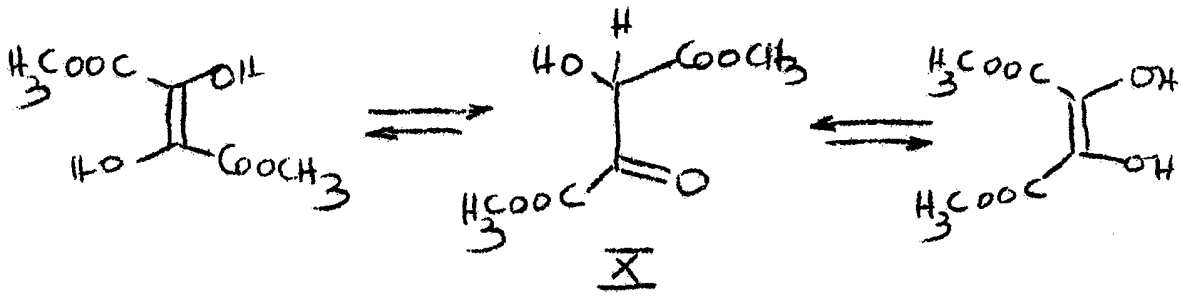
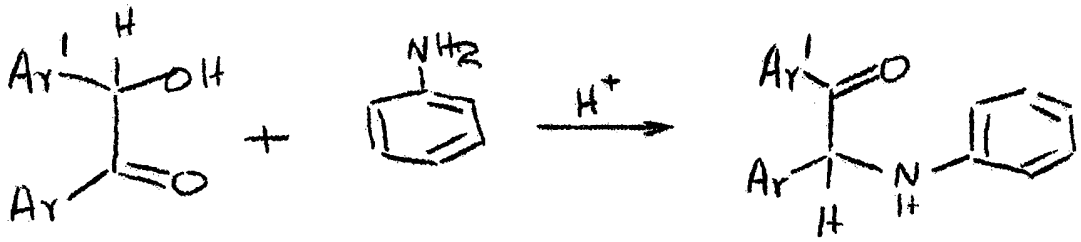
2. Preparation of Dimethyl Dianilinofumarate

Although dimethyl dihydroxyfumarate was shown to be structurally homogeneous in the solid state, it is quite conceivable that in solution a prototropic shift would give rise to an equilibrium between several chemical species:



X

Compounds analagous to X are known to undergo acid-catalyzed reactions with amines (see p. 3). One of the most extensive and best study in this field was carried out on the acid catalyzed condensation of benzoins with anilines[1].



This reaction was found to be first order with respect to each reactant and the catalyst. Electron-releasing groups para to the carbonyl group of the benzoin tended to decrease the rate, while in a group of eleven anilines the rate increased consistently as the electron releasing ability of the para or meta substituents increased. The ρ value obtained for the reaction with the substituted anilines was -2.204. The results of this study strongly favor the view of those who believe that aniline

[1]E.F.Pratt and M.J.Kamlet, J.Org.Chem. 28, 1366 (1963)

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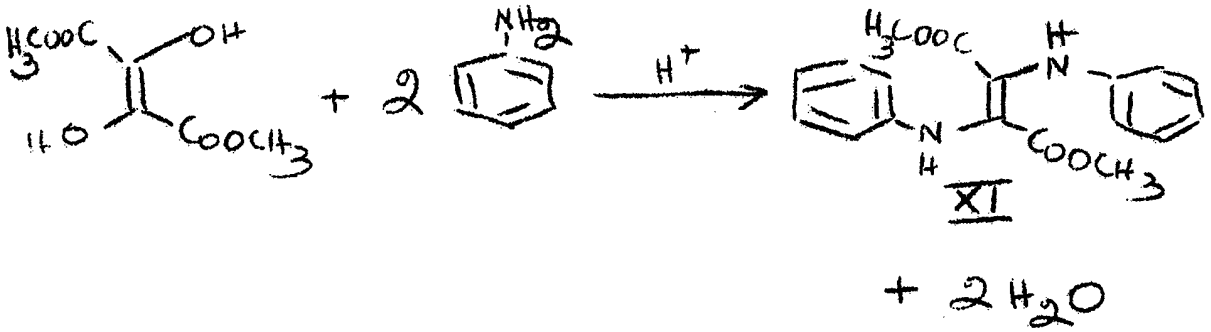
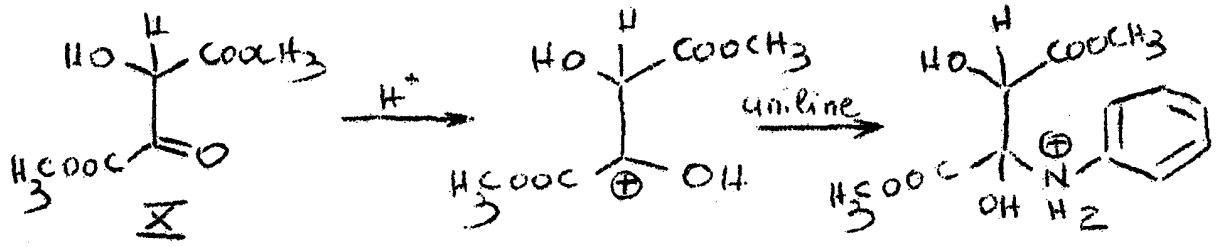
attacks the carbonyl group[1] rather than the hydroxymethylene group of the benzoin[2]. It is noteworthy that the results of the benzoin reaction closely parallel the factors which determine the rate of reaction of anilines with benzaldehyde ($\rho = -2.004$)[3]. This information was sufficient for the proposition of an acceptable mechanism for this reaction. The similarity of the above reaction with the one under consideration is readily apparent.



The reaction between dimethyl dihydroxyfumarate and aniline takes place in high yield (88%) in refluxing alcohol. The insoluble product, dimethyl dianilinofumarate (XI) precipitates out of solution as the reaction progresses.

It is assumed that in this reaction dimethyl dihydroxyfumarate is first isomerized to dimethyl hydroxyoxalacetate (X) which undergoes the acid-catalyzed reaction with aniline. The proposed mechanism for this reaction is analogous to the one proposed for the benzoin-aniline reaction and is outlined below.



[1] R. M. Cowper and T. S. Stevens, J. Chem. Soc. 347 (1940).
[2] A. Bischler and P. Fireman, Ber. 26, 1336 (1893); P. L. Julian, E. W. Meyer, A. Magnain and W. Cole, J. Am. Chem. Soc. 67, 1203 (1945)
[3] E. F. Pratt and M. J. Kamlet, J. Org. Chem. 26, 4209 (1961)

