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The Reaction of N-Magnesium Halides on Nitriles in the Synthesis of Amidines

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THE REACTION OF N-MAGNESIUM HALIDES ON NITRILES IN THE SYNTHESIS OF AMIDINES

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INTRODUCTION

Compounds of the amidine class have long been of interest because of their therapeutic and pharmacological properties. Members of this class of compounds have been shown to be effective in combating pathological conditions ranging from virus (11), bacterial (12), and protozoal infections (7) to diseases of the circulatory system (6), neoplasms (5) and hyperglucemia (21). Since many basic nitrogen compounds have been of interest in cancer chemotherapy, such as a variety of amino alcohols shown by the Upjohn Company to have anti-tumoral activity, it was felt that additional investigations into the use of amidines and amino amidines in this area would be justified.

Many different approaches have been applied to synthesize amidines. Among these are the reaction between imido esters and ammonium salts (1), the reaction between imido chlorides and amines (4), the use of nitriles and ammonium thiocyanates (16), the reaction of amines with amides in the presence of phosphorus trichloride (20), the reduction of amidoximes (10), the reaction between carboxylic acids and alkyl sulfonamides (14), the rearrangement of aldehyde aryl hydrazones (17), and various procedures involving the reaction between an amine and a nitrile. Included in this last category, Oxley, Partridge and Short describe methods of reacting these two intermediates in the presence of $AlCl_3$, $ZnCl_2$, $FeCl_3$ or $SnCl_4$ (15,22,2). Cooper and Partridge also facilitated

this reaction using powdered sodium (3). Hullen et al. and also Nagler and Wawzonek describe procedures which involve reaction of the N-magnesium halide derivatives of the amine with the nitriles (8,24).

This study was undertaken to investigate further the characteristics and limitations of synthesizing amidines through the N-magnesium halide derivatives and nitriles and was of special interest because of the possible anti-tumoral activity of the products. The general plan for the synthesis is as follows:

$$C_2H_5Br + Mg \longrightarrow C_2H_5MgBr$$

$$C_2H_5MgBr + HNRR' \longrightarrow BrMgNRR' + C_2H_6$$

$$R''CN + BrMgNRR' \longrightarrow R''-\overset{\overset{N\text{-}MgBr}{\|}}{C}-NRR'$$

$$R''-\overset{\overset{NMgBr}{\|}}{C}-NRR' + HOH \longrightarrow R''-\overset{\overset{N\text{-}H}{\|}}{C}-NRR' + Mg(OH)Br$$

EXPERIMENTAL RESULTS

All temperatures reported in this section are uncorrected. The micro analytical data were obtained from Galbraith Laboratories, Knoxville, Tennessee.

The Preparation of 4-Benzimidoylmorpholine

Eighty-seven and five-tenths grams (0.8 mole) of freshly distilled ethyl bromide dissolved in 200 ml. of tetrahydrofuran (THF) was added dropwise to 19.4 grams (0.8 mole) of magnesium turnings in a one liter, three necked flask fitted with reflux condenser, mechanical stirrer and addition funnel. After refluxing for 30 minutes, 69.7 grams (0.8 mole) of freshly distilled morpholine dissolved in 80 ml. of THF was added slowly producing a heavy greyish suspension of the N-magnesium bromide. Eighty-two and five-tenths grams (0.8 mole of benzonitrile was then added dropwise to the stirred, refluxing mixture producing a color change to a canary-yellow. After 68 hours, at which time the reaction mixture was mustard yellow in color, refluxing was stopped and the products were cooled to room temperature. The mixture was then hydrolyzed with a saturated ice water solution of ammonium chloride. After thorough mixing, a saturated solution of sodium hydroxide was added making the reaction mixture strongly basic and separating out a heavy dark oil. The oil was extracted with ether, the solution cooled to near $0^{o}C$, and then extracted with 4N hydrochloric acid.

The acid solution was made basic with a saturated sodium hydroxide solution separating again the dark oil which was extracted with ether. The ether was removed by evaporation and the remaining products were distilled until a temperature of 23°C was reached at a pressure of 2 mm. Hg, removing unreacted morpholine. The crude yield was 37.0 grams or 24% of the total theoretical yield. Other preparations gave yields in the range of 15% to 25%. Attempts to purify the product by vacuum distillation resulted in heavy decomposition. The product was ultimately isolated as the picrate. After three recrystallizations from alcohol, the product obtained had a melting point of 203° - 204°C.

