REACTIONS OF NITRILES WITH HYDROGEN HALIDES AND NUCLEOPHILIC REAGENTS

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CONTENTS

I. Introduction 615

II. Reactions of nitriles with hydrogen halides 615

A. Nitrile hydrohalides of composition RCN.*n*HX 615

B. Some properties of solutions of hydrogen halides in nitriles 617

C. Nitrile hydrohalides of composition 2RCN.*n*HX 618

D. Preparation of 1,3,5-triazines 618

E. Hydrogen cyanide hydrohalides 619

III. Reactions of nitriles with hydrogen halides and nucleophilic reagents 619

A. Reactions with water 619

B. Reactions with alcohols 621

C. Reactions with organic acids 624

D. Reactions with carbonyl compounds 625

E. Structure and chemical properties of amide hydrohalides 625

F. Selective reactivity of one cyano-group in adiponitrile 626

G. Reactions with amines 627

H. The Gattermann reaction 627

J. The Hoesch reaction 628

K. Reaction of dimeric nitrile salts (2RCN.*n*HX) with hydroxy-compounds 628

IV. Reduction of nitriles in the presence of hydrogen chloride 629

A. Preparation of aldehydes by the Stephen method 629

B. Preparation of bisamides in the reduction of nitriles by the Stephen method 629

C. Preparation of amines 630

I. INTRODUCTION

The ability of nitriles to form addition compounds with nucleophilic and electrophilic reagents derives from the electronic structure of the triple carbon–nitrogen bond[1]. We have recently reviewed the reactions of nitriles with electrophilic reagents[1], and these will be considered only to a limited extent. Because of the reduced electron density at the carbon atom of the cyano-group, nitriles should react very readily with nucleophilic reagents. Compounds such as hydrogen sulphide and hydroxylamine do in fact add to nitriles to form thioamides and amidoximes, but in general nitriles are very stable towards many other nucleophilic reagents (water, alcohols, amines, etc.). The reactivity of nitriles is increased and the range of their reactions with nucleophilic reagents broadened in the presence of acidic or alkaline compounds, the action of which is evidently due to the ready polarisability of the cyano-group; also the presence of acids creates suitable conditions for the appearance of electrophilic activity at the nitrile carbon atom and the formation of new bonds between this atom and atoms of oxygen, sulphur, nitrogen, carbon, etc.

Hydrogen halides are particularly important as acid catalysts for reactions of the cyano-group, and in many cases, especially with hydrogen chloride, they are specific catalysts. The Pinner reaction (preparation of imidate salts), Hoesch reaction (preparation of ketimine salts), Gattermann reaction, Stephen reaction (preparation of aldimine salts), and several other acid-catalysed reactions of nitriles are carried out in the presence of hydrogen halides, and do not occur with other protogenic or Lewis acids in the absence of hydrogen halides. In the literature these reactions are very often discussed without consideration of the nature of the products of the reaction of nitriles with hydrogen halides, which may be formed under the experimental conditions. These products are often formulated as imidoyl halides, although these have never been isolated and there is no proof of their existence in the reaction medium. There have been no attempts in the review literature to generalise the existing data on the reactions of nitriles with hydrogen halides in the absence of other reagents.

This review is intended to fill the existing gaps. We shall consider the structure of the hydrohalogenation products of nitriles and hydrogen cyanide, and describe the reactions of nitriles with hydrogen halides and other reagents: hydroxylic compounds (water, alcohols, and organic acids), aldehydes and ketones, amines and aromatic compounds (the Gattermann and Hoesch reactions). The reduction of nitriles in the presence of hydrogen halides and other matters related to these reactions of nitriles will also be considered.

II. REACTIONS OF NITRILES WITH HYDROGEN HALIDES

A. Nitrile Hydrohalides of Composition RCN.*n*HX

Nitrile hydrochlorination products were first isolated in 1866 by Gautier[2-4], and the hydrohalogenation of nitriles was much studied in the last century[5-10]. Several nitrile hydrohalides were apparently obtained in admixture with other compounds in the bromination of aliphatic nitriles[11,12]. Until 1931 it was thought that one or two hydrogen halide molecules could add to nitriles in the cold, to form imidoyl halides and amino-halides respectively, but, after more careful study of the composition of the very unstable reaction products of nitriles and hydrogen halides, Hantzsch concluded[13] that the monohydrochlorides were not obtained, and that only the saltlike dihydrochlorides exist. By hydrobromination, however, Hantzsch obtained mono- and di-hydrobromides. Hantzsch's experiments on hydrobromination were later repeated by Klages and Grill[14], who showed that Hantzsch's results on nitrile monohydrobromides were in error. In 1957 it was reported[15] that treatment of *N*-acylaminoacetonitriles with hydrogen chloride in the cold produces monohydrochlorides, and these were stated to be the first isolated imidoyl chlorides or nitrilium salts; however, hydrogen chloride can add not only to the cyano-group, but also to the amide group, and this possibility was not considered. Moreover, the hydrochlorides obtained melted above 100°, and it is improbable that imidoyl halides would melt at such high temperatures. Up

to the present, therefore, only nitrile dihydrohalides have been prepared (textbooks [16] and monographs [17] still erroneously refer to the existence of solid monohydrohalogenated nitriles).

The 1 : 2 reaction products of nitriles and hydrogen halides are also obtained by treating carboxylic acid amides with PCl_5; [18] these products have been shown to be identical with those obtained by direct hydrochlorination of nitriles [13]. Kirsanov has studied the reaction of carboxylic acid amides with PCl_5, [19-21] and his data confirm the earlier suggestion [22] that the primary reaction products are trichlorophosphazoacyl compounds:

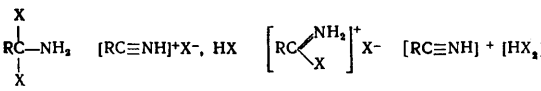
$$RCONH_2 + PCl_5 \rightarrow R\overset{\overset{O}{\|}}{C}-N=PCl_3 + 2\,HCl.$$

These can be obtained in high yields if the hydrogen chloride is removed from the reaction zone. In the presence of the hydrogen chloride they decompose into nitriles and $POCl_3$:

$$RC(=O)-N=PCl_3 \xrightarrow{HCl} RCN + POCl_3.$$

The resulting nitriles react further with the hydrogen chloride in the normal fashion, *i.e.* to form the 1 : 2 addition products.

The 1 : 2 addition products of nitriles with hydrogen halides have been given various structural formulae. In the older literature they were considered to be amino-halides (A).[23] In 1931 Hantzsch [13] suggested the formula (B), according to which they are hydrochlorides of nitrilium salts, and this formula is met with today [16]. Klages and Grill found [14] that the properties of the nitrile dihydrohalides correspond best to those of imidoyl halide salts [24], *i.e.* halogenoiminium halides (C). Finally, Janz has suggested [25] that the nitrile hydrochlorides may have formula (D):



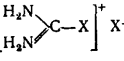
(A) (B) (C) (D)

The nitrile dihydrohalides show a high conductivity in liquid sulphur dioxide [14] and are therefore salts and cannot be amino-halides (A). The nature of the bond between the nitrilium salt and the hydrogen halide molecule in formula (B) is not clear. There can be no suggestion of the formation of a hydrogen bond between the hydrogen halide and the cation, since the nitrilium ion has no free electron pair to act as a base [14]. Formula (B) cannot therefore represent the true structure of the nitrile dihydrohalides. Unlike formula (B), the other nitrilium salt structure (D) is quite possible, since the existence of the dihalide anion HX_2^- has been proved [26-31]. It has been suggested [26] that the stability of the anion HCl_2^-, by analogy with HF_2^-, is due to the formation of a hydrogen bridge between the hydrogen atom in the HCl and the chloride ion ($Cl-H\cdots Cl^-$). There are also no particular objections to formula (C), representing a halogenoimonium structure for the salts RCN.2HX.

The infra-red spectra of acetonitrile dihydrobromide have shown it to be acetobromoimonium bromide [25]; an attempt was also made to obtain the infra-red spectra of solid acetonitrile dihydrochloride, but was unsuccessful because of its instability. The infra-red spectra of very dilute solutions (up to 1.15 M) of hydrogen chloride in acetonitrile revealed no band due to a C–Cl bond (750 cm^{-1}) but there was a band at 1180 cm^{-1} characteristic of the HCl_2^- anion [27]. It was therefore concluded that for the dihydrochloride, unlike the dihydrobromide or dihydriodide, the most probable formula is (D). Janz did not consider this structure as proved, because (a) the structure of nitrile dihydrochlorides may be different in dilute solution than in the solid state, and (b) the measurements were made [25] at room temperature, while even at +6° acetonitrile dihydrochloride dissociates into the nitrile and hydrogen chloride [32].

The existing data are therefore insufficient to ascribe to the dihydrochlorides a structure different from the structure of the other dihydrohalides. In order to establish finally the structure of nitrile dihydrochlorides, their spectra must be investigated under conditions such that their conversion into other nitrile–hydrogen chloride reaction products is excluded.

It is of interest that no difference has been found in the structures of solid cyanamide dihydrochloride and dihydrobromide [33] and both salts have been given the same halogenoformamidinium halide structure:



The dihydrohalides described in the literature, which are in all probability of structure (C), include the dihydrochlorides of acetonitrile [32], bromo- and fluoro-acetonitrile [34], benzonitrile [8], *p*-tolunitrile [13], and *p*-methoxybenzonitrile [35], the dihydrobromides of acetonitrile [25], bromoacetonitrile [34], phenylacetonitrile and benzonitrile [14], and *p*-tolunitrile [13], and the dihydriodides of acetonitrile [25], phenylacetonitrile, *o*-, *m*-, and *p*-tolunitrile, *o*-, *m*-, and *p*-nitrobenzonitrile, succinonitrile, terephthalonitrile, etc. [10].

Of the acetonitrile dihydrohalides, the hydriodide melts at the highest temperature (above 100°); the hydrobromide and hydrochloride melt at 75°–80° and about 20° respectively [25,36]. The thermal stability of the salts (ease of formation) also increases in this order:

$$CH_3CN.2HCl < CH_3CN.2HBr < CH_3CN.2HI.$$

The stability of the halogenoimonium halides is related to the polarisability of the hydrogen halides [36]: the least polarisable hydrogen chloride forms the least stable salts, and the most polarisable hydrogen iodide the most stable salts.

On heating, the halogenoimonium halides are usually decomposed into the nitriles and the hydrogen halides. The vapour pressure of certain bromoimonium bromides has been shown to depend on the temperature [14]. The heat of dissociation into the initial components was calculated; for benzobromoimonium bromide ΔH = 30 kcal per mole.

Nitrile dihydrochlorides enter into exchange reactions with other anions, and form stable salts with complex anions [14]. The following have been described: benzochloroimonium and acetochloroimonium hexachlorostannates, and benzochloroimonium, *p*-nitrobenzochloroimonium, and acetochloroimonium hexachloroantimonates [37].

Certain nitrogen-unsubstituted nitrilium salts with complex anions have been prepared where the corresponding halides are unknown. Benzo- and aceto-nitrilium hexachlorostannates and *p*-nitrobenzo- and aceto-nitrilium hexachloroantimonates have been prepared [37]. The reaction between benzonitrile, hydrogen chloride, and zinc chloride gave benzonitrilium trichlorozincate [38]. Their conductivity in liquid sulphur dioxide confirms their salt structure [37].

According to Klages[37], which complex is formed depends on the reaction temperature. There is no reaction between a nitrile, the complex-forming reagent, and hydrogen chloride at a very low temperature; in the intermediate region nitrilium salts are formed, and at higher temperatures two hydrogen chloride molecules react, with the formation of imonium salts. In some cases there is no intermediate region, *i.e.* nitrilium salts could not be obtained.

