Translated from *Uspekhi Khimii* **58** 250–274 (1989) U.D.C. 547.466

Synthesis and properties of α-aminonitriles

Yu M Shafran, V A Bakulev, V S Mokrushin
Kirov Ural Polytechnical Institute, Sverdlovsk

ABSTRACT. The information about the synthesis, chemical, physicochemical, and biological properties, and also the stereochemistry of α-aminonitriles has been classified. The bibliography includes 283 references.

Contents

I. Introduction 148
II. Synthetic methods 148
III. Stereochemistry 152
IV. Chemical properties 153
V. Physicochemical properties 158
VI. Biological activity 158

I. Introduction

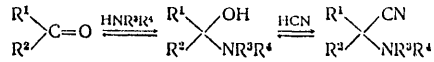
Throughout the period of over 130 years since their discovery, α-aminonitriles have been the subject of study for research scientists in different countries. There is continuous interest in this class of compounds mainly because they are intermediates in convenient preparative methods for obtaining α-amino acids [1] and nitrogen-containing heterocycles,[2] which are biologically important compounds. There has recently been a report about the possibility of the prebiological synthesis of the simplest example of an α-amino-nitrile—aminoacetonitrile—in an interstellar medium[3] as well as under conditions simulating the original atmosphere of the Earth.[4] There is theoretical interest in the mechanisms of the reactions used in the synthesis of α-aminonitriles and also the characteristics of the reactivity of the amino and cyano groups related to their close proximity in α-aminonitriles.

A brief review of methods for synthesising α-aminonitriles is given in one book.[5] The use of the Strecker reaction for obtaining α-aminonitriles has been examined.[6] A further review on α-amino-nitriles has been published in Danish[7] and is difficult to access as a literature source. Classification of the reactions involving α-amino-nitriles and examples of them have been reported in one study,[8] which, however, falls far short of including all known types of reactions of α-aminonitriles. The use of α-aminonitriles in organic synthesis is the topic of another review,[9] which appeared in Japanese in a journal that is difficult to obtain in the USSR.

II. Synthetic methods

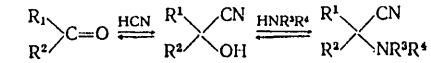
1. The Strecker reaction

In 1850 Strecker[10] carried out the synthesis of glycine and alanine by treatment of formaldehyde and acetaldehyde with aqueous solutions of ammonia and hydrocyanic acid followed by hydrolysis of the α-aminoacetonitrile and α-aminopropionitrile formed. This reaction was subsequently extended to ketones and amines and became known as the Strecker reaction.[11]



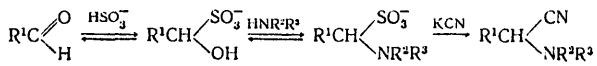
The replacement of volatile hydrocyanic acid and ammonia by a mixture of potassium or sodium cyanide and ammonium salts was proposed by Zelinskii and Stadnikov.[11] In this case ammonium chlorides or sulphates are reacted directly or are prepared *in situ*.

A modification of the Strecker reaction proposed by Tiemann[11] involves changing the order of mixing the reagents. It is suggested that the increase in yield of α-aminonitriles that often occurs in this case is due to participation of α-hydroxynitriles (cyanohydrins) (I) in the reaction.



(I)

When the aldehydes have low reactivity, their bisulphite adducts (II) are subjected to the Strecker reaction. When primary and secondary α-aminonitriles are prepared, the reaction is carried out in water with ammonium or alkylammonium salts in the presence of an excess of free base. This form of the Strecker reaction has become known as the Knoevenagel–Bucherer method.[6] The closest parallel with it in the Soviet literature[11] is given by the first two stages of the Bucherer–Bergs reaction,[12] in which adducts (II) are also frequently used.



(II)

In recent years the Strecker reaction itself[13–29] as well as the Zelinskii–Stadnikov,[6,16,30–48] Tiemann,[12,52–55] and Knoevenagel–Bucherer[6,55–58] modifications have been repeated many times on other substrates. Furthermore, the Strecker reaction in a broad sense has been considerably extended by the use of other solvents and sources of amino and cyano groups.