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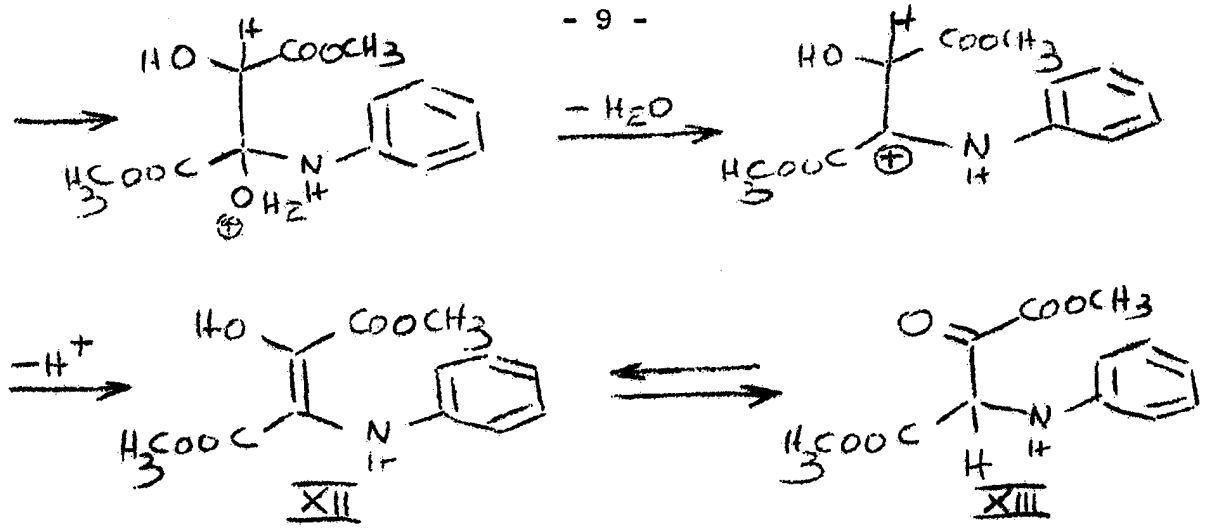
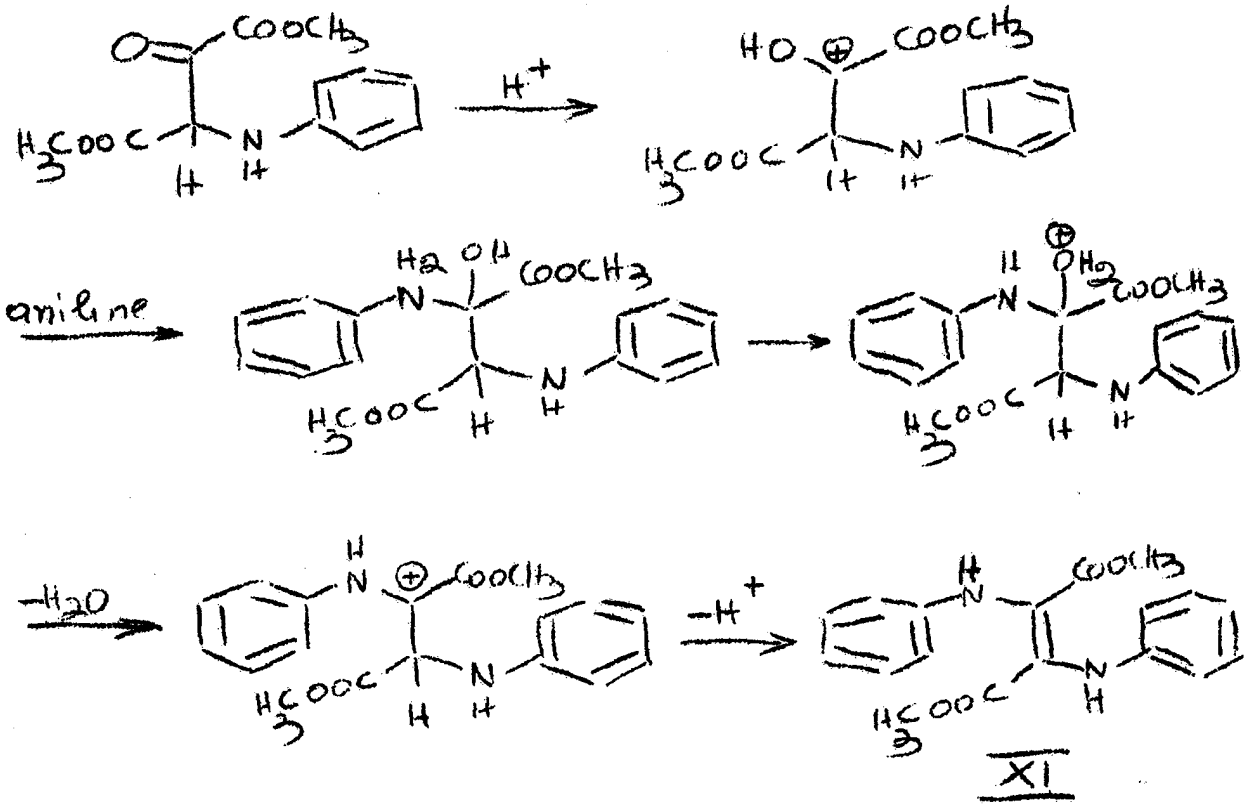


XII XIII

The formation of dialkyl anilinohydroxyfumarate (XII) follows well accepted mechanistic steps. A prototropic shift (enol-keto tautomerism) similar to the one assumed for the initial conversion of dialkyl dihydroxyfumarate to dialkyl hydroxyoxalacetate may afford an equilibrium concentration of dialkyl anilinooxalacetate (XIII). This intermediate can react with aniline by a similar mechanism to yield dialkyl dianilinofumarate (XI).



XI

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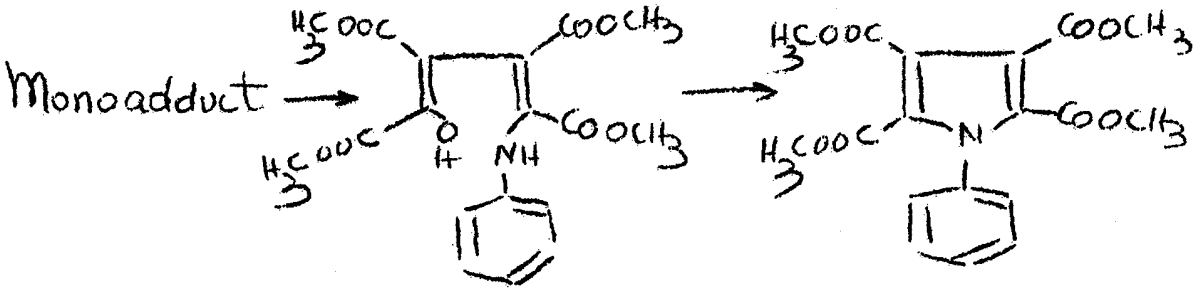
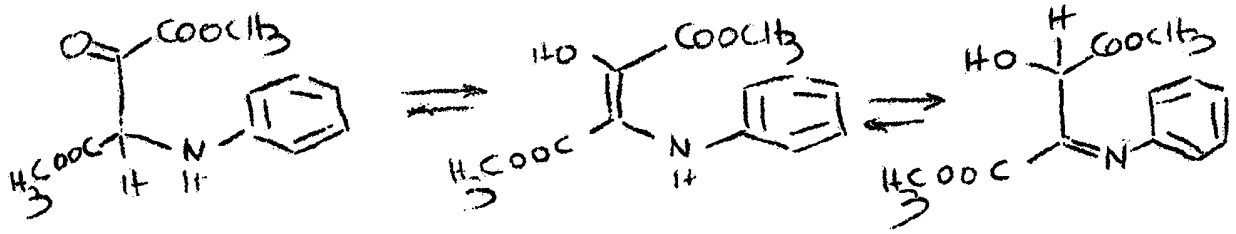
No attempt was made to stop the reaction at its first stage although this would appear to be an attainable goal. The latter assumption is based on the synthesis of XI, in low yield, from the monoadduct of N-phenylhydroxylamine and dimethyl acetylenedicarboxylate with aniline under acid-catalyzed conditions.

E. H. Huntress and co-workers[1] have shown that one mole of N-phenylhydroxylamine and one mole of dimethyl acetylenedicarboxylate form in ether at low temperatures an adduct which has a 1:1 mole ratio of the two reactants. The adduct is not stable for long periods, even at room temperature but decomposes to its original components. As a consequence of its behavior, the authors suggest that the adduct is a loose molecular complex of the two constituents in which no primary valence bonds have been formed.

The monoadduct can react with another mole of dimethyl acetylenedicarboxylate to form a new compound which can also be formed in good yield by simply refluxing the monoadduct in methanol. The resultant product has structure XIV based on its conversion to tetracarbomethoxy-N-phenylpyrrole.



Since the monoadduct reacts with aniline to form dimethyl dianilinofumarate, it is concluded that under the conditions of the reaction it is partially converted to a compound which is identical with one of the intermediates suggested in the mechanism of the reaction under consideration. The intermediate may be one of the three isomeric structures.



[1]E. H. Huntress, T. E. Leslie, and W. H. Hearon, J. Am. Chem. Soc. 78, 419 (1956)

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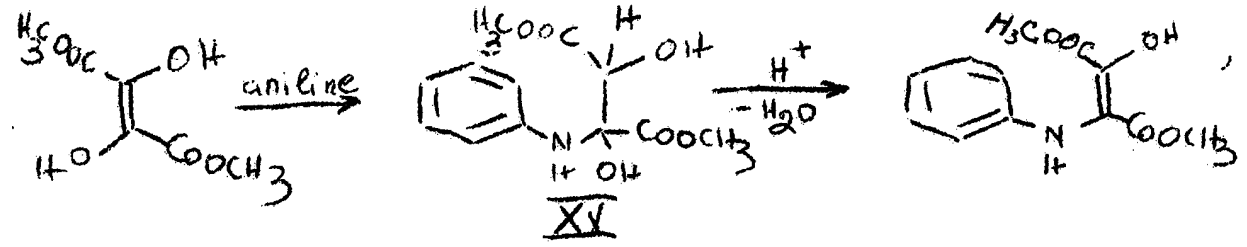
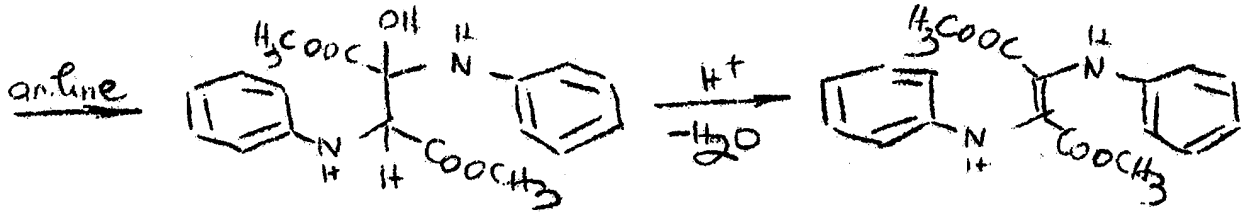
The participation of two of the above isomers is shown in the mechanistic scheme (p. 9); the involvement of the third cannot be rigidly excluded.