On heating, the complex nitrilium salts disproportionate to form the more stable chloroimonium salts.

$$2\,[RC{\equiv}NH]^{+}\,SbCl_6^{-} \rightarrow \left[RC\begin{matrix}NH_2\\Cl\end{matrix}\right]^{+} SbCl_6^{-} + RC{\equiv}N{\cdot}SbCl_5.$$

Study of the fusion diagrams of binary mixtures of hydrogen chloride with acetonitrile, propionitrile, butyronitrile, and benzonitrile has shown that these nitriles can form low-melting non-saltlike molecular compounds of formula RCN.HCl.[39] Thus CH_3CN.HCl melts at -63.2° and C_2H_5CN. .HCl at -97.2°. The molecular compounds RCN.HCl may be formed as a result of reaction between the unshared electron pair of the nitrile nitrogen and a molecule of hydrogen chloride. The above nitriles also form complexes of composition RCN.*n*HCl (where n = 5 or 7) and 2RCN.3HCl, which have even lower melting points than the compounds RCN.HCl. It is suggested[39] that in these compounds the unshared electron pair of the nitrogen and also π electrons act as donors, and the compounds RCN.*n*HCl are apparently therefore examples of the so-called π-complexes.

It must be emphasised that the compounds described by Murray and Schneider[39] are fundamentally different from all the other hydrohalogenation products of nitriles, which are salts. All the described molecular compounds retain the covalent bond between the hydrogen and chlorine in the hydrogen chloride molecule, and are apparently intermediates in the formation of the saltlike nitrile hydrohalides (see below).

B. Some Properties of Solutions of Hydrogen Halides in Nitriles

It has been known for a long time that hydrogen halides ionise comparatively readily in nitriles[40], and the conductance has been the most studied physical property of the solutions[25,37,41-44]. The polarographic behaviour of solutions of hydrogen chloride in acetonitrile has been investigated[45,46], and cryoscopic measurements have been made on dilute solutions of hydrogen chloride in benzonitrile[37].

The conductimetric study of the reaction between hydrogen chloride and acetonitrile[43], benzonitrile, β-chloropropionitrile, $\alpha\beta$-dichloropropionitrile, β-ethoxypropionitrile, and adiponitrile[44] shows that the conductance decreases as the HCl concentration is increased. In some cases the conductance curves pass through a minimum. Plots of λ (equivalent conductance) against $\sqrt{c}$ for solutions of HCl in adiponitrile and β-chloropropionitrile show two intersecting straight lines, *i.e.* within certain concentration limits the conductivity of these dilute solutions is described by Kohlrausch's formula for low concentrations of strong electrolytes. Plots of λ against $1/\sqrt{c}$, which are used for systems with chemical reaction[43], are linear for acetonitrile, adiponitrile, benzonitrile, and β-chloropropionitrile, the last two giving two intersecting lines[44].

The complexity of the conductance–concentration relationship, and in particular the presence of intersecting curves on the diagrams, can be explained by a given nitrile forming with the hydrogen halide, depending on the reaction conditions, not one but several compounds, some which ionise and some which do not[44]. The nitrile solutions may contain, for instance, the molecular compounds RCN.*n*HCl. Conductimetric and cryoscopic study of dilute solutions of HCl in benzonitrile has shown[37] that the compound C_6H_5CN. .HCl is formed. Of the known types of saltlike compounds, the nitrile solutions may contain halogenoimonium halides[14,47], compounds with the HX_2^- anion[25], and possibly also nitrilium salts and salts of composition 2RCN.*n*HX (see below). It must be assumed[44] that in general the nature of the reaction products between nitriles and hydrogen halides changes continuously in the qualitative and quantitative sense as the relative proportions of the reactants are varied.

The formation of compounds between nitriles and hydrogen halides is sometimes quite slow; for example, at 0° in ether (twice the reactant volume) the reaction between adiponitrile and hydrogen chloride in the molar ratio 1 : 2 is practically complete only after 24 h.[47] The conductance of freshly-prepared solutions of hydrogen halides in nitriles increases with time and reaches a maximum[42,44]. The slowness of the reaction enables the conductimetric method to be used to study the reaction mechanism[36,42].

The increase in conductance of solutions of hydrogen halides in nitriles with time means that the ionising compounds are not formed immediately. A similar effect was found with the systems acetonitrile–picric acid[48] and acetonitrile–iodine monohalides[49].

The donor-acceptor properties of the solvent and solute influence the rate of equilibration in the reaction of nitriles with hydrogen halides. It is assumed that the slow increase in conductance is due to the high ionisation potential of the nitrile, so that the latter is slowly protonated[42,48]. The polarisability of solvent and solute must also influence the rate of ionisation to a similar extent; the maximum conductance is reached earlier in the acetonitrile–HI and acetonitrile–HBr systems than in the acetonitrile–HCl system[42], the equilibrium conductances in these systems being in the ratio 60 : 20 : 1.[36]

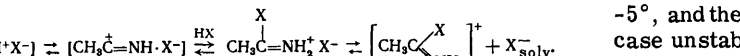
From the conductivity data, Janz and Danyluk suggested[42] two mechanisms for the reaction between nitriles and hydrogen halides. The primary reaction products are unionised molecular compounds ("outer complexes") which are then converted into saltlike compounds ("inner complexes")[49,50]. Mulliken and Reid associate the slow salt-formation with a considerable energy barrier for this reaction[51].

The first of Janz' and Danyluk's mechanisms[42] for the reaction of nitriles with hydrogen halides comprises the following stages:

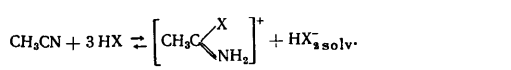
$$RCN + HX \rightleftarrows RCN{\cdot}HX \rightleftarrows RCNH^{+}X^{-} \rightleftarrows RCNH^{+} + X^{-}_{solv}.$$

In the compound RCN.HX, which is an "outer complex", the hydrogen halide molecule still retains its σ bond, but this is then broken to form the "inner complex", which ionises in solution to form the solvated anion X^{-}_{solv}; this then reacts with a second hydrogen halide molecule to form the anion HX^{-}_{2solv}.

The second mechanism[42] involves a nucleophilic attack by hydrogen halide on the "inner complex" to form the halogenoimonium halide, the anion of which is then solvated:



The solvated halide ion can obviously again react with a second hydrogen halide molecule to form the anion $HX_{2\,solv}^-$, so that the overall reaction in the solution is

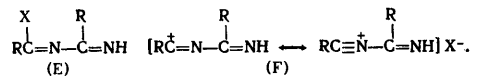


The compound $[C_6H_5CCl=NHC_6H_5]^+HCl_2^-$ has recently been prepared[52] by reacting *N*-phenylimidoyl chloride with hydrogen chloride.

The second mechanism was essentially that put forward[14] in 1955 as the only possible one for the reaction between nitriles and hydrogen halides. Attention was directed to the exceptional energetic instability of nitrogen-unsubstituted nitrilium salts, and to their strong tendency to add halide ions to yield undissociated imidoyl halides which, being bases, then react further with the hydrogen halide[14]. The addition of hydrogen halides to *N*-substituted imidoyl halides has been described[53,54].

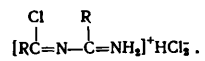
C. Nitrile Hydrohalides of Composition 2RCN.*n*HX

Certain halogenonitriles react with hydrogen halides under normal conditions to give saltlike products which have different chemical properties from the nitrile hydrohalides described above[55-59]. Although these salts were known to give secondary amides with water, the attempt to assign to them a more or less acceptable structure was for long unsuccessful, until Grundmann and coworkers convincingly demonstrated[60] that they are dimer salts of composition 2RCN.HX and have the *N*-alkylideneamidine structure (E) or (F):



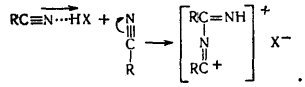
Alkylideneamidine chlorides of this type were prepared[60] from mono-, di-, and tri-chloroacetonitrile and α-dichloropropionitrile; the last reacts similarly with hydrogen bromide.

The *N*-alkylideneamidine structure has been assigned to the reaction product of hydrogen chloride with α-cyanoethyl acetate[61]. It has been reported that unsubstituted acetonitrile forms a dimer salt[32]; the reaction product was characterised as α-chloroethylideneamidine. The treatment of chloro-, fluoro- and bromo-acetonitriles with hydrogen chloride or bromide at about room temperature gives compounds of composition 2RCN.3HCl and $2ClCH_2CN$. .3HBr[34,62] having the same chemical properties as the salts 2RCN.HX; the products may therefore be formulated as, for instance,

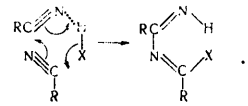


The reaction products of chloro- and bromo-acetonitrile with hydrogen chloride, which were formulated as imidoyl chloride hydrochlorides[63], are in fact dimer salts[38].

Lazaris and coworkers[34], using the reactions of fluoro- and bromo-acetonitrile with hydrogen chloride, were the first to show that, depending on the reaction conditions, the same nitriles may produce either halogenoimonium halides or dimer salts: the former were obtained between -50° and -5°, and the latter between 0° and 20° and above. In each case unstable outer and inner complexes are apparently first formed; at low temperatures these compounds are stabilised by addition of a hydrogen halide molecule to form the halogenoimonium halide. At a higher temperature the equilibrium in the formation of the unstable complexes is displaced towards the formation of the initial products, producing a higher concentration of the free nitrile. The cyano-group has both nucleophilic and electrophilic properties, and the unstable complexes are therefore stabilised by addition of the nitrile, giving the dimer salts:



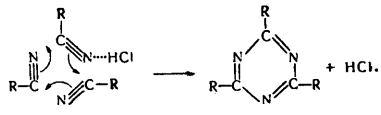
Cyclic electron transfer is also a probable mechanism in the formation of the dimer salts:



D. Preparation of 1,3,5-Triazines

In the presence of hydrogen halides some nitriles, chiefly α-halogenonitriles, polymerise at room temperature and above to produce 1,3,5-triazines[1,64]. Grundmann and coworkers[60] consider that the trimerisation of nitriles is preceded by the formation of the dimer salts (see above), which then react with the nitrile by the diene synthesis to form 1,3,5-triazines. However, this mechanism is inconsistent with their inability to prepare 1,3,5-triazines from the dimer salts and nitriles, and chloroacetonitrile, which forms the dimer salt more easily than any other nitrile, does not trimerise at all; on the other hand, trichloroacetonitrile, which gives the dimer salt with great difficulty[60], polymerises exceptionally readily. Hence the dimerisation of nitriles to dimer salts cannot be an intermediate stage in the production of 1,3,5-triazines, and these must be considered as competing reactions, as the early workers assumed.

The comparative ease of formation of 1,3,5-triazines may be due to cyclic electron transfer:



According to this mechanism, both the free nitrile and its hydrogen halide complex take part in the reaction. The required free nitrile content is met because the triazine synthesis is usually carried out at room temperature and above, when the nitrile hydrochlorides are already partially dissociated. Since the reaction proceeds less easily in the absence of the nitrile hydrohalide, an increase of reaction temperature above a certain limit should reduce the yield of triazine, and this has been confirmed experimentally[65]. The experimentally observed evolution of hydrogen chloride in the formation of 1,3,5-triazines[60] also does not contradict the suggested reaction mechanism.

Dimer salts and triazines are obtained most easily from α-halogenonitriles: electronegative α-substituents produce a comparatively low electron density at the nitrile carbon atom, and hence increase the electrophilic reactivity of the nitriles.

