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Nucleophilic Addition of Amino-groups to an Activated Carbon-Carbon Double Bond

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The review presents data on the effect of structural and steric factors, catalysts, and solvents on the mode and rate of condensation of activated olefins with amines, which indicate that the mechanisms of such condensations are to some extent general. The considerable importance of the steric inhibition of the reactions is evidence in favour of the hypothesis of a polar transition state characterised by a rigid structure. Proton transfer involving a proton donor and (or) acceptor or, more rarely, the ejection of a negative ion (see the reactions of β-halogeno-olefins) plays a significant role in the stabilisation of the transition state. The sequence of relative activities of the olefins $CH_2 = CHX$ is affected both by the polarising effect of the group X and the possibility of the delocalisation of the charges in the activated complex. Nevertheless the problems of the catalytic effect of proton-donating, alkaline, and particularly peroxidic additives are still not completely clear and require further study.
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1. INTRODUCTION

Reactions involving the addition of amines to an activated carbon–carbon double bond are widely known and are used in numerous syntheses (amino-nitriles, amino-acids, are various heterocyclic structures). The available reviews (the addition reactions of acrylic acid and its esters [1,2], acrylamide [3], vinylpyridines [4], and nitro-olefins [5]) are confined largely to the statement of the facts and the noting of a typical reaction conditions.

Usually the Michael reaction takes place in the presence of alkaline agents, i.e. via the formation of carbanions from the CH component with subsequent nucleophilic attack on the olefin [6]; on the other hand, for the condensation of compounds containing an amino- or imino-group, examples of non-catalytic reactions and of processes catalysed by both acids and bases or accelerated by the addition of proton-donor solvents have been described. Recently studies of the kinetics of these reactions have begun to be published. So far they have dealt with a narrow range of objects (particularly solvents) and the results cannot be correlated. Nevertheless the accumulation of experimental data, both preparative and kinetic, permits certain generalisations.

In this review attention is drawn to the effect of the medium, the catalytic additive, and steric factors in the structure of the amine (or imine). Heterocyclic imines such as pyrrole, indole, and phenothiazine and also acid amides are not considered as the amino-components since their alkylation by olefins usually takes place in the presence of alkaline additives (i.e. under typical conditions for the Michael reaction) via the formation of an anion at a nitrogen atom.

The capacity of unsaturated compounds of the type $CH_2=CHX$ for electrophilic addition is determined by the polarisation of the double bond under the influence of the electron-acceptor substituent X. Furthermore the reactivity is influenced by the type of the nucleophilic component and the polar and steric interactions in the transition stage. Thus, judging from the values of L_β (the localisation energy of the nucleophilic group), calculated for the anionic polymerisation of a number of monomers [7], we have the following sequence: nitroethylene > 2-nitropropene > acrylonitrile > methacrylonitrile > methyl vinyl ketone > methyl acrylate. However, a different sequence is usually found in the Michael condensation [6]: acrolein > vinyl ketones > αβ-unsaturated ethers ≥ acrylonitrile > > vinyl sulphones. A recent study of the kinetics of the reaction of alcohols with vinyl compounds [8] established that acrylonitrile is much more reactive than acrylates. Therefore, wherever this is allowed by the available data, we attempted to compare the nucleophilic properties of amines of different classes in relation to a given olefin †.

† See, for example, Ibne-Rasa [9], concerning the differences between the terms "nucleophilicity" and "basicity" (as applied to amines and imines) and also the conditions under which they have the same significance.

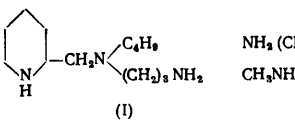
2. ACRYLONITRILE

Lower primary and secondary amines and also diamines are cyanoethylated with formation of mono-derivatives without catalyst at room temperature. With increasing length of the aliphatic group, the rate of reaction of the amines with acrylonitrile falls somewhat (probably due to a decrease in nucleophilic character) and brief heating is required to accelerate the process [10,11]. This method can be used to cyanoethylate a wide variety of amines containing up to 10–18 carbon atoms, benzylamines with ring substituents [12], arylalkylaminomethanes [13-15], etc. No difficulties are encountered in the reaction involving the simplest cyclic (polymethylene) imines: ethyleneimine, pyrrolidine, piperidine, morpholine, and their derivatives in which the NH group is sterically accessible [16,17].

Branching of the aliphatic chain of the amine hinders its cyanoethylation and to a greater extent when the branching point is closer to the amino-group [18-21]. This is shown most clearly for 2,2-disubstituted compounds of the type of t-octylamine [22,23]. Nevertheless the same amines behave normally in alkylation by alkyl halides. Another typical example is provided by 2,6-dimethylpiperidine with two substituents in the α-position relative to the imino-group [24]. In order to cyanoethylate amines with a sterically hindered amino-group, it has been suggested that water, lower alcohols, organic acids [21-26] and catalytic amounts of hydrochloric acid [22] be added to the reaction mixture or that the syntheses be simply carried out in a homogeneous aqueous solution. To increase the solubility of the amine in water, a second solvent may be added (dialkylamides, t-alkylaminopropionitriles, etc.), which in many cases increases significantly the yield [21,26]. It has been stated [27,28] that the cyanoethylation of various higher polymethyleneimines (starting with hexamethyleneimine) is also accelerated by Triton B (40% solution of trimethylbenzylammonium hydroxide). However, so far it is not clear whether the true catalyst is not in fact water, the mole fraction of which in the whole solution is 14/15.

Further studies elucidated the active role of the solvent also in the cyanoethylation of sterically unhindered amines [29-35]. It was established that the addition of the amino-group to the double bond of acrylonitrile is greatly accelerated by proton-donor substances of various classes (water, alcohol, glycols, formamide, organic acids, ammonium salts, ion-exchange resins). The most powerful promoting agent is water, which remains active also in mixtures with inert additives or in mixed solvents. Alcohols catalyse the reaction somewhat less, the promoting effect decreasing on going from methanol to higher members of the series. Branched-chain alcohols (isopropyl and s- and t-butyl alcohols) activate these reaction to only a slight extent [21,31]. Regardless of their polarity and chemical nature, all aprotic solvents (benzene, toluene, cyclohexane, ethyl methyl ketone, dioxan, tetrahydrofuran, ethyl and butyl acetates, acetonitrile, triethylamine, pyridine, etc.) under comparable conditions inhibit the addition of amines and hydrazines to an activated carbon–carbon double bond [29,31]. These findings are confirmed by data on the preparative cyanoethylation of methyl-, hexyl-, nonyl-, and decyl-amines in various media [33-35].

Comparison of the temperature conditions or yields for amines of different classes (primary and secondary aliphatic amines and cyclic imines) (for example, on the basis of the tables in the review of Terent'ev and Kost [10]) leads to the conclusion that a primary amino-group is the most active in the cyanoethylation reaction although the difference is usually small. This is consistent with the lower basicity of primary amines compared with secondary amines (see, for example, Girault-Vexlearchi [36] and Albert and Serjent [37]). When the molecule of the substance cyanoethylated contains various amino-groups, this difference may become distinct. Thus in the cyanoethylation of the triamine (I) [15] the product of addition to the cyclic amino-group was obtained almost quantitatively:



(I)

$NH_2(CH_2)_2N(CH_3)CH_2CH_2CN$ (II)

$CH_3NH(CH_2)_2NHCH_2CH_2CN$ (III)

The cyanoethylation of *N*-methylethylenediamine [38] leads to a mixture of nitriles (II) and (III) in proportions of 73 : 27.

In many cases steric factors can cause a sharp "reversal" of the relative reactivity. On being refluxed with acrylonitrile, 2-amino-1-isopropyl-amino-2-methylpropane forms a 2-cyanoethyl derivative (IV), with the cyanoethyl substituent attached to the NH_2 group and not the imino-group, the steric accessibility of which is much lower [39]:

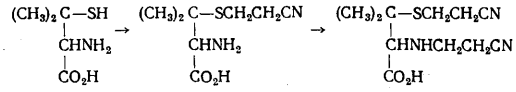
$(CH_3)_2CHNHCH_2C(CH_3)_2NHCH_2CH_2CN$ (IV)

The introduction into the structure of an aliphatic amine of a substituent with a terminal nitrile or ester group lowers appreciably its basicity [40-42]. This effect is particularly marked for CH_2CN and $(CH_2)_2CN$ groups. Thus while the esters of α- and β-amino-acids are cyanoethylated, albeit with difficulty, on being refluxed without catalyst in an inert solvent [43], there is virtually no cyanoethylation in the case of $RNH(CH_2)_2CN$, when R is an alkyl group with more than four carbon atoms [44]. However, the addition to the reaction mixture of methanol or ethanol (or their mixtures with water) greatly facilitates the dicyanoethylation of higher amines [33-35]. Acetic, propionic, and other organic acids have been recommended for the same purpose [45,46]. It is reasonable to suppose that the type of catalysis in these cases is similar to that obtaining for aliphatic amines [30,31].

Successful cyanoethylation of amino-acids requires the formation of an uncharged amino-group from the dipolar ion by the addition of, for example, at least an equivalent of an alkaline agent or a tertiary amine. When the content of alkali is low, the rate of reaction is proportional to its concentration. When an alkali metal salt of the amino-acid in aqueous solution is employed, the corresponding *N*-cyanoethyl derivatives are formed in almost quantitative yields even at room temperature. When the amount of acrylonitrile is raised to 2–3 moles, dicyanoethylation products can also be obtained after refluxing for a short time [43,47].

