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SOME REACTIONS OF NITRILES WITH THE FORMATION OF A NEW NITROGEN–CARBON BOND

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INTRODUCTION

Since the nitrogen atom is more electronegative than the carbon atom, the negative charge in nitrile molecules is displaced towards the former. The triple bond in the nitrile group is made up of one σ-bond and two π-bonds, and since a π-bond is more polarised than a σ-bond, nitrile molecules are particularly polar. In fact, with the interatomic distance in the nitrile group of 1.15 ± 0.02 Å [1,2], the dipole moments of aliphatic nitriles are 3.44–3.65 *D* in solution[3] and 3.94–4.09 *D* in the vapour phase[4]. The considerable polarity of the nitrile group is the cause of its ability to enter into addition reactions:

$$-\overset{\delta+}{C}\equiv\overset{\delta-}{N}$$

Moreover, as Newman pointed out[5], addition to the nitrile triple bond is less dependent on steric factors than addition to the double bond in carbonyl and other compounds.

The review literature has been mainly concerned with the reactions of nitriles with nucleophilic reagents (hydroxylamines, hydrazine, ammonia, etc.)[6]. The Hoesch synthesis, in which the nitrile group reacts in the presence of hydrogen halides to form a carbon–carbon bond, has been reviewed[7,8]. The preparation of iminoether hydrohalides (the formation of a carbon–oxygen bond) by the reaction of the nitrile group with alcohols and hydrogen halides was the subject of a large monograph[9] and has been treated in many reviews[7,10]. The literature on the Stephen reaction (the synthesis of aldehydes from nitriles in the presence of hydrogen chloride and stannous chloride) has been collated[11].

However, the reactions of the nitrile group involving the formation of a nitrogen–carbon bond has received very little attention in the review literature. Migrdichian's book "The Chemistry of Organic Cyanogen Compounds" contains only one chapter on this subject, relating to the polymerisation of nitriles[7]. Other reactions, particularly those discovered in the last 10–15 years, are barely mentioned in reviews.

The present review is an attempt to fill this gap, and is concerned with those reactions of nitriles in which a new nitrogen–carbon bond is formed, catalysed by protonic or Lewis acids.

The electrophilic reactivity of nitriles has never been in doubt. Remick[12] considered that since the tendency of the carbon atom, with a deficit of electrons, to accept electrons is greater than the tendency of the nitrogen atom, with an excess, to make these available, nitriles must possess predominantly electrophilic reactivity, but he supposed that they may also show nucleophilic properties. The considerable experimental and theoretical material accumulated since

the publication of Remick's book (1945), shows clearly that reaction at the nucleophilic nitrogen atom is important. The nucleophilic character of the nitriles is caused by the presence in the $-C\equiv N$ group of an unshared electron pair and the electron-donating π-bonds. The nucleophilic properties of nitriles are shown by the formation of molecular compounds with electrophilic reagents (see, for example, Tronov and Strel'nikova[13]). The addition of such reagents to the electron pair of the nitrogen atom of the nitrile group usually gives molecular compounds containing equivalent amounts of both substances. It has been suggested[14] that the addition to a nitrile of more than one equivalent of an electrophilic substance is due to the formation of so-called π-complexes.

The part played by acids in nucleophilic reactions of nitriles is primarily due to their increasing the electrophilic properties of the reagents reacting with the nitriles. The acid and the electrophilic reagent may form a carbonium ion by one of the following reactions:

$$RX + A \rightleftarrows R^+ + AX^-,$$
$$R_1 + HB \rightleftarrows R_1H^+ + B^-.$$

In the first reaction a protonic or Lewis acid (e.g. $AlCl_3$) reacts with the negative substituent X of the reagent RX (e.g. an alkyl halide or alcohol) to form a carbonium ion and an anion (e.g. $AlCl_4^-$). In the second reaction the hydrogen acid HB increases the electrophilic properties of compounds such as olefines or ketones and aldehydes (R_1) by protonating them.

The resulting carbonium ions then react with the unshared electron pair of the nitrile nitrogen, or, what is equivalent, with the π-electrons of the triple bond:

$$R'C\equiv\overset{\curvearrowright}{N}\!\!-\!\!\overset{\curvearrowright}{R}^+ \longrightarrow [R'C\cong NR]^+$$

The new cation, in which the positive charge is concentrated on two atoms (the nitrogen and the carbon), can be stabilised by the anion present in the reaction mixture, or can react with the solvent or any other nucleophilic substance, for instance:

$$[R'C\cong NR]^+ + AX^- \rightarrow R'C\!\!\begin{array}{l}\diagup\!\!\!\diagup NR\\ \diagdown\!\!\!\diagdown X\end{array} + A.$$

It is understood that the above schemes, like most of those used in this review, must be considered only as models of the more complex conversions which actually occur. In particular, the acids can react with compounds which act as electron acceptors in the reactions with the nitriles to form strongly electrophilic molecular compounds instead of cations[15]. Complete conversion to the nitrilium salt need not take place. It is possible that the addition of the electrophilic and nucleophilic components to the nitrile group takes place in one stage with the formation of a single transition state. However, the main scheme of nucleophilic reactions of nitriles is not changed by this.

Work on N-substituted nitrilium salts recently prepared by Meerwein[16] supports the above scheme. N-Alkyl and N-aryl nitrilium salts react chiefly by addition to the electrophilic carbon atom. With water they give N-substituted amides, with alcohols iminoethers, with amines amidines, and so on.

$$[R'C\overset{\curvearrowright}{\equiv}\overset{\curvearrowright}{N}R]^+X^- + H\ddot{O}C_2H_5 \longrightarrow \underset{\ddot{O}C_2H_5}{RC=\ddot{N}R} + HX$$

The structure of the nitrilium salts has been confirmed spectroscopically[17]. The reaction of the nitrilium salts with nucleophilic molecules or ions to form new nitrogen–carbon bonds (as well as the existence of these salts) confirms that the nucleophilic reactions of nitriles can take place by the above scheme.

We begin the review of reactions of nitriles as nucleophilic agents with a description of the nitrilium salts and their reactions. Other sections (3–7) are concerned with other reactions of nitriles as nucleophilic reagents (the synthesis of bis-amides from nitriles and aldehydes, the synthesis of N-substituted amides by the Ritter and analogous reactions, the polymerisation of nitriles to symmetrical triazines, etc.) which take place in acid medium or in the presence of acid catalysts. Probably in most of these there is direct reaction between the nitrile nitrogen and the electrophilic carbon.

As regards the polymerisation reactions of nitriles, the formation of the new nitrogen–carbon bond is achieved by the simultaneous appearance of nucleophilic and electrophilic reactivity in the nitrile group, as will be shown in section 6.

Nitriles can take part in the formation of a new nitrogen–carbon bond by sharing the electron pair of the nitrile nitrogen with a carbon atom of the electrophilic reagent, and also by other reactions. These include acid-catalysed reactions in which nitriles react as electron accepting substances, with the formation of a new carbon–oxygen bond. The nitrogen–carbon bond then arises by intramolecular rearrangement of the resulting compound. In these reactions the acids, by reacting with the nitrile nitrogen, cause a decrease in the electron density on the carbon atom of the $C\equiv N$ group and so increase its electron accepting properties, e.g.:

$$RC\equiv N + HB \rightleftarrows [RC\cong NH]^+ + B^-.$$

This group of reactions includes the synthesis of imides from nitriles and carboxylic acids (section 8) where the nitrogen–carbon bond arises by the rearrangement of the O-acyl compounds to the N-acyl compounds.

It should be noted that the considerations given above are insufficient to explain the mechanism of certain of the reactions reviewed here. The corresponding sections of the review will indicate the possibility of the reactions taking place by other mechanisms.

