SYNTHESIS AND STRUCTURE OF AMIDINES

A Thesis

by

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This thesis is dedicated
to my Father, the late
Constantinos John Grivas

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Primary and secondary aliphatic and saturated cyclic amines as well as primary aromatic and heterocyclic amines react with trichloro-, trifluoro-, and dichloro-acetonitriles to give the corresponding amidines. Sixteen trichloro-, seven trifluoro- and five dichloro-acetamidines were prepared by procedures characterized by their simplicity, the absence of catalysts and the high yields of the reaction products. Experimental evidence was produced to support the reaction mechanism and certain limitations to the above mentioned reactions were defined.

Infrared spectroscopic studies proved the following facts: N-alkyl- and N-aryl-, trichloro- and trifluoro-acetamidines associate strongly in the liquid and solid phases, and they exist only in the imino form, RC(=NH)NHR', at least in non-polar solvents; they can be characterized by a new absorption (Amidine II band) at 1510-1545cm.$^{-1}$ and 1570-1560 cm.$^{-1}$ respectively which is attributed to the deformation vibration of the secondary amino group. Proof for the structure of the amidiniumcation was also provided by infrared investigation of the amidine hydrochlorides obtained. The chemical evidence which supports the generally accepted concept regarding the tautomerism of the amidine systems is disproved or at least weakened seriously by this research. It can be stated that for the present time there is no reason to believe that the mobility of the amidine system is so high that an amidine exists as a mixture of its two tautomeric forms.

GENERAL INTRODUCTION

It has been firmly established that unsubstituted nitriles do not react with amines to form amidines even at high temperatures and it can be predicted that nitriles having electron attractive atoms or groups (-Is effect) at the α-carbon atom would show enhanced reactivity.

The reaction between these nitriles and amines has not yet been studied systematically. Moreover, a search of the literature revealed that the information available was often contradictory and indicative of the uncertainty which exists in this field.

The first objective of the present investigation is to make a systematic study of the non-catalyzed addition of amines across the carbon-nitrogen triple bond and to establish the limitations of this reaction. The following types of nitriles were examined: trifluoro-, trichloro-, dichloro-, chloro- and nitro-acetonitrile. These nitriles can be arranged in the following order of decreasing strength of the -Is effect on the carbon atom of the nitrile group.

$$F_3C- > Cl_3C- > Cl_2CH- > NO_2CH_2- > ClCH_2-$$

The second objective of this research is to provide experimental evidence of the mechanism of this reaction and to study the structure and tautomerism of the amidines isolated by infrared spectroscopic methods.

It has been generally accepted that the mobility of the amidine system is so high that neither of the two tautomers can be isolated and that amidines exist as tautomeric mixtures. The knowledge gained in the progress of this investigation led to a reexamination of this concept. As a consequence the chemical evidence which supports the above conclusions is now disproved or at least weakened seriously.

HISTORICAL INTRODUCTION

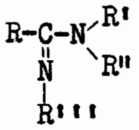
OPEN CHAIN AMIDINES

General:

An extensive review on amidines in general was written by Shriner and Newman (1) in 1944. Therefore in this introduction only the salient features of the chemistry of these compounds will be discussed.

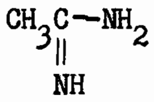
I Nomenclature and Classification

Open chain amidines are monoacid bases of the following structure



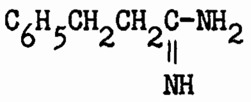
where R, R', R'' and R''' are hydrogen, alkyl or aryl radicals substituted or unsubstituted.

They are, in general, named after the acids or amides, which may be obtained by their hydrolysis, according to the system adopted by Chemical Abstracts, and this system will be used throughout this work. Thus (I) is acetamidine

 (I)

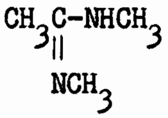
$$CH_3\underset{\underset{NH}{\|}}{C}-NH_2$$

The consecutive carbon atoms adjacent to the carbon atom of the amidine grouping are designated in the same manner as those adjacent to a carbonyl group (α, β, γ. . . etc.). Thus (II) is named β-phenylpropionamidine



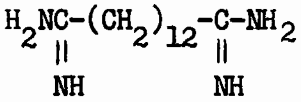
$$C_6H_5CH_2CH_2\underset{\underset{NH}{\|}}{C}-NH_2 \qquad (II)$$

The imino nitrogen and amino nitrogen atoms are not differentiated by this system and are referred to as N and N'; (III) is thus named N, N'-dimethylacetamidine



$$CH_3\underset{\underset{NCH_3}{\|}}{C}-NHCH_3 \qquad (III)$$

If it is difficult to name the compound as a derivative of an acid or amide, the amidine group is referred to as carboxamidine. For example,

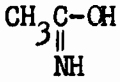


$$H_2N\underset{\underset{NH}{\|}}{C}-(CH_2)_{12}-\underset{\underset{NH}{\|}}{C}-NH_2 \qquad (IV)$$

(IV) may be named as dodecane-1,12-dicarboxamidine.

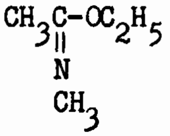
The nomenclature of compounds which are important intermediates in the synthesis of amidines should also be mentioned here. The addition of alcohols to the carbon-nitrogen triple bond of nitriles gives rise to compounds which have been called imino esters, imino ethers, imido esters or imido ethers.

These substances are esters of imidic acids according to Chemical Abstracts and are named after the parent acid. For example:



$$CH_3\underset{\underset{NH}{\|}}{C}-OH$$

Acetimidic acid

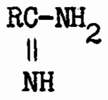


$$CH_3\underset{\underset{\underset{CH_3}{N}}{\|}}{C}-OC_2H_5$$

Ethyl N-methylacetimidate

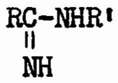
Open chain amidines can be classified into five general classes according to the number and distribution of the substituents on the nitrogen atoms.

(a) Unsubstituted amidines



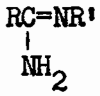
$\mathrm{R\underset{\underset{NH}{\|}}{C}-NH_2}$

(b) Monosubstituted amidines



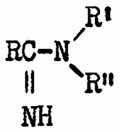
$\mathrm{R\underset{\underset{NH}{\|}}{C}-NHR'}$

or

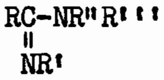


$\mathrm{R\underset{\underset{NH_2}{|}}{C}=NR'}$

(c) Unsymmetrical disubstituted amidines



(d) Trisubstituted amidines



$\mathrm{R\underset{\underset{NR'}{\|}}{C}-NR''R'''}$

II Structure of Amidines and their Salts

A considerable amount of chemical evidence indicates that monosubstituted and symmetrically disubstituted amidines exhibit tautomerism which is supported by the following facts:

(a) A mixture of amides and amines is always produced during hydrolysis of N,N'-substituted amidines.

(b) Attempts to prepare the two tautomers result in the isolation of a single amidine, and

(c) The alkylation of an amidine yields two products.

It is not intended in this introduction to discuss these aspects in detail. However, a few examples were considered helpful in the understanding of amidine structure.

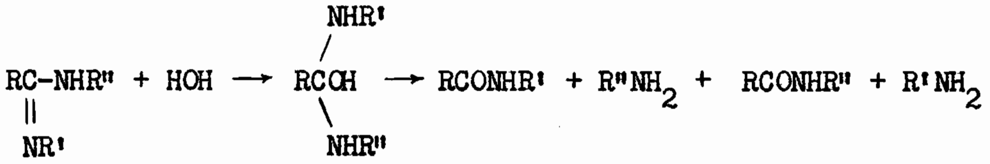
Amidines are relatively easy to hydrolyse (2, 3); hydrolysis usually takes place in water, alcohol or other solvents, depending on the solubility of the particular amidine. Dilute alkali or acid are usually used as a catalist to increase the rate of the reaction.

The nature of hydrolysis can be illustrated (4) by the general equation (V)

$$RC(=NH')NHR'' + 2H_2O \longrightarrow RCONHR'' + R'NH_2 + R''NH_2 + RCONHR' \qquad (V)$$

Identification of the reaction products often provides decisive information in the elucidation of the structure of amidines.

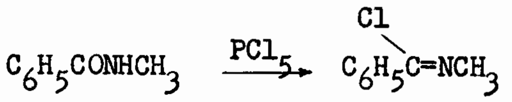
The above-mentioned facts led Markwald (5) in 1895 to suggest the following scheme for hydrolysis (VI)



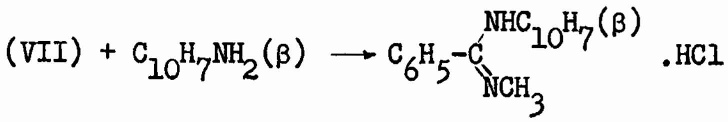
$$\underset{\underset{NR'}{\|}}{RC}\text{-}NHR'' + HOH \longrightarrow \overset{NHR'}{\underset{NHR''}{RCOH}} \longrightarrow RCONHR' + R''NH_2 + RCONHR'' + R'NH_2 \qquad (VI)$$

This mechanism, which involves the addition of water across the carbon-nitrogen double bond, is but of historical interest.

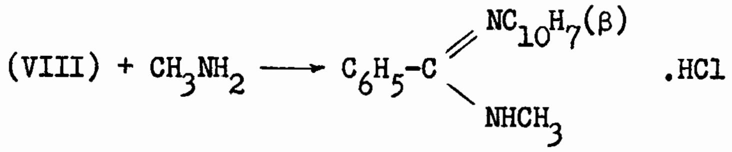
Many attempts have been made to isolate the two tautomers of a given amidine, but a single substance was always obtained (6, 7, 8, 10). Thus, von Pechmann (9) observed that the products obtained by the following reaction for the preparation of the tautomeric N-β-naphthyl-N'-methylbenzamidines (IX, X) were identical, so far as could be shown by comparison of melting points and other physical properties.



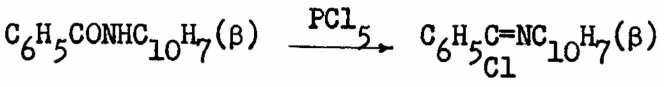
$$C_6H_5CONHCH_3 \xrightarrow{PCl_5} C_6H_5\overset{Cl}{C}{=}NCH_3 \qquad \text{(VII)}$$



$$\text{(VII)} + C_{10}H_7NH_2(\beta) \longrightarrow C_6H_5-C\begin{matrix} NHC_{10}H_7(\beta) \\ NCH_3 \end{matrix} .HCl \qquad \text{(X)}$$

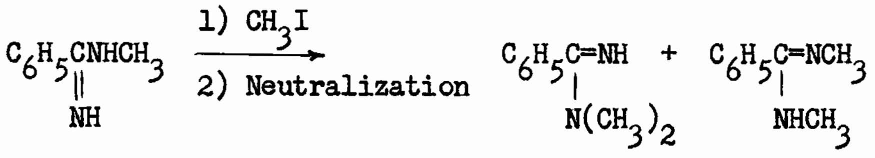


$$\text{(VIII)} + CH_3NH_2 \longrightarrow C_6H_5-C\begin{matrix} {/\!\!/} NC_{10}H_7(\beta) \\ \diagdown NHCH_3 \end{matrix} .HCl \qquad \text{(IX)}$$



$$C_6H_5CONHC_{10}H_7(\beta) \xrightarrow{PCl_5} C_6H_5\underset{Cl}{C}{=}NC_{10}H_7(\beta) \qquad \text{(VIII)}$$

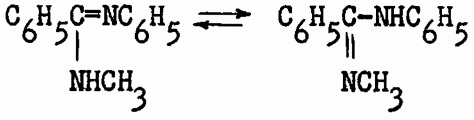
Alkylation studies conducted by Pyman (11) indicated also the existence of two tautomers in N-mono- and N,N'-disubstituted amidines. Thus N-methylbenzamidine (XI) gave equal amounts of products (XII, XIII) alkylated on each nitrogen.



$$\underset{\text{(XI)}}{C_6H_5\underset{\underset{NH}{\|}}{C}NHCH_3} \xrightarrow[\text{2) Neutralization}]{\text{1) } CH_3I} \underset{\text{(XII)}}{C_6H_5\underset{\underset{N(CH_3)_2}{|}}{C}{=}NH} + \underset{\text{(XIII)}}{C_6H_5\underset{\underset{NHCH_3}{|}}{C}{=}NCH_3}$$

(XI) (XII) (XIII)

The exact amount of each tautomer in the tautomeric equilibrium may be determined by the polar characteristics of the groups attached to the nitrogen atom. For example, the form (XIV) should exist in a greater proportion than the form (XV) in the tautomeric equilibrium, since the phenyl group has a greater tendency to attract electrons than the methyl group.

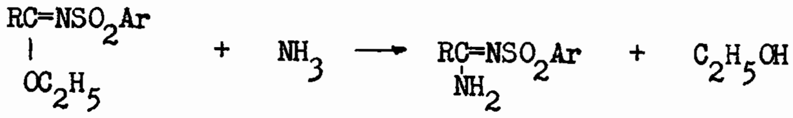


$$\underset{\text{(XIV)}}{C_6H_5\underset{\underset{NHCH_3}{|}}{C}{=}NC_6H_5} \rightleftarrows \underset{\text{(XV)}}{C_6H_5\underset{\underset{NCH_3}{\|}}{C}-NHC_6H_5}$$

(XIV) (XV)

Pyman (12) concluded that the formation of two isomeric alkyl derivatives by the action of methyl iodide upon open chain amidines is owing to the reaction of amidine in two tautomeric forms.

Nevertheless, the literature contains no authentic case of the isolation of two pure tautomers of a mono- or disubstituted open chain amidine, although a strong influence operating so as to immobilize the hydrogen atom could prevent tautomerism. Thus, Barber (13) isolated the two isomers (XVI , XVII) of an amidine substituted by a strong electronegative group, and this is the only example which has been reported.



$$\underset{\mathrm{OC_2H_5}}{\mathrm{RC{=}NSO_2Ar}} + \mathrm{NH_3} \longrightarrow \underset{\mathrm{NH_2}}{\mathrm{RC{=}NSO_2Ar}} + \mathrm{C_2H_5OH}$$

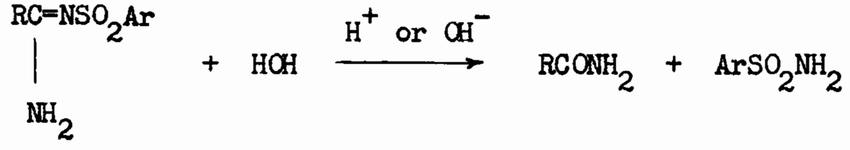
(XVI)

$$\underset{\mathrm{NH_2}}{\mathrm{RC{=}NH}} + \mathrm{ArSO_2Cl} \longrightarrow \underset{\mathrm{NHSO_2Ar}}{\mathrm{RC{=}NH}} + \mathrm{HCl}$$

(XVII)

Barber based the above structures on the hydrolysis products. The ease with which the nonstable isomer passed into the stable form precluded definite conclusions being drawn, but since sulphonamide was usually formed from the unstable amidine (XVI) whereas the stable form (XVII) was hydrolyzed exclusively to $\mathrm{RCONHSO_2Ar}$, the evidence was thought in favour of the above structural interpretation.

However, Northey, Pierce and Kertesz (15) concluded that sulphonamidines could be represented better by formula (XVIII), since their compounds did not form alkali salts and because of the nature of the products obtained from the hydrolytic cleavage.



$$\underset{\displaystyle \mathrm{NH_2}}{\mathrm{RC}}\mathrm{{=}NSO_2Ar} + \mathrm{HOH} \xrightarrow{\mathrm{H^+ \ or \ OH^-}} \mathrm{RCONH_2} + \mathrm{ArSO_2NH_2}$$

(XVIII)

In an attempt to study hydrogen bondings in general, Hunter and Marriot (14) measured the molecular weight of amidines and related substances and compared various physical constants. These studies led to the conclusion that amidines exhibit association far inferior to that of either glyoxalines or benzimidazoles. Furthermore, it was shown that the amidines examined fell into two distinct classes; those having a free imino hydrogen atom (XX) are associated to some extent and those without a free hydrogen atom (XXI) are not associated.

$RC(=NR)NHR'$

(XX)

$RC(=NR)NR'R''$

(XXI)

Acetamidines (XXII), showed stronger association than the corresponding benzamidines (XXIII).

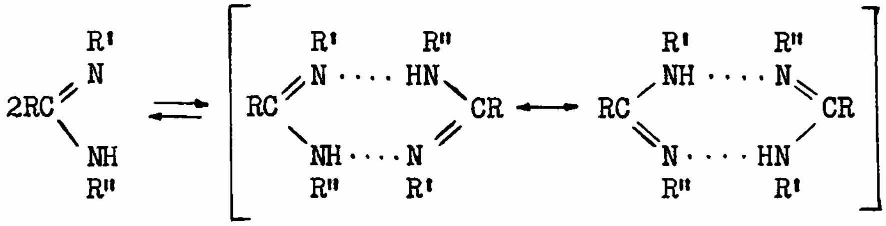
$CH_3C(=NR)NHR'$

(XXII)

$C_6H_5C(=NR)NHR'$

(XXIII)

Association (1) may be due to hydrogen bonding, with resonance occurring in the dimer in a fashion similar to that observed with carboxylic acids (XXIV).



(XXIV)

It is of historic interest to mention here that the failure to isolate the two tautomers of an amidine led Hunter (16) to the postulation of his "Theory of Mesohydric Tautomerism", according to which the true structure of an amidine is the hybrid of the two tautomeric structures.

Two years later Runner, Kilpatrick and Wagner (17, 18) without questioning the general validity of Hunter's theory, pointed out that it is so stated as to exclude the possibility that in any case a single tautomer can have a real existence. They suggested that an intramolecular immobilizing influence might be able to affect the normal mobility of the hydrogen atom in the amidine system of an unsymmetrical amidine so that it may stabilize one of the two tautomers to whatever extent this influence is able to prevail over the tendency to prototropy or hydrogen bonding. Such cases might be presented as follows:

(a) Existence of a strongly polar group located unsymmetrically with respect to the nitrogen atom.

(b) Steric hindrance.

(c) The possibility of stabilization of the amidine carbon-nitrogen double bond in one tautomer but not in the other through conjugation, and

(d) Intramolecular hydrogen bonding favouring one or the other tautomer by immobilizing the free hydrogen atom.

However, except in the above-mentioned special cases, it is generally accepted that a hydrogen atom attached to the amidine system is extremely mobile (19).

Recently infrared and Raman studies of some open chain amidines, to be discussed later, revealed that these compounds associate to a considerable extent, and provided indication of the existence of the two tautomers.

In contrast to the amides, which are very weak bases (dissociation constant near 10^{-15}), amidines are strong bases. Thus acetamidine (XXV) and benzamidine (XXVI) have Pk_a 12.52 (20) and 11.56 (21) respectively, whereas amidines of the formula (XXVII) are moderately strong bases (22) with Pk_a 7.22-7.26.

$CH_3C(=NH)NH_2$ (XXV) $C_6H_5C(=NH)NH_2$ (XXVI)

$p\text{-}PhC_6H_4NHCR{=}NH$

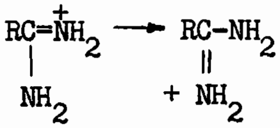
(XXVII)

The Pk_a is affected by the inductive and mesomeric effects which various R (XXXIV) groups can exert on the amidine system; for example when R = alkyl, Pk_a = 9-9.30, when R = secondary alkyl, Pk_a = 8.6-9.2 and if R = phenyl, Pk_a = 7.20-8.30.

Burtler and Pyman (12) suggested that, of the two nitrogen atoms of an amidine, that of the imino group is the one conferring basic properties in the molecule. Imido esters (XXVIII) are basic whereas amides (XXIX) are not markedly basic.

$RC(=NH)OR$ (XXVIII) $RC(=O)NH_2$ (XXIX)

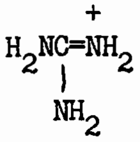
Amidines form monosalts with acids like hydrochloric, picric, chloroplatinic (23), sulphuric, acetic etc. Several authors have attempted to describe the nature of the amidinium cation which could be a resonance hybrid (24) of the structure (XXX)



$$\begin{array}{c}RC=\overset{+}{N}H_2\\ |\\ NH_2\end{array} \longrightarrow \begin{array}{c}RC-NH_2\\ \|\\ +\,NH_2\end{array}$$

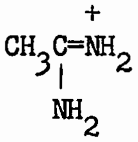
(XXX)

Guanidine is a much stronger base (Pk_a = 13.71) because its cation (XXXI) has three equivalent resonance structures in which each NH_2 group has a positive charge, whereas in acetamidine cation (XXXII) there are only two equivalent structures contributing to the resonance hybrid. This leads to a decrease in basic strength, partly compensated by the +Is effect of the methyl group.



$$\begin{array}{c}\overset{+}{H_2NC=NH_2}\\ |\\ NH_2\end{array}$$

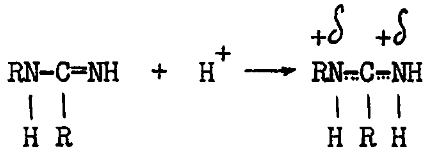
(XXXI)



$$\begin{array}{c}\overset{+}{CH_3C=NH_2}\\ |\\ NH_2\end{array}$$

(XXXII)

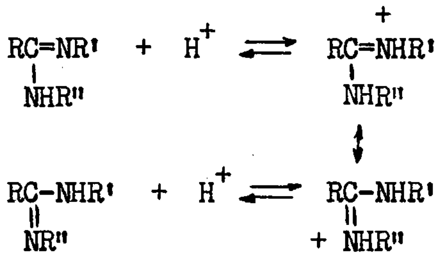
Addition of a proton to the N-mono-substituted amidines (22) may be written as in (XXXIII), but it is not true to say that the positive charge is distributed evenly over the two reaction centres.



$$\underset{\mathrm{H}}{\mathrm{RN}}\text{-}\underset{\mathrm{R}}{\mathrm{C}}\mathrm{=NH} + \mathrm{H}^+ \longrightarrow \underset{\mathrm{H}}{\overset{+\delta}{\mathrm{RN}}}\cdots\underset{\mathrm{R}}{\mathrm{C}}\cdots\underset{\mathrm{H}}{\overset{+\delta}{\mathrm{NH}}}$$

(XXXIII)

Shriner and Neumann (1) concluded that " . . . resonance is likely in the salts of unsubstituted amidines and in those of the symmetrically disubstituted amidines having <u>identical groups</u> on the nitrogen atom" and ". . . it seems likely that one of the resonance forms postulated by Sidgwick (24) should be partially stabilized when the two nitrogen atoms contain extremely unlike groups". The salts of the two tautomers should then be identical, since the common ion is a resonance hybrid (XXXIV).



$$\underset{\mathrm{NHR''}}{\mathrm{RC}}\mathrm{=NR'} + \mathrm{H}^+ \rightleftharpoons \underset{\mathrm{NHR''}}{\mathrm{RC}}\overset{+}{\mathrm{=NHR'}}$$

$$\updownarrow$$

$$\underset{\mathrm{NR''}}{\underset{\|}{\mathrm{RC}}}\mathrm{-NHR'} + \mathrm{H}^+ \rightleftharpoons \underset{+\,\mathrm{NHR''}}{\underset{\|}{\mathrm{RC}}}\mathrm{-NHR'}$$

(XXXIV)

III <u>Synthesis of Open Chain Amidines from Nitriles and Amines</u>

There is no record in literature of the production of an amidine by the addition of an amine or ammonia to an unsubstituted nitrile. The statement of Walter and Grossmann (25) that N-o-chlorophenylbenzamidine was obtained in 75% yield by heating o-chloroaniline and phenyl cyanide at 180° is probably due to an error, according to Oxley and Short (26). The last investigators repeated the reaction but failed to isolate any amidine.

One of the most practical and useful methods is that first described by Pinner (27, 28) in 1877. According to this procedure the nitrile is dissolved or suspended in anhydrous alcohol and treated with an excess of dry hydrogen chloride. The imido ester hydrochloride (XXXV) formed is then treated with ammonia, primary (29, 30) or secondary amines (31, 32, 33) to give unsubstituted (XXXVI) monosubstituted (XXXVII) and unsymmetrical disubstituted (XXXVIII) amidines.

$$\mathrm{RCN + R'OH + HCl \longrightarrow RC({=}NH)OR' \cdot HCl} \qquad \text{(XXXV)}$$

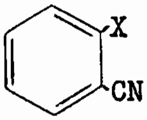
$$\text{(XXXV)} + \mathrm{NH_3 \longrightarrow RC({=}NH)NH_2 \cdot HCl + R'OH} \qquad \text{(XXXVI)}$$

$$\text{(XXXV)} + \mathrm{R''NH_2 \longrightarrow RC({=}NH)NHR \cdot HCl + R'OH} \qquad \text{(XXXVII)}$$

$$\text{(XXXV)} + \mathrm{R_1R_2NH \longrightarrow RC({=}NH)NR_1R_2 \cdot HCl + ROH} \qquad \text{(XXXVIII)}$$

Mononitriles as well as dinitriles, aliphatic or aromatic, have been used (34); Gautier (35) obtained even formamidine hydrochloride from cyanogen.

Nevertheless, Pinner's method involves the use of large volumes of anhydrous solvents and cannot be applied in some cases. Steric hindrance plays an important role in Pinner's reactions, but the exact limitations are unknown. For example, ortho-substituted aromatic nitriles (XXXIX) proved to be unreactive towards alcohols and hydrogen chloride, whereas their isomers did react with the same reagents (36).

(XXXIX) 

$X = CH_3, -NH_2, -NO_2, -C(=NH)OC_2H_5, -CN$

Similarly α-naphthonitrile gave no imido ester hydrochloride, whereas β-naphthonitrile was converted to the corresponding amidine (37).

The mechanism of the reaction between imido esters hydrohalides with amines has not yet been established. Knorr (38) claimed that it takes place between the free iminoether and ammonium chloride and that excess of ammonia plays no part in the reaction, i.e. the reaction involves an ammonium ion (XL).

$$RC(=NH)OR \cdot HCl + NH_3 \rightleftharpoons RC(=NH)OR + NH_4Cl \qquad (XL)$$

$$RC(=NH)OR + NH_4Cl \longrightarrow RC(=NH)NH_2 \cdot HCl + ROH$$

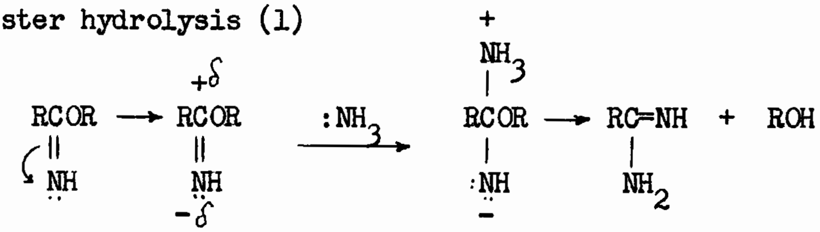
The fact that a large excess of absolute alcoholic ammonia is necessary may show that possibly the chief function of this excess is to displace the equilibrium (XL) in favour of the ammonium chloride and the imido ester base, the latter being much more stable to alcohol than is the imido ester hydrochloride.

Although the decomposition of imido ester hydrohalides by alcohol (XLI) must not be overlooked (39), Ashley et al. (40) found that the benzimido ester base does yield benzamidine base with alcoholic ammonia

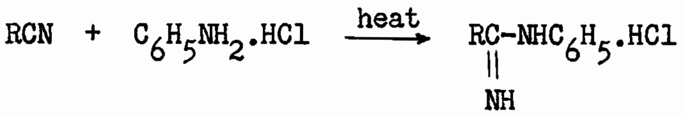
$$RC(=NH)OEt.HCl + 2EtOH \longrightarrow NH_4Cl + RC(OEt)_3 \qquad (XLI)$$

$$C_6H_5C(=NH)OEt + NH_3 \xrightarrow{EtOH} C_6H_5C(=NH)NH_2 + EtOH \qquad (XLII)$$

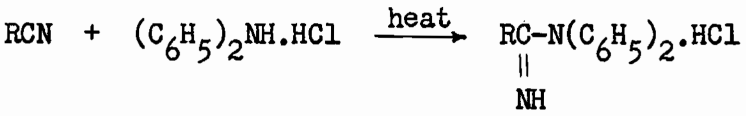
This points out that perhaps the reaction mechanism is similar to that of the ester hydrolysis (1)



Bernthsen (41, 42) first discovered that N-aryl- and N,N'-diarylamidines can be prepared by heating nitriles with the hydrochlorides of a primary aromatic amine or diphenylamine in yields from 10 to 30%.



$$RCN + C_6H_5NH_2.HCl \xrightarrow{heat} \underset{\displaystyle NH}{\overset{}{RC\!\!=}}\!-NHC_6H_5.HCl$$



$$RCN + (C_6H_5)_2NH.HCl \xrightarrow{heat} \underset{\displaystyle NH}{RC\!\!=}\!-N(C_6H_5)_2.HCl$$

He also stated that amidines could not be obtained from cyanides and ammonium chloride.

