A FEASIBILITY STUDY

OF A NEW UNIMOLECULAR REAGENT FOR NITROGEN DIOXIDE

by

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Chapter I

Introduction

In today's industrial society pollution of air and water has
become both a major problem and a major concern. One pollutant is ·
nitrogen dioxide. This compound to which the human body has a lack
of defensive respiratory reflexes is produced in several large in-
dustries. Among these industries are the manufacture of nitric
acid, the manufacture of dyes and explosives and the manufacture of
fertilizers and cyanamide.[1]

A concentration of 100 ppm NO_2 may cause illness if breathed
for a short period and 700 ppm is fatal if breathed for 30 minutes
or even less.[2,3] The generally allowable concentration[4] for daily
eight-hour exposures is 25 parts of nitrogen dioxide per million
parts of air. This low level makes trace analysis necessary.
There have been many methods developed for detection of nitrogen
dioxide. An early method, although tedious, involved conversion of
nitrogen dioxide to nitrate and the nitration of phenoldisulfonic
acid.[5,6] Another approach to this trace analysis is the Griess-
Ilosvay method,[7] which utilizes the nitrite formed from NO_2 to di-
azotize sulfanilic acid which in turn couples with 1-naphthylamine
to form an azo dye. Many variations of this method have been de-
veloped by changing the acid in the solvent[8,9] or the coupling a-
gent.[10] Instrumental methods have also been developed, such as
spectrophotometric determinations,[11] gas-solid chromatography,[12]
and ultraviolet photometry.[13] McMillan Electronics Corporation has
marketed a commercial nitrogen oxides analyzer based on chemilumin-
escence.

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The main drawback to the instrumental techniques is the initial cost of many of these instruments. They also suffer from a lack of portability. The colorimetric methods, which are cheaper have their own problems. In several of these techniques which utilize the nitrite present in aqueous solutions of nitrogen dioxide the coupling agent is of questionable stability and safety, as it is carcinogenic. This is particularly true of 1-naphthylamine. N,N-Dimethyl-1-naphthylamine is an improvement, but N-(1-naphthyl) ethylenediamine is preferred.

Nitrogen dioxide reacts with water to produce nitrous acid, which is the reactive species in a diazotization reaction:

$$2NO_2 + H_2O = HNO_2 + HNO_3$$
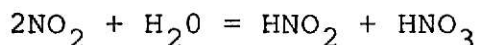
Only one-half of the NO_2 produces nitrous acid. Further reaction then takes place with a protonated diazotizable aromatic amine:

$$HNO_2 + RNH_3^+ = RN\equiv N^+ + 2H_2O$$
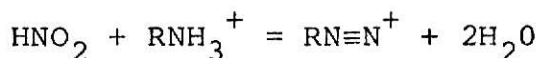
which can couple with an aromatic amine or hydroxy compound to form an azo dye:

$$RN\equiv N^+ + \begin{cases} R'OH = RN=NR'OH \\ R'NR_2'' = RN=NR'NR''_2 \end{cases}$$
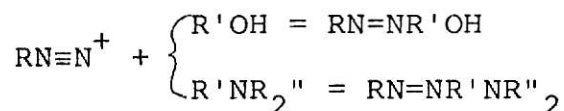
where R" = H or an alkyl radical.