The study of the cyanoethylation of mercapto-acids and amino-acids of similar basicities showed [48] that in general mercaptide ions are much more nucleophilic than the amino-group. However, the relative rates of reaction involving mercapto- or amino-groups depend on the structure of the compound and may vary from 1300 to 6–8. Thus in the case of dimethylcysteine (penicillamine) the mercapto-group reacts first, but, when the amine : acrylonitrile ratio is 1 : 1, the NH_2 group is also involved to some extent [48,49]; in the presence of acrylonitrile (at a slightly

elevated temperature) satisfactory yields of *NS*-dicyanoethyldimethylcysteine were obtained[50]:



Similar relations involving the ease of cyanoethylation of mercapto- and amino-groups are typical also for other classes of organic compounds ‡. For example, the cyanoethylation of 2-aminoethanethiol in an alkaline solution yields a mixture of *NS*-dicyanoethyl and *NNS*-tricyanoethyl derivatives; in a strongly acid medium the reaction does not take place. On the other hand, in the pH range 3.6–6.8 there is a possibility of the selective formation of 3-(2-aminoethylthio)propionitrile[51].

The cyanoethylation of aromatic amines with acrylonitrile encounters considerable difficulties owing to the low basicity of the amino-group (pK_b = 8.5–11.5). However, it is stated in patents that acrylonitrile can add non-catalytically to the most basic representatives of the series, namely to *p*-phenylenediamine[52] and *N*-hydroxyethyl-*m*-toluidine[53], but these findings have not been checked. Aniline is recovered unchanged after prolonged refluxing with acrylonitrile at 180°C[54,55].

The available methods for the cyanoethylation of aniline, its *N*-substituted derivatives, and homologues can be divided into three groups: (a) reactions in the presence of acid reagents; (b) reactions catalysed by copper salts; (c) reactions in proton-donor solvents §. Organic acids and their anhydrides, dialkylammonium and aluminium salts, and, with poorer results, inorganic acids, have been used as the acid catalyst[44,58-61].

The reaction can be conveniently carried out in the presence of added acetic acid and an excess of acrylonitrile with refluxing for 6–24 h, the product being the monocyanoethyl derivative and in rare cases also an admixture of the bisadduct. The yields increase if a large amount of acetic acid is added, since the latter can be used also as a high-boiling solvent[61]. It is possible to establish (albeit only approximately, since the basicity does not always correspond to nucleophilicity) a relation between the basicity of the aromatic amine and the ease of its cyanoethylation[59,61]. For compounds with very low basicity (for example diphenylamine and α- and β-aminoanthraquinones), the yields of the corresponding *N*-cyanoethyl derivatives do not exceed 10–15%; nitroanilines do not combine with acrylonitrile in acetic acid at all[61]. As a rule, for the same basicity, amines containing substituents at the nitrogen atom or in the *ortho*-position relative to the amino-group are cyanoethylated much less satisfactorily (because the reaction centre is sterically hindered).

Contradictory views have been expressed in the literature concerning the catalytic effects of the salts of copper, zinc, cobalt, nickel, iron, and chromium in different valence states and even of metallic mercury on the addition of acrylonitrile to aniline and its substituted derivatives[61-63]. The main practical use has been of copper acetate (or its hydrate), which can catalyse vigorously the monocyanoethylation of various anilines without acid additives[61].

‡ On the other hand, ethanolamine, its *N*-substituted derivatives, and other amino-alcohols are cyanoethylated exclusively at the amino-group without alkaline additives[10].

§ We exclude from consideration the rare examples of the cyanoethylation or aromatic amines in the presence of alkaline reagents (choline hydrate, Triton B, carbazolylpotassium)[44,56,57] for reasons stated above.

The reaction takes place when a mixture of the reagents is refluxed (2–12 h), but sometimes, after a thermal initiation stage, the temperature of the reaction mixture rises spontaneously by 10–15 deg¶.

A characteristic feature of the method is its low sensitivity to the position of the substituent in the ring and to the size of the *N*-alkyl substituent. Even *m*-nitroaniline is readily cyanoethylated in the presence of copper acetate but the *para*-isomer, the basicity of which is low, reacts much less well[61].

Specific co-catalysts of the dicyanoethylation of aromatic amines in acetic acid are copper(I) cyanide and chloride and cobalt (II) chloride[44,62]. The use of the most active of these (Cu_2Cl_2) permits the synthesis, in the presence of only a small excess of acrylonitrile, of dicyanoethyl derivatives of various anilines (including anilines containing electron-acceptor substituents). However, the limitations associated with the steric screening of the reaction centre remain effective. Thus, among *ortho*-substituted amines, only *o*-toluidine gives a dicyanoethyl derivative in a yield up to 35%, while α-naphthylamine and *o*-aminobiphenyl form only monoadducts.

During the last ten years a preparative method has been developed for the cyanoethylation of aniline and its *para*-substituted derivatives in the presence of water as the catalyst[55,65-67]. The yields and the rates of the reaction are determined both by the basicity of the amine and its solubility in water. An almost quantitative yield of 3-phenylaminopropionitriles can be achieved by carrying out the reaction in an aqueous solution, provided that the aniline and the acrylonitrile are fully soluble[66]. The yield of adducts is in most cases unaffected by the variation of the pH of the medium in the range 6.8–10.8.[67,68] Refluxing for 1–5 h with a slight excess of acrylonitrile in aqueous solution also results in the formation of the *NN'*-dicyanoethyl derivative of *p*-phenylenediamine and the monoadducts of *NN*-dimethylphenylenediamine and *o*-toluidine, although in the latter case the yield does not exceed 30%. However, the attempts to cyanoethylate nitroanilines even under more severe conditions (heating in a sealed tube at 150°C) were unsuccessful[69]. On the other hand, heterocyclic imines (pyrazolines, tetrahydroquinolines, aminopiperidines, etc.), whose basicity approaches that of aromatic amines, can be successfully cyanoethylated in the presence of water[30,70-72].

Butskus[73] showed that aliphatic diols and many phenols can be used as solvents for the cyanoethylation of aromatic amines. Thus phenols, hydroquinone, and naphthols (8–9 g per 0.1 mole of aniline) give rise to 98–100% yields after refluxing for 20 h with an excess of acrylonitrile, while ethylene glycol may be recommended as a solvent in preparative syntheses. However, the catalytic activity of lower aliphatic alcohols proved to be slight.

3. MECHANISM OF THE CYANOETHYLATION OF THE AMINO-GROUP

Numerous examples of appreciable steric control of the reaction, of the role of the polarity and the proton-donor

¶ There exists no definitely formulated view concerning the mechanism of the catalysis by metal salts of reactions involving the addition of an amine to the double bond of acrylonitrile and acrylic esters. The hypothesis that a Π-complex of the unsaturated compound with the metal cation takes part in the reaction appears to be the most likely[64].

properties of the solvent, and the possible acid catalysis can all be interpreted only on the assumption that the cyanoethylation of the amino-group (and related reactions) takes place with intermediate participation of ionic species. Earlier it was assumed that these are 1, 4-addition reactions[74,75]. Terent'ev and Kost[10] believed that the cyanoethylation involves the formation of an amine—acrylonitrile complex which rearranges to the corresponding adduct by intramolecular migration of a proton. Later Heininger[61], Luskin et al.[22], and also Bekhli[55,56] explained the sharp acceleration of the cyanoethylation of aromatic amines and t-alkylamines in the presence of various catalysts and water by postulating the protonation of the nitrile group of acrylonitrile by proton-donor elements of the medium:

$$\overset{+\delta}{CH_2}{=}CHC{\equiv}N + H^+ \longrightarrow \overset{+\delta_1}{CH_2}{=}CHC{\equiv}\overset{+}{N}H \qquad +\delta_1 > +\delta$$

The additional shift of electron density then occurring increases the electron deficiency at the terminal carbon atom in the double bond and consequently the alkylating activity of acrylonitrile. Similar views were put forward by workers who investigated the addition of acrylic acid esters to amines (see, for example, Baltrusis and Macinlis[76]).

Nevertheless, analysis of the experimental data currently available shows that these hypotheses are inadequate[29]. The point is that the cyanoethylation of aniline in the aqueous phase takes place most satisfactorily[67,68] at pH 6.8–8.8 and therefore does not require either alkaline or acid catalysis. Furthermore, an increase or decrease of the pH from the optimum value results in a decrease of the yield. In a study of the kinetics of the addition of acrylic acid esters to cyclic imines in protic solvents the catalytic effect of acid additives was also not observed[68,77,78]. The addition of acids in the cyanoethylation of sterically unhindered aliphatic amines usually does not facilitate but actually hinders the reaction. In reactions with aromatic amines the replacement of acetic acid by phosphoric or hydrochloric acid somewhat inhibits the process[59,65]. Furthermore, it is known that the catalytic effect of water and alcohols in cyanoethylation reactions is not fully correlated with their acidity. Thus methanol is a stronger acid than water (by a factor of 1.5–3 according to different estimates[79]) but it promotes the addition of amines to an activated double bond to a lesser extent[31]. The sharp fall of the yield of cyanoethylation products in alcoholic media on going from methanol to higher homologues and in particular to branched-chain alcohols shows the considerable role which steric factors play, together with acidity, in the catalytic capacity of alcohols[21,29,31].

In addition, nitriles, esters, ketones, and even amides are weak bases which are hardly protonated by weak acids[80]. On the other hand, when the molecule contains a conjugated carbon–carbon double bond, the basicity of a functional group of this type is even lower, and, for example, acrylonitrile in 85% sulphuric acid is only 50% protonated[81].