A number of syntheses of α-aminonitriles have been carried out under non-aqueous conditions—in alcohols,[29,59–64] tetrahydrofuran,[65] benzene,[66] in excess amine,[67] and also without any solvent.[68] When

the synthesis is carried out in liquid ammonia, it is necessary to use a low temperature and high pressure,[12,52,69] which makes it difficult to obtain primary α-aminonitriles by this method.[68] By using DMSO–H_2O (9 : 1, 19 : 1, and 20 : 1) systems as the solvent together with water and a water–methanol (1 : 1) mixture, it was possible to increase the yield of a number of α-aminonitriles by improving the solubility of the initial aldehydes.[70]

The role of water in the Strecker reaction is not simply that of a solvent. It was shown[67] that water, including that formed during the reaction, accelerates the epimerisation of a kinetically controlled α-aminonitrile and is therefore a catalyst for the process.

The nature of the products in the Strecker reaction is considerably affected by the pH of the medium, the ratio of reagents, and the reaction temperature. The primary or secondary α-aminonitriles formed initially are capable of undergoing a further *N*-α-cyanoalkylation reaction.[22–25,33–48,71,72] Thus in diamine (III) the hydrogen atoms of the primary amino groups are replaced first of all and then those of the secondary groups are replaced.[71] A high pH value of the medium helps to remove the primary α-aminonitrile (IV) from the reaction as an azomethine (V).[25,73] It is also possible to stop the process at the first or second stages by selecting the ratio of reagents[23,36,39,41,72] or the reaction temperature.[34,41] The exhaustive cyanomethylation of ammonia to give nitrilotriacetonitrile (VI) has been reported in a large number of patents.[22,23,33–48]

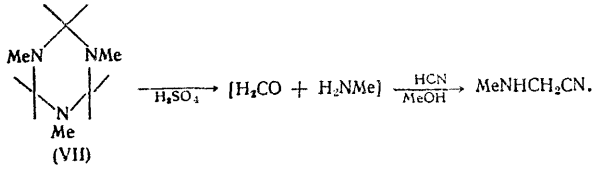
$$\underset{\text{(III)}}{H_2NC_2H_4NH_2} \xrightarrow{H_2CO,HCN} NCCH_2NHC_2H_4CH_2CN \xrightarrow{H_2CO,HCN} \rightarrow (NCCH_2)_2NC_2H_4N(CH_2CN)_2,$$

$$NH_3 + H_2CO + HCN \rightarrow \underset{\text{(IV)}}{H_2NCH_2CN} \underset{H^+}{\overset{H_2CO}{\rightleftharpoons}} \underset{\text{(V)}}{H_2C{=}NCH_2CN}$$

$$\text{(IV)} \xrightarrow{H_2CO,\ HCN} N(CH_2CN)_3 \xrightarrow{H_2CO,HCN} \underset{\text{(VI)}}{HN(CH_2CN)_2} \xrightarrow{H_2CO} H_4C(N(CH_2CN)_2)_2.$$

N-α-polycyanoalkylation reactions are catalysed by alkali metal cyanides.[71]

It is possible to use paraformaldehyde instead of formaldehyde in the synthesis of α-aminonitriles (VI). Urotropine [37,41–43,45,74] and 1,3,5-trimethylhexahydro-*sym*-triazine (VII) [49] can serve at the same time as sources of both formaldehyde and ammonia or methylamine. The thermolysis of formamide is a convenient method in the preparative sense for generating a mixture of hydrogen cyanide and ammonia.[75]



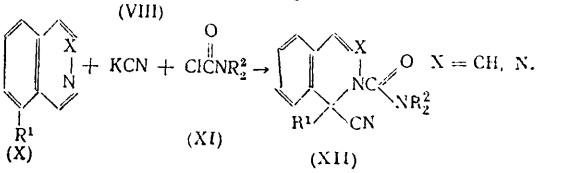
The most significant development of the Strecker reaction has been the introduction of new sources of cyano groups into synthetic use. Acetone cyanohydrin,[67,76,77] isobutyral cyanohydrin,[78] benzoyl cyanide,[79] diethylphosphonocyanide,[65] and trimethylsilyl cyanide (TMSCN) [59,60,68,80] have been used for this. The addition of TMSCN to aldehydes is catalysed by Lewis acids, in particular by zinc iodide,[59] and previously unobtainable α-aminonitriles can be prepared. However, this reagent is susceptible to hydrolysis, and therefore it is necessary to work under absolutely anhydrous conditions. The most acceptable methods for synthesising TMSCN are reported in two studies.[83,84]

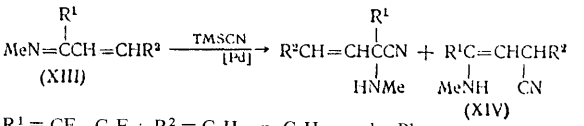
A scheme for the extended Strecker reaction has been drawn up to take account of these changes (see Scheme 1 below).