Cornell (43) reported that no reaction occurs when only nitrile and ammonia are heated but isolated benzamidine hydrochloride and aliphatic amidines in very low yields when the corresponding nitriles were heated in sealed tubes with ammonium chloride in liquid ammonia.

$$C_6H_5CN + NH_4Cl \xrightarrow{NH_3} C_6H_5C(=NH)NH_2.HCl$$

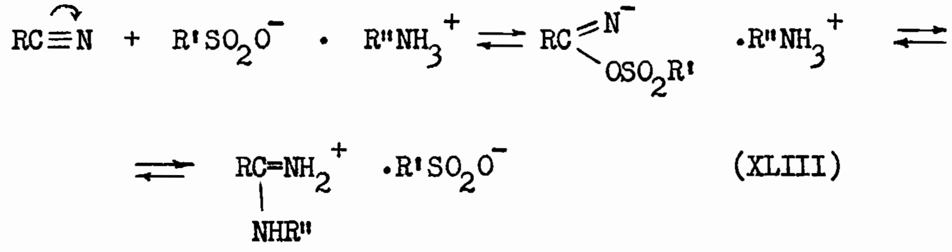
Aromatic and aliphatic nitriles also react with aryl or alkyl primary amine hydrochlorides to form amidines (44, 45) under the influence of heat. The disadvantage of this method is the formation of disubstituted amidines as by-products at higher temperatures.

$$C_6H_5CH_2CN + p\text{-}ClC_6H_4NH_2.HCl \xrightarrow{200°} C_6H_5CH_2C(=NH)NC_6H_4Cl\text{-}p$$

It should be pointed out here that the statment found in almost all the standard textbooks of organic chemistry, that unsubstituted amidines may be prepared by heating nitriles with ammonium chloride, is an extrapolation of Bernthsen's discovery and should be taken cautiously.

Suggesting that the additive capacity of the nitrile group may be enhanced by an "imported" stimulus, Oxley and Short (46) reported the preparation of unsubstituted and N-monosubstituted amidines from ammonium or alkyl- or aryl-ammonium salts of an aromatic acid at temperatures between 130 and 260°.

In a modification of this procedure the same authors (48) prepared some amidines and their N-substituted derivatives by heating the nitrile, ammonia or a primary or secondary amine and the corresponding ammonium or substituted ammonium sulphonates at temperatures between 150 and 220°. They represented the reactions as follows:



$$RC\equiv N + R'SO_2O^- \cdot R''NH_3^+ \rightleftharpoons RC\begin{matrix} \nearrow N^- \\ \searrow OSO_2R' \end{matrix} \cdot R''NH_3^+ \rightleftharpoons \underset{\displaystyle NHR''}{RC=NH_2^+} \cdot R'SO_2O^-$$

(XLIII)

The formation of amidines from phenyl cyanides was usually promoted by electron attracting groups (p-MeSO$_2$, p-Br, p-NO$_2$) and retarded by those which repulse electrons. The method having the advantage of being a one-stage process can be used without employing a solvent and is applicable to α-naphthyl cyanide and o-substituted phenyl cyanides which are inert at the conditions existing in Pinner's procedure.

Heating the nitriles with ammonium or alkylammonium thiocyanates, Partridge and Short (47) obtained increased yields in cases where a similar treatment with sulphonates resulted in very low yields.

$$RCN + H_4NSCN \longrightarrow RC(=NH)NH_2.SCNH$$

$$RCN + R'NH_3SCN \longrightarrow RC(=NH)NHR'.SCNH$$

The use of sulphonates and thiocyanates seems to be of importance, since attempts to react nitriles with a variety of other salts (49) were unsuccessful. Thus salts like ammonium chloride, sulphate, picrate, bromide etc. were heated with two reactive nitriles at temperatures between 200-250°, but no amidine could be isolated.

Catalysts capable of forming complexes with nitriles (50, 51) were found quite useful in the synthesis of amidines. These catalysts probably coordinate with nitriles enhancing the dipole conditions of the molecule and consequently its reactivity. A number of amidines have thus been prepared by Oxley, Partridge and Short (52), who used excess aluminum chloride, nitriles and temperatures around 100°. The reactions probably proceed according to the following scheme:

$$RCN + AlCl_3 \longrightarrow RC\underset{\curvearrowleft}{\equiv}\overset{+}{N} \longrightarrow \overset{-}{Al}Cl_3 \qquad (XLIV)$$

$$(XLIV) + HNR_1R_2 \longrightarrow RC(NR_1R_2)=\overset{+}{N}H \longrightarrow \overset{-}{Al}Cl_3$$

The complex of the amidine with the catalyst was carefully hydrolysed with water and the amidine hydrochloride was collected or the amidine liberated by excess aqueous sodium hydroxide

$$C_6H_5CN + NH_3 \xrightarrow{AlCl_3} C_6H_5C(=NH)NH_2.HCl$$

Various catalysts, e.g. ferric chloride, zinc chloride, stannic chloride and boron trifluoride, have been used to promote the formation of amidines in fairly good yields.

In certain cases aminomagnesium halides (53) were used for the preparation of amidines.

$$RCN + R'R''NMgBr \longrightarrow RC(=NMgBr)NR'R'' \qquad (XLV)$$

$$(XLV) \xrightarrow{H^+} RC(=NH)NR'R''$$

Another useful reaction involves the amination of aliphatic and aromatic nitriles with alkali metal amides:

$$RCN + KNH_2 \longrightarrow RC(=NK)NH_2$$

The reaction fails, however, when nitriles containing reactive methylene groups are used since they undergo condensation to a dimer (54, 55, 56). The conversion of the alkali metal salts to the amidines is accomplished by careful hydrolysis with water at low temperatures or by treatment with hydrogen chloride in absolute alcohol (57, 58, 59, 60).

Lathermoser (61) and others (62, 63) treated the free amine with powdered sodium and the isolated sodium salt of the amidine (XLVI) was converted into the free base by water hydrolysis.

$$o\text{-}CH_3C_6H_4CN + C_6H_5NH_2 + 2Na \xrightarrow{C_6H_6} o\text{-}CH_3C_6H_5C(=NC_6H_5)NHNa \quad (XLVI)$$

$$+ \; C_6H_5CH_3 \; + \; NaCN$$

$$(XLVI) \; + \; H_2O \longrightarrow o\text{-}CH_3C_6H_4C(=NC_6H_5)NH_2 \; + \; 2NaOH$$

The importance of this method is obvious since o-toluenenitrile does not react by Pinner's method.

It seems, nevertheless, that hydrogen cyanide reacts with amines to form amidines which, being unstable, hydrolyse to the corresponding amides. Contrary to the findings of Stewart and Fontana (64), who suggested that amines and hydrogen cyanide do not react, even to the limited extent of forming salts in alcoholic solutions, Erickson (65) reported that this reaction proceeds easily. Although he did not succeed in preparing the pure formamidines or their hydrochlorides, he isolated their hydrolysis products. For example, when a mixture of hydrogen cyanide and n-butylamine was allowed to stand at room temperature for 25 days n-butylformamide (XLVII) was formed. Diethylformamide (XLVIII) was also prepared by the reaction between dimethylamine and hydrogen cyanide.

$$HCN + n\text{-}CH_3(CH_2)_3NH_2 \longrightarrow \left[CH_3(CH_2)_3NHCH{=}NH\right] \xrightarrow{OH_2} CH_3(CH_2)_3NHCH{=}O \quad (XLVII)$$

$$HCN + (CH_3)_2NH \longrightarrow \left[(CH_3)_2N\text{-}CH{=}NH\right] \xrightarrow{\text{hydrolysis}} (CH_3)_2NCH{=}O \quad (XLVIII)$$

In general, amidines cannot be formed by the addition of ammonia or amines to an unsubstituted cyanide, but the introduction of electron attracting atoms or groups at the α-position of the carbon-nitrogen triple bond facilitates the reaction. Hydrochloric acid on the other hand seems to be necessary in the formation of imido esters from alcohols and unsubstituted nitriles. For the first time Steinkopf (66, 67) reported trichloroacetonitrile as an exception. Methylacetimidate (XLIX) was isolated when an excess of methanol and trichloroacetonitrile was refluxed for five hours, but no yield was given.

$$Cl_3CCN + CH_3OH \longrightarrow Cl_3CC(=NH)OCH_3 \qquad \text{(XLIX)}$$

Six years later Houben and Kauffmann (68) repeated the same reaction but recovered the trichloroacetonitrile in almost quantitative yield. Their remarks led Steinkopf (70) to a more detailed investigation of this reaction by conducting a series of tests under the same conditions, and using pure and non-pure reactants. These studies resulted in the conclusion that trichloroacetamide, present in the trichloroacetonitrile, and acetone-containing methanol are necessary for the reaction which did not proceed when 100% pure nitrile and acetone-free methanol were used. However, he did not explain the reason for the "catalytic" influence of acetone and trichloroacetamide. In the same communication, Steinkopf reported that, although absolute ethanol does not react with trichloroacetonitrile, ethyl acetimidate (L) was formed when these two compounds were refluxed in the presence of catalytic amounts of acetone

$$Cl_3CCN + EtOH \xrightarrow{\text{Acetone}} Cl_3CC(=NH)OEt \qquad \text{(L)}$$

Although hydrogen chloride is necessary for the conversion of an imido ester to the corresponding amidine, Steinkopf (66, 67) synthesized N-phenyltrichloroacetamidine (LI) by heating an ethanolic solution of methyl acetimidate with aniline in the absence of hydrogen chloride.

$$Cl_3CC(=NH)OCH_3 + C_6H_5NH_2 \rightarrow Cl_3CC(=NH)NHC_6H_5 + C_2H_5OH \quad (CH_3OH)$$

Another example of a straight addition of amines to the carbon nitrogen triple bond was demonstrated by Curtis and Nickel (71) when a solution of benzylamine was treated with ethyl cyanotartronate (LII) in ether. The addition product (LIII) was separated in fifteen seconds, but it was very unstable.

$$C_6H_5CH_2NH_2 + \underset{\text{(LII)}}{2NC(HO)C(COOC_2H_5)_2} \rightarrow \underset{\text{(LIII)}}{C_6H_5CH_2N\left[C(=NH)C(OH)(COOC_2H_5)_2\right]_2}$$

Trichloroacetonitrile also adds amines without any catalysts. Thus, Dachlauer (72), without giving any details in his patent, reported that trichloroacetonitrile was treated with ammonia or primary aliphatic or hydroaromatic amines or their derivatives at temperatures below the boiling point of trichloroacetonitrile to give the corresponding amidines. For example, excess of liquid ammonia was stirred with trichloroacetonitrile at -40° to give trichloroacetamidine (LIV). In a similar way N-n-propyltrichloroacetamidine (LV), ethyleneditrichloroacetamidine (LVI), N-stearyl- (LVII), N-benzyl- (LVIII), N-cyclohexyltrichloroacetamidine (LIX), and bis-trichloroacetamidoamine were isolated.

$$Cl_3CCN + H_2NCH_2NH_2 \rightarrow Cl_3CC(=NH)NHCH_2CH_2NH(HN=)CCCl_3 \quad \text{(LVI)}$$

$$CCl_3CN + RNH_2 \rightarrow Cl_3CC(=NH)NHR$$

(LIV): R=H

(LV) : $R=CH_3CH_2CH_2-$

(LVII) : $R=CH_3(CH_2)_{17}-$

(LVIII): $R=C_6H_5CH_2-$

(LIX) : $R=C_6H_{11}-$

A few years later Oxley repeated the preparation of trichloroacetamidine by passing dry ammonia for two hours at 0° into a benzene solution of trichloroacetonitrile. A liquid product was isolated instead of Dachlauer's solid compound. Its picrate, however, showed a correct analysis, whereas Dachlauer did not analyze his solid compound. Oxley and his co-workers attempted also to prepare N-phenyltrichloroacetamidine by treating equivalent amounts of aniline and the nitrile in benzene, but they were unsuccessful (48).

Recently Backer and Wanmaker (73) synthesized a few more N-substituted trichloroacetamidines by methods similar to that of Oxley et al. For example, N-methyltrichloroacetamidine was formed by passing dry methylamine in a dry benzene solution of trichloroacetonitrile and N-piperidyltrichloroacetamidine was produced by treating piperidine with trichloroacetonitrile in toluene at 0°. However, both compounds could be isolated only in the form of picrates. The same workers followed Steinkopf's method (70) for the preparation of N-phenyl derivatives. For example, a mixture of trichloroacetonitrile, aniline, excess methanol and a few drops of acetone was refluxed for five hours to give N-phenyltrichloroacetamidine in 36% yield. Without explaining the catalytic role of acetone, they suggested that the reaction proceeds via imido ester as in Pinner's procedure (LX).

$$Cl_3CCN \xrightarrow[\text{Acetone}]{CH_3OH} Cl_3CC(=NH)OCH_3 \xrightarrow[\text{Acetone}]{C_6H_5NH_2} Cl_3CC(=NH)NHC_6H_5$$

Trifluoroacetonitrile is expected to react in a way similar to trichloroacetonitrile owing to an even stronger -Is effect of the trifluoromethyl group. Thus, Husted (74) synthesized a series of perfluoroalkylamidines by allowing the corresponding nitriles to react with liquid ammonia in closed tubes at room temperature.

$$C_nF_{2n+1}CN \ + \ NH_3 \longrightarrow C_nF_{2n+1}C(=NH)NH_2$$

$$n = 1 - 11$$

In a modification of Husted's procedure Reilly and Brown (75, 76) isolated some N-alkyl- and N-dialkyl-perfluoroacetamidines by treating three perfluoronitriles with primary and secondary alkyl-amines at very low temperatures.

$$RCN \ + \ R'R''NH \longrightarrow RC(=NH)NR'R''$$

$$R = CF_3-, \quad C_2F_5-, \quad C_3F_7- \qquad R' \text{ and } R'' = H \text{ or } CH_3$$

The same authors pointed out that ". . . although the primary and secondary alkylamines reacted rapidly with the perfluoronitriles at the reflux temperature of the mixture, aromatic amines, for example aniline, did not react even at higher temperatures. This indicates that the basicity of the amine is an important consideration in this reaction. Aniline, being a weaker base than either ammonia or alkylamines, would furnish a relatively poor anionoid nitrogen to take part in the formation of the substituted amidines".

There is no information in the literature for the reaction between dichloroacetonitrile and amines since all dichloroacetamidines reported have been prepared by Pinner's method. In 1953 Ashley, Slack and Berg (77) reported the synthesis of ethyl dichloroacetimidate hydrochloride (LXI), dichloroacetamidine hydrochloride (LXII) and ethyl dichlorothioacetimidate hydrochloride (LXIII).

$$\underset{\text{LX}}{\mathrm{Cl_2CHCN}} + \mathrm{EtOH} \xrightarrow{\mathrm{HCl}} \mathrm{Cl_2CHC({=}NH)OEt.HCl} \qquad \text{(LXI)}$$

$$\text{LX} + \mathrm{NH_3} \longrightarrow \mathrm{Cl_2CHC({=}NH)NH_2.HCl} \qquad \text{(LXII)}$$

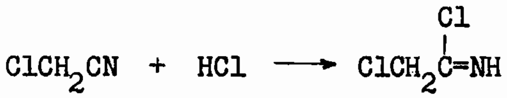
$$\text{LX} + \mathrm{EtSH} \longrightarrow \mathrm{Cl_2CHC({=}NH)SEt.HCl} \qquad \text{(LXIII)}$$

IV <u>Reaction of Chloroacetonitrile with Ammonia and Amines</u>

The same resistance of the carbon-nitrogen triple bond of acetonitrile towards ammonia and amines is encountered with chloroacetonitrile. However, Steinkopf and Bohrmann (80) succeeded in isolating the addition product (LXIV) by treating a water solution of chloroacetonitrile (LXV) and hydroxylamine with sodium carbonate.

$$\underset{\text{LXV}}{\mathrm{ClCH_2CN}} + \mathrm{H_2NOH} \xrightarrow{\mathrm{Na_2CO_3}} \underset{\text{LXIV}}{\mathrm{ClCH_2C({=}NOH)NH_2}}$$

Gaseous hydrogen chloride (81) is the only other compound which has been reported to add in a similar fashion to give α-chloroacetimidil chloride (LXVI)



$$ClCH_2CN + HCl \longrightarrow ClCH_2\overset{Cl}{C}{=}NH \qquad \text{(LXVI)}$$

The chlorine atoms of chloroacetonitrile enter preferentially in substitution reaction with ammonia since Bauer and Teter (82) isolated aminoacetonitrile (LXVII) by passing a stream of ammonia through a solution of concentrated ammonia and chloroacetonitrile

$$ClCH_2CN + NH_3 \longrightarrow \underset{\text{(LXVII)}}{H_2NCH_2CN.HCl}$$

The tendency of ammonia to attack chlorine at the α-carbon atom instead of the nitrile group may also be responsible for the formation of thiodiglycolonitrile (LXVIII) which occurred when ammonia and hydrogen sulphide passed together (83) through an ethereal solution of chloroacetonitrile.

$$2ClCH_2CN + H_2S + 2NH_3 \longrightarrow \underset{\text{(LXVIII)}}{S(CH_2CN)_2} + 2NH_4Cl$$

Diethylamine was also found to react by substitution, since Henry and Dewall (84) isolated diethylaminoacetonitrile (LXIX) by treating an ethereal solution of the amine with chloroacetonitrile in a molar ratio 2:1

$$2(C_2H_5)_2NH + ClCH_2CN \longrightarrow \underset{\text{(LXIX)}}{(C_2H_5)_2NCH_2CN} + (C_2H_5)_2NH.HCl$$

Alkyl chloroacetimidate hydrochlorides (LXX) have only been prepared (85, 86, 87, 88) by Pinner's method

$$ClCH_2CN + ROH \xrightarrow{HCl} ClCH_2C(=NH)OR$$

(LXX)

Klarer and Urech (89) prepared chloroacetamidine (LXXII), N-phenylethylchloroacetamidine (LXXIII) and N-piperidinochloroacetamidine (LXXIV) via imido esters

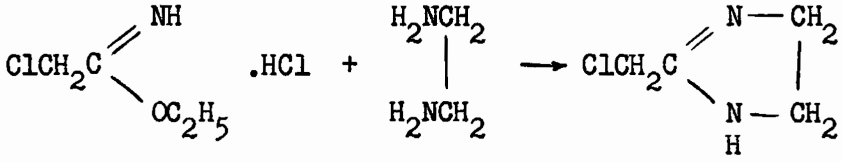
$$ClCH_2C(=NH)OC_2H_5.HCl + NH_3 \rightarrow ClCH_2C(=NH)NH_2.HCl \qquad (LXXII)$$

(LXXI)

$$(LXXI) + C_5H_{10}NH \rightarrow ClCH_2C(=NH)NHC_5H_{10}.HCl \qquad (LXXIV)$$

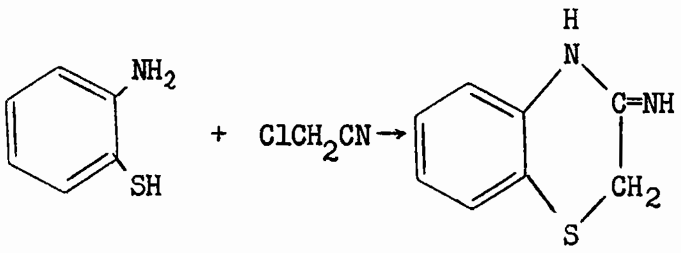
$$(LXXI) + C_6H_5CH_2NH_2 \rightarrow ClCH_2C(=NH)NHCH_2C_6H_5 \qquad (LXXIII)$$

Compounds like 2(chloromethyl)imidazoline (LXXV) have also been synthesized by cyclization reactions and proved to be therapeutically useful (91).



(LXXV)

Another cyclization reaction was achieved by Carla (92), by treating o-aminothiophenol (LXXVI) with chloroacetonitrile in the presence of sodium; however the structure of the product (LXXVII) was not proved decisively.



(LXXVI) (LXXVII)

V The Chemistry of Nitroacetonitrile

Very little is known concerning the chemistry of nitroacetonitrile which cannot be synthesized by the classical methods by dehydration of nitroacetamide with phosphorus pentoxide (93).

After several attempts Steinkopf (67) succeeded in its preparation. Methazonic acid (LXXVIII) can be isolated by the reaction of two molecules of nitromethane in concentrated aqueous sodium hydroxide. This acid can be dehydrated with thionyl chloride to give nitroacetonitrile in good yield.

$$2CH_3NO_2 + KOH \longrightarrow O_2NCH_2CH{=}NOK$$

$$O_2NCH_2CH{=}NOK + HCl \longrightarrow O_2NCH_2CH{=}NOH + KCl$$

(LXXVIII)

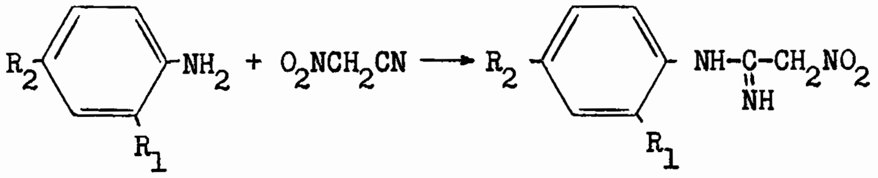
$$(LXXXIX) \xrightarrow{SOCl_2} O_2NCH_2CN$$

This procedure was modified slightly later by Steinkopf (63) and recently by Ried and Köhler (95).

Ammonium nitroacetonitrile was found to react (65) with hydroxylamine hydrochloride to give the addition product (LXXIX).

$$O_2NCH_2CN.NH_3 + HONH_2.HCl \longrightarrow O_2NCH_2C({=}NH)NOH + NaCl + H_2O \quad (LXXIX)$$

N-substituted amidines were reported to be formed quite easily (65). Thus, N-phenyl- (LXXX), N-o-tolyl- (LXXXI) and N-(2,4-dimethylphenyl)-nitroacetamidine (LXXXII) precipitated immediately, when an ethereal solution of nitroacetonitrile was added dropwise to the corresponding amine at 0°.

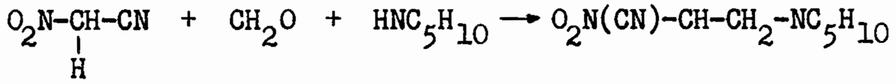


LXXX : $R_1 = R_2 = H$

LXXXI : $R_1 = CH_3$, $R_2 = H$

LXXXII: $R_1 = R_2 = CH_3$

Finally, the only other reaction known is the Mannich reaction, which takes place when nitroacetonitrile is brought together with amines and formaldehyde at low temperatures.



$$O_2N\text{-}\underset{\substack{|\\ H}}{C}H\text{-}CN \;+\; CH_2O \;+\; HNC_5H_{10} \longrightarrow O_2N(CN)\text{-}CH\text{-}CH_2\text{-}NC_5H_{10}$$

VI Infrared Spectra of Amidines

1. The NH Vibrations

Primary amines are known to give two absorption bands of medium intensity in the stretching region, characteristic of NH_2 group. The first of these is due to the asymmetric stretching mode and it occurs near 3500 cm.$^{-1}$, whereas the second one which involves the corresponding symmetric mode is found near 3400 cm.$^{-1}$ However, Orville-Thomas, Parsons and Ogden (96), using a Grubb-Parsons G.S.2 double-beam grating spectrophotometer found that primary aliphatic amines show the asymmetrical NH stretching vibration near 3400 cm.$^{-1}$ and the symmetrical stretching mode close to 3330 cm.$^{-1}$ The same frequencies occur near 3500 and 3400 cm.$^{-1}$

respectively in the case of primary aromatic amines. This frequency difference was explained in terms of the configuration of the nitrogen valency bonds. Thus the nitrogen atom is sp^3-hybridized (pyramidal) in aliphatic amines, but sp^2-hybridized (planar) in aromatic amines. This results in shorter and stronger N-H bonds, which account for the higher NH_2 stretching frequencies.

The same authors noticed that the ν_{sym} (NH_2) absorption of aliphatic amines is much more intense than the $\nu_{as.}$ (NH_2) band in the vapour phase. It seems that this difference in intensity is not so large in the case of aromatic amines (102).

Several attempts have been made to relate the two frequencies with the basicities of the NH_2 group (97, 98, 99) and also with its reactivity (100). Bellamy and Williams (101) arguing from the fact that both frequencies depend mainly upon the same force constant, developed equation (LXXXIII), useful for diagnostic purposes of the NH_2 vibrations.

$$\nu_{sym.} = 345.53 + 0.876\,\nu_{asym.} \qquad \text{(LXXXIII)}$$

This formula offers a sensitive method for the identification of non-equivalent NH bonds in primary amines and it was found to be obeyed, with a standard deviation of 4.8 cm.$^{-1}$, in sixty-four primary amines investigated with a high-resolution prism.

Intermolecular and/or intramolecular hydrogen bonding cause a displacement of these absorptions towards the lower frequencies; this shift is considerably less than 100 cm.$^{-1}$

The appearance of more than two bands, due to the simultaneous occurrence of both bonded and free NH vibrations was noted by Flett (103), who reported three peaks in the stretching region for the solid 2-aminoanthraquinone and β-naphthylamine. Other investigators (104) found also a similar effect with various other amines examined. It should be noted here that bands owing to intermolecular association vanish upon dilution in non-polar solvents.

Primary amines show one strong absorption of medium to strong intensity between 1590 and 1650 cm.$^{-1}$ corresponding to the NH deformation mode. This band, however, is obscured by the aromatic vibration near 1600 cm.$^{-1}$ in certain cases; its appearance near 1650 cm.$^{-1}$ in certain aminopyridines has been regarded as evidence that they exist in the amino rather than the imino form (105).

The free secondary amino group shows only one NH stretching absorption at 3500-3300 cm.$^{-1}$, but hydrogen bonding sometimes gives rise to a second one at lower frequencies. Marked differences occur between compounds of different classes both with respect to intensity and the frequency range. Thus, in aliphatic secondary amines the ν (NH) mode occurs between 3310-3350 cm.$^{-1}$ as a band of very low intensity, whereas the frequency rises sharply to about 3450 cm.$^{-1}$, and the intensity increases considerably in the case of alkylaryl amines (106).

A somewhat narrower frequency range (3400-3200 cm.$^{-1}$) has been established for the stretching vibration, ν (NH), of the unassociated imino group (=NH), as it is expected from the fact that the environment around this group is almost always the same.

The deformation vibrations, δ(NH), of both secondary amino and imino groups occur between 1650 and 1550 cm.$^{-1}$ and are usually too weak to be used for identification purposes (101). However, certain combinations of structural features are likely to enhance the intensity of the deformation vibrations, δ(NH), just as the NH deformation frequency is believed by some authors to be enhanced by the presence of the carbonyl group, with appearance of the Amide II band as a result. This has been recently substantiated by Barr and Haszeldine (107) who assigned the deformation frequency, δ(NH), to a strong band near 1510 cm.$^{-1}$ showed by secondary perfluoroalkylamines. The same mode has also been responsible for the absorption near 1510 cm.$^{-1}$, which was observed in the spectra of secondary aromatic amines (108), in addition to the normal aromatic vibration which occurs very close to this region.

2. The NH^+ Vibrations

The assignment of the $-NH_3^+$, $>NH_2^+$ and $\overset{+}{\geqslant}NH$ frequencies which have a formal analogy with the $-CH_3$, $>CH_2$, and $\geqslant CH$ vibrations, present a difficult problem which has not yet been solved successfully. Many investigations were concerned with the NH^+ frequencies in amine complexes, where the charge of the nitrogen atom is much smaller than in amine hydrohalides; as a consequence these frequencies occur close to those of the normal amines.

The infrared spectra of amine hydrohalides show many bands in the stretching region which cannot be fully assigned. This complexity is undoubtedly due to the strong hydrogen bonding in the solid phase, whereas the free vibrations are not well known since considerable difficulties are encountered in dissolving these salts in non-polar solvents.

These aspects have been reviewed by Bellamy (104), by Witkop (109) and by Heacock and Marion (110). The last investigators identified the $\delta\ (NH_2^+)$ deformation mode between 1620 and 1560 cm.$^{-1}$ in a series of secondary amine hydrochlorides and suggested their use in detecting the presence of secondary amino groups in the original molecule.

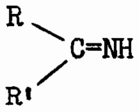
Generally, the stretching NH^+ vibrations are considerably displaced towards the lower frequencies, and many bands (4-13) have been reported between 3000 and 2400 cm.$^{-1}$, and near 2000 cm.$^{-1}$

Stone, Craig and Thompson (111) comparing the spectra of some amine salts with those of their deuterated compounds were able to arrive at more definite conclusions. The $>NH_2^+$ asymmetrical stretching frequency was thus found close to 2920 cm.$^{-1}$ for some secondary aliphatic amines and the corresponding symmetrical mode at 2780-2825 cm.$^{-1}$ They also located the $>NH_2^+$ deformation frequency between 1560-1600 cm.$^{-1}$ in agreement with the findings of Heacock and Marion. The same authors assigned the $>\!\!\!-NH^+$ stretching vibration to a band between 3330 and 2680 cm.$^{-1}$ shown by some tertiary amine hydrochlorides.

Recently Chenon and Sandorfy (112) reported the same complexity of the spectra in the NH^+ stretching region. A series of four to nine sharp or broad bands, usually well separated, were found between 2800 and 2300 $cm.^{-1}$ for aliphatic amine hydrohalides. On the other hand, aromatic amine hydrochlorides showed broad but composite bands. The bending vibrations of the NH_3^+ group were assigned to two absorptions present between 1510 and 1600 $cm.^{-1}$, whereas the existence of a strong band which appears in many cases near 2000 $cm.^{-1}$ was attributed to a combination frequency between the scissoring mode and a very anharmonic vibration near 400 $cm.^{-1}$

3. The C=N Stretching Frequency

This vibration has been firmly established as a very strong absorption between 1690 and 1640 $cm.^{-1}$ for open chain compounds. Pickard and Polly (113) quote this absorption at 1655-1615 $cm.^{-1}$ for ketimines of the structure (LXXXV).