Thus, under cyanoethylation conditions, acid additives should affect primarily the amino-group of the amines alkylated (which is present in a considerable excess relative to the acid). On the other hand, in the presence of water or alcohol the reversible protonation of the nitrile group when an amine is also present becomes altogether unlikely. One is virtually driven to the conclusion that only hydrogen bonds with participation of ammonium or oxonium salts are formed[82].

Finally, there is no unambiguous proof whether the activity of the carbon–carbon double bond is at all significantly increased (the electrophilic properties are increased) when the functional group of acrylic monomers is protonated[83,84]. Furthermore, hydrogen bonds formed between the solvent and the amine reduce the nucleophilicity of the amino-component and therefore must compensate the effect of monomer activation[85].

Without disproving completely the role of the protonation of the functional group in the activation of $\alpha\beta$-unsaturated compounds, the above findings show that this phenomenon cannot be responsible for the exceptionally high catalytic effect of the solvent.

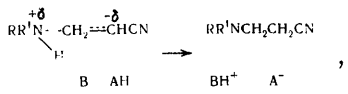
The available data are best explained on the assumption that the process takes place via an activated complex characterised by an appreciable or complete charge separation[21,29-31,50]. The probability of the formation of such an activated complex depends on the polarity of the medium. If the intermediate state is more polar than the initial components, then the reaction does not occur (or occurs with difficulty) in polar solvents[85]. This is probably so in our case. The polarity of amines is relatively low ($\epsilon = 3-7$) and, as their concentration in the mixture increases, the polarity of the medium falls[86,87]. The introduction of a protic solvent (water, alcohols) maintains the dielectric constant of the solution in the range 20–60 D. On formation of the transition state and its further stabilisation, the amino-group should be gradually converted into the ammonium form and the double bond of the monomer should be gradually converted into a single bond. We are thus dealing with the formation of an intermediate ylide structure †. There is at present no doubt that such structures occur as intermediates (and final) products in the reactions of acrylic esters with tertiary amines and in the condensation of nitrogen-containing heterocycles with acetylenecarboxylic acids[89]. A dipolar mechanism has been established for the reactions of acetylenecarboxylic esters with alkyl- and dialkyl-amines[86,90]. If in our case the reaction takes place via the ylide stage, this is of course because of the steric strain of the bonds and valence angles (the change of the sp^2 hybridisation of the carbon atom to sp^3 hybridisation and the conversion of the trigonal C–N–C angle into a tetrahedral angle)[91,92]. During the reaction, alkyl groups are somewhat displaced to the side opposite to that where the bulky alkylating group is introduced and there is steric interaction with the hydrogen atom of other substituents and hence repulsion. This repulsion (G. Brown's B-strain) will of course be a maximum if the reaction centre in the initial molecule is sterically hindered.

By solvating the intermediate ions, polar solvents should lower the activation energy for the reaction. In this respect, the most effective protic solvents (water, alcohols, and to some extent the excess of the amine introduced into the reaction) are capable of forming hydrogen bonds both with anions and with the ammonium ions formed ("specific solvation")[85]. Intermolecular proton migration has been demonstrated for almost all types of organic reactions catalysed by acids and (or) bases[93]. Even simple processes involving exchange between an amine and its conjugate acid and between an acid and its anion probably involve steps in which there is exchange with the medium[94]. In particular, this is why in acid-catalysed (prototropic) reactions proton transport is the rate-determining step over a definite pH range[93].

In our case the conversion of the transition complex (or the intermediate species close to it in structure) into

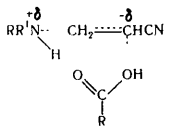
† The hypothesis of the intermediate formation of ionic species in the cyanoethylation of amines was first put forward by Timbekov and Sadykov[88].

the stable cyanoethylation product requires a double proton transfer and consequently the presence in the medium of a potential acid and base:



where B is a base and AH an acid—B and H may be part of the same molecule.

In a synchronous step of this kind[93] the bases may be the amines undergoing alkylation, other amino-components of the reaction mixture (for example reaction products, dimethylformamide, and other dialkylamides), solvent molecules when these are sufficiently basic or sterically accessible (water, alcohols), and hydroxide ions; the acids may be phenols, alcohols, water, and oxonium ions. When dipolar solvents and catalysts (ethylene glycol, organic acids) are employed, different centres of the same molecule function as acids and bases[95-97], so that the reaction complex is more compact. This can explain the higher rate of the reactions in such solvents:



In reactions with participation of metal ions (Cu^+, Cu^{2+}, Hg^{2+}) a metal ion with a vacant electron shell can serve as an acceptor for the electron pair of the CH group in the transition complex. According to some data[75], such solvation by transition metal ions may be more effective than solvation by many solvent molecules.

One can of course regard transfer processes, leading to the stabilisation of the transition state in reactions of amines with activated olefins, as reactions whose mechanism is not only of the synchronous (termolecular) type. Alcohols, water, dialkylamides, and, better still, the free amine can abstract a proton from the ammonium group and transfer it to the solution, whence it adds to the CH group[21], although energetically such a process is less favourable (retention of the charge on one side of the reaction complex). However, in both cases the solvents which show the greatest promoting effect are those which, while showing a considerable tendency towards the addition and dissociation of a proton, have molecules of small geometrical dimensions so that their incorporation in the complex or their approach to different centres of the binary ion is facilitated.

Under certain conditions, the protonation (or deprotonation) stage may compete with the primary alkylation stage as regards its importance for the overall rate of the process and to a greater extent the lower the concentration of the potential acid and the lower its donor capacity. Then the role of the base must of course be fulfilled largely by the amine undergoing alkylation. If the latter is sterically hindered or its basicity is low, both functions are carried out by the solvent (or catalyst) added. This is probably the reason for the anomalously high acceleration of the cyanoethylation of anabasine[86], 2,6-dimethylpiperidine[24], t-butylamine and related amines[21,22] following the introduction of several drops of water and acid, or dilute solutions of acid reagents. Here it is still too early to speak of changes in polarity, solvating capacity, and other macrocharacteristics of the medium. However, according to the literature, the presence of traces of proton-donor substances can strongly promote intermolecular proton transfer processes (see, for example, Giessner-Prettre and Oger[98]). On further dilution with a solvent or on further increase in the amount of catalyst, the rate of reaction increases but less appreciably and the effect is now determined by the sum of all factors. In reactions in highly dilute solutions the addition stage is of course rate-determining.

The kinetic literature data agree with the above mechanism. Cyanoethylation in aqueous or buffer solutions of ammonia[99,100], ethylamine, benzylamine, diethylamine[100], ethanolamine[78,100], amino-acids[48,50,101], and aromatic amines[69] follows second-order kinetics (or pseudo-first-order kinetics in the presence of an excess of one of the components), the non-protonated amine or the anion of the amino-acid with a free NH_2 group participating in the reaction. Therefore the pH probably affects only the concentration of the free amino-component. Thus, for amino-acids and mercapto-amino-acids, a satisfactory correlation has been found between pK_1 and pK_2 on the one hand and the kinetic characteristics of the system on the other; it is possible to estimate quantitatively the steric and polar factors with the air of a modified Hammett–Taft relation.

If one adopts as standard the rate constant for the cyanoethylation of glycine, then the following relation holds for other amino-acids: $\lg k_{A^-} = \rho\sigma^A + E_S$, where σ^A is a parameter representing the polar effect of the substituents and numerically equal to pK_2 (amino-acid) $- pK_2$ (glycine) and E_S is a steric constant, which depends on the size and the steric requirements of the substituent. Plots corresponding to substances with the amino-group at a primary, secondary, and tertiary carbon atom form separate branches with approximately the same slope ($\rho = 0.427 \pm 0.010$); their intercepts on the ordinate axis give E_S. A very sharp fall in the rate of cyanoethylation with increase of E_S (i.e. with increase in the number and bulk of substituents near the reaction centre) is typical, and has been attributed to an increase of the steric strain and steric interaction in the dipolar transition state (the telescopic effect)[50].

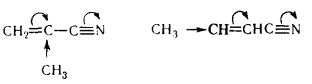
Unfortunately the kinetics of cyanoethylation in non-aqueous media have not been investigated at all[68]. To elucidate the role of proton-transfer processes, experiments in aprotic solvents with the addition of a certain amount of proton donors or acceptors would be particularly desirable.

4. SOME ANALOGUES OF ACRYLONITRILE

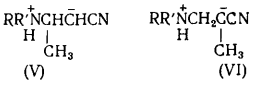
The substitution of a hydrogen atom in the acrylonitrile molecule by an alkyl group and (to a lesser extent) by an aryl group leads to decreased reactivity of the double bond in the addition reactions. Thus the nitrile of crotonic acid (or allyl cyanide, which is converted into the nitrile of crotonic acid in the presence of basic reagents) has been condensed with ammonia[102,103], methyl- and ethyl-amines[103], dimethyl- and diethyl-amines[104,105], pyrrolidine[106], ethylenimine[107], β-alanine[108], and other amino-acids[109]. As a rule these reactions take place at 70–100°C. Most of the syntheses have been carried out in dilute aqueous solutions, although the authors did not establish whether water promotes the reaction. Methods for the 2-cyanopropylation of aromatic amines (aniline, *o*- and *p*-toluidines, *o*-anisidine) are analogous to cyanoethylation methods: catalytic reaction of allyl cyanide at high temperatures in the presence of copper(I) chloride[104] and alkylation with the nitrile of crotonic acid by refluxing in

aqueous solution[105]. In both cases the yield does not rise above 10–40%. The study of the kinetics of the reaction of both isomers of crotononitrile with a number of amino-acids showed that the *cis*-compound is somewhat more reactive[101,110].