All the reactions positioned on the scheme above the continuous line are reversible. Moreover, the synthesis of α-aminonitriles is also carried out from individual compounds shown on the scheme between the horizontal dotted line and the continuous line. Thus, for example, the amination of cyanohydrins (I) with ammonia or amines[12,25,30,52,53,60,62,64,69,85–96] and even the reaction of α-mercaptobutyronitrile (VIII) with ammonia[30] can be regarded as specific examples of the Tiemann reaction.

The use of Schiff bases such as (IX) [3,19,21,77,79,80,97–100] and hydrazones[101–103] as substrates of CN^- ions has been reported. Aromatic nitrogen-containing heterocycles (X) can be regarded as Schiff bases with an endocyclic C=N bond; when they are treated with potassium cyanide and *N*,*N*-disubstituted carbamoyl chlorides (XI), analogues of Reissert compounds (XII) are obtained.[104] When they are reacted with TMSCN in the presence of palladium compounds, azomethines (XIII) also exhibit properties of 1-aza-1,3-dienes, leading to the formation of by-products (XIV) from 1,4-addition.[100]

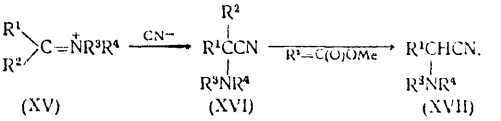
$$\underset{\text{(VIII)}}{EtCHCN(SH)} \xrightarrow{NH_3} \underset{NH_2}{EtCHCN}$$





$R^1 = CF_3, C_2F_5$; $R^2 = C_6H_{13}$-n, C_6H_{11}-cyclo, Ph, HC = CHMe-*trans*.

According to the modified method of Polonovskii–Potier[105] iminium salts of the type (XV) obtained *in situ* are treated with KCN. When a methoxycarbonyl group is present on the reaction centre it can be eliminated, and as a result demethoxycarbonylation products (XVII) are formed together with α-aminonitriles.[106,107]



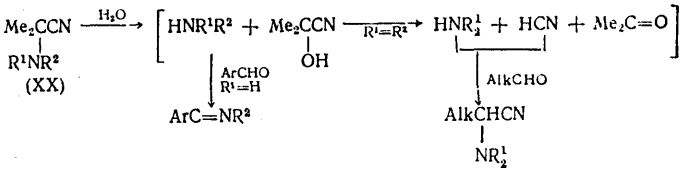
The addition of hydrocyanic acid to enamines such as (XVIII) in a basic medium also gives α-aminonitriles.[108] All this naturally raises the question about the mechanism of the expanded Strecker reaction.

This problem was examined in the greatest detail in two studies.[67,96] However, the results obtained in them are ambiguous. Thus, for example, in one article,[96] α-aminonitriles obtained by the Strecker and Tiemann reactions have the same optical purity. On the basis of this experiment the authors rejected a mechanism involving stereochemical control of the reaction due to steric hindrance in attack on cyanohydrins (I) and considered the stereoselective addition of HCN to geometric isomers of Schiff bases of the type (IX) more likely. In the other study[67] it was concluded that cyanide ions most probably add on to ketiminium cations of