Anal. Calc'd for N, 16.70. Found: N, 16.57.

The Preparation of N-(α-Methylbenzyl)-p-chlorobenzamidine

Using a procedure similar to that for the preparation of 4-benzimidoylmorpholine, and using 0.15 mole quantities, p-chlorobenzonitrile and α-methylbenzylamine were combined to yield the corresponding amidine. Butyl ether was used as a solvent which made it necessary to add the nitrile as a finely suspended solid in the solvent. The color of the reaction mixture changed from an initial deep buff color to a deep reddish orange at the end of 66 hours of refluxing. The crude yield (which was 5.2 grams or 14% of the total theoretical yield) was purified by vacuum distillation. The final product was a viscous amber colored oil having a boiling point of

192° - 193°C (at 1 mm. Hg) and a refractive index of 1.5714 at 29°C. Analysis of the liquid product was somewhat low in nitrogen.

Anal. Calc'd for N, 10.83. Found: N, 9.58.

On the basis of observations on a homologue of this amidine (see below) it is suspected that this variance from the theoretical was due to the presence of water.

The Preparation of N-(α-Methylbenzyl)benzamidine

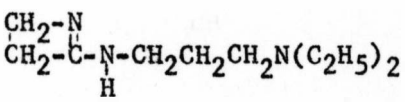
By a procedure similar to that used for the synthesis of 4-benzimidoylmorpholine, 0.5 mole of benzonitrile was reacted with 0.5 mole of the N-mangesium bromide derivative of α-methyl benzylamine. The reaction mixture changed from a clear amber to a clear wine red color during the course of 12 hours of refluxing. The crude yield of the amidine was 52.4 grams or 47% of the theoretical yield. Distillation of the product at a pressure of 3 mm. Hg produced 23.0 g. of a viscous oil having a boiling point (at this pressure) of 185° - 186°C. The product ultimately solidified and had a melting point of 65° - 69°C. On drying in vacuum over phosphorous pentoxide this melting point was raised to 81° - 82°C, indicating that on standing for several weeks in cork stoppered flasks, the amidine had absorbed water.

Anal. Calc'd for N, 12.49 Found: N, 12.38.

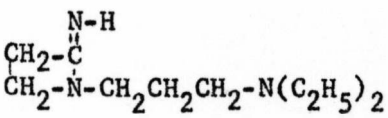
The Attempted Preparation of N-(3-Diethlyaminopropyl)-3-chloropropionamidine

By a procedure similar to that used for the synthesis of 4-benzimidoylmorpholine, 0.5 mole of β-chloropropionitrile was reacted with 0.5 mole of the N-magnesium bromide derivative of N,N-diethyl-1,3-propanediamine. After 48 hours of refluxing, the mixture was a clear brilliant reddish-amber color. It was hydrolyzed and worked up in the same manner as for 4-benzimidoylmorpholine to give 10.6 g. of a viscous oil (9.7% based on the proposed structure). An attempt to purify the product by vacuum distillation resulted in pyrolysis. A repeated sodium fusion test indicated the absence of chlorine which suggested an intramolecular cyclization involving the elimination of hydrochloric acid or dehydrohalogenation from the expected product or the formation of MgBrCl from the intermediate complex. The oil was purified as the picrate. Analysis indicated it to be the monopicrate of I, II or III.

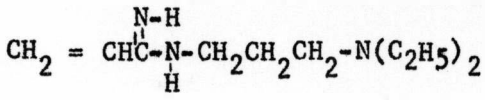
Anal. Calc'd. for N, 20.38 Found: N, 20.27.



I



II



III

The acrylamidine III was regarded as unlikely in view of the vigorous treatment required for such an elimination (18). The possibility of this compound was eliminated when the acrylamidine prepared from acrylonitrile and N,N-diethyl-1,3 propane diamine produced a picrate having a melting point of 195° - 196°C (refer p. 8) vs. a melting point of 144° - 145°C for the picrate of the amidine of questionable structure. The other possibility of cyclization back to the tertiary amine nitrogen to form the corresponding ammonium salt must also be eliminated because of the analysis and the expected insolubility of such a compound in ether and corresponding solubility in water, thus eliminating it in the work-up procedure. The only reasonable possibility appears to be 2-(3-diethylaminopropylamino)-1-azetine (I) or 1-(3-diethylaminopropyl)-2-iminoazetidine (II).