It has been established that α-substituted compounds passivate the double bond to a greater extent than substituents introduced at the β-carbon atom. Under the conditions indicated above, methacrylonitrile combines only with ethyleneimine[107], piperidine, and pyrrolidine[106] and does not alkylate diethylamine[106], benzylamine[13], aniline[105], and *p*-phenylenediamine (in the presence of acetic acid[60]). These facts are very interesting, since the +*I*-effect of the methyl group should be approximately the same in both positions[101,110].



In this connection, it has been suggested that in the transition state (VI) additional steric interactions between the CH_3 group and the substituent at the nitrogen atom are more likely than in the transition state (V)[101,107]:



(V) (VI)

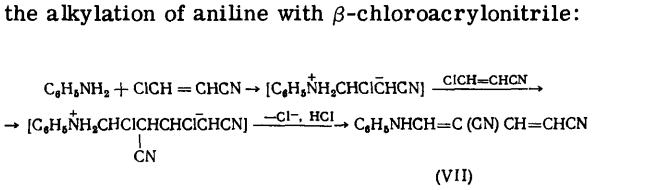
On the other hand the carbanion (V) with a negative charge at a tertiary carbon atom is apparently less stable than a similar carbanion with a negative charge at a secondary carbon atom[101].

Terent'ev and coworkers compared the relative reactivities of certain simplest αβ-unsaturated nitriles in reactions with an aqueous solution of potassium glycinate[111]. The yields of the adducts were as follows (acrylonitrile was adopted as 100): crotononitrile 23; allyl cyanide 5.3; methacrylonitrile 5; nitrile of *trans*-cinnamic acid 5; cyclohexylideneacetonitrile 8; cyclohexene-1-carbonitrile 8. Amines do not add to αβ- and ββ-dimethylacrylonitrile after prolonged refluxing both in the absence of additives and in the presence of an alkaline reagent[105,106]. 1,4-Dicyanobut-2-ene and β-cyanomethylacrylonitrile react with ammonia, various amines, and highly basic diamines at 60–70°C with formation of adducts of the type $NCCH_2CH_2CH(NRR')CH_2CN$. The addition is promoted by water as the solvent[112,113] or by 1–2% of a copper salt[114]. Dialkylamines are appreciably more active than primary amines or ammonia.

The chlorine atom is sterically similar to the methyl group but, in view of the −*I*-effect of the halogen, α-chloroacrylonitrile has a reactivity comparable with that of acrylonitrile[107,115]. If the chlorine atom is in the β-position, then in inert and even in proton-donor solvents, secondary amines are "cyanovinylated" according to the mechanism[116]:

$$ClCH{=}CHCN + RR'NH \rightarrow RR'NCH{=}CHCN$$

Similar substitution of functional groups has been noted for other classes of αβ-unsaturated compounds (β-chloroacrylates, β-halogeno- and β-alkoxy-vinyl ketones, β-chlorovinyl aryl sulphones). Nevertheless a mechanism involving initial nucleophilic addition with subsequent elimination of the hydrogen halide (or the alkoxy-group) is postulated for these reactions. In a kinetic study of the reaction of β-chloroacrylonitrile with piperidine (methanol, 0°C) appreciable differences between the rates for the *cis*- and *trans*-isomers were not observed (K_2 was respectively 2×10^{-2} and 2.67×10^{-2} litre mole^{-1} s^{-1}). Sterically homogeneous *trans*-2-piperidinoacrylonitrile was formed in both cases[116] (cf. ethyl β-chloroacrylate[117]). According to the authors[116], the intermediate dipolar ion has an appreciable lifetime, which permits isomerisation by rotation about the C–C bond. These views are indirectly confirmed by the formation of the bisadduct (VII) in the alkylation of aniline with β-chloroacrylonitrile:



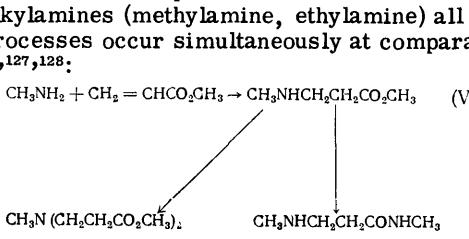
(VII)

5. ACRYLIC ACID ESTERS

Highly basic heterocyclic imines—ethyleneimine[107], pyrrolidine, piperidine[119,120], morpholine[16], and hexamethyleneimine[121]—readily add to the double bond‡ of methyl and ethyl acrylates, sometimes with a slight temperature rise, giving high yields of the corresponding esters of *N*-substituted aminopropionic acids. The reaction of lower dialkylamines is slower[120,122]. Even the reaction of dibutylamine requires a long time[120,123], probably due to the high steric hindrance at the nitrogen atom.

Similarly, 2-methylaminobutane (with an imino-group at a secondary carbon atom) reacts with ethyl acrylate only when the mixture is refluxed, and di-isopropylamine and di-s-butylamine do not react even on prolonged refluxing with ethyl acrylate[119,124]. However, recently it proved possible to carry out the addition of di-isopropylamine and 2,6-dimethylpiperidine to methyl acrylate in methanol[121].

The interaction of ammonia and primary amines with acrylic acid esters both without solvent and in methanol can take place in three ways. The weakening of the basicity of the alkylamine caused by the introduction of the group $CH_2CH_2CO_2R$ is relatively slight (see, for example, Holley and Holley[125]), so that the initially formed monoadduct can combine with a second molecule of acrylate. Furthermore, the addition reaction may be accompanied by the conversion of the ester group into an amide group, at least at elevated temperatures. Thus in the case of lower alkylamines (methylamine, ethylamine) all the above processes occur simultaneously at comparable rates[122,127,128]:



(VIII)

The yield of the amide then increases in proportion to the duration of the experiment. The formation of the monoadduct (VIII) appears to be favoured by the replacement of

‡ The same applies also to butyl, allyl, and other alkyl esters of acrylic acid, which are much more rarely used in chemical practice. It has been established that the amine may attack the C–O bond in cyanomethyl and *p*-nitrophenyl esters of αβ-unsaturated acids with formation of acid amides[18].

methanol by ethanol. As might have been expected, the reaction does not occur when ethylamine is introduced as the hydrochloride[129].

For less basic amines (butylamine, cyclohexylamine, β-tetrahydronaphthylamine, benzylamine, α-methylphenylethylamine), the formation of mono-2-alkoxycarbonylethyl derivatives takes place fairly smoothly in the mixture with acrylate kept in methanol for a period ranging from one day to several weeks[129-134]. Primary amines with tertiary substituents (t-butylamine, t-octylamine, 2-amino-1-ethoxycarbonyl-2-methylpropane) add to acrylic acid esters only under very severe conditions[20,130]. To accelerate the process, the latter is carried out in aqueous solution in the presence of alcohol or dilute acid[22,25,131,135]. According to patent data[136], acetic acid effectively catalyses the reactions of acrylates also with other strongly sterically hindered amines such as di(2-ethylhexyl)amine§. It is suggested that certain alkaline reagents be used as catalysts for the reactions of polymethyleneimines[107,138], but these data require verification.

In contrast to the cyanoethylation reaction, when aliphatic and aliphatic-aromatic primary amines are simply refluxed with 2–3 moles of acrylate, high yields of bisalkoxycarbonylethylation products are obtained[124,135,139]. According to other data, the latter reactions take place satisfactorily at lower temperatures too in alcoholic media[130]. This also applies to the addition of methyl and ethyl acrylates to amino-esters with the general formulae (IX)[139,140] and (X)[123,141,142]:

$$C_6H_5(CH_2)_n NHCH_2CHRCO_2R' \qquad RNHCH_2CHR'CO_2R^2$$
(IX) (X)

It is interesting that the shift of the branching point of the alkyl chain towards the nitrogen atom, which hinders the usual addition of acrylates, stimulates the "symmetrisation" reaction[142-144]:

$$C_6H_5(CH_2)_2NHCHCH_3CH_2CO_2C_2H_5 \xrightarrow[\Delta]{V} C_6H_5(CH_2)_3NCHCH_3CH_2CO_2C_2H_5$$
$$\rightarrow C_6H_5(CH_2)_2N(CH_2CH_2CO_2CH_3)_2 \qquad CH_2CH_2CO_2CH_3.$$

Methyl and ethyl acrylates can react, albeit with difficulty, with aniline in the presence of alkaline catalysts or methanol[145,146], but the yield of adducts is low. For preparative purposes, the 2-alkoxycarbonylethylation of aromatic amines is carried out with heating (8–15 h) in the presence of acetic acid[147]:

$$ArNH_2 + CH_2{=}CHCO_2R \xrightarrow{H^+} ArNHCH_2CH_2CO_2R$$

The reactions of methyl acrylate with aniline[38,148-150], toluidines[132-150], anisidines[148,149], halogenoanilines[132,148], *N*-alkylanilines, and α-naphthylamine and its analogues[150,151] have been achieved under these conditions. Amines of low basicity (diphenylamine, *o*-, *m*-, and *p*-aminobenzoic acids[151-153]) require more prolonged heating. Acetic acid can be replaced by acetic anhydride or an ammonium salt[120]. It has been stated that anhydrous stannous chloride has a catalytic effect[129,148].