1. N-SUBSTITUTED NITRILIUM SALTS

Recently Meerwein and his coworkers[16] have developed methods for the preparation of stable nitrilium salts of the general formula $[RC\cong NR']^+X^-$, where R is alkyl or aryl, R' is alkyl, aryl, or acyl, and X^- is an anion. The N-alkyl nitrilium salts are formed by the reaction of aliphatic or aromatic nitriles with trialkyloxonium salts of complex halogenoacids:

$$C_6H_5CN + [(C_2H_5)_3O]^+AlCl_4^- \rightarrow [C_6H_5C\cong NC_2H_5]^+AlCl_4^- + (C_2H_5)_2O.$$

Fluoroborates and hexachloroantimonates can also be prepared by this method. Another method which has been suggested for the preparation of N-alkyl nitrilium salts is the reaction between alkyl halides and the molecular compounds of nitriles with metal chlorides, for example:

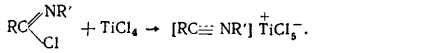
$$CH_3C\equiv\overset{+}{N}\cdot\bar{S}bCl_5 + C_2H_5Cl \rightarrow [CH_3C\cong NC_2H_5]^+SbCl_6^-.$$

The rate of addition in this reaction decreases in the series tertiary > secondary > primary alkyl chloride. The molecular compounds of nitriles with ferric chloride, aluminium chloride, and stannic chloride add alkyl halides

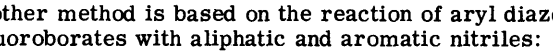
less readily than the compounds with antimony pentachloride.

Acyl chlorides add to the molecular compounds of nitriles with electrophilic metal chlorides analogously to the alkyl chlorides, forming salts which usually contain at least two molecules of nitrile for each acyl chloride molecule.

The above reactions are not applicable to the preparation of *N*-aryl nitrilium salts. These are easily obtained by the reaction of electrophilic metal chlorides with *N*-aryl iminochlorides[16,18]:

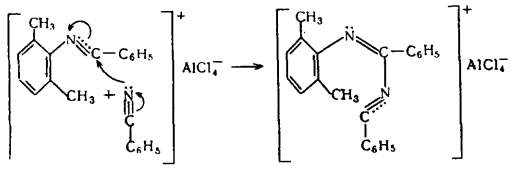


Another method is based on the reaction of aryl diazonium fluoroborates with aliphatic and aromatic nitriles:

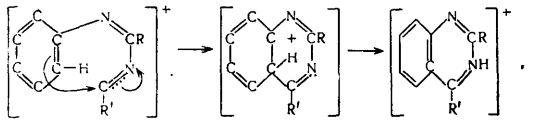


This synthesis was developed by Meerwein[16]. However, it had already been shown that *N*-aryl nitrilium salts are intermediates in the formation of substituted amides in the reaction of nitriles with diazonium salts[19,20].

The nitrilium salts can also add on a second molecule of nitrile[21]:

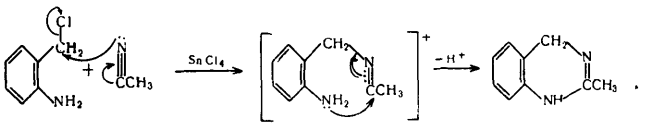


The same product is obtained by the reaction of *N*-aryl iminochlorides with the molecular compounds of nitriles and electrophilic metal chlorides. These new nitrilium salts correspond to the products of composition 2RCN.HCl described by Grundmann and coworkers[22] (see section 6). Nitrilium salts containing two nitrile molecules can only be obtained (as the above equation indicates) when the *o*-positions of the *N*-aryl group are substituted. In the presence of *o*-hydrogen atoms, intramolecular condensation occurs, with electrophilic substitution in the benzene nucleus, forming quinazolinium salts. On treatment with alkali these are converted to quinazolines:

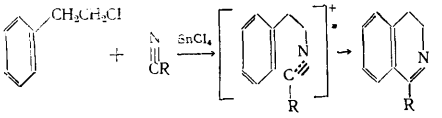


The quinazoline synthesis is simplified if it is combined with the preparation of the substituted iminochlorides. For example, heating a solution of benzanilide in benzonitrile with thionyl chloride and aluminium chloride produces 2,4-diphenylquinazoline in good yield. Iminoethers may be used instead of the substituted iminochlorides in the synthesis of quinazolines.

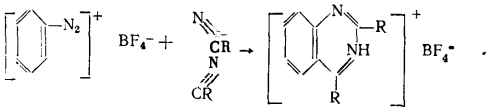
2-Methyl-1,4-dihydroquinazoline has been prepared from *o*-(chloromethyl)anilinium chloride, acetonitrile, and stannic chloride, by an intramolecular reaction in the nitrilium ion[23]:



Intramolecular reaction also results in the formation of 3,4-dihydroisoquinolines by heating equimolecular quantities of β-chloroalkylbenzenes and the complexes of stannic chloride with nitriles[23]:

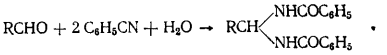


Quinazolinium salts are also formed when aryl diazonium tetrafluoroborates or other diazonium salts are heated with nitriles[21]:



2. PREPARATION OF BIS-AMIDES BY REACTION OF NITRILES WITH ALDEHYDES

In 1876 Hepp and Spiess[24] showed that at room temperature the reaction of aliphatic aldehydes with benzonitrile in the presence of excess concentrated sulphuric acid produces bis-amides:



This reaction was later carried out with benzyl cyanide[25,26] and a number of other compounds[27,28]. Comparatively recently it was found[29,30] that aliphatic nitriles also condense with aliphatic aldehydes. Methylene-bis-vinylacetamide has been prepared from allyl cyanide and paraformaldehyde in the presence of 85% phosphoric acid at 60°[31]. Sulphuric acid produces benzylidene-bis-acetamide from acetonitrile and benzaldehyde[32]. Formaldehyde has been used as the bisulphite compound for condensation with benzonitrile[26].

It is clear[33] that nitriles react smoothly only with those aliphatic aldehydes which do not contain α-hydrogen atoms. Under the reaction conditions, aldehydes with α-hydrogen atoms generally undergo autocondensation. Chlorosulphonic and other acids may be used as catalysts in place of sulphuric and phosphoric acids. Mixtures of sulphuric with acetic[25] or formic[33] acid are also used; the reaction temperature must not exceed 30°–50°. If formic acid alone is used as catalyst, the temperature must be raised to 100°[33].

Hydrogen chloride also influences the condensation of aldehydes with nitriles favouring formation of bis-amides[34,35]. A bis-amide is formed by passing hydrogen chloride into an ethereal solution of an aliphatic nitrile[36] or benzoylmandelonitrile[37] and an aromatic aldehyde and subsequently treating with water. A variation of this method, recently

patented[38], comprises passing hydrogen chloride into a mixture of nitrile, formalin, and concentrated hydrochloric acid.

Under the conditions of the Stephen reaction (passing hydrogen chloride into an ethereal solution of a nitrile in the presence of stannous chloride) certain aliphatic nitriles have produced bis-amides, apparently formed by condensation of the nitriles with their products of hydrochlorination[39]. The patent literature describes the catalytic vapour-phase preparation of bis-amides from aliphatic aldehydes and aliphatic or aromatic nitriles[40] (including halogen- and carboxyl-substituted mononitriles[41,42]) in the presence of water and hydrogen halides, formic acid, or acetic acid. The optimum temperature is 350°–380°, with a catalyst containing boron phosphate and alumina or other acidic compounds. For example, methylenebis(α,β-dibromopropionamide) has been obtained from acetaldehyde and α,β-dibromopropionitrile[41]. ω,ω'-Substituted bis-amides can be used to prepare high polymers[43,44], in particular by treating methylenebis(β-chloropropionamide) with metal sulphides or polysulphides[45].

