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A STUDY OF THE REACTION OF SOME
AROMATIC AMINES WITH GLYOXAL

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A THESIS

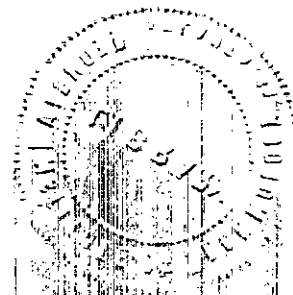
Presented to
the Faculty of the Graduate Division
Georgia Institute of Technology

In Partial Fulfillment
of the Requirements for the Degree
Master of Science in Chemistry

By

Robert Wade Collier

June 1955



A STUDY OF THE REACTION OF SOME
AROMATIC AMINES WITH GLYOXAL

Approved:

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Date Approved by Chairman:

March 17, 1955

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SUMMARY

It had been reported that quinoline could be obtained through a two-step reaction between glyoxal and o-toluidine. It was thought that this method could be extended to provide a convenient synthesis of 5-substituted quinolines which are not easily obtained by existing methods. This work was undertaken to study the feasibility of utilizing this reaction to obtain substituted quinolines and to separate and identify intermediate products which might be formed.

While the ultimate objective was to prepare substituted quinolines, it was deemed appropriate to study first the aspects of the reaction for quinoline itself. Repeated attempts under a wide variety of conditions failed to produce quinoline, however. In these attempts, glyoxal was used in several different forms or modifications, viz., a 30 per cent technical grade water solution, solid polyglyoxal, monomeric glyoxal, and glyoxal sodium bisulfite. o-Toluidine was used as the unmodified base and as the hydrochloride salt. In one series of experiments, the reaction was carried out as nearly as possible according to the original reference with the exception that glyoxal was prepared by a different method. In other attempts a variety of conditions were tried. In no case was quinoline obtained, nor was an intermediate isolated which could be converted to quinoline.

In the process of attempting to prepare quinoline a new compound was isolated, glyoxal-bis-o-tolylimine, melting point 127.3-128.5° (corr.), which was formed from glyoxal and o-toluidine. A synthesis was developed whereby this compound was obtained in 58 per cent yield.

Since quinoline was not obtained from o-toluidine, it was thought that perhaps the use of an amine having more highly reactive hydrogens on the methyl group would prove more successful. In the compound 4-nitro-2-aminotoluene (nitrotoluidine) the methyl group should be activated by the nitro group in the para position. Accordingly, nitrotoluidine was used with glyoxal in an attempt to produce 7-nitroquinoline. This product was not obtained. Instead, a low yield of a yellow solid resulted, apparently formed from glyoxal and nitrotoluidine. The solid was not identified, however, due to difficulties in purifying it.

In the course of trying to prepare 7-nitroquinoline another new compound was isolated. It was shown to have been formed by the reaction of nitrotoluidine with the formaldehyde impurity in the technical grade glyoxal which was used. The analysis of this compound and its molecular weight indicate that it is N-methylene-2-methyl-5-nitroaniline, although it may exist in a cyclic trimer structure. It has a melting point of 234.3-235.4° (corr.).

Infrared absorption spectra were obtained on the new compounds and on o-toluidine and nitrotoluidine. These were

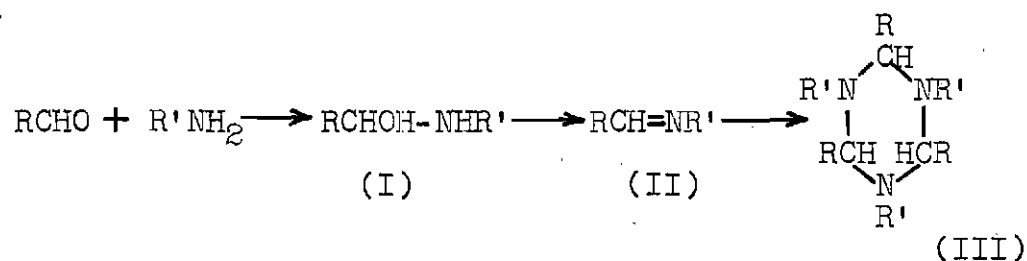
helpful in studying the structure of glyoxal-bis-o-tolylimine but provided no conclusive evidence in the case of N-methylene-2-methyl-5-nitroaniline.

A STUDY OF THE REACTION OF SOME
AROMATIC AMINES WITH GLYOXAL

CHAPTER I

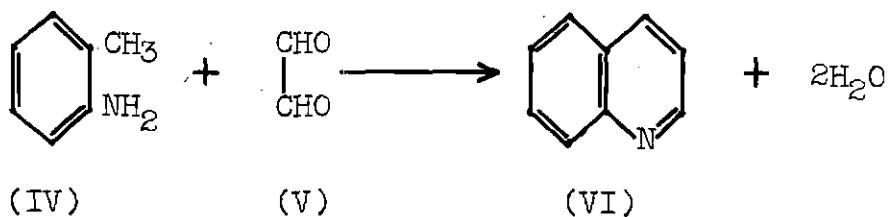
INTRODUCTION

Both aromatic and aliphatic amines are known to undergo reaction readily with aldehydes. Products of varying structure are obtained, depending upon the nature of the reactants and the conditions of reaction. Products which have been identified from the reaction with primary amines include alpha-hydroxy amines (I), substituted imines known as Schiff bases (II), and cyclic trimers of the Schiff bases (III). The step-wise formation of these substances is illustrated by the following equations in which R and R' may be either aromatic or aliphatic groups:



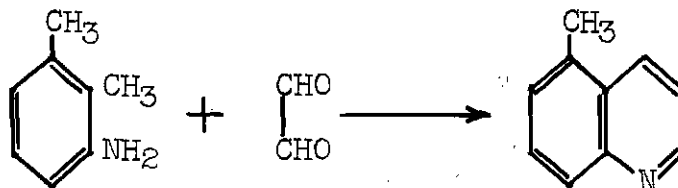
Kulisch (I) has reported a unique variation of this reaction in which *o*-toluidine (IV) and glyoxal (V) yield quinoline (VI). In its simplest form this reaction involves only the splitting out of water.

1. Kulisch, V., Monatsh., XV, 276 (1894).

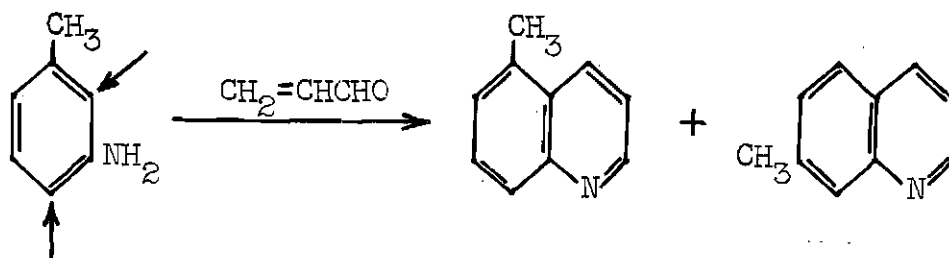


Kulisch suggested that a reaction first occurred by condensation of glyoxal with the methyl group of *o*-toluidine to form *o*-aminocinnamaldehyde. This intermediate was postulated as reacting further to give quinoline as a result of ring closure by a second condensation between the aldehyde function and the amino group.

Interest was shown in the Kulisch reaction not for its use as a synthesis of quinoline itself, but as a route to some substituted quinolines which are obtained only with difficulty. For example, 5-methylquinoline might be obtained as follows:



There are few attempts reported in the literature for the preparation of 5-substituted quinolines and these involve long, roundabout methods giving low overall yields. The well known Skraup synthesis if utilized for the preparation of 5-methylquinoline would occur as follows:



In this case ring closure can occur at either of the two positions indicated. It so happens that the formation of 7-methylquinoline is favored and 5-methylquinoline is produced only in small amounts.

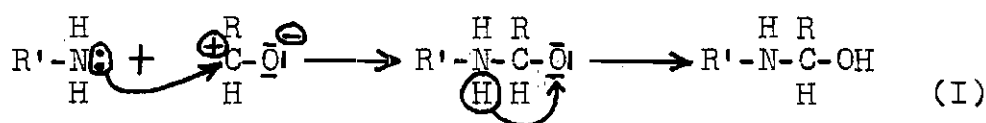
This work was undertaken to study the feasibility of utilizing the Kulisch reaction to obtain substituted quinolines. Another objective was to separate and identify intermediate products which might be formed, thus testing the validity of Kulisch's "mechanism" for quinoline formation.

CHAPTER II

GENERAL CONSIDERATIONS

Aldehyde-Amine Reactions.--The reactions of aldehydes with amines have been studied extensively and reported in the literature. Much of this work has been summarized in a review article (2).

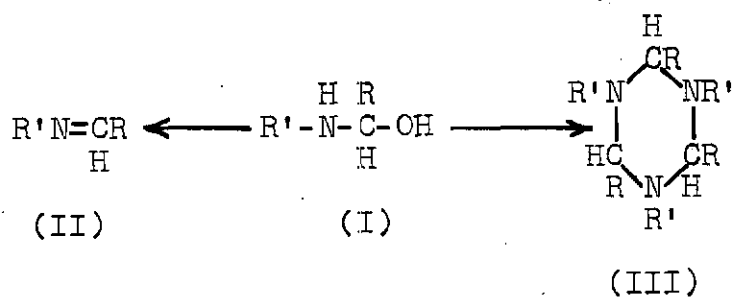
The reaction is believed to occur by the attack of the amino nitrogen on the electron deficient carbonyl carbon atom (3). A new carbon-nitrogen bond is formed and a proton migrates from the nitrogen to the oxygen atom of the new intermediate. The product of this step is the alpha-hydroxy amine (I) which is formed as shown in the following general equation, where R and R' represent either aromatic or aliphatic groups.



In most cases the hydroxy-amine cannot be isolated and reacts further in one of several ways (2,3). It may lose water to form either the imine Schiff base (II) or a cyclic trimer (III), depending upon the reaction conditions.

2. Sprung, M. M., Chem. Rev., 26, 297 (1940).

3. Alexander, E. R., "Principles of Ionic Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 163.



It is also possible for the Schiff base or the hydroxy-amine to react with other substances present, leading to the formation of complex products.

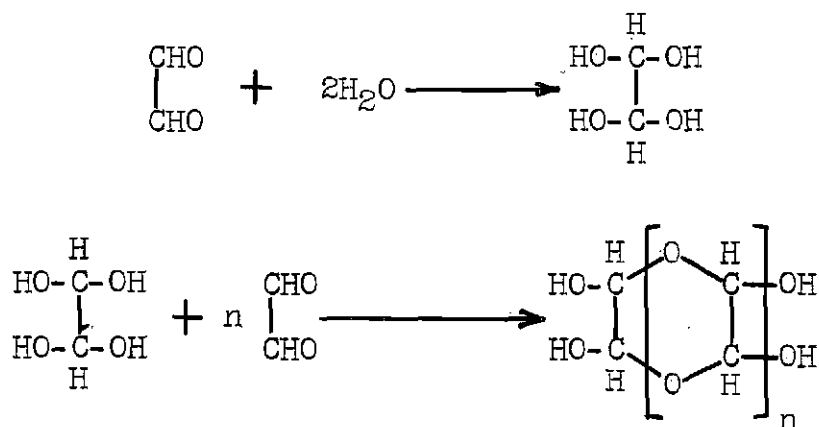
When an aromatic aldehyde reacts with either an aromatic or aliphatic amine (2), usually the Schiff base can be easily isolated. In the case where an aromatic amine is used with an aliphatic aldehyde, however, the isolation of the Schiff base seems to occur less readily, and the products usually are either the trimeric form or the di-(arylamino)alkanes, $\text{RCH}(\text{NHAr})_2$.

