# Kinetics of Styrylquinoline Formation (1)

*Steven M. Lynch (2) and Marshall Gordon (3)*

Department of Chemistry, Murray State University, Murray, Kentucky 42071

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A comprehensive kinetic investigation of reactions occurring in the formation of styrylquinolines has been conducted. Specific rate data such as rate equations, rate constants, and thermodynamic activation values have been determined and utilized in a study of which factors are of greatest importance in the reactions forming 2-styrylquinolines. A mechanism has been proposed for the condensation reaction which agrees with rate relationships found. Gas-liquid partition chromatography was used to follow the kinetics of the condensation reactions. A rate constant of $5.41 \times 10^{-2} M^{-1} min^{-1}$ was found for the reaction of benzaldehyde with 2-methylquinoline using zinc chloride as a catalyst at 104.0°. Rate constants of $1.28 \times 10^{-2} M^{-1} min^{-1}$ and $1.05 \times 10^{-2} M^{-1} min^{-1}$ were found for the reactions of *p*-methylbenzaldehyde and *p*-methoxybenzaldehyde with quinaldine to form 2-(*p*-methylstyryl)quinoline and 2-(*p*-methoxystyryl)-quinoline, respectively at 92.4°. A linear relationship was found using the Hammett equation. An Arrhenius plot was constructed from rate constants determined at five different temperatures for the reaction of benzaldehyde and quinaldine to form 2-styrylquinoline, using zinc chloride as a catalyst. The energy of activation, $E_a$, was found to be 22.2 kcal/mole for this reaction. The enthalpy of activation, $\Delta H^{\ddagger}$, free energy of activation, $\Delta F^{\ddagger}$, and entropy of activation, $\Delta S^{\ddagger}$, were found to be 21.4 kcal/mole, 27.7 kcal/mole and -16.7 eu/mole, respectively, at 104.0°. The mechanism proposed in the formation of 2-styrylquinoline involves the fast formation of a carbanion-zinc chloride complex, which then attacks, in the rate determining step, the aldehyde utilized in the reaction. The lack of reaction of certain methylquinolines is attributed to the inadequacy of the carbanion formed and not to the difficulty involved in the initial formation of the carbanion.

## Introduction.

Styrylquinolines have been synthesized for many years because most of the members of this group of compounds possess some type of biological activity. Substituted styrylquinolines have been shown to possess carcinogenic and/or carcinostatic activity (4-10), bacteriostatic and fungistatic properties (11-14), show value in the diminution of toxicity and physiological activity (15-16), cytogenic and culture activity (17), antimalarial (18,19), and antineoplastic activity (20), and certain of these compounds were shown to be most effective as an inhibitor of the α-chymotrypsin-catalyzed hydrolysis of acetyl L-valine methyl ester (21).

Many different procedures have been reported for the preparation of styrylquinolines. The most common methods are those of Kaslow and Stayner (22) and Shaw and Wagstaff (23) using acetic anhydride as a catalyst and Campbell (24) with zinc chloride as catalyst for the condensation of substituted methylquinolines and aromatic or aliphatic aldehydes. These authors and Izmail'skii (25) found that highest yields with the substituted styrylquinolines were obtained using acetic anhydride as a catalyst. For the preparation of the 4-substituted styrylquinolines, zinc chloride was a more effective catalyst. However, Tipson (26), using these catalysts in the preparation of 2-(*p*-dimethylaminostyryl)quinolines, reported a yield of 13% with acetic anhydride and a yield of 68% with zinc chloride. Tipson also noted the formation of a small amount of *p*-dimethylaminobenzylidenediquinaldine with equi-molar quantities of reactants, yet this compound was the main product when a 2:1 molar ratio of quinaldine to aldehyde was used. This result was in agreement with the predictions of Hamer (27). Gillman and Karmas (28) also noticed a difference in reaction characteristics when using either acetic anhydride or zinc chloride as catalysts. Other authors who have reported the use of acetic anhydride in the preparation of styrylquinolines are Bennett and Pratt (29), Mathur and Robinson (19), and Horwitz (30). Use of zinc chloride for a similar purpose

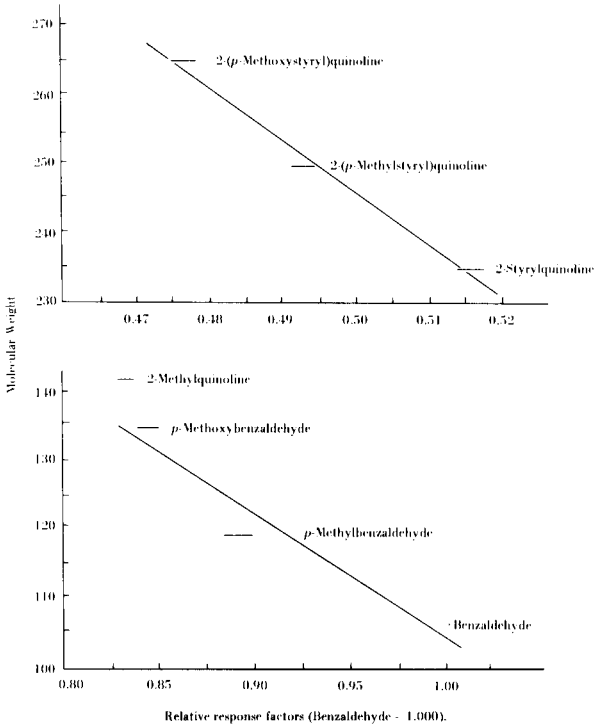


Figure 1. Relative response factors for substances used in this study.

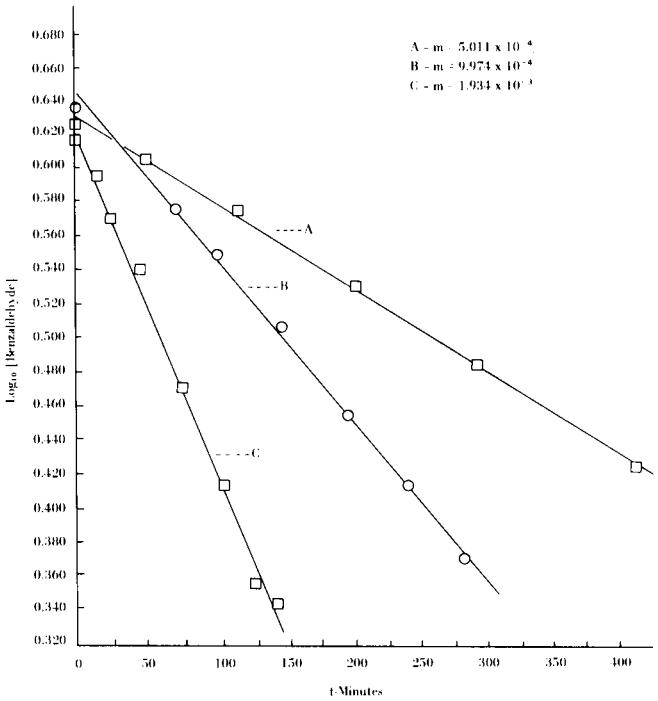


Figure 3. Effect of different concentrations of zinc chloride on the reaction rate.