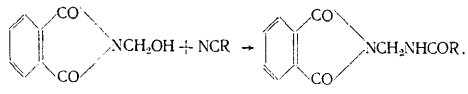
The mechanism of the synthesis of bis-amides has been studied in a number of researches[30,33,46]. It has been suggested that an amide is first formed, which then reacts with the aldehyde. However, the conditions for the preparation of bis-amides from amides and from nitriles are different. Since amides do not react with formaldehyde under the conditions for the synthesis of bis-amides from nitriles, Magat[33] has suggested a mechanism in which carbonium ions take part:

$$CH_2O + H^+ \rightleftarrows HOCH_2^+,$$

$$HOCH_2^+ + RCN \rightleftarrows \overset{-}{R}C{=}NCH_2OH \rightleftarrows \underset{OH}{RC{=}NCH_2^+},$$

$$\underset{OH}{RC{=}NCH_2^-} + RCN \rightleftarrows \underset{OH}{RC{=}NCH_2N{=}\overset{+}{C}R} \xrightarrow{H_2O} \underset{O}{RCNHCH_2}\underset{O}{NHCR}.$$

In agreement with this mechanism, *N*-(hydroxymethyl)-phthalimide reacts with certain nitriles in concentrated sulphuric acid to form methylene-bis-amides[47]:



The synthesis of methylene-bis-amides from *N*-(hydroxymethyl)amides and nitriles[48] is essentially the second step of Magat's mechanism:

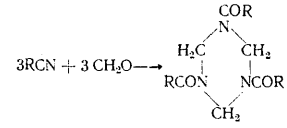
$$RCONHCH_2OH + R'CN \xrightarrow{H_2SO_4} RCONHCH_2NHCOR'.$$

The use of dinitriles in the synthesis of bis-amides has enabled a series of new polyamides to be prepared. The first high-molecular compound of this type (1-*n* polyamides) was obtained by reacting trioxane with azelaic acid dinitrile in sulphuric acid[30]:

$$CH_2O + NC(CH_2)_7CN \xrightarrow[H_2O]{H_2SO_4} \underset{O}{NC(CH_2)_7}\underset{O}{C}[\underset{O}{NHCH_2NHC}(CH_2)_7\underset{O}{C}]_n\underset{O}{NHCH_2NHC}(CH_2)_7CN.$$

Adiponitrile and other aliphatic dinitriles[49] and dinitriles obtained by the cyanethylation of glycols[50] have also been used in this reaction. The properties of the 1-*n* polyamides have been studied in detail[49–53]. Treating ω-cyanoundecanoic acid in acid medium with formaldehyde gave a dibasic acid containing the methylene-bis-amide group; a series of polyamides has been prepared by copolymerising the hexamethylenediamine salt of this acid with hexamethylenediamine adipate and ω-aminoundecanoic acid[54].

Heating nitriles to 70°–90° or above with formaldehyde in the presence of catalytic quantities of sulphuric acid gives hexahydro-1,3,5-triacyl-sym.-triazines[29,33,55]:



Aliphatic (saturated and unsaturated) and aromatic nitriles react. The formaldehyde may be used as paraformaldehyde[29,55], trioxane, or α-polyhydroxymethylene[56]. Aldehydes other than formaldehyde do not give this reaction with nitriles. For complete exclusion of water, the reaction may be carried out in the presence of acetic anhydride[55]. 2–20 wt.% of sulphuric acid, based on the initial nitrile, is used. Chlorosulphonic acid[29] is a less effective catalyst than sulphuric acid. An excess of nitrile over the stoichiometric quantity favours the reaction[56].

3. SYNTHESIS OF *N*-SUBSTITUTED AMIDES BY THE RITTER REACTION

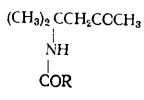
In 1948 Ritter[57] described a new reaction of nitriles with alkenes, with the production of *N*-substituted amides. The addition of isobutylene to acetonitrile and concentrated sulphuric acid in acetic acid at room temperature, with subsequent treatment with a large excess of water, produced *N*-t-butylacetamide in good yield:

$$(CH_3)_2C{=}CH_2 + CH_3CN + H_2O \xrightarrow{H_2SO_4} CH_3CONHC(CH_3)_3.$$

In analogous conversions tertiary and secondary olefines react with hydrocyanic acid, nitriles, and dinitriles of saturated and unsaturated aliphatic acids, and with aromatic nitriles[58–68]. The Ritter reaction has also been carried out with α-hydroxynitriles[63], *N*,*N*-dialkyl-substituted aminonitriles[69,70], β-chloropropionitrile[71], and 1-cyanoformamide[72].

Ritter and his coworkers and others have described the reaction of nitriles with various compounds containing other functional groups in addition to the double bond. *N*-substituted amides have been prepared from certain α,β-unsaturated acids and esters[60], non-conjugated diolefines[73], α-haloolefines[74], and oleic acid[75]. *N*-substituted amides could not be obtained from benzonitrile with methyl acrylate, methacrylate, or crotonate[60]. Formamido-acids have been prepared by the reaction of liquid hydrocyanic acid with oleic and other unsaturated acids[76].

Nitriles can react with certain α,β-unsaturated ketones; in the case of mesityl oxide[77] the reaction proceeds smoothly with the formation of 4-methyl-4-amido-2-pentanones:



It has been shown quite recently[32] that, under the conditions of the Ritter reaction, ketones which undergo the aldol condensation react with nitriles to form β-acylaminoketones.

Secondary and tertiary alcohols[58-60,62] and, less smoothly, their esters[78,79] react similarly to olefines in the Ritter reaction. Corresponding ethers also react with nitriles in the presence of sulphuric acid to form *N*-substituted amides, e.g. benzonitrile and methyl s-butyl ether produce *N*-s-butyl benzamide[80]. Other functional groups may be present in the alcohol; substituted amides have been obtained from β-hydroxyethers[60], α-haloalcohols[74], and 1-phenyl-3-piperidylpropanol[81]. In concentrated acids nitriles react with tertiary alkyl chlorides[82], in the same way as with olefines and alcohols, to form substituted amides.

In addition to 100% sulphuric acid, the catalyst for the Ritter reaction may be 85–95% sulphuric acid[75,76], phosphoric acid[83], benzenesulphonic acid[57], or 90% formic acid[82,84,85]. The reaction also takes place in polyphosphoric acid, although the yields of desired products are lower than with sulphuric acid[86]. Acetic acid, and also dibutyl ether, have been used successfully as solvents[57]. It has been reported[78] that metal salts inhibit the Ritter reaction.

With sulphuric acid as catalyst, the Ritter reaction is usually carried out at 20°–40°, but sometimes, depending on the reactants, a lower temperature (0°)[85], or heating to 55°–65°[69] is recommended. With formic acid as catalyst, the reaction is carried out by boiling the reaction mixture[82,84,85].

In addition to *N*-substituted amides, the reaction of nitriles with olefines may produce simple amides and the corresponding tertiary alcohols[87,88]:

$$RC{\equiv}N + CH_2{=}CR'R'' + 2H_2O \xrightarrow{H_2SO_4} RCONH_2 + R'R''(CH_3)COH.$$

The latter are obtained in good yield if the reaction is carried out in 92% sulphuric acid at 0°–5°. By this method 2,4-dimethylpentan-2-ol, 4-methylheptan-4-ol, and other tertiary alcohols have been obtained from the corresponding olefines. In the absence of nitriles the olefines were polymerised under the reaction conditions.

It is accepted that the first stage in the Ritter reaction is the reaction of the olefine with the mineral acid to form a carbonium ion, which then reacts with the nucleophilic nitrogen atom of the nitrile. This reaction may be schematically represented as follows[48,59,89]:

$$(CH_3)_2C{=}CH_2 + \overset{+}{H} \rightarrow (CH_3)_2\overset{+}{C}{-}CH_3$$

$$CH_3CN + {}^{+}C(CH_3)_3 \rightarrow CH_3\overset{+}{C}{=}NC(CH_3)_3 \xrightarrow{H_2O}$$

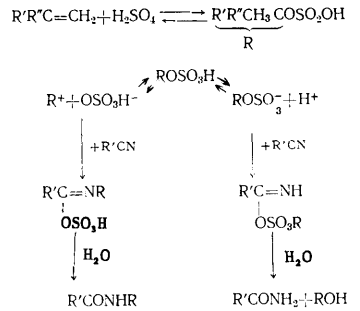
$$\rightarrow CH_3C(O^+H)=NC(CH_3)_3 \xrightarrow{-H^+} CH_3C(OH){=}NC(CH_3)_3 \rightarrow CH_3CONHC(CH_3)_3 .$$

In addition to the carbonium ion, a π-complex of the olefine and mineral acid may also be an intermediate. In this complex the electrophilic properties of the olefine are greater than in the non-complexed compound. Similarly the reaction of tertiary alcohols with nitriles must pass through the formation of a carbonium ion:

$$R\overset{+}{O}H_2 \rightarrow R^+ + H_2O.$$

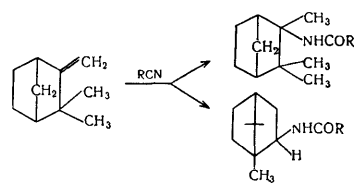
This point of view is confirmed by kinetic studies of the Ritter reaction between acrylonitrile and t-butyl alcohol, in which the t-butyl cation is not formed[15].