Glyoxal.--The work reported here was concerned primarily with glyoxal, which, under some conditions, can be represented by the formula $(\text{CHO})_2$. This substance reacts in many ways as a typical aldehyde, but in many ways it is singularly different. In the pure, anhydrous state it can exist in the monomeric form as a yellow liquid having a boiling point of 51° Centigrade^a at 776mm. It boils with the formation of a yellow-green vapor. Upon cooling, the liquid changes to a yellow

^aAll temperatures given in this report will be on the Centigrade scale.

crystalline material melting at 15° (4). The monomeric form is very unstable and polymerizes to a hard, yellow, very insoluble substance. This polymerization takes place instantaneously if traces of moisture are present but considerably slower in the anhydrous condition. When the monomer is exposed to a slight excess of water it polymerizes to a white, water-soluble solid, which is believed to be a cyclic polymer of the hydrated glyoxal. This form is frequently referred to as polyglyoxal. The hydrate is stable to the extent that fractional distillation of an aqueous solution will not liberate glyoxal, but rather removes water, eventually leaving behind the solid hydrated polymer. This property of glyoxal to polymerize and to hydrate so readily is attributed to the strongly activating effect of the adjacent carbonyl groups, one upon the other.

The hydration of glyoxal and the structure of its hydrated polymers are shown by the following reactions:



4. Harries, C. and P. Temme, Ber., 40, 165 (1907).

Since the second reaction is reversible, the value of n depends upon the concentration of glyoxal. For solutions up to 60 per cent the value is between 1.0 and 3.5 (5).

When an aqueous solution of glyoxal is vacuum distilled, the viscosity increases and the solution becomes syrupy. This syrup, if dried in a vacuum oven at 120° , yields a lightweight, tan-colored, friable resin. A procedure for the preparation of monomeric glyoxal consists of cautiously heating a mixture of this solid and phosphorous pentoxide and collecting the expelled vapor in a flask cooled by means of dry ice and acetone (4).

Reactions for the preparation of glyoxal, when carried out in the presence of moisture or in aqueous medium, result in the formation of the hydrated forms. The nitric acid oxidation of paraldehyde has been used as a method for preparing glyoxal in aqueous solution (6). The action of selenium dioxide upon acetaldehyde results in an almost quantitative yield of polyglyoxal (7). Selenious acid is the basis for a method in which the product is isolated as the bisulfite addition compound (8). The selenium dioxide oxidation of

5. Bohnfalk, J. F., Jr., R. W. McNamee, and R. P. Barry, Ind. Eng. Chem., 43, 786 (1951).

6. deForcrand, M. R., Bull., 41, 240 (1884).

7. Riley, H. L., J. F. Morley, and N. A. C. Friend, J. Chem. Soc., 1932, 1881.

8. Ronzio, A. R. and T. D. Waugh, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., 1944, Vol. 24, p. 61.

ethylene also leads to high yields of glyoxal bisulfite (9), and this method has been modified by the inclusion of phosphorous pentoxide to obtain anhydrous, monomeric glyoxal (10).

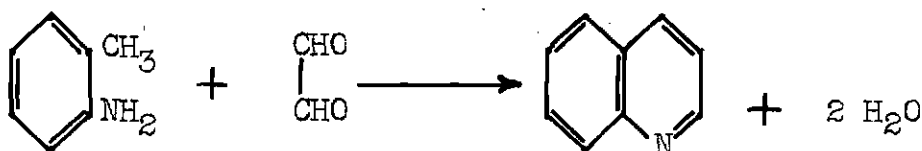
While several reactions have been studied for the commercial production of glyoxal, the air oxidation of ethylene glycol (5) is apparently the method currently favored in the United States. The product which is marketed from this process is an aqueous solution containing 30 per cent glyoxal and small amounts of formaldehyde, formic acid, glycolic acid, and acetals, which are formed in the reaction, together with a small amount of unreacted ethylene glycol.

In most cases the hydrated forms react chemically in the manner for aldehydes in general. Since glyoxal is a bifunctional molecule, its reactions may lead to polymer formation which may be troublesome.

The Kulisch Reaction.---Kulisch (1) reported that the reaction of glyoxal with *o*-toluidine resulted in the formation of quinoline. The simplest form of the reaction which involves only the splitting out of water is shown by the equation:

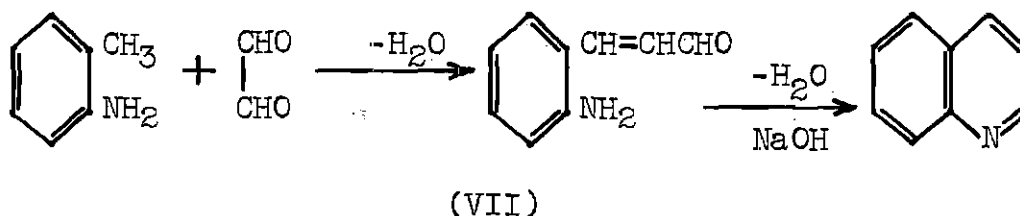
9. Riley, H. L. and N. A. C. Friend, J. Chem. Soc., 1932, 2342.

10. LuValle, J. E. and V. Schomaker, J. Am. Chem. Soc., 61, 3521 (1939).



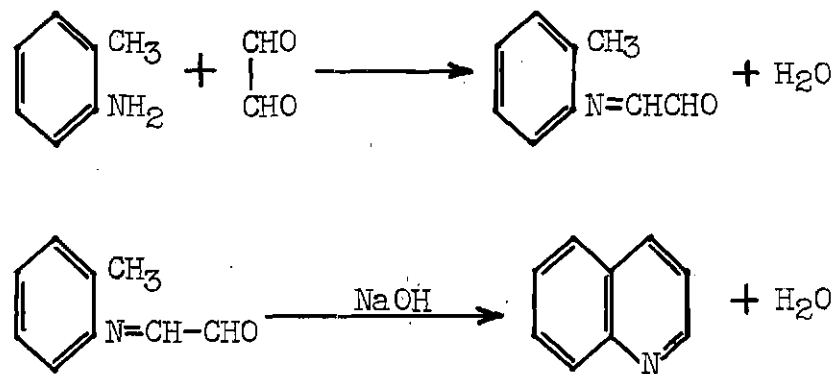
The glyoxal used by Kulisch was in the form of solid polyglyoxal prepared by the nitric acid oxidation of paraldehyde according to the method of deForcrand (6). Twenty grams of this polyglyoxal was added to 50 g. of *o*-toluidine and heated on the water-bath until solution was complete. Then 25 g. of 33-1/3 per cent sodium hydroxide solution was added and the mixture heated at reflux for 1.5 hours. The contents of the flask, which was dark brown and had an odor of quinoline, was diluted with water and extracted with ether. After further processing there was obtained a colorless oil, boiling between 226°-228° and having the odor of quinoline. The yield of crude quinoline was about 35 to 40 per cent of the theoretical.

Kulisch suggested that the formation of quinoline took place in two steps, with a condensation first taking place with the methyl group. It was postulated that *o*-aminocinnamaldehyde (VII) formed as an intermediate which reacted by intramolecular ring closure to form quinoline.



The basis for the postulation of the o-aminocinnamaldehyde was due to the report that the reduction of o-nitrocinnamaldehyde yielded quinoline, o-aminocinnamaldehyde presumably being an intermediate (11).

However, in the light of present concepts, it seems more likely that the initial condensation would occur first at the more reactive amino group. For example, the reaction of o-toluidine with formaldehyde has been reported to give two different products (12,13), neither of which was due to the reaction of formaldehyde with the methyl group but rather with the amino group. It seems more probable that the Kulisch reaction would proceed by the following reaction paths:

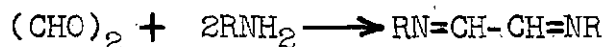


In our work it seemed advisable, therefore, to attempt isolation of the intermediate, or intermediates, in order to help clarify this point.

-
11. Baeyer, A. and V. Drewsen, Ber., 16, 2207 (1883).
 12. Wellington, C. and B. Tollens, Ber., 18, 3298 (1885).
 13. Eberhardt, C. and A. Welter, Ber., 27, 1804 (1894).

Other Reactions of Amines with Glyoxal.--A search of the literature revealed an almost complete absence of accounts of other reactions of glyoxal with amines. The notable few included the reactions of aniline (14) and o-toluidine (15) with glyoxal sodium bisulfite in alcoholic solution. The products of these reactions were the anilinoacetic acid anilide, $C_6H_5NHCH_2CONHC_6H_5$, and the corresponding compound of o-toluidine.

It has been reported that with primary amines the expected derivatives are obtained as shown in the following general equation (16,17):



No reference to a specific compound of this type could be found, however.

Glyoxal and o-phenylenediamine give good yields of quinoxaline (18). The sodium bisulfite addition compound also gives good results in the preparation of quinoxaline (19).

14. Hinsberg, O., Ber., 21, 112 (1888).

15. Hinsberg, O. and J. Rosenzweig, Ber., 27, 3254 (1894).

16. Kirk, R. E. and D. F. Othmer, "Encyclopedia of Chemical Technology," The Interscience Encyclopedia, Inc., New York, N. Y., 1951, Vol. 7, p. 246.

17. Carbide and Carbon Chemicals Co. pamphlet, Glyoxal and Pyruvic Aldehyde.

18. Hinsberg, O., Ber., 17, 320 (1884).

19. Billman, J. H. and J. L. Rendall, J. Am. Chem. Soc., 66, 540 (1944).

CHAPTER III

EXPERIMENTAL

The Starting Materials

Glyoxal.--A technical grade of glyoxal in the form of a 30 per cent water solution was obtained from the Eastman Kodak Company. Their designation for this product was number T4435. This number will be utilized frequently when referring to the 30 per cent solution used without any further treatment. As has been mentioned previously, this solution, having a pH of about 1, contains small amounts of other substances. The T4435 solution was the starting material for all forms of glyoxal used in this work.

A method for the preparation of solid polyglyoxal (20) consists of adjusting an aqueous solution to pH 4-5 and distilling off the water at 60° under reduced pressure. This technique was used to prepare viscous solutions as well as solid polyglyoxal. In our work it did not appear to make a difference whether the pH was adjusted or not, and after the first few times the pH was not adjusted. A viscous solution having a glyoxal content of approximately 48 per cent was made by distilling water from the T4435 solution. In another case

20. Walker, J. F., U. S. Patent, 2,379,555 (1945).

a solid rosin-like material having an estimated glyoxal content of 56 per cent was obtained by continuation of the distillation.