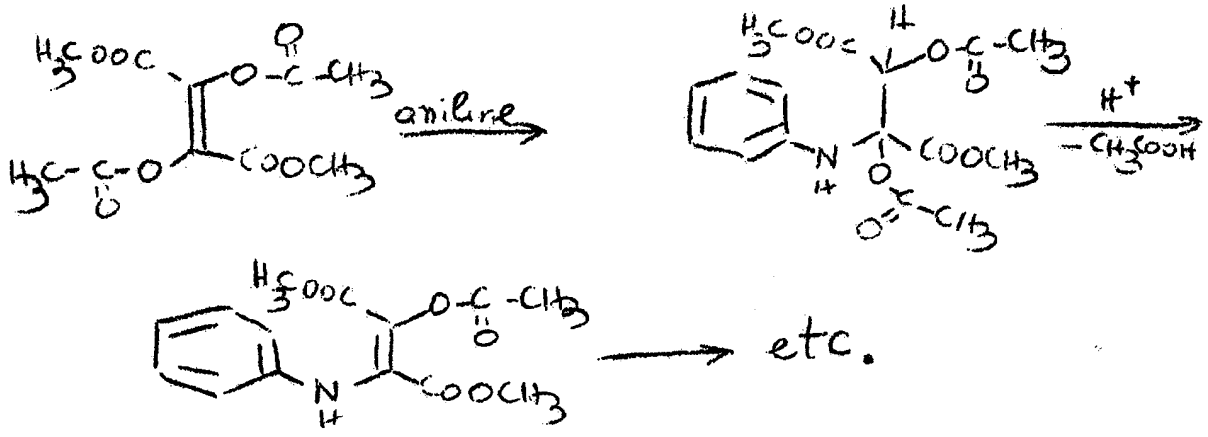
An alternate mechanism for the formation of dimethyl dianilinofumarate is outlined in the following sequence of reactions:



XV



This mechanism was considered and rejected on the basis of the following evidence. It is quite conceivable that aniline might add to the double bond of dimethyl dihydroxyfumarate to give the intermediate XV which would readily undergo an acid-catalyzed water elimination with the formation of dimethyl hydroxyanilinofumarate. A second addition of aniline followed by the elimination of water would give the desired product. This possibility could be tested by reacting the diacetyl derivative of dimethyldihydroxyfumarate with aniline. Were aniline to add to the double bond of the diacetoxy compound XVI to form dimethyl α,α^1-diacetoxy-α-anilino succinate (XVII), the latter compound would be expected to undergo acid catalyzed elimination of acetic acid. A second addition of aniline followed by the elimination of acetic acid would lead to dimethyl dianilinofumarate.



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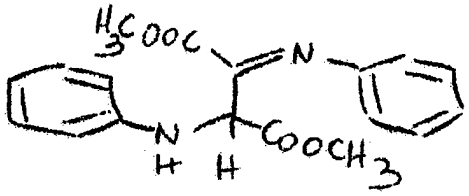
When dimethyl diacetoxyfumarate was reacted with aniline under the same conditions under which dimethyl dihydroxyfumarate gave rise to dimethyl dianilinofumarate, no such product was found and some unreacted material was recovered. Since the elimination of acetic acid would be expected to occur more readily than the elimination of water, the operation of this mechanism appears to be highly unlikely.

Although there is no unequivocal physical proof that the product of this reaction is dimethyl dianilinofumarate, it would appear quite unlikely that the compound is its geometric or other isomer.

The distinction from dimethyl dianilinomaleate could be made by dipole moment measurements since only the fumarate would be expected to have no dipole moment. The subsequent reaction in the quinolonoquinolone synthesis lends some support to the trans structure[1], and virtually eliminates any possibility of its existence in the other isomeric form.



In addition, Salmony and Simonis[2] report the preparation of dimethyl dianilinomaleate[3] from dimethyl dibromomaleate and aniline which is described as a yellow material having a melting point of 172°C. The intermediate in the quinolonoquinolone synthesis is a colorless compound which shows a melting point of 195-196°C. Furthermore, the fusion of theSalmony and Simonis product with potassium hydroxide is reported by these authors to have yielded a small amount of indigo. Under comparable conditions, the diester obtained in the present work failed to form any indigo.

[1] Assuming that heating in an inert, neutral solvent will not convert one geometric isomer into another.

[2] A. Salmony and H. Simonis, Ber. 38, 2580 (1905)

[3] One attempt to repeat this synthesis by G.R. Aldridge (KN Report 63-2) yielded α-anilino-N-phenylmaleimide.

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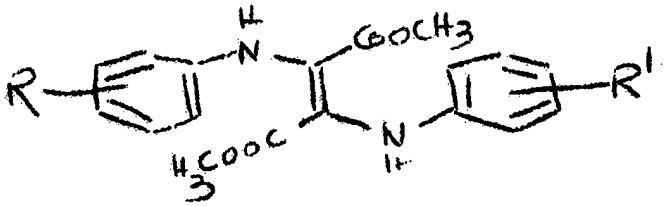
In view of the preparation of dimethyl dinailinofumarate, though in low yield, from the 1:1 N-phenylhydroxylamine-dimethyl acetylenedicarboxylate adduct and aniline it is certainly possible by this method, and possibly by the dimethyl dihydroxy-fumarate route to prepare non-symmetrical esters.



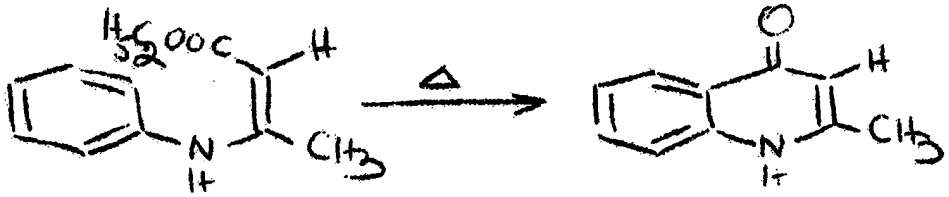
R = H R^1 = substituent

$R \neq R^1$ = substituents

This, in turn, would make possible the preparation of mono and unsymmetrically substituted quinolonoquinolones.

3. Preparation of 2-Carbomethoxy-3-anilino-4-quinolone

Cyclization of alkyl β-anilinoacrylates to 4-quinolones has been known since the discovery of this reaction by M. Conrad and L. Limpach[1] in 1887.



The Conrad-Limpach reaction as it is presently known, has been widely applied[2] in the synthesis of various 4-quinolones. Originally, this reaction entailed the pyrolysis of the requisite acrylate in the absence of a solvent at 240-250°C. More recently, mineral oil, diphenyl ether or Dowtherm A have been used widely as high boiling solvents for this cyclization reaction.

[1]M. Conrad and L. Limpach Ber., 20, 944 (1887); Ber. 21, 521 (1888)

[2]A. R. Surrey and H. F. Hammer, J. Am. Chem. Soc. 68, 113 (1946)
E. A Steck, L. L. Hallock and A. J. Holland, ibid., 68, 132, 380 (1946)
A. R. Surrey and R. A. Cutler, ibid., 68, 514 (1946)
B. Riegel et al, ibid., 68, 1264, 2685 (1946)

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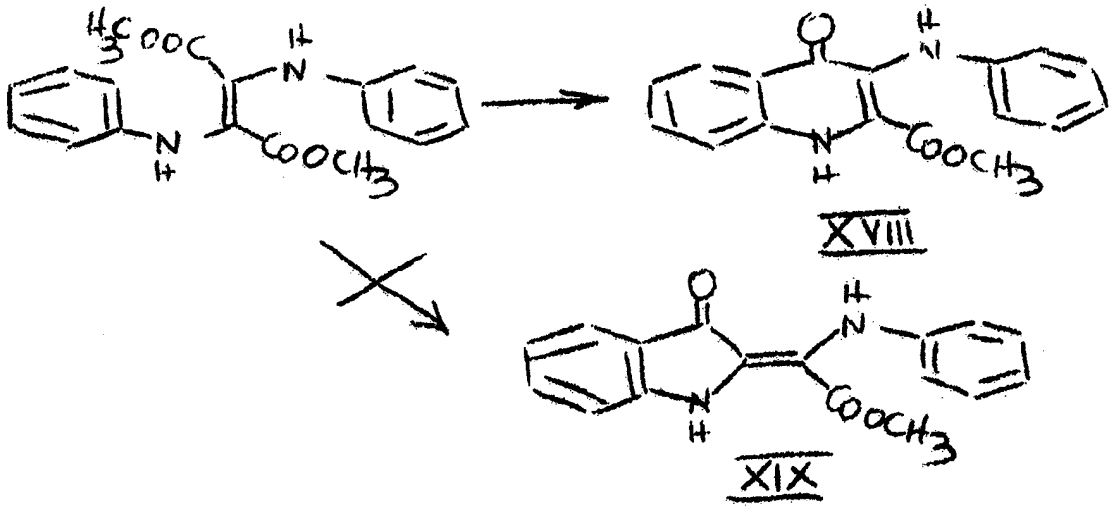
Dimethyl dianilinofumarate, being a trisubstituted acrylate, easily underwent a Conrad-Limpach reaction when heated in Dowtherm A for a few minutes at 250-255°C. to yield 2-carbomethoxy-3-anilino-4-quinolone XVIII.