(LXXXV)

When the C=N double bond is engaged in conjugation a general shift to the lower frequencies occurs, whereas a displacement towards the higher wave numbers has been observed when the nitrogen atom receives a positive charge. Thus, ethylphenaceturiminomethylate hydrochloride (LXXXVI) absorbs at 1694 $cm.^{-1}$ (114).

$$C_6H_5CH_2CONHCH_2C(OCH_3) = \overset{+}{N}H_2\ \overset{-}{Cl} \qquad (LXXXVI)$$

Goulden (115) substantiated the assignment by observing a 13 cm.$^{-1}$ increase in the frequency when (LXXXVII) is converted to its methiodide (LXXXVIII).

$$R_1R_2C = NR_3 \qquad\qquad R_1R_2 = \overset{+}{N}R_3R_4$$

(LXXXVII) (LXXXVIII)

Edwards, Clarke and Douglas (116) have assigned the band at 1682 cm.$^{-1}$ shown by the anhydronium perchlorate of 17-hydroxylupanine to the $C=N^+$ grouping (117, 118). Leonard and Gash (119) determined the infrared spectra of a series of α,β and β,γ unsaturated tertiary amines; they discovered that the absorption of the C=N stretching vibration did not shift appreciably on passing from the β,γ unsaturated amines to their salts, but a decisive displacement by 20-50 cm.$^{-1}$ towards higher frequencies was observed when an enamine transformed to its salt. The shift was attributed to the following structural transformation (120).

$$C=C-N \longrightarrow C=C-NH^+ \longrightarrow CH-C=\overset{+}{N}$$

4. The ν(C-N) Stretching Frequencies

The ν(C-N) vibration occurs in a wide range together with the C-C skeletal vibrations. This makes the assignment uncertain in many cases. Colthup (121) gave a range of 1100-1200 cm.$^{-1}$ for the C_{alk}-N stretching mode in secondary aliphatic amines. This was confirmed by Hadzi and Skrbljak (108) who mentioned a strong band between 1170 and 1140 cm.$^{-1}$ associated with skeletal vibrations, in which the C_{alk}-N bond participates strongly. Colthup's table shows also that the $\nu(C_{ar}$-N) of amines of the type Ar-NH-Alk occurs at 1350-1280 $cm.^{-1}$, and the second band of medium intensity at 1240-1290 $cm.^{-1}$ should correspond to the ν (C_{alk}-N) of the same type of secondary amines. Finally the ν(C_{ar}-N) was recently located at 1260-1240 $cm.^{-1}$ for a series of secondary aromatic amines (118).

Infrared Spectra of Open Chain Amidines

Fabian et al. (122, 123) assigned the ν(C=N) stretching vibration to a strong absorption between 1620 and 1627 $cm.^{-1}$ for compounds having the structure (LXXXIX), whereas the same mode was located at 1585-1595 $cm.^{-1}$ for the N-dialkyl compounds (XC).

$C_6H_5C(=NAr)NHAlk$ (LXXXIX) $C_6H_5C(=NAr)N(Alk)_2$ (XC)

This shift of the ν(C=N) absorption to the lower frequencies on going from the N-alkyl- to the N-dialkyl compounds was attributed to the existence of these compounds (LXXXIX) mainly in their tautomeric form (XCI), although implications were observed in some case.

$$(LXXXIX) \rightleftharpoons C_6H_5C(=NAl)NHAr$$

(XCI)

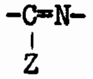
It should be noted here that three absorptions at 1600-1610 $cm.^{-1}$, 1575-1580 $cm.^{-1}$ and 1502-1508 $cm.^{-1}$ were attributed to the skeletal in-plane vibrations of the aromatic ring.

The ν(NH) stretching vibrations in compounds having the formula

(LXXXIX) was found between 3430 and 3465 cm.$^{-1}$, but a second band of low intensity at 3370-3410 was always present. Since their relative intensities were independent of the concentration, this observation was attributed to rotational isomerism, which was absent for the type (XC) compounds.

Nevertheless, an association-sensitive absorption was noticed close to 1500 cm.$^{-1}$ in the spectra of the N-alkyl derivatives. Since it was displaced by 30-40 cm.$^{-1}$ to the higher frequencies upon dilution it could be related to the δ (NH) mode, although the frequency was too low for this vibration.

The intensity of the ν (C=N) absorption in compounds having the grouping (XCII) was also found (124) to be related to the type of substitution. Thus, it is maximum when Z represents an oxygen (imidates) or a nitrogen atom (amidines), and decreases when Z is sulphur (thioimidates), carbon (ketimines) or hydrogen (aldimines).

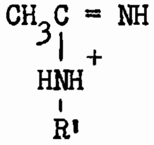


$$-\underset{\displaystyle Z}{\underset{|}{C}}{=}N- \qquad \text{(XCII)}$$

Acetamidines of the type (XCIII), with R', R" = aryl groups, have been reported (125, 126) exhibiting four bands in the region 1550-1200 cm.$^{-1}$ which were affected by dilution and deuteration. Two of them near 1540 and 1330 cm.$^{-1}$, were assumed to originate from the coupling of the deformation vibrations, δ (NH), and the antisymmetric mode of the group -C(=N)N, and the other two at 1440 and 1220 cm.$^{-1}$ from the coupling mode of the δ (NH) and the ν (N-R) vibration.

$$CH_3\underset{\displaystyle NHR'}{\underset{|}{C}} = NR \qquad \text{(XCIII)}$$

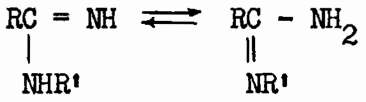
The same compounds showed two absorption bands at 3500-3300 cm.$^{-1}$, whereas one only was expected. This phenomenon was explained by the suggestion that the amino nitrogen atoms attained a trigonal and planar configuration due to resonance. In this case two stereoisomers could be formed differing in the relative position of the single hydrogen atom below or above this plane. A further evidence for such a type of molecule was assumed to be found in the spectra of their hydrochlorides of the structure (XLIV).



$CH_3C(=NH)\overset{+}{N}H_2R'$

(XLIV)

Very recently, Prevorsek (127) studying the spectra of a series of N-substituted amidines (XCV) suggested that the tautomeric equilibrium in this type of compound is a function of the electronegativity of the group R'.



$RC(=NH)NHR' \rightleftharpoons RC(=NR')NH_2$

(XCV) (XCVI)

Thus, when R' = alkyl groups, the equilibrium is displaced completely to the left (XCV), whereas, if R' is an aryl group, formula (XCVI) is predominant. The latter was based on the following grounds:

a) No absorption sensitive to a change of physical state and isotopic exchange was found.

b) The Amidine II band was found near 1540 cm.$^{-1}$ in the N,N'-

diaryl-substituted amidines, but it was absent in N-arylamidines.

c) The observed ν(NH) vibrations were in excellent agreement with those calculated by the Bellamy equation for the symmetric and asymmetric ν (NH_2) frequencies.

DISCUSSION

A. Inductive effect in the reaction of nitriles with amines

GENERAL

It has been firmly established that unsubstituted nitriles do not react with amines to form amidines even at high temperatures, and it can be predicted with certainty that aliphatic nitriles with electron-attracting groups (-Is effect) at the α-carbon atom would show enhanced reactivity towards amines.

The first objective of the present work was a systematic study of the influence of electron-attracting groups in the non-catalyzed addition of amines across the carbon-nitrogen triple bond of nitriles and to find the scope and limitations of this reaction. The following types of nitriles were examined: trifluoro-, trichloro-, dichloro-, chloro- and nitro-acetonitriles. These nitriles can be brought into the following order of the decreasing strength of the negative inductive effect (-Is) on the carbon atom of the nitrile group:

$$Fe_3C- > Cl_3C- > Cl_2CH- > O_2NCH_2- > ClCH_2-.$$

The second objective of this research was to provide experimental evidence for the mechanism of this reaction, and to study the structure and tautomerism of amidines by infrared spectroscopy.

I. Reaction of trichloroacetonitrile with amines

The preparation of N-substituted trichloroacetamidines involved three general procedures:

(a) the lower primary and secondary aliphatic amines were treated with trichloroacetonitrile in aqueous solutions,

(b) the reactions of higher aliphatic and cyclic amines were carried out in the absence of solvents, and

(c) the aromatic and heterocyclic primary amines were allowed to react with trichloroacetonitrile in methanol, water-methanol, ether-methanol and acetonitrile solutions.

The three procedures are characterized by their simplicity, the absence of catalysts and the high yields of the reaction product.

The first method consisted mainly of the addition of trichloroacetonitrile to aqueous solution containing an equivalent amount of the amine. Vigorous stirring or shaking of the mixture caused such strongly exothermic reaction that the reaction vessel had to be cooled to prevent evaporation and side reactions. There is no limitation with respect to the concentration of the amine solutions applied, and therefore amine solutions available on the market can be used.

The reaction was completed in a few minutes in the case of primary aliphatic amines, but required half an hour at least with secondary aliphatic amines. The end of the reaction can be easily detected by the disappearance of the strong lachrymatory smell of the trichloroacetonitrile.

The amidines produced, being insoluble in water, formed a liquid bottom layer which was separated and distilled. Since the products are high boiling liquids, sensitive to hydrolysis, it is recommended to remove the volatile reactants and traces of water at reduced pressure in dry nitrogen atmosphere. Such treatment is preferred to the use of even relatively inert dehydrating reagents. The fractionation or distillation must be carried out at low pressure, otherwise a vigorous uncontrollable decomposition occurs at temperatures near 150°.

The above-mentioned procedure can undoubtedly be used in the case of higher primary and secondary amines, however, the following method is more convenient and even simpler, and the yields are higher. Trichloroacetonitrile and the amine were mixed and the mixture distilled or fractionated after a certain period of time.

$$Cl_3CCN + H_2NR \longrightarrow Cl_3CC(=NH)NHR$$

(XCVII)

$$Cl_3CCN + HNR_1R_2 \longrightarrow Cl_3CC(=NH)NR_1R_2$$

When primary aliphatic amines are used the mixture must be cooled to 5° because of the fast rate of the reaction and the large amount of heat evolved. The reaction is complete in a few minutes, whereas it requires at least half an hour if secondary aliphatic or cyclic amines are used. Distillation or fractionation of the products has to be carried out at low pressure and in nitrogen atmosphere.

It has been observed that traces of a solid substance remained after the distillation of the reaction mixture. This was identified as the hydrochloride of the amine used in the reaction and was the main product isolated when n-dibutylamine or di-n-amylamine were treated with trichloroacetonitrile. The only explanation which can be given is that preferential substitution occurs in these cases (IC).

$$\underset{}{Cl_3CCN} + \underset{\text{(XCVIII)}}{HN(CH_2CH_2CH_2CH_2CH_3)_2} \longrightarrow \underset{\text{(IC)}}{(CH_3CH_2CH_2CH_2CH_2)_2NCCl_2CN} + HCl$$

$$\text{(XCVIII)} + HCl \longrightarrow (CH_3CH_2CH_2CH_2CH_2)_2NH.HCl$$

All but one of the lower amidines synthesized are colourless liquids, possessing an unpleasant characteristic smell and a density higher than water.

The striking feature of these methods is that, although amidines hydrolyze easily, they show perfect resistance to water under the experimental conditions employed. This is in contrast to the German patent (72) in which anhydrous media and very low temperatures were reported for the preparation of a few N-alkyl trichloroacetamidines, and to the methods applied by Oxley, Partridge and Short (48) and by Backer and Wanmaker (73). These investigators used dry benzene as a solvent but the amidines could be isolated only in the form of picrates.

Methyl alcohol cannot be used as a solvent at least in the reactions between trichloroacetonitrile and secondary aliphatic amines, because it reacts with the nitrile to give methyl trichloroacetimidate in goods yields. Thus, when piperidine or diethylamine was added to a solution of trichloroacetonitrile in methanol an exothermic reaction occurred, which led to the isolation (70-80%) of methyl trichloroacetimidate.

$$Cl_3CCN + CH_3OH \xrightarrow[\text{amines}]{\text{Secondary aliphatic}} Cl_3CC(=NH)OCH_3$$

It is suggested that, if necessary, solvents like acetonitrile can be used in these cases with excellent results.

The fact that methyl alcohol reacts preferentially with trichloroacetonitrile in the presence of secondary aliphatic amines manifests the strong catalytic action of basic compounds in the addition of alcohols at the carbon-nitrogen triple bond; advantage can be taken of this in the synthesis of imido esters. It should be mentioned here that methyl trichloroacetimidate is formed only after reflux of a methanolic solution of trichloroacetonitrile for 5 to 8 hours.

The synthesis of N-aryltrichloroacetamidines was modified considerably because of the slow rate of the reaction. Generally equivalent amounts of trichloroacetonitrile and an aromatic amine were dissolved in methanol, ethanol, water-methanol, ether methanol and left at room temperature for 3-5 days. The product could be isolated by precipitation with water, or evaporation of the solvent at reduced pressure. Precipitation by water was found to give the best results in most cases where water-miscible solvents were used.

Acetonitrile proved to be an excellent solvent because of its strongly polar character and its miscibility with water. It was used in the preparation of two compounds, namely N-2(5-methylpyridyl)-trichloroacetamidine and N-{2(5-methylpyridyl)}-trifluoroacetamidine.

Aromatic amines reacted very slowly with trichloroacetonitrile in non-polar solvents or not at all. Thus aniline did not react with trichloroacetonitrile in carbon tetrachloride when it was left at room temperature for eleven days.

In the course of this work trichloroacetamidine was prepared for infrared investigations. This compound has been reported as a solid, m.p. 41-42°, by Dachlauer (72) and as a liquid by Oxley, Partridge and Short (48). Following Oxley's procedure isolated the liquid product which was distilled to give Dachlauer's solid product. The picrate of the solid trichloroacetamidine had the same m.p. as the picrate prepared from the liquid product. This experiment proved definitely that both the liquid and the solid compounds correspond to trichloroacetamidine.

N-Substituted trichloroacetamidines are very soluble in alcohols, benzene, chloroform, ether etc. and insoluble in water. They are, with a few exceptions, stable compounds and can be stored for a long period.

They were characterized by their monosalts with picric and hydrochloric acids. Their picrates can be purified by crystallization from water, contrary to their hydrochlorides or sulphates which are extremely sensitive and hydrolyse very quickly on heating with water; attempts to recrystallize them from absolute ethanol failed, since the hydrochlorides decomposed to unknown products.

Since the yields of the reactions in general were high and the experimental conditions most favourable, the optimum conditions of this reaction were not investigated.

However, it is certain that the yields were not the highest possible, and modifications could be found to promote the reaction between higher aliphatic secondary amines and secondary aromatic amines which reacted by substitution with the experimental conditions employed.

A more precise study, in order to discover the most suitable solvents in each particular case on the one hand, and the establishment of the detailed mechanism of this interesting reaction, on the other, will undoubtedly improve the yields and reduce considerably the reaction time.

II. Reaction of trifluoroacetonitrile with amines

Trifluoroacetonitrile, a gas boiling at -61.5°, was prepared by a standard procedure, by dehydration of trifluoroacetamide with phosphorus pentoxide. Ethyl trifluoroacetate which was used for the preparation of trifluoroacetamide is generally obtained by treating a mixture of anhydrous sodium trifluoroacetate and ethanol with sulphuric acid.

In this work a method was developed, similar to the common one applied for the preparation of esters, which consists of the slow fractionation of equivalent amounts of trifluoroacetic acid, absolute ethanol in a large volume of sulphuric acid. The yields were as high as by the other method and it had the advantage of using directly the trifluoroacetic acid without preparing its very hydroscopic sodium salt.

The reactions of trifluoroacetonitrile with ammonia, methylamine and dimethylamine have been reported recently. Liquid ammonia and the nitrile were allowed to react (74) in closed ampoules at room temperatures for two weeks to yield trifluoroacetamidine; N-methyl and N-dimethyl trifluoroacetamidines were obtained (75, 76) by refluxing the two reactants at very low temperatures (-60°).

The latter reaction, however, could not be applied to higher aliphatic amines as they solidified at such low temperatures.

On looking for more general methods for the preparation of higher N-alkylamidines, necessary for infrared study, new, less complicated procedures were found.

Thus, N-n-butyltrifluoroacetamidine was obtained in high yields by passing a slow stream of trifluoroacetonitrile through n-butylamine at room temperature. Although the unreacted nitrile escapes and cannot be recovered, this procedure is very general, and, if suitably modified, might prove an excellent method for large-scale preparations. Its disadvantage when being applied to liquid or low melting amines can be easily overcome by using amine solutions.

According to the second general method a liquid amine or its solution was allowed to react with trifluoroacetonitrile which exerted a pressure slightly over the atmospheric in a closed system at room temperature. Any inert solvent is suitable. This method was applied in the preparation of N-benzyltrifluoroacetamidine in acetonitrile solution.

Reilly and Brown (75) pointed out that "...aromatic amines, for example aniline, did not react even at higher temperatures".

This conclusion seemed very unlikely since fluorine is more electronegative than chlorine.

A series of experiments was thus conducted in closed tubes at room temperature; it was found that not only aniline, but also primary aromatic and heterocyclic amines reacted with trifluoroacetonitrile in a fashion similar to that observed with the trichloroacetonitrile. The yields were excellent and the reaction products of very high purity.

In general, the liquid amidines obtained were colourless liquids and showed a boiling point much lower than the corresponding trichloroacetamidines. They were purified by distillation at normal pressure. With the higher amidines, these operations had to be conducted at reduced pressure in nitrogen atmosphere. Solid amidines were purified by sublimation and crystallization from petroleum ether, if desired, was possible.

The hydrochlorides of trifluoroacetamidines hydrolyze easily on heating. Picrates could not be made, since they separated as oils which crystallized with difficulty. Also certain low melting hydrochlorides were obtained in a soft solid form and they were not useful for characterization of the parent compounds.

Finally, attempts to prepare N-(p-nitrophenyl)-trifluoroacetamidines failed and the p-nitroaniline was recovered quantitatively.

III. Reaction of dichloroacetonitrile with amines

Dichloroacetamide, an intermediate compound leading to dichloroacetonitrile by dehydration with phosphorus pentoxide, has been prepared by a number of methods involving the treatment of ethyl dichloroacetate with alcoholic ammonia (141), or aqueous ammonium hydroxide (142). Slightly better yields (67-78%) could be obtained by the reaction of chloral hydrate and concentrated ammonium hydroxide (143).

$$Cl_3CCH(OH)_2 + 2NH_4OH \xrightarrow{KCN} Cl_2CHCONH_2 + NH_4Cl + 3H_2O$$

In this work, dichloroacetamide was obtained in comparable yields by a less elaborate procedure which consisted of passing dry gaseous ammonia through ethyl dichloroacetate cooled to 0°.

A search in the literature revealed that no investigation had been made regarding the synthesis of dichloroacetamidines. Only ethyl dichloroacetimidate hydrochloride (LXI) was reported in a British patent (77) in 1953. It was obtained by treating ethyl dichloroacetimidate hydrochloride with ammonia according to Pinner's method.

The dichloromethyl group exerts -Is effect weaker than the trichloromethyl or trifluoromethyl groups, and it was decided to investigate the effectiveness of this group in promoting a non-catalyzed addition of amines across the nitrile carbon-nitrogen triple bond. The methods used for the preparation of N-substituted dichloroacetamidines were essentially similar to those applied in the preparation of trichloroacetamidines, because comparable results were needed. The N-methyl-α,α-dichloroacetamidine was obtained from dichloroacetonitrile and a water solution of methylamine (25%) at room temperature.

$$Cl_2CH_2CN + CH_3NH_2 \longrightarrow Cl_2CHC(=NH)NHCH_3$$

(25% in water)

The reaction was strongly exothermic and the yield high, but the product decomposed partially during distillation at low pressure in a nitrogen atmosphere, and changed to a black tar on standing at room temperature for two days.

Diethylamine and piperidine formed the corresponding dichloroacetamidines when left with an equimolar amount of the nitrile in benzene solution for five days. It was found that this procedure gave higher yields and more stable compounds than the first one. Nevertheless, the product decomposed in the same way after three weeks. Not only primary and secondary aliphatic amines reacted at room temperature with dichloroacetonitriles; primary aromatic amines, for example aniline, also showed a reactivity towards this nitrile, comparable to that towards the trichloro- and trifluoro- acetonitriles. Thus, N-phenyl-α,α-dichloroacetamidine was obtained in 60% yield by allowing equivalent amounts of dichloroacetonitrile and aniline to react in methanol for one week.

$$Cl_2CHCN + H_2NC_6H_5 \longrightarrow Cl_2CHC(=NH)NHC_6H_5$$

These experiments led to the conclusion that the -Is effect of the Cl_2C- group is strong enough to promote the non-catalyzed reaction between dichloroacetonitrile and amines in general.

Obviously the reaction requires a longer period of time for completion and the isolation of the reaction products is more complicated owing to their instability.

While trichloro- and trifluoro-acetamidines can be stored for years, the dichloro compounds, whether liquids or solids, decompose at room temperature after a time varying from two days to four weeks.

No attempts were made to determine optimum conditions in each particular case; it seems certain, however, that yields could be improved considerably and the decomposition which occurred during distillation or fractionation could be avoided by applying very low pressures, i.e., below 1 mm. Hg. Selection of solvents would also affect both yields and stability.

Comparison of the structural differences between trichloroacetamidines on the one hand and the dichloro-compounds on the other might provide an answer to the stability of the first and the instability of the latter. Dichloroacetamidines possess an acidic hydrogen atom due to an electron deficiency of the α-carbon atom, which is imposed by the two chlorine atoms and the amidine grouping. Since amidines are fairly strong basic compounds a nucleophilic attack on this electrophilic center is very likely. This would result in the formation of a carbonium ion and an amidinium cation which could start a chain reaction in a variety of ways.

$$2Cl_2CHC(=NH)NHR \longrightarrow Cl_2\underset{\ominus}{C}-C(=NH)NHR + Cl_2CH\overset{\delta+}{C}(=\overset{\delta+}{N}H_2)NHR$$

In spite of the instability of the free bases the picrates were quite stable and permitted characterization of the amidines and analysis for the elements.

IV. Reaction of chloroacetonitrile with amines

Although it has been reported that diethylamine reacted (84) with chloroacetonitrile in ether by substitution, studies were resumed to investigate the interaction of this nitrile with various aliphatic amines, in the hope that addition at the nitrile group instead of substitution at the α-carbon atom could be achieved.

Little success was foreseen in these experiments since both types of reaction proceed with mechanisms involving ionic intermediates and change of solvent or other conditions would not favour the addition only.

Several attempts were made with primary and secondary aliphatic amines under conditions similar to those already mentioned. The reactions were studied in water, methanol or in the absence of solvents. Nitriles and amines were used in molar ratios 1:1, 1:2 and 2:1. A fast exothermic reaction occurred in each case yielding the corresponding aminoacetonitrile according to the following equations:

$$ClCH_2CN + 2RNH_2 \longrightarrow RNHCH_2CN + RNH_2.HCl$$

$$ClCH_2CN + 2R_1R_2NH \longrightarrow R_1R_2NCH_2CN + R_1R_2NH.HCl$$

Since aminoacetonitriles were less basic than primary or secondary aliphatic amines the hydrochlorides of the latter were always obtained. The free aminoacetonitriles were isolated and identified in the form of hydrohalides and picrates.

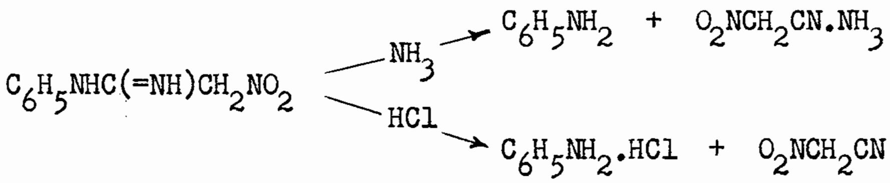
It should be noted that the yields of the substitution reaction were very high; this suggested that the procedure could be used for the preparation of aminoacetonitriles or aminoacids by hydrolysis of the nitriles.

The study of the reaction involving aromatic amines and chloroacetonitriles was given up after the above-mentioned results.

V. The reaction of nitroacetonitrile with aromatic amines

Studies have been made of the reactions of nitroacetonitrile with various amines in an attempt to examine the influence of nitro groups attached to the α-carbon atom of acetonitrile on the formation of the amidines. The reaction forming alleged N-phenyl-, (LXXX), N-o-tolyl-, (LXXXI) and N-(2,4-dimethylphenyl)- (LXXXII) nitroacetamidine has been reported (67) to occur almost instantaneously in ether at about 0°C.

Early observations were made, showing that ammonia gas decomposed the alleged N-phenylnitroacetamidine in ether solution, to give a precipitate of ammonium salt of nitroacetonitrile while aniline remained in solution. Passing hydrogen chloride gas through a similar solution caused the amidine to decompose into aniline hydrochloride and nitroacetonitrile



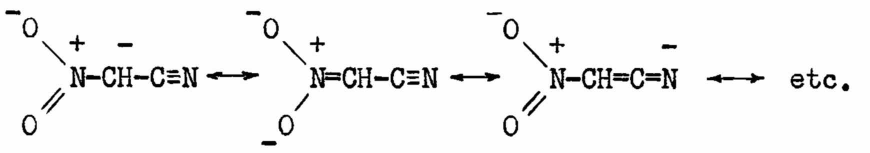
$$C_6H_5NHC(=NH)CH_2NO_2 \begin{cases} \xrightarrow{NH_3} C_6H_5NH_2 + O_2NCH_2CN.NH_3 \\ \xrightarrow{HCl} C_6H_5NH_2.HCl + O_2NCH_2CN \end{cases}$$

The hydrolysis of these alleged amidines to their starting materials was attributed recently (95) to the formation of a resonance-stabilized carbonium ion, although no other amidines are known to hydrolyze in this way.

However, it seems doubtful that the amidines of nitroacetonitrile and aromatic amines could form so readily, since the reaction between the more electropositive carbon atom of the carbon-nitrogen triple bond of trichloroacetonitrile and primary aromatic amines takes place only very slowly at room temperature, even in polar solvent. Furthermore, the reported behaviour of the reaction products towards ammonia and hydrogen chloride, and their solubilities, could be explained better if they were salts rather than amidines, since nitroacetonitrile is approximately as acidic as acetic acid.

In view of these contradictory facts, the three addition compounds in question were prepared according to procedures described, and their infra-red spectra investigated, together with that of the ammonium salt of nitro-acetrile, $NH_4^+ \left[O_2NCHCN\right]^-$. The results are summarized in Table I.

The presence of the very sharp strong absorption bands in the infrared spectra of the four compounds, due to the $\nu(C\equiv N)$ vibrations being very close to 2200 cm.$^{-1}$, suggested immediately that no addition occurred across the carbon-nitrogen triple bond. The four salts absorbed at a frequency even lower than the conjugated aliphatic nitriles (2235-2215 cm.$^{-1}$), as one might expect for a strongly resonating carbanion structure.



(C)

On the other hand, the two NH stretching vibrations, characteristic of the N-substituted amidines, which occur between 3300 and 3500 cm.$^{-1}$ were completely absent. New wide strong bands appeared in the region 2500-3100 cm.$^{-1}$, corresponding to the ν (NH_3^+) modes and indicating that the aromatic amines were present in the form of salts.

Finally, resonance within the carbonium ion caused a remarkable frequency shift in the asymmetric stretching vibration of the $-NO_2$ group to the lower part of the absorption range (1500 cm.$^{-1}$), whereas the similar symmetric mode showed absorption at 1320-1345 cm.$^{-1}$

Numerous attempts to prepare N-alkyl nitroacetamidines failed, proving that nitroacetonitrile did not react with primary and secondary aliphatic amines, at least with the mild conditions used. Thus nitroacetonitrile was recovered unchanged in the form of its complex with silver nitrate from the reaction mixture.

It should be mentioned here that, due to the explosive character of unknown compounds formed by heating the nitroacetonitrile itself or its mixtures, any reactions involving nitroacetonitrile must be conducted in the hood and safety glasses have to be used.

The inertness towards addition of amines at the carbon-nitrogen triple bond of nitroacetonitrile can be easily explained: because of the acidity of this compound, formation of salts with amines cannot be avoided. In this case resonance-stabilization of the nitroacetonitrile cation (C) decreases the positiveness of the carbon atom of the CN group to such an extent that it prevents the nucleophilic attack of the amine at this carbon centre and the formation of an ionic intermediate similar to (CII).

Thus, when a water solution of ammonium salt of nitroacetonitrile and n-butylamine hydrochloride was left at room temperature for two weeks, a product (m.p. 53°) soluble in water and insoluble in non-polar solvents was isolated and was proved by infrared analysis to be the salt of nitroacetonitrile with n-butyl amine (CI).

$$O_2NCH_2CN.NH_3 \;+\; n\text{-}CH_3(CH_2)_2NH_2.HCl \longrightarrow$$

$$\longrightarrow O_2NCH_2CN.H_2N(CH_2)_2CH_3 \;+\; NH_4Cl$$

Nevertheless hydroxylamine hydrochloride reacted with ammonium salt of nitroacetonitrile to give the addition compound (LXXIX) which showed the characteristic ν (NH) absorption of 3330 and 3170 cm.$^{-1}$, ν(C=N) at 1650 cm.$^{-1}$ and the absence of the ν(C≡N) mode, which occurs near 2200 cm.$^{-1}$.

This comes as an additional proof for the existence of the alleged N-aryl nitroacetamidines in the form of salts of nitroacetonitrile with the aromatic amines.