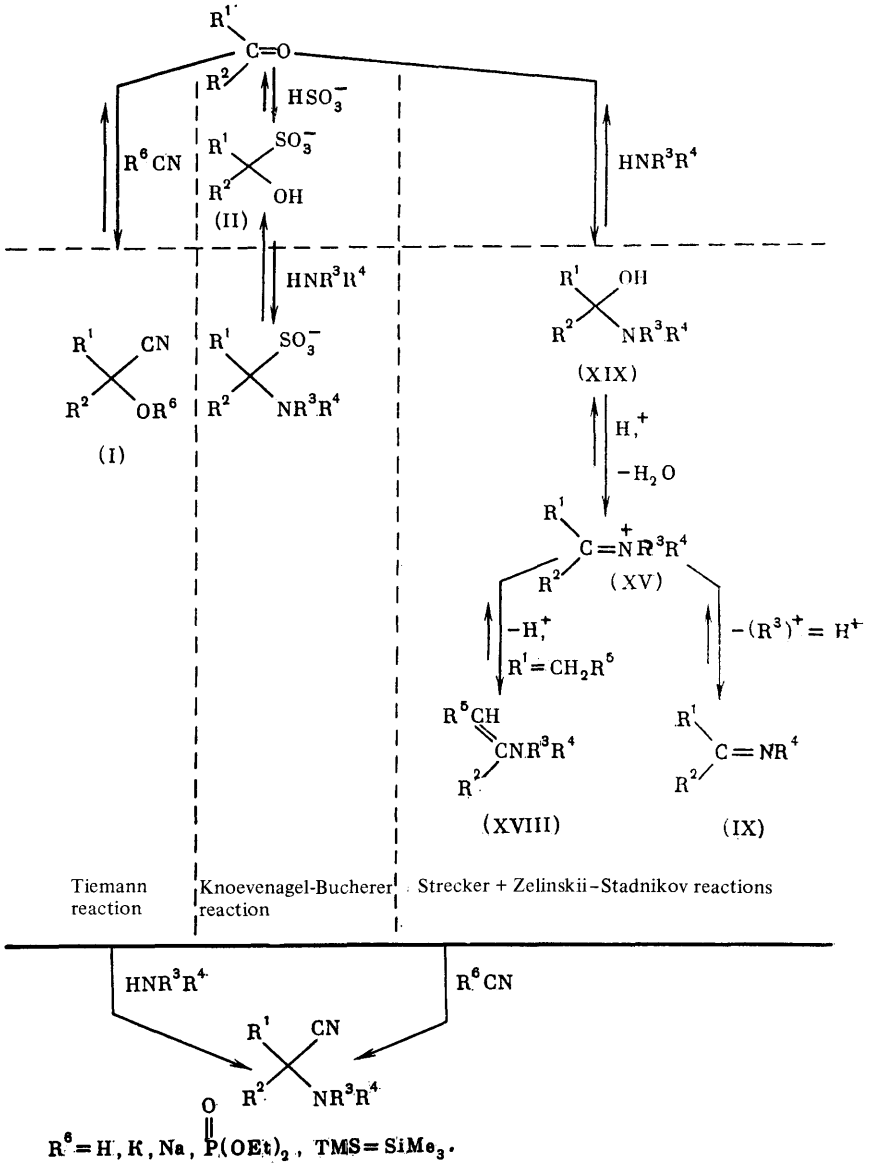
the type (XV), the presence of which in the reaction mixture was reliably detected. Moreover, the authors did not rule out the possibility of α-aminonitriles being formed by S_N2 attack of CN^- on aminoalcohols such as (XIX).

Valuable information about the mechanism of this reaction was obtained when the "retro-Strecker" decomposition of α-aminonitriles was analysed. This process occurred in water at different pH values,[109,110] during mass spectrometry,[111] during vacuum flash thermolysis, gas-phase pyrolysis, and thermolysis.[112] It was shown that the decomposition of *N*, *N*-dialkyl-α-aminonitriles occurs via ketiminium ions such as (XV).[109] In the case of primary and secondary α-aminonitriles, intermediates of the type (XV) are also formed, but they are much more difficult to identify because of their rapid conversion to Schiff bases.

The molecular ions generated from primary and secondary α-aminonitriles eliminate HCN to give Schiff bases, and only in the case of tertiary α-aminonitriles does the elimination of an amino group predominate, corresponding to a "retro-Tiemann" reaction.[111] The latter type of decomposition was also demonstrated for aqueous solutions of isobutyronitriles (XX) from the chemical reaction of its products.[113]



Scheme 1



A reliable determination of the mechanism of the Tiemann reaction is made possible by comparing the yield of α-aminonitriles obtained by this and other methods. In one study[63] it was shown that the yield of a number of α-aminonitriles from cyanohydrins such as (I) is invariably higher than from azomethines such as (XVIII). The difference between the Tiemann reaction and the "classical" Strecker reaction is also exhibited when TMSCN is used as the cyano group donor. In this case, however, the Strecker variant is more favourable because of the low thermal stability of cyanohydrins of the type (I) (where R^6 = TMS).[68]

The data given indicate that in some cases cyanohydrins of the type (I) lie within the sphere of the Tiemann reaction. By and large the mechanism of the Strecker reaction is not universal and depends on the nature of the solvent and the reagents and also on the order in which they are mixed.