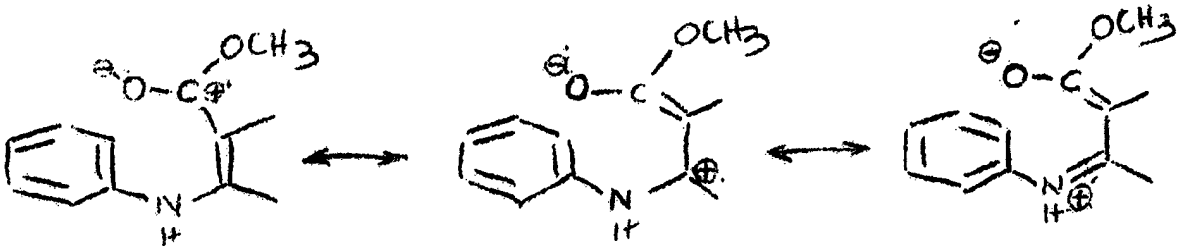
XVIII

XIX

XVIII was the only product of the reaction, no cyclization had occurred to yield any of the isomeric product XIX.

The pyrolytic cyclization is believed not to be a free radical reaction. Although the reaction is carried out at a relatively high temperature (255°C), it is known that esters do not undergo homolytic fission up to about 700-1000°C.

The postulated ionic mechanism takes under consideration the fact that only β-anilinoacrylates are known to undergo this reaction and that there is no known recorded example in which an alkyl β-anilinopropionate underwent a pyrolytic cyclization. It is proposed that under the influence of heat, the normal charge separation within the carbonyl function of the ester group is enhanced, and that the cyclization reaction will occur only if the molecule possesses the necessary structural features to allow greater charge separation by means of mesomeric stabilization of the partial positive charge.



XX XXI XXII

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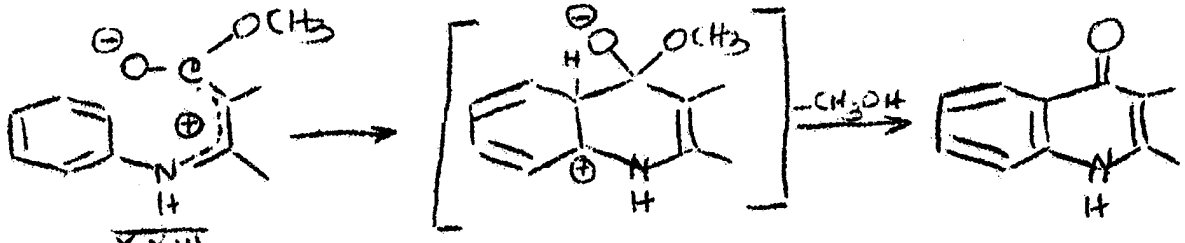
This charge is situated at one end of a modified allylic system (XX, XXI) and is further significantly stabilized by the presence of the electropositive group in conjugation with the carbolkoxy group (XXII). It is postulated that these structures which partake in the stabilization of the ionic system bring about a facile electrophylic substitution unto the benzene ring with simultaneous or subsequent elimination of alcohol which is one of the products of this reaction.



XXIII

It was previously intimated with considerable uncertainty that barring thermal isomerization of the starting ester, its structure was very likely trans based on the nature of the product of the reaction. This argument is valid only if structure XX contributes very significantly toward the stabilization of XXIII, so that a substantial amount of doublebondedness is retained between the α and β carbons. If, on the other hand, the other structures XXI and XXII are important contributors toward the stabilization of XXIII, geometric isomerization may become possible since in either of these structures the α and β carbons are joined by a single bond with substantial freedom of rotation around it. Should the latter be correct, then regardless of the geometry of the starting ester, the cyclization product would be expected to be the same[1].

The failure to obtain five member ring cyclization, regardless of the degree of possible geometric isomerization of XXIII, can be attributed to the known greater facility of six versus five member ring formation.

[1]A study of the pyrolytic cyclization of dimethyl dianilinomaleate would greatly enhance the knowledge on which a more definite mechanism could be based.

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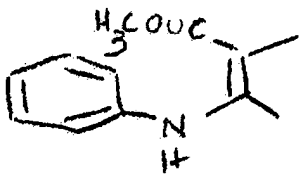
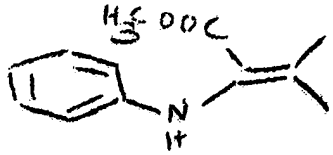
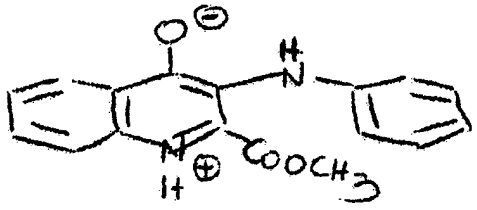
This is particularly accentuated in this case, since the newly formed six membered ring is in effect an aromatic system. It is





interesting to note that XVIII (p. 14) fails to undergo a second cyclization under the described conditions or indeed under extended or higher temperature pyrolysis conditions. This is entirely consistent with the proposed cyclization mechanism and the known failure of 2-carbolkoxydiphenylamine to undergo pyrolytic cyclization. As stated above, the newly formed ring is aromatic in nature to which structure XXIV makes a considerable contribution.



Thus, any stabilization of the potentially polarizable ester group similar to be the one shown for the first cyclization step would require some loss of resonance in the pyridone ring, which is energetically unfavorable and consequently leads to the failure to achieve pyrolytic cyclization.

4. Preparation of Quinolonoquinolone

2-Carbomethoxy-3-anilino-4-quinolone was easily cyclized to quinolonoquinolone in polyphosphoric acid (PPA) in quantitative yield. The cyclization in this medium afforded an opportunity to prepare a pigmentary product directly[1]. This was achieved by liberating the pigmentary product from its acid salt by an alcoholysis reaction. The cyclization is an acid catalyzed reaction which can be carried out in 60% sulfuric acid but is much more effectively carried out in PPA since the latter acid cyclizes the ester without otherwise attacking the starting material.

[1]E.E.Jaffe Report KN-62-11

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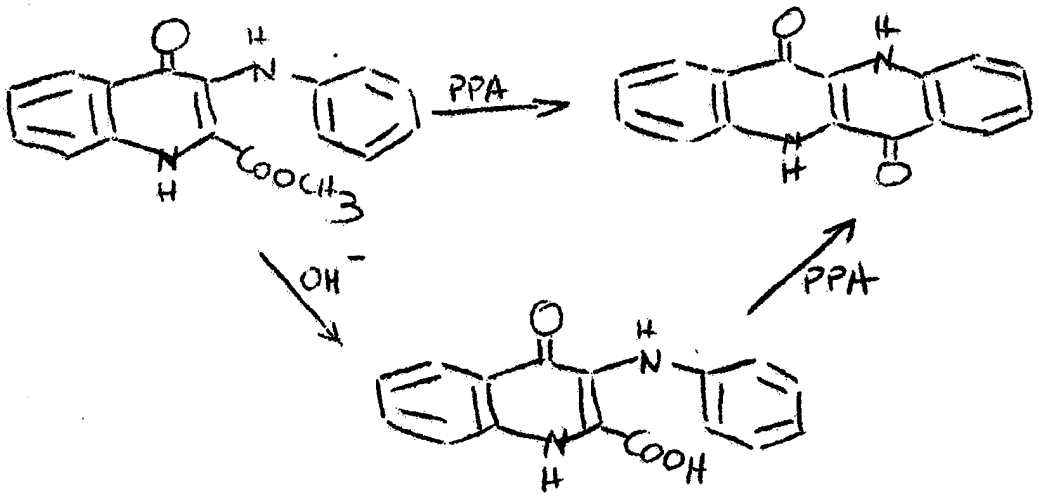


Although direct cyclization to quinolonoquinolone is the preferred method for its synthesis, it has been shown that the ester can be hydrolyzed to 2-carboxy-3-anilino-4-quinolone and the latter cyclized in PPA to quinolonoquinolone. The synthesis via the acid has been successfully applied in the preparation of 2,9-dimethoxyquinolonoquinolone[1].