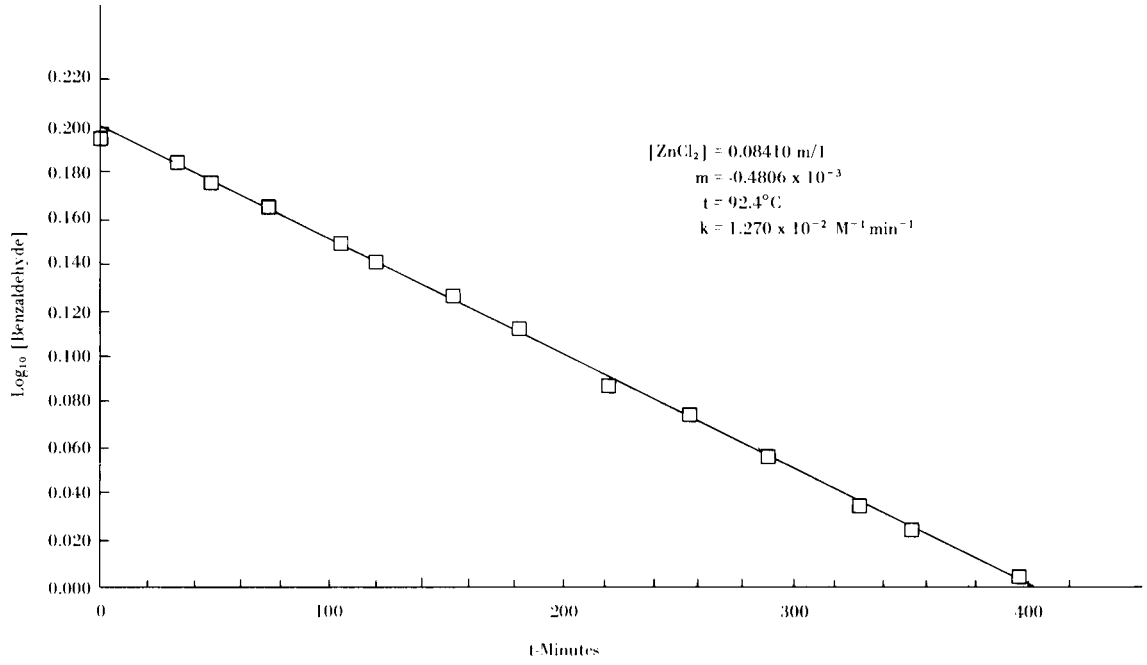


Figure 2. Plot illustrating first order kinetics.

has been reported by Clapp and Tipson (26), Dentimalli (31), and Bahner (9). Of the other catalysts used, the most common include hydrochloric acid (26), piperidine (25,30,32) and potassium hydroxide (33). Tipson (26) compares many of the methods used in his syntheses of dimethylamino-substituted styrylquinolines. He found that a modification of the Bramachari method (13), where the reactants are heated to the boiling point, and from time-to-time, the unreacted reactants removed for further reaction, gave the best results with yields up to 86% of the theoretical. Michalski (34) prepared 2-styrylquinoline in 50% yield by mixing diethyl-2-quinolylmethyl phosphate and benzaldehyde in benzene with finely cut potassium metal. Andrews (35) found that only a 17% yield of 2-styrylquinoline could be obtained by heating benzaldehyde and quinaldine for thirty hours at 100° in a sealed tube. Avramoff and Spinzak (33) obtained poor yields of this product by using potassium hydroxide in benzyl alcohol and heating with quinaldine and a molar excess of aldehyde. Tramontini (36) reported a unique method for the preparation of styrylquinolines, *i.e.*, the cyclization of a suitable substituted 1-aryl-5-arylaminopent-1-en-3-ones in the presence of stannous chloride and zinc chloride. For example, 1-phenyl-5-anilinopent-1-en-3-one was cyclized in ethanol with stannous chloride and zinc chloride to give 4-styrylquinoline in 30% yield. Several articles give excellent comparisons of optimum conditions for styrylquinoline formation (25,26,37,38).

## Results and Discussion.

### Analytical Method.

To follow the reaction kinetics of this system, analysis was achieved by glpc. The actual quantitative analysis interpretation of results is that currently used in the industrial treatment of glpc data in the most quantitative applications and achieves theoretical accuracy approaching that of the ball and disc integrator used in this study of about 2-3% (39).

To relate the areas of the peaks on the resulting chromatograms in the study with the corresponding quantitative amounts of substance present at any time, relative response factors were used. These are only correction factor coefficients to allow for the variation in the response of the thermal detector. To assume that the response of a thermal detector is the same for all of the compounds used, is an evaluation which could be capable of over 35% error (40).

The relative response factors were calculated for each substance used during any period of analysis by the use of initial known standards. Two standards were sufficient to allow for proper factor determination. The factors were calculated by the use of the following equation:

$$Rf_x = \frac{As}{Ax} \times \frac{Mx}{Ms} \times Rf_s \qquad (1)$$

where

$Rf_x$ = Relative response factor of substance x.

As = Area of standard used (Peak area).

Mx = Mole % of substance x in standard solution mixture.

Ms = Mole % of internal standard in standard solution mixture.

$Rf_s$ = Relative response factor of internal standard (arbitrarily chosen as 1.000).

The internal standard denoted above was chosen as one of the reacting substances involved in the reaction, specifically, either the methylquinoline or aldehyde used and assigned the relative response factor shown in equation 1. Thus, the other areas are normalized to the area of the internal standard and the "corrected areas" are then obtained from equation 2:

$$A_a' = A_a \times Rf_a \qquad (2)$$

where

$A_a'$ = Corrected area of peak for substance a.