Up to the present, therefore, the reaction of nitriles with hydrogen halides has given three main types of stable compound: the dihydrohalides (apparently halogenoimonium halides), dimer salts (*N*-alkylideneamidines), and 1,3,5-triazines. The reactions commence with the formation of unstable complexes between the reactants, and these are then stabilised by one of the above mechanisms, depending on the properties of the initial components and the reaction conditions.

E. Hydrogen Cyanide Hydrohalides

Hydrogen cyanide reacts with hydrogen chloride to produce two compounds, of composition 2 : 3 and 2 : 1.

The sesquichloride 2HCN.3HCl [66] has been assigned the dichloromethylformamidine hydrochloride structure [67,68]:

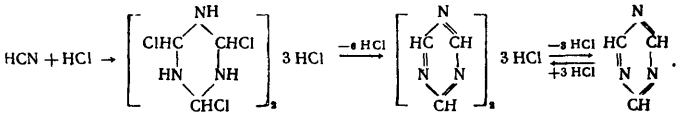
$$Cl_2CHNHCH{=}NH\cdot HCl,$$

or, in more recent work, the following non-saltlike structure [69-74]:

$$Cl_2CHNHCHClNH_2.$$

The sesquichloride readily loses two-thirds of its hydrogen chloride to form the compound 2HCN.HCl, which was earlier considered to be chloromethyleneformamidine ClCH = NCH = NH.[69] Further dehydrochlorination, *e.g.* by means of quinoline, gives the so-called "dimeric hydrocyanic acid",[75] which has been given the iminoformylcarbylamine structure C = NCH = NH.[76]

The structure of these reaction products was considered afresh by Grundmann and coworkers [77-80], who put forward completely new formulae for them. According to Grundmann, the product initially formed is 2,4,6-trichlorohexahydro-1,3,5-triazine hydrochloride, the compound thought to be chloromethyleneformamidine is 1,3,5-triazine sesquichloride, and exhaustive dehydrochlorination produces 1,3,5-triazine, which is unstable:

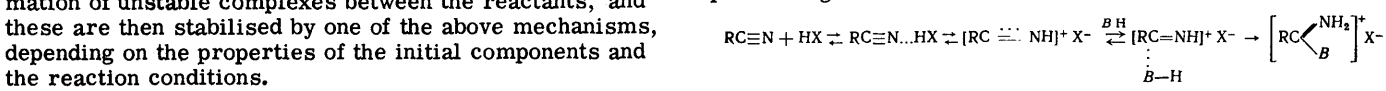


At various times the reactions of the hydrogen cyanide hydrochlorination products with water, alkali, alcohols [66], amines [68], aromatic compounds (in the presence of aluminium chloride) [67,73,74], and other compounds have been studied. The compositions of the molecular compounds formed between aluminium chloride and all three of the HCN–HCl reaction products have also been investigated [80].

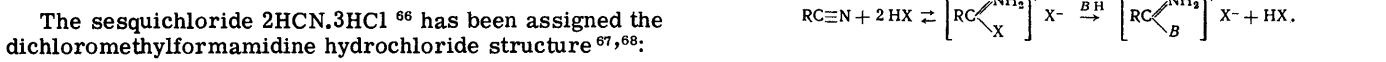
Hydrogen cyanide reacts with hydrogen bromide to give the analogous bromine compounds 2HCN.3HBr and 2HCN. .HBr.[71,81]

III. REACTIONS OF NITRILES WITH HYDROGEN HALIDES AND NUCLEOPHILIC REAGENTS

As stated above, in the absence of acids nitriles do not as a rule react with hydroxylic or other nucleophilic reagents. The addition of a proton to the nitrile nitrogen atom "opens up" the triple bond, and hence considerably increases the ability of the cyano-group to react with electron-donating compounds; it must be assumed, therefore, that the reaction of nitriles with water, alcohols, organic acids, mercaptans, and other nucleophilic reagents is preceded by the formation of nitrile–hydrogen halide addition products. Possible intermediates in these reactions of nitriles are the unstable strongly polarised 1 : 1 nitrile–hydrogen halide complexes described in the previous section; these are then stabilised by addition of the nucleophilic reagent:



Since nitriles also form extremely stable reaction products with hydrogen halides, the halogenoimonium halides, these must also be considered to take part in the reactions between nitriles, hydrogen halides, and nucleophilic reagents:



We shall consider below the reactions occurring, in the presence of hydrogen halides, between nitriles and hydroxylic compounds and amines, and also the Gattermann and Hoesch syntheses. In discussing these reactions, we shall show that in many cases there has been experimental confirmation of two main reaction stages: reaction between the nitrile and the hydrogen halide, and, subsequently, addition of the electron-donating compound. In some cases the experimental results have been sufficient to decide which of the two mechanisms is predominant in the first stage, *i.e.* whether only the unstable complexes are formed, or whether the saltlike nitrile dihydrohalides are also produced. Some of the results do not exclude the possibility, in individual cases, of synchronous reactions, *i.e.* reactions passing through a single transition state. Knowledge of the mechanism of the electrophilic reactions of nitriles has enabled known syntheses to be improved and new ones developed.

This section includes a subsection devoted to the reactions of the nitrile dimer salts with hydroxylic compounds. Since the previously little known amide hydrohalides are often the final products in the reaction of nitriles with hydrogen halides and hydroxylic compounds, a separate subsection is devoted to their properties. Finally, we shall consider the selective reactivity of one of the cyano-groups of adiponitrile, which is particularly evident in the presence of hydrogen chloride.

A. Reactions with Water

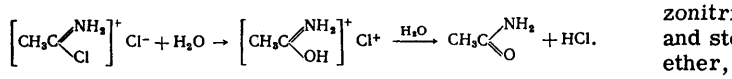
1. Preparation of amides and their hydrohalides. Amides are obtained when nitriles are treated with concentrated hydrochloric acid at room temperature [82-94], or, more rapidly, at 50°–60°. At higher temperatures carboxylic acids are formed [90,95]. Nitriles containing reactive groups are hydrated at room temperature or at 0°.

The hydrolysis of nitriles with hydrochloric acid of various concentrations has been investigated [96]; with concentrated acids hydrolysis stops at the amide stage, while in dilute acids carboxylic acids are obtained. Since the HCl content of concentrated hydrochloric acid at room temperature is at most 36–38%, the amides formed by the hydration of nitriles are sometimes partially or completely

hydrolysed to carboxylic acids even at low temperatures[97]. To suppress hydrolysis of the amides the nitriles must be hydrated under conditions such that there is no large excess of water. In some cases the nitriles have been dissolved in concentrated hydrochloric acid, or mixed with a little water, and the solution cooled to between -5° and 0° and saturated with hydrogen chloride[17,98-101]. Treatment of the reaction products of nitriles and dry hydrogen chloride with water usually gives the initial nitriles[13,17,32], but in certain cases nitrile–hydrogen chloride reaction products have been said to be intermediates in the production of amides from nitriles[92,102,103]. The formation of amides from nitriles and water in the presence of hydrogen chloride is the basis of proposed methods for the dehydration of acids[104] and esters[105].

As early as 1877 Pinner and Klein[8] passed hydrogen chloride into a mixture of equivalent quantities of water and acetonitrile or benzonitrile and obtained compounds which they described as amide hydrochlorides, but the reaction conditions and the yield and properties of the salts were not given. Later it was stated[25,99,103] that amide hydrochlorides are intermediates in the preparation of amides from nitriles, water, and hydrogen chloride, but here also the amide hydrochlorides were not identified. Treatment of adiponitrile with water and hydrogen chloride[106] gave a chlorine-containing product which was wrongly described as an imidoyl chloride hydrate.

According to Zil'berman and Kulikova's results[47,107-112], earlier statements[13,32] that the action of water on nitrile–hydrogen halide reaction products can only produce the initial reactants are only partly correct. With an excess of ice water acetochloroimonium chloride does in fact dissociate to give the initial nitrile, but the addition of small quantities of water to an ether solution of the chloride gives a precipitate of acetamide hydrochloride (acetimidic acid hydrochloride), which on hydrolysis produces the free amide:



Treatment of mixtures of equivalent quantities of nitriles and water with hydrogen chloride has given high yields of amide hydrochlorides derived from aliphatic acid amides[47,110], aliphatic acid diamides[111], and ring-substituted benzamides[35]. In some cases the amide hydrochlorides are very unstable, readily losing hydrogen chloride, and even before hydrolysis are partially converted into the free amides. Some nitrile hydration products (*e.g.* from chloroacetonitrile[110]) contained so little hydrogen chloride that they should be classed as free amides rather than amide hydrochlorides. Hydration of trichloroacetonitrile[110] and αβ-dichloropropionitrile[112] gives the free amides. The considerable negative inductive effect of the chlorine atoms in these amides apparently so weakens the nucleophilic properties of the oxygen atom that it becomes unable to add a proton. Unlike these, however, capronitrile[109], methacrylonitrile, and lactonitrile[112] do apparently form amide hydrochlorides, but they could not be isolated from the reaction mixture. The corresponding amides were obtained immediately on hydrolysis of the reaction mixture.

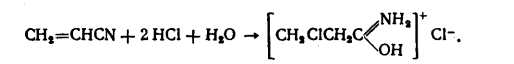
As a rule, the order of addition of the nitrile, hydrogen chloride, and water to the reaction mixture plays substantially no part in the reaction, but in certain specific cases a particular order of addition is essential for obtaining optimum yields of hydrochlorides or free amides. In the preparation of most amides equivalent quantities of nitrile and water are added to an organic solvent, and hydrogen chloride is passed into the solution; after a definite time the precipitate is filtered off. Because of the reactivity of the hydroxy-groups in lactonitrile and acetonecyanohydrin, the corresponding amides can only be prepared by adding the nitrile to a solution of hydrogen chloride in aqueous ether[112]. Adiponitrile was converted quantitatively into δ-cyanovaleramide hydrochloride by passing hydrogen chloride into a solution of adiponitrile in ether for at least four hours and then adding the calculated quantity of water[47]. This procedure was also the most suitable for preparing diamides of dibasic acids[111].

The larger the excess of hydrogen chloride with respect to the nitrile, the more rapidly is the amide hydrochloride formed[110]; evidently excess of hydrogen chloride increases the concentration of primary nitrile–hydrogen chloride reaction products, which then react with the water. An excess of hydrogen chloride is not necessary in the hydration of nitriles of high electrophilic reactivity. In the preparation of lactamide, α-hydroxyisobutyramide hydrochloride[112], and δ-cyanovaleramide hydrochloride the molar ratio of nitrile to hydrogen chloride should be 1 : 2. The formation of most amide hydrochlorides is complete within 24 h, but in some cases (*e.g.* with stearamide, adipamic acid methyl ester[110], *p*-toluamide[35], etc.) the reaction had to be continued for 5–10 days.

Amide hydrochlorides are usually prepared at ~0°,[110] but with some nitriles of low reactivity (*e.g.* stearonitrile, capronitrile, and benzonitrile) room temperature was preferred.

Amide hydrochlorides can be prepared from nitriles, water, and hydrogen chloride in the presence or absence of inert organic solvents, so long as the nitrile dissolves in the reaction mixture. The amide salts are often prepared in ether[110]. Substituted benzamides are prepared in dioxane, which unlike ether partially dissolves substituted benzonitriles[35]. The comparatively slow-reacting capronitrile and stearonitrile have been hydrated in toluene, since ether, dioxane, and similar oxygen-containing compounds were not found to be suitable solvents. The reaction between hydrogen chloride and the ethers apparently displaces the equilibrium of the nitrile–hydrogen chloride reactions towards the initial reactants, and the reduced concentration of intermediate products in the reaction mixture lowers the rate of formation of the amides.