Direct cyclization of dimethyl dianilinofumarate in PPA to quinolonoquinolone was not successful, presumably because of intermolecular amide formation as suggested by the IR spectrum of the product. Dianilinofumaric acid which would be less likely to undergo an intermolecular amidation reaction eluded our limited attempts at its synthesis.

The quinolonoquinolone obtained by the present synthesis is sufficiently pure for direct utilization as a pigment. If desired, however, the product can be further purified by acid recrystallization since this compound is insoluble in any of the usually available solvents.

As stated earlier, quinolonoquinolone can be obtained in pigmentary form directly from the cyclization reaction mixture. However, despite the realization of the full tinctorial strength, the product is not sufficiently transparent to impart adequate "flip-flop" to metallic finishes. The transparency can be achieved by either HF, salt or dispersion milling of crude quinolonoquinolone which is generated from its PPA solution by the addition of water.

[1]H. Matrick Report KN-62-18

DUP050054008

Regardless of the method of pigment generation from PPA solution, the major polymorphic phase was always alpha[1].

5. Color of Quinolonoquinolone

The origin of color in the quinolonoquinolone molecule can be inferred from the known ultraviolet spectra of open chain β-amino-α,β-unsaturated ketones. The absorption of UV light at the longer wave lengths exhibited by these compounds has been ascribed[2] to the electronic transition A ⟷ B



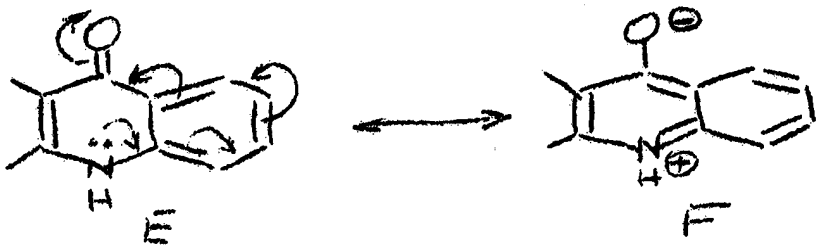
A B

In quinolonoquinolone, there is a similar conjugative distribution of electrons within the vinylogous amido groups giving rise to the electronic transition C ⟷ D.



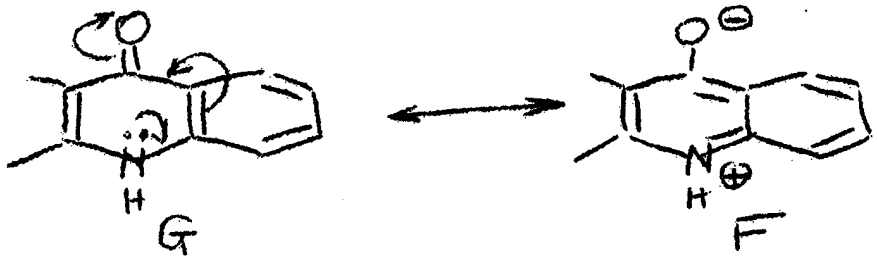
C D

In addition, there is a mutual interaction between the two vinylogous amido groups within the molecule. The side benzene rings can be assumed to be auxochromes, that is, color-aiding groups, which allow the conjugative displacement of electrons to proceed with greater ease due to the delocalization of a greater number of electrons. A plausible theoretical argument can be made by noting



E F

that the resonance system E ⟷ F in which No π bonds avoid delocalization during a charge transfer, should involve a larger uncertainty of electron position than the resonance system G ⟷ F.



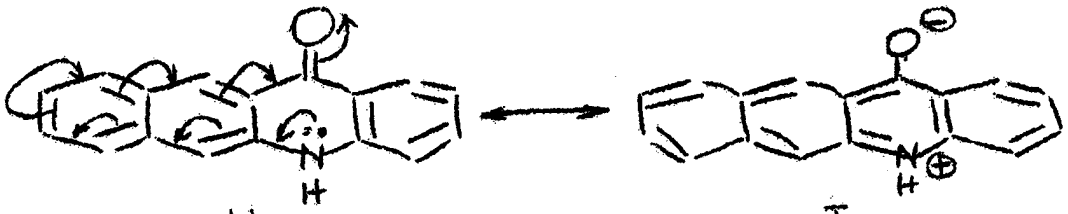
G F

[1]G. R. Aldridge Report KN-63-2

[2]N. H. Cromwell and W. R. Watson, J. Org. Chem., 14, 411 (1949)

DUP050054009

in which two π bonds could remain static during charge separation. By virtue of this argument, the electronic transition E $\longleftrightarrow$ F is most likely involved. This is supported by several observations. Whereas 4-quinolone is colorless, acridone is weak yellow while 2,3-benzoacridone is yellow. In the latter compound, charge separation involves the delocalization of all π electrons of the naphthalene system, thereby lowering the energy required for charge separation. (H $\longleftrightarrow$ I)



H I

The interaction of one pyridone (vinylogous amide) system upon the other within the quinolonoquinolone molecule could be explained by the well-known electron donating effect of one amino group on the other, thus enhancing the electron density on a given amino group. This, in conjunction with the withdrawal of electrons by one keto group from the other making the carbon of the latter carbonyl group more positive, further minimizes the energy required for charge separation within a pyridone ring. It is assumed, without any corroborative physical data, that quinolonoquinolone shows a bathochromic shift and a higher extinction coefficient relative to 2,3-benzoacridone.

By introducing a benzene ring between the two pyridone rings the interaction between the two pyridone rings is further facilitated by involving a greater number of π electrons, thus giving rise to a further bathochromic shift as is observed in quinacridone.

6. Other Properties of Quinolonoquinolone

Quinolonoquinolone does not melt below 400°C. and is very insoluble in many solvents. Its extinction coefficient was determined in DMF (12 mg. per liter) and found to be 14,300 at 444mμ where its absorption in the visible spectrum is at a maximum.

The infrared spectrum of quinolonoquinolone in the solid state in the form of a Nujol mull shows a broad band in the hydrogen bonded N-H stretching region at 3.17μ.

In view of the low solubility and high melting point, it is assumed that most hydrogen bonding is intermolecular in nature. The strength of this bonding is no doubt enhanced by the contribution of the charge separated structures to the resonance of the quinolonoquinolone molecule.

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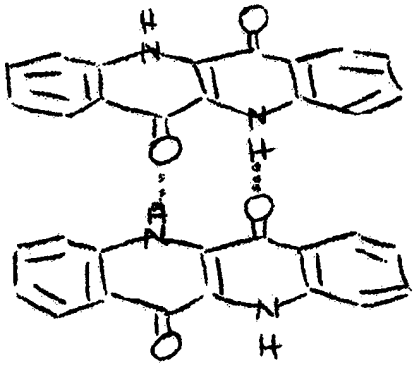
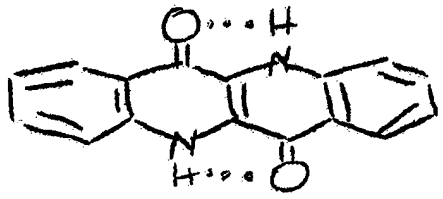
The carbonyl stretching vibration occurs at 6.14μ which is shifted to longer wave lengths by 0.3-0.4μ relative to ordinary aromatic ketones and resembles those of amides. Some intramolecular hydrogen bonding in this molecule cannot be positively excluded. Because of the proximity of the amide hydrogen to a





carbonyl function, intramolecular hydrogen bonding can be visualized and in fact is indirectly supported by the ability of quinolonoquinolone to form chelates.

The formation of chelates is a serious drawback in the use of quinolonoquinolone in polyvinyl chloride application systems where under the influence of heat it undergoes chelation with Zn^{+2} and/or Cd^{+2} present in vinyl stabilizers. The resultant chelates show both migration and poor lightfastness. When a less commonly used tin stabilizer was used, chelation did not occur and the integrity of quinolonoquinolone was preserved in the plastic system.

Quinolonoquinolone has been shown to be about 50% stronger than Green Gold by rubout. In 30J alkyd, it is 30% stronger than Green Gold and equal to flavanthrone.

For a discussion of substituted quinolonoquinolones, see Report KN-62-18 by H. Matrick.