When the Ritter reaction is carried out in aqueous sulphuric acid, another mechanism may play an important part, i.e. one involving an alkylsulphuric acid. As shown below, these acids can react with a nitrile in two ways, to form either a substituted or an unsubstituted amide[87]:



It is interesting that when succinonitrile reacts with isobutene under conditions expected to give the *N*,*N*'-disubstituted amide, one nitrile group reacts with the organic cation, and the other with a proton to form an unsubstituted amide group. The *N*-monosubstituted amide $(CH_3)_3CNHCOCH_2CH_2CONH_2$ was obtained[59].

When racemic camphene reacts with hydrocyanic acid in the presence of sulphuric acid, 3-formamidoisocamphane is obtained, instead of the isomeric *N*-formylisobornylamine expected as a result of the Wagner rearrangement. Under the same conditions, *N*-acylisobornylamines have been synthesised from camphene and nitriles[90].



The behaviour of camphene in the Ritter reaction has recently been studied in detail by Kochetkov and coworkers[91], who showed that it condenses with hydrocyanic acid in the presence of one mole of concentrated sulphuric acid at 0° in dibutyl ether, acetic acid, or propionic acid, giving 3-formamidoisocamphane containing 20% *N*-isobornylformamide. The formation of the isobornyl derivative is reduced to a minimum by reducing the reaction temperature to -15° or -20° and carrying out the reaction for 24 h. They also showed[91] that the highly active trichloro- and dichloroacetonitriles react with camphene under the conditions of the Ritter reaction at a reduced temperature similarly to hydrocyanic acid, i.e. without the Wagner rearrangement.

The widest use of the Ritter reaction is found in the synthesis of substituted amides, although it is also of interest as a method of preparation of compounds with an amino group on a tertiary[57,58,68,73] or secondary[75] carbon atom. Yields of compounds with the amino group on a primary carbon atom are low[92]. A number of papers[92-95] have described the synthesis of amines by the reaction of cycloalkanols, secondary aliphatic alcohols, cycloalkyl-substituted aliphatic alcohols, and alicyclic alcohols of spiro structure, with potassium cyanide in the presence of sulphuric acid. In many cases there is intramolecular rearrangement, sometimes leading to an expansion or contraction of the ring.

The reaction of dinitriles with tertiary diolefines has been used to prepare linear polyamides[48,78,82-85]:

$$NC(CH_2)_nCN + R_1CH{=}CR_3C{=}CHR_5 \rightarrow$$
$$\rightarrow NC(CH_2)_nCO[NHCR_2{-}R_3{-}CR_4NHCO(CH_2)_nCO]_m{-}NHCR_2{-}R_3{-}CR_4{=}CHR_5,$$

where R_1, R_2, R_3, R_4, and R_5 are hydrocarbon groups. In addition to aliphatic dinitriles, polyamides have been synthesised from nuclear aromatic (terephthalonitrile), side-chain aromatic (*p*-phenylenediacetonitrile), carbocyclic, heterocyclic, and other dinitriles. Polyamides are also formed by reacting dinitriles with di-secondary alcohols [1,10-dimethyldecan-1,10-diol-1,4-bis-(3-hydroxybutyl)-benzene] and their esters, di-tertiary alcohols (1,1,10,10-tetramethyldecan-1,10-diol), *N*,*N*'-di(hydroxymethyl)-amides, and di-tertiary alkyl chlorides.

Polyamides can similarly be produced from compounds having two different functional groups (hydroxynitriles and chloronitriles in which the hydroxy and chloro groups are tertiary, etc.), for instance from 2-methyl-6-cyanohexan-2-ol. Polymers are formed even when the functional groups are separated by only three carbon atoms; it is known[96] that to prepare polymers by homopolycondensation, the initial monomers must be separated by at least six carbon atoms, or rings are formed.

A patent[97] describes the continuous preparation of *N*-substituted amides from secondary and tertiary alkenes or alcohols at 45°–95° in the presence of sulphuric acid.

In the presence of concentrated acids, certain olefines react with a number of other compounds containing the cyano group as well as with acid nitriles. *N*-t-Pentylbiuret has been prepared from 1-cyanoguanidine and 2-methylbut-2-ene[57]:

$$H_2NCNHCN + (CH_3)_2C{=}CHCH_3 \longrightarrow H_2NCONHCONHC(CH_3)_2C_2H_5.$$
(NH)

The reaction of olefines with cyanogen chloride to form amines has been studied in detail[98] and the following mechanism suggested:

$$>C{=}C< + H^+ \rightleftharpoons >CH{-}\bar{C}<;\quad >CH{-}\overset{+}{C}< + ClC{\equiv}N \longrightarrow >CH{-}C<\ (N{=}\overset{+}{C}Cl) \xrightarrow{H_2O}$$
$$\longrightarrow >CH{-}C<\ (N{=}C(OH)Cl) + H^+ \longrightarrow >CH{-}C<\ (HN{-}C(=O)Cl) \xrightarrow{H_2O} >CH{-}C<\ (NH_2) + CO_2 + HCl.$$

The best catalyst is 96% sulphuric acid, although methanesulphonic, fluorosulphonic, and other acids are also effective. Cyanogen chloride reacts with such olefines as 2-methylbut-1-ene, but-2-ene, and cyclohexene, but not with oct-1-ene or dodec-1-ene.

Thiocyanates react similarly to the nitriles under the conditions of the Ritter reaction[99]; with alcohols and olefines in the presence of sulphuric acid *N*-substituted thiocarbamates are formed:

$$RSCN + R'OH \xrightarrow{H_2SO_4} RSCONHR'.$$

Benzyl thiocyanate and camphene give the corresponding *N*-substituted isobornylamine as a result of the Wagner rearrangement.

4. OTHER SYNTHESES OF *N*-SUBSTITUTED AMIDES

Wieland[100,101] achieved a conversion analogous to the Ritter reaction in 1930 by using hydrogen chloride in the presence of aluminium chloride. Under these conditions *N*-formylcyclohexylamine was synthesised from cyclohexene and hydrocyanic acid. Later[102] cyclohexene was similarly reacted with acetonitrile, phenylacetonitrile, and benzonitrile.

In the presence of aluminium chloride and hydrogen chloride, secondary alkyl halides react with nitriles to form *N*-alkylamides. Apparently $AlCl_3$ removes the halogen from the alkyl halide to form a carbonium ion, this being followed by the formation of a substituted iminochloride, which, when water is added, is converted into the substituted amide[102]:

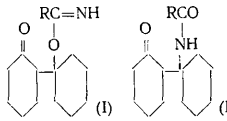
$$RCl + AlCl_3 \longrightarrow R^+ + AlCl_4^-,$$
$$R^+ + R'C{\equiv}N \longrightarrow [R'C{=}\overset{+}{N}R],$$
$$[R'C{=}\overset{+}{N}R] + AlCl_4^- \longrightarrow R'C(=NR)Cl + AlCl_3;$$
$$R'C(=NR)Cl + H_2O \longrightarrow R'C(=NR)OH \longrightarrow R'CONHR.$$

N-alkylamides are formed comparatively smoothly from cyclohexyl and cyclopentyl chlorides. Under these reaction conditions tertiary alkyl halides produce liquid polymers.