It was proposed that the introduction of both the diazotizing agent and the coupling agent into a single molecule would improve the method by reducing reaction times, and the use of a quaternary ammonium salt to stabilize the color once formed. The reagent first proposed for study was N-(3-dimethylaminobenzyl)-N'-2-amino-5-trimethylammoniumiodobenzyl)-N,N'-dimethylethylenediamine.
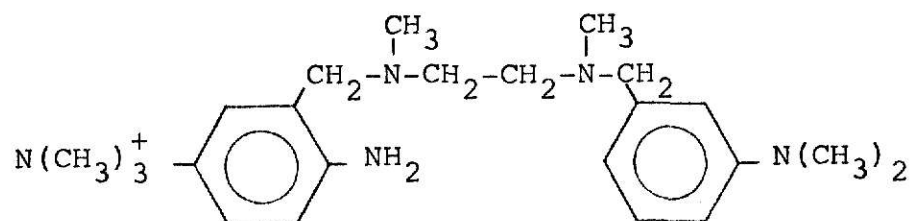
Although at this writing the molecule itself has not been synthe-
sized, it has been prepared in two fragments, (3-hydroxymethyl-4-
aminophenyl)trimethylammonium iodide and N-(3-dimethylaminobenzyl)-
N,N'-dimethylethylenediamine.
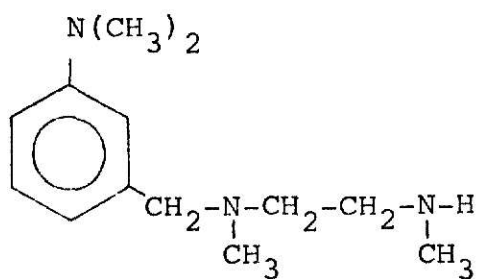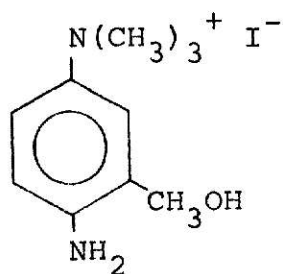
It has proved impossible thus far to produce the alkyl chloride of the alcohol fragment to combine with the amine fragment.

It was decided to run a short study of the two ends of the molecule to determine if the idea behind the research was valid, while still attempting to complete the molecule. Among the factors studied were the conditions which most readily facilitated diazotization and coupling, rate of color development and stability of the color reagent once produced.

Chapter II

Experimental

This chapter will describe the synthetic steps involved in pre-
paring the reagents tested. The starting materials for both parts
of the reagent were obtained from the Aldrich Chemical Company.
The starting material for the (3-hydroxymethyl-4-aminophenyl)tri-
methylammonium iodide was 3-dimethylaminobenzoic acid. For the N-
(3-dimethylaminobenzyl)-N,N'-dimethylethylenediamine the starting
materials were sym-dimethylethylenediamine and 3-dimethylaminoben-
zoic acid.

(3-Hydroxymethyl-4-aminophenyl)trimethylammonium Iodide

The following is the procedure used to prepare the (3-hydroxy-
methyl-4-aminophenyl)trimethylammonium iodide. The first step was
the reduction of 3-dimethylaminobenzoic acid to 3-dimethylamino-
benzyl alcohol. This was done by a $LiAlH_4$ reduction modified from
that used by Conover and Tarbell[14] for reduction of similar com-
pounds.

Six grams (0.158 mole) of $LiAlH_4$ were suspended in 250 ml of
absolute ethyl ether. To this suspension was added slowly over a-
bout a two-hour period a solution of 20 grams (0.121 mole) of 3-
dimethylaminobenzoic acid in a minimum of dry tetrahydrofuran.
After complete addition the mixture was hydrolyzed with 10% NaOH
over a period of 90 minutes. After complete hydrolysis the suspen-
sion of $LiAlO_2$ remaining was extracted several times with a total
volume of 1500 ml of ether. The ether was removed under reduced
pressure and the liquid remaining was 3-dimethylaminobenzyl alco-
hol. Average yields were 92%.

The second step involved introduction of a nitrogen atom para

to the dimethylamino group. This was done by coupling the 3-dimethylaminobenzyl alcohol with diazotized sulfanilic acid. Coupling was used to introduce the nitrogen instead of nitration because of its more selective attack at the para position. The preparation of the p-benzenediazonium sulfonate was done according to the method presented by Fieser,[15] and the coupling by the method described by Randall, Lewis and Slagan.[16]

Sulfanilic acid, 12.3152 grams (0.071 mole), was dissolved in 70 ml of water with the aid of 3.7729 grams (0.036 mole) Na_2CO_3. This solution was cooled to 15° C, treated with 5.3084 grams (0.077 mole) $NaNO_2$ in 11 ml of water and poured over a mixture of 20 ml concentrated HCl and 107 grams of ice. This mixture was allowed to stand 15-25 minutes. At the end of that time 10.7491 grams (0.071 mole) of 3-dimethylaminobenzyl alcohol dissolved in water with the aid of a minimum amount of concentrated HCl was added in one portion. Immediately, solid $NaC_2H_3O_2$ was added to adjust the pH to approximately 5. A thick red paste soon formed which was allowed to stand overnight. This intermediate need not be isolated to reduce the azo bond to an amine, which is the next step.