$A_a$ = Integrated area of peak for substance a.

$Rf_a$ = Relative response factor of substance a.

The corrected areas are directly proportional to the molar amount of substance present at any time, t, according to equation 3:

$$(\text{Mole }\%)_a = \frac{A_a'}{A_a' + B_b' + C_c' + \ldots} = \frac{A_a'}{\Sigma D'} \qquad (3)$$

where

$B_b'$ = Corrected area of substance b.

$C_c'$ = Corrected area of substance c.

$\Sigma D'$ = Total of corrected areas.

Knowing the mole % of each component at any time, t, one need only apply equation 4 to determine the total moles/liter (m/l) of each component.

$$(M_a)_t = (\text{Mole }\%)_{a_t} \times Z' \qquad (4)$$

where

$(M_a)_t$ = Moles of component a, at time t.

$a_t$ = Component a, at time t.

$Z'$ = Initial total moles or total moles/liter.

With the use of $Z'$ in the above equation with concentration units, a negligible total volume change was assumed during the course of a reaction.

The merit in using this system of analysis is that relative response factors are unique in that they are independent of sample volume injection, concentration, temperature, flow rate, and carrier gas (41).

An interesting relationship indicated by Messner (39) stated that the response values of substances in a structurally similar homologous series of compounds exhibit a linear, inverse relationship, relative to the corresponding molecular weights. This could be of importance when there is a limited amount of substance available for determination of relative response values.

The relative response values, as indicated in Figure 1, did seem to follow the predictions of Messner (39) for the substances used in this study. It should be noted that the relative response values did change in the third significant place from time to time and for this reason, the values plotted are represented as a line and not as a point. It is also noted that *p*-methylbenzaldehyde and 2-(*p*-methylstyryl)quinoline showed slight deviation from the relationship which may be due to some molecular feature of the *p*-methylbenzaldehyde nucleus.

Effect of Catalysts.

Much information was obtained from the experimentation with different catalysts, concentrations of catalysts and control reactions, and these data are summarized in Table I.

The reaction studied involved the condensation of an aldehyde with a methylquinoline, specifically benzaldehyde and 2-methylquinoline. It was at first necessary to eliminate the possibility of catalysis of the reaction by any substance other than that added to the mixture for this purpose. Since benzaldehyde could be air oxidized to benzoic acid, this potential source of error had to be checked for its influence because as indicated in Table I, benzoic acid is capable of catalyzing the reaction. A control reaction was run in an atmosphere of helium and the test reaction was subjected to the same conditions that would be present during the course of a kinetic run, specifically sampling at fifteen-minute intervals for ten seconds. The frequency of sampling was done to insure that no loss of aldehyde and gain of catalyst would take place *via* this route even at the maximum conditions of air exposure to the reaction.

Of the other catalysts tested and also shown in Table I, zinc chloride and acetic anhydride were the best agents for catalyzing the reaction in terms of speed of product formation and yield. Aluminum chloride was not as strong a catalyst as would be expected in a proton removal reaction, but this discrepancy could be attributed to the

TABLE I

Summary of Catalysts Tested in the Preparation of 2-Styrylquinoline

| Catalyst | Concn. (m/l) | A (m/l) (a) | B (m/l) (b) | Temp. (°C) | Time Lapse (min.) | % Styryl Formed |
|---|---|---|---|---|---|---|
| Benzoic acid | 0.0841 | 4.216 | 4.216 | 104.0 | 90 | 1.12 |
| Magnesium sulfate | 0.0841 | 4.216 | 4.216 | 92.4 | 90 | 0.51 |
| Aluminum chloride | 0.0841 | 4.216 | 4.216 | 92.4 | 90 | <1.0 |
| Trifluoroacetic acid | 3.982 | 2.958 | 2.958 | 92.4 | 98 | 0.913 |
| Zinc chloride | 0.0841 | 1.568 | 1.568 | 92.4 | 90 | 9.65 |
| (c) Zinc chloride | 0.400 | 0.400 | 0.400 | 60.0 | 52 | ------ |
| Acetic anhydride | 3.018 | 3.018 | 3.018 | 92.4 | 131<br>363 | 15.7<br>49.9 |
| Acetic anhydride | 4.700 | 2.350 | 2.350 | 92.4 | 113<br>345 | 10.8<br>31.2 |
| (d) None-purged with helium | | 4.216 | 4.216 | 104.0 | 375 | 1.91 |
| (d) Air introduced into reaction vessel every 15 seconds for 10 seconds | | 4.216 | 4.216 | 104.0 | 371 | 1.85 |

(a) A = Concentration of benzaldehyde. (b) B = Concentration of quinaldine. (c) Quinaldine was seen to disappear very quickly while the rate of disappearance of benzaldehyde was less. No styrylquinoline peak was observed even when the quinaldine was completely gone, yet the solution turned color indicating product formation. Benzylidenediquinaldine was isolated and the hydrochloride derivative of this compound gave a melting point of 158° which was in agreement with the literature value of 156° (27). The m.p. of the pure benzylidenediquinaldine was 125-126° and the nmr (deuteriochloroform) of this material consisted of doublet, $\delta$ 3.25; triplet, $\delta$ 5.30; multiplet, $\delta$ 7.0. (d) Done to check the possibility of oxidation of benzaldehyde to benzoic acid and it in turn, serving to catalyze the reaction. It would seem that the loss of aldehyde and gain of acid *via* this route is negligible.

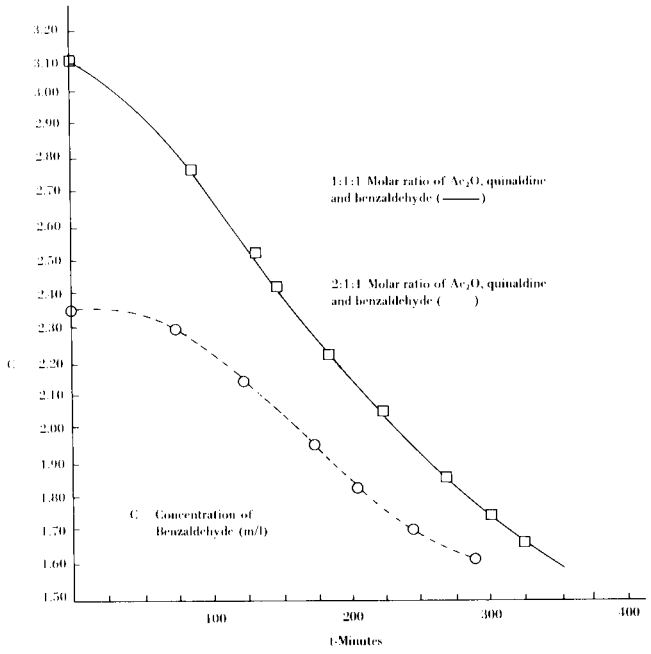


Figure 4. Rate of decrease of benzaldehyde when a molar ratio of 1:1:1 (solid line) and 2:1:1 (dashed line) of reactants to acetic anhydride was used.

lack of solubility of this catalyst in the comparative quantity used.