Solid polyglyoxal also was prepared by a simpler modification of the above procedure. The T4435 solution was evaporated on the water-bath in an evaporating dish until a thick viscous mass was obtained. The dish and contents were then placed in a vacuum oven and held between 100° and 120° for about 4 hours at a pressure of approximately 25 mm. This procedure yielded a lightweight, foamed, brittle resin containing about 64 per cent glyoxal. This product actually contained little free water as the difference between 64 and 100 per cent is mostly accounted for by water combined in the hydrated polymer and the other non-aqueous materials originally present in the technical grade solution.

Monomeric glyoxal was prepared from solid polyglyoxal by the method of Harries and Temme (4). Ten g. of the polyglyoxal, 25 g. of phosphorous pentoxide, and 10 g. of dry sand were intimately mixed in a 200 ml., three-necked flask. A thermometer was inserted into the dry reaction mixture through a rubber stopper which closed the center neck of the reaction flask. One side neck was connected to a source of dry nitrogen and the other was connected to a receiver cooled by means of dry ice and acetone. A plug of glass wool was inserted between the flask and the receiver to prevent carry-over of

phosphorous pentoxide into the receiver. A long, slender tube or flask, similar in design to an ordinary cold-trap, served as the receiver. With all connections made, a slow current of nitrogen was allowed to sweep the assembly.

The flask was heated cautiously with an electric mantle since the reaction proceeded rapidly and vigorously when started. A temperature of slightly over 100° was required to start the reaction. It took about 30 minutes to reach this temperature. Once started, a copious evolution of heavy green vapor of glyoxal was observed which lasted only a minute or two, after which the release of glyoxal ceased. The monomeric glyoxal which collected in the receiver weighed 3 g.

Glyoxal Sodium Bisulfite.--One hundred ml. of the T4435 solution (0.72 mole of glyoxal) was added to one liter of freshly filtered, saturated sodium bisulfite solution. The white solid addition product soon began to form and after sitting overnight was removed by filtration. It was transferred to 300 ml. of cold water, stirred well, and filtered again. After air-drying overnight it was free of the odor of sulfur dioxide and weighed 181 g. which was 94 per cent of theoretical.

o-Toluidine.--This material was the best grade supplied by Merck and Company. A large batch, to serve as the supply for the entire work, was distilled from zinc dust using a Claisen-type distilling flask. The distillate was stored in several small brown bottles, tightly capped, until used.

o-Toluidine Hydrochloride.--Fifty-two ml. (0.5 mole) of distilled o-toluidine was poured slowly into 200 ml. of concentrated hydrochloric acid cooled in an ice bath. Crystals of the hydrochloride salt began to form and the mixture was cooled for an hour in the ice bath. The product was collected on a fritted glass suction filter after which the resulting cake was washed on the filter with ether, then twice with acetone, in order to remove adsorbed hydrogen chloride from the product. This yielded 32 g. of white crystals which was 44.6 per cent of theoretical.

4-Nitro-2-aminotoluene.--This material was obtained from the Eastman Kodak Company. It was their best grade and was used without further purification.

Formaldehyde.--This material, obtained from Merck and Company, was a U. S. P. Grade aqueous solution containing 37 per cent formaldehyde. It was used without further purification.

Attempted Preparation of Quinoline

While the ultimate objective was to prepare 5-substituted quinolines, it seemed appropriate to study first the aspects of the reaction for preparing quinoline itself. The most direct manner was to investigate what results could be obtained from the 30 per cent glyoxal solution and o-toluidine. A test tube experiment showed that when portions of each were poured together that a strongly exothermic reaction took place

with the formation of a dark colored solid. This was repeated under more refined conditions as described below.

Thirty-five g. of the T4435 solution (0.18 mole of glyoxal) was placed in a 100 ml. three-necked flask fitted with a mechanical stirrer, a dropping funnel, and a thermometer. The solution was heated to 50° and o-toluidine was added dropwise slowly enough that the temperature did not rise above 52° . Immediately upon contact of the amine with the solution, a brown color developed and, as the addition was continued, a dark solid increased in quantity in the dark-colored liquid. A total of 0.15 mole of o-toluidine was used. Upon sitting, the contents of the flask became a semi-solid mass. This material was stirred with a glass rod, made free of lumps, and washed with dilute sodium hydroxide solution. The solid which was obtained upon filtering was refluxed with 50 ml. of 33-1/3 per cent sodium hydroxide solution for two hours. The product of refluxing was comprised of a large lump of black tar in a dark-colored liquid. It gave no suggestion of the presence of quinoline and the aqueous phase failed to yield quinoline upon extraction with benzene.

A variation of the above procedure was made using the 48 per cent concentrated glyoxal. Fifty g. (0.47 mole) of o-toluidine and 41.5 g. (0.345 mole) of the viscous glyoxal solution were placed in a 200 ml. flask. They did not become miscible after sitting at room temperature for two hours so the flask was heated slowly on the water-bath. Upon heating

and stirring, the two phases slowly changed to a brown liquid. This was removed from the water-bath but in a few minutes a vigorous exothermic reaction occurred. The flask was cooled under the tap and the contents stirred. A black viscous tarry mass formed which was refluxed for 1.5 hours with 25 g. of 33-1/3 per cent aqueous sodium hydroxide. The product was a thick, black tar, which was not processed further since it did not appear that quinoline was present. In this experiment all materials were used in the same stoichiometric proportions as described by Kulisch (1).

The use of solid polyglyoxal (64 per cent) led to essentially the same results. The solid did not dissolve in o-toluidine, but when a mixture was heated slowly on the water-bath for one hour, the temperature reached about 80° and a strongly exothermic reaction occurred as before.

In the experiments above, apparently undesirable polymerization reactions occurred between the glyoxal and the amine. It is to be expected that polymerization would decrease as the concentration of reactants is decreased. Accordingly reactions were carried out in aqueous media at higher dilutions.

In the preparation of quinoxaline from glyoxal sodium bisulfite and o-phenylenediamine (19) it was found necessary to use dilute solutions of both reagents, otherwise polymeric substances formed and yields were low. Using this procedure

an attempt was made to prepare quinoline. A solution was prepared by dissolving 66.5 g. (0.25 mole) of glyoxal bisulfite in 400 ml. of water at 70°. In another container, 26.75 g. (0.25 mole) of *o*-toluidine was placed in 500 ml. of water and heated to 70°. Even though all of the amine did not dissolve, the mixture, nevertheless, was poured into the solution of glyoxal bisulfite and the flask was shaken vigorously. The amine soon became completely dissolved and upon continued shaking a cloudy brown color slowly developed. After standing overnight the flask contained a clear, light yellow colored solution with a small amount of black resinous material which had settled on the bottom. The solution was divided and portions treated differently in an attempt to isolate the products of the reaction.

A portion was distilled under reduced pressure to remove some of the water. Upon addition of ethanol to the concentrate, a white crystalline solid was obtained. This solid, apparently unreacted glyoxal bisulfite, was removed by filtration and amounted to about two-thirds of the original weight of glyoxal bisulfite. The filtrate was made basic, extracted with benzene, then made acidic and extracted again. These extractions yielded only small amounts of dark amorphous material.

The other portion was treated with sodium hydroxide whereupon a yellow precipitate formed. This was removed from the aqueous phase by extraction with benzene. The crude yellow

solid amounted to about 7.6 g. based upon the reaction as a whole. An ether extraction following the benzene extraction failed to yield anything more from the aqueous solution. The yellow solid was recrystallized several times from benzene and melted at 126.5-127.5^o.^b Further characterization of the yellow solid and methods for its synthesis are described in sections which follow.

In another attempt to produce quinoline, o-toluidine hydrochloride was used since the amine salt is more water-soluble. A dilute solution of glyoxal was made by adding 25 ml. of the T4435 solution to 250 ml. of water. An equal molar amount of o-toluidine hydrochloride, 24 g. or 0.175 moles, was dissolved in 100 ml. of water. The glyoxal solution was placed in a flask provided with a mechanical stirrer, heated to 70^o, and maintained at this temperature throughout the reaction. The amine hydrochloride was added drop-wise over a period of 1.25 hours. During this time the solution became cloudy due to the formation of a dark solid. After holding the temperature for an additional half-hour at 70^o the solution was allowed to cool and left overnight at room temperature. A dark brown powder weighing 13 g., was collected upon filtering the reaction mixture. This powder was a low-melting amorphous substance and was not processed further. In other

^bMelting points in all cases were determined with an electrically heated aluminum block using an ordinary calibrated thermometer. No stem corrections have been applied unless specifically stated.

experiments similar materials had failed to yield quinoline upon refluxing with sodium hydroxide and this did not appear to offer any greater possibility of doing so. In like manner, no attempt was made to extract material from the filtrate since similar experiments had been followed through by extractions without yielding quinoline.

The hydrochloride salt was used also with glyoxal bisulfite. Ten g. (0.0375 mole) of glyoxal sodium bisulfite was dissolved in 200 ml. of water. To this was added a solution of 4.3 g. (0.03 mole) of *o*-toluidine hydrochloride dissolved in 50 ml. of water. After standing at room temperature overnight a yellow solution resulted. Nothing was obtained upon extracting this solution with benzene and with ether. The solution was treated further by heating for five hours at 60° which caused the evolution of sulfur dioxide. After filtering off a small amount of black residue a clear yellow solution again resulted which yielded nothing upon extracting with ether. An equal volume of ethanol was added to the solution. This yielded a white solid, apparently glyoxal bisulfite, weighing 4.5 g. Further processing of the ethanolic solution yielded negligible amounts of unidentified material. Upon evaporating the solution to dryness, 2.5 g. of a solid which appeared to be inorganic was obtained.

Conditions of still higher dilution were tried using *o*-toluidine and solutions of glyoxal. Several experiments

were performed in which such factors as temperature, and rate and order of addition of reactants were varied. These were all carried out in aqueous solution at relatively high dilution. The following is a typical example. Twenty-seven ml. (0.25 mole) of *o*-toluidine was placed in 1500 ml. water (approximately the amount found necessary to dissolve the amine at 80°). An equal molar quantity of glyoxal T4435 (38 ml.) was dissolved in 300 ml. of water and heated to 70°. The amine solution was heated to about 80° and the glyoxal solution was poured into it, with moderate stirring being maintained. No further heating was provided. In this case the immediate formation of a large amount of bright yellow solid was observed. The color rapidly darkened, however, and the product of this reaction was 23 g. of a black low-melting amorphous solid. Here again no attempt was made to convert this to quinoline as it appeared unlikely to be successful due to the nature of the material. When the order of addition was reversed with the amine added to the glyoxal over a period of 1.5 hours, essentially the same results were obtained. However, the slow addition of glyoxal to the amine solution led to the isolation of the yellow solid (melting point 126.5-127.5°) previously mentioned on p. 20.

Thus far all efforts using some form of the technical grade glyoxal failed to produce quinoline. It was thought that the monomeric glyoxal, obtained from the phosphorous pentoxide

treatment, would be free of impurities or other agents which might be the cause of the failure to produce quinoline. Since the monomeric glyoxal must be kept strictly free from water, the reaction was carried out in dioxane which had been dried over sodium wire. Approximately 2 g. (0.035 mole) of monomeric glyoxal was dissolved in 10 ml. of dioxane. An equal molar amount (3.7 ml.) of o-toluidine was added to the dioxane solution. A strongly exothermic reaction ensued and the container was cooled under the tap. The solution turned jet-black. Two and one-half g. of sodium hydroxide dissolved in five ml. of water was added, and the mixture refluxed for two hours. This resulted in a jet-black liquid which was diluted with 150 ml. of water and extracted with 100 ml. of benzene. Upon distillation of this extract, about two ml. of an acid-soluble oil was obtained which did not appear to be quinoline. This was not characterized further but was concluded to be o-toluidine due to its similarity in odor.