In this step the azo bond was reduced with sodium hydrosulfite to the amine by the procedure described by Fieser.[17] The product from this reaction, 2-amino-5-dimethylaminobenzyl alcohol, is air and light sensitive. To reduce its exposure time to both of these elements the product was immediately reacted with acetic anhydride to form both the amide and the ester. This reduction was carried out on small portions of the dye intermediate to reduce the time necessary to extract the light-sensitive product.

In small portions the azo dye was dissolved in warm sodium

hydroxide solution. The temperature was raised to 70° C and $Na_2S_2O_4$ was added until the deep red color disappeared. The solution was then heated to $80 - 85^\circ$ C, cooled in an ice bath to 60° C and extracted with chloroform. The chloroform extract was drained into a flask containing an excess of acetic anhydride. The chloroform was distilled off and recycled. After all the azo dye was reduced the chloroform-acetic anhydride mixture was cooled and the solution neutralized with $NaHCO_3$ and water was added to extract the sodium acetate salt. The chloroform was removed under reduced pressure and the solid remaining, 2-acetamido-5-dimethylaminobenzyl acetate, recrystallized from benzene. The average yield from the alcohol to this point was 42%.

The next step in the sequence was the preparation of the quaternary salt of the above compound. This was patterned after the procedure described by Singh.[18] One gram of 2-acetamido-5-dimethylaminobenzyl acetate was dissolved in a minimum of chloroform. A one molar excess of methyl iodide was added, the reaction flask stoppered and allowed to stand two days. The crystals formed were collected by suction filtration. The average yield of this step was 78%.

This next step, the last in this sequence, was run only once. Normally only the ester was hydrolyzed and attempts made to convert the resulting alcohol to the alkyl chloride. To date this has not been accomplished. However, in this last step 1 gram of the 2-acetamido-5-trimethylammoniumiodobenzyl acetate was suspended in 20 ml of absolute alcohol. To this suspension was added 0.2568 gram sodium hydroxide dissolved in methanol. After a few minutes the starting material dissolved and the solution was then refluxed for two hours. At the end of this time the 3-hydroxymethyl-4-

aminophenyltrimethylammonium iodide crystallizes out when cooled
in an ice bath. The product was collected by suction filtration
and recrystallized from absolute alcohol.

The ester alone can be similarly hydrolyzed by using only one
molar equivalent of sodium hydroxide and allowing the mixture to
stir for 4-5 hours at room temperature. In this case ether must
be added to precipitate the product.

N-(3-Dimethylaminobenzyl)-N,N'-dimethylethylenediamine

The coupling end of the molecule was prepared from the 3-di-
methylaminobenzyl chloride and sym-dimethylethylenediamine. The
sym-dimethylethylenediamine was used in large excess to minimize
the possibility of the alkyl chloride attaching to both ends. The
3-dimethylaminobenzyl chloride was prepared from the previously
synthesized 3-dimethylaminobenzyl alcohol.[19] To minimize the time
the 3-dimethylaminobenzyl chloride was allowed the opportunity to
polymerize by forming the quaternary salt, the alkyl chloride was
isolated during one of the preparations to be sure it was forming.
In subsequent runs, it was left in solution.

To a solution of 5 grams (0.0331 mole) of 3-dimethylamino-
benzyl alcohol in 20 ml of chloroform was added slowly a solution
of 2.4 ml (0.0334 mole) thionyl chloride in 10 ml of chloroform.
This solution was stirred at room temperature for 20 minutes. Af-
ter this time, a one molar equivalent of triethylamine was added.
A large amount of ether was added next to precipitate the triethyl-
amine hydrochloride, which was separated by suction filtration.
The filtrate was poured into a solution of 15 ml (0.1411 mole) sym-
dimethylethylenediamine in 25 ml of chloroform. This solution was
stirred at room temperature for one hour and the solvent and excess

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sym-dimethylethylenediamine removed under reduced pressure. The remaining liquid was N-(3-dimethylaminobenzyl)-N,N'-dimethyl-ethylenediamine.