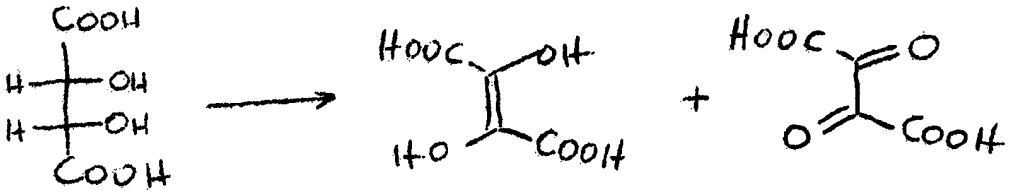
7. Preparation of Dihydroxyfumaric Acid and Alternate Syntheses of its Methyl Ester

Dihydroxyfumaric acid which was previously called dihydroxymaleic acid, was prepared for the first time by Fenton[1] by the oxidation of tartaric acid with hydrogen peroxide in the presence of ferrous ion (Fenton's Reagent). An improved procedure for this reaction is described by Hartree. It involves the oxidation of tartaric acid in an aqueous solution at -5° to -10°C. with dilute hydrogen peroxide in the presence of ferrous sulfate and a small amount of Rochelle Salt. After the completion of the slow hydrogen peroxide addition, concentrated sulfuric acid is added which slowly causes the precipitation of dihydroxyfumaric acid in the form of its dihydrate. In our hands, a study of variables of this reaction has shown that under the most favorable conditions, the yield of dihydroxyfumaric acid is 26.8% (N.B. 1725/57, 78). Since the reaction is quite exothermic and

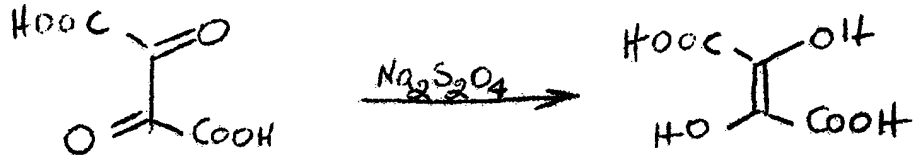
[1]H.J.H.Fenton, J.Chem.Soc., 87, 811 (1905)

DUP050054011

since dihydroxyfumaric acid can be assumed to be subject to further oxidation, it was assumed that subsequent reactions may be responsible for the low yield of the required acid. This was shown to be the case by treating the diluted strongly acidic filtrate with phenylhydrazine. A large amount of yellow phenylhydrazones ~~was~~ formed. (N.B. 1725/57G, 78A). Indirectly, it has been shown that one of the phenylhydrazones is that of diketo succinic acid. The latter is formed either directly by the oxidation of tartaric acid or by the step-wise oxidation via dihydroxyfumaric acid.



The formation of diketosuccinic acid is inferred from the product of the reduction of the acidic filtrate with sodium dithionate which shows a melting point and infrared spectrum identical with authentic dihydroxyfumaric acid dihydrate. The yield of the reduction reaction was 7.9%.



Based on the yield of dihydroxyfumaric acid and the large amount of phenylhydrazine derivatives which was obtained, it appears that either tartaric acid undergoes an oxidative scission to two carbon compounds and/or decarboxylation leads to carbonyl compounds containing less than four carbons. It is interesting to note that the diketo acid is fairly stable in very strong acid (pH $<$ 0) but is progressively less stable in less concentrated acid. This was shown in the following way. After the removal of dihydroxyfumaric acid dihydrate by filtration the strongly acidic filtrate was divided into four equal parts and each treated with sodium dithionate after adjusting the acid concentration to the required pH (N.B. 1725/91).

pH	Yield of dihydrate
0	2.0g
2.5	1.8g
5.0	very small
7.0	no yield

The above decrease in yield suggests a progressive increase in decarboxylation of the diketo acid as its ionization increases with a decrease in acid concentration.

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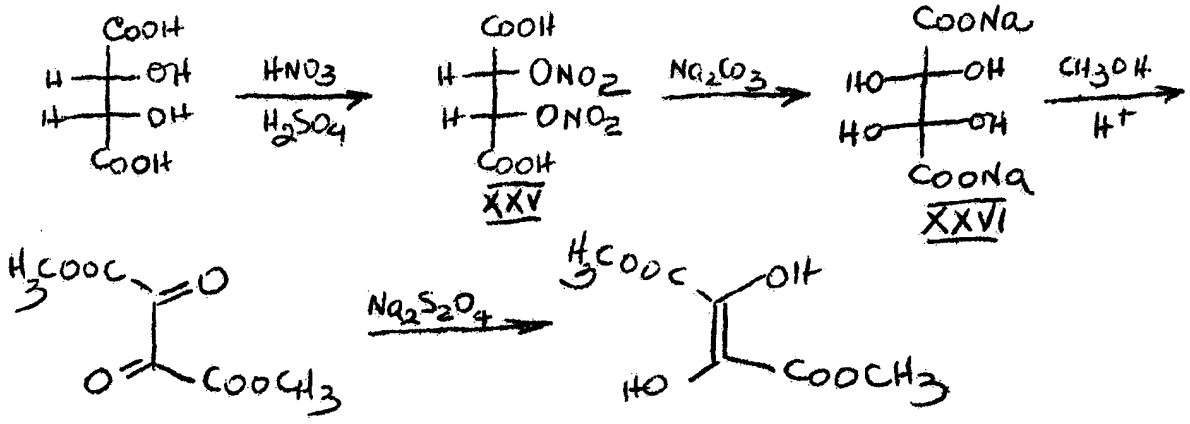
A potentially more economical method for the preparation of dimethyl dihydroxy fumarate is based on the following sequence of reactions.



The initial reaction is the known[1] nitration of tartaric acid to the dinitrate XXV. Without isolating XXV or any other intermediates, it is rearranged to the dinitrite (not shown) and hydrolyzed[1] to disodium dihydroxy tartrate XXVI. In a brief investigation of variables of these reactions (N.B. 1725/83) the disodium salt was obtained in as high a yield as 66.8% based on tartaric acid. There is a potential for a further increase in the yeild of this reaction.

Isolated disodium dihydroxy tartrate is esterified[2] with methanol and gaseous HCl to give dimethyl diketosuccinate. After removing excess HCl and methanol under vacuum, the residue was treated with sodium dithionite to give a 71.4% yield of dimethyldihydroxyfumarate (N.B. 1725/23C, 86). The product of this reaction reacted with aniline under acid catalyzed conditions to give a good yield of dimethyl dianilinofumarate (N.B. 1725/89).

Several other approaches to the synthesis of dimethyldihydroxyfumarate were tried with little or no success.

A very low yield of the desired ester was obtained on reacting dimethyl oxalate with methyl acetoxyacetate in the presence of sodium methoxide.

[1]A. Lachman, J. Am. Chem. Soc., 43, 577 (1921); J. Am. Chem. Soc. 43, 2091 (1921)
[2]H. H. Fox, J. Org. Chem., 12, 535 (1947)