TABLE I

Positions of absorption maxima (cm.$^{-1}$) in the infrared spectra of nitroacetonitrile salts

$$\left[O_2NCHCN\right]^- \quad H_3\overset{+}{N}R$$

Assignment	R=H	R=C_6H_5N-	R=O-$CH_3C_6H_5$-	R=2,4$(CH_3)_2C_6H_3$-
$\nu(NH_3^+)$		3060 m (2)	3100 sh	3100 m
		2540 m	3010 m (3)	3000 s (3)
			2710 m	2730 s
			2560 s	2580 vs
			2360 sh	2100 m
$\nu(NH_4^+)$	3060 vs (1)			
	2780 s			
$\nu(C\equiv N)$	2210 s	2200 s	2200 s	2205 s
$\delta(NH_3^+)$		1578 m	1535 m	1623 m
		1525 m		
$\nu_{as}\ NO_2$	1500 vs	1480 vs	1500 vs	1505 vs
$\delta(NH_4^+)$	1430 vs			
$\nu_{sym}\ (NO_2)$	1345 vs	1320 vs	1330 vs	1328 vs
$\nu(C-N)$	1185 vs	1260 s	1235 vs	1222 vs
			1222 vs	1207 vs
$\nu(C-C)$	977 vs	945 s	955 s	948 vs

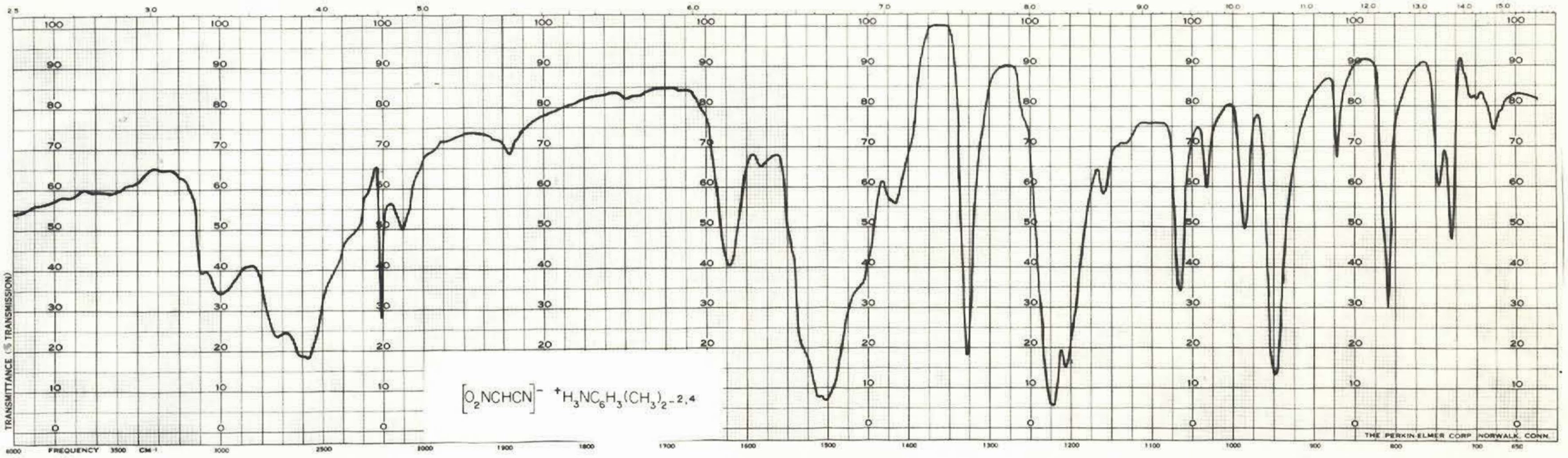
(1) Broad band at 3200-2900 cm.$^{-1}$ including Nujol absorptions
(2) Broad band at 2600-3100 with inflections at 3130 and 2740 cm.$^{-1}$
(3) Broad bands.

FIG. 1

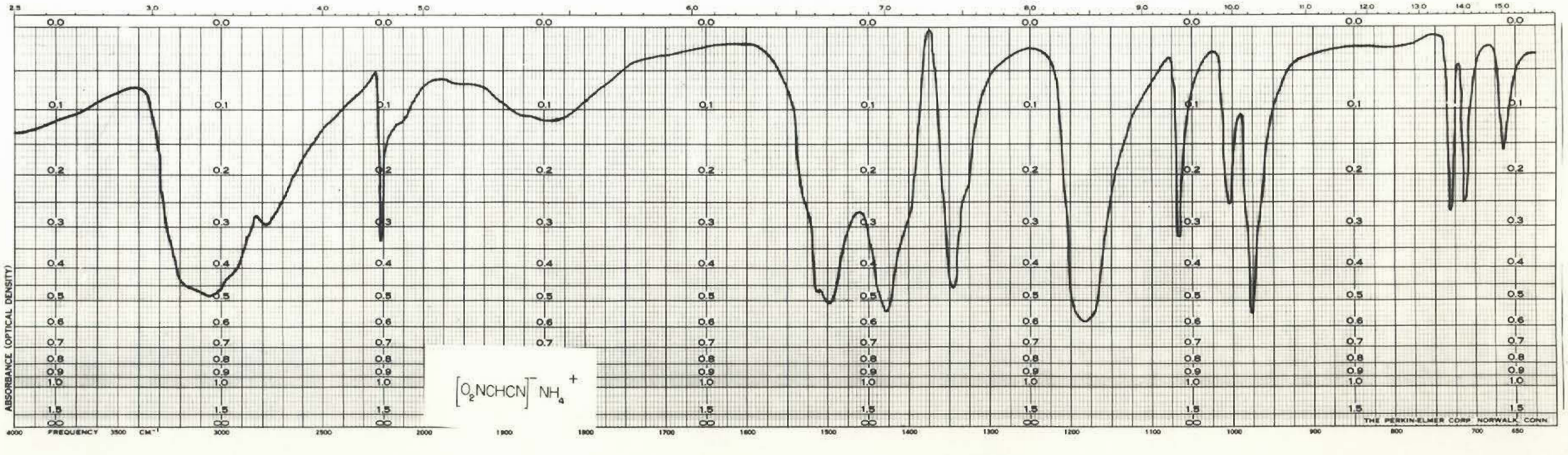
Infrared Absorption Spectra of

nitroacetonitrile salts of:

1. ammonia
2. 2,4-dimethylaniline



$[O_2NCHCN]^- \ {}^+H_3NC_6H_3(CH_3)_2\text{-}2,4$



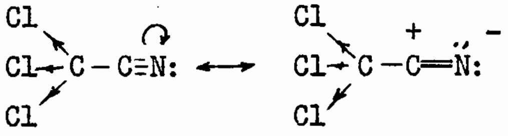
$[O_2NCHCN]^- NH_4^+$

VI. Mechanism and limitations of the reaction between trichloro-, trifluoro-, and dichloro-acetonitrile with primary and secondary amines

In the absence of physicochemical data, no suggestions for a mechanism can be made. However, theoretical considerations combined with the chemical evidence accumulated in the present work gives information for the mechanism of the reaction between the nitriles in question with the various amines.

The molecule of trichloroacetonitrile is a strong dipole with a dipole moment of 1.93 D., according to Davies and Jenkins (147); the dipole moment was measured in terms of the dielectric constant, refractive index and the density of the pure liquid. On the assumption that the group moments are constant, this value should be equal to the difference between the moments of acetonitrile and chloroform, which is 2.1 D., and the agreement is reasonable.

From a careful examination of the molecular structure of the trichloroacetonitrile it can be assumed that the carbon atom of the carbon-nitrogen triple bond is the centre of electron displacements in the opposite directions.



The three strongly electronegative chlorine atoms of the trichloromethyl group attract the electrons of the carbon atom to which they are attached, and impose on it a partial positive charge; this inductive effect can be transmitted to the carbon atom of the nitrile group to an extent of 10-20% of its original value. At the other end of the molecule the nitrogen atom produces a shift of the electrons to the opposite direction, increasing the electron deficiency of this carbon centre.

These effects undoubtedly account for the enhanced reactivity of the trichloroacetonitrile in the Hoesh reaction, for the decomposition suffered by the trichloroacetic acid in boiling water and the alkaline hydrolysis of the chloral.

$$Cl_3CCOOH \longrightarrow Cl_3CH + CO_2$$

$$Cl_3CCHO + NaOH \longrightarrow Cl_3CH + HCOONa$$

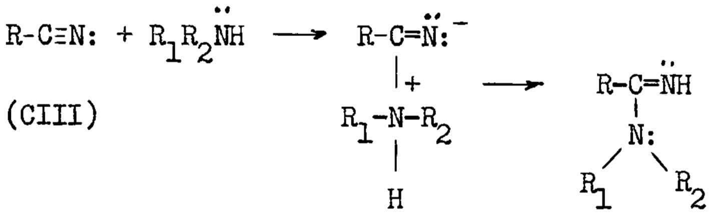
That the nitrile carbon atom is the centre of a nucleophilic attack is supported by the observations of Oxley and Short (26) that the preparation of amidines from phenylcyanides is usually promoted by groups acting as electron acceptors and retarded by those which are electron sources.

One hydroxy and two carbethoxy groups in cyanotartronate (LII) increase the electron deficiency of the carbon atom in the nitrile group to such an extent that amines add (71) in a manner exactly similar to that observed in the reactions of trichloro- and trifluoro-acetonitrile with amines.

A comparison of the apparent rates of the reaction as determined by a rough measurement of the completion time shows that the latter nitriles react faster than dichloroacetonitrile because of the smaller -Is effect of the dichloromethyl group.

Thus the carbon atom of the nitrile group is the electrophilic centre responsible for the reactions in question which occur even at -60° with trifluoroacetonitrile and primary and secondary aliphatic amines.

Once this is accepted the following general mechanism which is also supported by other evidence can be postulated.



(CIII)

(CII)

$R = Cl_3C-$ or F_3C- or Cl_2CH-

$R_1 = H$, R_2 = alkyl or phenyl, or heterocyclic radicals and their substituents

R_1, R_2 = alkyl.

The nucleophilic attack of the unshared electron pair of the amine nitrogen atom on the electrophilic carbon is followed by the formation of a bond between these atoms, the liberation of a proton, and the subsequent addition of the proton to the negatively charged nitrogen atom.

The failure of chloroacetonitrile to yield any amidine, while the dichloro-, trichloro-, and trifluoro-acetonitrile give amidines in excellent yields leads to the following limitation:

Limitation I: At least two strongly electronegative atoms or groups at the α-carbon atom of a nitrile are necessary to promote its non-catalyzed addition of primary and secondary amines.

Important evidence for the mechanism (CIII) was provided by the failure of methylamine or ethylamine hydrochlorides to react with trichloroacetonitrile at room temperature, due to the electrophilicity of both reagents.

The suggested mechanism involves an ionic intermediate (CII); as a consequence polar solvents should facilitate the reaction whereas non-polar media should inhibit or prevent the formation of the amidines. Evidence for this was given by the following experimental observations:

(a) The reaction of primary and secondary amines cannot be prevented by non-polar solvents but it does proceed faster in polar media.

(b) Primary aromatic amines do not react in non-polar solvents. For example when aniline was left with an equimolar amount of trichloroacetonitrile in carbon tetrachloride or cyclohexane at room temperature for eleven days no reaction occurred.

It should be noted here that infrared analytical methods were used for determination of changes of concentration with time. The $\nu(C\equiv N)$ absorption was followed in these quantitative measurements. However, the rate of the reaction could not be investigated due to technical difficulties and lack of time.

As it was mentioned previously, when secondary aliphatic amines were treated with trichloroacetonitrile in methanol methyl trichloroacetimidate was isolated in good yield; this indicated the catalytic influence of the amines used.

Two further limitations can therefore be put forward.

Limitation II: Methanol and probably ethanol cannot be used as solvents in the reaction of trichloroacetonitrile with secondary aliphatic amines; this might be extended to trifluoro- and dichloroacetonitrile although no experiments were conducted with these nitriles.

Limitation III: Non-polar solvents prevent the reaction between aromatic amines and the nitriles in question.

Most of the N-aryl substituted amidines were prepared in methanol or water methanol mixtures. This raises the point regarding the suggestions of Baker and Wanmaker (73) that methanol is essential in the reaction of trichloroacetonitrile with aromatic amines by forming first the methyl trichloroacetimidate which subsequently reacts with the aromatic amines to give the corresponding amidines. The same authors considered that "a few drops of acetone" acting catalytically are essential in this reaction. These views were disproved for the following reasons.

(a) Acetone was not used in any of the experiments involved in this work

(b) Aniline reacts with trichloroacetonitrile even in the absence of methanol or other solvents

(c) This reaction occurs also in ethanol which, contrary to methanol, has been reported not to react with trichloroacetonitrile

(d) 2-Amino-5-methyl pyridine reacted with trichloro- and trifluoro-acetonitrile in acetonitrile with excellent yields.

The mechanism (CIII) indicates that the rate of the reaction is not only a function of the electron deficiency of the nitrile carbon atom (which depends on the magnitude of the -Is effect at the α-carbon atom, i.e., $F_3C- > Cl_3C- > Cl_2CH- > ClCH_2-$) but is also a function of the basicity of the amine. Indeed, the free electron pair of the amino nitrogen atom is the stronger will be the interaction between the two reactive centres and the faster the reaction will go.

A comparison of the Pk_a of the amines used in this work gives the following order with respect to the rate of the reaction with a certain nitrile i.e. trichloroacetonitrile.

Secondary aliphatic amines > primary aliphatic amines >
primary aromatic amines

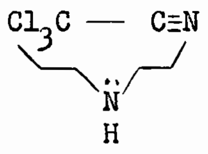
TABLE II

Dissociation constants ($pK_a^{25°}$) of some amines in aqueous solution

Primary aliphatic		Secondary aliphatic	
Methylamine	10.64	Dimethylamine	10.70
Ethylamine	10.67	Diethylamine	11.00
iso-Propylamine	10.63	Piperidine	11.12
n-Butylamine	10.61		
	Primary aromatic		
Aniline	4.58	p-Toluidine	5.07
o-Toluidine	4.39	p-Nitroaniline	2.00
m-Toluidine	5.07	p-Phenetidine	5.30

The reaction of primary aliphatic amines with trichloroacetonitrile was over in a few minutes, whereas that of the aromatic amines with the same nitrile required about three days for completion. These findings, combined with the fact that p-nitroaniline does not react with trichloro- and trifluoro-acetonitrile, are in excellent agreement with the theory and support the proposed mechanism (CIII).

On the other hand, primary aliphatic amines reacted distinctly faster than the secondary aliphatic compounds, although the latter are more basic than the first. This discrepancy indicated that some other factor interfered, namely a stereochemical effect. Indeed, the probability for an effective collision of the two reactants is decreased considerably when one hydrogen atom of the primary amino group is replaced by an additional alkyl radical. As a consequence the longer the chain of the two alkyl groups, of a secondary alkylamine, the greater is the stereochemical interference and the less likely the reaction.



The above interpretation is in agreement with the experimental findings. Thus, n-dibutylamine and n-diamylamine react mainly with substitution (IC) at the α-carbon atom, instead of addition across the carbon-nitrogen triple bond to yield the corresponding amidines. This behaviour brings about another limitation which can be applied to these reactions.

Limitation IV: Secondary aliphatic amines with alkyl groups containing more than three carbon atoms react preferentially with substitution at the α-carbon atom.

Stereochemical interference may also be responsible for the unreactivity of secondary aromatic amines, α-naphthylamine, etc.

Finally, the reaction mechanism (CIII) may not be as simple as it seems. There were indications that the rate of the reaction was slower when dry reactants and solvents were used than when these contained small amounts of water. This catalytic influence of water is obvious, since it provides the mixture with protons which facilitate the transformation of the ionic intermediate (CII) to the reaction product.

B. Study of the Structure of Trichloroacetamidines by Infrared Study

The uncertainty which exists in the literature with respect to the structure of the amidines in general indicated that a structural investigation of the trichloroacetamidines was needed. The correlations between the infrared absorption spectra and the structure of thirteen N-mono- and N-di-substituted trichloroacetamidines led to the following general conclusions:

(a) N-alkyl and N-aryl-trichloroacetamidines associate strongly in the liquid and solid phases,

(b) they exist only in the imino form (CIV) in non-polar solvents,

(c) they can be characterized by a strong band (Amidine II) at 1510-1525 cm.$^{-1}$ and 1570-1580 cm.$^{-1}$ respectively, which is attributed to the deformation vibration δ (>NH) of the secondary amino group, and (d) the degree of association of N-substituted trichloroacetamidines changes in the following order of substitution

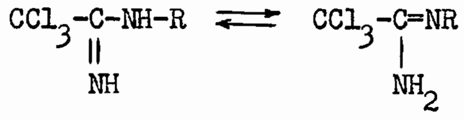
N-alkyl- > N-aryl- > N-dialkyl.

The results have been summarized in Tables III and IV.

Correlation of infrared spectra and the structure of trichloroacetamidines

I. Region 4000-1800 cm.$^{-1}$

If trichloroacetamidines existed in two tautomeric forms (CIV) and (CV)



$$CCl_3\text{-}\underset{\underset{NH}{\|}}{C}\text{-}NH\text{-}R \rightleftharpoons CCl_3\text{-}\underset{\underset{NH_2}{|}}{C}\text{=}NR$$

(CIV) (CV)

present in dilute solutions then more than two absorption bands should appear between 3500-3200 cm.$^{-1}$. Or, if the tautomeric equilibrium had been displaced to the right completely (CV), two absorption bands characteristic of the stretching vibrations of the primary amino group should appear, although modified by the double bond at the α-carbon atom. However, the infrared spectra of the N-monosubstituted trichloroacetamidines revealed only two, very sharp, absorptions at 3450-3520 cm.$^{-1}$ and at 3350-3415 cm.$^{-1}$ in dilute solutions. The intensity of the two bands showed a general increase on passing from N-alkyl to N-phenyl derivatives, where both were almost of the same intensity. The second absorption band was of a much lower intensity in the spectra of the N-alkyl-trichloroacetamidines. No inflections were recorded. The results indicate that amidines do not exhibit any tautomerism at least not in dilute tetrachloroethylene solutions.

Furthermore, a comparison of the infrared spectra of N-dialkyl substituted trichloroacetamidines with those of the N-alkyl homologues revealed that the first and the second stretching band of the imino group =NH appear in the same regions and are very close to each other. Thus, in dilute solution N-ethyl- and N-amyltrichloroacetamidines showed the second band at 3350 and 3347 cm.$^{-1}$ respectively, while the N-dimethyl-, N-diethyl- and N-morpholyl- derivatives exhibited only one band of the free =NH group in this region at 3362, 3382 and 3365 cm.$^{-1}$ respectively.

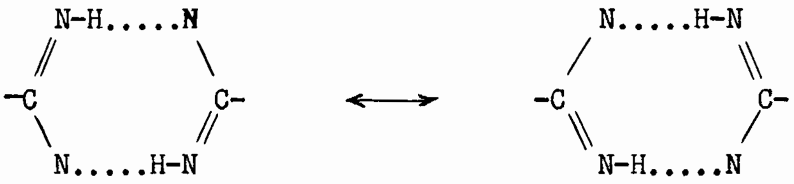
The NH stretching vibration of the secondary amino group was thus assigned to the 3450-3520 cm.$^{-1}$ band and the ν(NH) of the imino group to 3350-3415 cm.$^{-1}$ absorption. Further evidence in favour of the above assignments was obtained from the position of the ν(C=N) in different types of substitution, which will be discussed later in this paper.

The infrared spectra of all the compounds show that hydrogen bonding is involved to a considerable extent in liquid and solid phases, except the liquid N-dialkyl substituted amidines. The general trend of the displacement of the ν(>NH) and ν(=NH) to the higher frequencies is shown when the substances are diluted, in accordance with what is expected from a breaking of hydrogen bonding. This displacement is very slight for the change from the liquid to the solution and it is more pronounced in the case of the solid derivatives.

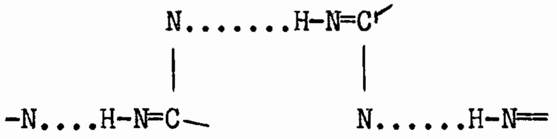
More than two bands appear in the spectra of solid or liquid compounds in addition to the two NH vibrations; their behaviour resembles that of the secondary amides, since they disappear upon dilution. Many of the liquids examined possess a weak absorption near 3040 cm.$^{-1}$ and it is expected that other bands exist because of the fact that the ν(=NH) band is very broad and exhibits one or two inflections. Its intensity is also higher than the ν(>NH) while the opposite is true with the spectra obtained by solutions of these substances.

The existence of these absorption bands in addition to the ν(>NH) and ν(=NH) was established in four of the six solid amidines examined; i.e. N-(p-ethoxyphenyl) trichloroacetamidine absorbed rather strongly at 3450, 3360, 3330 and 3110 cm.$^{-1}$ The last two bands vanished upon dilution, while the first two were displaced to 3498 and 3398 cm.$^{-1}$ respectively. Solid N-(m-tolyl) trichloroacetamidine showed absorption maxima at 3470, 3365, 3320 and 3160 cm.$^{-1}$; these four bands were replaced by only two strong absorptions at 3500 and 3400 cm.$^{-1}$ in dilute solutions. The 3050 cm.$^{-1}$ weak absorption observed with the N-alkyl-trichloroacetamidines, may be confused with the stretching motion of the aromatic C-H group with the N-phenyl derivatives.

Of the two hydrogen atoms of the imino and secondary amino groups, the first one seems to be involved in hydrogen bonding to a greater extent since it is the band near 3350 cm.$^{-1}$ which undergoes greater transformation on changing from the condensed phase to the solution. Although more work is necessary in this field, it can be assumed that the absorption near 3300 and 3150 cm.$^{-1}$ are due to hydrogen bonding and originate from a <u>trans</u> and <u>cis</u> arrangement respectively. These absorption bands correspond to the dimer and polymer structures (CVI) and (CVII), from which the dimer may be stabilized by resonance occurring in a fashion similar to that observed with the carboxylic acids.



(CVI)



(CVII)

In conclusion, secondary amidines possess hydrogen bonding to a smaller extent than secondary amides and the N-alkyl trichloroacetamidines are more strongly associated than the N-aryl derivatives.

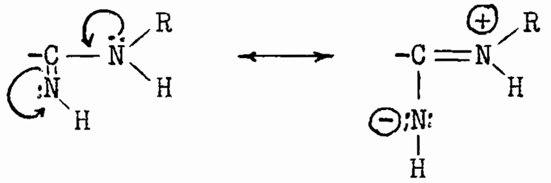
II. Region 1800-1200 cm.$^{-1}$

(a) The stretching, ν(C=N), absorption

These vibrations were easily recognizable in all the spectra taken, since they appeared as a very strong band between 1590 and 1670 cm.$^{-1}$ and did not show any appreciable change in intensity and position, whether the sample was a solid, a liquid or a solution. The small displacement

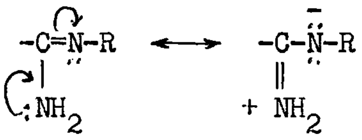
(5-25 cm.$^{-1}$) to the lower wave lengths upon dilution is quite characteristic in all cases and excludes the possibility of being an NH bending vibration. The position of the ν(C=N) seems to be a function of substitution on the amino nitrogen atom. Thus N-alkyl trichloroacetamidines absorbed between 1630 and 1645 cm.$^{-1}$, whereas the N-dialkyl compounds at 1590-1610 cm.$^{-1}$ The opposite shift to higher frequencies (1650-1670 cm.$^{-1}$) was recorded with the N-phenyl trichloroacetamidines.

This behaviour can be easily explained and it comes as additional evidence for the non-existence of tautomerism in the amidines examined. Amidines are the resonance hybrid of the following structures (CVIII).



(CVIII)

Substitution of the amino hydrogen atom by another alkyl group increases the electron density around the amino nitrogen atom owing to the greater +Is effect. As a consequence the contribution of the polar structure increases, the double bond character of the C=NH double bond decreases and hence causes a displacement of the ν(C=N) to the lower frequencies which is in fact observed. When R is an electron attracting group (phenyl) its -Is effect should oppose such an electron movement and depress the resonance within the amidino group. As a result N-phenyl derivatives should absorb at higher frequencies than the corresponding N-alkyl derivatives in agreement with our findings. If tautomerism exists, one of the two tautomers (CIV,CV) should be present. In this case the resonance hybrid can be represented as (CIX)



$$\underset{\overset{|}{NH_2}}{-C}{=}\ddot{N}{-}R \longleftrightarrow \underset{\overset{\|}{{}^{+}NH_2}}{-C}{-}\overset{-}{\ddot{N}}{-}R$$

(CIX)

and the pattern of the displacement going from the N-alkyl to the N-dialkyl and N-phenyl trichloroacetamidines is expected to be the opposite of that observed.

(b) The amidine II band, δ (N-H)

The second very strong absorption in this region appeared near 1515 cm.$^{-1}$ for all N-alkyltrichloroacetamidines, and was absent from all the infrared spectra of N-dialkyl derivatives. This immediately suggested that it could be related to the δ (NH) of the secondary amino group. The displacement of this band (1-5 cm.$^{-1}$) to the lower frequencies upon dilution was negligible, since association is weak in the liquid phase, but was indicative of an NH deformation frequency. A rather pronounced shift to lower frequencies was recorded for the N-benzyl derivative, the only aliphatic solid which showed a strong displacement. This compound had a very strong band at 1545 cm.$^{-1}$, in addition to the aromatic absorptions at 1602 and 1495 cm.$^{-1}$. The 1545 cm.$^{-1}$ band was displaced to 1510 cm.$^{-1}$ upon dilution and the 1495 cm.$^{-1}$ absorption peak appeared as a distinct inflection of this band.

In the case of the N-aryl derivatives, the δ (NH) seems to be located near 1580 cm.$^{-1}$, in addition to the two aromatic vibrations. A normal aromatic stretching mode, nevertheless, has been identified between 1600 and 1560 cm.$^{-1}$; although it is always weak, external conjugation increases its intensity, when it becomes a readily recognizable medium band (104).

This possibility was excluded on the following grounds:

1) The band is very strong in all the spectra
2) In the case of the solid N-(p-ethoxyphenyl)-trichloroacetamidine, which associates strongly, it appeared at 1627 cm.$^{-1}$ as a strong absorption, whereas it was found at 1578 cm.$^{-1}$ upon dilution.
3) Richards and Thompson (144) reported only two bands for the aromatic modes near 1600 and 1500 cm.$^{-1}$ with the N-aryl acetamides, for which a similar increase in intensity of the 1560-1600 cm.$^{-1}$ frequency could be expected.
4) Since the resonance within the amidine system C(=NH)-NH is opposed to that arising from the aromatic ring, such a conjugation should be reduced greatly, if it existed at all. The assignment of the δ (NH) to the 1515 cm.$^{-1}$ absorption for the N-alkyl trichloroacetamidines and to the 1580 cm.$^{-1}$ for the N-aryl analogues might be supported by the findings of Barr and Haszeldine (107), Hadzi and Skrbljak (108) who located the δ (NH) of the secondary aromatic amines and the secondary perfluoroalkyl amines in the same region. It is obvious that the otherwise weak δ (NH) is enhanced through resonance which imposes a partial positive charge on the nitrogen atom.

(c) The stretching ν(C-N) frequencies

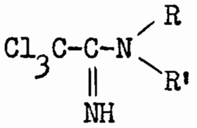
Amidines should give rise at least to two absorption bands related mainly to the C-N stretching vibrations. It was clearly understood that only two absorptions of strong and very strong intensity were suitable for the ν(C-N) vibrations in the 1400-1100 region for the N-aryl substituted trichloroacetamidines, i.e. the 1330 cm.$^{-1}$ band for the ν(C_{ar}-N) and the 1240 cm.$^{-1}$ for the ν(C-N) of the amidino grouping. Both values agree with those given by Colthup's table and permit the assumption that the phenyl group "localizes" the C=N double bond to some extent; in agreement with our observation the C=N groups in the phenyl derivatives absorb at higher frequencies than the N-alkyl and N-dialkyl derivatives.

The ν(C-N) of N-alkyltrichloroacetamidines occur at higher frequencies; alkyl groups facilitate the resonance within the amidine system, thus imposing a partial double bond character to its (C-N) bond, which therefore should absorb at higher frequencies than the C_{alk}-N bond. This was revealed from a comparison of the infrared spectra recorded for the different classes of substituted amidines on the one hand and from their absorption in the ultraviolet region on the other. Indeed the amidine ν(C-N) was found to be located near 1310 cm.$^{-1}$, very close to the ν(C_{ar}-N) in the aromatic compounds, whereas the 1150-1170 cm.$^{-1}$ strong absorption should involve mainly ν(C_{alk}-N) modes, with the N-alkyltrichloroacetamidines.

No general conclusion could be drawn, for the N-disubstituted derivatives. Nevertheless, a strong band near 1270 cm.$^{-1}$ was attributed to the amidine ν(C-N) absorption and the ν(C_{alk}-N) could be related also to a strong band occurring near 1100 cm.$^{-1}$ It should be pointed out that the ν(C-C) of the Cl_3C-C group was definitely found near 1050 cm.$^{-1}$, in agreement with the spectrum obtained for the trichloroacetonitrile which was used in the preparation of the amidines mentioned above and with the data found in the literature (145).