When αβ-unsaturated nitriles (acrylonitrile, methacrylonitrile) are treated with hydrogen chloride and water, they are hydrated and also hydrochlorinated at the double bond[112]:



Some nitriles (β-ethoxypropionitrile, azodiisobutyronitrile[110], *o*-nitrobenzonitrile[35], etc.) have proved impossible to hydrate to amides, presumably because of steric hindrance. *Ortho*-substituted benzonitriles are known[113,114] to be inactive in other reactions also: *e.g.* they do not form imidate hydrochlorides with hydrogen chloride and alcohols. The stability of β-ethoxypropionitrile under normal conditions for the preparation of amide hydrochlorides may be because, as has been suggested[115], β-substituents in the aliphatic series produce the same steric hindrance as is found in *ortho*-substituted aromatic compounds.

The reaction of nitriles with deuterium chloride and deuterium oxide is a convenient method for preparing

ON-deuterated imidic acid hydrochlorides [116]:

$$RCN + DCl + D_2O \rightarrow \left[RC\begin{matrix}ND_2\\OD\end{matrix}\right]^+ Cl^-.$$

Treatment of these salts with heavy water causes deuterium exchange at the α-carbon atom, forming *NC*-deuterated amides with a high deuterium content. Trichloroacetonitrile, which has no α-hydrogen and does not form the imidic acid hydrochloride, reacts with deuterium chloride and deuterium oxide to produce deuterotrichloroacetamide in high yield. Obviously, other isotopic varieties of water will react with nitriles in the same way as D_2O.

2. Mechanism of the reactions of nitriles with hydrogen halides and water. Two reaction mechanisms for the reaction between nitriles, hydrogen halides, and nucleophilic reagents were given at the commencement of Section III: (a) the formation of unstable complexes between nitriles and hydrogen halides, and (b) the formation as intermediates of saltlike nitrile hydrohalides (halogenoimonium halides).

Investigation of the reaction of substituted benzonitriles [35] and aliphatic dinitriles [111] with hydrogen chloride and water has confirmed that the reaction proceeds in stages. The possibility of carrying out the reaction by way of chloroimonium chloride was shown experimentally in the selective hydration of one nitrile group of adiponitrile [47]. To obtain the theoretical yield of δ-cyanovalerimidic acid hydrochloride, the 1:2 nitrile–hydrogen chloride reaction product (δ-cyanovalerochloroimonium chloride) must first be prepared:

$$NC(CH_2)_4CN + 2HCl \rightleftarrows \left[NC(CH_2)_4C\begin{matrix}NH_2\\Cl\end{matrix}\right]^+ Cl^- \xrightarrow{H_2O}$$

$$\rightarrow \left[NC(CH_2)_4C\begin{matrix}NH_2\\OH\end{matrix}\right]^+ Cl^- + HCl.$$

There are cases, *e.g.* in the hydration of chloroacetonitrile [62], when the chloroimonium chloride formation is unnecessary or even impossible. In the treatment of certain reactive nitriles, particularly halogenoacetonitriles, with water and hydrogen chloride, the unstable outer and inner complexes RCN.HCl may be intermediate products. It is also possible that in this case the addition of water and hydrogen chloride takes place in a single transition state.

It must be assumed that in most actual cases of the hydration of nitriles in the presence of hydrogen halides the reaction mechanism is more complex than those given above. The addition of water may proceed simultaneously, for example, by two or three mechanisms.

In each stepwise reaction mechanism there are at least two stages: (1) reaction of the nitrile with hydrogen chloride, and (2) reaction with the nucleophilic hydroxy-compound. To decide which is the rate-determining step, the influence of substituents in benzonitrile on the rate of formation of the corresponding benzimidic acid hydrochlorides has been studied [35]. The activating effect of the substituents on the rate of reaction decreases in the series:

(1) *p*-substituents: $NO_2 > COOH > Br, Cl > CH_3 > H \gg \gg OCH_3$;

(2) $p\text{-}NO_2 > m\text{-}NO_2 \gg o\text{-}NO_2$.

The more electronegative the *p*-substituent, the more readily, as a rule, is the nitrile hydrated in the presence of the hydrogen chloride. Since the inductive effect and the effect of conjugation of electronegative substituents in benzonitrile reduce the electron density at the nitrile carbon atom, the rate-determining step in the reaction of nitriles with hydrogen chloride and hydroxy-compounds is the nucleophilic attack by water. In one case, however, this rule is not obeyed: *p*-tolunitrile has an electropositive substituent but stands above benzonitrile in the above series. The comparative ease with which *p*-tolunitrile is hydrated is apparently due to the activating effect of the *p*-methyl substituent on the first reaction step (reaction of the nitrile with hydrogen chloride). The presence of the electropositive substituent in the tolunitrile molecule causes additional displacement of electrons towards the nitrogen (the dipole moment of *p*-tolunitrile is 4.37 D, against 4.08 D for benzonitrile [117]) and so facilitates its nucleophilic reactions. Thus in the case of *p*-tolunitrile the rate of formation of the imidic acid hydrochloride is determined both by the reaction with the nucleophilic reagent and by the reaction of the nitrile with the hydrogen chloride. The reaction of *p*-tolunitrile with hydrogen chloride in the absence of water [35] supports this conclusion: it readily forms the chloroimonium chloride, while under the same conditions benzonitrile does not. *p*-Methoxybenzonitrile forms the chloroimonium chloride even more readily than *p*-tolunitrile, even in the presence of water, but because of the electropositive methoxy-group, the nucleophilic attack is completely suppressed, and *p*-methoxybenzimidic acid hydrochloride is not produced.

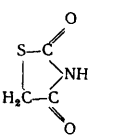
3. Reaction of alkyl thiocyanates with hydrogen chloride and water. Organic thiocyanates often react in the same way as nitriles. Treatment of methyl, ethyl, *n*-propyl, and *n*-butyl thiocyanates with hydrogen chloride and water produces the corresponding *S*-alkyl esters of monothiocarbamic acid in moderate yields [118]:

$$RSCN + H_2O \xrightarrow{HCl} RSC\begin{matrix}O\\NH_2\end{matrix}.$$

The comparatively slow hydration of alkyl thiocyanates is due to the presence in the SCN group of the sulphur atom, which has unshared electron pairs and by conjugation increases the electron density of the thiocyanate carbon atom, so hindering nucleophilic attack on this atom by a water molecule.

Heating methyl thiocyanoacetate with hydrochloric acid produces 2,4-dioxothiazolidine [119]:

$$NCSCH_2COOCH_3 \xrightarrow{HCl,\ H_2O}$$



B. Reactions with Alcohols

1. Preparation of imidate hydrohalides. Boiling a mixture of a nitrile, alcohol, and water with strong acids produces esters [120], and these are also obtained by passing hydrogen chloride into hot mixtures of nitriles, alcohols, and water [121]. In an anhydrous medium the reaction between nitriles, alcohol, and hydrogen chloride (the so-called Pinner synthesis [122]) produces imidate hydrochlorides (imino-ether hydrochlorides): [8,123]

$$RCN + R'OH + HCl \rightarrow \left[RC\begin{matrix}NH_2\\OR'\end{matrix}\right]^+ Cl^-$$

Under the same conditions nitriles, mercaptans, and hydrogen halides produce thioimidate hydrohalides:

$$\left[RC\begin{matrix}NH_2\\SR'\end{matrix}\right]^+X^-.$$

Imidate hydrochlorides, unlike amide hydrochlorides, are well known in organic chemistry. The preparation and chemical properties of imidates have been described in recent detailed reviews [17,122] covering the literature up to 1959, and we shall therefore consider here only matter outside the scope of these reviews and data which have appeared only after the date of submission of Roger and Neilson's review [122].

Although three reactants participate in the formation of imidate hydrohalides, it is usually presented as a single-stage reaction [17,122], but the mechanism of the reaction of nitriles and hydrogen halides with alcohols is close to the mechanism of their reaction with water. The imidate hydrohalides are formed by way of the corresponding halogenoimonium halides [124] and also directly from unstable reaction products of nitriles and hydrogen halides with alcohols. The halogenoimonium halide mechanism is also confirmed by the treatment of acetochloroimonium chloride [32], bromoacetochloroimonium chloride, and bromoacetobromoimonium bromide [34] with alcohols, when the corresponding imidate salts are obtained.

Imidate hydrochlorides are formed not only from nitriles, but also from other compounds containing the cyano-group, when treated with alcohols and hydrogen chloride. Cyanamide, methanol, and hydrogen chloride give methylisourea hydrochloride [125]:

$$H_2NCN + CH_3OH + HCl \longrightarrow H_2NC\begin{matrix}NH\cdot HCl\\OCH_3\end{matrix}.$$

Organic thiocyanates react similarly [126]:

$$RSCN + R'OH + HCl \longrightarrow \left[RSC\begin{matrix}NH_2\\OR'\end{matrix}\right]^+Cl^-.$$

Various quantities of hydrogen halide have been used in the preparation of imidates. In his first study of imidates Pinner [8] gave the following structure for the reaction products of nitriles, alcohols, and hydrogen chloride:

$$\begin{matrix}OR'\\|\\RC{-}NH_2\cdot HCl\\|\\Cl\end{matrix}.$$

When dried, these split out one molecule of hydrogen chloride, leaving the imidate hydrochloride. On this basis, in his early work [8,127] on the preparation of imidate salts Pinner used the nitrile, alcohol, and hydrogen chloride in the ratio 1:1:2, but later he apparently realised that the imidate group usually combines with only one hydrogen chloride molecule, and in his monograph [123] he gave the optimum reactant ratio as 1:1:1. Up to the present this ratio of 1:1:1 has very frequently been used in the production of imidate salts, or a slight excess (10–25%) of hydrogen chloride is used [128–130]. However, as in the preparation of amide hydrochlorides (see above), an excess of hydrogen chloride accelerates the reaction, and therefore, when free hydrogen chloride does not cause decomposition of the resulting imidate hydrochloride, it is useful to saturate the reaction mixture with hydrogen chloride [131–136]. The use of a large excess of hydrogen halide is particularly effective when nitriles of low electrophilic reactivity are reacted with alcohols. There are particular cases [124] when the reaction product can only be obtained in a pure state by using a reactant ratio of 1:1:2; as will be shown below, this ratio is not due to addition of two hydrogen chloride molecules to the imidate, but is necessary because the intermediate reaction product is sometimes the corresponding chloroimonium chloride.

The compound 6-methoxy-2-naphthimino-ether dihydrochloride was prepared in 1947. [137] The formation of this imidate with two molecules of hydrogen chloride can be explained either by one of the HCl molecules adding to the oxygen of the methoxy-group, or by the imidate salt having the HCl_2^- anion.

It has recently been suggested that hydrogen bromide or iodide be used to accelerate imidate salt formation and increase the yield of product [138].

Ethyl ethoxycarbonylacetimidate hydrochloride has been prepared from ethyl cyanoacetate and ethanol in the presence of hydrogen chloride formed *in situ* from equimolar quantities of thionyl chloride and water [139].

In addition to the solvents previously used [122], CCl_4 has also been employed as reaction medium for the preparation of imidate hydrohalides [140]. When imidate salts are to be prepared from nitriles which are insoluble in the usual organic solvents, the reaction can be carried out in suspension [133,141]. In the preparation of the imidate salt from β-cyanoethyl *p*-toluenesulphonate a saturated solution of hydrogen chloride in absolute alcohol was shaken at room temperature with the solid nitrile until a homogeneous solution was obtained [142].

In the preparation of the overwhelming majority of imidate salts, the order of addition of the nitrile, alcohol, and hydrogen halide to the reaction mixture is immaterial; usually the nitrile and alcohol are mixed with an inert organic solvent, into which the hydrogen halide is passed at ~0°. In individual cases other procedures have proved convenient. To prevent side reactions in the preparation of the imidic acid hydrochloride derived from ethyl β-chlorolactate acid, hydrogen chloride is passed into the alcohol and then the nitrile is added while continuing the addition of hydrogen chloride [143].