A number of studies have been made on the kinetics of the reaction of amines with acrylic acid esters[48,77,101,145,154]. The reactions of morpholine and piperidine with acrylates in methanol are of second order, are not inhibited by alkalis, but are somewhat inhibited in the presence of acid reagents (acetic or perchloric acid). Replacement of part of the methanol by benzene greatly reduces the rate of the process, the rate decreasing faster than the dielectric constant of the mixture. The reactivity of methyl acrylate is higher than that of ethyl acrylate, but the latter scarcely differs from that of the butyl ester.

Table 1 lists the rate constants for the pseudounimolecular reaction of methyl acrylates with various amines in tetrahydrofuran (THF)[145].

It is striking that ethanolamine reacts 150 times faster than allylamine which has the same pK_a and ten times faster than the highly basic butylamine. A similar anomaly has been noted also for the diethanolamine–benzylamine pair. The reactivity of amino-alcohols $HO(CH_2)_nNH_2$ is almost independent of the number of methylene groups n,[154] and therefore in all cases it is necessary to assume an accelerating effect of the HO group, probably as a result of intermolecular interactions.

Table 1.

Amine	pK_a	K_1^{30}, min^{-1}
Ethanolamine	9.50	$2.4 \cdot 10^{-2}$
Butylamine	10.59	$2.1 \cdot 10^{-3}$
Allylamine	9.49	$1.6 \cdot 10^{-4}$
Diethanolamine	8.80	$9 \cdot 10^{-5}$
Benzylamine	9.34	$5 \cdot 10^{-5}$

Indeed when the reaction of ethanolamine with methyl acrylate is carried out at 20°C in dioxan, pyridine, dimethylformamide, and acetonitrile, a very slight increase of k_1 (from 2×10^{-2} to 4×10^{-2} min^{-1}), corresponding to the increase in the polarity of the medium, was observed[145]. However, in methanol, which has a smaller dielectric constant but is a potential proton donor, $k_1 = 9 \times 10^{-2}$ min^{-1}. (The high value $k_1 = 7 \times 10^{-2}$ min^{-1} quoted for the reaction in tetrahydrofuran may be due to the effect of peroxy-compounds[155]). Similarly it has been shown that the condensation of butyl-amine with ethyl acrylate in tetrahydrofuran[154] is very markedly accelerated (by a factor of 5–350) on introduction of alcohols, water, and butanethiol. These findings agree well with the hypothesis that the reactions of amines and activated olefins have the ionic mechanism discussed above for acrylonitrile[29].

A group of American workers[48,101] compared the reactivities of vinyl compounds of the acrylic series in reactions with 11 amino-acids. At pH 8.5 (30°C) methyl acrylate proved to be 3.6 times more reactive in relation to glycine than acrylonitrile. This is somewhat inconsistent with other observations[6,8] according to which the nitrile group has more pronounced electron-acceptor properties than the ester group. To account for this fact, it was suggested[101] that, in condensation with neutral nucleophilic reagents, one of the additional factors determining the reactivity of the olefins $CH_2{=}CHX$ is resonance stabilisation of the transition state by the functional group X. This is of course more likely for $COOCH_3$ than for CN.

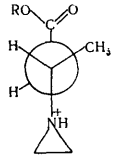
There are few data for the reactions of alkylacrylic acid esters with amines. The introduction of a methyl substituent at the double bond of methyl acrylate has little effect on the bond polarity, but, as in the case of acrylonitrile, it significantly reduces the steric accessibility of the reaction centre. The relative rates of reaction of methyl *trans*-crotonate and methyl methacrylate with glycine in aqueous buffer solutions are respectively 0.24 and 0.0116 of the rate of cyanoethylation of glycine[101].

§In reactions with participation of acrylic and methacrylic esters in an aqueous medium, an anomalous reaction involving the migration of alkyl groups may take place to some extent as well as the addition of amines to the double bond[137].

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It is interesting that crotonates exhibit more stringent steric requirements as regards the structure of the amine. Thus ethyl crotonate combines with piperidine [156], dimethylamine [157], propylamine [124], and methylamine [156,158] only on refluxing. In the last case variable amounts of the *N*-methylamide of 3-methylaminobutyric acid are also formed [158]. Diethylamine scarcely reacts with ethyl crotonate without heating, while at 200°C the main product is *N*-ethylcrotonamide. Normal, albeit slow, addition to the double bond occurs only in alcoholic solution [158]. On the other hand, the condensation of ethyl crotonate with butyl-, cyclohexyl-, benzyl-, and phenylethyl-amines takes place in alcohol even at room temperature [143,159,160], high yields of monoalkylation products being achieved.

Another unexpected observation of the steric inhibition of the reaction was made in a comparative study of the condensation of ethyleneimine with methyl and ethyl crotonates [107]. At 75°C methyl crotonate reacts completely, while its homologue gave only 2% of the adduct. Probably this is due to the mutual repulsion of the methyl and ester groups in the transition state (Newman's projection), which increases sharply with increasing size of the substituent R.



p-Anisidine and *p*-chloroaniline add to ethyl crotonate on refluxing in the presence of small amounts of acetic acid [161]. Ethyl and methyl ββ-dimethylacrylates combine slowly with methylamine [162] and very slowly with ammonia [156] in alcoholic solutions. On heating with anhydrous ethylamine, the main product is the *N*-methylamide; in the absence of additives, there is no reaction with piperidine [156]. Dimethylamine condenses with the β-dimethylaminoethyl ester of ββ-dimethylacrylic acid in the presence of acetic acid [163].

Methyl methacrylate readily reacts with piperidine [164], but the reaction with dimethyl- and diethyl-amines requires prolonged heating [44,124]. As already mentioned above, the ethyl ester proved to be even less reactive under comparable conditions [153,157]. Non-catalytic reactions of methacrylates with a number of aliphatic and aliphatic-aromatic amines have also been described [124,140,165]. However, the addition of methyl methacrylate, on refluxing the mixture, to dibutylamine [123], ethyl *N*-methylaminopropionate [123,141], and t-butylamine [166] could not be achieved. Aniline reacts with methyl methacrylate at 200°C to give a low yield of a mixture of three substances: the normal addition product, the anilide of 3-anilino-2-methylpropionic acid, and methacrylanilinide [120].

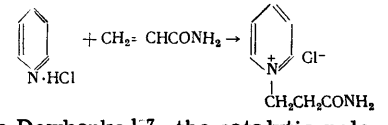
When alcohols are used as solvents, the reaction is either initiated or the temperature required is appreciably reduced. Thus in the presence of methanol the reactions of lower amines and dialkylamines (and also benzylamine) give, after a fairly long time, high yields of the corresponding monoadducts even at a low temperature [123,127,128,137,142,160,164]. With methylamine, a small amount of the double addition product is also obtained [123]. Hexamethyleneimine, β-tetrahydronaphthylamine, and cyclohexylamine react with methyl methacrylate on heating in the presence of added alcohol—the reaction takes place smoothly without the formation of side products [121,167]. For aniline, it is recommended that the synthesis be carried out in the presence of acetic acid [44,164], while methanol is inactive as a catalyst [121]. Acid catalysis can probably be used also in the reactions of other weakly basic amines, for example carboline derivatives [168].

The ethyl ester of α-ethylacrylic acid does not react with ammonia and dimethylamine on prolonged heating [156]. However, in an alcoholic medium it proved possible to add methyl-, butyl-, and benzyl-amines to a number of α-alkylacrylates with high yields [140,169].

6. ACRYLAMIDE

Diethylamine adds to acrylamide on refluxing (2–3 h), while without heating the reaction scarcely occurs [170]. It has been stated that with ammonia there is a possibility of the formation of a bis- or even a tris-adduct [171,172]. When acrylamide is added to an alcoholic solution of piperidine and morpholine, the process begins exothermically [121,170,173], although heat is required to complete the reaction. The method of 2-carbamoylethylation in alcoholic media has been successfully applied to dimethyl-, dipropyl-, and dibutyl-amines [173] and to a number of ring-substituted benzylamines [121,165,174]. For amines of low basicity (pyrazolines, pyrazoles, amino-acids), aqueous solutions are employed, sometimes with the addition of tertiary amines [108,121,172,175]. The effect of solvents on the addition of acrylamide to an amino-group proved to be more pronounced than in the case of acrylonitrile [29,121,165], but the overall nature of the catalysis by proton-donor solvents is probably the same. In particular 3-arylaminopropionamides may be obtained by condensing substituted anilines with acrylamides in the presence of both water and acetic acid in alcohol [147,176]. The kinetics of 3-carbamoylethylation of amino-acids have also been described [48,101].

Acrylamide can combine with the hydrochloride of pyridine (and a number of other heterocyclic bases) on refluxing in methanol [177]:



According to Dowbenko [177], the catalytic role of the acid is not associated with the protonation of the functional group of acrylamide.

N-Dodecylacrylamide (and dodecyl acrylate) reacts slowly by a similar mechanism with trimethylammonium and pyridinium salts [178]. Triethylamine proved to be inactive, probably for steric reasons or because of the impossibility of charge delocalisation of the type which occurs in pyridinium salts.