In another experiment equal molar proportions of monomeric glyoxal and o-toluidine were brought together without the use of solvent. These reacted vigorously as before, forming an amorphous product which failed to yield quinoline when refluxed with sodium hydroxide in the usual manner.

Other Experiments With Glyoxal and o-Toluidine

More information was obtained on the yellow solid, melting point 126.5-127.5°, which was first produced from o-toluidine and glyoxal bisulfite as described on p. 20. A study

was made to characterize the compound, to develop a satisfactory synthesis of it, and to investigate its role in the formation of quinoline.

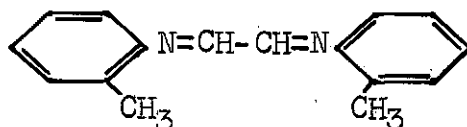
In order to prepare more compound, another experiment was performed similar to that in which the compound was first isolated. A solution was prepared by dissolving 66.5 g. (0.25 mole) of glyoxal bisulfite in 500 ml. of water at 70°. To this hot solution was added directly 26.75 g. (0.25 mole) of o-toluidine. It was added in small portions, with shaking, as fast as it was taken up by the solution. After sitting for two days, a small amount of dark resin was filtered off to give a clear, golden colored solution. The solution was made strongly basic by the addition of 75 ml. of 20 per cent sodium hydroxide solution which caused the formation of dark colored material suspended in the liquid. Since the solution was difficult to filter, the solid product was removed by extraction with benzene. After evaporation of the benzene, the remaining solid was recrystallized three times from benzene to a constant melting point of 126.5-127.5°. A very poor yield of 0.23 g. was obtained.

After drying to constant weight in a vacuum oven, a sample was analyzed^c with the following results:

^cAnalyses were made by the Galbraith Microanalytical Laboratories, Knoxville, Tenn.

	Found, duplicate results		Calculated (for C ₁₆ H ₁₆ N ₂)
Carbon	81.46%	81.47%	81.30%
Hydrogen	6.68	6.82	6.83
Nitrogen	11.87	11.73	11.86

On the basis of its method of preparation and the analytical results, the compound was considered to have the following structure:



Glyoxal-bis-o-tolylimine

As additional evidence to substantiate this structure, attempts were made unsuccessfully to convert the compound by hydrogenation to a known derivative, N,N'-di-o-tolyl-ethylene-diamine, melting point 78° (21). Three experiments were carried out using a Parr low-pressure hydrogenation apparatus. In each case 2.36 g. (0.01 mole) of the glyoxal-bis-o-tolylimine was dissolved in a solvent. In one experiment 175 ml. of 95 per cent ethanol was used, whereas 65 ml. and 100 ml. of benzene, respectively, was used in the other two. Platinum oxide served as a catalyst. In the experiment when ethanol was used, the catalyst weighed 0.25 g.; in the others with benzene it weighed 0.15 g. each. Hydrogen was admitted to a gauge pressure of 50 pounds per square inch and reduction was

21. Bischoff, C. A. and A. Hausdorfer, Ber., 23, 1982 (1890).

carried out with shaking. With the benzene solutions hydrogen was absorbed for about 30 minutes and then no further pressure drop was observed. The ethanol solution absorbed more slowly, however. In every experiment a pressure drop was observed which corresponded to the absorption of approximately 0.02 mole of hydrogen. After reaction the solvents were evaporated to obtain the product. When heated in the air, such as on the water-bath, the solutions rapidly darkened, and thus distillation at reduced pressure was found to be more satisfactory. Upon removing the solvents, dark colored oils were obtained which could not be induced to crystallize. The products were not further identified.

Tests were made on the solubility of glyoxal-bis-o-tolylimine (for brevity referred to as tolylimine) to learn how it could best be recrystallized. The compound was found to be very soluble in benzene and moderately soluble in ethanol. It was only slightly soluble in isopropyl alcohol at room temperature, but its solubility was sufficiently high when hot so that isopropyl alcohol could be used quite satisfactorily for recrystallizing the tolylimine. The compound was only slightly soluble in acetone at room temperature. This fact was utilized in purification of crude samples of the tolylimine. The crude material could be covered with a little acetone, stirred and filtered, with the result that the acetone removed resinous impurities leaving behind the compound with

much improved purity. It was advantageous to use this treatment, followed by recrystallization with isopropyl alcohol.

Several experiments were performed in a study of the conditions of reaction which would give a high yield of the tolylimine. Previous work had indicated that too high a temperature tended to lower the yield but it seemed reasonably satisfactory in the range of 70°.

Another factor which appeared to have a pronounced effect upon the yield was the pH at which the reaction was carried out. It was first observed in simple exploratory experiments that improved results were obtained if the glyoxal solutions were neutralized with sodium hydroxide before reacting with o-toluidine. It became the practice to follow this procedure.

A series of reactions was carried out in which the reaction time and ratio of reactants were varied in order to study their effects upon yield. All of these reactions were alike in certain respects. A volume of from one to two liters of water was used in each. The amounts of reactants used, for a given ratio, was such that the theoretical yield of the tolylimine would be either 0.025 or 0.05 mole. A typical experiment will be described to illustrate the procedure.

The reactants were used in a ratio of four moles of o-toluidine to one mole of glyoxal. A solution was made by dissolving 7.6 ml. (0.05 mole) of the T4435 glyoxal in 1500 ml.

of water. This was exactly neutralized with 20 per cent sodium hydroxide, as indicated by litmus paper, and heated to 70° . The solution was stirred in a beaker with a mechanical stirrer and 21.4 ml. (0.20 mole) of the amine was added. Stirring was continued and the temperature was maintained for 15 minutes, during which time a yellow cloudiness formed which gradually darkened. The solution was cooled to room temperature by placing the beaker in running water, after which stirring was continued for two hours. The product was collected on a filter as a brown solid weighing 8.5 g. after air-drying to constant weight. After sitting overnight the filtrate yielded additional crude material which was filtered and weighed 1.5 g., air-dried. The quality of the crude material obtained from this experiment was high enough that the acetone wash was omitted. After one recrystallization from isopropyl alcohol, 6.85 g. of material was obtained having a melting point of 126° - 128° . This is a yield of 58.0 per cent, the theoretical yield in this case being 11.8 g. or 0.05 mole.

A summary of the experiments in this series is tabulated in Table 1.

Table 1. Summary of Experiments on the Preparation of Glyoxal-bis-o-tolylimine

Experiment Number	Mole Ratio, <u>o</u> -Toluidine: Glyoxal	Conditions of Heating	Percentage Yield of Product, m. p. 126-128°
36	1:4	15 minutes at 70°, cooled quickly, then two hours at 30°.	42.4
37	1:4	Four hours at 70°.	None.*
41	2:1	Same as 36.	29.7
42	4:1	Same as 36.	58.0
45	4:1	One hour at 70°, cooled slowly to 40° in one hour.	48.3

*The product was 3.0 g. of black solid, acetone-soluble, which could not be crystallized.

The tolylimine was also formed by the reaction of monomeric glyoxal with o-toluidine. An unmeasured amount of the amine was added drop-wise to one ml. of monomeric glyoxal. A very vigorous reaction occurred and o-toluidine was added until no further reaction was detected. A dark solid was formed which was recrystallized twice from isopropyl alcohol. The recrystallized material had a melting point of 126-127.5°. It showed no depression of the melting point when mixed with a known sample of the tolylimine. This information is not

important for preparative purposes but may have theoretical significance.

It was considered that the tolylimine itself might be an intermediate in the Kulisch reaction, and that it might be converted to quinoline by the influence of sodium hydroxide. A sample of the tolylimine was placed in a solution of one part sodium hydroxide and two parts water. After standing several days at room temperature it was recovered unchanged. Another sample did not undergo reaction readily upon refluxing in a similar sodium hydroxide solution. Six hours of refluxing were required to convert all of it to an insoluble brown oil. This oil was extracted with benzene, then extracted from the benzene with hydrochloric acid solution. Upon neutralizing the acid extract, an oil was recovered which did not have the odor of quinoline. It was identified as o-toluidine by preparing a derivative with acetyl chloride which had a melting point of 109-110°. The recorded value for acet-o-toluide is 110° (22). A mixed melting point of this derivative with an authentic sample of acet-o-toluidide was unchanged.

To determine the melting point of glyoxal-bis-o-tolylimine precisely, a sample was selected that had been recrystallized from isopropyl alcohol and had a melting point of 126-128°. It showed a constant melting point when further

22. Alt, H., Ann., 252, 319 (1889).

recrystallized from benzene and then again with isopropyl alcohol. The melting point was determined with an electrically heated aluminum block using an Anschütz thermometer. The observed melting point for glyoxal-bis-o-tolylimine was 127.0-128.2°; the corrected melting point was 127.3-128.5°.

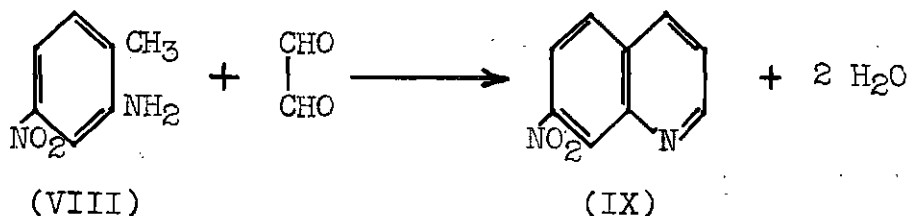
The tolylimine was found to be soluble in approximately 17.5 per cent hydrochloric acid and formed a purple solution. After sitting overnight this solution was made basic with sodium hydroxide. A brown oil which appeared to be o-toluidine separated on top of the water solution.

Experiments With Glyoxal and 4-Nitro-2-aminotoluene

It was thought that the inability to obtain quinoline from glyoxal and o-toluidine might be due to the low order of reactivity of the methyl group hydrogens. A more favorable condition for the formation of the quinoline nucleus would exist if the reactivity of the methyl hydrogens could be increased by the substitution of an activating group on the aromatic nucleus of o-toluidine. In the compound 4-nitro-2-aminotoluene (nitrotoluidine) the methyl group should be activated by the nitro group in the para position and would result in the methyl group having an increased reactivity in condensation reactions.^d Nitrotoluidine (VIII) by reaction with

^dFor a discussion of activating effects of nitro groups in condensation reactions, see Alexander, E. R., "Principles of Ionic Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 22, 129.

glyoxal should lead to the formation of 7-nitroquinoline (IX).



Experiments were performed using nitrotoluidine to investigate the possibility of obtaining 7-nitroquinoline in this manner.

Reactions were carried out both in water and in an organic solvent. Due to the low solubility of the nitrotoluidine, some of the experiments resulted in heterogeneous reactions when water was used. If a large volume and a sufficiently high temperature were used, however, the amine could be dissolved in water.