Once these two pieces of the molecule were made, difficulty was encountered in connecting them into one molecule. It was decided to try them out together in solution to determine if they could be used to detect or analytically determine NO_2 and/or nitrite concentrations.

Reagents used for this determination were of reagent grade. The deionized water was distilled water which had been passed through a column of deionizing resin and prewashed 6-14 mesh activated coconut charcoal (Fisher-Scientific Co.).

The apparatus used to measure the absorption spectra was a Coleman 124 spectrophotometer. Standard 1.0-cm glass cells were used, and narrow range pH paper was used to determine approximate pH's.

The preparation of the colorimetric reagent was done by placing 0.2252 gram of N-(3-dimethylaminobenzyl)-N,N'-dimethylethylenediamine and 0.0619 gram of (3-hydroxymethyl-4-aminophenyl)trimethylammonium iodide in a 25 ml volumetric flask and diluting to the mark. The pH was then adjusted to 1.2 with concentrated hydrochloric acid. This pH was selected after finding that hydrochloric acid concentrations of 10 N, 7.5 N, 5 N, 2.5 N, 1 N, and 0.5 N were too concentrated to allow coupling to take place.

Sodium Nitrite Solutions were used to determine if the reagent would work and at what concentration ranges. A stock solution of 100 ppm nitrite was prepared by dissolving 0.1500 gram sodium nitrite in 1 liter of water. Volumetric dilutions were made to obtain a series of concentrations: 75 ppm, 50 ppm, 25 ppm, 10 ppm,

5 ppm, 2 ppm, and 1 ppm. A 100 ml sample of each was prepared.

The procedure involved placing 2 ml of the appropriate sodium nitrite standard prepared above in a 10 ml flask and adding 2 ml of the mixed reagents. This combination was mixed thoroughly and transferred to a 1 cm UV cell. Absorbance readings were taken at 1, 5, 10, 15, 30, 45, 60, 90, and 120 minutes. These results are shown in Table 1. A wavelength of 495 nm was employed in all measurements. This wavelength was determined from the peak of the absorbance curve for the coupled reagent, Figure 1.