The substitution of hydrogen atoms in the amide group of acrylamide by alkyl groups alters the reactivity of the double bond but not always in the same way [8,107,179]. Thus *N*-benzylacrylamide reacts smoothly on heating with hydrazine hydrate in the presence of alcohol and dimethylformamide [180]:

$$N_2H_4 \cdot H_2O + CH_2{=}CHCONHCH_2C_6H_5 \rightarrow NH_2NHCH_2CH_2CONHCH_2C_6H_5 .$$

With phenoxycarbonylhydrazine, similar condensation takes place on refluxing with added acetic acid [181]. The reactions of *N*-methyl-, *N*-benzyl-, and *NN*-dimethylacrylamides with the most basic aromatic amines, which occur relatively readily in the presence of organic acids, have been described [182].

Diacrylamidomethane and 1,3,5-triacryloyl-1,3,5-triazine react similarly [183,184]. In the condensation of bisacrylamides (particularly 1,4-diacryloylpiperazine) with

primary and secondary amines in proton-donor media, polymers were obtained [185]. The reactions of α- and β-methyl-acrylamides have been described [172,186,187].

7. ACRYLIC ACID

Acrylic acid itself and its alkyl-substituted derivatives are the least reactive among acrylic olefins in condensations with amino-compounds. Thus aqueous ammonia (in a large excess) adds to crotonic and $\beta\beta$-dimethyl-acrylic acids after prolonged heating in an autoclave [188]. The same reaction involving crotonic acid takes place more readily on irradiation with ultraviolet light, the product being N-methyl-β-alanine and also its amide [189].

One of the factors inhibiting the reactions of acrylic acids with amines is undoubtedly salt formation and the consequent decrease of the activating effect of the carboxylate group on the adjacent double bond. Thus when crotonic acid is mixed in alcohol with 2-aminoethanol, 2-hydroxyethylammonium crotonate is precipitated [190]. After heating to 100°C, the latter is converted into β-(2-hydroxyethylamino)butyric acid.

Recently several ways have been suggested for overcoming these difficulties. For example, benzylamine, some of its substituted derivatives, isobutylamine, and hexylamine have been added to crotonic acid with high yields on heating an equimolar mixture of the reactants in pyridine solution [134,191,192]; when optically active α-phenylethylamine is introduced into this reaction, a mixture of diastereoisomers is formed, which can be separated [193]. The use of proton-donor solvents (water, lower alcohols, ethylene glycol) has been recommended in patents [194,195] for the synthesis of the adducts of unsaturated acids with higher aliphatic amines and polyamines. Nevertheless in a few cases the reaction in aqueous solution takes place in different ways and polymeric substances are formed together with alkylaminopropionic acids. Probably this can be explained by the addition of the monomer to the intermediate ion (XI) [192]:

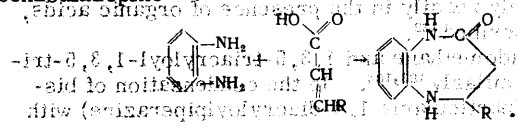
$$RNH_2 + CH_2=C(CH_3)CO_2H \rightarrow R\overset{+}{N}H_2CH_2\overset{-}{C}(CH_3)CO_2H\ .$$

Acrylic and methacrylic acids interact with an excess of aniline only at 180–190°C, the reaction involving both the double bond and the carboxy-group [196]:

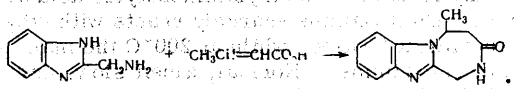
$$C_6H_5NH_2 + CH_2=CHCO_2H \rightarrow C_6H_5NHCH_2CH_2CONHC_6H_5\ .$$

Adducts of aromatic amines and $\alpha\beta$-unsaturated acids (1:1 composition) can be obtained in a low yield by exposing toluene solutions of the reactants to ultraviolet light [188]. Equivalent amounts of p-chloroaniline and crotonic acid were successfully condensed on refluxing in benzene [161]. According to the authors [161], in this case crotonic acid behaves at the same time as an acid catalyst. In a 1937 patent application by I.G. Farbenindustrie [197] the adducts of acrylic acid with a number of aromatic amines were described, but these data have not been reproduced so far.

The condensation of $\alpha\beta$-unsaturated acids and also their esters with difunctional amines leads to the formation of seven-membered heterocyclic compounds. For example, o-phenylenediamine is converted into the corresponding benzodiazepine [198]:



The structure of products of similar condensations is determined both by the reaction conditions and the relative nucleophilicity of the functional groups. When 2-aminomethylbenzimidazole is heated with crotonic acid, the double bond attacks a ring nitrogen atom [199]:



When the molecule contains a mercapto-group (o-aminothiophenol, β-aminoethanethiols), the reaction takes place with initial 2-carboxyethylation of the sulphur atom [200].

8. VINYL KETONES

Vinylketones (CH_2=CHCOR) have a highly activated double bond and their reactions with aliphatic dialkylamines and heterocyclic imines take place very vigorously [107,201–203]:

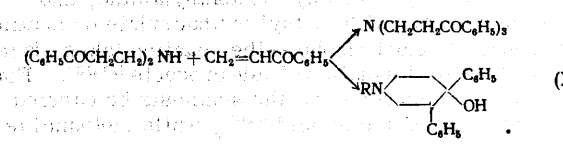
$$RR'NH + CH_2=CHCOR^2 \rightarrow RR'NCH_2CH_2COR^2\ .$$

Therefore the reaction is usually carried out either with cooling [204] or in ethereal and benzene solutions; in some cases alcohols have also been used as solvents [205].

When the rate of reaction is high, it is difficult to estimate qualitatively the effect of the basicity of the amino-component [204]; on the other hand, the effect of steric factors is very distinct. Thus a very bulky substituent in the 2-position of the piperidine ring (or two small substituents) greatly hinders the reactions with aryl vinyl ketones. Whereas dimethyl- and diethyl-amines react quantitatively with methyl vinyl ketone even at −5°C, the preparation of the corresponding adducts of methylcyclopentyl- and methylcyclohexyl-amines requires heating to 40°C [204]; the reaction of di-isopropylamine and dicyclohexylamine with methyl vinyl ketone would not proceed at all. The relative decrease of the rate of reaction is characteristic also of 2-alkylcarbonylethylation of amines with low basicity [206].

Primary aliphatic amines usually react with vinyl ketones without solvent, a complex mixture of products being formed (probably because of the simultaneous attack on the double bond and the carbonyl group). The process can be regulated by adding acetic or formic acid to the reaction mixture, so as to bind part of the amine [202]. Under these conditions, propylamine with ethyl vinyl ketone yields a mixture of mono- and di-adducts. Likewise, while aqueous ammonia and vinyl ketones form a mixture of di- and tri-alkylation products [207], with ammonium acetate it is possible to obtain a small amount of the monoadduct [201]. However, there are data [208,209] showing that ammonia and methylamine in the form of their hydrochlorides do not react with phenyl vinyl ketone even on heating in aqueous alcohol. In another method the monoadducts of primary amines and methyl vinyl ketone are synthesised at room temperature or with cooling in ethereal solution [210].

By heating an aqueous alcoholic solution of β-benzoylethylamine with phenyl vinyl ketone, the triadduct $N(CH_2CH_2COC_6H_5)_3$ was obtained, while the reaction of di(benzoylethyl)amine with the same unsaturated ketone yields a mixture of the same triadduct and a piperidinol (XII, R' = $C_6H_5COCH_2CH_2$) [208,209]:

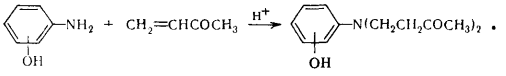


(XII)

On the other hand, the hydrochloride of *N*-benzoylethyl-*N*-methylamine and phenyl vinyl ketone form the adduct $(C_6H_5COCH_2CH_2)_2NCH_3$ or its mixture with a piperidinol of type (XII), with R = CH_3, depending on the medium (water or aqueous alcohol). Probably in both cases the reaction proceeds via a dipolar intermediate state, which is stabilised by the addition of a proton or by intramolecular aldol condensation[208].

Aromatic amines (aniline, *p*-toluidine, certain *N*-alkylanilines) add to methyl vinyl ketone[210,211], ethyl vinyl ketone[211,212], phenyl vinyl ketone[213-215] on slight heating or standing for a long time at room temperature. It has actually been stated that the addition of aniline to phenyl vinyl ketone causes an exothermic reaction[214], but the less basic anthranilic acid gives high yields only at 60°C[216]. The addition of an unsaturated ketone to an aromatic amine is the first stage in the synthesis of quinolines by the Döbner–Miller method[217]. In the presence of a proton-donor solvent (methanol, 50% ethanol) these processes appear to be accelerated[215,216]. When *N*-methylaniline and dimethylamine hydrochlorides are introduced into the reaction under these conditions, a mixture of Mannich bases is formed from both amines as a result of a mobile equilibrium[215]. The addition of an inert solvent appears to inhibit 2-carbonylalkylation of amines[216].

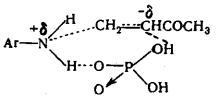
The products of the addition of methyl vinyl ketone to *p*-phenylenediamine and its analogues have been described[216]. In methanol in the presence of a slight excess of the unsaturated component, a bismonadduct is formed, while refluxing with an excess of methyl vinyl ketone leads to double alkylation of both amino-groups. When an acid catalyst (acetic acid) is used, it is also possible to obtain dialkylation products of other, somewhat less basic aromatic amines but there are few such examples yet[218]:



The study of the kinetics of the addition reactions has shown[101] that in aqueous solutions methyl vinyl ketone reacts with glycine eighty times faster than does acrylonitrile. Zuman and coworkers[219,220] determined polarographically the first-order rate constant for the reaction of phenyl vinyl ketone with a tenfold excess of morpholine and a number of primary amines in the presence of the corresponding hydrochlorides. The reaction with ethanolamine and cyclohexylamine goes almost to completion, while for other amines an equilibrium was observed after 37–60% conversion. Within the limits of experimental error, k_1 proved to be independent of ionic strength and pH. A direct correlation between the rate of 2-phenylcarbonylethylation and the basicity of the amine has not been found and therefore the different values of k_1 have been attributed mainly to the effect of steric factors[101]. This interesting result has not been adequately explained.