TABLE III

POSITIONS OF ABSORPTION MAXIMA (CM.$^{-1}$) IN THE INFRARED SPECTRA OF N-SUBSTITUTED TRICHLOROACETAMIDINES



$$Cl_3C-\underset{\underset{NH}{\|}}{C}-N\begin{matrix}\diagup R\\ \diagdown R'\end{matrix}$$

Assignments	R = H R' = Alkyl	R = H R' = Aryl	R,R' = Alkyl
Free ν (>N-H)	3440-3480	3490-3520	
Free ν (=N-H)	3300-3370	3390-3420	3360-3380
Bonded (N-H) (trans)	3180-3300	3270-3330	
Bonded (N-H) (cis)		3100-3160	
ν(C=N)	1630-1650	1650-1670	1590-1610
Free δ (>NH) (Amidine II band)	1510-1525	1570-1580	
ν(C_{ar}-N)		1320-1340	
ν(C-N) in HN=C-N	1300-1340	1230-1270	1260-1280
ν(C_{alk}-N)	1150-1170		1090-1120(?)
ν(C-C) in Cl_3C-C	1025 - 1070		

TABLE IV

POSITIONS OF ABSORPTION MAXIMA (CM.$^{-1}$) IN THE INFRARED SPECTRA OF N-SUBSTITUTED TRICHLOROACETAMIDINES

TABLE IV

POSITIONS OF ABSORPTION MAXIMA (CM.$^{-1}$) IN THE INFRARED SPECTRA OF N-SUBSTITUTED TRICHLOROACETAMIDINES

No.	Trichloro-acetamidine	State$^{(1)}$	(N-H)	(N-H)	Hydrogen bonded NH	(CH_3) and (CH_2)	(C=N)	(C=C) aromatic	(N-H) Amidine II	(C=C) aromatic	(C_{ar}-N)	(C-N) HN=C-N	(C_{alk}-N)
1	N-Methyl	L	3490s	3300vs(2)	3200(sh)-3045s	2950s,2905s	1635vs		1522vs			1313vs	1152vs
		L	3465s	3340vs(3)	3280(sh)-3050s	2970m,2940s,2875s	1637vs		1515vs			1314vs	1168vs
2	N-Ethyl												
		Sol	3465m	3350w	None	2970m,2930m,2870w	1642vs		1510vs			1308m	
3	N-n-Butyl	L	3445s	3325vs	3200(sh)-3040m	2920vs,2850s	1633vs		1515vs			1313s	1155vs
		L	3440m	3320s(3)	3180(sh)-3030m	2915vs,2845s	1632vs		1513vs			1312s	1155s
4	N-n-Amyl												
		Sol	3455m	3350w	None	2950(sh),2925vs, 2855s	1642vs		1512vs				
		S	3330m	3205s(3)		2915vs,2890vw	1635vs	1602m	1545vs	1495s		1338	1168vs
5	N-Benzyl												
		Sol	3475m	3370w			1642vs	1602m	1510s	1500sh			
		S	3485s	3370s	3270sh-3150vw		1657vs	1594vs	1584vs	1483s	1337s	1237m	
6	N-Phenyl												
		Sol	3520m	3415m	None		1672vs	1594vs	1580vs	1484s	1327s	1240m	
7	N-o-Tolyl	Sol	3500s	3400s		2915vw,2860(sh)	1670vs	1596s	1577s	1483s	1327s	1239m	
		S	3470m	3365m	3320m-3160(sh)	2915vw,2860(sh)	1652vs	1595vs	1585vs	1486s	1337s	1265m	
8	N-m-Tolyl												
		Sol	3500m	3400m	None	2915vw,2860(sh)	1670vs	1595vs	1580vs	1484s			
		S	3480m	3370m	3150w	2915w-2850w	1660vs	1610s(sh)	1580vs	1504vs	1337	1237s	
9	N-p-Tolyl												
		Sol	3505m	3400m	None	2918w-2860vw	1667vs	1611m	1580vs	1505vs			
		S	3450m	3360m	3300m-3110m	2990m;2930m;2890vw	1660vs	1606vs	1627vs	1507vs	1332	1232vs	
10	N-p-Ethoxyphenyl												
		Sol	3500m	3400m	None	2980m;2920sh;2895w	1667vs	1604m	1577vs	1503vs	1322s	1236vs	
		L		3340m		2895s	1603vs					1267vs	1090vs
11	N,N-Dimethyl												
		Sol		3360m		2895s,2820(sh)	1607vs					1267vs	
		L		3380s		2985vs,2945vs,2885s	1593vs						
12	N,N-Diethyl												
		Sol		3380m		2985vs,2945vs,2880m	1600vs						
		L		3360m								1275vs	1117vs
13	N-Morpholyl												
		Sol		3365m		2975m-2920m; 2900m-2858s	1601vs					1277vs	

NOTES: (1) L = liquid, S = solid, Sol = solution.
(2) a wide band between 3250 and 3350 cm.$^{-1}$
(3) wide bands.

FIG. 2

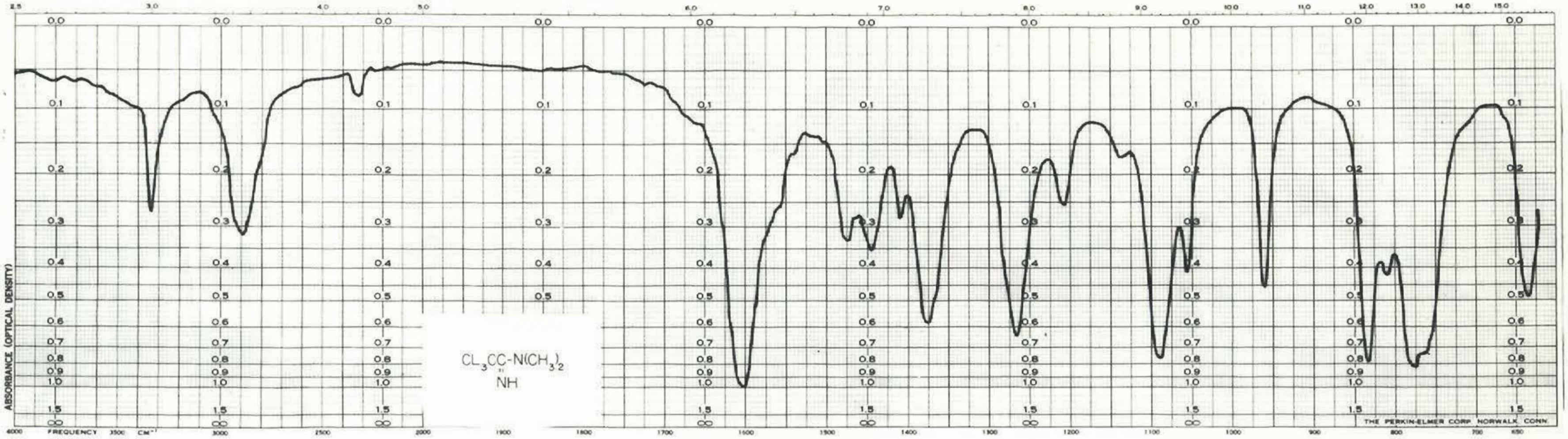
Infrared Absorption Spectra of:

1. N,N-Dimethyl-α,α,α-trichloroacetamidine
2. N-Methyl-α,α,α-trichloroacetamidine

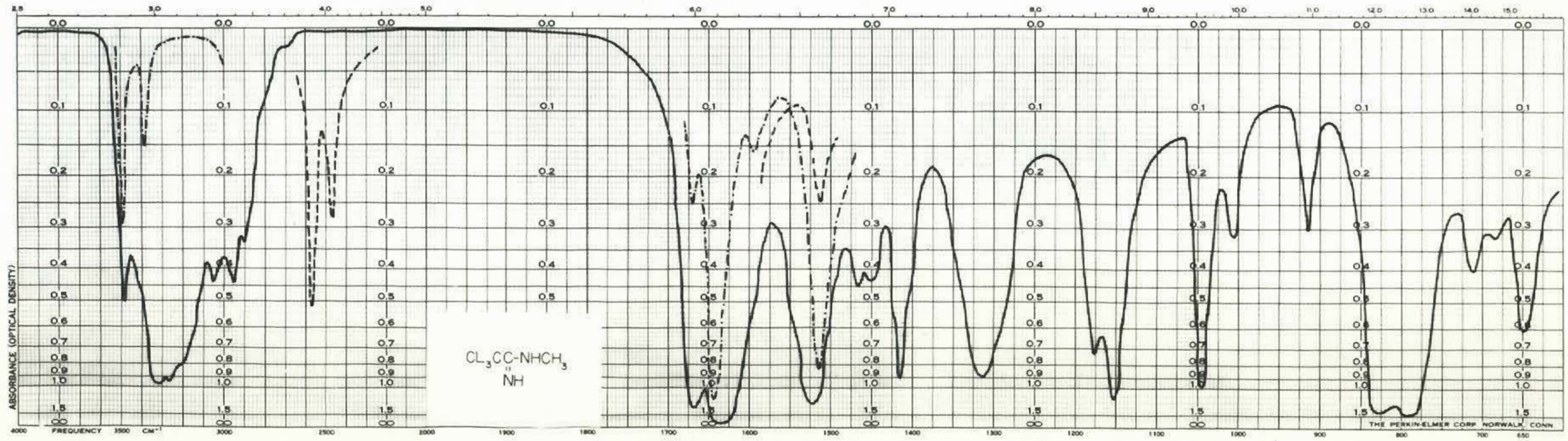
——— Liquid

—·— Dilute solution

— — Deuterated compound, dilute solution



$CL_3CC\text{-}N(CH_3)_2$
NH
ABSORBANCE (OPTICAL DENSITY)
FREQUENCY CM⁻¹
THE PERKIN-ELMER CORP NORWALK, CONN



$CL_3CC\text{-}NHCH_3$
NH
ABSORBANCE (OPTICAL DENSITY)
FREQUENCY CM⁻¹
THE PERKIN-ELMER CORP NORWALK, CONN

FIG. 3

Infrared Absorption Spectra of:

1. N-Benzyl-α,α,α-trichloroacetamidine

———• in KBr

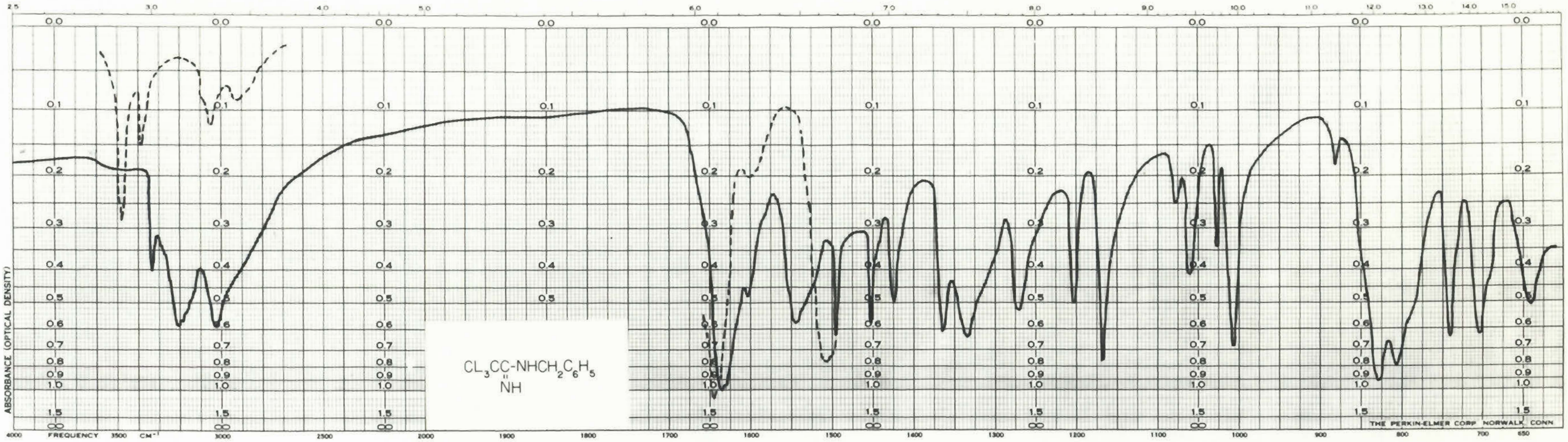
— — Dilute solution

2. N-Phenyl-α,α,α-trichloroacetamidine

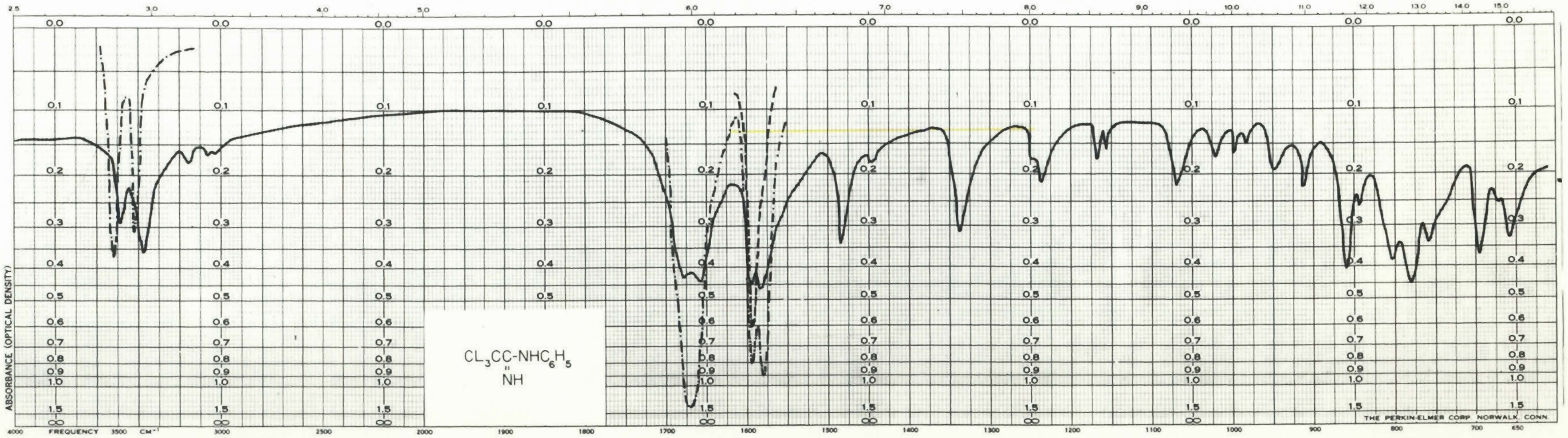
——— in KBr

—•— Dilute solution

—-— Deuterated compound, dilute solution



$CL_3C\underset{NH}{\underset{\|}{C}}\text{-}NHCH_2C_6H_5$



$CL_3C\underset{NH}{\underset{\|}{C}}\text{-}NHC_6H_5$

C. Study of the structure of trifluoroacetamidines by infrared spectroscopy

As was expected the infrared spectra of N-substituted trifluoroacetamidines presented no considerable differences with those of the corresponding trichloro compounds. However, the possibility that individual compounds of both series could exist in a tautomeric equilibrium or in the form (XCVI) was reexamined. More evidence was accumulated which favoured the interpretation given previously and provided further information for the existence of these amidines in the form (CV). The results are summarized in Table V.

Correlation between the infrared spectra and the structure of trifluoroacetamidines

1. Region 4000-1800 cm.$^{-1}$

The stretching, ν (NH), vibrations

The spectra of trifluoro- and trichloro-acetamidines showed definitely at least three absorption peaks in dilute tetrchloroethylene solutions corresponding to the asymmetrical and symmetrical ν (NH_2) absorptions and the ν (=NH) of the imino group in agreement with the spectrum of $C_3F_7C(=NH)NH_2$ reported (74). This excluded the possibility of overlapping of the ν_{sym}(NH_2) and ν (=NH) absorption, and left only one of the two tautomeric forms for consideration.

Assuming that the validity of Bellamy's equation (LXXXIII), which seems to offer a sensitive method for the detection of non-equivalent NH bonds in primary amines, holds in compounds having the structure (XCVI), and in spite of the fact that our spectra were not taken with a high resolution prism, the difference ν_{sym}calc. - ν_{sym} observed was computed and tabulated (Table V). Although these values cannot be considered accurate, they still are far over the standard deviation (4.8 cm.$^{-1}$) reported for sixty-four compounds so far examined. Such evidence favours the formula (XCV) for both N-alkyl and N-aryl series, though decrease of this value was observed in passing from the first to the second series.

N-Substituted trifluoroacetamidines were shown to exhibit strong association in the liquid and solid phases, except the N-dialkyl compounds, which presented only one inflection at the position of the sharp ν (=NH) band in the condensed phase.

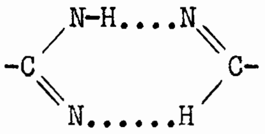
Thus, more than two bands were found in the spectra of the solid and liquid compounds and these bands appeared in such a way that it was difficult to distinguish between the free and bonded NH stretching vibrations in some cases. Dilution in tetrachloroethylene produced two very sharp absorption peaks; i.e. four strong absorptions appeared in the spectrum of N-benzyl-α,α,α-trifluoroacetamidine and were still persistent near 3475, 3340, 3270 and 3200 cm.$^{-1}$ at 1.3 M concentration in tetrachloroethylene. They were replaced by a sharp band of medium intensity, ν (>NH), at 3465 cm.$^{-1}$ and a weak one, ν (=NH), at 3360 cm.$^{-1}$ upon further dilution.

In trifluoro- and trichloro-acetamidines there are two hydrogen atoms which might be involved in hydrogen bonding. Theoretical considerations demonstrate that one of these, namely the amino hydrogen bears a partial positive charge, owing to resonance and thus is more acidic than the other. This provides a ready explanation of the fact that the degree of association decreases in the order shown:

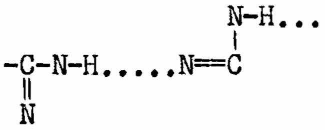
N-Alkyl > N-phenyl ≫ N-dialkyl.

Indeed the $\delta +$ charge of the hydrogen atom of the secondary amino group would be expected to be greater when R' = alkyl (+Is) than when R' = Aryl (-E) (XCV), and the presence of only the imino hydrogen atom in N-dialkyl derivatives would result in a very small association. These findings are in complete harmony with the protonation of the amidines which will be discussed later.

Association might then be better expressed as follows in both the trichloro- and trifluoro-series.



cis



$-\underset{\underset{N}{\|}}{C}-N-H\cdots\cdot N{=}\overset{\overset{N-H\cdots}{|}}{C}$

trans

Consequently the 3100-3200 cm.$^{-1}$ band was assigned to the <u>cis</u> arrangement and the absorption 3200-3300 cm.$^{-1}$ to <u>trans</u> association.

The ν (C=N) vibrations

This easily recognizable absorption appeared as a very strong band at 1615-1690 cm.$^{-1}$ in all the spectra taken and was displaced slightly to higher frequencies upon dilution, as is expected from a C=N vibration. The frequencies at which they occurred in the N-aryl-, N-alkyl- and N-dialkyl-trifluoroacetamidines followed exactly the same pattern as those of the trichloro compounds, and provided further evidence for the existence of these compounds in the imino form (XCV), as discussed previously.

A comparison of the ν(C=N) frequencies of the following compounds in dilute solution showed the occurrence of this mode exactly at the same frequency.

$Cl_3CC(=NH)NH_2$: 1670 $cm.^{-1}$, $Cl_3CC(=NH)NHAr$: 1667-1672 $cm.^{-1}$

$F_3CC(=NH)NH_2$: 1690 $cm.^{-1}$, $Cl_3CC(=NH)NHPh$: 1690 $cm.^{-1}$

This may not be pure coincidence but may indicate that the presence of aryl groups does not influence the resonance within the amidine system at all, whereas substitution by one or two alkyl radicals at the amino group does facilitate the progressive displacement of the ν(C=N) frequency, which takes its lowest value in the case of N-dialkyl amidines.

δ (NH), the "Amidine II" band

This absorption appeared as a medium or as a strong band in the spectra of four N-alkyl trifluoroacetamidines. It was absent from the spectra of the N-dialkyl compounds and was displaced to the higher frequencies (10-20 $cm.^{-1}$) when association came into play to indicate a δ(NH) absorption. Nevertheless, it was not found in the spectrum of solid N-benzyl-α,α,α-trifluoroacetamidine, but appeared as usual when solutions in tetrachloroethylene were used. It was also found when the spectrum of the melted compound was taken but vanished when the melt was left to resolidify, this being done several times with the same results.

Since the melting point of the compound was low, decomposition by heating could not take place and the spectra of the solidified melt were exactly the same as those of the pure compound in Nujol mull or potassium bromide pellets. The behaviour which is an example unique to the literature, could only be attributed to changes related to the crystal lattice and could be the answer to the absence of the amide II band in the spectrum of N-chloromethyl acetamide (146).

A strong band with two well separated peaks at 1607 and 1582 cm.$^{-1}$ was found in the spectrum of solid N-phenyl-α,α,α-trifluoroacetamidine, but was replaced by only one very strong absorption band at 1582 cm.$^{-1}$ upon dilution. The 1607 peak was taken as evidence for the "Amidine II" absorption, which was displaced and coincided with the aromatic absorption.

The assignment of the amidine II band to the 1570-1590 absorption in N-aryl trifluoro- and trichloro-acetamidines was supported by the deuteration studies of the N-phenyl-α,α,α-trichloroacetamidine. The absorption at 1580 cm.$^{-1}$ disappeared gradually by progressive deuteration. The same phenomenon was noted with the deuterated N-methyl-, trichloro-, and trifluoro derivatives.

ν(C-N) frequencies

The very strong absorptions of the F_3C-group, which vary in number from two to five even for simpler molecules occurred in the same region (1100-1250 cm.$^{-1}$) where the ν(C-N) vibrations appeared and produced complicated spectra.

However, the $\nu(C_{ar}\text{-}N)$ could be related to a very strong absorption at 1407 cm.$^{-1}$ in the N-phenyl-α,α,α-trifluoroacetamidine. This was clearly understood, since it was the only strong band between 1225 and 1480 cm.$^{-1}$ and was not present in the spectrum of trifluoroacetamidine. The existence of a strong absorption near 1080 cm.$^{-1}$, could be attributed to a $\nu(C_{alk}\text{-}N)$ in the N-dialkyl compounds, since it was absent in the case of the N-alkyl derivatives.

TABLE V

POSITIONS OF ABSORPTION MAXIMA ($CM.^{-1}$) IN THE INFRARED SPECTRA OF N-SUBSTITUTED TRIFLUOROACETAMIDINES

No.	Trifluoro-acetamidine	State	ν(>NH)	ν(=NH)	$\Delta\nu$ (ν_{sym}calc.- ν_{sym}obs.)	Hydrogen bonded ν(NH)	ν(C=N)	δ(NH) "Amidine II"	$\nu(C_{ar}$-N)	$\nu(C_{alk}$-N)
1	N-Methyl	L	3515m	?		3350sh,3300 sh,3220s	1655vs	1555m		
		Sol	3515m	3380w	+34	None	1660vs	1530m		
2	N-Ethyl	L	3475s	?		3250vs(1), 3090vs	1645vs	1545s		
		Sol	3475s	3355m	+35	None	1655vs	1530m		
3	N-n-Butyl	L	?	3300s(1)		3500w, 3100m	1650vs	1455s		
		Sol	3460m	3340w	+35	None	1653vs	1527m		
4	N-Benzyl	S(Nujol)	3485m	?		3300m,3260 m,3150s(1).	1650vs	Absent (3)		
		Sol(1.3M)	3475m	3340s		3270s, 3200s				
		Sol	3465m	3360w	+20	None	1655vs	1517s		
5	N-Phenyl	S	3465s	?		3270s(1), 3140s(1)	1670vs	1607vs		
		Sol	3535s	3425m	+17		1690vs	1582vs(4)	1410vs	
6	N,N-Dimethyl	L		3375m(2)		3330sh	1615vs			1090vs
		Sol		3355m		None	1620vs			1090vs
7	N,N-Diethyl	L		3365s(2)		3330sh	1625vs			1070vs
		Sol		3375m		None	1625vs			1070vs

(1) Broad bands with inflections
(2) Sharp bands
(3) It disappeared in the solid state
(4) Together with the C=C aromatic mode.

FIG. 4

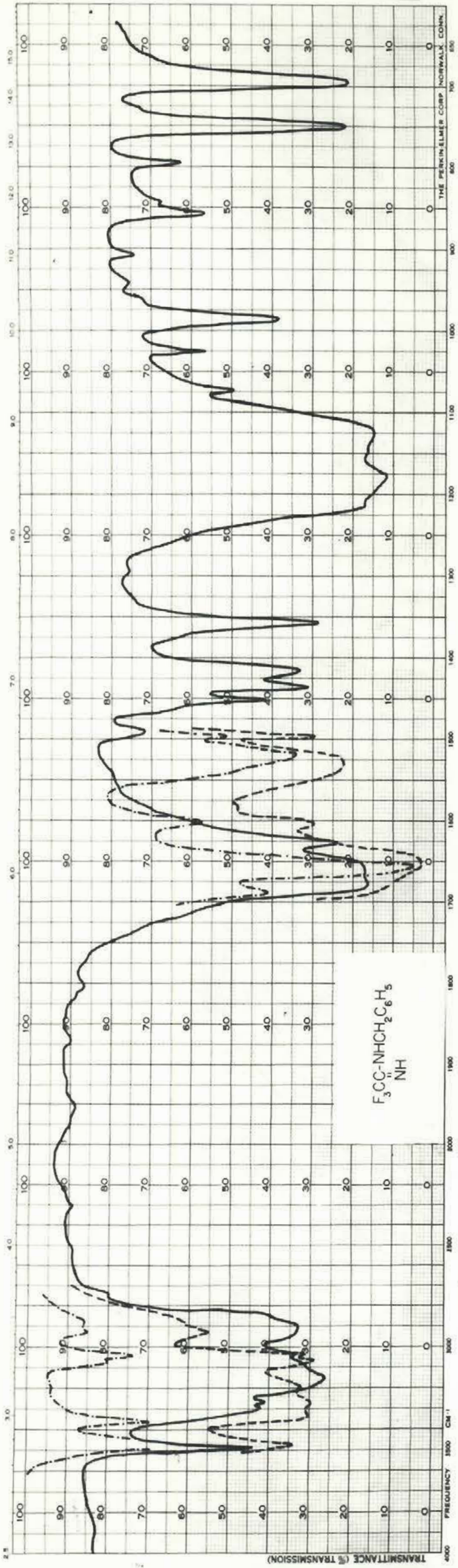
Infrared Absorption Spectra of:

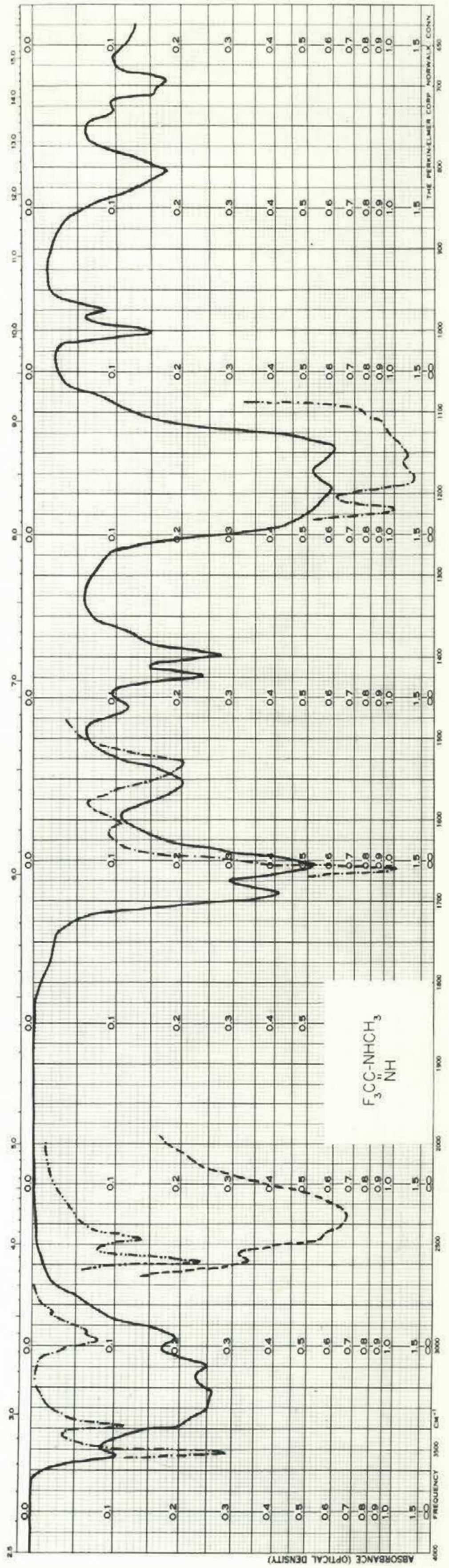
1. N-Benzyl-α,α,α-trifluoroacetamidine

———	Nujol mull
— — —	1.3 M solution
—·—	Dilute solution

2. N-Methyl-α,α,α-trifluoroacetamidine

———	Liquid
—·—	Dilute solution
— —	Deuterated compound, liquid
—··—	Deuterated compound, dilute solution


$F_3C\underset{\underset{NH}{\|}}{C}\text{-}NHCH_2C_6H_5$
TRANSMITTANCE (% TRANSMISSION)
FREQUENCY CM⁻¹
THE PERKIN-ELMER CORP. NORWALK, CONN.


$F_3C\underset{\underset{NH}{\|}}{C}\text{-}NHCH_3$
ABSORBANCE (OPTICAL DENSITY)
FREQUENCY CM⁻¹
THE PERKIN-ELMER CORP. NORWALK, CONN.

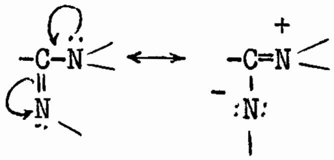
D. Structure of amidinium cation in the light of infrared study

The infrared spectra of fourteen trichloro- and trifluoro-acetamidine hydrochlorides showed that protonation occurs at the imino nitrogen atom of the N-substituted amidines. Both nitrogens of the amidine grouping, C(=N)N, become electron deficient due to resonance leading to the single structure (CXIII), regardless of which of the tautomers is present in the equilibrium mixture, and of the number and type of substituents on the amidine nitrogen atoms. These findings predestine to failure any attempts to isolate the two amidine tautomers, whenever amidinium salts are involved as intermediates.