In an example of a heterogeneous reaction, 300 ml. of a neutral solution of glyoxal was prepared containing 7.6 ml. of the T4435 solution (0.05 mole of glyoxal). This solution was placed in a 500 ml. flask equipped with a mechanical stirrer and heated with a Glas-Col mantle. To the solution at room temperature was added 7.6 g. (0.05 mole) of nitrotoluidine. Stirring was maintained and the temperature was raised slowly to 96° in four hours. At all times there was a large amount of solid present in the reaction mixture. The liquid was filtered but a large amount of the solid product adhered to the walls of the flask in a fused condition. Solid which

had been removed by filtering was returned to the flask and the entire solid product was extracted by heating for an extended period in 300 ml. of ethanol. The solid was loosened from the walls of the flask by scraping and stirring, but not all of it dissolved. A brown colored material weighing 1.98 g. was obtained by filtration. The clear alcoholic filtrate was concentrated by distillation at reduced pressure. This caused the precipitation of an intermediate portion weighing 1.13 g. Final removal of the alcohol to dryness yielded 3.49 g. more of brown solid. The melting points of the first and middle products were not sharp, and were roughly of the order of 150° . The solid obtained last melted at about 80° . Solubility considerations and the fact that some material melting at $105-108^{\circ}$ was separated from this last fraction led to the conclusion that it was a mixture of amorphous material and unreacted nitrotoluidine. The recorded melting point for nitrotoluidine is $105-107^{\circ}$ (23).

The alcohol insoluble portion which was obtained first was the product of main interest. Washing with acetone was found to improve the color of the material considerably. One treatment yielded a jet-black filtrate and an 84 per cent return of a bright yellow solid. However, little improvement of

23. Lange, N. A., "Handbook of Chemistry," eighth edition, Handbook Publishers, Inc., Sandusky, Ohio, 1952, p. 618.

the melting point resulted. The amount of acetone used for washing was not critical inasmuch as the solubility of the yellow product was very low in this solvent. Recrystallization of the acetone washed material was attempted from a large number of the commonly used solvents, but the solubility of the solid was too low in all except chlorobenzene. It was found that the substance dissolved satisfactorily when heated in chlorobenzene, and that a solid reformed upon cooling. The substance was not readily soluble in nitrobenzene, and upon heating in this solvent, it appeared to decompose and would not recrystallize from the solution. Even though it was found that the solid could be recrystallized from chlorobenzene, its identity was not determined at this time. Data will be given later to elucidate this point. 7-Nitroquinoline did not appear to be formed in the reaction. Any appreciable amount of it would have been insoluble in the aqueous reaction liquid. It is reported to be slightly soluble in alcohol and has a melting point of 132-133° (24). These properties would have enabled it to be detected easily in the procedure used in handling the product.

Several other heterogeneous reactions were carried out with only minor modifications of the one described above. In two cases the reactions were carried out with agitation

24. Claus, A. and C. Massau, J. prakt. Chem. [2], 48, 170 (1893).

provided by a mechanical shaker instead of by a stirrer, and in these cases the temperature was lower. The yields of acetone washed material in all of these reactions was of the same order as for the one described.

Attention was given to the identification of the yellow solid obtained in these experiments. Simple recrystallization did not yield a pure product, and it became apparent that two or more substances were present in this material. It was observed further that part of the material sublimed, this fact being utilized to separate one component in a fairly pure state. The yellow solid was first recrystallized from chlorobenzene and then subjected to sublimation. Part of the material sublimed and part of it was left behind. The sublimate was again recrystallized to yield golden colored plates which were washed with benzene. Due to sublimation, all melting points of this compound were determined in sealed melting point tubes. It was observed that the compound tended to decompose upon heating to its melting point, especially if it were not in a high state of purity. For this reason, samples in sealed tubes were placed in a block at 225° as it was being heated up. Following this procedure, the melting point of the golden colored plates was found to be $233-235^{\circ}$. It was uncertain whether or not decomposition occurred upon melting. It appeared that very pure samples of this compound melted without decomposition.

The residue left behind in the above sublimation was recrystallized from isopropyl alcohol to yield light yellow colored, fine crystals. The melting point, as determined in the block preheated to 200° , was $223-224^{\circ}$ (dec.). There was not enough of the material isolated to allow it to be identified. As compared with the sublimable compound, this compound is much more soluble in chlorobenzene. Contrary to the other, it can be recrystallized from isopropyl alcohol and it is not easily sublimed.

A small portion of the acetone washed yellow solid was treated with concentrated sodium hydroxide to see if it could be converted to 7-nitroquinoline in this manner. A sample weighing 0.1 g. was placed in a solution formed from one part sodium hydroxide and one part water. This was heated by immersing the container in boiling water for one hour. The solid was stirred frequently but did not dissolve, and did not appear to change. After heating was stopped, the mixture was diluted with a little water and filtered. The solid was washed with water followed by ethanol. The melting point was $221-223^{\circ}$ (dec.). This material did not appear to be readily sublimable. While this and its melting point are similar to that observed for the compound described in the paragraph above, it is not known whether or not they are identical. The solid recovered here had a much more intense yellow color than the other.

Other experiments were carried out in the study of the reaction of nitrotoluidine and glyoxal in aqueous medium. An example of using a larger volume is an experiment in which 15.2 g. (0.1 mole) of nitrotoluidine was placed in three liters of water. The reaction was carried out in a beaker heated on a hot plate with the solution stirred by a mechanical stirrer. Due to the large volume of water used, all of the nitrotoluidine was dissolved upon heating to 80°. A separate solution was made by dissolving 15.2 ml. (0.1 mole) of the glyoxal T4435 solution in 200 ml. of water and neutralizing with sodium hydroxide. This was added to the amine solution causing the temperature to drop to 75°. The temperature was slowly increased to 92° over a period of two hours. The hot plate was removed and stirring continued while the solution cooled. The product, a brown granular solid, was collected on a filter. It weighed 12.5 g. after air-drying. A portion of this was washed with acetone and only 6.3 per cent was recovered as a slightly dark yellow colored solid. After one recrystallization in chlorobenzene and washing the crystals with benzene the product had a melting point of 233-234°. A 59 per cent recovery was obtained from the recrystallization. It should be noted that in this experiment only one of the components discussed above was isolated, also that it was easily obtained in a pure form without resorting to sublimation.

It was thought that the yield might be improved by making use of an organic solvent in which the nitrotoluidine

would be more soluble. Dioxane was selected for this purpose. The procedure for carrying out the reaction was based upon Experiment No. 45 (see Table 1, p. 29) which gave a good yield in the reaction of o-toluidine with glyoxal. It was desired to carry out the reaction in about one liter of a dioxane-water mixture, containing just enough dioxane to dissolve 28.8 g. (0.19 mole) of nitrotoluidine. A mixture of 600 ml. dioxane and 400 ml. of water was found to be satisfactory. When nitrotoluidine was dissolved in this mixture it produced a clear red solution. Another solution was made by dissolving 7.2 ml. (0.047 moles) of the glyoxal T4435 solution in 30 ml. of water and neutralizing with sodium hydroxide. The nitrotoluidine solution was heated to 70° in a beaker by means of a hot-plate and stirred with a mechanical stirrer. The glyoxal was added and in about ten minutes the red color, which was initially present, began to darken. The temperature was held at 70° for two hours. During this time the solution turned progressively darker until at the end it was completely opaque and the color was dark brown to black. Heating was stopped and, with stirring continued, the solution cooled to 45° in one hour. No solid appeared to have settled out. The reaction mixture was cooled in the refrigerator overnight, whereupon a small amount of crystals formed. These were removed by filtration and after air-drying weighed 0.56 g. Upon washing this solid with two 5 ml. portions of acetone, 0.50 g. of golden colored crystals was obtained. This material

sublimed upon heating. Its melting point was $230-232^{\circ}$. A mixed melting point determination indicated that this compound was the same as the compound with similar properties which had previously been isolated.

The dioxane-water filtrate was concentrated to about one-half its original volume by distillation under reduced pressure such that its temperature did not exceed 55° . A dark insoluble oil formed on the bottom of the container. After cooling in the refrigerator the oil solidified and could be removed by filtration. A clear filtrate was obtained but the material left on the filter consisted of a mixture of a solid and a very thick black liquid. This was washed with three 20 ml. portions of acetone and 4.18 g. of an orange-yellow powder was recovered. This material melted over a wide range starting at approximately 160° .

Difficulty was encountered in attempting to recrystallize the above material. It proved to be insoluble when heated in a variety of common solvents. In certain high boiling solvents, such as chlorobenzene, nitrobenzene, and anisole, it dissolved upon heating but only very minute quantities could be recovered when the solutions were cooled. This seemed to indicate that the solid changed when it was heated in these solvents, and that the product formed by this change was soluble in the respective solvents.

It appeared, therefore, that the reaction in the dioxane-water mixture led to the formation of two or more products, as was noted before for the reactions carried out in water alone. One advantage to be noted is that with the use of dioxane a virtually complete separation of the golden colored compound, melting point $233-235^{\circ}$, from the other products of reaction was achieved. It may be concluded, furthermore, that reactions in both solvents led to the formation of a yellow powder. It is not certain that the yellow powder had the same composition in all cases, but it has been observed to be similar in several respects, and no apparent difference was noted.

The identification of these substances was the object of continued study. As previously mentioned, the yellow powder could not be recrystallized as the only solvents which dissolved it apparently caused it to undergo a change. Small portions of the yellow powder from the dioxane reaction were used in recrystallization attempts. A sample was dissolved upon heating in chlorobenzene but when the solution was cooled crystals did not form. Part of the solvent was removed by vacuum distillation and the concentrated solution was cooled in the refrigerator. This yielded a small amount of pale yellow crystals which was filtered off and washed with benzene. The material melted at 212° , not sharply. Anisole and nitrobenzene were tried in like manner on samples of the yellow powder.

Minimum amounts of the solvents were used and it was not necessary to remove any by vacuum distillation. Pale yellow colored needles were collected and washed in benzene. The melting point of the material from anisole was 217-218^o(dec.); that from nitrobenzene, 218^o(dec.). A mixed melting point of these two showed no depression. A sample which had been recrystallized from nitrobenzene, with a melting point of 213-216^o, was found to be soluble in isopropyl alcohol and benzene, and upon further recrystallization from benzene it had a melting point of 222^o(dec.). Benzyl alcohol was also tried. A small sample dissolved in a little benzyl alcohol when boiled vigorously. While still hot, two volumes of isopropyl alcohol was added and upon cooling a good recovery of fine crystals resulted. The filtered material was washed with isopropyl alcohol and had a melting point of 220-221^o(dec.).

In order to characterize the yellow powder it was desirable to have a pure sample, and to obtain its analysis. Since it did not seem possible under the circumstances to isolate the material in a pure form, it appeared that an alternative was to isolate the material that was formed from the yellow powder upon heating in the solvents mentioned. It seemed that the best results in the small scale experiments described above had been obtained by the use of benzyl alcohol followed by diluting with isopropyl alcohol.