The various forms of the Strecker reaction differ slightly with respect to their synthetic possibilities. Thus, out of the very large number of α-aminonitriles obtained by the Strecker reaction only compound (XXI) contains a substituent with distinct electron-withdrawing properties on the α-carbon atom.[17] When TMSCN was it was possible to add to this a number of compounds such as 2-amino-(4-cyano- and 4-carboxymethyl-phenyl)acetonitriles (XXII).[59] It should be noted that the yield of α-aminonitriles (XXII) is considerably lower than for the analogous compounds not containing strong electron-withdrawing groups at the α-position (15%, 17%, and 90–99% respectively).[59] α-Aminonitriles with strong electron-withdrawing groups at the 2-position, synthesised from cyanohydrins, also constitute a small proportion of the total number of compounds obtained by such methods, but nevertheless ten 2-amino-2-fluorocarbonitriles (XXIII) [86] and six 2-carbonyl-amino-2-(2-, 3-, and 4-nitrophenyl)acetonitriles (XXIV) [66] are among them.

$$R^1C_6H_4CHO + H_2NR^2 \xrightarrow[AcOH+H_2O]{KCN} \underset{\displaystyle HNR^2}{\underset{|}{R^1C_6H_4CHCN}},$$

(XXI)

$R^1 = NO_2$-2; R^2 = Ph, C_6H_4Me-4.

$$4\text{-}R^1C_6H_4CHO + TMSCN + NH_3 \xrightarrow[MeOH]{} \underset{\displaystyle NH_2}{\underset{|}{4\text{-}R^1C_6H_4CHCN}},$$

R^1 = CN, $\underset{\displaystyle O}{\underset{\|}{COMe}}$.

(XXII)

$$\underset{\displaystyle OH}{\underset{|}{R^1R^2CFCHCN}} \xrightarrow{H_2NR^3} \underset{\displaystyle HNR^3}{\underset{|}{R^1R^2CFCHCN}},$$

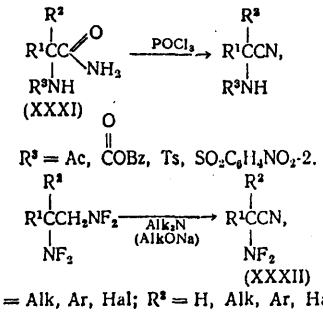
(XXIII)

R^1 = Alk[1], R^2 = Alk[2], $R^1 + R^2 = (CH_2)_n$, $n = 4.5$.

$$\underset{\displaystyle OH}{\underset{|}{R^1C_6H_4CHCN}} + \underset{\displaystyle O}{\underset{\|}{HNCR^3}}\overset{\displaystyle R^2}{\overset{|}{}} \rightarrow \underset{\displaystyle R^2NCR^3}{\underset{\|}{\underset{|}{R^1C_6H_4CHCN}}},$$

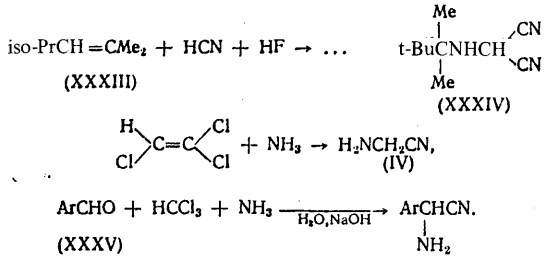
$\quad\quad\quad

formally the reverse of reduction of α-aminonitriles forms the basis for obtaining *N*,*N*-difluoro-α-aminonitriles (XXXII).[130]



The simultaneous introduction of amino and cyano groups is achieved when the olefin (XXXIII) is reacted with hydrocyanic and hydrofluoric acids. 2-*N*-Alkylaminomalononitrile (XXXIV) has been identified among the products of this reaction.[131] Treatment of 1,2,2-trichloroethylene with ammonia at high pressure is the most effective method for synthesising aminoacetonitrile.[132,133]

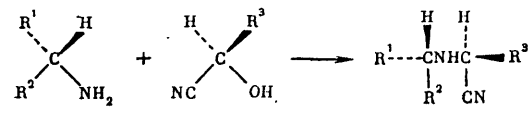
The synthesis of primary α-aminonitriles from aromatic aldehydes (XXXV), chloroform, ammonia, and water in the presence of alkali at a raised temperature and pressure[134] should be noted in particular. A study of the mechanism of this reaction could show whether its resemblance to the Strecker reaction is purely superficial. The scope for applying this method,[134] however, is limited to aldehydes (XXXV) that are readily soluble in chloroform.



III. Stereochemistry

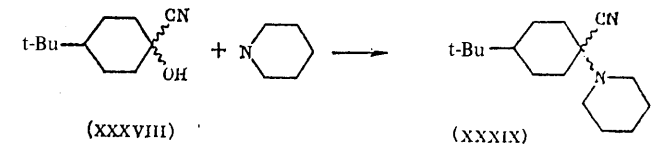
α-Aminonitriles are widely used for the synthesis of α-amino acids, whose biological activity depends fundamentally on their configuration.[1] Therefore, a considerable amount of attention has been given by synthetic chemists to stereoselective methods for obtaining α-aminonitriles.