An analogous synthesis of *N*-substituted amides occurs in the reaction of diphenylmethyl bromide with acetonitrile or propionitrile in the presence of silver sulphate[103]. It has been suggested that the primary product is a carbonium ion which then reacts with the nitrile as described above:

$$(C_6H_5)_2CHBr + Ag^+ \rightarrow (C_6H_5)\overset{+}{C}H + AgBr.$$

On adding a mixture of cyclohexanone or its autocondensation product (2-cyclohexylidenecyclohexanone) and acetonitrile (or propionitrile or benzonitrile) to a cooled suspension of anhydrous aluminium chloride in carbon disulphide or dichloroethane and subsequently hydrolysing, a solid made up of two cyclohexanone molecules and one nitrile molecule is obtained; the iminoether structure I[104] was assigned to this compound:

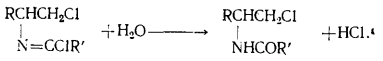


but later it was suggested[30] and then confirmed[32] that the reaction between cyclohexylidenecyclohexanone and the nitrile takes place by a mechanism analogous to that of the Ritter reaction, the resulting product being 2-(1-acetamidocyclohexyl)cyclohexanone (II).

The preparation of *N*-(2-haloalkyl)amides from nitriles, olefines, and chlorine or bromine, discovered by Cairns and his coworkers[105] is of interest. The first stage of the reaction is the formation of an *N*-(2-chloroalkyl)iminochloride and a 1,2-dichloroalkane:

$$RCH{=}CH_2 + Cl_2 \longrightarrow \overset{+}{R}CHCH_2Cl + Cl^-$$
$$\bar{R}CHCH_2Cl \xrightarrow[Cl^-]{R'CN} \begin{cases} RCHCH_2Cl\ (N{=}C^+R') \xrightarrow{Cl^-} RCHCH_2Cl\ (N{=}CClR') \\ RCHClCH_2Cl \end{cases}$$

If the nitrile does not contain an α-hydrogen atom, the resulting iminochloride can be separated from the dichloroalkane by distillation; if the nitrile contains an α-hydrogen atom, the iminochloride is unstable and undergoes thermal bimolecular condensation with loss of hydrogen chloride. With water the N-(2-chloroalkyl)iminochlorides are converted into the more stable N-(2-chloroalkyl)amides:



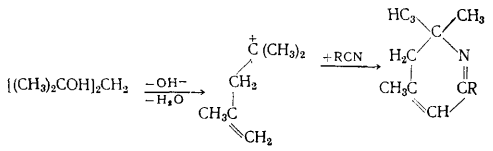
In the case of hydrocyanic acid, the N-(2-chloroalkyl)-formamide is very easily hydrolysed to the 2-chloroalkylamine. Aromatic and aliphatic nitriles and acrylonitrile react in this reaction with ethylene, cyclohexene, oct-1-ene, and styrene.

N-Substituted amides have been prepared by the reaction of nitriles[106-109] and hydrocyanic acid[110] with amines in water at 100°–150° in the presence of acid catalysts. In these studies N-benzylacetamide was obtained from acetonitrile and benzylamine in yields of 1% (in the presence of carbon dioxide), 10% (thiophenol), 20% (hydrochloric acid), 40% (acetic acid), 73% (hydrogen sulphide), and 76% (thioacetamide). Under the same conditions, dinitriles, cyanoamides, and cyanoethers have given N,N'-substituted diamides[111,112]. Unlike other dinitriles, adiponitrile and tetramethylsuccinonitrile do not react; however, there is a patent[113] for the preparation of polyamides from adiponitrile and hexamethylenediamine. In some cases the reaction proceeds without catalysts.

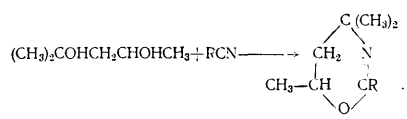
The reaction of hydrocyanic acid with equivalent quantities of an amine and hydrogen sulphide may be used as a general method for the preparation of N-substituted thioformamides[110].

5. PREPARATION OF HETEROCYCLIC COMPOUNDS UNDER THE CONDITIONS OF THE RITTER REACTION

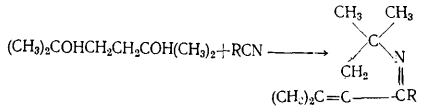
In many cases the Ritter reaction proceeds untypically, with the formation of heterocyclic compounds. The reaction of 2,4-dimethylpentan-2,4-diol with acetonitrile, benzonitrile, or acrylonitrile has produced the corresponding 4,6,6-trimethyl-5,6-dihydropyridines[114]; the reaction may be represented schematically as follows:



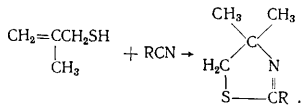
An analogous reaction takes place with 2,4-dimethylhexa-2,4-diene and acetonitrile[88]. The synthesis of dihydro-1,3-oxazines from 2-methylpentan-2,4-diol and nitriles has been described[88,115]:



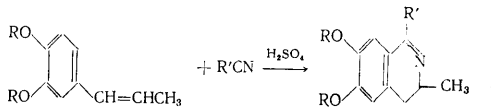
The reaction products of 2,5-dimethylhexan-2,5-diol (or 2,5-dimethylhexa-2,4-diene) with nitriles in concentrated sulphuric acid were 5,5-dimethyl-3-isopropylidene-1-pyrrolines[114]:



The same paper describes the synthesis of 4,4-dimethyl-2-thiazolines from methylallyl mercaptan:

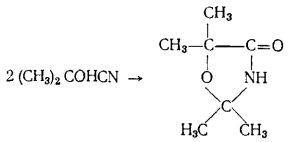


3,4-Dihydroisoquinolines are formed by the reaction (in the presence of concentrated sulphuric acid) of isosafrol, methyleugenol, or methylisoeugenol with veratronitrile, anisonitrile, and certain other nitriles[116,117]:

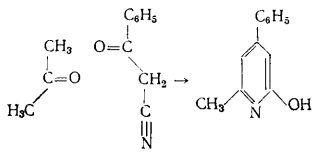


This reaction has been considered as an internal diene synthesis[117].

2,2,5,5-Tetramethyl-4-oxazolidone has been obtained by heating α-hydroxyisobutyronitrile at 85° in the presence of polyphosphoric acid[118]:



Polyphosphoric acid is also a catalyst for the condensation of β-ketonitriles (α-acetyl-α-toluonitrile, benzoylacetonitrile, α-nicotinoylpropionitrile, etc.) with ketones (acetone, phenylacetone, cyclohexanone, etc.) to form substituted 2-pyridones[119], for example:



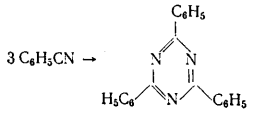
This reaction comprises both condensation and reaction of the nitrile nitrogen atom with an electrophilic carbon atom.

6. PREPARATION OF 1,3,5-TRIAZINES

Even in the early days of organic chemistry it was known[120,121] that nitriles, like simple cyanogen compounds, could polymerise to form triazines. For a long time it was thought[7,122] that triazines could be obtained only from nitriles not containing α-hydrogen atoms; this is not so, for a triazine is also obtained from dichloroacetonitrile[123], but not from trimethylacetonitrile[22].

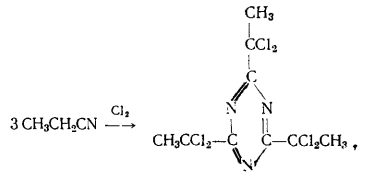
The polymerisation of nitriles is induced by a number of acidic substances, as well as by alkaline[7] and other agents[124]. In the presence of sulphuric acid, alcoholic

hydrogen chloride[34,120,125,126], or chlorosulphonic acid[127,128], benzonitrile has been converted into cyaphenine (2,4,6-triphenyl-1,3,5-triazine):



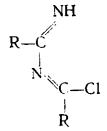
Chlorosulphonic acid has also been successfully used for the conversion of toluonitriles and *p*-chlorobenzonitrile into triazines. It has been reported[129,130] that by treating 3,4-methylenedioxybenzonitrile, 3-methoxy-4-ethoxybenzonitrile, and other substituted nitriles, with chlorosulphonic acid in chloroform, so-called "anthraquinone-diimines" are formed; but Wilson[131] showed that the reaction products are sym.-triazines. The decomposition of phenyl diazonium fluoroborate in aromatic nitriles gives the anilides with the nitrile trimers as by-products[20].