Table 1

Absorbance vs Time Measurements for Various NO_2^- Concentrations

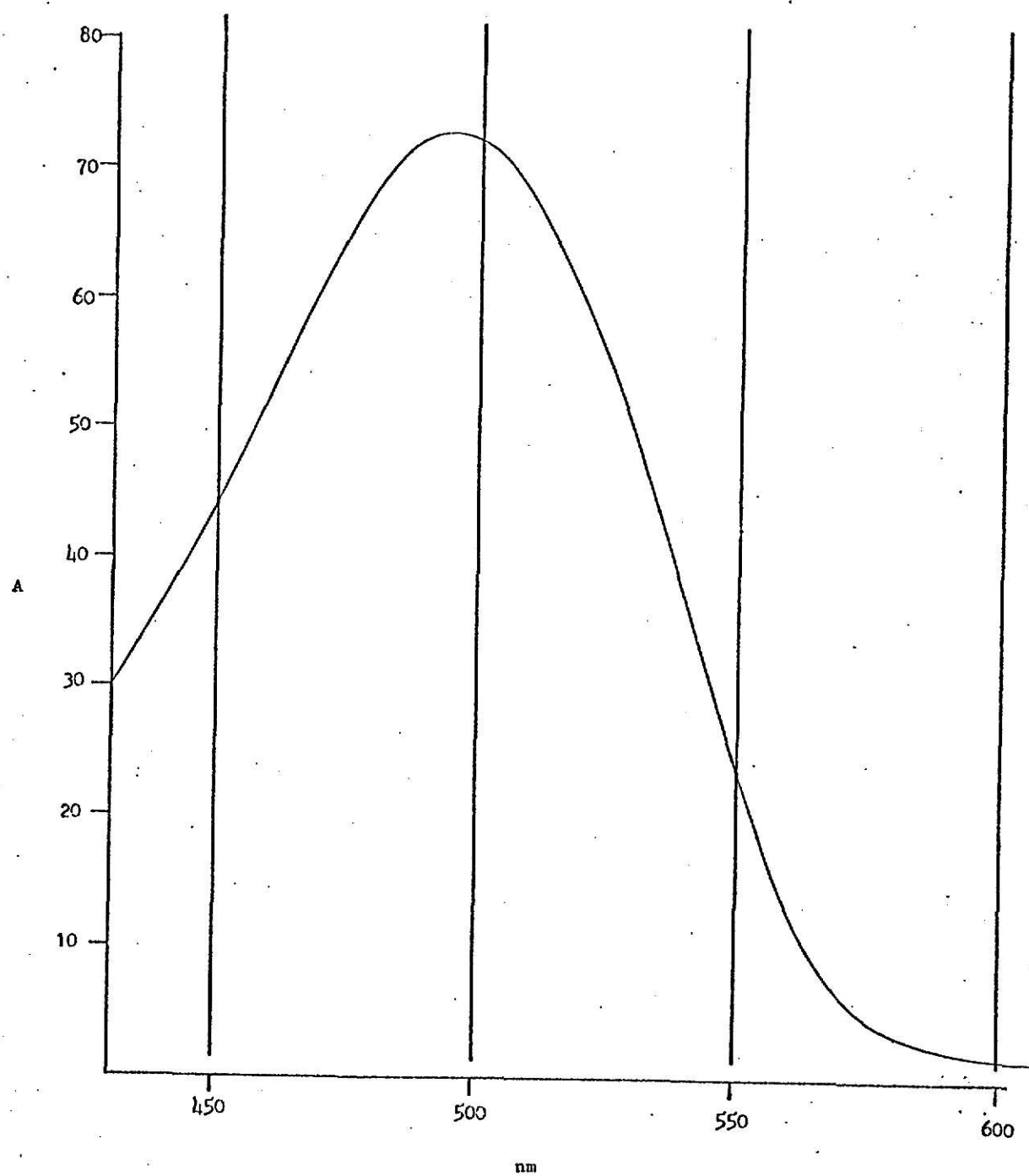| ppm	1 min	5 min	10 min	15 min	30 min	45 min	60 min	90 min	120 min
100	.24	.795	1.56	*	*	*	*	*	*
75	.158	.565	1.10	1.62	*	*	*	*	*
50	.11	.395	.801	1.19	*	*	*	*	*
25	.07	.215	.395	.580	1.07	1.45	1.76	*	*
10	.059	.119	.195	.265	.443	.570	.685	.900	1.06
5	.055	.080	.110	.140	.208	.265	.313	.381	.445
2	.040	.050	.065	.079	.115	.131	.149	.171	.188
1	.040	.045	.052	.060	.070	.081	.089	.095	.100

Figure 1

Absorbance Curve of Reagent

Chapter III

Results and Discussion

Before the synthetic route described previously was decided
upon a number of other routes were attempted. The first of which
used 5-amino-2-nitrobenzoic acid as the starting material. This
material was converted, using formaldehyde and formic acid, to 5-
dimethylamino-2-nitrobenzoic acid. This reaction gave only a rel-
atively low yield and the product could not be readily isolated
due to having both a basic site and an acid site in the molecule.
Due to these factors this synthetic approach was abandoned.

The remaining synthetic routes attempted were based on 3-di-
methylaminobenzoic acid as the starting material. The first at-
tempt was to couple this starting material with aniline
diazotized with sodium nitrite and hydrochloric acid. This reaction
did introduce the nitrogen into the desired position in the ring,
but introduced problems later when the azo bond was cleaved to the
amine group. It was not possible to easily separate the desired
product from the aniline also produced in the reaction. This also
proved to be the case when the ethyl ester of 3-dimethylaminoben-
zoic acid was used as the starting material, or when the azo com-
pound was esterified.

The next attempt to overcome this problem was to convert 3-
dimethylaminobenzoic acid to 3-dimethylaminobenzyl alcohol to re-
move the possibility of internal ionization. This compound was
then converted to 2-nitroso-5-dimethylaminobenzyl alcohol to remove
the problem of separating reduction products of the azo bond. This
product proved to be very unstable and, therefore, this route was
also abandoned.