Imidate hydrochlorides are used in the preparation of certain polymerisable acrylates [144]. When hydrogen chloride is passed through a mixture of alcohol and an αβ-unsaturated nitrile, β-chloroimidate hydrochlorides are obtained [142,145], for example [144]:

$$CH_2{=}\overset{OCOCH_3}{\overset{|}{C}}CN + C_2H_5OH + 2HCl \longrightarrow CH_2Cl\overset{OCOCH_3}{\overset{|}{C}}H{=}NH\cdot HCl.$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad OC_2H_5$$

Hydrolysis of the imidate hydrochlorides produces esters of β-chlorocarboxylic acids, which in the presence of dehydrohalogenation agents are converted into esters of αβ-unsaturated acids.

Imidate hydrochlorides derived from dibasic aliphatic acids can be used as additives, *e.g.* for food products and synthetic polymers, to prevent the catalytic action of metals on the organic materials; they inhibit, for example, their autoxidation [146].

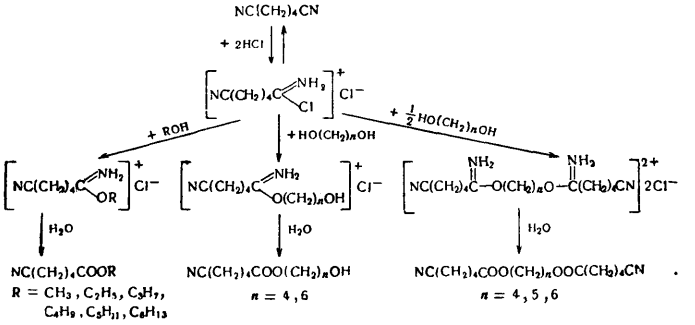
2. New syntheses from dinitriles. A large number of diimidate salts obtained from dinitriles and monohydric alcohols or mononitriles and glycols have been described [122]. Woodburn and coworkers [147] have studied the reaction of cyanogen with hydrogen chloride and certain

glycols; diimidate hydrochlorides were prepared from propane-1,2-diol, propane-1,3-diol, and butane-2,3-diol:

$$2HOROH + NCCN + 2HCl \longrightarrow HOROC(=NH\cdot HCl)-COR(OH)(=NH\cdot HCl)$$

In most other reported reactions between dinitriles, glycols, and hydrogen chloride, however, mixtures of unidentified imidate salts were obtained [148].

In 1959 Zil'berman and Kulikova showed [124,149] that for successful preparation of individual compounds from certain dinitriles, glycols, and hydrogen chloride, the hydrochlorination of the dinitrile and the reaction of the product with the alcohol must be carried out separately, *i.e.* the dinitrile should first be treated with the calculated amount of hydrogen chloride, and then the alcohol added after a definite time. This procedure gave a number of interesting compounds from adiponitrile, which, because of the selective reactivity of one of its cyano-groups, gave the following series of reactions [124,149-152]:



The yields of alkyl δ-cyanovalerates [124], ω-hydroxyalkyl δ-cyanovalerates, and alkylene (from alkanediols) di(δ-cyanovalerates) [152] were close to theoretical. Earlier procedures for the preparation of alkyl δ-cyanovalerimidates [129,153,154] gave the desired products in low yields and in admixture with a molecular compound formed between the alkyl imidate hydrochloride and adiponitrile [124]. It is important to obtain alkyl δ-cyanovalerates in high yields because they are starting materials for the production of caprolactam [155]:

$$NC(CH_2)_4COOR \xrightarrow{H_2} H_2N(CH_2)_5COOR \longrightarrow \text{(cyclic)} + ROH.$$

The reaction between aliphatic dinitriles and hydrogen chloride in a molar ratio of at least 1:4 in the cold produces solid products, apparently di(chloroimonium) dichlorides, which precipitate if insufficient solvent is used. These were treated with twice the molar quantity of glycols without separation from the reaction mixture. The resulting diimidate hydrochlorides when treated with an excess of water gave di(ω-hydroxyalkyl) esters of dibasic acids:

$$NC(CH_2)_mCN + 4HCl \rightleftharpoons \left[H_2N\text{-}C(Cl)\text{-}(CH_2)_m\text{-}C(Cl)\text{-}NH_2 \right]^{2+} 2Cl^- \xrightarrow{2HO(CH_2)_nOH}$$

$$\rightarrow [HO(CH_2)_nO\text{-}C(=NH)\text{-}(CH_2)_m\text{-}C(=NH)\text{-}O(CH_2)_nOH]^{2+} 2Cl^- \xrightarrow{H_2O} HO(CH_2)_nOOC(CH_2)_mCOO(CH_2)_nOH.$$

This reaction has been carried out with such glycols as butane-1,4-diol, pentane-1,5-diol, and hexane-1,6-diol. [151,152,156] Di(ω-hydroxyalkyl) esters were not obtained from ethyleneglycol or *p*-xylyleneglycol, since under the reaction conditions the hydroxy-groups of these glycols are partly replaced by chlorine [151,157].

The reaction between dinitriles, hydrogen chloride, and glycols in the ratio $1:n:1$, where $n \geq 4$, has been used to prepare polyimidate hydrochlorides, which on hydrolysis give polyesters [151,157-160]:

$$NCRCN + 4HCl \rightleftharpoons \left[H_2N\text{-}CRC(Cl)\text{-}NH_2 \right]^{2+} 2Cl^- \xrightarrow{HOR'OH}$$

$$\rightarrow HOR'O\text{-}[CRC(Cl)=NH\cdot HCl\text{-}OR'O]_n\text{-}CRC(Cl)=NH\cdot HCl \xrightarrow{H_2O} HOR'O\text{-}[OCRCOOR'O]_n\text{-}OCRCN.$$

Polyesters of molecular weight 650-1650 have been obtained from the dinitriles of adipic, azelaic, sebacic, and *p*-phenylenediacetic acids and ethyleneglycol, butane-1,4-diol, diethyleneglycol, and *p*-xylyleneglycol. In addition to nitrile and hydroxy-groups, chlorine was also found as an end-group in some cases. Increasing the reaction temperature from 0 to 20° considerably increased the chlorine content of the polyester and lowered its molecular weight. Excess of glycol or dinitrile also reduces the molecular weight of the final polyester. Unlike the pasty polycondensation products obtained from dibasic acids and glycols, which are slightly coloured, the polyesters obtained from polyimidate hydrochlorides are often white powders, because of the mild conditions under which they are prepared.

3. Preparation of amides and their hydrochlorides. The reaction products obtained from nitriles, hydrogen chloride, and tertiary alcohols remained unidentified for a long time [161,162]. Zil'berman and Sladkov showed [163] that many nitriles react in the cold with hydrogen chloride and tertiary alcohols to yield not imidate ester salts, but imidic acid hydrochlorides (amide hydrochlorides) and tertiary alkyl chlorides:

$$RCN + R'OH + 2HCl \longrightarrow \left[RC(NH_2)(OH) \right]^+ Cl^- + R'Cl.$$

Nitriles with strongly electronegative substituents in the α-position give the free amides and not the amide hydrochlorides.

Several mechanisms are possible for the formation of amides and their hydrochlorides in this reaction [163]; for example, tertiary alcohols react with hydrogen chloride to give tertiary alkyl chlorides and water, and the latter may be expected to react with the nitrile-HCl reaction products to give imidic acid hydrochlorides.

According to a second mechanism, the initial nitrile-hydrogen chloride reaction products, particularly the chloroimonium chlorides, which have a high electrophilic reactivity, dehydrate the tertiary alcohols, the liberated water reacting with the nitrile and HCl in the normal way.

In a third possible mechanism, the nitriles and hydrogen chloride react initially with the tertiary alcohols in the same way as with primary and secondary alcohols, *i.e.* to form imidate hydrochlorides, which then undergo the Pinner rearrangement [8,122,164]:

$$\left[RC(NH_2)(OR') \right]^+ Cl^- \xrightarrow{HCl} \left[RC(NH_2)(OH) \right]^+ Cl^- + R'Cl.$$

Normally this last reaction is carried out by heating the imidate salts in the absence of free hydrogen chloride, and the products are then the free amides and not the amide hydrochlorides. The basic literature on this reaction has

been reviewed[122], and we only mention here that this splitting of imidate hydrochlorides has been shown to involve a bimolecular nucleophilic substitution reaction (S_N2)[165,166], although in some cases the reaction follows an S_N1 mechanism[167,168]. With increasing electron-donating properties of the alkyl radical, a carbon atom of which undergoes substitution in such reactions, the rate of reaction first decreases (S_N2 mechanism) and then increases (S_N1 mechanism)[169], and it may therefore be assumed that when the alkyl radical R′ is the strongly electropositive tertiary alkyl group, the splitting will proceed by an S_N1 mechanism. This also explains the ease with which tertiary alkyl imidate hydrochlorides are split, even at the moment of their formation.

Experiments on the hydration of a number of substituted benzonitriles using hydrogen chloride and dimethylethylmethanol aimed at establishing whether the reaction of the nitrile with the hydrogen chloride or the hydration is the rate-determining step gave the same results as in the study of the mechanism of the reaction between nitriles, HCl, and water[35] (see p. 621).

Amides or their hydrochlorides are also sometimes obtained in the reaction of nitriles and hydrogen chloride with primary or secondary alcohols; this was observed, for example, in attempts to prepare primary alkyl imidate hydrochlorides from trichloro-, dichloro-, tribromo-, nitro- and dichloronitro-acetonitrile[162,170-172]. Chloroacetonitrile, which has only one electronegative chlorine atom in the α-position, gives the imidate hydrochloride on reaction with hydrogen chloride and methanol[171]; the use of a secondary alcohol (cyclohexanol) in this reaction gives the imidate or amide hydrochloride, depending on the reaction conditions[163]. α-Phenylaminoacetonitrile gives the amide instead of the imidate[173].

Unlike tertiary alkanols, tertiary alkyl mercaptans react normally with nitriles and HCl, to form the corresponding thioimidate hydrochlorides[161,174].

The scission of imidate salts into amides and alkyl halides may be used preparatively[122]; it has been used for the production of oligomeric amides from adipic acid and hexamethylenediamine[175]:

$$NC(CH_2)_5NHCO(CH_2)_4CONH(CH_2)_5CN \xrightarrow{2C_2H_5OH,2HCl}$$

$$\rightarrow ClH\cdot HNC(OC_2H_5)(CH_2)_5NHCO(CH_2)_4CONH(CH_2)_5C(OC_2H_5)NH\cdot HCl \xrightarrow{-2C_2H_5Cl}$$

$$\rightarrow H_2NOC(CH_2)_5NHCO(CH_2)_4CONH(CH_2)_5CONH_2.$$

C. Reactions with Organic Acids

Treatment of mixtures of nitriles and carboxylic acids with hydrogen halides gives amide hydrochlorides and the acid anhydrides or chlorides[176-180]:

$$RCN + HCl + 2R'COOH \rightarrow \left[RC(NH_2)(OH)\right]^+ Cl^- + (R'CO)_2O,$$

$$RCN + 2HCl + R'COOH \rightarrow \left[RC(NH_2)(OH)\right]^+ Cl^- + R'COCl.$$

A similar reaction is obtained with hydrocyanic acid, hydrogen chloride, and carboxylic acids[181].