Hydrogen halides are the most frequently used reagents for the polymerisation of nitriles to triazines. In the presence of hydrogen chloride, sym.-triazines have been obtained from trichloroacetonitrile[123,132-134], tribromoacetonitrile[135], trifluoroacetonitrile[136], dichloroacetonitrile[123], benzonitrile[22], and other nitriles. Trichloroacetonitrile is comparatively rapidly polymerised with hydrogen bromide[137]. The polymerisation of trichloroacetonitrile by the combined action of aluminium chloride and hydrogen chloride has been proposed[138]. The formation of 2,4,6-tris-(α,α'-dichloroethyl)-1,3,5-triazine[139,140],

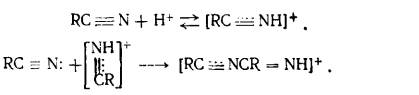


by the chlorination of propionitrile and the formation of 2,4,6-tris(dibromomethyl)-1,3,5-triazine[141] by the reaction of equimolecular quantities of bromine and acetonitrile (in the presence of red phosphorus and calcium carbonate) may be explained by the action of the hydrogen chloride and bromide liberated in these reactions.

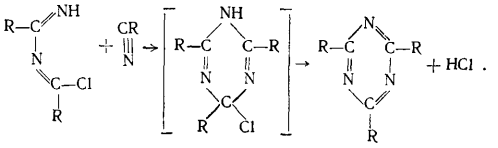
The mechanism of the synthesis of triazines from nitriles in the presence of hydrogen halides has been studied in detail by Grundmann and coworkers[22], who showed that a compound of the nitrile and the hydrogen halide is an intermediate. At normal or elevated temperatures and pressures, depending on the reactivity of the initial nitrile, the intermediate disappears from the reaction mixture and a triazine is formed. In some cases, for example, in the polymerisation of trichloroacetonitrile, the intermediate can be separated as a crystalline material very sensitive to moisture, with a composition corresponding to the combination of hydrogen chloride with two molecules of nitrile; it is apparently a substituted iminochloride:



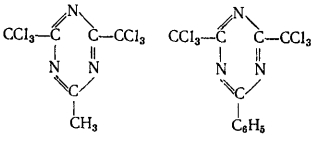
The insolubility of the intermediate in non-polar solvents and its comparatively high decomposition temperature suggest that it has a salt-like structure. The formation of the substituted iminochloride can be considered as a nucleophilic reaction of the nitrile group, with the same nitrile as the electrophilic reagent:



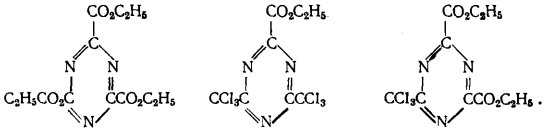
The reaction between the iminochloride and a third nitrile molecule may take place analogously. Grundmann relates the reaction of iminochlorides with nitriles to the diene synthesis:



In certain cases the dienophile nitrile is different from the nitrile forming the iminochloride. Trichloroacetonitrile condenses with acetonitrile or benzonitrile, taken in the ratio 2 : 1, to give 2-methyl-4,6-bis(trichloromethyl)-1,3,5-triazine and 2-phenyl-4,6-bis(trichloromethyl)-1,3,5-triazine respectively[22,142]:



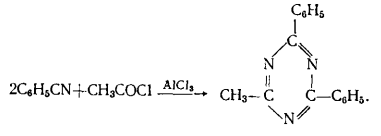
The possibility of mixed condensation for each pair of nitriles is determined by the rates of formation of both possible iminochlorides and their reaction with the nitriles. Sometimes a mixture of triazines is obtained: depending on the reaction conditions, trichloroacetonitrile and ethyl cyanoformate give mixtures of variable composition containing tris(trichloromethyl)triazine, tris(ethoxycarbonyl)-triazine, 2-ethoxycarbonyl-4,6-bis(trichloromethyl)-1,3,5-triazine and 2-trichloromethyl-4,6-bis(ethoxycarbonyl)-1,3,5-triazine:



In the presence of a small quantity of cold water, the substituted iminochlorides which take part in the formation of triazines give secondary amides (imides) in high yield[22,143,144]:

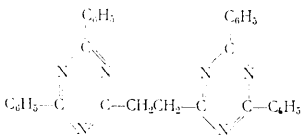


In the presence of aluminium chloride, benzonitrile reacts with aliphatic-acid chlorides to form diphenylalkyltriazines[145,146]:



Benzonitrile reacts analogously with dibasic-acid chlorides[147], forming compounds having two rings, e.g.

1,2-ethylenebis(4,6-diphenyl-1,3,5-triazine):



Under these conditions benzonitrile forms dibenzamide with benzoyl chloride[148], but by heating benzonitrile with *m*- or *p*-nitrobenzoyl chloride in the presence of ammonium chloride and aluminium chloride, *m*- and *p*-nitrocyaphenine respectively were obtained[127]. The same method produced the corresponding dinitrocyaphenines from *m*- or *p*-nitrobenzonitrile and benzoyl chloride.

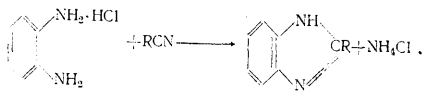
The source of the third nitrogen in the alkyldiaryltriazines was not clear until recently[149]; but in 1956 Meerwein and his coworkers[16] showed that the formation of the triazine is preceded by exchange of functional groups between the nitrile and the acid chloride:

$$C_6H_5CN + CH_3COCl \rightarrow CH_3CN + C_6H_5COCl.$$

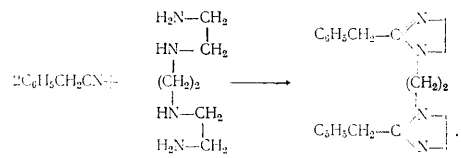
Hence, this triazine synthesis becomes the mixed condensation of two aromatic nitriles and one aliphatic.

7. OTHER SYNTHESES OF HETEROCYCLIC COMPOUNDS

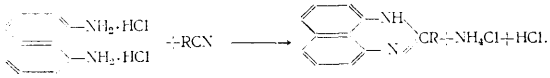
The condensation of *o*-diamines with acid anhydrides, acid chlorides, acids, amides, esters, and substituted amides produces imidazoles. It has been found that an analogous reaction takes place by heating *o*-diamines with nitriles in the presence of hydrogen halides[150,151] or polyphosphoric acid[152]:



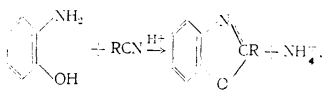
Hydrogen sulphide is a catalyst for the condensation of aliphatic 1,2-diamines with nitriles[153,154]. The reaction of diethylenetriamine and triethylenetetramine with nitriles in the presence of hydrogen sulphide[155] has given aminoethylimidazolines and ethylenebisimidazolines respectively, e.g.