The Preparation of N-(3-Diethylaminopropyl)acrylamidine

By a procedure similar to that used for the synthesis of 4-benzimidoylmorpholine, 0.5 mole of acrylonitrile was reacted with 0.5 mole of the N-magnesium bromide derivative of N,N-diethyl-1,3-propanediamine. After refluxing for 40 hours, the products were hydrolyzed in an ice-cold saturate solution of NH_4Br. The product

was rather insoluble in ether and a continuous method for extraction with ether was used. In other respects the work-up was similar to that used for 4-benzimidoylmorpholine. The product largely decomposed on vacuum distillation, but a minute portion of the distillate was converted to the picrate having a melting point of 195° - 196°C.

The Attempted Preparation of N,N-Bis-(β-chloroethyl)-benzamidine

The following general procedure evolved in an attempt to prepare N,N-bis-(β-chloroethyl)-benzamidine converting β,β'-dichlorodiethylamine to its magnesium halide derivative and reacting the latter with benzonitrile, hydrolyzing the product to the corresponding amidine.

The β,β'-dichlorodiethylamine hydrochloride was prepared according to the procedure given by Ward (23). A 93% yield was obtained of a product which after three recrystallizations melted at 216°C (literature value was 215°C). Approximately 0.25 mole of the hydrochloride was dissolved in water and the solution was then made strongly basic, liberating a non-viscous yellow oil. The oil was extracted with ether and reclaimed by evaporating the ether. Exactly 0.2 mole of the dichlorodiethylamine was then weighed out and promptly dissolved in 100 ml. of THF. Two-tenths of a mole (21.8 grams) of ethyl bromide dissolved in 50 ml. of THF was added dropwise to 0.2 mole (4.9 grams) of magnesium turnings. After refluxing for 30 minutes, the ethyl magnesium bromide was cooled to

room temperature and transferred to an additional funnel. The THF solution of β,β'-dichlorodiethylamine was then transferred to the reaction flask, and the Grignard reagent was added very slowly to the nitrogen mustard solution at room temperature evolving the expected ethane gas. After the addition was completed, the reaction mixture was allowed to reflux for a few minutes. Then 0.2 mole (20.6 grams) of benzonitrile dissolved in 80 ml. of THF was added dropwise. The reaction was refluxed for about 48 hours after which the procedures used for isolating 4-benzimidoylmorpholine were followed. The product, immediately after evaporation of the final ether extract, was a highly viscous, dark brown oil. An infrared spectrum of this oil showed significant absorption at 1625 cm^{-1}, an absorption characteristic of the imine nitrogen. Since reactants, solvents, and other reasonable end products do not absorb in this region, this peak is fairly strong evidence for the presence of the desired amidine. The product was stored at room temperature for several days during which time much evidence of decomposition took place (see p.14).

Several attempts to synthesize the amidine by alternative procedures resulted in similar observations. Efforts to isolate and purify the product by vacuum distillation, chromotography, and by fractional crystallization of various amidine salts before decomposition, were unsuccessful.

DISCUSSION

The preparation of amidines from nitriles and amines by way of amino magnesium halide intermediates has been found to be generally satisfactory, except that poor yields were frequently encountered. Since the reaction between the amine and nitrile involves an attack by the nucleophilic amine nitrogen on the electrophilic cyanide carbon, conditions which would enhance the anionoid character of the former and/or the cationoid character of the latter should augment the reaction. Thus, primary or secondary amines, by the power of their active hydrogens, can be readily converted in good yields to amino magnesium halides by a suitable alkyl magnesium halide. The resulting Grignard reagents thus having greater polarity than the corresponding amines should provide much more reactive intermediates.