This brought us back to the use of the azo bond to introduce the nitrogen into the benzene ring. To aid in the separation of the reduction products later in the sequence, sulfanilic acid was used instead of aniline as the diazonium salt. In the basic reduction of the azo bond with sodium hydrosulfite the sulfanilic acid remained in the water layer when the reaction product solution is extracted with chloroform.

This was where the real problems began. Attempts to convert the azo intermediate to the quaternary ammonium salt proved futile. The azo bond would methylate prior to the dimethylamino group. Attempts to convert the alcohol group in this azo compound to the chloride also proved futile. The thionyl chloride reacted with the amines first. This showed the azo bond had to be cleaved before joining both ends of the molecule as was considered a possibility. About the only synthetic route available was the one described in the second chapter of this thesis.

In the attempt to convert the (4-acetamido-3-hydroxymethyl-phenyl)trimethylammonium iodide to an alkyl chloride thionyl chloride could not be used because it reacted with the nitrogen groups. An attempt was made to use concentrated hydrochloric acid to form the chloride, but upon neutralization of the solution the chloride reverts to the alcohol. A possibility of getting around this problem is the use of the ion pairing technique of HPLC. That is adjust the pH to approximately 4-5 and add a large anion to the solution, such as heptane sulfonic acid. The large slightly polar ion pair, if formed, could be extracted by chloroform and then reacted further to obtain the desired compound.

The study done on the effects of HCl concentration showed, as was expected, that the more concentrated the acid the less coupling

took place. This would be due to the acid protonating all the amine sites and, therefore, rendering the reagent inactive. Protonated amines are not reactive enough to couple. At a pH of 2.4 the coupling goes well. It might be well to try even higher pH's. At this stage the exact optimum conditions were not sought. That will come when the pieces are combined into one molecule.

The results of absorbance versus time as stated before are in Table 1. Another set of knowns are run closely following the initial trial with closely similar results. But a repeat the next day showed no reproducibility of the original study. This indicates that the reagent is unstable and should be made up just before use. Combining the two pieces into one molecule will eliminate two reactive sites, the alcohol and the amine, and this will hopefully increase the stability of the reagent.

Figure 2 shows a plot of absorbance versus time for each of the standard concentrations of sodium nitrite. This figure indicates that the reagent, in its present fragmented form, is only good to approximately 1 ppm on instantaneous determinations, which is good enough to detect acceptable limits. This also indicates that although the rate of color development tapers off with time the color does not fade within two hours. Color stability is essential to the use for which the complete reagent is intended, and is confirmed by the trimethylammonium group in the azo dye formed by diazotization and coupling.