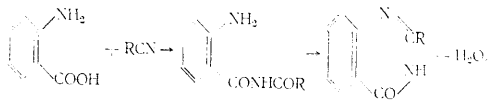
[2-C^{14}]-2-Benzylimidazoline has been synthesised from benzyl[C^{14}]cyanide and ethylenediamine mono-*p*-toluenesulphonate[156]. Certain aromatic diamines produce pyrimidine derivatives[150]:



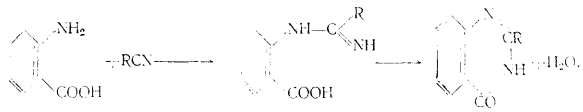
Nitriles react analogously with *o*-aminophenols, the reaction serving as a preparative method for the synthesis of benzoxazoles[150]:



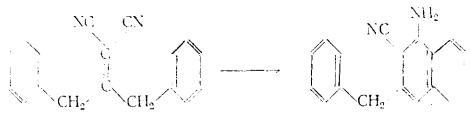
As early as 1898 it was found[157] that on heating to 220°–230° anthranilic acid easily condenses with acetonitrile. The reaction products were later identified, and it was shown that this is a general reaction for aliphatic, nuclear aromatic, and side-chain aromatic nitriles, quinazoline derivatives being formed[158–161]. It was suggested[161] that a secondary amide is the first product:



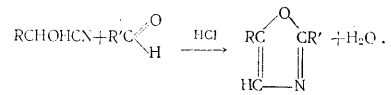
A substituted amidine may also be an intermediate in this synthesis of 2-substituted 4-oxo-3,4-dihydroquinazolines:



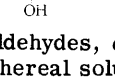
In the presence of polyphosphoric acid, sym.-diphenylisopropylidenemalonitrile undergoes intramolecular condensation to form 3-benzyl-2-cyano-1-naphthylamine[162]:



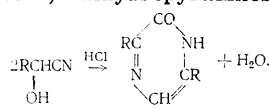
The action of hydrogen chloride on ethereal solutions of aromatic aldehydes and aldehyde cyanhydrins has produced 2,5-disubstituted oxazoles[37,163,164]:



The presence of moisture favours the formation of substituted amides from the same components[37,164]:

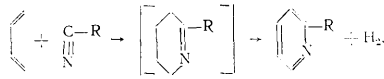


In the absence of aldehydes, α-hydroxynitriles undergo autocondensation in ethereal solutions of hydrogen chloride, to form substituted 3,4-dihydropyrazines[37,165,166]:



The conditions for the above reactions of aldehyde cyanhydrins are identical with those for the synthesis of iminoether hydrochlorides, so that the primary products of these reactions with nitriles, both substituted and unsubstituted with a hydroxy group in the α-position, may be the same. It is also possible that the iminoether hydrochlorides are intermediates in the condensation of aromatic aldehyde cyanhydrins.

Janz and his coworkers[167–179] have developed a vapour-phase synthesis of substituted pyridines from dienes and nitriles:



This is a variation of the diene synthesis. The reaction is carried out at 400° in the presence of mixed aluminium and chromium oxides. If the dienophile component is dicyanogen or trifluoroacetonitrile, the condensation also takes place in the absence of a catalyst. The synthesis of 2-ethylpyridine, from butadiene and propionitrile at 600° in the presence of aluminium oxide, has been described[180].

8. REACTIONS OF NITRILES WITH CARBOXYLIC ACIDS

The reaction of nitriles with carboxylic acids produces secondary amides:

$$RCN + R'COOH \rightarrow RCONHCOR'; \quad (1)$$

but they are not the only reaction products. Often exchange between the nitrile and carboxyl groups occurs:

$$RCN + R'COOH \rightarrow RCOOH + R'CN. \quad (2)$$

In the presence of hydrogen halides, particularly in the cold, the same reagents produce amide hydrohalides and acid anhydrides or chlorides:

$$RCN + 2R'COOH + HCl \rightarrow RCONH_2 \cdot HCl + (R'CO)_2O, \quad (3)$$

$$RCN + R'COOH + 2HCl \rightarrow RCONH_2 \cdot HCl + R'COCl. \quad (4)$$

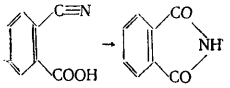
Of reactions (1)–(4), only the first leads to the formation of a new nitrogen–carbon bond, but since the mechanisms of all these reactions have much in common, this review will consider material relating to them all.

The reaction between carboxylic acids and their nitriles was intensively studied at the end of the last and the beginning of the present century, after which practically nothing appeared in the literature for a considerable period. Recently, this reaction has again begun to receive attention.

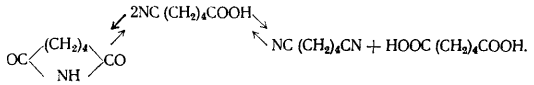
Gautier[181,182] was the first to report on the reaction between aliphatic acids and nitriles. On heating acetonitrile with acetic acid in a sealed tube, he obtained a secondary amide (diacetamide) as product. Similarly, propionitrile and propionic acid give dipropionamide[183]. According to Colby and Dodge[184], a small amount of acetic anhydride may be added to the reaction mixture to increase the yield of secondary amide, in certain cases. They studied the reaction of aliphatic and aromatic nitriles with various acids at 200°–280°, and concluded that: (a) aliphatic nitriles and aliphatic acids form secondary amides according to Eqn. (1); (b) aliphatic nitriles and aromatic acids exchange the acid and nitrile groups according to Eqn. (2); (c) aromatic nitriles and aliphatic acids form mixed secondary amides; and (d) at moderate temperatures aromatic nitriles and aromatic acids form secondary amides; at elevated temperatures reaction (2) is possible.

This classification of the reactions of nitriles with acids is over-simplified. Depending on the reaction conditions, each pair of reactants can form a nitrile and an acid, or a secondary amide, or can undergo both reactions simultaneously. König[158] studied the change in the reactivity of nitriles and acids when they are substituted by electronegative substituents, and found that the greater the number of electronegative substituents on α-carbon atoms in the nitrile or acid, the lower the temperature at which the reaction proceeds at a satisfactory rate, and the greater the yield of secondary amide. The favourable influence of electronegative substituents in the nitrile and acid on reaction (1) was also evidenced in the study of the synthesis of diphenylacetamide and α,α'-di(*p*-nitrophenyl)diacetamide[185]. This work also showed that the reaction between the nitrile and the acid is an equilibrium one.

The reaction between nitriles and acids has also been studied when one or both reactants are bifunctional compounds. Treating adipic acid with excess acetonitrile over a short time at 300° produces industrially important adiponitrile[186]. Heating equivalent quantities of succinonitrile and succinic acid gave succinimide in good yield[158]. The reaction temperature can be reduced if the reaction is carried out in the presence of excess mineral acid[187], preferably sulphuric[188]. Succinimide is also formed by heating β-cyanopropionic acid with excess sulphuric acid at 200°–230°. The reaction between the acid and nitrile groups to form secondary amides sometimes takes place even in the cold; thus, on standing, *o*-cyanobenzoic acid is converted to phthalimide[189]:



Nitrile and acid groups in higher cyano-acids also react. On heating, ω-cyanopelargonic acid does not form a cyclic imide, but the functional groups of different molecules react with each other, forming sebacic acid and its dinitrile[190]. In accordance with Carothers' study[96], which showed that the homopolycondensation of compounds with six or seven carbon atoms can take place both by cyclisation and by the formation of linear macromolecules, it has been established that on heating δ-cyanovaleric acid, two reversible reactions occur, producing adipimide and adipic acid and adiponitrile[191]:



The reactions between nitriles and acids, which have often been considered as thermal reactions[158,181,192], are accelerated by catalytic amounts of acids[193,194] and some of their derivatives[193]. The preparation of succinimide from β-cyanopropionic acid, in the presence of $SOCl_2$, PCl_3, $POCl_3$, PCl_5, $AlCl_3$, and CH_3COCl, has been described[188].