Accordingly, all that remained of the yellow solid from the dioxane reaction, 2.86 g., was placed in five ml. of benzyl alcohol contained in a small beaker. This made a thick paste which was heated by placing the beaker on an asbestos covered wire gauze over a burner. It was stirred while heating and gave off a considerable amount of cloudy vapor. The material slowly changed to a dark brown liquid. It was boiled momentarily, then removed from the heat, and 10 ml. of isopropyl alcohol was added. This solution was heated to boiling and filtered hot to remove foreign material. A considerable amount of dark tar formed when the dark liquor was cooled in the freezer and a clear solution was decanted from the tar. Solvent was removed from this solution by vacuum distillation to yield a yellow-brown pasty residue. Recrystallization was attempted from benzene, but instead of crystallizing upon cooling, the material came out of solution as a yellow powder. Filtration yielded about 0.2 g. of yellow solid which was not identified. The overall result of the benzyl alcohol treatment was that most of the material decomposed to resinous substances and the expected compound was apparently not formed.

The following résumé summarizes the results described above of work done with the products derived from nitrotoluidine:

a. Reactions carried out in aqueous medium yielded a crude residue, insoluble in alcohol. By washing the crude

residue with acetone, a yellow solid of much improved quality was obtained. This solid could be recrystallized from chlorobenzene but it appeared to decompose when heated in nitrobenzene. Sublimation indicated that this yellow solid was a mixture. The sublimate was recrystallized from chlorobenzene to yield the golden colored compound melting at $233-235^{\circ}$. The non-sublimable residue was recrystallized from isopropyl alcohol to yield light-yellow colored crystals, melting point $223-224^{\circ}$ (dec.).

b. A small portion of the acetone washed yellow solid was treated with concentrated sodium hydroxide solution on the water-bath. A yellow solid was recovered, melting point $221-223^{\circ}$ (dec.), which did not appear to be readily sublimable.

c. In the reaction carried out in dioxane-water mixture, the golden colored compound, melting point $230-232^{\circ}$, was obtained as a residue, insoluble in the reaction medium.

d. The dioxane-water filtrate was concentrated by vacuum distillation and a residue was obtained which yielded an orange-yellow powder upon washing with acetone. This powder dissolved upon heating in high boiling solvents but did not recrystallize in appreciable quantities, suggesting that decomposition occurred. The use of such solvents yielded very small samples of crystals having various melting points between about 212° and 222° .

e. An attempt to treat a sample of the orange-yellow powder with benzyl alcohol on a large scale was unsuccessful. A large proportion of the material decomposed and the small amount recovered was not identified.

A study was also made to identify the other substance, besides the yellow powder, derived from nitrotoluidine. As previously mentioned, 0.5 g. of the golden colored crystals, melting point $230-232^{\circ}$, was obtained from the reaction in dioxane-water mixture. This was purified further by recrystallizing three times from chlorobenzene to provide a sample suitable for analysis. After filtering from the liquor the crystals were washed with benzene to aid in complete removal of the solvent. The melting point of the final purified form was determined using an Anschütz thermometer. The observed melting point was $233.5-234.6^{\circ}$; corrected was $234.3-235.4^{\circ}$. After drying in a vacuum oven a sample was analyzed with the following results of duplicate analyses:

	Found		Average
Carbon	57.45%	57.27%	57.36%
Hydrogen	5.14	5.09	5.11
Nitrogen	17.77	17.62	17.70

Oxygen, by difference, was 19.83 per cent. The empirical formula was calculated to be C_4H_4NO .

Molecular weight determinations were made on the compound by the Rast method. A procedure was employed in which the necessary freezing points were determined on samples

sealed in thin-walled glass tubes, similar to but larger than melting point tubes. A small amount of camphor was introduced into a tube (sealed at one end) after which the other end was sealed. The tube was fastened to an Anschultz thermometer and immersed in an oil bath. By carefully controlled heating, a point was reached where all the camphor was melted except for one small crystal. At this point the temperature was allowed to drop very slowly and the temperature was determined where new crystals just began to form. This was taken as the freezing point of the camphor. Next, a small amount of the compound was introduced into another tube sealed at one end which had been carefully weighed previously. After weighing again, camphor was introduced. The tube was sealed and a final weighing made. The camphor and sample were heated above the melting point to insure complete solution and mixing. The freezing point of this mixture was then determined in the manner described above for pure camphor. Two determinations were made using mixtures of significantly different concentrations. The values calculated for the molecular weight of the compound were 151 and 161.

A correlation of the molecular weight with the empirical formula C_4H_4NO , suggests that the molecular formula is $C_8H_8N_2O_2$ corresponding to a molecular weight of 164.08. These data are in accord with the structural formula (X), which is



(X)

the substituted methyleneimine that might be formed from the reaction of nitrotoluidine with formaldehyde. It is not surprising that such a reaction might occur, inasmuch as formaldehyde is known to be an impurity in the glyoxal T4435 solution which was used in this work. It is somewhat surprising, however, that a compound of this structure would exhibit the observed properties, viz., the high melting point and the low degree of solubility. These properties suggest that the product may be polymeric but which dissociates under the influence of heat. This idea will be discussed further in Chapter IV.

As additional confirmation of the origin of this compound, a reaction was carried out between nitrotoluidine and formaldehyde. A solution was prepared by dissolving 0.47 g. (0.0031 mole) of nitrotoluidine in 175 ml. of water at 70°. A hypodermic syringe was used for introducing 0.15 ml. of the 37 per cent formaldehyde solution into the amine solution. This was a ratio of approximately two moles of formaldehyde to three moles of nitrotoluidine. The reactants were mixed by swirling the flask and a yellow color immediately appeared in the liquid. The mixture was left for several hours at room

temperature and a large amount of yellow solid formed. This was collected by filtration and the product was washed with water followed by acetone. The yield of yellow solid, melting point $231-233^{\circ}$, was 0.24 g. or 71 per cent of theoretical. This material was recrystallized from chlorobenzene to form bright yellow-golden plates which were washed with benzene. The observed melting point, determined with an Anschultz thermometer, was $234.0-235.4^{\circ}$; the corrected value was $234.8-236.2^{\circ}$.

To establish that the product from the formaldehyde reaction was the same, a mixed melting point was determined with the compound obtained from the reaction carried out in dioxane-water solution. No depression of the melting point resulted. Further proof that they are the same compound was shown by infrared analysis (see following section). Absorption curves of the two samples were identical.

This compound was found to be soluble in approximately 17.5 per cent hydrochloric acid solution. After sitting overnight the solution was made basic with sodium hydroxide. This caused the formation of a yellow solid which was collected by filtration. The melting point was $105-108^{\circ}$, agreeing well with that for nitrotoluidine.

Infrared Absorption Spectra

A study was made of the infrared absorption spectra of the compounds encountered in this work to aid in the determination of the structure of the new compounds. The Perkin-Elmer, Model 21, Infrared Recording Spectrophotometer was used

for obtaining the absorption curves. Reproductions of these curves appear in the Appendix.

The spectrum was obtained on a redistilled sample of o-toluidine. A cell was used having a nominal sample thickness of 0.025 mm. and a matched empty cell was placed in the reference beam.

The other materials whose spectra were needed were solids in their normal state. Due to the low solubility of the compound formed from formaldehyde, a suitable solvent was not found in which it could be dissolved for obtaining its spectrum. This made it necessary to obtain its spectrum in the solid state. A satisfactory method has been described for doing this by mixing the solid sample with potassium bromide and pressing the mixture into a thin tablet or disk (25). It was thought that for the purpose intended, it would be appropriate to obtain the spectra of the other solids by the same procedure. Modifications in the basic technique were necessitated by the equipment available. The procedure used in preparing a sample for spectrum analysis involved grinding potassium bromide, C. P., in a mortar until it passed a 100 mesh sieve. After drying to remove adsorbed moisture it was ready for use. It was found that approximately one milligram of sample mixed with 0.15 g. of potassium bromide gave the best

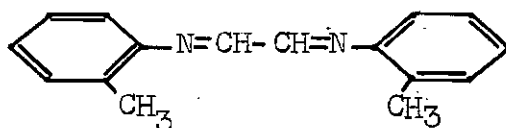
25. Stimson, M., Molecular Spectroscopy Symposium, Ohio State University, Columbus, Ohio, June, 1951.

results as judged by the spectra obtained. The sample and potassium bromide were weighed out and ground together in a small agate mortar. The mixture was poured into the mold, or die, of a hydraulic tablet machine and subjected to a pressure of 20,000 pounds per square inch. It was necessary to spread the sample evenly in the die before pressing to get a well-formed tablet. This resulted in the formation of a tablet measuring 13 mm. in diameter and approximately 0.5 mm. in thickness. A tablet to serve as a reference blank was prepared in the same manner from 0.15 g. of potassium bromide alone. For mounting in the spectrophotometer, the tablets were fastened over slits made in small cards. These cards were placed in the slots designed for mounting the conventional sample cells. The instrument was then operated in the regular manner to produce the absorption curve. In this manner the absorption spectra were obtained for nitrotoluidine, glyoxal-bis-tolyimine, the compound formed by reaction of nitrotoluidine with formaldehyde, and the compound formed from the T4435 solution and nitrotoluidine.

CHAPTER IV

RESULTS AND CONCLUSIONS

It has been shown that the reaction of o-toluidine with glyoxal results in the formation of a new compound which has been obtained in good yields. It is proposed that the compound has the structure:

Glyoxal-bis-o-tolylimine

The infrared absorption spectrum of this compound is shown in Fig. 3. Further information regarding its structure was developed by a comparison with the spectrum for o-toluidine, Fig. 1. Certain absorption bands of these spectra were given functional group assignments on the basis of data recorded in the literature (26). It should be noted that the curves were obtained on one compound in the liquid state and the other in the solid state, which in itself introduces slight differences in the position and intensity of certain absorption bands. In the three micron region o-toluidine has

26. Randall, H. M., R. G. Fowler, N. Fuson, and J. R. Dangle, "Infrared Determination of Organic Structures," D. Van Nostrand Company, Inc., New York, N. Y., 1949, p. 20.

a strong absorption at 3.00 microns due to the N-H bonds, and two medium bands at 3.30 and 3.45 due to the methyl group. In the spectrum of the tolylimine the N-H absorption at 3.00 microns is completely absent, while that due to the methyl group is faintly evident as a horizontal break in the curve from about 3.2 to 3.55. o-Toluidine shows two strong bands at 6.30 and 6.70 which are assigned to N-H bending vibrations and two strong bands at 7.68 and 7.90 which are characteristic of the aniline structure. This region also contains bands caused by C-H bending vibrations. The tolylimine spectrum is radically different in this region, having only weak bands between seven and eight microns, and two medium bands at 6.21 and 6.75. This is interpreted to mean that upon reaction with glyoxal, the amino group of o-toluidine has been modified extensively causing its characteristic absorptions to be erased in the new compound.

It will be noted that the tolylimine has three narrow bands straddling 6.25 microns. The general rule is that the C=N- vibrations give rise to a medium band very close to six microns. The band at 6.21 was, therefore, assigned to the C=N- group. The other two adjacent bands and the slightly stronger one at 6.75 are probably due to C-H bending vibrations which are characteristic for this region. A medium intensity absorption near six microns is the only characteristic band for the imine type structures.