When a molar ratio of 1:1:1 of zinc chloride, benzaldehyde and quinaldine was used, with 1,2-dimethoxyethane as a solvent, and the reaction kinetics followed, the peak for quinaldine disappeared in a short time. The solution was treated as if styrylquinoline had formed and when added to water after potassium hydroxide treatment, an insoluble product formed which was identified as benzylidenediquinaldine; the same product obtained when two moles of quinaldine are condensed with one mole of benzaldehyde (27). This gave strong indications in support of the carbanion intermediate proposal. This supposition was further confirmed on the basis of the speed at which the 2-methylquinoline disappeared. Identification of benzylidenediquinaldine was made by a comparison of the melting point of the hydrochloride salt of this product with that reported in the literature, by elemental analysis and by nmr.

Reaction Order.

When using zinc chloride as a catalyst in a concentration of 0.0841 m/l, the kinetic monitoring of the reaction of equi-molar amounts of benzaldehyde and quinaldine yielded data which when plotted as $\log_{10}$ reactant concentration *versus* time, gave the straight line illustrated in Figure 2. This plot indicated a first order reaction. The true rate constant was determined by dividing the rate constant obtained by the use of equation 5 by the concentration of zinc chloride. It will be shown that the

$$k = -2.303 \text{ (slope)} \qquad (5)$$

reaction is actually a pseudo-first order reaction where the concentration of zinc chloride remains constant during the course of a run. The rate constant in this solvent was calculated to be $1.270 \times 10^{-2} M^{-1} min^{-1}$ at 92.4°.

Zinc Chloride and Acetic Anhydride as Catalysts.

Zinc chloride and acetic anhydride were shown to be the best condensing agents of those tested in this study. From a review of the literature, other experimenters have shown these compounds to be the best, and most widely used catalysts in the condensation reactions of the type conducted in this study (22-24,26). Because of this fact, a more detailed study of the role of these catalysts in the condensation reaction of benzaldehyde and quinaldine to form 2-styrylquinoline was deemed necessary.

When three different quantities of zinc chloride were used to determine the role of this catalyst in the condensation reaction to form 2-styrylquinoline, a plot of the $\log_{10}$ of the concentration of reactant (equi-molar) *versus* time for this reaction with the concentrations of catalyst given in Table II, yielded the curves shown in Figure 3. The slopes of these lines were found and subsequent "true" rate constants were obtained by dividing the constants obtained from equation 5 by the concentration of zinc chloride used in each case.

These results indicated a pseudo-first order reaction had occurred. The average rate constant obtained in this case using neat liquids was $5.420 \times 10^{-2} M^{-1} min^{-1}$ at 104.0°. A solvent effect was shown to be present when performing the reaction in a solvent such as 1,2-bis(2-methoxyethoxy)ethane as indicated previously in this section, and when performing the reaction with the neat liquids.

TABLE II

Values Indicating the Dependence of the Rate Constant on Concentration of Zinc Chloride at 104.0°

| Curve | Zinc Chloride Concentration Moles/liter | $k_1$, $min^{-1}$ | $k_1(ZnCl_2)$ |
|---|---|---|---|
| A | $2.107 \times 10^{-2}$ | $1.154 \times 10^{-3}$ | 0.0548 |
| B | $4.214 \times 10^{-2}$ | $2.297 \times 10^{-3}$ | 0.0545 |
| C | $8.410 \times 10^{-2}$ | $4.454 \times 10^{-3}$ | 0.0530 |

When using acetic anhydride as a catalyst, a plot of the data for the decrease in concentration of reactants *versus* time resulted in the curves illustrated in Figure 4. There

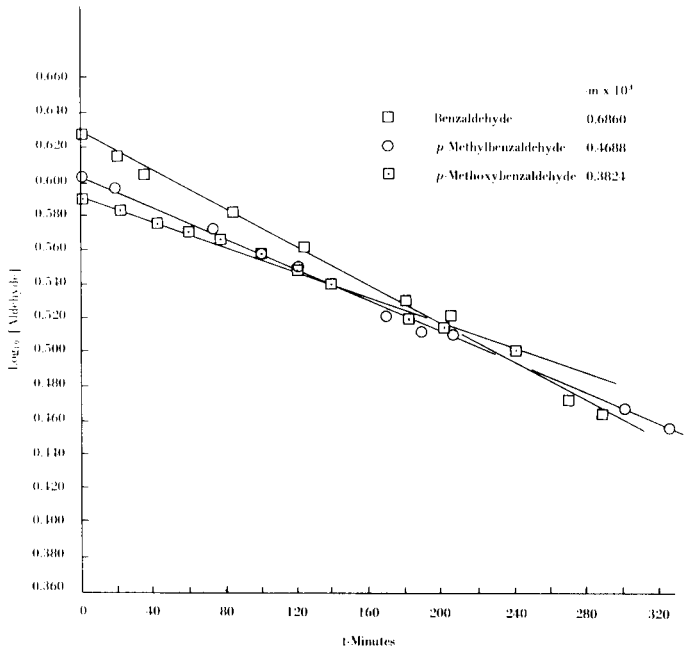


Figure 5. Effect of different aldehydes on rate of reaction.