An excess of hydrogen halide accelerates the formation of the amide salt[179]. The reaction proceeds in any solvent, polar or non-polar. Under otherwise the same conditions, the basicity of the solvent greatly affects the yield of imidic acid hydrochloride. It must be supposed that the reaction of the HCl with solvents having nucleophilic properties competes with the main reaction and noticeably reduces its rate[180]. However, as in reactions of nitriles and hydrogen chloride with other nucleophilic reagents, the determining factor in the choice of solvent is not its acid-base properties, but the solubility of the reaction components in it.

An excess of the hydrating acid may be used as solvent, and this is particularly useful when the nitrile is poorly soluble in other organic solvents, *e.g.* with *p*-nitrobenzonitrile and *p*-cyanobenzoic acid[180].

Hydration of the cyano-group under the influence of hydrogen bromide and acetic acid or acetic anhydride is evidently the basis of the production of caprolactam from ε-alkoxycapronitriles by way of ε-bromocapramide[182].

Study of the liquid reaction products of acetonitrile, hydrogen chloride, and butyric acid has shown that the acid is converted partly into the anhydride and partly into the acid chloride.

These data and the study of the reaction of a number of substituted benzonitriles with hydrogen chloride and acetic acid[35] show the general relationship between the hydration of nitriles using carboxylic acids and the other reactions described above between nitriles, nucleophilic reagents, and hydrogen halides; we may assume that the initial stages in all these reactions are the same, the reaction products of nitriles and hydrogen halides with acids being converted into the unstable isoimide salts[179]. Since these should possess considerable acylating activity, they react with the acids to form imidic acid hydrochlorides and the acid anhydrides or halides:

$$RC(=\overset{+}{N}H_2Cl^-)(-O-CH(H)-COR')(-O-CR'=O) \rightarrow \left[RC(NH_2)(OH)\right]^+ Cl^- + (R'CO)_2O.$$

N-substituted imidoyl chlorides react with carboxylic acids by an analogous mechanism[183].

The reactive imidoyl derivatives (isoimides) of trichloroacetic acid have been widely used in recent years as reagents for the selective esterification of phosphoric acid derivatives[184-188]. The isoimides are also intermediates in other acylation reactions[189,190].

Nitriles react with thio-acids in the presence of hydrogen chloride by the mechanism[191] given above for carboxylic acids:

$$RCN + R'COSH \rightleftharpoons RC(=NH)(-SCR'=O) \xrightleftharpoons{HCl} RCSNH_2 + R'COCl.$$

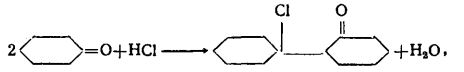
In the presence of hydrogen chloride nitriles react with thio-amides in ether in the cold[192] or in dimethylformamide on heating[193] in the same way as with acids:

$$RCN + R'CSNH_2 \rightleftharpoons RC(=NH)(-S-CR'=NH) \rightleftharpoons RC(NH_2)(=S) + R'CN.$$

This reaction has been proposed for the preparation of thio-amides[193].

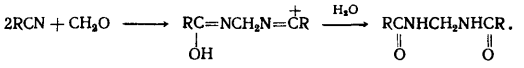
D. Reactions with Carbonyl Compounds

Aldehydes and ketones react with nitriles and hydrogen chloride in the cold to give imidic acid hydrochlorides [194,195] or compounds with a new carbon–nitrogen bond [1]. A necessary condition for the formation of imidic acid hydrochlorides is the ability of the carbonyl compound to undergo autocondensation with the splitting out of water [196]. For example, when a mixture of a nitrile and cyclohexanone is treated with hydrogen chloride, the ketone condenses with itself:



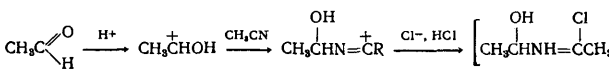
and the liberated water then reacts with the nitrile and hydrogen chloride in the normal way.

In a second process the nitrile and an aldehyde, taken in the molar ratio 2 : 1, react in the presence of hydrogen chloride to form a solvated carbonium ion, which with water gives a bisamide:



The preparation of bisamides from nitriles and aldehydes has been reviewed [1]. In a recent work [196] benzonitrile and hydrogen chloride were reacted with acetaldehyde and benzaldehyde to obtain ethylidene- and benzylidene-bisbenzamide. A bisamide is obtained from *p*-nitrobenzaldehyde, hydrogen cyanide, and hydrogen chloride [72].

The reaction between acetonitrile, acetaldehyde, and hydrogen chloride did not give either a primary amide salt or a bisamide [197]. The salt obtained in the absence of water contains the initial reactants in the ratio 1 : 1 : 2; [196] its chemical properties indicate it to be an *N*-substituted chloroimonium chloride, and the following mechanism has been put forward for its formation:



E. Structure and Chemical Properties of Amide Hydrohalides

Amide hydrohalides were earlier prepared by reacting the corresponding amides with hydrogen halides in inert organic solvents in the cold [198–201]. However, most *N*-unsubstituted amides are insoluble in organic solvents, and this method can therefore only be used to obtain hydrohalides of some of the simplest aliphatic and aromatic amides. Until recently there were almost no published data on the properties of amide hydrohalides, apparently because adequate general methods for their preparation were unavailable. Since, as described above, treatment of nitriles with various hydroxy-compounds can easily yield various amide hydrochlorides, the study of their structure and chemical properties is now of interest.

1. Structure of amide hydrohalides. Carboxylic acid amide salts have one of the following structures:



(G) (H)

The question of which is the actual structure is related to the question of the nucleophilic centre of the amides.

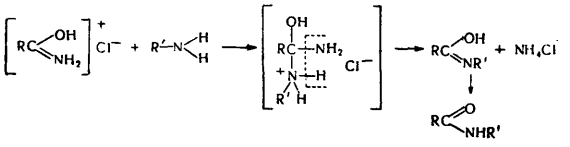
Davidson [202] reviewed a number of reactions between amides and nucleophilic reagents (acids, anhydrides, acid chlorides and amides, and alkyl halides), and concluded that the oxygen atom is the nucleophilic centre of amides. Nuclear magnetic resonance spectra of amides in the pure state and in solution in water, deuterium oxide, and hydrogen and deutero-acids indicate [203–204] that the products are protonated predominantly on the oxygen. Kinetic data on the hydrolysis of amides in concentrated acids [205] and the basicity of amides [206,207] are in accord with the view that it is the amide oxygen and not nitrogen to which the proton attaches. This *N*-protonated imidic acid structure of amide hydrochlorides finds confirmation in the infra-red and nuclear magnetic resonance spectra of the complexes of amides with boron halides and titanium halides [208], the infra-red spectrum of the dimethylacetamide–iodine complex [209], and in other studies [210–213].

In the comparatively old literature [214] amide salts are also given the structural formula (G), and this is still sometimes preferred [215–217]; for example, Spinner [216] attempted to base structure (G) on his infra-red spectroscopic studies. In the spectrum of acetamide hydrochloride he found a band with ν_{max} = 1695 cm^{-1}, which coincides with $\nu_{C=O}$ for acetamide, and he therefore concluded that the proton is attached to the amide nitrogen. However, it has been demonstrated [218] that the presence of this band is due to free amide impurity, and not to the amide hydrochloride.

Comparison of the frequencies observed with acetic, δ-cyanovaleric, adipic, and benzoic acid amide hydrochlorides indicates that the *N*-protonated imidic acid group has the following characteristic frequencies [218]: (*a*) three bands in the 3500–3000 cm^{-1} region, of which the one of shortest wavelength corresponds to ν_{O-H} (this band is not always resolved and is often observed as a shoulder); $\nu_{as}NH_2$ is at 3250 cm^{-1} and νNH_2 at 3160–3200 cm^{-1}; (*b*) a single band in the 1600–1700 cm^{-1} region, the 1650–1660 cm^{-1} frequency corresponding to vibrations of the C=N group.

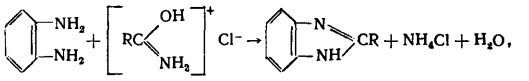
2. Reactions of amide hydrochlorides. Acid amides are weak acylating agents. Fatty acid amides do not react with aniline even at 100°: only on boiling are anilides produced in small amounts [219]. Formylation of amines with formamide proceeds slightly more readily [220], but in practice, because of their comparatively low reactivity in the absence of catalysts, amides are rarely used for acylation [221]. The aminolysis of amides is considerably accelerated in the presence of acid catalysts [222–224]. Good yields of *N*-substituted amides have been obtained in the reaction of amides with amine hydrohalides [225–227]. Jaunin has suggested [223] that the function of the acid catalysts is to add a proton to the amide oxygen to form an imidic acid structure, and this increases the electrophilic reactivity of the carbon atom.

In accordance with these results, the reaction between amines and amide hydrochlorides, which already have the imidic acid hydrochloride structure, would be expected to give a very smooth acylation reaction by the mechanism

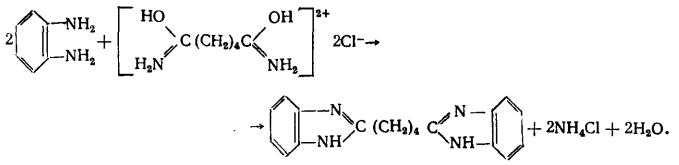


When aniline[228,229] or other aromatic amine[230] was heated with acetimidic acid hydrochloride, δ-cyanovalerimidic acid hydrochloride, and benzimidic acid hydrochloride at 160°–170°, the *N*-acylated amines were sometimes obtained in high yield. Aliphatic amines are acylated with considerably more difficulty than aromatic amines. In the benzoylation of hexamethylenediamine with benzimidic acid hydrochloride, the diamine hydrochloride had to be used in place of the free amine[230].

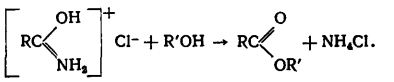
Heating imidic acid hydrochlorides with *o*-phenylenediamine at 140°–190° produces benzoimidazoles in high yields:



where R = CH_3, $(CH_2)_4CN$, C_6H_5;

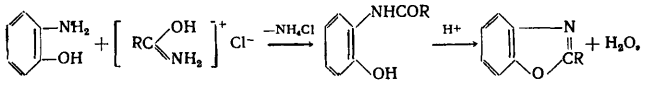


These imidic acid hydrochlorides react at 100°–170° with alcohols (n-butanol, ethylene glycol) and phenols (phenol, *o*- and *m*-cresol, resorcinol monomethyl ether, *p*-nitrophenol) to form the corresponding esters[231]:



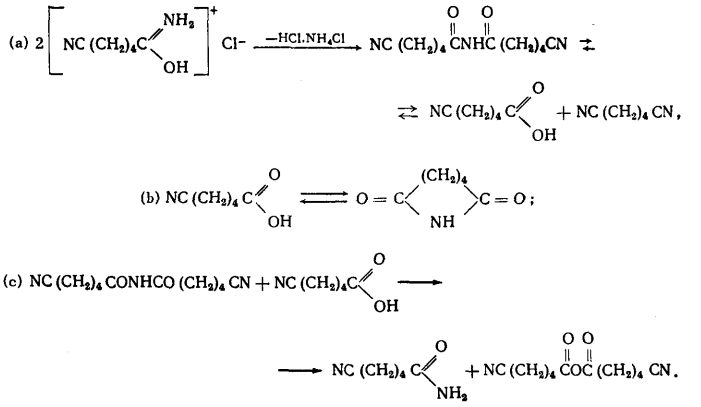
The aliphatic alcohol esters were obtained in 61–75% yields, and the phenol esters in somewhat lower yields. In some cases, *e.g.* in the preparation of ethylene and *p*-phenylene di(δ-cyanovalerates) (from ethylene glycol and hydroquinone), acylation with the imidic acid hydrochloride is more convenient than earlier methods for the preparation of esters.