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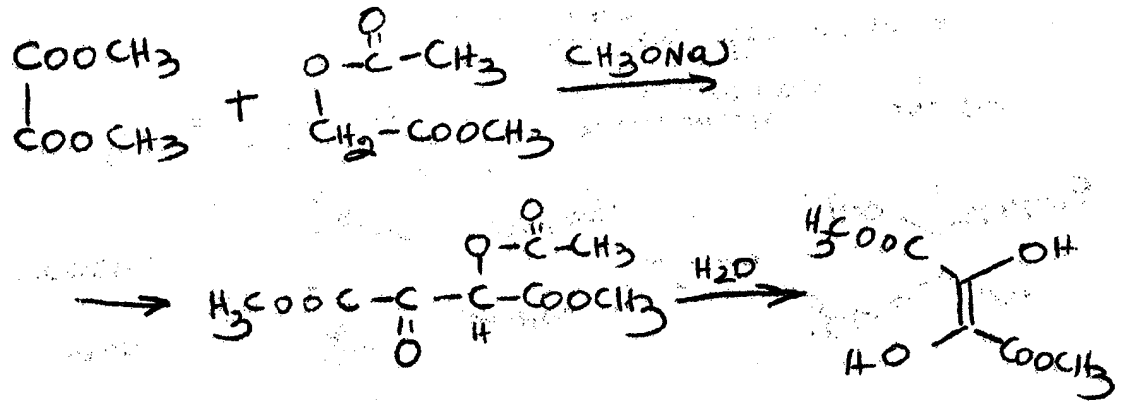
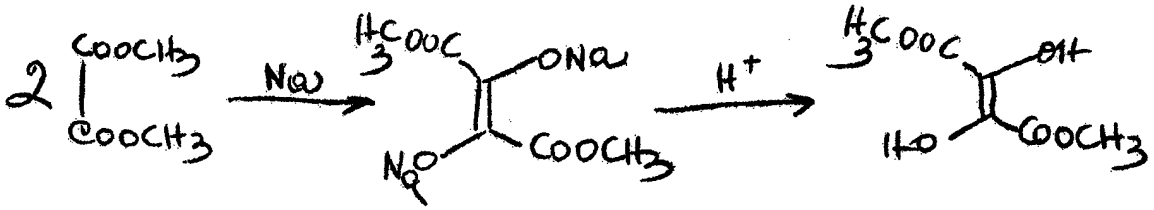
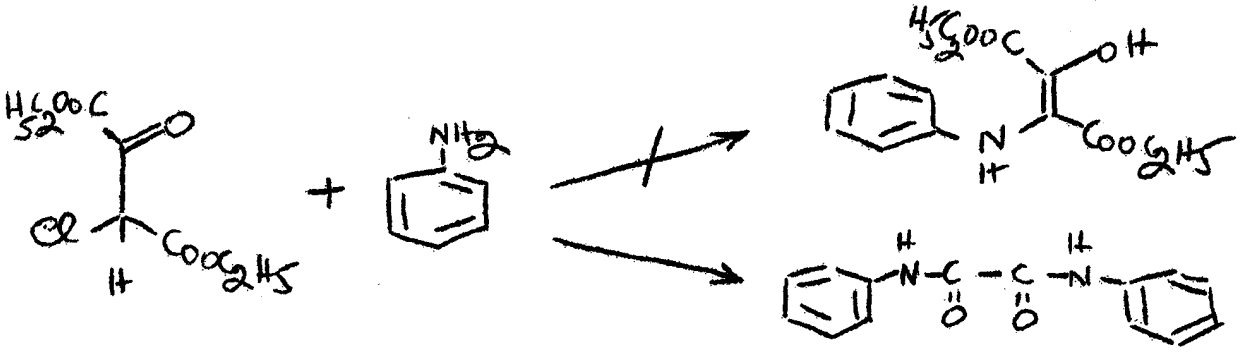


Oxidation or dehydrogenation of dimethyl tartrate to dimethyl dihydroxy fumarate or dimethyl diketo succinate over a variety of catalysts was unsuccessful (N.B. 1725/44). Equally unsuccessful was the attempt to carry out an intermolecular acyloin condensation with dimethyl oxalate.



The reaction of diethyl chlorooxalacetate with aniline failed to yield the expected diethyl anilinohydroxyfumarate. (diethyl α-anilinooxalacetate) but instead gave oxanilide, confirmed by mixed melting point and comparison of infrared spectra with that of an authentic sample.



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8. Lightfastness of Quinolonoquinolone

a. 30J Alkyd

In 30J alkyd, quinolonoquinolone has shown good outdoor durability in metallic and fair durability in tint after one year Florida exposure. The best results were obtained with products which were prepared in pigmentary form by alcoholysis or particle size reduced by HF milling. Dispersion or salt milled products were inferior (by 2 units) both in metallic and tint. None of the products were as durable as Green Gold. However, 2,8-dimethoxyquinolonoquinolone[1] has shown excellent durability after one year Florida exposure. The results are summarized below.

Series 62441
One Year Florida Exposure

	Metallics	Tints
N.B 1725/26, methanolysis of PPA soln. of QQ	9d	6f
N.B. 1725/33A, HF milled QQ	9d	7f
N.B. 1725/33B, dispersion milled QQ	7d	5f
N.B. 1725/33C, salt milled QQ	7d	5f
N.B. 1721/58C_3, salt-milled 2,8-diCH_3OQQ	9.5d	10
Flavanthrone	9d	10
YT-562-D	10	9

In another exposure series, an HF milled product was inferior to the one shown above, however, the precipitation of 10% $NiCO_3$ on the pigment had a marked beneficial effect on the durability of the pigment, particularly in tint (Series 62477). Nevertheless, the pigment was inferior to Green Gold after one year Florida exposure.

b. Acrylic Lacquer

Acrylic lacquer metallics of quinolonoquinolone have shown good durability, comparable to the 30J alkyd counterparts. However, in tint considerably inferior performance has been recorded. Similar differences have been observed for 2,8-dimethoxyQQ.

Series 62449
One Year Florida Exposure

	Metallics	Tints
N.B. 1725/26, methanolysis of PPA soln. QQ	8	3
N.B. 1725/33A, HF milled QQ	8	3
N.B. 1725/33B, dispersion milled QQ	7	4
N.B. 1721-58C_3 salt milled 2,8-dimethoxyQQ	7	4f
Flavanthrone	7	8d
YT-562-D	9.5	8

[1]Exposed by H. Matrick

DUP050054015

Unlike the performance in 30J alkyd, precipitation of 10% $NiCO_3$ on HF milled QQ (series 62481) failed to show any durability improvement in acrylic lacquer.

The reasons for the inferior durabillity of QQ vs. quinacridone are difficult to delineate in the absence of sound experimental evidence.

The following speculative reasons are offered:

1. QQ possesses a central double bond which is part of the two adjacent pyridone rings. Although these rings are aromatic in character, unlike benzene rings they possess contributing structures which freeze the double bond in the position suggested by the ordinary formula of QQ and thus impart to the double bond some olefinic character and as a consequence chemical or photochemical reactivity.

2. Because of the proximity of the keto and amine functions, intramolecular hydrogen bonding may be present[1] (ease of chelation with metals) at the expense of intermolecular bonding weakening the links between molecules by which photochemical energy may be dissipated.

3. The considerable disparity between the durability of QQ in 30J alkyd and acrylic lacquer coupled with the knowledge that the latter system is transparent to UV radiation suggests the possibility of predominant decomposition by UV radiation. This condition is probably common to many pigments which do not possess a high degree of lightfastness. While quinacridone is probably a good and stable UV absorber, QQ absorbs UV radiation without displaying sufficient stability. The incorporation of a stable UV absorber either by physical or chemical means may be of some help in achieving desired durability.

VII. EXPERIMENTAL PART

1. Esterification of Dihydroxyfumaric Acid (NB 1725/32B)

222 g. (1.5 moles) dihydroxyfumaric acid was added to 1.2 liters of methanol in a flask equipped with an agitator, a drying tube, a gas inlet and means for external cooling. To the solution was added 300 g. (2.5 moles) of anhydrous magnesium sulfate and after cooling the mixture to 0-5°C., treated with a stream of anhydrous hydrogen chloride. The mixture was stirred well and treated with the HCl for 4.5 hours while the temperature was maintained at 0-5°C. The mixture was kept at room temperature over a weekend. The solid was removed by filtration, washed with little methanol, reslurried in cold water, filtered again and washed free of acid and sulfate. The wash water reduced Ag^+ to Ag, and an aqueous suspension of the ester reduced cupric acetate to cuprous oxide. After drying, the yield of ester was 245.7g. (93.2%) m.p. 173-174.5°C.

[1]This problem should be possible to resolve by NMR.

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2. Condensation of Dihydroxyfumaric Acid with Aniline (NB 1725/22A)

66 g. (0.375 mole) of dimethyl dihydroxyfumarate was added to 400 ml. methanol in a round-bottom flask equipped with a stirrer, reflux condenser and means for external heating. To the mixture was added 77 g. (0.75 mole + 10% excess) of aniline together with 7.5 g. aniline hydrochloride. The mixture was refluxed for 5.5 hour. After a short period of reflux, a solid began to precipitate out of solution. At the end of the reflux period a heavy, nearly colorless precipitate was out of solution. The slurry was cooled to room temperature, filtered, washed with little methanol and then with water until free of acid. After drying the yield was 102 g. (83.4%). A small sample was recrystallized from n-butanol. Dimethyl dianilinofumarate showed a m.p. of 195-196°C. The elemental analysis was as follows:

Calculated for $C_{18}H_{18}N_2O_4$		Found
% C	66.2	66.68
% H	5.52	5.46
% N	8.58	8.97

3. Cyclization of Dimethyl Dianilinofumarate

a. Direct Addition (NB 1713/79B)

5 g. of dimethyl dianilinofumarate was introduced into 50 ml. Dowtherm and the mixture heated and kept at 250°C. for 5 minutes. Cooled to 10°C. Precipitated product filtered, washed with ligroin and air dried. Yield of yellow crystals 3.5 g. (77.6%). A small sample was recrystallized from methanol. 2-Carbomethoxy-3-anilino-4-quinolone showed a m.p. of 204-205°C. Mixed m.p. with precursor was about 180°C. The elemental analysis was as follows:

Calculated for $C_{18}H_{14}N_2O_3$		Found
% C	69.4	69.18
% H	4.76	4.82

b. Slow Addition (NB 1725/20D)

100 g. of dimethyl dianilinofumarate was dissolved in 1 l. of Dowtherm at 130°C. While keeping the temperature of the solution at 125-130°C. it was added over a 1/2 hour period to 400 ml. of Dowtherm kept at 250-256°C. After completion of the addition, the temperature was maintained at 250-256°C. for another five minutes. The solution was cooled and the precipitated solid filtered, washed with ligroin and dried to give 79 g. (87.6%) of product. M.p. of non-crystallized material 190-191.5°C.