It was possible to obtain optically active products from the Tiemann reaction by introducing just one optically pure reagent into it. Thus, for example, the reaction of optically active cyanohydrins with ammonia or amines occurs with a considerable degree of inversion of the chiral centre.[86] From a racemic mixture of cyanohydrins (XXXVII), the (*R*)-form predominantly reacts with (*S*)-amines (XXXVI).[96] When the latter reaction was carried out according to the Strecker method this also gave an optically active product, which had an optical purity that differed slightly from that achieved in the first method (36–51% and 44–48% respectively).[96]



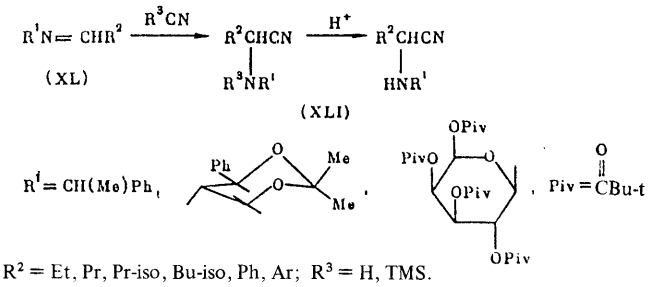
R^1 = Me, COOH; R^2 = Ph; $C_{10}H_7$; R^3 = Me, Et, Pr-iso, CH_2Pr-iso.

Under quasi-kinetic conditions, piperidine mainly attacks axially the conformer of 4-t-butylcyclohexanone cyanohydrin (XXXVIII) with an equatorial configuration of the cyano group.[67] In the presence of water the kinetically controlled α-aminonitrile (XXXIX) rapidly epimerises.



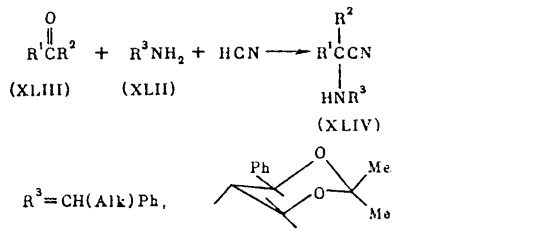
The correspondence between the thermodynamic properties of the racemisation of optically active secondary α-aminonitriles and those for their decomposition to Schiff bases and hydrocyanic acid indicates that there is a common mechanism for these two processes.[135]

The addition of HCN and TMSCN to the C=N bond of Schiff bases (XL) also takes place stereoselectively; the optical purity of α-aminonitriles (XLI) is improved when a bulky R^1 substituent is introduced into compounds (XL) and when the addition of TMSCN is carried out in the presence of Lewis acids.[4,20,61,97,98,136–139]



R^2 = Et, Pr, Pr-iso, Bu-iso, Ph, Ar; R^3 = H, TMS.

An asymmetric Strecker synthesis has also been used widely to obtain optically active α-amino acids.[20,61,96,136–140] The amino components used in it are amines that are readily separated into enantiomers and containing those substituents which are readily eliminated from the required α-amino acids. Among such substituents are *N*-phenylalkyl, removed by hydrogenation of palladium, and *N*-(2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl), which is eliminated on oxidation. The presence of the latter substituent in amine (XLII) gives better results.[20,61,136–140] Thus, the (*S*)-(−)-α-amino acid is obtained from amine (XLII) with a (4*S*,5*S*)-(+)-configuration, while the (*R*)-(+)-α-amino acid is obtained from the (4*R*,5*R*)-(−)-amine. It should be noted that only ketones (XLIII) (R^1 and $R^2 \neq$ H) are suitable for conducting the asymmetric synthesis; otherwise asymmetric transformation of the chiral centre formed in α-aminonitriles (XLIV) will occur during the reaction.[136]

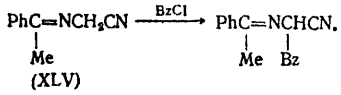


In contrast to the Tiemann reaction, dehydration of α-amino-amides occurs with retention of configuration.[128]

In the remaining cases a racemic mixture of enantiomeric α-aminonitriles is formed. In order to resolve this, either fractional crystallisation[135] or salt formation with optically pure organic acids such as tartaric acid[57,141-143] and its derivatives[143] and brucine[89] are used. In one study[141] it was possible to obtain pure isomers only when this reaction was carried out in the presence of ketones.