Correlation between the infrared spectra and the trichloro- and trifluoroacetamidine hydrochlorides

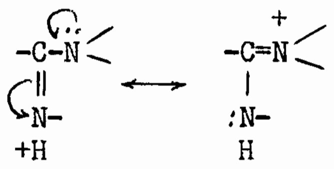
A literature search revealed that very little is known with respect to the structure of the amidinium cation, which must have an important bearing on the understanding of the chemical behaviour of the amidine grouping. Some authors do not draw any distinction between the two nitrogen atoms of amidines.

Theoretical considerations, however, combined with the results of this investigation by the infrared spectroscopy method may definitely elucidate the course of protonation. Irrespective of the type and number of substituents on the nitrogen atoms, the amidine system is represented by formula (CX)



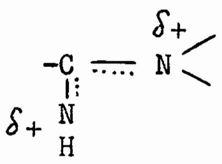
(CX)

Such a structure as shown allows for only one charged resonance form having a negative charge on the imino nitrogen and a positive charge on the other. Consequently, the imino group would be expected to accept the proton during the salt formation. Such protonation should yield a resonance hybrid receiving contributions from the two structures shown in formula (CXII). As a result both nitrogen atoms would become electron



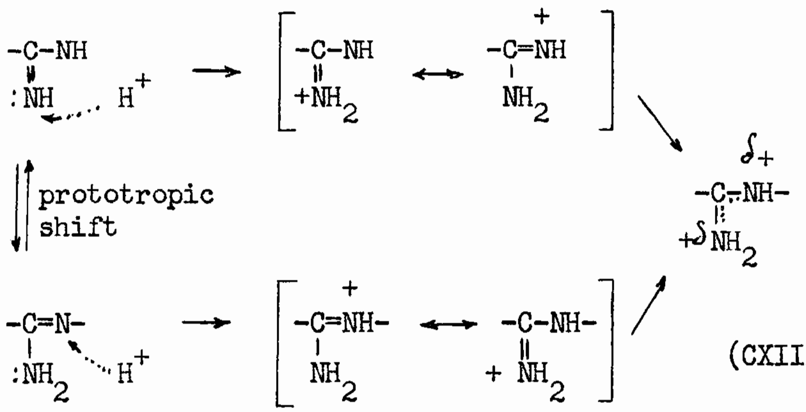
(CXI)

deficient to a degree (CXII) which should depend on the substituents to



(CXII)

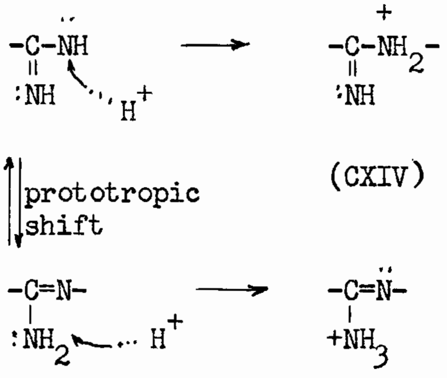
some extent. The decreased electron density on nitrogen atoms should prevent any further protonation. The protonation of both plausible tautomeric forms of amidines must give one and the same compound (CXIII) stabilized by resonance, as outlined in the following scheme:



(CXIII)

This course must be valid in any case, independently of the kind of substitution and predestines to failure any attempts to isolate the two tautomers, whenever intermediate salt formation occurs. It should be mentioned here that many such unsuccessful attempts have been made, even recently, and in all cases methods leading to salt intermediates were used.

An alternative course of protonation can be written as follows:



(CXIV)

(CXV)

It is obvious that formulae (CXIV) and (CXV) represent two relatively unstable isomers, since resonance stabilization is prevented. The infrared spectra of the amidine hydrochlorides examined showed characteristically only the stretching vibrations of the $\overset{+}{\text{NH}}$ group and the complete absence of any absorption bands of free or bonded NH groups (Tables VI, VII and VIII).

A broad and very strong band was shown instead, between 2600 and 3000 cm.$^{-1}$, which possessed two to three well defined inflections. This absorption includes of course, the CH stretching vibrations, their separation being impossible with the low dispersion prism used. In addition a broad weak absorption band appeared near 2350 cm.$^{-1}$ in all cases.

The striking feature of all the spectra was the complete absence of the strong bands near 2000 $cm.^{-1}$ (111, 112) and between 2600 and 2000 $cm.^{-1}$ Furthermore the strongest absorption occurred at higher frequencies than in the corresponding amines, as was firmly established from a comparison of two amidine hydrochlorides with their deuterated analogues (Table VIII). Since the greater the positive charge on a nitrogen atom the greater is the displacement of its NH^+ stretching vibrations towards the lower frequencies (104), this observation may definitely demonstrate that only partial positive charges are present in the amidinium cation, which does not agree with structures (CXIV) and (CXV).

The stretching $\nu(C{=}N^+)$ vibrations were easily detected since they showed the strongest band between 1600 and 1700 $cm.^{-1}$ Moreover, deuterium chloride salts of the two deuterated N-alkylamidines established this assignment, since they displaced all $\delta\ (NH^+)$ absorptions. This frequency seems to be quite sensitive to small changes, because substitution of the two amino and imino hydrogen by deuterium in N-methyltrifluoro- and N-methyltrichloroacetamidine salts reduced the absorption frequency by about 20 $cm.^{-1}$, and formula (CXIII) indicates that some distortion of the almost planar configuration of the molecule is likely to occur.

There was no difficulty in the identification of the $\delta\ (=NH_2^+)$ modes with the N-dialkyl compounds, since only one band was present and suitable for this assignment between 1530 and 1590 $cm.^{-1}$

Two peaks of medium to strong intensity appeared in the spectra of the N-substituted compounds. Although no decisive conclusions could be drawn, the one existing very close to the Amidine II band in the

the corresponding free bases, was attributed to the $\delta(\rangle NH^{+})$ of the secondary amino group, and the other to the $\delta(=\overset{+}{N}H_2)$ frequency.

The present study suggest quite clearly that protonation is always initiated at the imino group, and the distribution of the positive charge over the two nitrogens takes place in agreement with this theory.

TABLE VI

Positions of absorption maxima (cm.$^{-1}$) in the infrared spectra
of N-substituted trichloroacetamidine hydrochlorides

No.	Trichloroacetamidine hydrochloride	M.P. (dec.)	ν(>NH) and ν(=NH$_2$)(2)				ν(C=N)	δ(=NH$_2$)	δ(>NH)
1	N-Methyl	229°	3100sh,	(1) 2930vs,	2800sh,	2300w	1680vs	1620m	1500m
2	N-Ethyl	224-225°	3060sh,	(1) 2950vs,	2800sh,	2340w	1687vs	1640m	1520s
3	N,N-Dimethyl	175-176°	2970sh,	2910sh,	(1) 2860vs,	2340w	1617vs	1530s	None
4	N,N-Diethyl	202°	3040sh,	2990sh,	(1) 2860vs,	2340sh	1607vs	1540s	None
5	N-Phenyl	182-183°	2820sh,	(1) 2710vs,	2600sh,	2360m	1630vs	?	1550s
6	N-o-Tolyl	214-216°	2800sh,	(1) 2680vs,	2600sh,	2360m	1625vs	1555m	1575m
7	N-m-Tolyl	193-195°	(1) 2830vs,	(1) 2740vs,	2600sh,	2360w	1635s	1550m	1585m

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[1] Very broad strong bands

[2] Bands have no sharp peaks; positions of absorption maxima represent only approximate values.

TABLE VII

Positions of absorption maxima (cm.$^{-1}$) in the infrared spectra of N-substituted trifluoroacetamidine hydrochlorides

No.	Trifluoroacetamidine hydrochlorides	M.P. (dec.)	$\nu(>\overset{+}{\mathrm{N}}\mathrm{H})$ and $\nu(=\overset{+}{\mathrm{N}}\mathrm{H}_2)$(2)				$\nu(\mathrm{C}=\overset{+}{\mathrm{N}})$	$\delta(=\overset{+}{\mathrm{N}}\mathrm{H}_2)$	$\delta(>\overset{+}{\mathrm{N}}\mathrm{H})$
1	N-Methyl	219-221°	3150m,	2970vs,	2910vs,(1)	2780m	1717vs	1655vw	1560vw
2	N-Ethyl	189-191°	3130m,	2900vs,(1)	2760sh,	2360w	1707vs	1650m	1560m
3	N,N-Dimethyl	169-171°	3000sh,	2850vs,(1)	2780sh,	2330w	1655vs	1585s	-
4	N,N-Diethyl	133-135°	2960sh,	2780vs,(1)	2360w		1645vs	1580s	-
5	N-Phenyl	179-180°	2840vs,(1)	2770sh,	2630sh,	2360m	1685vs	1537s	1525s

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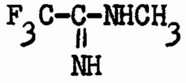
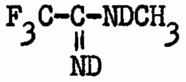
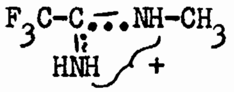
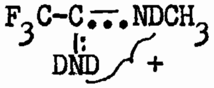
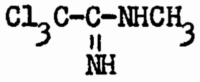
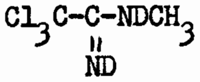
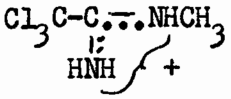
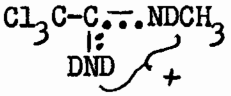
[1] Very broad strong bands

[2] Bands have no sharp peaks; positions of absorption maxima represent only approximate values.

TABLE VIII

Absorption maxima (cm.$^{-1}$) in the infrared spectra of N-methyltrichloro-, and N-methyltrifluoroacetamidines and their salts

No.	Compound	ν(NH)	ν(=NH)	ν(ND)	ν(=ND)	ν(NH^+)	ν(ND^+)
1	 $F_3C-\underset{\overset{\Vert}{NH}}{C}-NHCH_3$	3515	3380				
2	 $F_3C-\underset{\overset{\Vert}{ND}}{C}-NDCH_3$			2585	2470		
3	 $F_3C-\underset{HNH}{C}\cdots NH-CH_3\ +$					2910	
4	 $F_3C-\underset{DND}{C}\cdots NDCH_3\ +$						2200vs (1)
5	 $Cl_3C-\underset{\overset{\Vert}{NH}}{C}-NHCH_3$	3480	3355				
6	 $Cl_3C-\underset{\overset{\Vert}{ND}}{C}-NDCH_3$			2570	2465		
7	 $Cl_3C-\underset{HNH}{C}\cdots NHCH_3\ +$					2930	
8	 $Cl_3C-\underset{DND}{C}\cdots NDCH_3\ +$						2260vs

(1) Also 2420 (s), 2190 (s) and 2110 (s) peaks.

TABLE VIIIa

Comparison of ν(NH)/ν(ND) ratios of absorption maxima (cm.$^{-1}$) in the infrared spectra of N-methyltrichloro-, and N-methyltrifluoroacetamidines and their salts

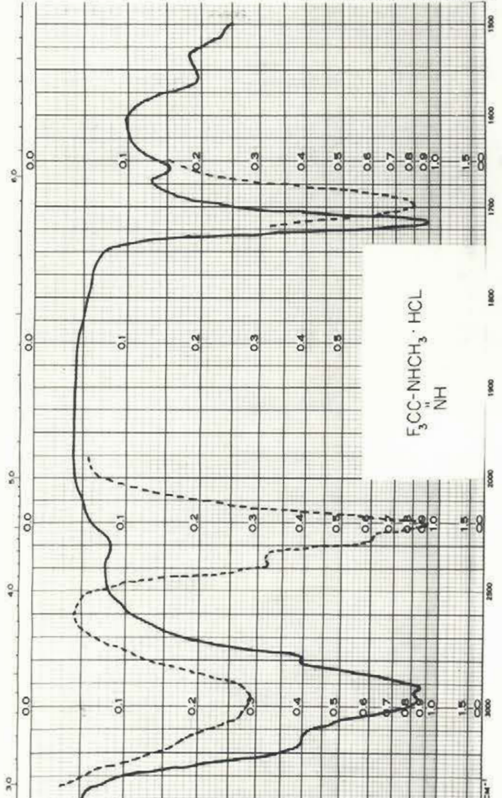
Compound Nos.	$\frac{\nu(NH)}{\nu(ND)}$	$\frac{\nu(=NH)}{\nu(=ND)}$	$\frac{\nu(NH^+)}{\nu(ND^+)}$
1/2	1.36	1.37	
3/4			1.32
5/6	1.31	1.31	
7/8			1.30

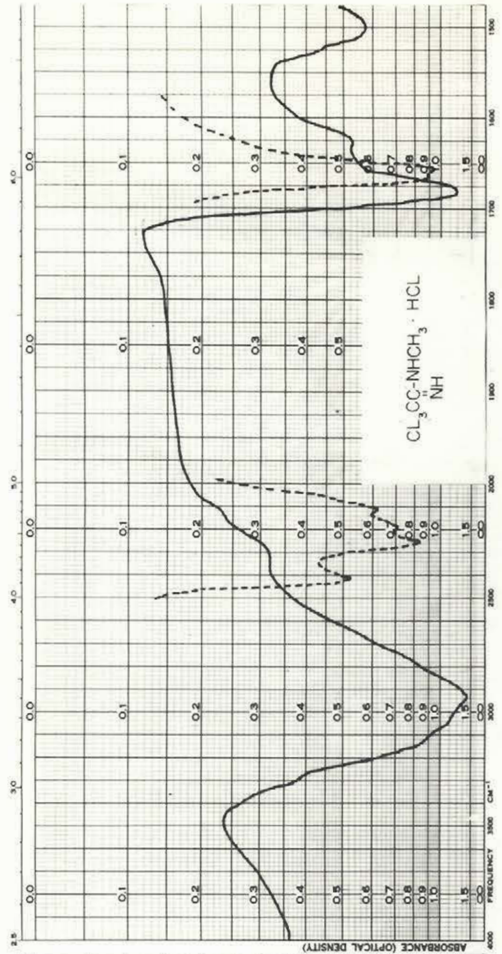
FIG. 5

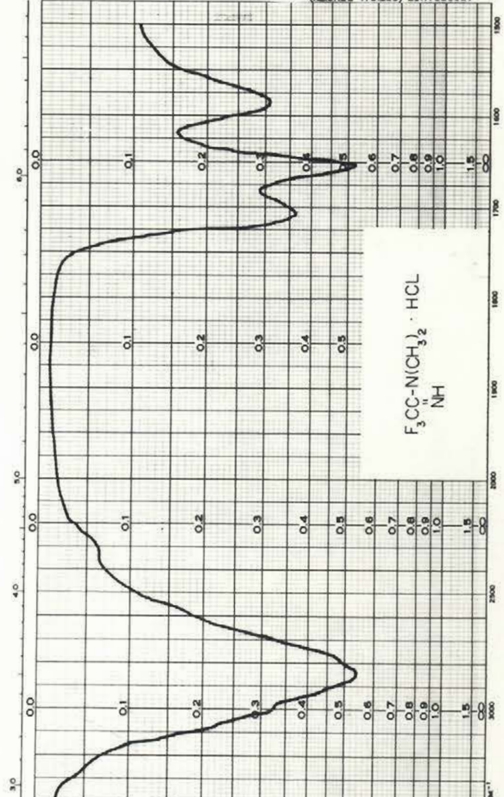
Infrared Absorption Spectra of:

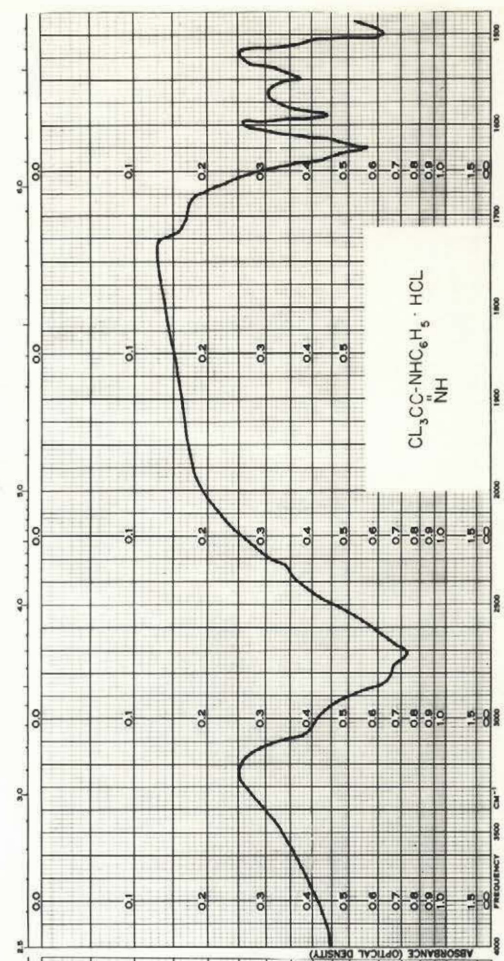
1. N-Methyl-α,α,α-trifluoroacetamidine hydrochloride
2. N-Methyl-α,α,α-trichloroacetamidine hydrochloride
3. N-Phenyl-α,α,α-trichloroacetamidine hydrochloride
4. N,N-Dimethyl-α,α,α-trifluoroacetamidine hydrochloride

———	Fluorolube T-45 mull
— — —	Fluorolube T-45 mulls of deuterium hydrochlorides of the deuterated parent compounds


$F_3C\underset{\underset{NH}{\|}}{C}-NHCH_3 \cdot HCL$


$CL_3C\underset{\underset{NH}{\|}}{C}-NHCH_3 \cdot HCL$


$F_3C\underset{\underset{NH}{\|}}{C}-N(CH_3)_2 \cdot HCL$

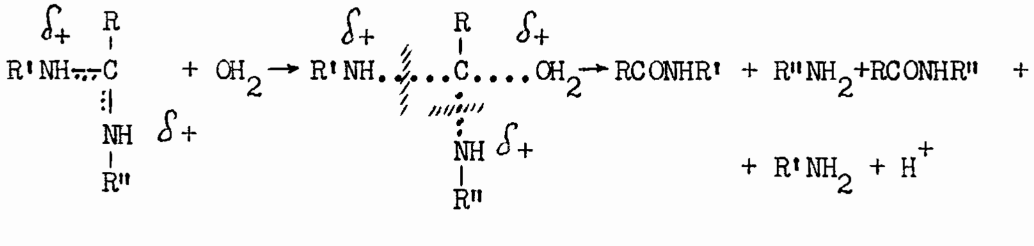

$CL_3C\underset{\underset{NH}{\|}}{C}-NHC_6H_5 \cdot HCL$

E. The mobility of the hydrogen atom in the amidine system

It has been generally accepted that the mobility of the amidine system is so high (19) that neither of the two tautomers can be isolated and "there is certainly every reason to believe that the amidine is a mixture (148) of the two tautomers".

The considerable amount of the chemical evidence (1) which supports the above conclusions, however, is now disproved or at least weakened seriously after the findings of this work.

The hydrolysis of a given N,N'-disubstituted amidine to four products (5) does not necessarily proceed through that of the two tautomers assumed to be present. Marckwald's experiment involving the acidic hydrolysis of an amidine of this structure is a typical example. In this case it is not the free amidine which hydrolyzes, but its amidinium cation which is the same whether the original amidine exists as a tautomeric mixture or as one of the two possible tautomers. The amidinium cation should then hydrolyze according to the following mechanism which is similar to that given for the acidic hydrolysis of amides

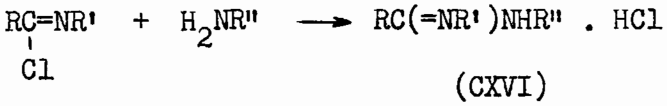


$$\overset{\delta+}{R'NH}\cdots\underset{\underset{R''}{|}\,\overset{\delta+}{NH}}{\overset{R}{C}} + OH_2 \rightarrow \overset{\delta+}{R'NH}\cdots\underset{\underset{R''}{|}\,\overset{\delta+}{NH}}{\overset{R}{C}}\cdots\overset{\delta+}{OH_2} \rightarrow RCONHR' + R''NH_2 + RCONHR'' + R'NH_2 + H^+$$

(CXVIII)

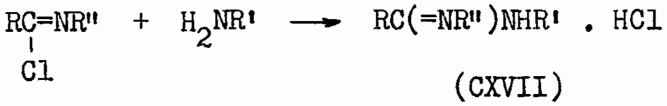
The distribution of the electron deficiency over the three centres will, of course, depend on the electronegativities of the nitrogen and oxygen atoms and the inductive effect of the substituents. Thus, the amount of the products formed during the hydrolysis will be related to the extent to which the carbon-nitrogen single bonds are weakened. This mechanism is most likely even in neutral media due to the solvolysis of the basic amidines. It is thus obvious that hydrolysis does not provide any evidence for the mobility of the amidine system.

The attempts to isolate the two tautomers of an amidine have not failed because the amidine is a mixture of the two tautomers but because an amidinium cation was involved as an intermediate. For example the following reaction was generally used, and the free amidine was liberated by treatment with base.



$$\mathrm{R\underset{\underset{Cl}{|}}{C}{=}NR'} + \mathrm{H_2NR''} \longrightarrow \mathrm{RC({=}NR')NHR''\ .\ HCl}$$

(CXVI)



$$\mathrm{R\underset{\underset{Cl}{|}}{C}{=}NR''} + \mathrm{H_2NR'} \longrightarrow \mathrm{RC({=}NR'')NHR'\ .\ HCl}$$

(CXVII)

But (CXVI) and (CXVII) yield the same amidinium cation (CXVIII), which on neutralization gives the more stable product.

A unique example of the isolation of two tautomers (XVI, XVII) was reported by Barber (13), but no decisive conclusions could be drawn due to the ease with which the unstable tautomer passed into the stable form. However the following important remarks can be mentioned.

a) The reaction which leads to the temporary isolation of the unstable tautomer does not involve an amidinium cation intermediate.

b) The $ArSO_2$-group does not operate so as to immobilize (1) the amidine hydrogen atom, but accelerates the tautomeric change by withdrawing electrons from the dissociation centre.

c) There is evidence that the imino form (XVII) is the most stable.

The above-mentioned are in accord with this theoretical discussion and with the structures assigned to the N-substituted trichloro-, and trifluoro-acetamidines.

The results of the alkylation of an amidine are also ambiguous, since the reaction is complicated and the hydrogen halide evolved during the procedure must form salts with the products as well as with the reactants which influences the reactive centres.

Finally, the following conclusions can be made.

a) For the present time there is no reason to believe that the mobility of the amidine system is so high that the amidine exists as a mixture of the two tautomers.

b) Reactions not involving the intermediate formation of an amidinium cation are needed for the preparation of the two tautomers of an amidine and the tautomeric studies.

c) Accumulated evidence indicates that N-substituted amidines exist in the form $RC(=NH)NHR_1$, which is the more stable thermodynamically.

d) Since the mobility of a hydrogen on a triad system depends on basic catalysis, the more thermodynamically stable form will always be favoured, due to the basic nature of the amidines themselves.

e) An amidine might exist as a tautomeric mixture when both tautomers possess the same or about the same thermodynamic stability.

The identity of the tautomers obtained by Wheeler and Johnson (149) may be explained by paragraphs (d) or (e) or both.

EXPERIMENTAL

Infrared Absorption Spectra Determinations

The infrared absorption spectra were taken on a Perkin-Elmer model 21 double beam spectrophotometer equipped with a sodium chloride prism. The settings of the instrument during measurements were as follows: response 1:1, gain 4.5-5, speed 5-6, resolution 927 and suppression 0. The scale was 100 cm.$^{-1}$/1 cm. in the absorption range 4000-2000 cm.$^{-1}$ and 100 cm.$^{-1}$/ 4 cm. in the range of 2000-600 cm.$^{-1}$

Solid trichloroacetamidines were examined in potassium bromide pellets. Nujol mulls were prepared for the spectra of solid trifluoroacetamidines and the nitroacetonitrile salts. The mulls were spread between the sodium chloride plates of a mounted cell and a similar unit containing Nujol was used for compensation. The spectra of amidine hydrochlorides were examined in Fluorolube T-45 (Hooker-Electrochemical Co. of Niagara Falls, N.Y.) mulls. A similar cell provided excellent compensation in the region 4000-1400 cm.$^{-1}$

All spectra of the liquid compounds were determined by spraying a layer between the sodium chloride plates of a mounted cell. Cells of constant width (1 mm.) were used for the determination of the spectra of all the compounds in solution. The substance (10 mg.) was weighed accurately in 1 ml. glass-stoppered volumetric flask and dissolved by addition of 1 ml. of tetrachloroethylene. A similar compensation cell containing pure solvent was used in all cases.

A. Synthesis of trichloroacetamidines

Ethyl trichloroacetate (128)

A strong stream of dry gaseous hydrogen chloride was passed for 3.5 hours through a mixture of 450 g. of trichloroacetic acid (2.76 moles) and 164 ml. of absolute ethanol (2.76 moles). The mixture was cooled by means of an ice-water bath. At the end of this time separation into two layers was observed. The slightly yellow coloured lower layer was separated by means of a separatory funnel and washed four times with distilled water until the washing water gave no acidic reaction with blue litmus paper. The liquid was distilled at normal pressure and the fraction boiling at 166-167° was collected. Reported b.p. 167.5-168° (corrected). Yield 456 g., 87%.

Trichloroacetamide (129)

Ethyl trichloroacetate (480 g.) was placed in a one-litre round-bottomed flask, and cooled in an ice-water bath. A strong stream of ammonia gas was passed through the liquid ester for a period of four hours. Trichloroacetamide started to precipitate immediately in the form of fine colourless crystals.

The alcohol liberated was poured out and the product was dried in vacuum desiccator. M.p. 136°; yield 400 g., 90%.

Trichloroacetonitrile (129)

Trichloroacetamide (395 g., 2.37 moles) was placed in a two-litre round-bottom Pyrex flask and mixed with about 340 g. of phosphorus pentoxide (2.37 moles).

The mixture was shaken well and left for six hours at room temperature. The flask was then connected for distillation at normal pressure and was heated by means of an electric mantle. The trichloroacetonitrile obtained was redistilled and the portion boiling at 86° was collected.

Yield 252 g., 75% of the theoretical.

I. Preparation of trichloroacetamidines in water solutions

N,N-Dimethyl-α,α,α-trichloroacetamidine

Trichloroacetonitrile (7.2 g., 0.05 moles) was placed in 4 ml. of a 25% water solution of dimethylamine containing 2.25 g. of the amine. The mixture separated into two layers and was shaken vigorously for one hour. A slightly exothermic reaction took place, enough to keep the mixture at about 30°. It was then left to cool at room temperature and the lower layer was separated by means of a separatory funnel.

The crude liquid obtained was distilled under nitrogen atmosphere at 2 mm. Hg. The heating started one hour after the application of the vacuum to remove the low boiling point reactants and the water. 6.45 g. of a transparent colourless liquid possessing the characteristic smell of amidines was collected. B.P. 51-52°. Yield 68%.

After a second distillation the product was analyzed for nitrogen.

Calc. for $C_4H_7Cl_3N_2$: N, 14.77%

Found: N, 14.67%.

N,N-Dimethyl-α,α,α-trichloroacetamidinium picrate

N,N-dimethyl-α,α,α-trichloroacetamidine (1 g.) was diluted with 10 ml. of benzene and treated with an equimolar quantity of picric acid in the same solvent. The yellow crystals precipitated had m.p. 157-159° and after two recrystallizations from water showed a m.p. 162-163° (dec.).

N-Methyl-α,α,α-trichloroacetamidine

To 15 ml. of a 25% water solution of methylamine, 8 ml. of trichloroacetonitrile (11.1 g.) was added dropwise from a funnel over a period of ten minutes. The solution was stirred and the reaction became so exothermic that it had to be cooled with an ice-water bath.

During the addition of the trichloroacetonitrile, separation of a layer was observed; when all the nitrile had been added the stirring was continued for two more minutes. The lower layer was separated by means of a separatory funnel, one gram of anhydrous sodium sulphate was added and it was left overnight. The solid drying reagent was filtered off and the colourless liquid was distilled at 129° and 60 mm. Hg pressure in a dry nitrogen atmosphere. Yield 11.5 g., 86% of the theoretical.

Calc. for $C_3H_5Cl_3N_2$: N, 15.93%

Found: N, 15.85%.

N-Methyl-α,α,α-trichloroacetamidinium picrate

To N-methyl-trichloroacetamidine (1 g.) in 10 ml. of benzene an equimolar quantity of picric acid in benzene was added slowly. The precipitated yellow picrate was filtered off and dried. The melting point of the crude product was 150-153°; after two recrystallizations from water it melted at 163-164°. Reported m.p. 163-164° (73).

N-Ethyl-α,α,α-trichloroacetamidine

Into 10 ml. of a 72% water solution of ethylamine trichloroacetonitrile (8.5 ml., 12.1 g.) was added dropwise under continuous vigorous stirring. The reaction became so exothermic that it had to be cooled with an ice-water bath. The lower layer formed was separated by means of a separatory funnel, dried over one gram of anhydrous sodium sulphate, filtered off and distilled at low pressure in a dry nitrogen atmosphere. After a second distillation 11.9 g. (74%) of a colourless transparent liquid, boiling at 62° at 2 mm. Hg was collected.

Calc. for $C_4H_7Cl_3N_2$: N, 14.77%

Found: N, 14.68%.

N-Ethyl-α,α,α-trichloroacetamidine hydrochloride

Through one gram of N-ethyl-α,α,α-trichloroacetamidine in 30 ml.

of dry ether a slow stream of dry hydrogen chloride gas was passed until no further precipitation occurred. The white salt was filtered, washed twice with a small amount of dry ether and dried in vacuum. Ten degrees below its melting point the colourless salt became dark brown and melted finally at 222° (dec.).