The reaction of methyl vinyl ketone with aromatic amines (in an acetate or phosphate buffer solution) up to a conversion in excess of 80% is satisfactorily described by a second-order equation[210]. The Hammett equation with $\rho = -1.60$ holds ($r = 0.998$; $s = 0.09$) for p-$RC_6H_4NH_2$ (R = CH_3O, CH_3, H, Cl, NO_2). The activation energy for the reaction in the temperature range 20–50°C is 5.2–6.1 kcal mole^{-1} and the entropy is between −48 and −50 e.u. By varying the composition of the buffer solution and its concentration, the authors established that the process is catalysed by both acids and bases (Table 2).

The activity of the $H_2PO_4^-$ ion is striking; it greatly exceeds the catalytic effect of acetic acid which has a much higher pK_a value. The phosphate ion may be involved in the transition state as a bifunctional catalyst:



If the reaction is carried out in dioxan–water mixtures, the catalytic effect of aniline itself (and similarly pyridine) is clearly shown. Evidently the amino-component in some form can participate in the formation of the transition complex, functioning, together with water, as a proton-transfer agent.

Table 2. Catalytic constants (k_1) for the reaction of methyl vinyl ketone with aniline at 31°C under different conditions.

Catalyst	Water	Solvent (40% aqueous dioxan)	Catalyst	Water	Solvent (40% aqueous dioxan)
CH_3COOH	0.02	—	H^+	10^3	
CH_3COO^-	0.26	—	Water	$5.5\cdot10^{-3}$	$1.6\cdot10^{-4}$
$H_2PO_4^-$	0.45	—	Aniline	—	$4.3\cdot10^{-3}$
HPO_4^{2-}	0.42		Pyridine	—	$7\cdot10^{-2}$

Alkyl substituents at the double bond of vinyl ketones (usually a methyl group) lower its reactivity only slightly. Thus the ketones RCOCH=$CHCH_3$, where R = methyl, phenyl, or alkoxyphenyl, combine with aliphatic amines, piperidines, and morpholine at room temperature[221,222]. High yields of monoalkylation products are attained after 1–4 h if the reaction is carried out in methanol or water.

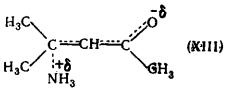
α-Benzylidene-ketones react with secondary amines somewhat more slowly[223] and the reaction depends more on steric factors than on the basicity of the amine. For example, diethylamine already adds with difficulty to methyl styryl ketone.

Among multiply substituted vinyl ketones, the condensations of amines with mesityl oxide has been most thoroughly investigated[224]. In the presence of water mesityl oxide combines with ammonia, methylamine, benzylamine, and hydroxylamine and its *N*-alkyl derivatives. However, the adducts formed are thermally unstable and can be isolated only as salts:

$$(CH_3)_2C{=}CHCOCH_3 + C_6H_5CH_2NH_2 \rightarrow (CH_3)_2\underset{\displaystyle NHCH_2C_6H_5}{CCH_2COCH_3}.$$

Diethylamine adds to mesityl oxide without solvent at 50°C[225]. Aromatic amines react with difficulty and do not give high yields. Mesityl oxide and other vinyl ketones react with diamines and amino-thiols forming seven-membered heterocyclic nitrogen-containing compounds[198].

On the basis of the study of the kinetics of the reaction of mesityl oxide with ammonia under pressure in aqueous solution or in methanol[226], the intermediate formation of the dipolar ion (XIII) has been suggested:



(XIII)

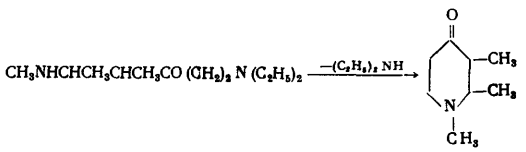
The rate of reaction in methanol increases with pressure appreciably faster [$\ln(k_p/k_1) = 1.224$] than in water (0.737) but nevertheless remains lower by a factor of 3–5. Calculation based on activation volumes shows a considerable

separation of charges in the transition state (0.42–0.65 of electron charge).

Compounds of the type $R_2C{=}CHCOCH{=}CH_2$, where one vinyl group is markedly screened, undergo smooth addition of aliphatic dialkylamines, piperidine, isopropylamine, and aniline to the sterically accessible double bond on brief heating to 60°C[207]. The yields fall somewhat with increasing length of the alkyl group R. The reaction with isopropylamine is accelerated by the addition of a few drops of water:

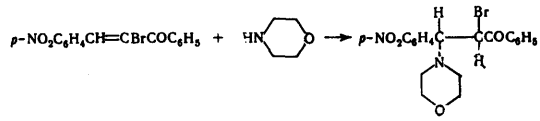
$$(CH_3)_2C{=}CHCOCH{=}CH_2 + (CH_3)_2CHNH_2 \rightarrow (CH_3)_2C{=}CHCO(CH_2)_2NHCH(CH_3)_2 .$$

In an alcoholic or aqueous medium it is possible to achieve a condensation involving the second double bond as well. Thus 1-diethylamino-4-methylhex-4-en-3-one combines with methylamine and certain other primary amines, forming a linear diadduct[228]. However, on heating these reactions lead to cyclisation with formation of γ-piperidones[228,229]:

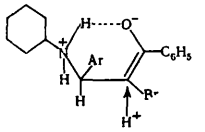


It is possible to use directly mixtures of a primary amine with divinyl ketones or β-methoxyalkyl vinyl ketones[230]. The cyclisation reaction, which consists essentially in a dialkylation process involving the amino-group, is of course controlled both by steric factors and by basicity[228,230,231]. A large number of γ-piperidones with various substituents in the ring and at the nitrogen atom have been obtained by this process.

A number of studies dealing with the stereochemistry of the addition of amines to the double bond of $\alpha\beta$-unsaturated ketones have been published. In the condensation of morpholine in benzene with *cis*- and *trans*-isomers of α-bromo-4-nitrochalcone, the same sterically homogeneous *threo*-adducts were obtained regardless of the configuration of the ketone, although the yield was somewhat higher when the *trans*-isomer was used[223]:



Primary amines (for example cyclohexylamine) react with α-bromochalcones forming diastereoisomeric β-amino-α-bromo-ketones, which cyclise spontaneously during the reaction, with retention of the configuration, to the corresponding *cis*- and *trans*-ethyleneimines[233,234]. It was found that the ratio of the isomers, as in the case of heterocyclic imines, is almost independent of the configuration of the initial $\alpha\beta$-unsaturated ketone, but may vary with the solvent. From these data, it was concluded[232,234] that the alkylation reaction proceeds via an intermediate complex incorporating the enolic form of the ketone:



The protonation of the α-carbon atom by the bulky cyclohexylammonium ion (in inert media) is responsible for the preferential formation of *trans*-adducts. Methanol probably attacks the complex less specifically, which results in an increase of the yield of products with a *cis*-configuration. These results have been analysed in greater detail by Hughes[23].

9. NITRO-OLEFINS

In a discussion of reactions involving a double bond activated by an adjacent nitro-group, it is necessary to take into account not only the polarity of the bond[5,6] but probably also the greater possibility of the delocalisation of a negative charge in the activated complex. On the other hand, the properties of nitro-compounds as carbon acids play a certain role, so that sometimes the process may occur autocatalytically. This is the reason for the exceptional ease of the reaction, of even highly substituted nitro-olefins, with nucleophilic reagents, including amines.

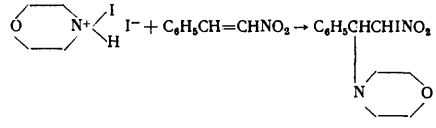
A typical example is provided by nitroethylene[236,237]. In an inert solvent (ether, dioxan, xylene, nitrobenzene) it combines with benzylamine, cyclohexylamine, and *N*-methylcyclohexylamine even at −20°C with formation of the corresponding 2-nitroalkylamines. Under the same conditions, benzylamine gives with an excess of the olefin the diadduct $C_6H_5CH_2N(CH_2CH_2NO_2)_2$. Two adducts (1 : 1 and 1 : 2) can also be obtained from aniline at 20° and 40°C respectively[236–238]. On slight heating, naphthylamines, *N*-alkylanilines, aminoanthraquinones, and aromatic diamines are 2-nitroethylated[227].

Homologues of nitroethylene combine with ammonia, diethylamine, and aromatic amines at room temperature without solvent or in ethereal solution[238]. Because of their instability, the acids are usually isolated as salts. The nitro-olefin $CH_3OCOCH_2[CH(OCOCH_3)]_3CH{=}CHNO_2$ has been successfully condensed (in the presence of methanol) with ammonia, benzylamine, cycloalkyleneimines, 2-aminoethanol, and isopropylamine. Under comparable conditions, aromatic amines give lower yields[239].