In general, the amino magnesium halides have been found to be extremely insoluble in ethyl ether and formed thick greyish-white suspensions which have made mechanical stirring very difficult. With similar periods of refluxing, poor yields of the amidine have been observed to correlate well with this lack of solubility. Also, when benzonitrile was used, significant amounts of an acid-insoluble, white solid were formed, having a melting point of 226°C which is presumably the cyclic trimer of benzonitrile, 2,4,6-triphenyl-1,3,5-triazine (cyaphenin) (Lit: m.p. = 224°C) indicating that homogeneous polymerization occurred in preference to

heterogeneous nucleophilic attack. As a rule, much greater solubilities of the N-magnesium halide and better yields of amidine have been achieved by the use of THF which frequently produced a one phase system. It is well known that THF is a suitable solvent for Grignard reactions and yet is sufficiently polar to dissolve in water and therefore would be more likely to solvate the salt-like N-magnesium halide. According to Kharasch and Reinmuth (9) on the basis of kinetic studies, Grignard reagents probably react with nitriles in ethyl ether with the aid of an intermediate complex of Grignard and solvent. Since this requirement is most likely also valid for N-magnesium halides in THF, the solubility of the amine-Grignard would provide a favorable condition for a reaction with a nitrile. These views would satisfy the observed phenomena in that increased concentrations of the amine-Grignard would enhance intermolecular reactions to form amidines and thus would divert the tendency of benzonitrile (and possibly other nitriles) to form polymers.

Several factors other than solubility and, of course, unfavorable equilibria may be contributing to the relatively small yields observed. One of these involves the hydrolysis. Apparently, (at least in the reaction of nitrile with Grignard reagents) a great range of stabilities of the resulting compounds of the general formula RRC = N-MgX exist. According to Kharasch and Reinmuth (9), the subsequent acid hydrolysis of such a compound could result in one which is so readily hydrolyzed to the ketone that isolation of the

imine would be very difficult. By analogous reasoning, if the amidine resulting from the acid hydrolysis of the corresponding N-magnesium halide compound were unstable, an acid amide would be formed. According to the extraction procedure used, this compound would most likely be carried along with unreacted nitrile. Because of this possibility, a saturated solution of ammonium chloride cooled to near zero or below zero was used as the hydrolysis medium.

Many of the amidines prepared or attempted in this study proved to decompose either partially or completely under vacuum distillation. 4-Benzimidoylmorpholine decomposed rather extensively when vacuum distilled with a tantalum spiral column, but yielded some distillate by using a short column with no packing. Although the product from this distillation was not adequately purified, much less difficulty was encountered in converting it to the picrate than when the picrate was attempted on the undistilled material. N-(α-methylbenzyl) benzamidine and its p-chloro homologue proved to be more heat stable and no difficulties were encountered with these distillations.

Recourse was taken to purify the heat-labile amidines by fractional crystallization of their corresponding salts. The hydrochlorides of all of the amidines synthesized in this study were deliquescent as were most of the hydrobromides, oxalates, sulfates, benzoates and salicylates. In spite of some concern over the

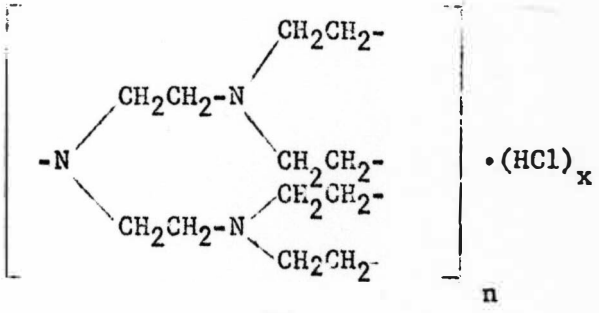
possible toxicity of picrates, the conversion of the heat-labile amidines to these salts proved to be the only convenient method of isolation and purification.

Sax (19) lists picric acid as only moderately toxic (not severe enough to threaten life or produce serious physical impairment) in its chronic systemic action. In view of this, it was felt that the therapeutic usefulness of the various amidine picrates was not significantly diminished. It was determined that picrates could be converted back to the amidine, but this was deemed unnecessary.