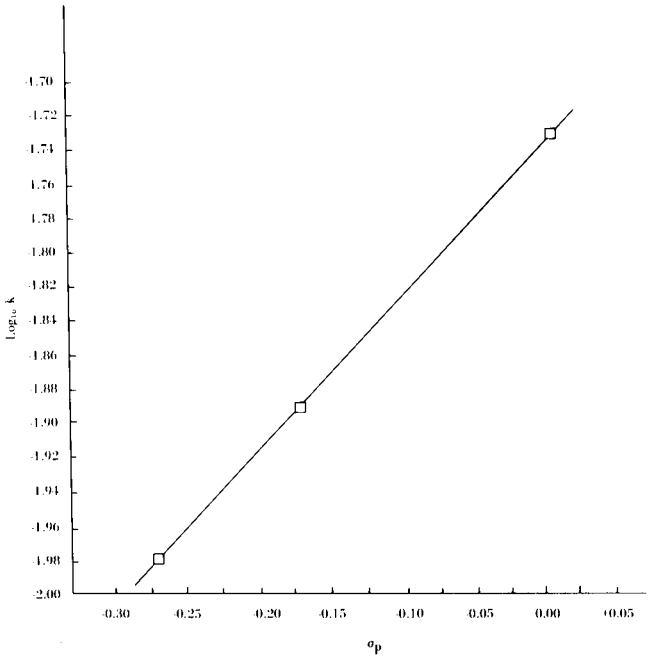


Figure 6. Hammett plot for different aldehydes.

is a close resemblance between these curves and those of autocatalytic reactions (42). This is readily understandable since as the reaction proceeds with this catalyst, hydrolysis of one mole of acetic anhydride yields two moles of acetic acid which further catalyzes the reaction. It would seem from the comparative results of Table I with the two concentrations of acetic anhydride, that the majority of the catalytic effect in these cases was, in fact, the acetic acid and not the anhydride since the 1:1:1 molar ratio reaction between acetic anhydride, benzaldehyde and quinaldine proceeded at a faster rate than the reaction between these components when the molar quantity of acetic anhydride was doubled. This is also understandable since when one considers that upon the hydrolysis of one mole of anhydride to give two moles of acid, the resulting solution would be more concentrated in hydrogen ions since a smaller volume would be present in a 1:1:1 molar ratio solution than in a 2:1:1 molar ratio solution of acetic anhydride, benzaldehyde and quinaldine.

Effect of Substituent Groups on Benzaldehyde.

Three aromatic aldehydes substituted in the *para* position with different electron-donating groups were examined to determine the effect on the rate of the reaction of aldehyde with 2-methylquinoline in the presence of zinc chloride. A plot of the $\log_{10}$ of the concentration of each aldehyde *versus* time yielded the straight lines given in Figure 5, which gave the constants indicated in Table III. A Hammett plot was then constructed (Figure 6) using the $\sigma_p$ values for each group given by Gould (43). This plot indicated that electron donating groups in the *para* position of the benzaldehyde nucleus, when reacting

TABLE III

Rate Constants Obtained for Aldehydes Tested at 92.4°

| Aldehyde | Zinc Chloride Concentration Moles/liter | $k_1$, $min^{-1}$ | $k' = k_1/(ZnCl_2)$ (a) |
|---|---|---|---|
| Benzaldehyde | $8.410 \times 10^{-2}$ | $15.80 \times 10^{-4}$ | $1.879 \times 10^{-2}$ |
| *p*-Methylbenzaldehyde | $8.410 \times 10^{-2}$ | $10.75 \times 10^{-4}$ | $1.278 \times 10^{-2}$ |
| *p*-Methoxybenzaldehyde | $8.410 \times 10^{-2}$ | $8.807 \times 10^{-4}$ | $1.047 \times 10^{-2}$ |

(a) The "true" rate constant = k′.

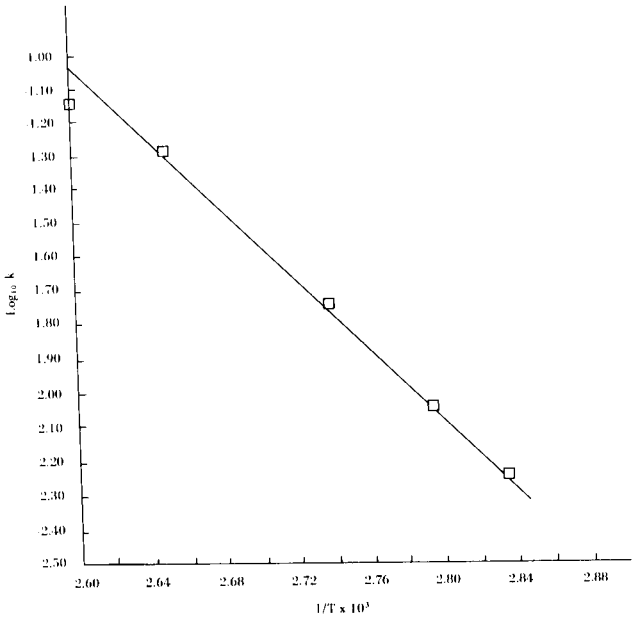


Figure 7. Arrhenius plot for the formation of 2-styrylquinoline.

in this type of condensation reaction, tended to decrease the reaction rate. These results also indicated that the reaction was not only first order in the aldehyde, but in addition, supported the carbanion mechanism, since resonance stabilization of the aldehyde nucleus by a more electron donating group than hydrogen would create a site less likely to be attacked by a negatively charged carbanion.

Electron withdrawing groups, such as *p*-chloro or *p*-nitro, would be expected to increase the rate of reaction, but these reactions could not be followed kinetically since 2-(*p*-chlorostyryl)quinoline, the product of the reaction between *p*-chlorobenzaldehyde and quinaldine, was not soluble enough in the reactants to follow the rate of the reaction in the usual manner. The *p*-nitrobenzaldehyde and quinaldine reaction to form 2-(*p*-nitrostyryl)quinoline could not be followed since the reactants could not be separated conveniently by glpc. It was noted that the rate of formation of 2-(*p*-chlorostyryl)quinoline did take place in 1,2-bis(2-methoxyethoxy)ethane without a catalyst in a much shorter time than it took 2-styrylquinoline to form in the same solvent without a catalyst.

Activation Values.