Two products were obtained by heating *o*-aminophenol with imidic acid hydrochlorides[230], the *o*-hydroxyanilides or the 2-substituted benzoxazoles; the former were the main product if the reaction were carried out under reflux, and the latter if the water of reaction were removed as it formed. Heating the *o*-hydroxyanilides with catalytic amounts of acids converted them into the benzoxazoles; the former are apparently intermediates in the preparation of benzoxazoles from *o*-aminophenol and imidic acid hydrochlorides:



where R = CH_3, $(CH_2)_4CN$ or C_6H_5. In the single-stage production of benzoxazoles (without intermediate separation of the *o*-hydroxyanilides from the reaction mixture) the unreacted imidic acid hydrochloride or the ammonium chloride may act as the acid catalyst. The presence of the acid catalyst should promote lactimisation of the amide group of the *o*-hydroxyanilide; this increases the reactivity of the amide group and the intramolecular interaction of the functional groups thus becomes possible.

Thermal decomposition of imidic acid hydrochlorides gives the acid, acid halide, nitrile, and a secondary amide[199,200]. The mechanism of the decomposition was investigated by studying the pyrolysis products (180°) from δ-cyanovalerimidic acid hydrochloride[232]; hydrogen chloride, ammonium chloride, di(δ-cyanovaleramide), δ-cyanovaleric acid, adiponitrile, adipamide, δ-cyanovaleramide and, apparently, δ-cyanovaleric anhydride were found. The following mechanism based on these results was suggested:



The pyrolysis of other imidic acid hydrochlorides shows the same features. This reaction may be used for the preparation of secondary amides[232]. The reaction between formamide hydrochloride and *m*-nitrobenzaldehyde gives *m*-nitrobenzylidenebisformamide[72].

The thermal decomposition of amide hydrochlorides thus gives products which are formed from the free amides only at considerably higher temperatures[224,233,234]. This difference in the behaviour of amides and their hydrochlorides is apparently due to the latter existing in the more reactive imidic acid form.

F. Selective Reactivity of One Cyano-Group in Adiponitrile

Several instances of the selective reactivity of one of the two cyano-groups of adiponitrile with hydrogen chloride and nucleophilic reagents (water, primary alcohols, and diprimary glycols) have been described above. Aliphatic dinitriles with a hydrocarbon chain shorter or longer than adiponitrile do not exhibit this selective reactivity of one cyano-group[111]. The different reactivities of the cyano-groups in adiponitrile and such compounds as, for example, δ-cyanovalerimidic acid hydrochloride and alkyl δ-cyanovalerimidate hydrochlorides are apparently due to the particular molecular configuration of adipic acid derivatives with the formation of cyclic systems[111,235].

One cyano-group of αα′α′-tetrachloroadiponitrile could not be selectively hydrated in the presence of hydrogen chloride; the mutual repulsion between the chlorine atoms and the nitrile nitrogen apparently hinders the formation of cyclic systems during the hydrochlorination and hydration. However, treatment of β-methyladiponitrile with HCl and water in the ratio 1 : 2 : 1 with subsequent hydrolysis gave a mixture of nitrile-amides in high yield. The introduction of the β-methyl substituent into adiponitrile apparently restricts its internal rotation, so that "convoluted" configurations are more easily formed and the reacting groups approach each other more closely[235].

With adiponitrile itself, the selective reactions of one cyano-group with hydrogen chloride take place under rigorously defined conditions. The interaction between the solvent, dinitrile, and hydrogen chloride has a large influence on the reactivity of adiponitrile. In the reaction

between adiponitrile, hydrogen chloride, and water (in the ratio 1:2:1) at 0° selective reactivity is found in isopropyl, ethyl or butyl ether as solvent, but not in solvents which are more basic (tetrahydrofuran, tetrahydropyran or dioxane) or less basic (benzyl ether, β-chloroethyl ether, carbon tetrachloride, toluene, benzene, dichloroethane, or chloroform) than the above ethers [235]. At room temperature there is no selective reaction of one cyano-group of adiponitrile with hydrogen chloride and water, even in ether [235].

There is no selective reaction of one cyano-group of adiponitrile with hydrogen chloride and such nucleophilic reagents as acetic acid [179] and alkanethiols [235], apparently because of the high reactivity of the hydrogen atom of mercapto- and carboxy-groups, which readily interact with the cyano-group and so destroy the unstable intramolecular ring of the reacting molecule; this straightens out, and both adiponitrile cyano-groups become energetically equivalent.

A non-equivalent reactivity of the two cyano-groups of adiponitrile is also sometimes found in the absence of hydrogen chloride. The formation of the unsymmetrical amidoxime has been described [236]:

$$NC(CH_2)_4CN + NH_2OH \longrightarrow NC(CH_2)_4C\begin{matrix}NOH\\NH_2\end{matrix}.$$

Hydrogenation of adiponitrile can produce ε-aminocapronitrile in high yield [237-240]:

$$NC(CH_2)_4CN + 2H_2 \longrightarrow NC(CH_2)_5NH_2.$$

G. Reactions with Amines

The most general method for the preparation of amidines from nitriles is based on the reaction between imidate hydrohalides and amines [241]. Many attempts have been made to obtain amidines directly from nitriles without the intermediate stage of imidate salt formation, but the direct addition of amines only proceeds readily with nitriles having two or three α-halogen atoms, *e.g.* trichloroacetonitrile and trifluoroacetonitrile [242-248]:

$$CF_3CN + NH_3 \longrightarrow CF_3C\begin{matrix}NH\\NH_2\end{matrix}.$$

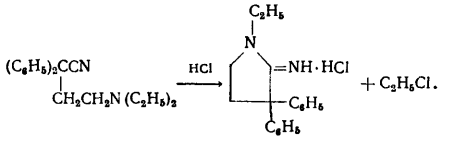
The amination of α-halogeno-nitriles is accelerated in the presence of hydrogen halides (in practice, amine hydrohalides) [242]. Primary and secondary aliphatic amines add to hydrogen cyanide to form unstable formamidines, which with water are converted into *N*-substituted formamides [249,250].

When nitriles free of electronegative substituents react with ammonia or amines in the presence of the base hydrohalide, amidines are generally not formed or are formed in only moderate yields. The rather sparse literature on these reactions has been given in a review on the chemistry of amidines [241].

Amidine hydrohalides are usually prepared from nitriles and amine hydrohalides at 170°–200° or above [241,251,252]. The thermally unstable nitrile–hydrogen halide compounds cannot participate in the reaction under these conditions, and compounds of the halogenoimonium halide type easily lose hydrogen halide in the presence of amines. The activating effect of hydrogen halides in the preparation of amidines from nitriles may be explained by a mechanism similar to those already given (see p. 619).

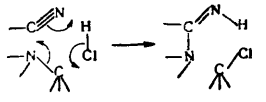
One case has been described in which a chloroimonium chloride reacts with an amine in the cold [32]: at -16° acetonitrile dihydrochloride and dimethylaniline yield α-tri(dimethylaminophenyl)ethane.

The amidine group is formed by intramolecular condensation when various γ-, δ-, and ε-amino-nitriles are heated with hydrogen chloride or hydrochloric acid [253-257]; for example, at 275° αα-diphenyl-γ-diethylaminobutyronitrile gives 1-ethyl-2-imino-3,3-diphenylpyrrolidine hydrochloride:



Certain 2-iminopyridine and 2-iminohexamethyleneimine hydrochlorides have been prepared analogously. Hydrolysis of 2-iminopolymethyleneimines sometimes yields the corresponding lactams.

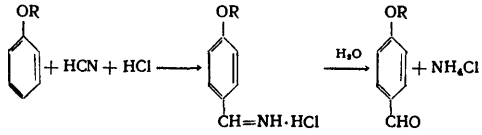
Since the 2-iminohexamethyleneimines are obtained at high temperatures, it is difficult to see how the unstable hydrochlorides of the initial nitriles can be intermediates [257]. A more probable interpretation of the intramolecular reaction between the functional groups is cyclic electron transfer:



H. The Gattermann Reaction

The Gattermann and Hoesch (Houben–Hoesch) reactions differ from the reactions between nitriles, hydrogen halides, and nucleophilic reagents described above, in that new carbon–carbon bonds are formed.

In the Gattermann reaction [258] an aromatic compound reacts in an inert solvent in the cold with hydrogen chloride and hydrocyanic acid to yield an aldimine hydrochloride, which on hydrolysis is converted to the aldehyde:



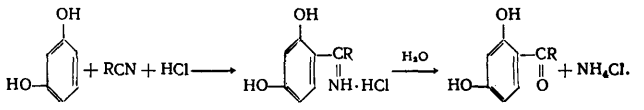
According to Gattermann, hydrogen cyanide and hydrogen chloride react under the above conditions to produce formimidoyl chloride HC(:NH)Cl, but as in the case of hydrochlorination products of nitriles, hydrogen cyanide monohydrochloride does not apparently exist (see p. 619).

Hinkel and coworkers [259] suggested that in the Gattermann synthesis the hydrogen cyanide and hydrogen chloride react as chloromethyleneformamidine (2HCN.HCl), so that the reaction product is not an aldimine hydrochloride, but an arylmethyleneformamidine hydrochloride RCH=NCH=NH.HCl. Later [70] Hinkel showed that this view of the intermediates in the Gattermann reaction is incorrect, and he put forward [260] a new mechanism, according to which the aromatic compound reacts with the sesquichloride 2HCN.3HCl; however, this also is not supported by the experimental data on the Gattermann synthesis of aldehydes, and contradicts more recent views on the structure of hydrogen cyanide hydrochlorides [78].

Hydrogen cyanide dihydrochloride (a compound of the chloroimonium chloride type) is unknown, or at least is not formed in the Gattermann reaction, and the only remaining possibility is that stable hydrogen cyanide hydrochlorides are not intermediates when the reaction is carried out in the normal manner (by passing hydrogen chloride into a mixture of the aromatic compound, hydrogen cyanide, and $ZnCl_2$ or $AlCl_3$ as catalyst). The reaction apparently involves the formation of unstable complexes between hydrogen chloride, hydrogen cyanide, and the catalyst, with a reduced electron density at the cyano-carbon atom. Analogous mechanisms for reactions of nitriles are given above. The Gattermann synthesis has been reviewed [261,262].

J. The Hoesch Reaction

The first studies describing the synthesis of ketones by the Hoersch reaction were developments of the Gattermann reaction. The Hoesch ketone synthesis [263] is based on the reaction, in a solvent, between a nitrile, hydrogen chloride, and a phenol (usually a polyhydric phenol) to form a ketimine hydrochloride, followed by hydrolysis:



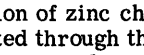
The suggestion [264] that the primary reaction products are imidate hydrochlorides which then rearrange to ketimine hydrochlorides has not been confirmed [265]. Most workers consider that under the conditions of the Hoesch synthesis the nitrile and hydrogen chloride react to form the imidoyl chloride, which then condenses with the phenol [264,266,267]. Zil'berman and Rybakova have put forward [268] new mechanisms for the formation of ketimine hydrochlorides in the Hoesch synthesis, similar to those described above for the reaction of nitriles with hydrogen chloride and hydroxy--compounds.

The utility of the Hoesch synthesis is considerably increased when it is carried out in accordance with these mechanisms [268]. Unlike the usual procedures [266] for preparing ketones by the Hoesch reaction, the reaction between the nitrile and hydrogen chloride and the subsequent electrophilic attack on the phenol are carried out separately. In many cases it has also been found preferable to carry out the reaction not at room temperature, but at 0° (decreasing the temperature increases the stability of the saltlike nitrile hydrohalides [14]). The use of the new procedure has shown that, contrary to published opinion [266], ketimine hydrochlorides can be obtained from aromatic nitriles in yields as high as those obtained with aliphatic nitriles [268]. Diketones have been obtained in high yields from resorcinol and various dinitriles (adiponitrile, pimelonitrile, sebaconitrile, *p*-xylylene dicyanide, etc.) [269], although it had previously been considered [266] that the Hoesch synthesis is of little value for the production of diketones.