Figure 3 shows a plot of absorbance versus concentration at various times. At the shorter time periods a nearly linear plot is obtained. The scattering around the line increases with the time allowed for color development. The optimum time for taking readings would be after approximately 10-15 minutes.
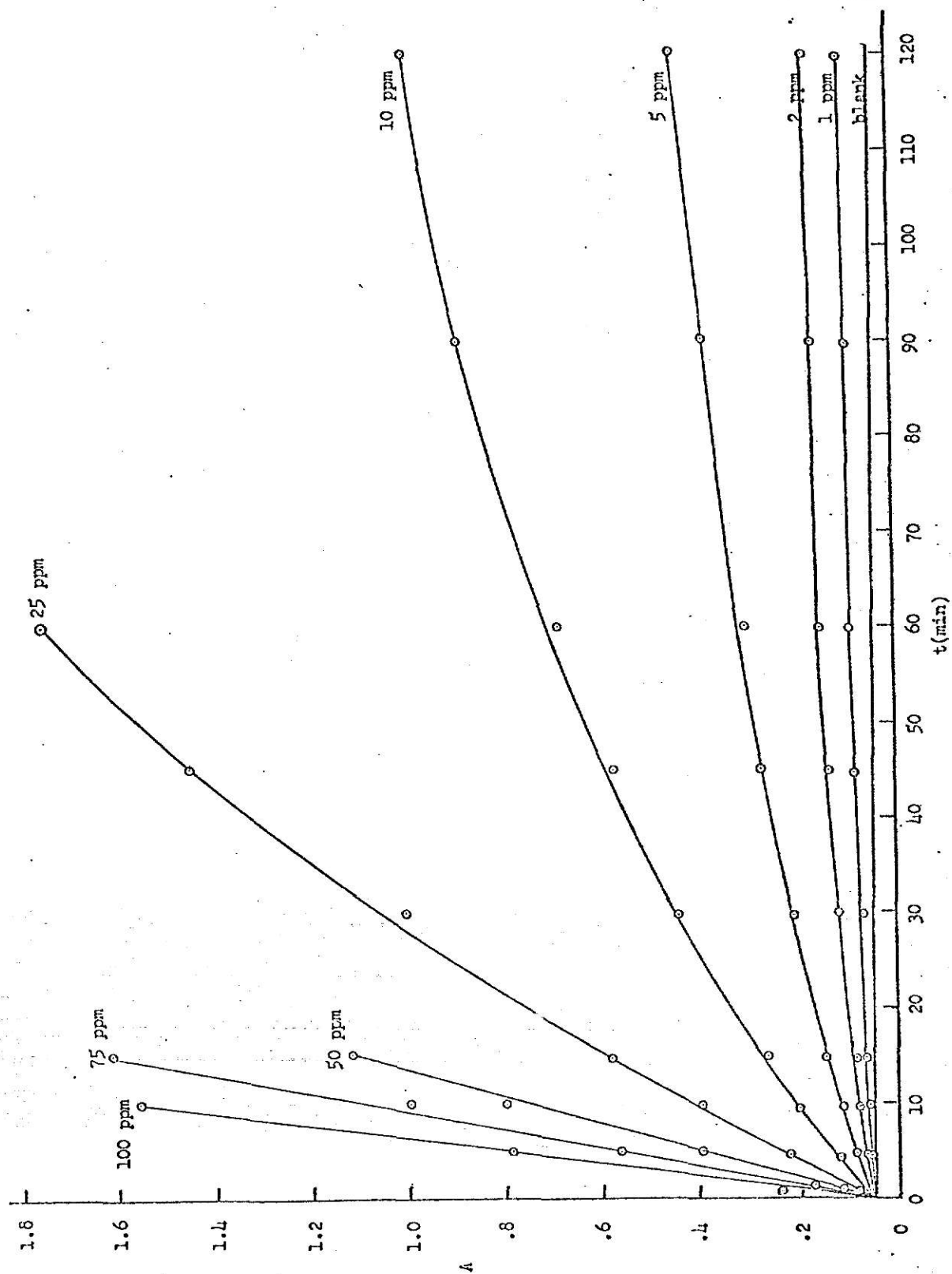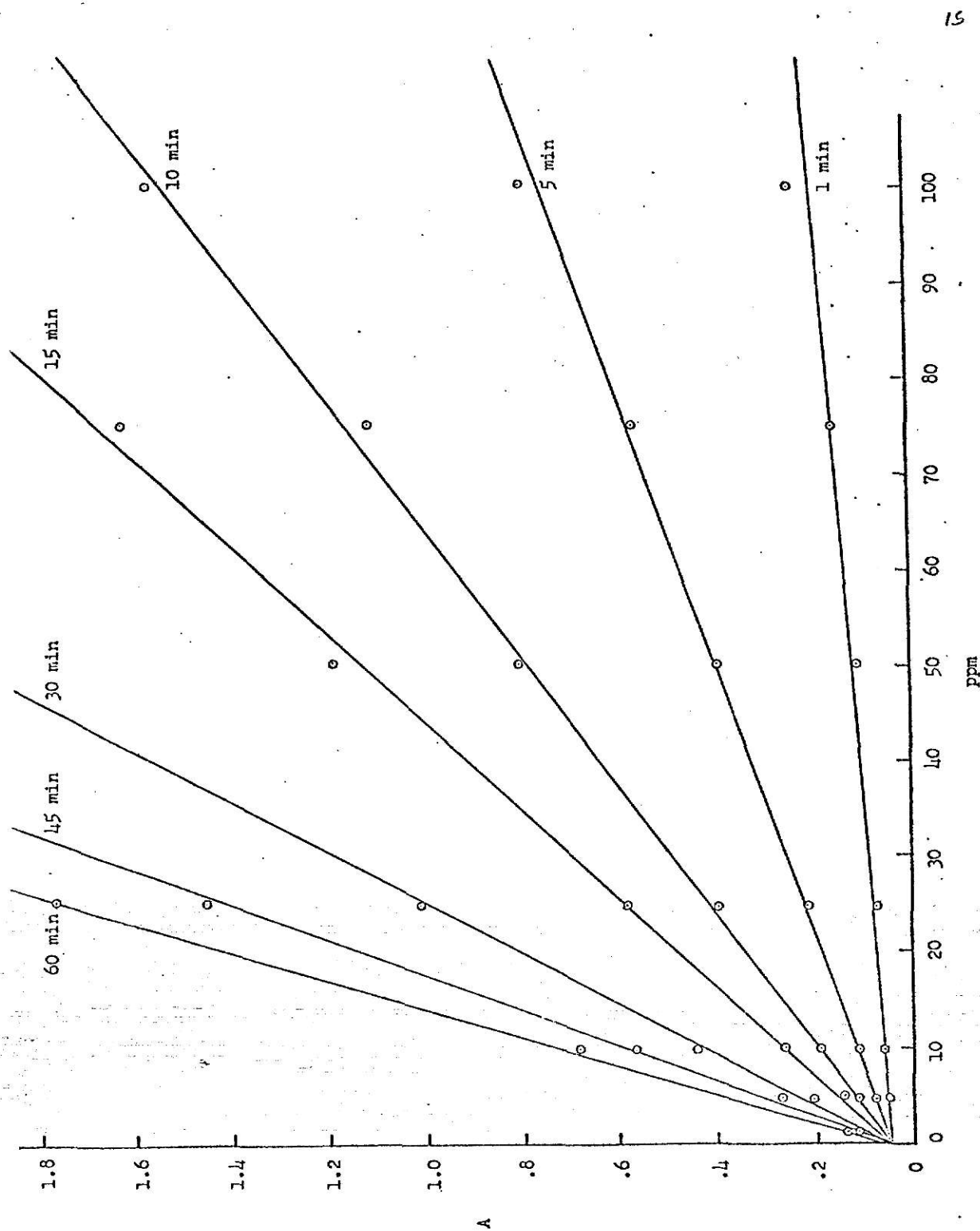
Rate of Color Development of Reagent