The Arrhenius rate data for the five temperatures are summarized in Table IV. A plot of this data is given in Figure 7. From equation 6, the energy of activation, $E_a$, was calculated to be 22.2 kcal/mole. From equation 7, $\Delta H^{\ddagger}$ was calculated to be 21.4 kcal/mole at 104.0°. From equation 8, $K^{\ddagger}$, the equilibrium activation constant, was calculated to be $1.12 \times 10^{-16} M^{-1}$ at the same temperature. From equations 9 and 10, $\Delta F^{\ddagger}$ and $\Delta S^{\ddagger}$ were calculated to be 27.7 kcal/mole and -16.7 eu/mole at 104.0° (44).

$$E_a = \Delta E^{\ddagger} = -4.576 \times \text{slope} \quad (6)$$

$$\Delta H^{\ddagger} = E_a - RT \quad (7)$$

$$k_r = kT/h \times K^{\ddagger} \quad (8)$$

$$\Delta F^{\ddagger} = -RT \ln K^{\ddagger} \quad (9)$$

$$\Delta S^{\ddagger} = \frac{\Delta H^{\ddagger} - \Delta F^{\ddagger}}{T} \quad (10)$$

Kinetic Mechanism.

The kinetic mechanism which would be indicated to this author from the results of this study is illustrated in Figure 8. It would seem that the abstraction of the proton from the methylquinoline is a fast step; whereas, the actual rate of the reaction is governed by the attack of the zinc chloride-quinaldine carbanion complex, I, on the aldehyde. Both the formation of the intermediate, III, and subsequent loss of water from this intermediate are believed to be fast steps.

Thus, the rate expression given in equation 11 would hold true when using zinc chloride as a catalyst where

$$-dC/dt = k(ZnCl_2 \cdot \text{Quinaldine}^-)(\text{Aldehyde}) \quad (11)$$

TABLE IV

Values Used in the Construction of the Arrhenius Plot

| t(°C) | T(°K) | 1/T x $10^3$ | Slope (m) x $10^4$ | k x $10^2$ (a) | $Log_{10}$ k |
|---|---|---|---|---|---|
| 111.5 | 384.5 | 2.600 | -25.64 | 7.051 | -1.152 |
| 104.0 | 378.0 | 2.653 | -19.34 | 5.296 | -1.276 |
| 92.4 | 365.4 | 2.737 | -6.860 | 1.879 | -1.726 |
| 85.0 | 358.0 | 2.793 | -3.331 | 0.9121 | -2.041 |
| 80.0 | 353.0 | 2.833 | -2.115 | 0.5792 | -2.237 |

(a) Calculated with the zinc chloride concentration = 0.0841 m/l.

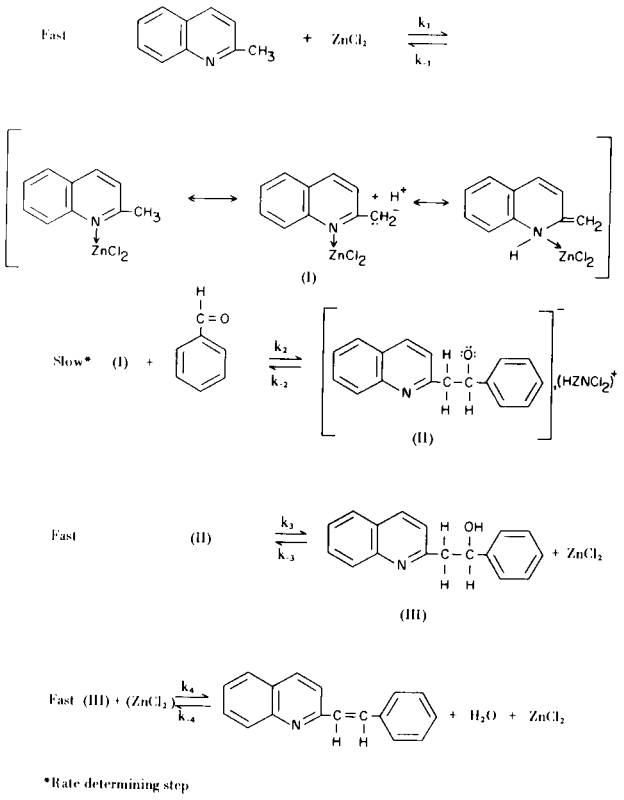

Figure 8. Proposed mechanism for the formation of 2-styrylquinoline with rate relationships.

the quantity shown in the first parentheses is the complex formed in the first step of the mechanism scheme depicted in Figure 8. Since the concentration of complex is constant and equal to the concentration of zinc chloride, a pseudo-first order reaction is indicated.

Several conditions must be stipulated before equation 11 would hold completely true. Since the possibility of equation 12 representing the reaction scheme under certain conditions exists, then the kinetic equation given in

$$2\,(ZnCl_2\cdot Quinaldine^-) + Bz = \begin{matrix} H \\ | \\ Q\text{-}C\text{-}Q \\ | \\ C_6H_5 \end{matrix} + H_2O + 2\,ZnCl_2 \qquad (12)$$

equation 13 must be said to be applicable:

$$-dC/dt = k_1\,(ZnCl_2\cdot Quinaldine^-)\,(Bz) + k_2'\,(ZnCl_2\cdot Quinaldine^-)^2\,(Bz) \qquad (13)$$

where in all of the equations above

Q = Quinaldine minus the reacted proton and/or a second proton.

Bz = Benzaldehyde nucleus plus or minus the oxygen as the case may be.

$$\begin{matrix} H \\ | \\ Q\text{-}C\text{-}Q \\ | \\ C_6H_5 \end{matrix}$$ = Benzylidenediquinaldine.

Thus, other rate constants may play a role in this reaction unless conditions are carefully maintained. Equation 11 represents the rate expression when the concentration of zinc chloride is low and when the concentration of quinaldine is less than or equal to the concentration of benzaldehyde. If the concentration of zinc chloride is too great, or if the concentration of quinaldine is increased over that of the aldehyde used, then $k_2'$ of equation 13 plays a more significant role in the rate expression. Since the solubility of zinc chloride in the neat liquid reactants (methylquinoline and aldehyde) does not approach that required to involve $k_2'$ of equation 13 to a great degree, then little trouble is encountered when using the reactants in this form to yield the required styrylquinoline product. If a solvent is used which allows the concentration of zinc chloride to increase significantly, then product yield may decrease because of the increasing significance of $k_2'$.