Under mild conditions, ω-nitrostyrene combines with piperidine, ammonia, semicarbazide, aniline, phenylhydrazine, benzidine, and a number of other amines[238,240]. Probably the yield of adducts is determined mainly by the isolation conditions and cannot be related to the basicity of the amine used. Thus with *p*-toluidine the reaction is completed after several minutes. Nevertheless aromatic amines of low basicity (for example, *p*-chloro- and *p*-nitro-anilines) do not react with ω-nitrostyrene at room temperature. Condensations of this kind are usually not carried out with heating to avoid secondary reactions. For example, it has been shown that certain 1-aryl-2-nitroethylation products are cleaved at elevated temperatures with formation of nitromethane[241]:

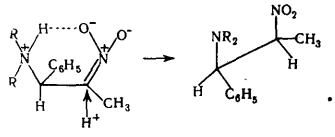
$$C_6H_5NHNH_2 + ArCH{=}CHNO_2 \rightarrow C_6H_5NHNHCHArCH_2NO_2 \rightarrow C_6H_5NHN{=}CHAr + CH_3NO_2 .$$

The addition of hydrazine and a number of acylhydrazines to ω-nitrostyrene has been achieved in absolute alcohol[242]. When the iodonium complex of morpholine is introduced into the condensation reaction in the presence of acetic acid, a positively charged iodine atom enters into the molecule of the alkylation product[243]:



The reactions of β-methyl-β-nitrostyrene with pyrrolidine, piperidine, morpholine, and certain aliphatic

amines have been investigated stereochemically[244]. In petroleum ether with equimolar proportions of the reactants, the *erythro*-isomers are formed preferentially while in the presence of an excess of the amine or in an alcoholic medium the main products are the corresponding *threo*-isomers. It was assumed[244] that the reaction takes place via an intermediate *aci*-compound, which exists as the inner complex (XIV):



(XIV)

The proton donor should attack it preferentially from the unhindered side, which leads to the *erythro*-disposition of the substituents. The gradual isomerisation of the *erythro*-isomers gives the more stable *threo*-adducts.

A number of studies have been made to elucidate the effect of substituents in the aromatic ring on the reactivity of arylnitro-alkenes. Methyl, methoxy-, or hydroxy-groups in the para-position of the benzene ring occasionally deactivate the double bond and the corresponding nitro-olefins cannot be condensed with *p*-toluidine and *p*-phenylenediamine (slight heating in the presence of alcohol)[245,246]. The introduction of an additional nitro-group or halogen atom leads, on the other hand, to an increase of the electrophilicity of the double bond[245-247]. Thus 2-chloro-4-nitro-ω-nitrostyrene readily reacts with many aromatic amines and hydrazines[247].

The nitro-group in the *ortho*- or *para*-position relative to the double bond of the styrene molecule activates the latter sufficiently for certain nucleophilic reactions[248]. On being refluxed in alcoholic solutions with an excess of secondary amines (pyrrolidine, piperidine, dimethylamine), *p*-nitrostyrene forms the corresponding adducts in yields in excess of 90%; the yield gradually falls on going to diethyl- and dipropyl-amines. When di-isopropylamine is used, only traces of the desired product are obtained, and di-isobutylamine does not react with *p*-nitrostyrene at all. In all cases *o*-nitrostyrene is less reactive. t-Butylamine reacts with difficulty with *p*-nitrostyrene and in particular with *o*-nitrostyrene (yields 45 and 7% respectively). It has been shown that these effects are not associated with the interaction between the amines and the nitro-group but are caused by direct frontal hindrance of the addition reaction.

Recently very interesting results were obtained in the study of the kinetics of the reaction of butylamine and benzylamine in dioxan with various nitrostyrenes, β-nitropropenylbenzenes and β-nitrobutenylbenzenes[249]. The pseudo-first-order constants obtained can be represented by the equation

$$K_{tot} = [RNH_2]^2/[A(RNH_2] + B)$$

where A and B are constants which can be roughly correlated with Hammett's σ coefficients. In other words, the authors believe that the transition state of the reaction includes, together with the αβ-unsaturated compound, two molecules of the amine. On the other hand, if the condensation (for example with aniline) is carried out in an alcoholic solution of a phosphate buffer, the reaction is of first order with respect to the amino-component. Consequently in such cases the protic solvent assumes the functions of the second amine molecule.

10. VINYL SULPHONES

The available information about the condensation of vinyl sulphones with nucleophilic reagents is insufficiently systematic[6]. For a long time the problem of the nature of the interaction between the double bond and the sulphonyl group also remained unresolved[250,251]; it is most reasonable to assume a purely inductive effect of the SO_2R group. This makes even more unexpected the appreciable reactivity of vinyl sulphones in reactions with amino-compounds[101].

Aryl vinyl sulphones have been thoroughly investigated in this respect, particularly the readily available p-$CH_3C_6H_4SO_2$-$CH{=}CH_2$ [252-255]. The latter sulphone gives quantitative yields of adducts with various amines in benzene solution at room temperature[256,257]. However, the addition of sterically hindered amines such as diazopropylamine could not be achieved[256]. In preparative experiments methanol as solvent has a favourable effect[254,255]. Condensations involving allyl aryl sulphones, which are evidently first isomerised to the αβ-unsaturated isomers, also take place comparatively readily at 50–70°C [255,258]:

$$ArSO_2CH_2CH{=}CH_2 + R_2NH \rightarrow ArSO_2CH_2CH(CH_3)NR_2 .$$

Table 3. First-order rate constants for the reaction of *p*-tolyl vinyl sulphone with amines in alcohol at 25°C.

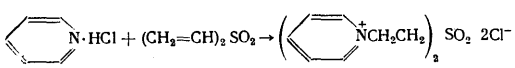
Amine	pK_a	$k_1 \cdot 10^3$	Amine	pK_a	$k_1 \cdot 10^3$
Piperidine	11.1	585	Hexylamine	10.6	10.6
Dimethylamine	10.8	451	Butylamine	10.6	8.0
Morpholine	8.4	33.8	Isopropylamine	10.6	4.32
Diethylamine	11.0	23.3	s-Butylamine	10.6	4.24
Dibutylamine	11.3	12.5	2-Ethylpiperidine	—	3.78
2-Methylpiperidine	11.0	10.9	t-Butylamine	10.7	0.86
Isobutylamine	10.7	10.8	2,6-Dimethylpiperidine	11.1	0.085

The addition of numerous amines of different classes to the double bond of aryl vinyl sulphones was recently investigated by kinetic methods[256,257,259]. It was found that, as in the case of vinyl ketones, the reactivity of the amines depends more on the steric environment of the nitrogen atom than on its basicity[256] (Table 3). In alcohol the reaction is definitely of first order with respect to each component; in benzene solution the rates of all the reactions are greatly reduced (approximately by a factor of 40) and the order with respect to the amine becomes non-integral, approaching two in the presence of an excess of the amino-component. Probably the second amine molecule enters into the transition state and evidently functions, instead of alcohol, as a proton transfer agent[256]. The rate of addition of t-butylamine to *meta*- and *para*-substituted aryl vinyl sulphones $RC_6H_4SO_2CH{=}CH_2$ (R = H, CH_3, CH_3O, Cl, NO_2, or CH_3SO_2) is satisfactorily correlated with the Hammett relation ($\rho = 1.59$)[257]. This also suggests that the reactions take place via a co-ordinated mechanism with very marked charge separation and a high degree of new bond formation in the transition state. According to kinetic data[259], the introduction of a methyl group in the β-position in the double bond of the *p*-tolyl vinyl sulphone molecule lowers the rate of addition of piperidine by a factor of 840 and in the case of α-substitution the rate falls by a factor as high as 6500. The explanation given for this behaviour is similar to that

discussed above for substituted acrylonitriles—destabilisation of the carbanionic centre in the transition state as a result of the donor properties of the methyl group[259].

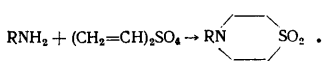
There are data (mainly in patents) on the addition of aromatic amines, but these probably require experimental verification: thus *N*-ethylaniline can add to *p*-tolyl vinyl sulphone on heating to 100°C[253], β-naphthylamine reacts satisfactorily on being refluxed in methanol, and *o*-aminobenzenesulphonic acid and amines of similar structure react in aqueous sodium carbonate solutions[252,253]. Data have also been published on the acceleration of the reaction in the presence of benzoyl peroxide or zinc acetate[253]. Weakly basic aromatic amines such as *p*-nitroaniline and diphenylamine apparently react only in the presence of alkaline additives (metallic potassium, sodium hydroxide)[253,254].

Divinyl sulphone, which can interact with secondary amines in proportions of 1 : 1 and 1 : 2, exhibits high chemical reactivity[260-263]. Most of the bis-addition reactions take place with high yields in the presence of an excess of the amino-component even at room temperature or with slight heating[260,262]. For this reason, the formation of monoadducts is favoured by dilution of the reactant mixture with a non-polar solvent and by cooling (for example in ether at a temperature between −1° and −3°C)[263]. The condensation of divinyl sulphone and pyridine hydrochloride and some of its substituted derivatives has been described[260,264]:



The reaction is reversible and takes place rapidly only in an almost neutral alcoholic medium (pH 6.5—7.5). An increase of acidity, which leads to binding of part of the tertiary amine, sharply inhibits addition processes.

On heating with divinyl sulphone, primary amines cyclise in most cases to 1,1-dihydroxy-1,4-thiazane derivatives[256,266]:



Diamines, aniline, hydroxylamine, phenylhydrazine, and amino-acids and their esters react by the same mechanism. The reactions are accelerated in the presence of alcohol. Somewhat longer heating and a somewhat greater amount of solvent are required for higher and especially aromatic amines[266].

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