IV. Chemical properties

α-Aminonitriles can contain a different number of reaction centres. Thus, for example, *C*-benzylation of compound (XLV) occurs on its methylene group.[144]



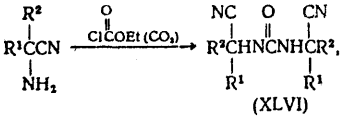
C-Alkylation,[145] *C*-bromination,[146] and intramolecular interaction between the cyano and methylene groups[147] have also been reported. Ammonia[148] and hydrazine[149] replace the ethoxyl group in ethyl 2-amino-2-cyanoacetate.

However, the overwhelming majority of reactions of α-aminonitriles involve their amino and cyano groups. In making a convenient presentation of the material, these two classes of reactions are described in the respective sections. The syntheses that involve both amino and cyano groups also shed light on the reactivity of these functional groups in α-aminonitriles. Moreover, intermediates have been isolated in some of them. However, in view of the importance of α-aminonitriles for heterocyclic chemistry, reactions of the latter type have been grouped in a separate section of this review.

1. Reactions of the amino group

The amino group in α-aminonitriles is quite basic and therefore readily undergoes characteristic reactions. Primary and secondary α-aminonitriles undergo *N*-acylation,[26,58,77,84,90,120,123,124,135,142,150-155] which is a reason for their use in peptide synthesis.[156,157] Removal of the protecting group causes certain difficulties since the cyano group in α-aminonitriles is sensitive to both acids and bases. In this respect it is convenient to use a 2-nitrophenylsulphenyl protecting group, which is readily removed on treatment with hydrochloric acid.[128]

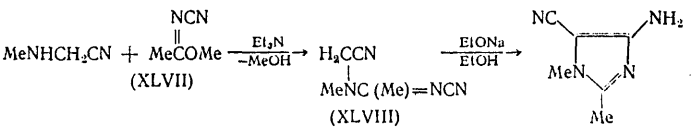
When primary α-aminonitriles are treated with half the quantity of ethyl chloroformate or an equimolar quantity of carbon dioxide[12,159] it is possible to obtain symmetrical ureas (XLVI).



(XLVI)

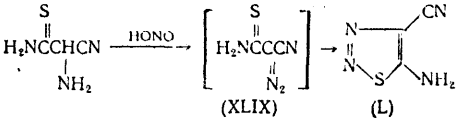
$R^1 = H$, Me; $R^2 = H$, Me, Et.

The synthesis of asymmetric ureas and thioureas starting from α-aminonitriles can be achieved with the use of isocyanates[160] and isothiocyanates[149,161] respectively. The reaction of primary α-aminonitriles with aldehydes[70,73,162] and ketones[163-165] gives azomethines. When primary α-aminonitriles were treated with ortho esters and imidates under mild conditions, the corresponding *N*-substituted imidates were obtained.[166-172] On the other hand, the base-catalysed addition of *N*-cyanoimidate (XLVII) to *N*-methylaminoacetonitrile results in elimination of the methoxyl group and formation of amidine (XLVIII), which cyclises under these conditions without participation of the cyano group from the initial α-aminonitrile.[173]



(XLVII) (XLVIII)

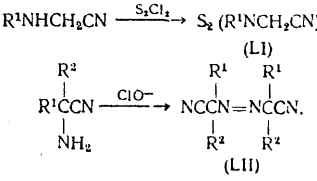
N-Alkylation of primary and secondary α-aminonitriles was carried out using derivatives of acrylic acid;[174-176] tertiary α-aminonitriles were quaternised with alkyl halides in propanol and acetone.[177] 9-Chloroacridine derivatives arylate the amino group of primary α-aminonitriles.[178,179] Diazotisation of primary α-aminonitriles gives 2-diazonitriles;[117,150,180-183] the diazothioamide (XLIX) generated in this way cyclises to 5-amino-1,2,3-thiadiazole (L) during the reaction.[184,185]



(XLIX) (L)

Primary α-aminonitriles undergo an azo–amino interaction with diazonium salts to form triazenes, which then cyclise to heterocycles containing three nitrogen atoms.[186,187]

N-Chlorination of primary and secondary α-aminonitriles is carried out with chlorine[188] and isopropyloxonium chloride.[189] Replacement of the hydrogen atoms of the amino group in α-aminonitriles by a cyano group is carried out using cyanogen chloride.[190] The reaction of secondary α-aminonitriles with 98% nitric acid results in the formation of *N*-nitro derivatives.[191] The synthesis of diaminodisulphides (LI) from secondary α-aminonitriles and sulphur monochloride has been reported in a patent.[192] Oxidation of primary α-aminonitriles with alkali metal hypochlorites in an organic solvent gives azobisnitriles (LII).[193]