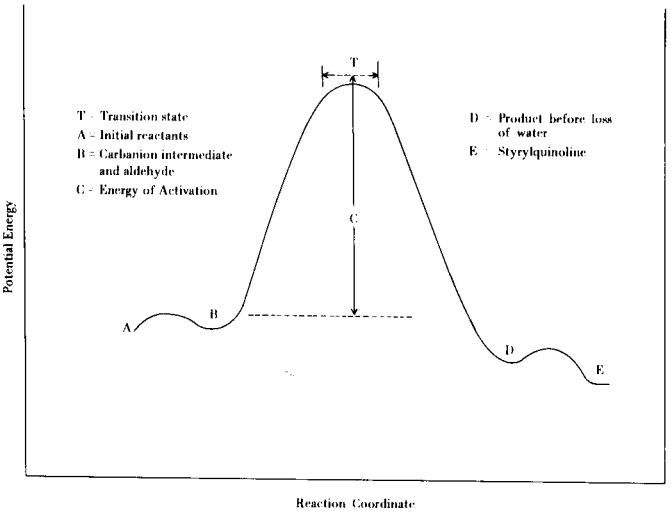


Figure 9. Free energy diagram for styrylquinoline formation.

Free Energy Diagram.

The free energy diagram predicted for the reaction of benzaldehyde and quinaldine in the presence of zinc chloride to give 2-styrylquinoline is illustrated in Figure 9. The relative sizes of the energy barriers are by no means quantitative but it is felt that the first barrier is small for the 2-methylquinoline reacting with benzaldehyde in the presence of a catalyst to give a carbanion intermediate and even smaller for the other methylquinolines. The non-reactivity of the methylquinolines other than those

with the methyl group in the 2 and 4 positions of the quinoline nucleus is attributed to the inadequacy of the carbanion formed after proton removal to attack the aldehyde and not to the degree of difficulty initially involved in the removal of the proton.

## EXPERIMENTAL

### A. Kinetics of Styrylquinoline Formation.

#### 1. Apparatus.

All reactions studied in this work concerning the kinetics of styrylquinoline formation were conducted in 50 ml. stoppered flasks. The flask and contents were equilibrated in a constant temperature oil bath capable of a temperature stability of plus or minus 0.15°.

#### 2. Analysis of Data.

The analytical tool used in this investigation was gas-liquid partition chromatography (glpc). The glpc measurements were made using a Varian, Model 1525-C, Dual Column, Matrix Temperature Programmed Gas Chromatograph (45) equipped with dual flame and dual thermal conductivity detectors. Both detectors were used during the kinetic runs, but the TC detectors were those used to evaluate results with the integration of peaks accomplished using a Honeywell, Model 16, recorded equipped with a disc chart integrator and an Infotronics, Model CRS 104, Digital Integrator.

The samples were injected into the chromatograph and the program started. After the integrated areas were obtained for the peaks, the necessary calculations, such as least squares treatment, were made with the aid of an IBM, Model 1130, computer.

Initial relative response factors for the substances used in this study were calculated using known standards with the use of equation 1 of the Results and Discussion Section. Injections were made until a constant value was obtained for each substance studied at that time. These values were confirmed before each run.

#### 3. Procedure for Kinetic Run.

The condensing agent was mixed with the aldehyde being used in each run until it dissolved or became homogenized. Infrared spectra of benzaldehyde and of a mixture of this liquid and zinc chloride in a molar ratio of 1.00:0.02, respectively, indicated that no complexation of the zinc chloride with the aldehyde oxygen was taking place (based on the carbonyl absorption). The methylquinoline was then added in an equi-molar amount to the aldehyde and the mixture was then immediately equilibrated to the constant temperature chosen. Aliquots of the mixture were removed periodically and a sample large enough to give adequate results at the attenuation chosen was obtained. It is not of importance that the sample size be constant because of the relative response factors used in this study. The time needed to sample the reaction was usually around ten seconds.

### B. Synthesis of Styrylquinolines (46).

During the course of the investigation it became necessary to synthesize certain styrylquinolines for various reasons. The synthetic procedures are given below.

#### 1. Preparation of 2-styrylquinoline.

2-Methylquinoline (2.00 g., 0.014 mole, Eastman Organic Chemical Co.) was mixed with benzaldehyde (1.50 g., 0.014 mole, J. T. Baker Chemical Co.) and acetic anhydride (1.45 g., 0.014 mole, J. T. Baker Chemical Co.) and heated at 100° for 24 hours. The resulting oil mass was treated with 20 ml. of 20% potassium hydroxide until a tan solid was obtained. The solid was recrystallized from 40 ml. of 95% ethanol yielding 2-styrylquinoline (2.47 g., 76%) as light tan needles, m.p. 99-100° (lit. (47) m.p. 98-99°).

#### 2. Preparation of 6-Chloro-2-styrylquinoline.

6-Chloro-2-methylquinoline (2.00 g., 0.0113 mole, K and K Chemicals) was mixed with benzaldehyde (1.20 g., 0.0113 mole) and acetic anhydride (1.17 g., 0.0113 mole) and heated at 100° for 24 hours. The oil which resulted was treated directly with 35 ml. of 20% potassium hydroxide solution and the resulting solid was recrystallized from 40 ml. of 95% ethanol to yield the title compound (2.80 g., 75%) as light yellow needles, m.p. 153.5-154.5° (lit. (48) m.p. 156-157°).

#### 3. Preparation of 2-(*p*-Dimethylaminostyryl)quinoline.

2-Methylquinoline (2.00 g., 0.014 mole) was added to *p*-dimethylaminobenzaldehyde (2.10 g., 0.014 mole, Eastman Organic Chemicals) and acetic anhydride (1.49 g., 0.014 mole) and heated for 24 hours at 100°. The oil which resulted was treated directly with 35 ml. of 95% ethanol yielding crystals within the solution. The solvent was vacuum evaporated and the residue dissolved in 35 ml. of absolute ethanol, decolorized with adsorbent charcoal and recrystallized from the same solvent to yield 2-(*p*-dimethylaminostyryl)quinoline (1.49 g., 39%) as flaky orange crystals, m.p. 184-185° (lit. (31) m.p. 186-187°).

#### 4. Preparation of 2-(*p*-Methylstyryl)quinoline.

2-Methylquinoline (7.15 g., 0.0499 mole) was added to *p*-methylbenzaldehyde (6.00 g., 0.0499 mole, Eastman Organic Chemicals) and anhydrous zinc chloride (0.1481 g., 0.0011 mole, Eastman Organic Chemicals) and the solution was heated for 13 hours at 92.4°. The entire mixture was treated with 20 ml. of 20% potassium hydroxide solution until complete solidification of product was attained. The solid was dissolved in 40 ml. of 95% ethanol, decolorized with adsorbent charcoal and crystallized from the same solvent to yield the title compound as light fluffy crystals. Recrystallization from acetone yielded the title compound (9.41 g., 77%) as dense white needles, m.p. 136.5-138° (lit. (49) m.p. 140°).