Of the more interesting studies of the Hoesch synthesis appearing after Spoerri and Du Bois' review [266], mention may be made of the condensation of resorcinol or its derivatives with trichloroacetonitrile and hydrolysis of the reaction products to the corresponding benzoic acid derivatives [270].

Under the conditions of the Hoesch synthesis, cyanopyridines react with pyrroles and indoles to yield the corresponding ketimines and hence the corresponding ketones [271]. Dihydroisoquinolines have been obtained by condensation of the chlorination products of various amides with isosafrole and methylisoeugenol; the suggested mechanism for this reaction is close to that of the Hoesch synthesis [272].

The most frequently used catalyst in the Hoesch synthesis is zinc chloride [266]; in individual cases ferric chloride [273] or aluminium chloride [274,275] is a more suitable catalyst. The catalytic action of zinc chloride has recently been investigated in more detail [38]. It might have been expected that the catalytic action of zinc chloride on the Hoesch synthesis is manifested through the complexes $RCN.ZnCl_2$ and $(RCN)_2.ZnCl_2$ or the nitrilium salt $[RCNH]^+ZnCl_3^-$, but stable complexes of such structures were tested and found not to react with resorcinol in many cases, particularly at low temperature. It has been suggested that in the presence of zinc chloride the Hoesch synthesis involves the formation of unstable complexes with a covalently-bonded $ZnCl_3$ group, *e.g.*:

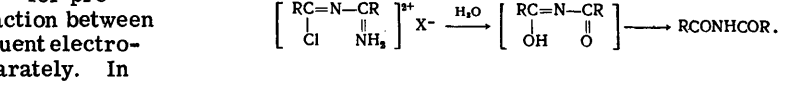


The part played by the zinc chloride in the production of ketimine hydrochlorides from nitriles which under the conditions of the Hoesch synthesis react with hydrogen chloride to form salts of the *N*-alkylideneamidine type [38], is interesting; it was found that in the reaction between resorcinol, hydrogen chloride, and chloroacetonitrile the catalyst acts primarily to prevent dimerisation of the nitrile.

In the presence of $SnCl_4$ and $TiCl_4$, which readily form stable complexes with nitriles, ketimine hydrochlorides are produced only in very low yields [38].

K. Reaction of Dimeric Nitrile Salts (2RCN.*n*HX) with Hydroxy-Compounds

1. Reaction with water. The structures of most of the known dimer salts of composition 2RCN.*n*HX, where *n* is 1 or 3, have been proved by reaction with water:

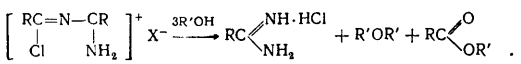


This method for the production of secondary amides was known [59,63] even before Grundmann and coworkers suggested [60] this formula for the dimer salts. The reaction is usually carried out by dissolving the dimer salt in water at room temperature or at 0°. A modified procedure has been used to prepare hexachlorodiacetamide without further hydrolysis of the product at the moment of its formation: a suspension of the trichloroacetonitrile dimer salt in chloroform was shaken with an excess of finely ground ice [60].

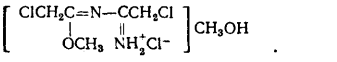
Hydrolysis of the dimer salts derived from chloroacetonitrile and hydrogen bromide yields $\alpha\alpha'$-dichlorodiacetamide having some of the chlorine atoms replaced by bromine. A similar exchange also took place in the reaction of bromoacetonitrile dimer salt with hydrogen chloride [34].

The $\alpha\alpha'$-dichlorodiacetamide obtained from chloroacetonitrile, deuterium chloride, and deuterium oxide contained 1.5 atoms of deuterium. The infra-red spectrum of the deuterated dichlorodiacetamide indicated the presence of N–H, N–D, C–H, and C–D bonds [116].

2. Reaction with alcohols (amidine hydrochloride synthesis). Treatment of dimer salts of composition 2RCN.*n*HX derived from fluoro-, chloro-, and bromo-acetonitrile with primary and secondary alcohols at room temperature causes unsymmetrical scission, with the formation of halogenoacetamidine hydrochlorides, ethers, and esters [34,62,276]:



Methanol reacts anomalously; instead of the chloroacetamidine salt, it gives a compound of empirical formula $2ClCH_2CN.2CH_3OH.HCl$, which with water gave chloroacetamidine hydrochloride. The primary reaction product probably has the constitution

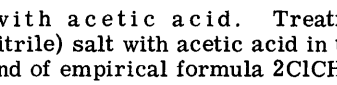


The reaction of the dimer salts with other alcohols apparently also involves a first step in which a labile chlorine atom is replaced by an alkoxy-group, but the resulting intermediates are unstable and cannot therefore be isolated.

The fact that alcoholysis of the dimer salt produces (in addition to the amidine hydrochloride) a mixture of ester and ether, and not an ortho-ester, merits attention. Certain imidate salts also react with alcohols to yield a mixture of ester and ether instead of an ortho-ester [277].

Cyclohexanol reacts with the di(chloroacetonitrile) salt to form a molecular compound of chloroacetamidine hydrochloride with cyclohexanol [34].

3. Reaction with acetic acid. Treatment of the di(chloroacetonitrile) salt with acetic acid in the cold produces a compound of empirical formula $2ClCH_2CN.CH_3COOH.HCl$, most probably having the structure



With water it yields *sym*-dichlorodiacetamide [34].

IV. REDUCTION OF NITRILES IN THE PRESENCE OF HYDROGEN CHLORIDE

According to the data available, the reduction of nitriles in the presence of hydrogen chloride may produce three types of compound: (*i*) aldimines, which on hydrolysis yield aldehydes; (*ii*) acyclic trimerisation products, which give bisamides with water; and (*iii*) amines.

A. Preparation of Aldehydes by the Stephen Method

Nitriles can be reduced in the presence of hydrogen chloride by the Stephen method [278] with stannous chloride; stannous bromide also gives good results. Chromous chloride, vanadium trichloride, and titanium trichloride could not be used as reducing agents in this reaction [279]. The reaction is usually carried out in ether, dioxane, chloroform, ethyl acetate, or other solvent at about room temperature. Aromatic nitriles, as a rule, give good yields of aldimines and hence of aldehydes. Adehydes cannot always be obtained from aliphatic nitriles [280].

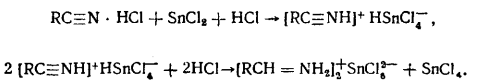
The Stephen reaction has been reviewed [281,282]. After the appearance of these reviews, it was shown that a reaction competing with the reduction of the nitrile to the aldimine is the conversion of the nitrile to the imidate, which takes place under the action of the alcohol formed as a result of scission of the ethyl ether by the hydrogen chloride. At elevated temperatures this process may completely suppress the reduction of the nitrile [283].

The effect of steric hindrance in the reduction of substituted benzonitriles has been investigated [284].

The order in which the various reactants enter into the reaction has not been studied. It must be assumed that, as in other reactions of nitriles in the presence of hydrogen halides, outer and inner complexes of nitriles with hydrogen halides and chloroimonium chlorides are formed in the Stephen synthesis of aldehydes also; Stephen's last study [285] supports this assumption.

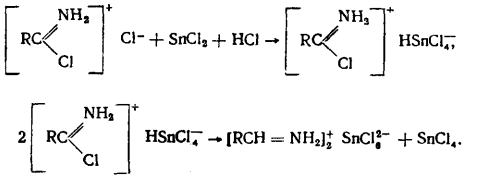
Although earlier the reaction was usually carried out [281] by adding the nitrile to the solution of stannous chloride and hydrogen chloride, according to a modified procedure [285] a solution of the nitrile in the inert solvent is saturated with hydrogen chloride at 0°, and then a solution of stannous chloride and hydrogen chloride in the same solvent is added. The modified Stephen method gives higher yields of aldehydes, presumably because of preliminary reaction between the nitrile and hydrogen chloride at the low temperature.

The mechanism of the Stephen reaction with the intermediate formation of nitrilium salts [282] may be represented as follows:



The aldimine hexachlorostannates very often separate from the reaction mixture as easily crystallising precipitates [281].

If the intermediates are chloroimonium chlorides, the probable mechanism is

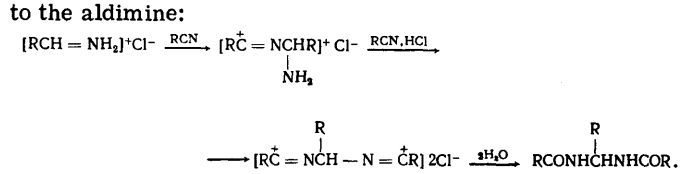


B. Preparation of Bisamides in the Reduction of Nitriles by the Stephen Method

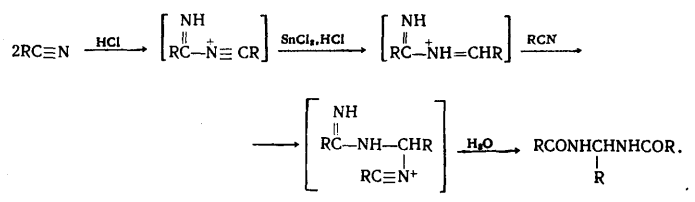
Stephen showed [278] that aliphatic nitriles are reduced to aldimines as readily as aromatic nitriles; however, more recent workers have found [286] that the reduction of lauric acid nitrile by stannous chloride followed by hydrolysis produces not the aldehyde [287], but the *NN'*-alkylidenebisacylamide RCONHCH(R)NHCOR.

Two mechanisms have been suggested for the formation of bisamides in the reduction of nitriles. The intermediate which is hydrolysed to the bisamide may be

formed[286] by the stepwise addition of two nitrile molecules to the aldimine:



According to Meerwein[282], there is first formed a product from two nitrile molecules, similar to the dimer salts of α-halogenoacetonitriles (see p. 618), which is then reduced. The reduction product reacts with a third nitrile molecule to form a salt, which is hydrolysed to the bis-amide:



C. Preparation of Amines

In certain extremely rare cases the reduction of nitriles by the Stephen method does not stop at the aldimine stage, but proceeds further to form primary amines[288]. An analogous effect is observed in the stannous chloride reduction of various heterocyclic *N*-phenylimidoyl chlorides, where the reaction products were not the aldimines expected by Sonn and Müller[289], but secondary amines[290].

Hydrogen chloride also promotes the catalytic hydrogenation of nitriles[291-295]; for example, mandelonitrile is reduced on a palladium catalyst to phenylacetonitrile in the absence of hydrogen chloride and to phenylethylamine in its presence. The influence of hydrogen chloride on the catalytic reduction of nitriles is apparently due to the formation of reactive complexes between the nitriles and HCl.[294]

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CHEMICAL ADVANCES IN SYNTHESIS AND REACTIONS OF DIARYLUREAS

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CONTENTS

I. Introduction 634
II. Synthesis of diarylureas by phosgenation of aromatic amines 634
III. Conditions for and mechanism of the phosgenation of aromatic amines 636
IV. Synthesis of diarylureas and arylalkylureas by the reaction of amines with aryl isocyanates 639
V. Synthesis of dialkylureas and diarylureas by the reaction of amines with urea 641
VI. Conditions for and mechanism of the reaction of diarylureas with aromatic amines 644
VII. Synthesis of substituted diarylureas by nitration, chlorination, and sulphonation of diphenylurea 646
VIII. Hydrolysis and other reactions of diarylureas 648
IX. Synthesis of aromatic amines *via* diarylureas and by other new methods 650