II. Preparations in the absence of solvents

N-Isopropyl-α,α,α-trichloroacetamidine

Trichloroacetonitrile (7.2 g., 0.05 moles) was added dropwise under continuous stirring into 2.95 g. (0.05 moles) of isopropylamine cooled in an ice-water bath. The liquid product formed with evolution of heat solidified quickly to colourless crystals. The unreacted volatile substances were evaporated in vacuum to give 9.3 g. of the crude amidine. M.p. 50-55°, yield 91.6%. The product was purified by repeated sublimation at 45-48°/2 mm. Hg giving well developed colourless crystals melting at 56°. Yield 90%.

Calc. for $C_5H_9Cl_3N_2$: N, 13.77%

Found: N, 13.92%.

N-n-Butyl-α,α,α-trichloroacetamidine

Trichloroacetonitrile (7.2 g., 0.05 mole) was added dropwise with continuous stirring into a small three-necked flask containing 3.65 g., (0.05 mole) of n-butylamine. The reaction mixture was cooled in an ice-water bath. The flask was then arranged for vacuum distillation.

After the elimination of the unreacted volatile substances at low pressure in nitrogen atmosphere the flask was heated slowly in an oil bath and 9.98 g. of a colourless transparent liquid boiling at 71-72°/2 mm. Hg was collected. Yield 92%.

Calc. for $C_6H_{11}Cl_3N_2$: N, 12.87%

Found: N, 12.67%.

N-n-Amyl-α,α,α-trichloroacetamidine

The substance was prepared by the procedure described previously except that the mixture was cooled at about 0°. The addition of trichloroacetonitrile in an equimolar quantity of n-amylamine lasted for fifteen minutes. The colourless transparent liquid boiled at 89-90°/2 mm. Yield 94%.

Calc. for $C_7H_{13}Cl_3N_2$: N, 12.09%

Found: N, 11.97%.

N,N-Diethyl-α,α,α-trichloroacetamidine

Diethylamine (3.66 g., 0.05 mole) was mixed with an equimolar amount of trichloroacetonitrile (7.2 g., 0.05 mole) and the mixture was left for three hours at room temperature. An exothermic reaction took place, while the mixture turned yellow. The unreacted compounds were eliminated in vacuum at room temperature in a distillation apparatus and the product distilled had a b.p. 61-61.5°/2 mm. Yield 91%.

Calc. for $C_6H_{11}Cl_3N_2$: N, 12.87; C, 33.12; H, 5.09%

Found: N, 12.69; C, 32.77; H, 4.84%.

N,N-Diethyl-α,α,α-trichloroacetamidine picrate

The free amidine (2 g.) was diluted in 15 ml. of benzene and added dropwise under stirring to an equimolar amount of picric acid in benzene. The yellow solid precipitate was filtered, dried and recrystallized twice from water, in the form of yellow needles melting at 153° (corrected).

N-Benzyl-α,α,α-trichloroacetamidine

Benzylamine (3.57 g., 0.033 mole) was added dropwise under stirring and cooling into an equivalent (0.033 mole) amount of trichloroacetonitrile. The mixture solidified in three minutes into a yellow crystalline substance, which was dissolved in a small volume of methanol and precipitated by addition of distilled water with continuous stirring.

A second precipitation from methanol by addition of water gave colourless crystals melting at 83.5°.

Calc. for $C_9H_9Cl_3N_2$: C, 42.98; H, 3.60; N, 11.19%

Found: C, 43.22; H, 3.64; N, 11.14%.

N-Piperidino-α,α,α-trichloroacetamidine

Equimolar quantities (0.02 mole) of trichloroacetonitrile and piperidine were mixed and left at room temperature for twenty-four hours. The reaction was exothermic. Fractionation of the mixture at low pressure and in nitrogen atmosphere gave a colourless product boiling at 80-81°/1.5 mm. Yield 87%.

Calc. for $C_7H_{11}Cl_3N_2$: N, 12.20%

Found: N, 12.09%.

N-Piperidino-α,α,α-trichloroacetamidine picrate

Benzene solutions containing equimolar quantities of the amidine and picric acid were mixed under stirring. The yellow crystals were filtered off and recrystallized twice from water. M.p. 140-140.5°. Reported m.p. 139.5-140° (73).

N-Morpholino-α,α,α-trichloroacetamidine

The substance was obtained by the procedure described previously in the preparation of the N-piperidino compound. The mixture was fractionated and the liquid boiling at 89°/1 mm. was collected. Yield 92%.

Calc. for $C_6H_9Cl_3N_2O$: N, 12.10%

Found: N, 11.99%.

III. Preparation of amidines in various solvents

N-Benzyl-α,α,α-trichloroacetamidine

Benzylamine (5.36 g., 0.05 mole) was dissolved in 30 ml. of methanol in a 100 ml. conical flask and cooled in an ice-water bath. Addition of trichloroacetonitrile (7.22 g., 0.05 mole) dropwise with stirring over a period of five minutes caused an exothermic reaction. When allthe nitrile had been added, addition of fifteen ml. of distilled water resulted in the precipitation of almost colourless crystals, which were separated by filtration and dried. The crystals melted at 76-81°.

The product was dissolved in a small volume of methanol and reprecipitated by addition of distilled water dropwise with stirring. M.p. 83.5° (corrected). Yield 89%.

N-Phenyl-α,α,α-trichloroacetamidine

Trichloroacetonitrile (50 ml., 0.5 mole) and 46 ml. of freshly-distilled aniline (0.5 mole) were dissolved in 60 ml. of methanol and 25 ml. of distilled water in a 300 ml. round-bottom flask, and left at room temperature for three days.

A large amount of crystals precipitated; addition of 50 ml. of water caused further precipitation. The almost colourless crystalline precipitated was filtered off and recrystallized twice from a methanol-water mixture or petroleum ether. Yield 107 g., 90% of the theoretical. M.p. 101-102 (corr.). Reported (67) m.p. 101°.

Calc. for $C_8H_7Cl_3N_2$: C, 40.45; H, 2.98; N, 11.80%

Found: 40.60; H, 3.07; N, 11.80%.

N-Phenyl-α,α,α-trichloroacetamidine hydrochloride

A stream of dry hydrogen chloride was passed through a solution of one gram of N-phenyl-α,α,α-trichloroacetamidine in 50 ml. of dry ether until no further precipitation occurred. The white salt was filtered off, washed twice with 10 ml. of dry ether and dried in vacuum.

The product turned brown 10-15° below its melting point and darker at higher temperatures melting finally at 183°. Reported (67) m.p. 183 (dec.).

N-m-Tolyl-α,α,α-trichloroacetamidine

Trichloroacetonitrile (7.22 g., 0.05 mole) was added to a freshly redistilled m-toluidine (5.36 g., 0.05 mole) in fifteen ml. of methanol and the solution was left for six days at room temperature.

Addition of one ml. of distilled water caused the precipitation of a solid product which was separated by filtration. When fifteen ml. of water was added to the filtrate a second crop of almost pure white crystals was precipitated and collected by filtration. The total yield of the crude product was 11.54 g., or 95%. M.p. 97-99°. After three recrystallizations from ligroin (b.p. 100-120°) the compound melted at 100° (corrected).

Calc. for $C_9H_9Cl_3N_2$: N, 11.13%

Found: N, 10.96%.

N-m-Tolyl-α,α,α-trichloroacetamidine hydrochloride

A stream of dry hydrogen chloride was passed through 30 ml. of dry ether containing 100 mg. of the amidine. The mixture was cooled in ice-water bath and stirred continuously by a magnetic stirrer. When no further precipitation occurred the white crystals were filtered off, washed with two portions of 5 ml. of dry ether, and dried in vacuum. M.p. observed

193-195° (dec.).

N-o-Tolyl-α,α,α-trichloroacetamidine

Trichloroacetonitrile (1.44 g., 0.01 mole) was added to a solution of 1.08 g. of freshly redistilled o-toluidine (0.01 mole) in 5 ml. of methanol and left at room temperature for four days. The volatile solvent and nitrile were eliminated by vacuum distillation to leave a yellow solid melting at about 50°. It was dissolved in 5 ml. of methanol and precipitated by dropwise addition of distilled water under continuous stirring. This was repeated once more. The colourless crystalline solid (1.73 g., 83% in yield) melted at 73° (corrected). After one sublimation at 70°/2 mm. a sample was analyzed for nitrogen.

Calc. for $C_9H_9Cl_3N_2$: N, 11.13%

Found: N, 11.13%.

N-o-Tolyl-α,α,α-trichloroacetamidine hydrochloride

It was prepared by a method similar to that described above for the preparation of N-phenyl-2,2,2-trichloroacetamidine hydrochloride. M.p. observed 214-216° (dec.).

N-p-Tolyl-α,α,α-trichloroacetamidine

p-Toluidine (5.36 g., 0.05 mole) and an equimolar amount of trichloroacetonitrile were dissolved in fifteen ml. of methanol and left at room temperature for three days. After twenty-four hours the first crystals precipitated in the form of big colourless parallelograms. At the end of the three-day period ten ml. of distilled water was added, the white solid filtered off and dried in vacuum. 11.66 g. of a very pure product melting at 135-137° was collected. Yield 92%. Two recrystallizations from ligroin (b.p. 100-120°) raised the m.p. to 138.5° (corrected).

Calc. for $C_9H_9Cl_3N_2$: N, 11.13%

Found: N, 10.99%.

N-p-Ethoxyphenyl-α,α,α-trichloroacetamidine

Freshly distilled p-phenetidine (6.86 g., 0.05 mole) was dissolved in 10 ml. of methanol; 7.2 g. (0.05 mole) of trichloroacetonitrile was then added and the mixture left at room temperature for four days. The solid precipitated was then filtered off, washed with 10 ml. of ethanol-water (1:5) mixture and dried to give 13.12 g. (94%) of the crude product.

It was recrystallized from ligroin (b.p. 90-95°) to give a very pure compound melting at 104° (corrected). A small quantity was sublimed at 100°/2 mm. (m.p. 104°).

Calc. for $C_{10}H_{11}Cl_3N_2O$: N, 9.95%

Found: N, 9.90%.

N-(2-Thiazolyl)-α,α,α trichloroacetamidine

2-Aminothiazole (2 g., 0.02 mole) was dissolved in a mixture of

10 ml. of ether and 3 ml. of methanol together with 2.88 g. (0.02 mole) of trichloroacetonitrile and left at room temperature for two weeks.

The solution was then subjected to fractional distillation at progressively reduced pressure in nitrogen atomosphere. After the evaporation of the volatile solvents and the unreacted nitrile 4.2 g. (86%) of a light yellow liquid was distilled over which solidified immediately. The product was dissolved in methanol and precipitated by addition of distilled water under stirring to obtain an almost white solid which was sublimed at 80°/2 mm. The first portion (m.p. 85-90°) sublimed was rejected and the sublimation continued to give pure white crystals melting at 87°.

Calc. for $C_5H_4Cl_3N_3S$: N, 17.2%

Found: N, 17.2%.

Mixed melting point of the product with 2-aminothiazole (m.p. 90°) showed a melting range 60-70°.

N-[2-(5-Methylpyridyl)]-α,α,α-trichloroacetamidine

2-Amino-5-methylpyridine (2.16 g., 0.02 mole) was dissolved in 6 ml. of acetonitrile and 2.88 g. (0.02 mole) of trichloroacetonitrile and left at room temperature for four days. Then, addition of distilled water (10 ml.) caused the precipitation of a light yellow liquid which solidified in ten minutes to a soft yellow crystalline substance. The compound was filtered, dissolved in a small amount of methanol and reprecipitated by addition of distilled water. 4.1 g. of an almost colourless product melting at 78-79° was collected. Yield 81%. Two sublimations at 70°/2 mm. raised the melting point to 83.5°.

Calc. for $C_8H_8N_3Cl_3$: N, 16.64%

Found: N, 16.66%.

Methyl trichloroacetimidate (66, 67)

Trichloroacetonitrile (5 g.) was dissolved in 14 ml. of methanol and refluxed for ten hours. Fractional distillation of the mixture yielded 4.7 g. (77%) of methyl trichloroacetimidate boiling at 147-149°.

Reactions of trichloroacetonitrile and di-n-amylamine

Di-n-amylamine (3.15 g., 0.02 mole) was mixed with an equivalent amount of trichloroacetonitrile (2.88 g., 0.02 mole) and left at room temperature for forty-four hours. The mixture turned black and the solid substance deposited was separated by filtration, and washed twice with a small amount of dry ether. A white product (1.5 g.) soluble in water and insoluble in non-polar solvent was collected. M.p. 272-274°. Reported m.p. for di-n-amylamine hydrochloride 275° (130).

Attempted fractional distillation of the liquid filtrate failed, due to decomposition.

Reaction of di-n-butylamine with trichloroacetonitrile

The same procedure as in the reaction of di-n-amylamine with trichloroacetonitrile was followed. Starting with 0.02 moles of the reactants, 1.4 g. of a white salt was isolated. M.p. 280-282°. Reported m.p. of di-n-butylamine hydrochloride 283-284° (131).

Methylamine hydrochloride and trichloroacetonitrile

Trichloroacetonitrile (4.81 g., 0.033 mole) was added to a solution of 2.27 g. of methylamine hydrochloride (0.033 mole) in 10 ml. of distilled water and 10 ml. of methanol. The mixture was allowed to stand at room temperature for two hours and then subjected to fractional distillation. The reactants were recovered almost quantitatively.

Ethylamine hydrochloride and trichloroacetonitrile

A mixture of 2.7 g. of ethylamine hydrochloride, 4.81 g. of trichloroacetonitrile, 10 ml. of water and 10 ml. of methanol was prepared and left at room temperature for two hours. The four components of the mixture were recovered by fractional distillation almost quantitatively.

Reaction of trichloroacetonitrile and piperidine in methanol

Piperidine (4.25 g.) was added quickly to a solution of 7.7 g. (0.5 mole) in 20 ml. of methanol. An exothermic reaction started which was allowed to complete in a two-hour period. Fractional distillation of the mixture gave 4 g. of piperidine and 7 g. (80%) of methyl trichloroacetimidate, b.p. 148-149°.

Reaction of trichloroacetonitrile and diethylamine

Equimolar quantities of the reactants in methanol were treated as in the reaction of trichloroacetonitrile and piperidine. About 75% of methyl trichloroacetimidate was isolated and most of the diethylamine.

Trichloroacetamidine (48, 72)

Dry ammonia was passed into a solution of trichloroacetonitrile (7.22 g., 0.05 mole) in 20 ml. of dry benzene for two hours at 0°, and the solvent was then removed in vacuum below 0°. A viscous oil was isolated and distilled at low pressure and in a nitrogen atmosphere. The product solidified quickly into a soft solid, m.p. 41-43°. Yield 65%.

Trichloroacetamidine picrate (48)

Solid trichloroacetamidine (1 g.) in 20 ml. of benzene was treated with a benzene solution containing an equivalent amount of picric acid. The picrate was crystallized from water twice to yellow needles which melted at 273-275° (dec.).

Preparation of N-Phenyl-α,α,α-trichloroacetamidine in the absence of solvents

Trichloroacetonitrile (1.44 g., 0.01 mole) was mixed with 0.93 g. of aniline (0.01 mole) and left at room temperature for 5 days. The mixture turned red, brown and finally black and after 48 hours, crystals started to precipitate in small quantity. The mixture was diluted with

7 ml. of methanol and the product was precipitated by addition of water, filtered, and crystallized from a water-methanol mixture. M.p. 101-102°. Yield 1.27 g. (54%).

Preparation of N-Phenyl-α,α,α-trichloroacetamidine in ethanol

Equimolar quantities of the reactants were dissolved in 5 ml. of ethanol and left at room temperature for five days, when the product was precipitated by the addition of water. Filtration and recrystallization of the crude product gave 1.8 g. (76%) of the amidine which showed a m.p. 101-102°.

B. Synthesis of trifluoroacetamidines

Ethyl trifluoroacetate

Absolute ethanol (52 ml., 0.877 mole) was added in small portions to 200 ml. of concentrated sulphuric acid while the mixture was kept in an ice-water bath and stirred continuously. After the addition of an equimolar amount (0.877 mole) of trifluoroacetic acid, it was left in a closed flask for six hours at room temperature. Two layers were formed, the top one containing mainly ethyltrifluoroacetate.

The flask was provided with a Widmer column and the content was fractionated over a period of six hours. The crude ester, boiling at 60-68°, was collected in a receiver, immersed in an ice-water bath to prevent evaporation during the distillation period. The ester was then washed once with 100 ml. of cold sodium carbonate solution (5%), dried over 15 g. of calcium chloride and redistilled, finally, over 10 g. of phosphorus pentoxide. The ester boiling at 61-62.5° was collected. Yield 108 g. (86%).

Trifluoroacetamide (132)

Ethyl trifluoroacetate (108 g., 0.76 mole) was mixed with 70 ml. of anhydrous ether. The mixture cooled in an ice-water bath, was saturated with a stream of dry gaseous ammonia over a period of two hours. The resulting clear colourless solution was then distilled by heating in a water bath at 60-70°. When no more distillate was collected at this temperature, the pressure was reduced by an aspirator and the heating at 60-70° was continued until the residue in the flask began to crystallize. At this point the heating bath was removed, but the vacuum was maintained until crystallization was complete. 64.4 g. of trifluoroacetamide, melting at 75°, was collected. The distillate was redistilled to give an additional 13 g. of trifluoroacetamide, which was carried over during the first distillation. The total yield was 77.4 g. or 90% of the theoretical.

Trifluoroacetonitrile (132)

A mixture of 60 g. of powdered trifluoroacetamide and 150 g. of phosphorus pentoxide was placed in a one-litre round-bottomed flask provided with a coil condenser, from the top which a tygon tube led to a trap cooled in an ice-salt mixture. This trap, in turn, was connected to two other traps in series cooled in dry ice-acetone baths. A calcium chloride tube protected the end trap, and consequently the whole system, from atmospheric moisture.

The flask containing the reaction mixture was heated gradually in an oil-bath up to 145-150° and held at this temperature for three hours. The trifluoroacetonitrile was evolved rapidly at first and was collected as a colourless liquid in the first dry-ice acetone trap. The yield was 36 g. or 72% of the theoretical. Part of the trifluoroacetamide (1-2 g.) sublimed unchanged and accumulated at the entrance of the condenser.

N-Butyl-α,α,α-trifluoroacetamidine

A fine stream of trifluoroacetonitrile was passed through 2.9 g. of pure n-butylamine kept in a test tube which was surrounded with an ice-water mixture. The reaction was exothermic.

The stream of trifluoroacetonitrile was stopped after ten minutes and the crude liquid was transferred into a semi-micro distillation apparatus and distilled at low pressure in a dry nitrogen atmosphere.

5.5 g. of a colourless liquid boiling at 39-40° at 2 mm. pressure was collected and redistilled. It possessed the characteristic smell of the liquid amidines. Yield 82%.

Calc. for $C_6H_{11}F_3N_2$: N, 16.65%

Found: N, 16.41%.

N-Ethyl-α,α,α-trifluoroacetamidine

Trifluoroacetonitrile (6 g.) was condensed in an 80 ml. cylindrical flask immersed in a dry ice-acetone bath and fitted with a delivery tube and dry ice-cooled reflux condenser. A slight excess of liquid ethylamine (3 g.) was then added and the mixture allowed to reflux for one hour. The system was protected from atmospheric moisture by a calcium chloride tube.

The excess of ethylamine was distilled from the mixture and the remaining liquid fractionated at normal pressure to yield 8 g. of the colourless N-ethyltrifluoroacetamidine. The product was redistilled at 125-126°, yield 90%.

Calc. for $C_4H_7F_3N_2$: N, 20%

Found: N, 19.83%.

N-Ethyl-α,α,α-trifluoroacetamidine hydrochloride

A stream of dry gaseous hydrogen chloride was passed through a small quantity (100 mg.) of N-ethyltrifluoroacetamidine dissolved in 10 ml. of dry ether until no further precipitation was observed. The mixture was cooled by means of an ice-salt bath and stirred continuously by a magnetic stirrer. The fine white cyrstals were filtered, washed twice with dry ether and dried in vacuum. M.p. 189-191° (dec.).

N-Methyl-α,α,α-trifluoroacetamidine (75, 76)

Trifluoroacetonitrile (5 g.) was condensed in a 40 ml. cylindrical glass flask immersed in a dry ice-acetone bath. The flask was provided with a delivery tube and dry ice-cooled reflux condenser and protected from atmospheric moisture by a calcium chloride tube. Twice an equimolar quantity (3.1 g., 0.1 mole) of dry gaseous methylamine was then condensed in the flask and the mixture was allowed to reflux for one hour. Excess methylamine was distilled from the mixture and the remaining high boiling liquid was fractionated under reduced pressure. 6 g. (95%) of N-methyl-α,α,α-trifluoroacetamidine boiling at 39-40° at 15 mm. Hg was collected.

N-Methyl-α,α,α-trifluoroacetamidine hydrochloride

A stream of dry hydrogen chloride was passed through a solution of N-methyltrifluoroacetamidine in dry ether, which was cooled in an ice-salt bath. The mixture was stirred continuously by a magnetic stirrer and the hydrogen chloride stream was stopped when precipitation was complete.

The fine white crystals were filtered out, washed twice with dry ether and dried in vacuum. The hydrochloride melted at 219-221° with the evolution of a gas.

N-Benzyl-α,α,α-trifluoroacetamidine

A solution of 2.15 g. of benzylamine (0.02 mole) in 10 ml. of benzene was prepared and placed in a 100 ml. pear-shaped glass flask, which was closed tightly with a ground glass stopper provided with a delivering tube. The end of this tube was connected to a tightly closed long glass tube (20") by means of tygon tubing. The long tube which was immersed in a dry ice-acetone mixture contained an equimolar amount of trifluoroacetonitrile.

The benzene solution was kept at room temperature and stirred continuously by a magnetic stirrer. A slight over-pressure of trifluoroacetonitrile was kept in this closed system; the pressure was controlled by keeping the surface of the liquid nitrile slightly above the surface of the acetone in the cooling mixture.

A slow exothermic reaction was noticed in the reaction vessel. After half an hour the trifluoroacetonitrile had been used but the reaction was continued for 30 minutes more.

Then, the benzene solution was transferred to a 20 ml. flask and distilled at 20 mm. reduced pressure at room temperature. When the benzene solution had evaporated the temperature of the liquid bath was raised slowly, while the pressure was decreased to 3 mm. Hg. The distillation which took place in a dry nitrogen atmosphere, gave 3.84 g. of a colourless liquid boiling at 88-90° at 3 mm. pressure, which solidified to white transparent crystals in a few hours. This crystalline solid after two sublimations under vacuum (2 mm. at room temperature) gave very pure N-benzyltrifluofoacetamidine, m.p. 51°. Yield of the liquid product 91%.

Calc. for $C_9H_9F_3N_2$: N, 13.86%

Found: 13.78%.

N-Phenyl-α,α,α-trifluoroacetamidine

Trifluoroacetamide (8.5 g.) was mixed with 20 g. of phosphorus pentoxide in a 200 ml. round bottom flask provided with a coil condenser from the top of which Tygon tubing extended. The other end of the Tygon tubing was connected to a glass tube which passed through a tightly placed rubber stopper and stopped 10 cm. from the bottom of a 20" high pressure tube with a side arm at the top carrying a calcium chloride tube to protect the system from atmospheric moisture. The high pressure tube contained 5 g. of aniline in 20 cc. of methanol and was immersed in a dry ice-acetone mixture.

The round-bottomed flask was then heated by means of an oil bath to 140-150° for three hours. The trifluoroacetonitrile produced was thus condensed in the high pressure tube which was sealed at the end of the reaction and left at room temperature for 4 days. The sealed tube was then cooled once more in order to condense any unreacted trifluoroacetonitrile, opened and the methanol was removed at reduced pressure by an aspirator.

An almost white crystalline product was collected together with the unreacted aniline. The crystals were washed twice with 25 ml. of distilled water to eliminate the aniline. The product showed a high degree of purity and melted at 78-80°. Yield of the crude substance was 9.2 g. or 91%. The N-phenyltrifluoroacetamidine melted at 91° after two sublimations.

Calc. for $C_8H_7F_3N_2$: N, 14.89%

Found: N, 14.80%.

N-Phenyl-α,α,α-trifluoroacetamidine hydrochloride

N-phenyl-α,α,α-trifluoroacetamidine (50 mg.) was dissolved in 10 ml. of dry ether and cooled with continuous stirring at 0°. A stream of dry hydrogen chloride was passed through this solution until no more hydrochloride was precipitated. The white solid substance was filtered, washed twice with a small amount of dry ether and dried in vacuum. It melted at 179-180° decomposing with the evolution of a gas, to a solid compound which sublimed on further heating to 300-320°.

Attempted preparation of N-(p-nitrophenyl)-α,α,α-trifluoroacetamidine

p-Nitroaniline (2.76 g., 0.02 mole) dissolved in 20 ml. of acetonitrile was placed in a long high pressure tube similar to the one used in the preparation of N-phenyltrifluoroacetamidine. An approximately equimolar amount of trifluoroacetonitrile was then condensed in the tube using the apparatus described previously. The tube was then sealed and left at room temperature for two weeks.

At the end of this time the liquid mixture was cooled in a dry ice-acetone mixture and when it reached room temperature the tube was opened and 20 ml. of distilled water was added. The precipitated yellow compound was removed by filtration, dried, and recrystallized from a mixture of equal volumes of methanol and water. The dried crystalline solid (2.4 g.) had a m.p. of 147-148°. Reported m.p. for p-nitroaniline is 148°.

N-[2-(5-Methylpyridyl)]-2,2,2-trifluoroacetamidine

2-Amino-5-methylpyridine (2.16 g., 0.02 mole) was dissolved in 10 ml. of acetonitrile in a high pressure tube similar to the one used in the preparation of N-phenyltrifluoroacetamidine. The same apparatus was used. An approximately equivalent (0.01 mole) amount of trifluoroacetonitrile was condensed in the tube which was sealed and left at room temperature for ten days.

At the end of this period the mixture was cooled in a dry ice-acetone bath for one hour. The tube was then opened and left at room temperature for another hour to eliminate the unreacted trifluoroacetonitrile.

Addition of 20 ml. of water to the reaction mixture caused the separation of a liquid layer which solidified in five minutes. The crude yellow-white crystalline product, m.p. 95-98°, was dissolved once more in a small amount of acetonitrile and precipitated again by addition of distilled water. Yield of the product after the second precipitation was 3.2 g. (71%). It was sublimed twice at 2 mm. pressure and 95-98° to a white crystalline solid, m.p. 102°.

Calc. for $C_8H_8F_3N_3$: N, 20.7%

Found: N, 20.85%.

Trifluoroacetamidine (74)

Equimolar quantities (0.1 mole) of trifluoroacetonitrile and dry gaseous ammonia were condensed in a 17 x 22 x 700 mm. Pyrex tube, which was then sealed and left at room temperature for four days. At the end of this period the end of the tube containing the reaction mixture was cooled in a liquid air bath, the tube was opened and the mixture allowed to reach room temperature in a dry nitrogen atmosphere. The viscous, colourless liquid was subsequently transferred to a semi-micro distillation apparatus and distilled at low pressure in a nitrogen atmosphere. B.p. 43-45°/15 mm. Yield 60%.

N,N-Dimethyl-α,α,α-trifluoroacetamidine (75, 76)

Into a 50 ml. cylindrical flask immersed in a dry ice-acetone bath and fitted with a delivery tube and dry ice-cooled reflux condenser 4.52 g. (0.05 mole) trifluoroacetonitrile was condensed. Dimethylamine (4.5 g., 0.1 mole) was then added and the mixture allowed to reflux for one hour.

Excess dimethylamine was distilled from the mixture and the remaining liquid was fractionated at normal pressure to yield 6.3 g. of a colourless liquid, boiling at 92°.

N,N-Dimethyl-α,α,α-trifluoroacetamidine hydrochloride

A stream of dry gaseous hydrogen chloride was passed into a solution of dimethyltrifluoroacetamidine in dry ether at 0° and stirred continuously by a magnetic stirrer until no further precipitation occurred. The precipitated white crystals were filtered out, washed twice with dry ether and dried in vacuum. M.p. 169-171° (dec.).

N,N-Diethyl-α,α,α-trifluoroacetamidine

Equimolar quantities (0.05 mole) of trifluoroacetonitrile and diethylamine were allowed to react in a sealed 17 x 22 x 700 mm. Pyrex tube at room temperature for twenty-four hours. The mixture was subsequently fractionated twice at normal pressure to give 7.6 g. of a colourless liquid boiling at 119°. Yield 91%.

Calc. for $C_6H_{11}F_3N_2$: N, 16.66%

Found: N, 16.73%.

N,N-Diethyl-α,α,α-trifluoroacetamidine hydrochloride

The method previously described for the preparation of hydrochloride was used. The white crystalline solid was washed twice with dry ether and dried in vacuum. M.p. 133-135° (observed).

N-Methyl-α,α,α-trifluoroacetamidine-d_2

Freshly prepared dry trifluoroacetonitrile (0.04 mole) was condensed in a Pyrex tube (17 x 22 x 700 mm.) previously flushed with dry nitrogen for half an hour, the lower part of which, 30 cm. in length, was immersed in a dry ice-acetone mixture. Methylamine-d_2 (2 ml.) was then allowed to condense in a long glass tube leading to about 5 cm. above the bottom of the Pyrex tube, the top of which was closed with a well-fitting rubber stopper carrying two short tubes of 4 and 0.5 mm. in diameter. The tubes allowed the slow circulation of dry nitrogen through the upper third of the Pyrex tube during the whole operation, thus preventing the condensation of atmospheric moisture in the reaction mixture. Finally the stream of nitrogen was stopped and the tube was sealed as quickly as possible, and left at room temperature for four hours.