#### 5. Preparation of 4-Styrylquinoline.

4-Methylquinoline (7.15 g., 0.0499 mole, K and K Chemicals) was added to benzaldehyde (5.29 g., 0.0499 mole) and anhydrous zinc chloride (0.1360 g., 0.0010 mole) and the mixture was heated at 104° for 48 hours. The oil mass which resulted was treated in two equal portions with the first being treated with 30 ml. of absolute ethanol and the second being treated with 40 ml. of 3% potassium hydroxide solution. Both solutions were allowed to stand for 48 hours. After this time, clear crystals appeared in both oils which were then separated and recrystallized from acetone. The title compound was obtained in 51% yield (5.88 g.), m.p. 88.5-90.5° (lit. (25) m.p. 92-92.5°).

#### 6. Preparation of 2-(*p*-Chlorostyryl)quinoline.

2-Methylquinoline (7.15 g., 0.0499 mole) was mixed with *p*-chlorobenzaldehyde (7.01 g., 0.0499 mole) and anhydrous zinc chloride (0.1446 g.) and heated at 92.4° for 24 hours. A precipitate formed readily and was observed to form within one hour of initial mixing. The precipitate plus solution was treated with 30 ml. of 10% potassium hydroxide solution and the resulting solid mass separated from the mixture by decanting the liquid from the solid. The mass was then dissolved in 30 ml. of absolute

ethanol to yield, after crystallization from this solvent, 2-(*p*-chlorostyryl)quinoline (9.08 g., 68%) as flaky, green-yellow crystals, m.p. 139-140° (lit. (50) m.p. 142.8-143.2°).

7. Preparation of 2-(*p*-Methoxystyryl)quinoline.

2-Methylquinoline (7.15 g., 0.0499 mole) was added to *p*-methoxybenzaldehyde (6.80 g., 0.0499 mole, Eastman Organic Chemicals) containing 0.1470 g. of zinc chloride. The mixture was heated at 92.4° for 24 hours and the oil mass which resulted was treated with 30 ml. of 5% potassium hydroxide solution. The yellow solid which then resulted was separated from the mixture by decanting, dissolved in 30 ml. of acetone, decolorized with adsorbent charcoal and crystallized from acetone to give 2-(*p*-methoxystyryl)quinoline (9.64 g., 74%) as small, light yellow needles, m.p. 123.5-124.5° (lit. (51) m.p. 127.5°).

8. Preparation of 6-Methyl-2-styrylquinoline.

2,6-Dimethylquinoline (2.00 g., 0.0129 mole, K and K Chemicals) was added to benzaldehyde (1.37 g., 0.0129 mole) and acetic anhydride (1.34 g., 0.0129 mole) and the mixture heated for 24 hours at 100°. The residual mass was then treated with 20 ml. of 5% potassium hydroxide solution and decolorized with adsorbent charcoal in 30 ml. of absolute ethanol. Crystallization from ethanol yielded 6-methyl-2-styrylquinoline (1.38 g., 43%) as small white granules, m.p. 136-137.5° (lit. (52) m.p. 137-138°).

9. Preparation of 6-Ethoxy-2-(*p*-methoxystyryl)quinoline.

6-Ethoxy-2-methylquinoline (2.00 g., 0.0106 mole, Aldrich Chemical Co.) was added to 4-methoxybenzaldehyde (1.61 g., 0.0117 mole, 10% excess) and 0.140 g. of zinc chloride was dissolved in the mixture. The solution was heated at 95° for 72 hours until a solid residue was obtained. The mass was treated with 15 ml. of 10% potassium hydroxide solution and stirred for 15 minutes. The brownish solid was filtered off and dissolved in 25 ml. of absolute ethanol, decolorized with adsorbent charcoal and crystallized from the same solvent to yield small yellow needles of 6-ethoxy-2-(*p*-methoxystyryl)quinoline (1.53 g., 47%, m.p. 152.4-154°). The proton nmr spectrum consisted of the following: triplet, δ 1.4; singlet, δ 3.85; quartet, δ 4.1; multiplets, δ 6.9, 7.4, 7.85.

*Anal.* Calcd. for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27. Found: C, 78.57; H, 6.37.

10. Preparation of 6-Ethoxy-2-styrylquinoline.

6-Ethoxy-2-methylquinoline (2.00 g., 0.0106 mole), was added to benzaldehyde (1.13 g., 0.0106 mole) and acetic anhydride (1.11 g., 0.0106 mole), and the mixture heated for 24 hours at 100°. The resulting oil was treated with 25 ml. of 20% potassium hydroxide solution and stirred for 15 minutes. The solid obtained was dissolved in 20 ml. of absolute ethanol, decolorized with adsorbent charcoal and crystallized from the same solvent to yield 6-ethoxy-2-styrylquinoline (2.16 g., 72%) as fiery yellow needles, m.p. 120-121°. The nmr spectrum consisted of the following: triplet, δ 1.3; quartet, δ 4.0; multiplets, δ 6.8, 7.3, 7.8.

*Anal.* Calcd. for $C_{19}H_{17}NO$: C, 82.88; H, 6.22. Found: C, 82.77; H, 6.21.

11. Preparation of 6-Dimethylamino-2-styrylquinoline.

6-Dimethylamino-2-methylquinoline (2.00 g., 0.0107 mole, Eastman Organic Chemicals) was added to a mixture of benzaldehyde (1.13 g., 0.0107 mole) and acetic anhydride (1.11 g., 0.0107 mole) and heated for 24 hours at 100°. The oil which was air dried and sublimed (100°, 0.1 mm Hg) to give yellow crystals which, when crystallized from absolute ethanol, yielded 6-dimethylamino-2-styrylquinoline (1.89 g., 63%) as dense yellow-green crystals, m.p. 163.5-165°. The nmr spectrum consisted of the following: singlet, δ 2.9; multiplets, δ 6.7, 7.4, 7.8.

*Anal.* Calcd. for $C_{19}H_{18}N_2$: C, 83.12; H, 6.61. Found: C, 82.98; H, 6.70.

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(46) Melting points were performed on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Microanalyses were performed by the Galbraith Laboratories, Knoxville, Tenn. The nmr's were performed on a Varian A-60A instrument using deuterated chloroform as the solvent.
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