The equilibrium nature of the reactions in the system nitrile–acid–secondary amide has been used for the quantitative exchange of nitrile and carboxyl groups in aromatic compounds. Heating a high-boiling nitrile with a low-boiling acid produces an equilibrium mixture containing also the low-boiling nitrile and the high-boiling acid; the equilibrium is displaced by distillation of the low-boiling nitrile. Thus benzonitrile and isophthalic acid are obtained by heating benzoic acid and isophthalonitrile at 237°–287° for 3 h[195]. Similar methods are the basis for the preparation of isophthalic and terephthalic acids[196,197] and their nitriles[198] from the corresponding xylenes. Oxidation of the latter first produces toluic acids; these are oxidised to phthalic acids more slowly than their derivatives, and in particular, their nitriles[195]. To accelerate the process, suggestions have been made to carry it out in accordance with the scheme

$$CH_3C_6H_4CH_3 + 3/2\ O_2 \rightarrow CH_3C_6H_4COOH + H_2O,$$

$$CH_3C_6H_4COOH + NCC_6H_4COOH \rightarrow CH_3C_6H_4CN + HOOCC_6H_4COOH,$$

$$CH_3C_6H_4CN + 3/2\ O_2 \rightarrow HOOCC_6H_4CN + H_2O.$$

To investigate the mechanism of the reaction between nitriles and acids, the reaction between adiponitrile and adipic acid has been studied in the presence of small amounts of additives which accelerate or retard the process[193]. Experiments using equivalent amounts of acids as the catalysts showed that in general the catalytic effect increases with increase of the dissociation constant of the acid catalyst. Acids weaker than adipic do not catalyst the reaction. Solvents having basic properties (dioxan, pyridine, and acetic anhydride) inhibit the reaction between the nitrile and acid to a noticeable extent. On the basis of these results and of studies of the influence of electronegative substituents in the reactants on the course of the reaction[158,185], it has been suggested that the process commences with reaction of the unshared electron pair of the nitrile nitrogen atom with the acid (see the introduction). In the resulting complex the electron density on the carbon atom of the nitrile group decreases (the positive charge increases) as a result of which it reacts with the carboxylic acid to form a protonated isoimide.

$$RCN + HA \rightleftarrows RCN\cdots HA$$

$$RCN\cdots HA + HOOCR' \rightleftarrows \left[\begin{array}{l} RC{=}NH \\ | \\ HO^{+}{-}C{=}O \\ | \\ R' \end{array}\right]^{-} \quad (A = \text{anion}).$$

The greater the lability of the proton in the acid, the more positive is the charge on the carbon atom in the nitrile-acid complex, the closer are the properties of this complex to those of the carbonium ion $RC^{+}{=}NH$, and the more favourable are the conditions for its reaction with the carboxylic acid to form the protonated isoimide molecule. It is known that the interconversion of *N*-acyl and *O*-acyl compounds is accomplished comparatively easily[190-202]; probably this conversion is also possible under the conditions for the reaction of nitriles with acids, leading to the formation of a protonated secondary amide[203-205]. Depending on the reaction conditions and the nature of the radicals R and R', the amide may react with the anion to form a secondary amide, or may rearrange to an ion isomeric with the original cation; this ion easily decomposes into a nitrile and an acid. It has been shown[194] that the formation of the secondary amide,

$$RC(=\overset{+}{N}H_2)(-\bar{O}-CR')=O \rightleftarrows RC(=\overset{+}{N}H-CR')(-OH)=O \rightleftarrows RC(=\overset{+}{N}H=CR')(-O-H)=O$$

$$\downarrow A^{-}\uparrow$$

$$RCNHCR'(=O)+HA$$

$$RC(=\overset{+}{N}H=CR')(-OH)=O \rightleftarrows RC(=\overset{+}{O}H-CR')(=O)=NH \xrightleftarrows{A^{-}} RCOOH + R'CN + HA$$

predominates in the presence of considerable quantities of acid catalysts.

However, a direct reaction of the nucleophilic nitrile molecule with the acid in the presence of an electrophilic agent (scheme *a*) or with an acylcarbonium ion (scheme *b*) cannot be excluded:

(*a*) $R{-}C{\equiv}N: + \overset{R'}{\underset{O}{C}}{-}OH + H^{+} \xrightarrow{-H_2O} R{-}\overset{+}{C}{=}N{-}\overset{R'}{\underset{O}{C}} \xrightarrow[-H^{+}]{+H_2O} R{-}\underset{O}{C}{-}NH{-}\underset{O}{C}{-}R'$;

(*b*) (*a*) $R'COOH + H^{+} \longrightarrow R'CO^{+} + H_2O$;

$$R'CO^{+} + R{-}C{\equiv}N \longrightarrow R{-}\overset{+}{C}{=}N{-}\underset{O}{C}{-}R' \xrightarrow[-H^{+}]{+H_2O} RCONHCOR'.$$

The decomposition of the mixed secondary amide to form a new nitrile and a new acid may be represented as follows:

$$R{-}\underset{O}{\overset{H}{\overset{|}{C}}}{-}\overset{H}{O}{-}C{\equiv}N{-}R' \xrightarrow{-H_2O} [RCOOH_2]^{+} + N{\equiv}C{-}R' \qquad [RCOOH_2]^{+} \xrightarrow{-H^{+}} RCOOH + H^{+}$$

Sometimes, in addition to the formation of a secondary amide and the exchange of the nitrile and acid groups, heating mixtures of nitriles and acids also produces small quantities of the amides and anhydrides or acid diborides [reactions (3) and (4)][194]. A stoichiometric excess of acid over nitrile favours this reaction.

If the nitriles and acids are reacted at low temperatures in the presence of a large amount of hydrogen chloride, this reaction is the main one. Colson[206,207] was the first to show that in the presence of acetic acid and hydrogen chloride, acetonitrile and propionitrile are converted at 0° into the corresponding amides, the acetic acid forming acetyl chloride. The same products were obtained when the acetic acid was replaced by acetic anhydride. Krieble[208] suggested carrying out this reaction in an organic solvent, and used it for the synthesis of anhydrides of chloro-substituted acetic acids.

Colson[206] assumed that the first stage in this process is the reaction of the acetic acid with the hydrogen chloride to form acetyl chloride and water, which then adds on to the nitrile. Closer to modern views on the mechanism of such reactions is the suggestion[208] that initially the nitrile and hydrogen chloride form an iminochloride, which produces a secondary amide with the carboxylic acid. A second carboxylic acid molecule is acylated by the secondary amide, with the formation of the final reaction products:

$$RCN \xrightarrow{HCl} RC(=NH)Cl \xrightarrow{R'COOH} RCONHCR'(=O)=O \xrightarrow{R'COOH} RCONH_2\cdot HCl + (R'CO)_2O.$$

It has recently been shown[209] that in the presence of large amounts of inert solvents, the nitrile and hydrogen chloride first form a chloroimonium chloride, which reacts with the carboxylic acid to give a protonated isoimide, which is a more effective acylating agent than a secondary amide[205]:

$$RC{\equiv}N + 2HCl \rightleftarrows \left[RC(=NH_2)Cl\right]^{+}Cl^{-} \xrightleftarrows{R'COOH} \left[RCOCR'(=O)=NH_2O\right]^{+}Cl^{-} \xrightarrow{R'COOH}$$

$$\rightarrow \left[RC(=NH_2)OH\right]^{+}Cl^{-} + (R'CO)_2O.$$

The acid chloride may be formed as a result of a secondary reaction between the anhydride and the hydrogen halide[207,210], and possibly also by the direct reaction of the isoimide with hydrogen chloride.

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REVERSIBLE PHOTOCHEMICAL REDUCTION OF CHLOROPHYLL AND ITS ANALOGUES AND DERIVATIVES

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INTRODUCTION

One method of obtaining knowledge about the photochemical stage of photosynthesis is to study the changes undergone by plant pigments on exposure to light. In 1948 we succeeded in detecting the ability of chlorophyll and its analogues to undergo reversible photochemical reduction[1]. This reaction is accompanied by the formation of active photoproducts, which "store" the energy of the light quanta, reacting reversibly after the termination of the exposure to regenerate the original pigment molecule. Further research showed that reversible photoreduction forms the basis of the photosensitising action of chlorophyll in solution, and can be used to explain the mechanism of several photobiological processes. During the past decade much work in the USSR and abroad has been concerned with the photoreduction of chlorophyll and its analogues and derivatives, and it is timely to review this work now. Brief summaries have been given in previous papers by the present author[2].

The Laboratory of Photobiochemistry of the Institute of Biochemistry of the Academy of Sciences of the USSR has carried out a comparative study of the properties of chlorophyll and its analogues and derivatives, which has enabled us to determine the significance of individual molecular groupings in the pigments and of the nature of the central metal atom in the development of photochemical properties. Investigations have been carried out on pigments isolated from various organisms and purified by chromatography, and also on pigments in the form of natural proteins directly in biological structures (in suspensions of granules and chloroplasts) and the leaves of plants.

Studies have been made on chlorophylls *a* and *b* of green leaves, bacteriochlorophyll of photosynthesising bacteria, protochlorophyll of etiolated leaves and the seed capsules of the Cucurbitaceae, the corresponding phaeophytins, various