The mixture was then transferred quickly to a semi-micro distillation apparatus and distilled at reduced pressure in a nitrogen atmosphere. B.p. 39-40° at 15 mm. Yield 80%.

Deuterium chloride salt of N-methyl-α,α,α-trifluoroacetamidine-d_2

About 100 mg. of N-methyltrifluoroacetamidine-d_2 was dissolved in 20 ml. of dry ethyl and cooled to about 0°. A stream of dry gaseous deuterium chloride was passed through this solution which was stirred continuously by a magnetic stirrer, until no further precipitation was observed.

The white solid salt was filtered, washed twice with a small quantity of dry ether and dried in vacuum. All the operations were conducted as quickly as possible in a dry nitrogen atmosphere. M.p. 219-221° (dec.).

The purity of the salt is believed to be very high.

C. Synthesis of dichloroacetamidines

Ethyl dichloroacetate (133)

Dichloroacetic acid (176 g., 1.36 mole) was mixed with absolute ethanol (80 ml., 1.36 mole) in a 500 ml. flask, and the mixture was cooled in an ice-water bath. A stream of dry hydrogen chloride gas was then passed through this mixture for four hours with continuous cooling and two layers separated.

The flask was then disconnected and 100 ml. of concentrated hydrochloric acid was added. The lower layer was separated by means of a separatory funnel, washed once with 100 ml. of 5% sodium bicarbonate solution and five times with distilled water (5 x 100 ml.) until there was no acidic reaction to litmus paper. The ester obtained was dried over 20 g. of calcium chloride, decanted in a 500 ml. round bottom flask and distilled. B.p, 157-158°, yield 167 g. 78% of the theoretical.

Dichloroacetamide

A stream of dry ammonia was passed for four hours through ethyl dichloroacetate (167 g.) in a 500 ml. round bottom flask cooled by means of an ice-water bath. The clear solution obtained was then distilled at reduced pressure produced by a water pump. The reddish crystals obtained after the elimination of the liquid phase were recrystallized once from benzene with charcoal treatment. M.p. 97.5°, yield 114 g. or 84% of the theoretical.

Dichloroacetonitrile (134)

Dichloroacetamide (84 g., 0.65 mole) was mixed with phosphorus pentoxide (144 g., 1 mole) in a one-litre round bottom flask arranged for distillation. The flask was then heated slowly by means of an electric mantle and the nitrile was collected as a colourless liquid in the receiver, which was protected from atmospheric moisture by a calcium chloride tube. A small amount of dichloroacetamide probably decomposed with evolution of hydrogen chloride.

The nitrile obtained was then treated with a small amount of anhydrous potassium carbonate and redistilled to give 60 g. of dichloroacetonitrile boiling at 112-113°. Yield 83% of the theoretical.

N-Methyl-α,α-dichloroacetamidine

Dichloroacetonitrile (6.87 g., 0.062 mole) was added to a 25% water solution of methylamine containing an equimolar amount of the amine; the nitrile formed a separate layer. When the mixture was shaken for a short time, a strong exothermic reaction was observed. The lower reddish-brown layer was then separated by means of a separatory funnel and distilled at reduced pressure in a dry nitrogen atmosphere.

4.8 g. of an almost colourless liquid was collected at 80-85°/ 6 mm. pressure. Yield 55%.

Part of the product decomposed in the distillation flask to a black tar, although a liquid bath was used. The compound isolated turned black on standing for two days.

N-Methyl-α,α-dichloroacetamidine picrate

Dichloroacetonitrile (0.0125 mole) was placed in a small conical flask containing an equimolar amount of methylamine (25% in water). The mixture was shaken for a few minutes with the evolution of heat. The reddish-brown bottom layer was removed by means of a separatory funnel, dissolved in 10 ml. of benzene, and added to 20 ml. of a benzene solution of picric acid containing an equimolar quantity of the acid. The picrate formed as a liquid and solidified on standing in an ice water bath. The crude picrate (2.8 g.) had a m.p. of 142-147°. The calculated yield of the N-methyl-2,2-dichloroacetamidine based on 1.07 g. of the crude picrate was 61% of the theoretical. The yellow salt was recrystallized three times from water. M.p. 164.5° (observed).

Calc. for $C_9H_9Cl_2N_5O_7$: N, 18.92%

Found: N, 18.73%.

N,N-Dimethyl-α,α-dichloroacetamidine

Dichloroacetonitrile (0.062 mole) was added to a 25% water solution of dimethylamine containing an equimolar amount of the amine, and shaken vigorously for half an hour. A slow exothermic reaction occurred. The lower red layer which formed was separated by means of a separatory funnel and distilled at 2 mm. in a nitrogen atmosphere. Almost all the product decomposed in the distilling flask to a black tar; 0.5 g. of a slightly yellow liquid was collected, but it changed to a tarry material after two days.

N,N-Dimethyl-α,α-dichloroacetamidinine picrate

Dichloroacetonitrile (1 ml., 0.0125 mole) was shaken with 2.3 ml. of a 25% water solution of dimethylamine (0.0125 mole) for one hour, with the evolution of heat. The lower brown layer was separated, washed twice with 4 ml. of distilled water and dissolved in 10 ml. of benzene. 2.8 g. of picric acid in 10 ml. of benzene was then added to the solution. The yield of the crude picrate, m.p. 142-150°, was 52%. It was recrystallized twice from water. M.p. 159-160° (observed).

Calc. for $C_{10}H_{11}Cl_2N_5O_7$: N, 18.19%

Found: N, 17.85%.

N,N-Diethyl-α,α-dichloroacetamidine

Diethylamine (3.65 g., 0.05 mole) was added to a solution of 4 ml. (0.05 mole) of dichloroacetonitrile in 60 ml. of benzene, and left at room temperature for five days in a well closed flask. The mixture was then fractionated under reduced pressure in a nitrogen atmosphere. 7.2 g. of a clear, very slightly yellow liquid, boiling at 80-83° at 5 mm., was collected. Yield 80%. The product decomposed to a black gummy mixture in three weeks.

N,N-Diethyl-α,α-dichloroacetamidine picrate

Benzene solutions containing equimolar amounts of the amidine and picric acid were mixed with stirring. The precipitated picrate was recrystallized twice from a water-methanol mixture. M.p. 127.5° (obs.).

Calc. for $C_{12}H_{15}Cl_2H_5O_7$: N, 17%

Found: N, 17%.

N-Piperidino-α,α-dichloroacetamidine

Piperidine (3.15 g., 0.037 mole) was added to 15 ml. of benzene containing 4.7 g. (0.037 mole) of dichloroacetonitrile in a 25 ml. conical flask. The mixture turned red after three days at room temperature. It was then fractionated at reduced pressure in a nitrogen atmosphere.

After the elimination of the volatile components 6.4 g. of a colourless liquid boiling at 63-66° at 1 mm. Hg was collected. Yield 88%. The product decomposed to a black tar in three weeks.

N-Piperidino-α,α-dichloroacetamidine picrate

Equimolar quantities of the amidine and picric acid in benzene were mixed slowly with stirring. The precipitated picrate was filtered and recrystallized twice from a water-ethanol mixture. M.p. 142°.

Calc. for $C_{13}H_{15}Cl_2N_5O_7$: N, 16.51%

Found: N, 16.57%.

N-Phenyl-α,α-dichloroacetamidine

Dichloroacetonitrile (0.025 mole) was added to a solution of 2.3 g. (0.025 mole) of aniline in 6 ml. of methanol and the mixture was left in a tighly closed flask at room temperature for one week.

After evaporation of the volatile components at reduced pressure a dark brown solid compound was collected as well as the unreacted aniline. It melted at 45-50°. The product was then sublimed and the small quantity of aniline and a portion of the desired compound were collected first. Continued sublimation of the remainder gave very pure white crystalline N-phenyl-α,α-dichloroacetamidine. M.p. 62° (observed). Yield 3 g., 60% of the theoretical.

Calc. for $C_8H_8Cl_2N_2$: N, 13.80%

Found: N, 13.86%.

D. Reaction of chloroacetonitrile with amines

Ethyl chloroacetate (135, 136)

Chloroacetic acid (211 g., 2.23 mole) was dissolved in 260 ml. absolute ethanol (4.46 mole) in a one-litre round bottomed flask and the mixture was cooled in an ice-water bath. After the addition of 50 ml. concentrated sulphuric acid the mixture was refluxed for five hours with a calcium chloride tube protecting the system from atmospheric moisture.

The mixture separated into two layers,and was allowed to cool to room temperature when 400 ml. of water was added. The lower layer was removed, washed twice with 100 ml. of water, twice with 100 ml. of 5% sodium bicarbonate solution and once with 100 ml. of water. The ester was then dried over anhydrous magnesium sulphate, filtered and distilled over a small fractionation head. The first 10 ml. were rejected and the ester boiling at 140.5-141° was collected. Reported b.p. 144.2 (corrected). Yield 210 g., 76.8% of the theoretical.

Chloroacetamide (137)

A) A stream of dry ammonia gas was passed for four hours through ethyl chloroacetate (200 g., 1.63 mole) at 0°. A small amount of crystals appeared but most of the product remained in solution.

When the ethanol produced was removed by fractional distillation, most of the chloroacetamide precipitated. After cooling in an ice-water bath to complete the crystallization, the white product was filtered out and the filtrate was fractionated. 120 g. of unreacted ester was recovered. The solid amide (45 g.) was washed twice with cold water and dried. 37 g. of chloroacetamide m.p. 117°-118° was collected. Yield 24%.

B) In a 2 l. round bottom three-necked flask fitted with a mechanical stirrer, thermometer and surrounded by an ice-salt bath 217 g. (1.75 mole) of ethyl chloroacetate was added and stirred vigorously. To the cold ester 200 ml. of chilled aqueous ammonia (sp. gr. 0.9) was added and the solution was stirred for about fifteen minutes, while the temperature was maintained below 5°. Another 200 ml. portion of chilled aqueous ammonia was added and the stirring was continued for another fifteen minutes. The mixture was then allowed to stand for 30 minutes while a heavy precipitate of colourless crystals formed. It was then filtered by suction and washed with two 25 ml. portions of cold water to remove most of the ammonium chloride.

Traces of ammonium chloride were removed by crystallization from 700 ml. of water. The yield of the air-dried compound was 115 g. or 70% of the theoretical. M.p. 119-120°.

Chloroacetonitrile (129, 138).

A) In a 1 l. round-bottomed three-necked flask fitted with an efficient mechanical stirrer, a reflux condenser, and a thermometer were placed 30 g. of chloroacetamide (0.32 mole), 50 g. of phosphorus pentoxide (0.32 mole) and 100 ml. of dry paraffin oil (b.p. 260-300°).

The mixture was then refluxed gently with vigorous stirring which was interrupted after half an hour because of the formation of a spongy mass.

The reaction mixture was allowed to cool to about 100° and then fractionated. The crude nitrile was separated from a small layer of paraffin oil which passed over during the fractionation, treated with sodium bicarbonate to neutralize the small amount of hydrogen chloride present, filtered and redistilled. 16 g. (67%) of chloroacetonitrile boiling at 123-124° was collected.

B) Chloroacetamide (50 g., 0.53 mole) and 90 g. phosphorus pentoxide (0.64 mole) were mixed well in a half-litre round-bottomed flask arranged for distillation. The mixture was then heated slowly by means of an electric mantle and the crude nitrile (33 g.) distilling at 123-124° was collected. It was then treated with 2 g. of sodium bicarbonate to neutralize any hydrogen chloride present,filtered and fractionated over

3 g. of phosphorus pentoxide. The nitrile boiling at 123-123.5° was collected. Yield 28.7 g., 71% of the theoretical.

Reaction of chloroacetonitrile and methylamine

Chloroacetonitrile (3.77 g., 0.05 mole) was placed in a 25 ml. three-necked flask provided with stirrer, thermometer and dropping funnel. To this solution, cooled to about 0°, 12.5 ml. of a 25% water solution of methylamine containing 3.1 g. of the amine (0.1 mole) was added dropwise with continuous stirring until the lower nitrile layer was dissolved completely. An exothermic reaction occurred and the mixture was left overnight.

The volatile constituents were then removed by the vacuum of an aspirator and the precipitated crystals were separated from a dark liquid with filtration by suction. The product was recrystallized once from absolute ethanol. M.p. 224-226°. Yield 70%. Reported m.p. for methylamine hydrochloride 226° (139).

Reaction of chloroacetonitrile and diethylamine

Diethylamine (7.31 g., 0.1 mole) was placed in a 25 ml. three-necked flask provided with thermometer, stirrer and dropping funnel and was cooled in an ice-water bath. 3.77 g. (0.05 mole) of chloroacetonitrile was then added dropwise with continuous stirring. The exothermic reaction was controlled in such a way that the temperature of the mixture did not exceed 40°. After four hours at room temperature the precipitated white crystals were filtered, washed four times with five ml. dry ether (4 x 5) and recrystallized once from absolute ethanol. M.p. 219-220°. Yield of the crude product 5.2 g., 95%. Yield of the crystallized product diethylamine hydrochloride 4.35 g., 79%.

The original filtrate together with the ether washings was separated from the solvent by distillation and then redistilled under reduced pressure. 6.2 g. of a colourless liquid boiling at 60-62° at 14 mm. was collected. Yield 81%. Reported b.p. for diethylaminoacetonitrile (62.5°/14 mm.) (84).

Diethylaminoacetonitrile hydrochloride (84)

A stream of dry hydrogen chloride was passed through an ethereal solution of the liquid isolated from the reaction between chloroacetonitrile and diethylamine. The colourless crystals were filtered and recrystallized once from absolute ethanol. M.p. 186-187°.

Reaction of chloroacetonitrile and ethylamine

Chloroacetonitrile (3.77 g., 0.05 mole) was added dropwise with continuous stirring to 2.25 g. of ethylamine (0.05 mole) cooled to about 0° by an ice-water bath. The reaction was allowed to proceed for four hours, after which the precipitate was filtered from the mother liquid, washed twice with a small amount of dry ether and dried. 1.5 g. of ethylamine hydrochloride was collected. M.p. 106-108°.

The filtrate was then fractionated to give 1.3 g. of colourless ethylaminoacetonitrile boiling at 61-62° at 13 mm. pressure.

Ethylaminoacetonitrile hydrochloride (140)

Dry gaseous hydrogen chloride was passed through a chilled ethereal solution of ethylaminoacetonitrile. The salt was crystallized from absolute ethanol once. M.p. 124-128°.

E. Reaction of nitroacetonitrile with amines

Methazonic acid (67, 95)

I. A solution of 20 g. NaOH in 40 ml. of water was added to a three-necked flask provided with a thermometer, electrical stirrer and a dropping funnel, and was warmed to about 45-50°. To this solution 20 g. of nitromethane was added dropwise during a period of 15 minutes with vigorous stirring. The rate of addition was so regulated that the temperature did not exceed 50°. This was accomplished by the aid of an ice-water mixture which was used whenever the temperature rose to 50°. At the end of the reaction the temperature was raised to 55° for 6-7 minutes. After addition of the nitromethane the reaction was left to go to completion until the solution started cooling. It was then cooled further to about 0° by an ice-salt bath. A small amount of sodium methazonate precipitated. To this cooled mixture 45 ml. of hydrochloric acid (sp. gr. 1.18) was added dropwise with constant vigorous stirring at such a rate that the temperature of the solution did not exceed 10°.

The methazonic acid was filtered by very strong suction, dried on a clay plate and later in a desiccator. The product, a creamy-white to yellow crystalline material was contaminated with NaCl, which was eliminated by dissolving the crystals in 70 ml. of absolute ether, and filtering. The ether solution was dried by calcium chloride and the product was recovered by evaporation.

II. To a three-necked flask provided with thermometer, dropping funnel and stirrer, a solution of 20 g. sodium hydroxide in 40 ml. of water was added. To the solution warmed to 47-48° 20 g. of nitromethane was added dropwise with stirring, in such a way that the temperature remained between 45-50°. The reaction mixture was then left to cool to room temperature and was further cooled to about 0° by means of an ice-salt mixture. 45 ml. of concentrated hydrochloric acid was then added drop by drop with vigorous stirring, in such a way that the temperature of the solution did not exceed +10° until the red colour had changed to yellow. The colourless methazonic acid deposited was filtered out by very strong suction, dried on a clay plate and dissolved in 100 ml. of ether after standing one hour. The solution was then dried over calcium chloride and the ether was removed by a dry air current. The operation was repeated once more and the substance was dissolved in 80 ml. of dry ether. Yield 6-8 g.

<u>Nitroacetonitrile</u> (63, 95)

15 g. of methazonic acid was dissolved in 75-80 ml. of absolute ether and heated to boiling in a flask provided with a condenser and a dropping funnel. The condenser was equipped with a calcium chloride tube.

To the boiling solution 17.5 g. of thionyl chloride was added dropwise, while the addition was so regulated that the solution was kept boiling. After the addition of the thionyl chloride the solution was refluxed for one hour. After cooling a trace of a solid substance was removed by filtering and the ether was dispelled by a dry air current. The remaining red liquid was dissolved in 60 ml. of ether and agitated once with 30 ml. of water in a separatory funnel. The ether layer was separated, dried over calcium chloride, decolorized with charcoal at room temperature, and after filtering the ether was expelled by a dry air current. Yield 4-5 g. Nitroacetonitrile obtained in this way was pure enough to be used in the majority of the experiments.

Pure ammonium nitroacetonitrile (94)

Nitroacetonitrile obtained after the first elimination of the ether by means of a dry air current had a deep red colour. It was dissolved in about 60 ml. of ether and agitated with 30 ml. of water. The ether layer was separated, dried over calcium chloride, decolorized with carbon black at room temperature and filtered.

The ethereal solution was cooled by means of an ice-water bath and dry ammonia was passed through it until precipitation was complete. A yellowish-brown product which was contaminated with ammonium chloride was obtained. The solid was dissolved in 5% sulphuric acid and the nitrile was extracted with ether five times (5-20 ml.).

The ether extract was dried with calcium chloride, decolorized with carbon black and the nitrile was precipitated again by dry ammonia with cooling. The yellowish-white solid melted at 130-135°. It was finally purified in small quantities by sublimation at 2 mm. Hg and at 60-70°. M.p. 134-135°.

Nitroacetamidoxime (67)

Freshly purified by sublimation ammonium nitroacetonitrile (0.04 g.) was dissolved in as little water as possible. To this solution a very concentrated solution of an equimolar amount (0.027 g., 4.10^{-4} mole) of hydroxylamine hydrochloride in water was added and the mixture was left at room temperature for 24 hours. The yellowish crystals which deposited were recrystallized from hot water. The compound was suddenly decomposed at 108° with the violent evolution of a gas.

Salt of aniline and nitroacetonitrile (67)

Freshly purified nitroacetonitrile (0.86 g., 0.01 mole) was dissolved in 1.5 ml. of dry ether and placed in a small three-necked flask provided with a stirrer and a dropping funnel. To the solution, cooled to about 0°, an equimolar amount of freshly distilled aniline in 1.5 ml. of dry ether was added dropwise with good stirring and cooling. The slightly yellow solid which precipitated in one minute, was removed by filtration, washed with a little dry ether, dried in the air and sublimed at 3 mm. Hg and 45-50°. The white crystalline solid collected melted at 80°.

Salt of o-toluidine and nitroacetonitrile (67)

The same procedure as above was used. The yellow product was purified by sublimation at 3 mm. Hg and 45-50°. Slightly yellow crystals were isolated. M.P. 77-78°.

Salt of 2,4-dimethylaniline and nitroacetonitrile (67)

The above procedure was used for the preparation and purification of the product. White to slightly yellow crystals were collected. M.p. 86-86.5°.

Attempted preparation of N-butylnitroacetamidine

Ammonium nitroacetonitrile (0.103 g., 0.001 mole) was dissolved in as little water as possible. To this solution 0.18 ml. of n-butylamine (0.002 mole) was added and the mixture was left at room temperature for two weeks.

The solution, which had turned yellow, was then subjected to micro-distillation at 5 mm. Hg and up to 100°. 0.13 g. of a white solid substance was collected at the cool part of the tube and melted at 53° (obs.). Yield 74%. This product proved, by infrared analysis, to be the salt of n-butylamine and the nitroacetonitrile was not analyzed.

Attempted preparation of nitroacetamidine

Ammonium nitroacetonitrile (0.103 g., 0.001 mole) was dissolved in an excess of ammonium hydroxide (sp. gr. 0.9, NH_3 28%) and left at room temperature for two weeks. The volatile parts of this solution were then removed by evaporation at low pressure and the remaining solid was sublimed at 70-80° and 2 mm. pressure. 0.85 g. of the unreacted ammonium nitroacetonitrile was recovered.

Attempted preparation of N-(n-butyl)-nitroacetamidine

n-Butylamine (2 ml., 0.02 mole) was dissolved in 2 ml. of water and the solution was cooled by an ice-water bath. To this solution 0.86 g. of nitroacetonitrile (0.01 mole) was added dropwise with stirring and the mixture was left at room temperature for two weeks.

After the evaporation of all the volatile components at reduced pressure a red syrup (1.5 g.) which could not be distilled or separated remained. When 0.2 g. of the red syrup was treated with an equivalent amount of 0.21 g. of silver nitrate in 2 ml. of water, 0.38 g. of the yellow complex of silver nitrate and the nitroacetonitrile was collected. The complex exploded violently on heating. 92% of the unreacted nitroacetonitrile was recovered.

SUMMARY AND CLAIMS TO ORIGINAL RESEARCH

1. Aqueous solutions of the lower primary and secondary aliphatic amines were treated with trichloroacetonitrile to give the corresponding amidines.

2. The reactions of higher primary and secondary aliphatic or cyclic amines with trichloroacetonitrile were carried out in the absence of solvents at room temperature. The yield of the N-substituted trichloroacetamidines formed were very high (85-95%).

3. It was found that aromatic and heterocyclic primary amines reacted with trichloroacetonitrile in methanol, water-methanol, ether-methanol and acetonitrile solutions at room temperature to yield the corresponding N-aryl-trichloroacetamidines in excellent yields.

4. It was shown that the solid compound obtained by Dachlauer was identical to Oxley's liquid trichloroacetamidine.

5. Liquid trichloroacetamidines could be purified by distillation at low pressure and in nitrogen atmosphere, whereas they decomposed vigorously at about 150° at normal pressure.

6. The following new N-substituted trichloroacetamidines have been prepared and characterized.

(a) N-Methyl-α,α,α-trichloroacetamidine
(b) N-Ethyl-α,α,α-trichloroacetamidine
(c) N-n-Butyl-α,α,α-trichloroacetamidine
(d) N-n-Amyl-α,α,α-trichloroacetamidine
(e) N,N-Dimethyl-α,α,α-trichloroacetamidine
(f) N,N-Diethyl-α,α,α-trichloroacetamidine

(g) N-Piperidino-α,α,α-trichloroacetamidine
(h) N-Morpholino-α,α,α-trichloroacetamidine
(i) N-Isopropyl-α,α,α-trichloroacetamidine
(j) N-p-Ethoxyphenyl-α,α,α-trichloroacetamidine
(k) N-p-Tolyl-α,α,α-trichloroacetamidine
(l) N-m-Tolyl-α,α,α-trichloroacetamidine
(m) N-o-Tolyl-α,α,α-trichloroacetamidine
(n) N-(2-Thiazolyl)-α,α,α-trichloroacetamidine
(o) N-[2-(5-Methylpyridyl)]-α,α,α-trichloroacetamidine
(p) N-Methyl-α,α,α-trichloroacetamidine-d_2

7. Contrary to what has been suggested, methanol and acetone were proved not to be essential in the reaction of trichloroacetonitrile with primary aromatic amines, by forming the intermediate methyl trichloroacetimidate. This was demonstrated by the following:

(a) Acetone was not used in the preparation of N-aryltrichloroacetamidines

(b) Aniline reacted with trichloroacetonitrile even in the absence of methanol or other solvents

(c) The reaction occurred also in ethanol, which does not react with trichloroacetonitrile

(d) 2-Amino-5-methylpyridine formed the corresponding trichloroacetamidine in acetonitrile solution with excellent yield.

8. Salts of primary and secondary amines did not react with trichloroacetonitrile.

9. Attempts to synthesize N-p-nitrophenyl-α,α,α-trichloroacetamidine failed. The failure was attributed to the fact that p-nitroaniline is a very weak base.

10. Ethyl trifluoroacetate was prepared for the first time by the action of concentrated sulphuric acid on a mixture of absolute ethyl alcohol

and trifluoroacetic acid.

11. Two new general procedures were developed for the preparation of N-alkyl- and N-dialkyl-trifluoroacetamidines at room temperature.

12. It was discovered that, contrary to what has been reported, trifluoroacetonitrile reacts with primary aromatic and heterocyclic amines to form the corresponding amidines at room temperature and in excellent yields.

13. The following previously unreported N-substituted trifluoroacetamidines have been prepared and characterized:

(a) N,N-Diethyl-α,α,α-trifluoroacetamidine
(b) N-Methyl-α,α,α-trifluoroacetamidine-d_2
(c) N-Ethyl-α,α,α-trifluoroacetamidine
(d) N-n-Butyl-α,α,α-trifluoroacetamidine
(e) N-Benzyl-α,α,α-trifluoroacetamidine
(f) N-Phenyl-α,α,α-trifluoroacetamidine
(g) N-{2-(5-Methylpyridyl}-α,α,α-trifluoroacetamidine

14. Attempts to synthesize N-p-nitrophenyl-α,α,α-trifluoroacetamidine failed due to the very low basicity of the p-nitroaniline.

15. Primary and secondary aliphatic or cyclic amines and primary aromatic amines add across the carbon-nitrogen triple bond of dichloroacetonitrile in a manner similar to that observed for trichloro- and trifluoro-acetonitrile.

16. The following new dichloroacetamidines have been prepared and characterized:

(a) N-Methyl-α,α-dichloroacetamidine
(b) N,N-Dimethyl-α,α-dichloroacetamidine
(c) N,N-Diethyl-α,α-dichloroacetamidine
(d) N-Piperidino-α,α-dichloroacetamidine
(e) N-Phenyl-α,α-dichloroacetamidine.

17. An explanation was offered for the instability of N-substituted dichloroacetamidines.

18. For the first time dichloroacetamide was obtained in good yields by a less elaborate procedure which consisted of passing dry ammonia through ethyl dichloroacetate cooled to 0°.

19. It has been shown by infrared spectroscopic study that the alleged N-phenyl-, N-o-tolyl- and N-(2,4-dimethylphenyl)-nitroacetamidines are in fact the salts of nitroacetonitrile with the corresponding aromatic amines.

20. Attempted synthesis of N-alkyl and N-dialkyl-nitroacetamidines failed, due to the formation of a strongly resonating nitroacetonitrile carbanion .

21. Attempts to promote the non-catalyzed addition of amines across the carbon-nitrogen triple bond of chloroacetonitrile at various conditions were unsuccessful. Instead, the reactants gave aminoacetonitriles which were isolated in high yields and identified by their derivatives.

22. The experimental evidence obtained in this work clearly supported the mechanism which has been proposed. It involves a nucleophilic attack of the unshared electron pair of the amine nitrogen atom on the positively charged carbon atom of the nitrile group.

23. The following limitations were found concerning the reaction of the nitriles with amines:

(a) At least two strongly electronegative atoms or groups at the α-carbon atom of a nitrile are necessary to promote the non-catalyzed addition of primary and secondary amines.

(b) Methanol and probably ethanol cannot be used as solvent in the reaction of trichloroacetonitrile with secondary aliphatic amines. This might be extended to trifluoro- and dichloro-acetonitrile although no experiments were conducted with these nitriles.

(c) Non-polar solvents prevent the reaction between aromatic amines and the nitriles in question.

(d) Secondary aliphatic amines containing alkyl groups with more than three carbon atoms react preferentially by substitution at the α-carbon atom.

24. Infrared spectroscopic studies of the trichloro- and trifluoroacetamidines were carried out for elucidating the structure of these products. The results could be summarized as follows:

(a) N-alkyl and N-aryl trichloroacetamidines associate strongly in the liquid and solid phases.

(b) They can be characterized by a new band (Amidine II) at 1510-1540 cm.$^{-1}$ and 1570-1580 cm.$^{-1}$ respectively; this absorption is attributed to the deformation vibration of the secondary amino group.

(c) N-substituted amidines exist only in the imino form (RC(=NH)NHR') in non-polar solvents.

(d) The degree of association of N-substituted trichloroacetamidines changes in the following order of substitution:

N-alkyl- > N-aryl- > N-dialkyl

25. The correlation between the infrared spectra and the trifluoroacetamidines provided additional information in support of the above conclusions.

26. For the first time the structure of the amidinium cation was established by the infrared spectroscopic study of fourteen trichloro-, and trifluoro-acetamidines. Protonation occurs on the imino nitrogen atom and both nitrogens of the amidine system become electron deficient due to resonance. This leads to a single structure regardless of which of the tautomers is present in the equilibrium mixture and of the number and type of substitution.

27. The chemical evidence supporting the current views concerning the structure of amidines is disproved or at least weakened seriously after the findings of this work.

28. The following general conclusions can be drawn regarding the tautomerism and structure of amidines in general.

(a) Reactions not involving the intermediate formation of amidinium cations are needed for the isolation of the two tautomers of an amidine.

(b) Accumulating evidence indicates that N-substituted amidines exist in the form $RC(=NH)NHR_1$, which is thermodynamically the more stable.

(c) Since the mobility of hydrogen atom in a triad system depends on the basic catalysis, the more stable form will always be favoured due to the basic nature of the amidines themselves.

(d) An amidine might exist as a tautomeric mixture when both tautomers possess the same or about the same thermodynamic stability.

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