The presence of a halogen on either the amine or alkyl nitrile complicated synthesis procedures in the examples studied. The attempt to synthesize N-(3-diethylaminopropyl)-3-chloropropionamidine resulted in a reaction involving the elimination of the chlorine. An infrared spectrum of this compound, however, showed a strong absorbence peak for the imine nitrogen, strongly supporting the supposition that the amidine structure was present. The exact structure of the compound was not established, but is most certainly either structure I or II (refer p. 6). To further ascertain the structure is beyond the scope of this thesis problem. The product from the reaction of p-chloro-benzonitrile and α-methylbenzylamine gave a strong test for halogen and thus apparently did not undergo any secondary reactions. This may be the result of steric factors as well as the relative low reactivity of the chlorine on the

aromatic ring. Thus, in the presence of an amine hydrogen, an imine hydrogen and especially the rather reactive hydrogen on the carbon of benzylamine, apparently no elimination reaction occurred either inter or intramoleculary involving the chlorine which is stably attached to a benzene ring.

Because of the unusual reactivity of β,β'dichlorodiethylamine (nitrogen mustard), a variety of difficulties became apparent in the attempted synthesis of N,N-bis-(β-chloroethyl)-benzamidine. The synthesis of this amine involves the conversion of the hydrochloride of diethanolamine directly into the hydrochloride of the nitrogen mustard by treatment with thionyl chloride (23). The stable hydrochloride was first converted to the base form by treating a water solution of the salt with strong base and extracting with ether. The evaporation of the ether produced a yellow oil which proved to be unstable on standing for short periods of time. Apparently intermolecular alkylation takes place with ease liberating HCl and producing an obvious polymer and a free chloride ion such as IV (as the hydrochloride).



IV

This difficulty was avoided by keeping the ether extract cool during evaporation and promptly re-diluting the required weight of amine in THF.

Since ethyl magnesium bromide appeared to react with the chlorine ends of the nitrogen mustard, efforts were made to avoid high localized concentrations of Grignard reagents relative to the nitrogen mustard. This was achieved by adding dropwise, and with rapid stirring, the solution of the Grignard reagent to the nitrogen mustard (the reverse of the normal procedure). In doing this, it was hoped that the slower alkylation reaction would not take place to any significant extent if only enough of the Grignard reagent was present to react with the N-hydrogen.

Isolation of the corresponding benzamidine was not achieved although the reaction between nitrile and amino magnesium bromide apparently took place as evidenced by the liberation of heat on addition of nitrile and by IR spectra of the crude yield, which was a dark brown viscous oil. The oil, if stored at room temperature for several days, changed into a semisolid having the consistency of damp brown sugar. Attempts to vacuum distill the product resulted in a similar phenomenon. The possibility existed that unreacted nitrogen mustard had polymerized to furnish enough HCl to partially convert the amidine and amine polymer to their corresponding hydrochlorides. A pilot attempt was made to vacuum distill the nitrogen

mustard from a solution dilute enough to hinder polymerization in a solvent having an expected higher boiling point than nitrogen mustard. A 10% solution of nitrogen mustard in acetophenone (B.P. = 203°C) was prepared and vacuum distilled after which time heat was removed. The undistilled material in the flask contained, in addition to excess acetophenone, apparently the complete amount of original nitrogen mustard now solidified and probably polymerized.

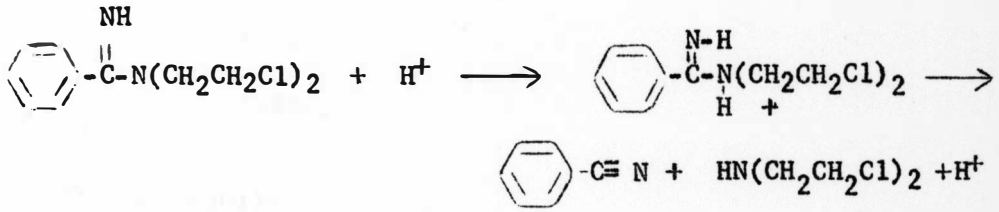
To circumvent this difficulty, an attempt was made to synthesize the amidine by first preparing and purifying the N,N-bis-(β-hydroxyethyl)-benzamidine and then converting the purified product to its dichloro homologue by treatment with thionyl chloride. Thus, diethanolamine was treated with C_2H_5MgBr in a 1:3 ratio producing the tri substituted amino-alkoxy-magnesium bromide. The latter was then treated with benzonitrile. No complications at this point were anticipated because it has been shown that alkoxy-magnesium bromides do not show Grignard reagent behavior toward nitriles (13). This N-Grignard reagent was apparently so slightly soluble even in THF, however, that the nitrile reverted to its alternative reaction and only the cyclic trimer could be isolated.