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The 2-carbomethoxy-3-anilino-4-quinolone can be isolated in two forms, a yellow form when the solution is cooled rapidly and a brown form when the solution is cooled slowly. They have substantially the same melting points and show the same chemical reactions but have distinctive x-ray patterns and are, therefore, judged to be polymorphic forms.

4. Cyclization to Quinolonoquinolone

a. Generation by Hydrolysis (NB 1725/20E)

79 grams of 2-carbomethoxy-3-anilino-4-quinolone was added to 790 g. of polyphosphoric acid (83% P_2O_5) and the well stirred mixture heated over one hour to 150°C., then held at 145-150°C. for 2 hours. After cooling to 40-50°C., water was slowly added, maintaining the temperature about 50°C. until the vigorous reaction had ceased, after which an excess of water was added. The mixture was stirred well and then filtered. The product was washed until free of acid and dried to give 70 g. (100%) of quinolonoquinolone (α phase). At least on one occasion, a mixture of α and β phases was obtained.

b. Generation by Methanolysis (NB 1725/26)

The reaction was carried out exactly as described under a. After cooling the PPA solution (containing 240 g. PPA) to 40°C., it was treated with 750 ml. methanol over about 50 minutes while maintaining the temperature at 40-50°C. The mixture was then heated and kept under reflux for 80 mins. The product was filtered and washed with water until free of acid. After drying, the yield was quantitative. The product showed full strength by rubout in tint.

5. Integration of the Condensation and the First Cyclization Reaction (NB 1725/38D)

17.6 g. (0.1 mole) of dimethyl dihydroxyfumarate was added to 152 ml. of Dowtherm in a round-bottom flask equipped with an agitator and vacuum distillation set-up. 65.1 g. (0.7 mole) of aniline was added to the mixture followed by 1 g. aniline hydrochloride. Vacuum was applied and maintained at 35 mm. Hg. while the mixture was heated to 70-75°C. and held at that temperature for six hours. After cooling to room temperature, the acid was neutralized by adding a solution of 0.8 g. Na_2CO_3 in 5 ml. water. The vacuum was again applied to about 3-5 mm. Hg. and the excess aniline removed by distillation along with a considerable amount of Dowtherm which was periodically replaced with fresh material. When the total distillate was about 400 ml., the vacuum was released and the volume of the remaining solution adjusted to contain about 300 ml. of Dowtherm. The mixture was heated to 125°C. to bring about complete solution of the dianilino ester. The solution was filtered hot to remove inorganic salts and the filtrate added over a 20 min. period to 80 ml. of boiling Dowtherm. After completion of addition, the solution was kept at 255°C. for 5 min., then cooled to room temperature and filtered. Dowtherm was washed out from the precipitate with ligroin and the solid dried to give 17 g. of 2-carbomethoxy-3-anilino-4-quinolone.

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6. Integration of the Two Cyclization Reactions(NB 1725/85A)

4 g. of 2-carbomethoxy-3-anilino-4-quinolone was dissolved in 70 ml. Dowtherm and the solution added to 40 g. of PPA. The mixture was stirred and heated to 150°C. and maintained at this temperature for two hours.

Due to the ester's basicity it was immediately extracted from the Dowtherm into the acid layer where the cyclization reaction took place. Most of the Dowtherm was decanted and the residue cooled to 50-60°C. and treated slowly with 100 ml. methanol. The suspension was refluxed for 1.5 hours and the pigment isolated by filtration. Yield of product 3.3 g. (92.8%).

7. Purification of Quinolonoquinolone (NB 1725/28A)

127 g. of quinolonoquinolone was pulverized and an attempt made to dissolve the powder in a mixture of 800 g. 100% H_2SO_4 and 400 g. conc. H_2SO_4. However, the solution was far from being complete. Complete solution at ~8°C. was obtained when the amount of 100% H_2SO_4 was increased to 2.4 kg..

The cold solution was treated slowly with a calculated amount of water. At 96% acid concentration sulfate began to precipitate. The acid concentration was lowered to 89% allowing the temperature to rise to 20°C. The sulfate was filtered on a sintered funnel and washed with 85% sulfuric acid. To effect hydrolysis, the sulfate was slurried with ice and water. The generated product was filtered and washed free of acid and sulfate. Yield of dry product was 103.9 g.

The elemental analysis was as follows:

Calculated for $C_{16}H_{10}N_2O_2$		Found
% C	73.35	73.65
% H	3.82	3.89

8. Preparation of Dihydroxyfumaric Acid (NB 1725/78B)

100 g. of tartaric acid was dissolved in 50 ml. water and to the solution was added another solution of 2.0 g. ferrous sulfate and 2.4 g. Rochelle Salt in 50 ml. water. The resulting solution was cooled to 0° to -5°C. and while maintaining this temperature, 72.5 ml. 30% H_2O_2 diluted with 160 ml. water was slowly added over a period of 2 hours and 13 min. After completion of the addition, stirring was continued for 1 hr. while maintaining the temperature at 0° to -5°C. Then the temperature was lowered to -10 to -20°C. and 60 ml. conc. H_2SO_4 added over a period of 10 min. The resulting solution was stored in the refrigerator overnight and 24 hours at room temperature. The precipitated acid was filtered and washed with 150 ml. cold water. The product was air dried. Yield of dihydroxyfumaric acid dihydrate was 32.8 g. (26.8%).

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The filtrate of a similar run (NB 1725/78A) was diluted with 2 liters water and treated slowly with 162 g. phenylhydrazine. The mixture was kept 1 hr. on the steam bath. The precipitated yellow product was filtered and washed acid-free. After air drying, its weight was 51.5 g.

9. Reduction of Diketosuccinic Acid (NB 1725/91)

After the preparation of dihydroxyfumaric acid dihydrate and its isolation by filtration, the filtrate was treated with a solution of 32 g. sodium dithionite dissolved in 200 ml. water. The reduction product immediately precipitated out of solution. After a few minutes of stirring at room temperature, the product was filtered and dried at room temperature. Yield = 9.7 g. (7.9% based on tartaric acid)..

10. Preparation of Disodium Dihydroxytartrate Dihydrate (NB 1725/83B)

30 g. Tartaric acid was introduced into a 250 ml. round-bottom flask, and to it was added 30 ml. nitric acid and 30 ml. fuming nitric acid. The suspension was stirred and treated slowly over a period of 35 min. with 64 ml. conc. sulfuric acid not allowing the temperature to rise above 50°C. The resulting slurry was stirred at room temperature for three hours and the contents poured into 500 ml. finely chopped ice, using additional ice to complete the transfer into a beaker. The solution was stirred and cooled to 0-10°C. and while maintaining this temperature, treated (over two hours) with 155 g. dry sodium carbonate until the pH of the solution rose to 1. The solution was kept overnight. The precipitated salt was filtered and washed with water to remove soluble salts. Yield 35.0 g. (66.8%).

11. Esterification of Dihydroxytartaric Acid and Its Reduction to Dimethyl Dihydroxyfumarate (NB 1725/23C)

25 g. of disodium dihydroxytartrate dihydrate was suspended in 100 ml. methanol and the suspension saturated with gaseous HCl at 0°C. The mixture was kept in the refrigerator for four days. The inorganic salt was filtered off and the filtrate concentrated under vacuum (water pump) not allowing the temperature to rise above 30°C. The residue was treated at once with a solution of 19 g. $Na_2S_2O_4$ in 200 ml. water. As soon as the formed brown color disappeared, the solid was removed by filtration and washed with water. Yield of dimethyl dihydroxyfumarate was 12 g. (71.4%) m.p. 157-159°C. The product readily condensed with aniline to give dimethyl dianilinofumarate.

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12. Preparation of Dimethyl Diacetoxyfumarate (NB 1725/65)

20 g. of dimethyl dihydroxyfumarate was added to a mixture of 200 ml. acetic anhydride and 100 ml. pyridine. The resulting solution was warmed on the water bath for one hour and allowed to stand at room temperature overnight. The solvents were removed in vacuo maintaining the temperature of 30-40°C. The wet solid residue was recrystallized from methanol. Yield of white product was 4 g. m.p. 103.5-104.5°C.

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