Figure 2

Calibration Curve for Reagent

Figure 3

The data collected thus far would indicate that further research along these lines would be warranted, and quantitative work could be possible. The first step would be to combine both of the present molecules into a single molecule. This would reduce the number of reactive sites, which should increase the stability of the reagent. Further studies of this molecule would then be necessary to determine the optimum conditions of pH, time, and reagent concentration at which it detects NO_2. More studies should be run to determine detection limits, a calibration curve plotted and studies of the reagents stability before use and color stability after color development.

Other coupling agents could be used in place of the dimethylaminophenyl group, such as the corresponding dimethylaminonaphthyl group. This would shift the color of the coupled reagent more toward the red and possibly increase the sensitivity of the reagent. The potential use of both of these reagents and possibly others as a solid reagent should not be overlooked.

The usefulness of this reagent would come mainly in industry where NO_2 pollution is most common. A moist reagent could possibly be placed in a tube and the tube placed in an exhaust vent to the outside and the amount of NO_2 released to the atmosphere monitored by the reagents color change. Hopefully, the dry reagent would be sensitive to NO_2. If not, a water-containing support such as silica gel or crystals such as potassium, cesium, ammonium or tetraalkylammonium acid sulfate which contain surface-adsorbed water[21] could be used. A membrane selective for NO_2 would eliminate variables due to air currents and make the solid reagent responsive only to the partial pressure of NO_2 in the air. Quantitative analysis could then be done by dissolving the coupled reagent in water

and observing its absorbance in a uv-visible spectrophotometer. The possibilities of such a reagent should definitely be explored further.

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AN ABSTRACT OF A THESIS

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Manhattan, Kansas

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ABSTRACT

The synthesis of a new unimolecular reagent for NO_2 is described. Although never completely synthesized the functional parts of the molecule were used to determine if the intended use of the final molecule would be reasonable. The research shows that such a molecule could be used for detection of NO_2 to a concentration of 1 ppm determined instantaneously.