Subsequent study of the reaction products of the nitrogen mustard-benzonitrile reaction provided some indication that the resultant amidine decomposes on standing. This was based on the

observation that the product after standing for several days contained significant amounts of nitrile. Going through the extraction procedure removed the nitrile, but subsequent storage again revealed significant quantities of nitrile. After a third extraction procedure, the final liquid product did not possess aromatic character (as judged from the flame test) and was thin and light colored, closely resembling the original nitrogen mustard.

Another indication of decomposition appeared during an attempt to isolate the hydrochloride of the amidine. The salt, prepared by bubbling dry HCl gas through an ether solution of the reaction products, was highly deliquescent, providing a water phase instantly. Vacuum dessication produced crystals which completely went into solution within a few seconds after exposure to air. The dry salt was then recovered by vacuum dessication and stored in this state for one week. At this time, the crystals had taken on the appearance of somewhat damp brown sugar, but exposure to air indicated an essentially complete disappearance of deliquescent properties.

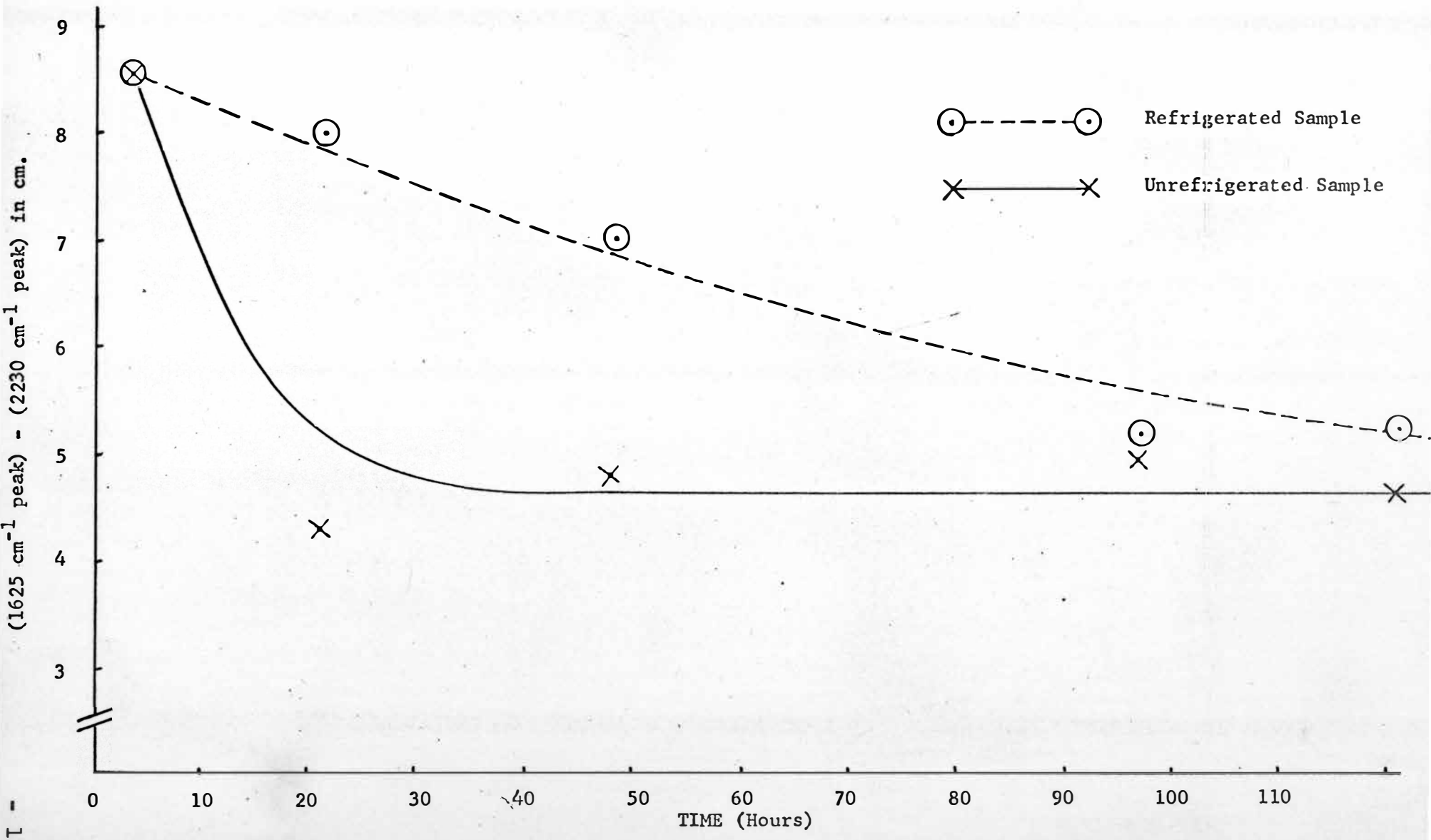
A reasonable mode of decomposition was theorized involving an intermediate protonated amidine.