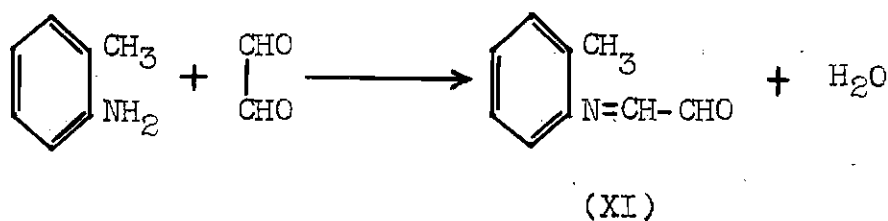
Between eight and eleven microns both curves show medium strength bands. This is the region of C-N stretching vibrations which would be present in both compounds. Primary amines show absorptions in the 12-15 micron range such as those at 13.40 and 14.05 for o-toluidine. These have been replaced in the tolylimine spectrum by three strong narrow bands the origins of which were not determined.

In Chapter III it was reported that hydrogenation of the tolylimine was attempted. If the known compound, N,N-di-o-tolylethylenediamine (21), had been produced it would have been added proof of the structure of the tolylimine. The catalytic reduction of imines may lead to coupling reactions in which tertiary amine groups are formed and the product is polymeric. In view of this, the failure to obtain the desired compound should not be taken as evidence against the imine structure.

As a result of this work, a procedure has been developed whereby the glyoxal-bis-o-tolylimine can be easily prepared in good yields. The procedure should be capable of being easily extended to numerous analogous amines. These products, having the two reactive imine linkages, may prove to be useful intermediates for further reactions.

The study of the reaction of glyoxal with o-toluidine was undertaken because it was reported by Kulisch (1) that quinoline had been obtained by this reaction. The results

of this work show that the method must be viewed with considerable reservation. Kulisch's statement that *o*-aminocinnamaldehyde probably formed as an intermediate is subject to doubt in view of presently accepted theories on the reactivity of amines with aldehydes. The existence of this intermediate is further to be questioned since our work has shown that the reactants readily form glyoxal-bis-*o*-tolylimine, thus showing initial condensation taking place with the amino group, not the methyl group. Since the tolylimine was not converted to quinoline when treated with concentrated alkali, it also would not likely be an intermediate in the Kulisch process. Throughout the work efforts were made to isolate substances which might have been intermediates that would produce quinoline upon further treatment. Reactions were carried out with equal molar amounts of the reactants, or with an excess of glyoxal. These conditions would be favorable for the formation of a compound (XI) by the reaction of one molecule of amine with one molecule of the aldehyde in the following manner:

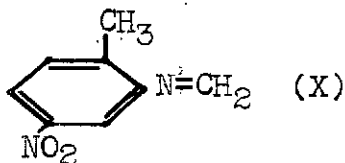


This compound (XI) could not be isolated, however, either as the free aldehyde by extraction, or by the formation of a

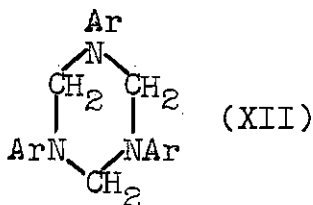
sodium bisulfite addition product. This intermediate certainly would be very reactive. Apparently it reacted more readily with the amine than did glyoxal since only the compound formed from two moles of amine per mole of glyoxal was obtained, regardless of the mole ratios of reactants used.

In further attempts to bring about the ring closure, as claimed by Kulisch, a molecule was used having more highly reactive hydrogens on the methyl group. 4-Nitro-2-aminotoluene was substituted for *o*-toluidine and several reactions were carried out with glyoxal. This compound, if it reacted by the Kulisch process, would produce 7-nitroquinoline, which, however, was not the case. The product of the reaction of glyoxal with nitrotoluidine was a yellow powder which was not fully identified.

The technical grade of glyoxal used in this work contains a small percentage of formaldehyde. In addition to the yellow powder, a compound was isolated in small amounts which was shown to be a product formed from the nitrotoluidine and formaldehyde. This is a new compound and its structure is of theoretical interest. The results of analyses indicate its empirical formula to be C_4H_4NO and a molecular weight determination in camphor corresponded to the formula $C_8H_8N_2O_2$. This suggests that the compound has the methyleneimine structure (X).



The aniline analog (27) of this structure has never been isolated, as such, but a form has been obtained which is the trimer of the hypothetical Schiff base of aniline and formaldehyde. It has a six-membered ring structure similar to the general formula (XII) shown below. It showed a molecular weight in

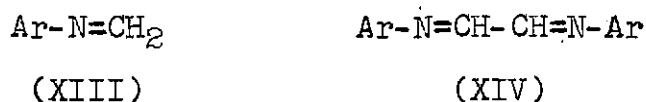


camphor of about twice that of the hypothetical monomer. In the vapor state the molecular weight corresponded to that of the monomer. The question arises then as to whether the new compound has the methyleneimine structure (X) or the cyclic structure (XII). Its melting point of 234.3-235.4° (corr.) and its low degree of solubility in organic solvents are more consistent with the cyclic form. Molecular weight data, however, suggest that it exists as the monomer.

The infrared absorption curve of this compound was studied in an effort to differentiate between the two structures. First, a comparison of the spectrum of nitrotoluidine, Fig. 2, with that for the compound, Fig. 4, is helpful. In the nitrotoluidine spectrum, two medium bands due to N-H vibrations are present just below 3 microns and C-H vibrations of the methyl group are represented by the weak absorption

at 3.45 microns. In the other spectrum, Fig. 4, the C-H absorption is present in approximately the same place, and an absorption also appears at 2.95 microns which is stronger and sharper than the N-H bands in nitrotoluidine. Its origin is not known. In both curves weak bands are present at about 6.3 microns and medium bands at 7.25 microns which are due to the presence of nitro groups in both compounds. A striking similarity is seen between these two curves in the 6 to 8 micron region and the 11 to 14 region. An almost one to one matching, with very little difference in wave lengths of corresponding bands is possible.

A comparison now can be made between the tolylimine spectrum, Fig. 3, and the nitro compound, Fig. 4. The basic structure for the methyleneimine (XIII) is closely similar to that for the glyoxal-bis-arylimine (XIV), having in common



the Ar-N=CH- group. If the nitro compound exists in the methyleneimine form their infrared spectra should be similar, the presence of nitro groups not causing major changes. In both curves similar bands are present between 6 and 7 microns. Between 7 and 8 microns, however, a great difference is observed. (The band at 7.22 microns in Fig. 4, due to the nitro group, is an expected difference). From 8 microns throughout the rest of the spectrum a general similarity exists. In view

of the difference in the 7 to 8 micron region, and the absorption at 2.95 in the nitro compound which is absent in the other, it is apparent that the compounds do not have completely similar spectra. While this situation does not support the methyleneimine structure, on the other hand neither does it provide support for the other. Another fact which should be noted is that both spectra have a medium intensity absorption near 6.2 microns. In the tolylimine spectrum the band at 6.21 was assigned to the C=N- group (see p. 51). In like manner the band in Fig. 4 at 6.19 microns also may be due to the imine linkage.

From these considerations it is apparent that the spectrophotometric data is not conclusive. Likewise, considering all the evidence, a choice cannot be made between the monomeric and cyclic structures with any degree of certainty. Therefore, until further information is available on this question, it does not seem to be improper to assign tentatively the methyleneimine structure to the compound. Accordingly, the compound may be considered to be the N-methylene-2-methyl-5-nitroaniline.

In the study of the reaction of glyoxal with *o*-toluidine, an analogous compound, formed by reaction of the amine with the formaldehyde impurity, was not isolated. A reaction between *o*-toluidine and formaldehyde undoubtedly took place, however, as two compounds are known which are formed from these reactants in neutral solution. The anhydro formaldehyde

o-toluidine has been reported by Wellington and Tollens (12) and the bis(o-tolylamino)methane by Eberhardt and Welter (13). Both compounds are solids but they are reported to be soluble in organic solvents. Consequently they would have been easily removed from the product derived from glyoxal, upon washing with acetone or recrystallizing in isopropyl alcohol, as was done in the procedures followed in this work. The situation was different, however, in the work with nitrotoluidine in aqueous medium. The compound formed with formaldehyde is not acetone soluble and hence remained in evidence.

The results and conclusions of this work will be summarized briefly in closing. Reaction of glyoxal with o-toluidine did not produce quinoline as reported by Kulisch (1) and arguments are given against his proposed reaction mechanism. This reaction was shown to produce glyoxal-bis-o-tolylimine instead, and conditions are described for synthesizing this new compound in good yields. In addition to analytical results, infrared absorption studies support the glyoxal-bis-o-tolylimine structure for the new compound. When the supposedly more reactive nitrotoluidine was used in place of o-toluidine, the expected 7-nitroquinoline was not obtained. The product which resulted could not be identified despite intensive efforts. Another new compound was isolated as a result of the reaction of nitrotoluidine with formaldehyde, present as an impurity in the glyoxal. An attempt was made

to determine the structure of this compound from infrared studies and by a consideration of molecular weight data and physical properties of the compound. A choice could not be made conclusively between the monomeric imine structure and the trimeric cyclic form. Until further evidence is available the compound may be considered to be N-methylene-2-methyl-5-nitroaniline. In view of the complete failure to obtain quinoline or 7-nitroquinoline, it is concluded that the Kulisch reaction should not be given further consideration as a possible means for obtaining substituted quinolines.

APPENDIX

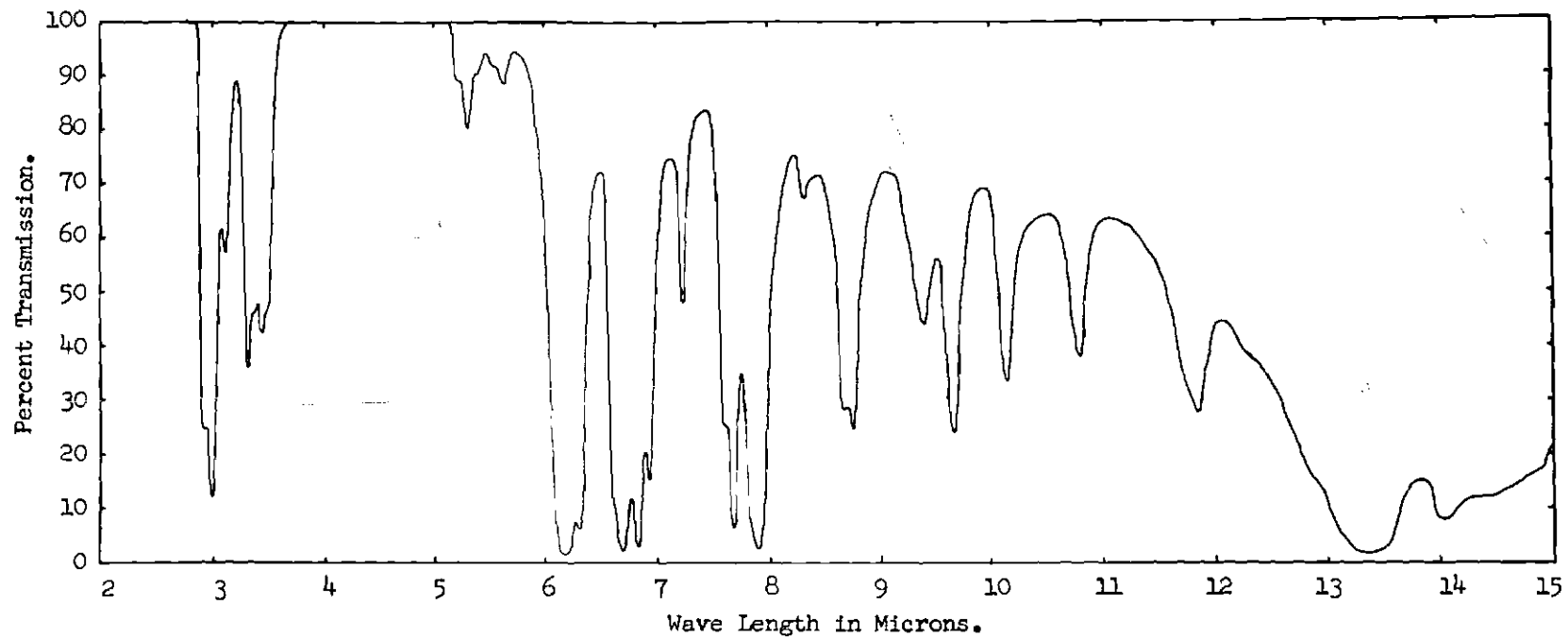


Figure 1.
Infrared Absorption Spectrum of o-Toluidine
(Pure liquid in 0.025 mm. cell.)