The proton could be provided by an alkylation reaction between the chloro end of the molecule and the imine hydrogen thus forming a cyclic amidine and HCl. Whether this reaction actually occurs to any significant extent at room temperature was not established. Bromoethane alkylates rather readily on amidines at room temperature, but the corresponding reaction with chloroethane appears to be very sluggish. The proton could be provided as well by the polymerization reaction of unreacted nitrogen mustard.

An attempt was made to follow this decomposition by infrared spectrophotometry. An IR spectrum was run on the oil immediately after its recovery. One-half of the sample was then stored in an acetone-dry ice mixture and the other half at room temperature. IR spectra were run on both samples at periodic intervals throughout a five day period. Trends were noted by observing the differences in the peak at 1625 cm^{-1} (imine nitrogen) and the peak at 2230 cm^{-1} (nitrile). Thus, if decomposition into benzonitrile and nitrogen mustard actually occurs, then the values should get smaller with time since the 1625 cm^{-1} peak would become smaller and the 2230 cm^{-1} peak would become larger. Such a negative slope was observed with both samples during the first 90 to 100 hours approximately (refer to figure I). Also, as expected, the unrefrigerated sample appeared to decompose at a faster rate. Beyond 100 hours, however, there was some indication that no further decomposition took place in

FIGURE I. The Decomposition of β,β' Dichlorodiethylbenzamidine



either sample.

Additional work to establish the mode of decomposition of this amidine is of interest, but is beyond the scope of this study.

SUMMARY

Benzonitrile reacts with the magnesium bromide derivatives of morpholine and α-methylbenzylamine to give, after hydrolysis, 4-benzimidoylmorpholine and N-(α-methylbenzyl)-benzamidine respectively. The former was isolated as the picrate and the latter, because of its greater heat stability, was readily purified by vacuum distillation. The p-chloro homologue of the latter was also prepared in a similar fashion and purified by distillation.

The reaction between β-chloroproprionitrile and the magnesium bromide derivative of N,N-diethyl-1,3-propane diamine gives presumably a cyclic amidine, the exact structure of which has not been established. Because of the absence of chlorine in the final product, a secondary alkylation reaction apparently occurs involving the elimination of the chlorine either as hydrogen chloride or as magnesium chlorobromide. The product, which is most likely, either 2-(3-diethylaminopropyl amino)-1-azetine or 1-(3-diethylaminopropyl)-2-iminoazetidine, was isolated as the picrate.

Acrylonitrile reacts with the magnesium bromide derivative of N,N-diethyl-1,3-propane diamine to give N-(3-diethylaminopropyl)-acrylamidine. The product which is heat labile was isolated as the picrate.

The reaction between benzonitrile and β,β'-dichlorodiethyl amino magnesium bromide gives, on the basis of IR spectra, an unstable amidine. Isolation and purification of the product was not achieved. Difficulties in purification were brought about, at least in part, by the unusual reactivity of the amine as well as the apparent instability of the amidine. Some evidence of instability of this amidine (at room temperature) was accumulated on the basis of IR spectral studies.

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VITA

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