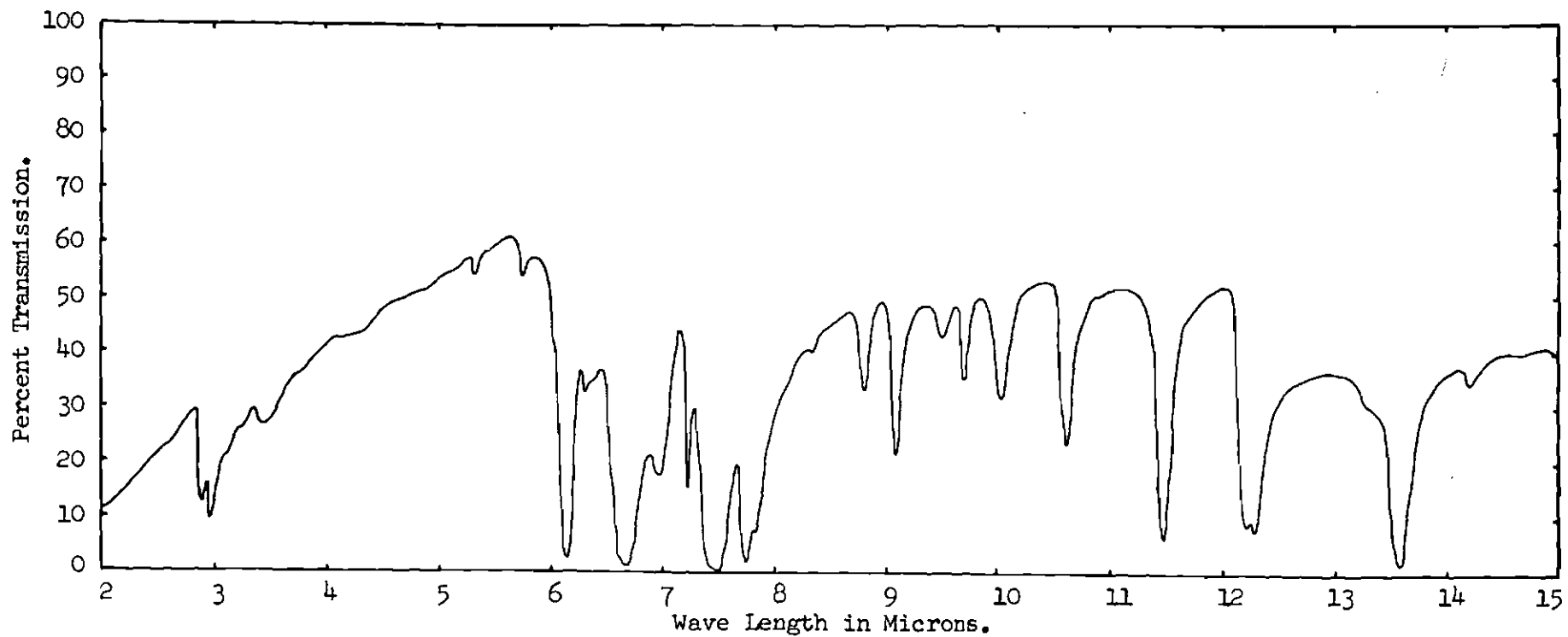


Figure 2.
Infrared Absorption Spectrum of 4-Nitro-2-aminotoluene.
(1.5 mg. of solid sample and 150 mg. of KBr pressed into tablet
approximately 13 mm. in diameter and 0.5 mm. thick.)

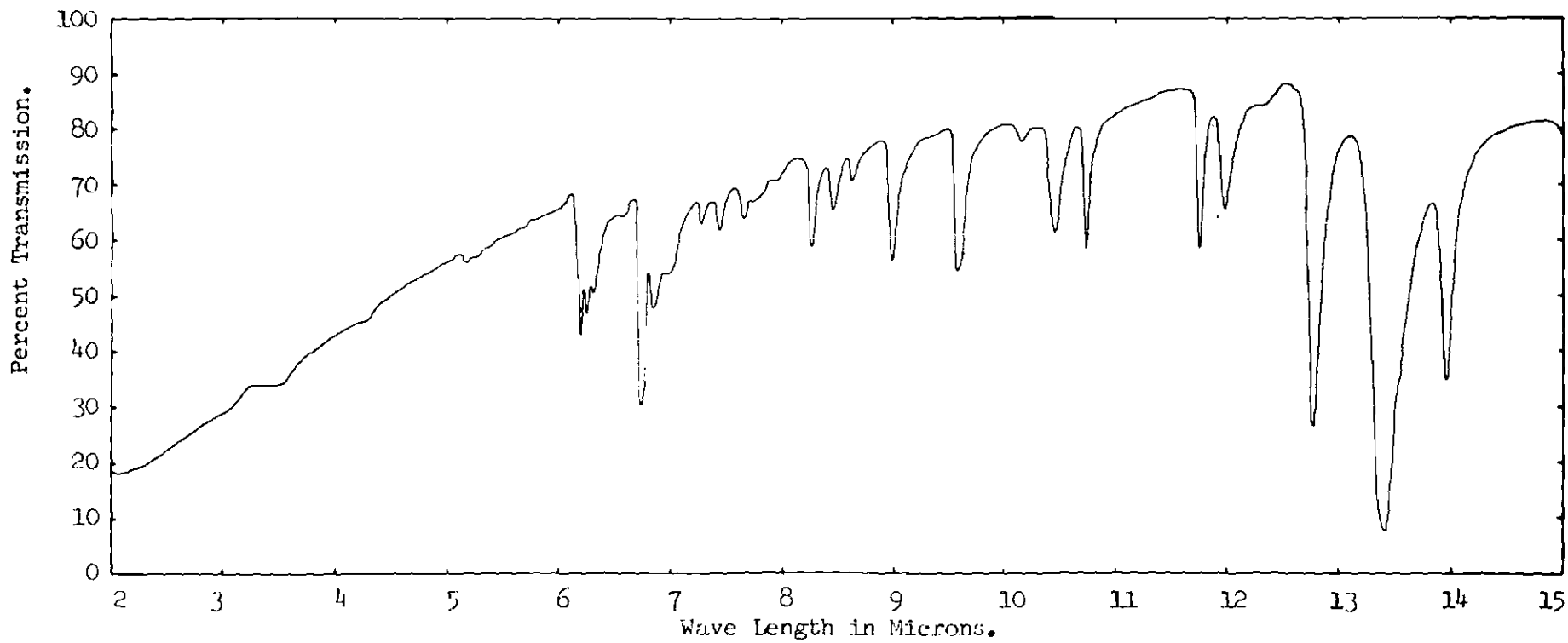


Figure 3.
Infrared Absorption Spectrum of Glyoxal-bis-o-tolylimine.
(1 mg. of sample and 150 mg. of KBr pressed into tablet
approximately 13 mm. in diameter and 0.5 mm. thick.)

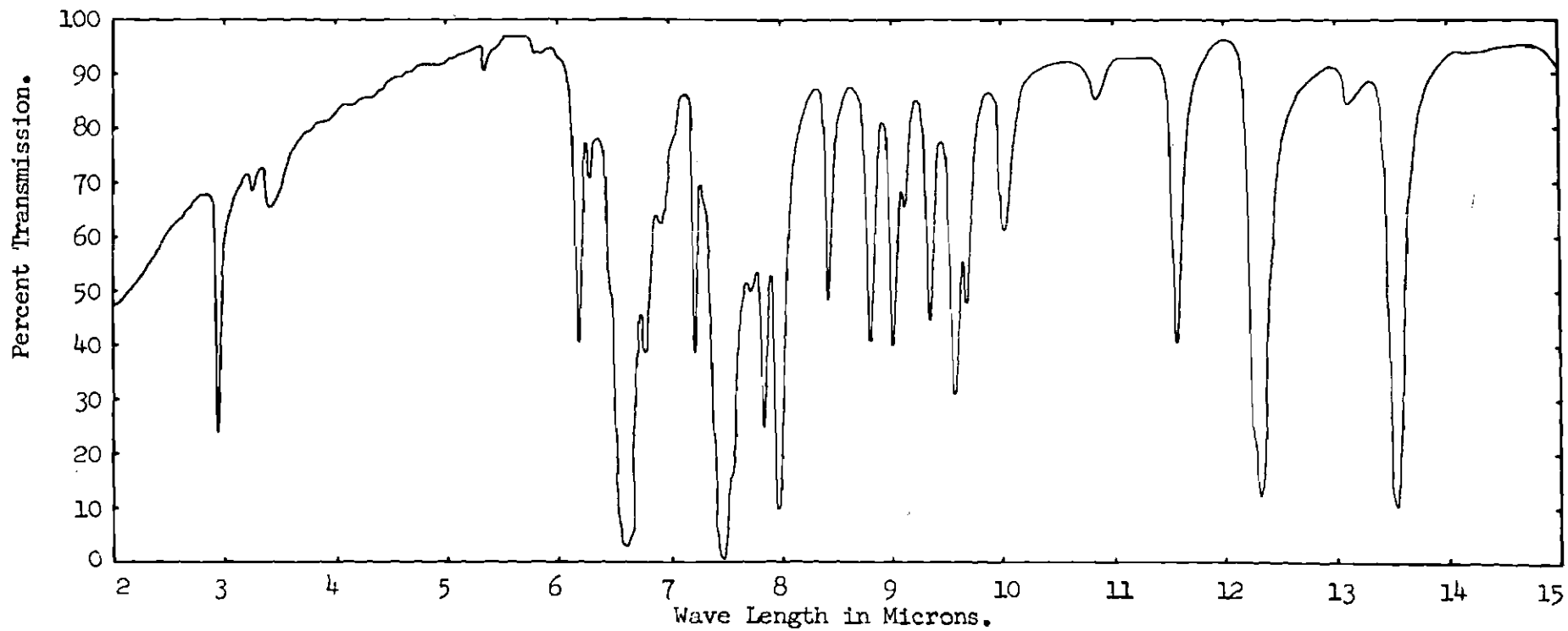


Figure 4.
Infrared Absorption Spectrum of N-Methylene-2-methyl-5-nitroaniline
(1 mg. of sample and 150 mg. of KBr pressed into tablet
approximately 13 mm. in diameter and 0.5 mm. thick.)

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