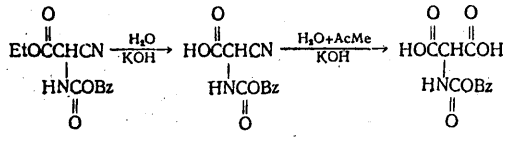
(LI)

(LII)

2. Reactions of the cyano group

Historically the first and most important use of α-aminonitriles has been their hydrolysis to the corresponding α-amino acids,[1] which are widely used in organic synthesis, medicine, agriculture, and other areas of the economy. The hydrolysis is carried out in aqueous and water–ethanol solutions[99] of mineral acids (hydrogen halide[50,51,71,80,86,88,96-99,141] or sulphuric acids[71] and also bases.[10,47,71,72,133,142,194-199] In one patent[200] the hydration of α-aminonitriles on polymer-bonded *N*-acyl-4-piperidones is reported.

When there are other groups that are susceptible to hydrolysis in the α-aminonitrile molecule, the reaction can be caried out selectively by choosing a suitable solvent.[201]

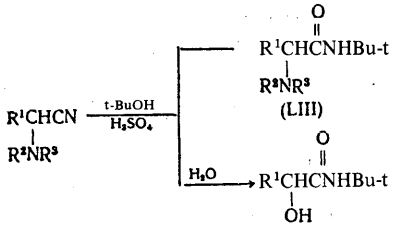


The reaction of α-aminonitriles with water is catalysed by compounds and alloys of zinc, cadmium, and boron,[64,87] and also by iron(III) chloride.[90]

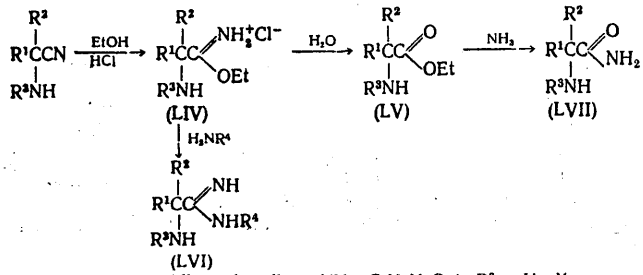
When suitable conditions (concentrated sulphuric acid at room temperature[202] or aqueous alkali in the presence of ketones[197,203]) are chosen, it is possible to discontinue the hydrolysis of α-aminonitriles at the stage when α-aminoamides are formed. On the other hand, dilution of the sulphuric acid and raising the reaction temperature[202] or increasing the time of contact with alkali[197] results in the conversion of aminoamides to amino acids.

The directed synthesis of α-aminoamides is carried out by treating α-aminonitriles with aqueous hydrogen peroxide.[204] It is possible to hydrate selectively one cyano group in polycyanomethylamines using this method.[204]

N-t-Butyl α-aminoamides (LIII) were obtained by the Ritter reaction, which was complicated in a number of cases by hydrolysis of the tertiary amino group.[205]

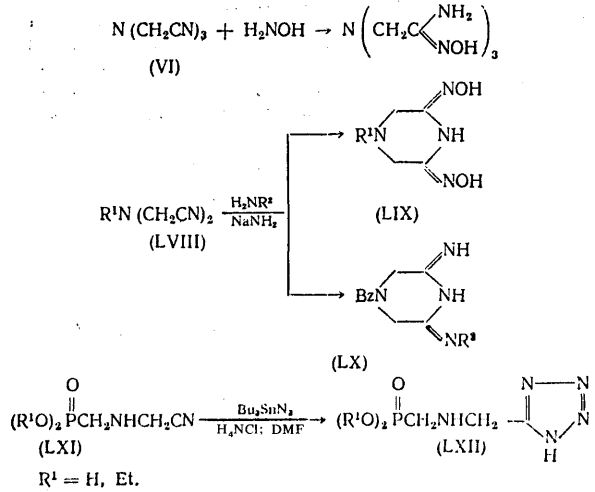


The reaction of α-aminonitriles with alcohols in the presence of hydrogen halides under anhydrous conditions gives the corresponding imidates (LIV),[86,206,207] which can then be converted to esters (LV) [128] or amidines (LVI).[206] In aqueous ethanol in the presence of hydrogen chloride the initially formed imidates (LIV) are spontaneously hydrolysed to esters (LV),[27] which can be converted to the corresponding amides (LVII).[207]



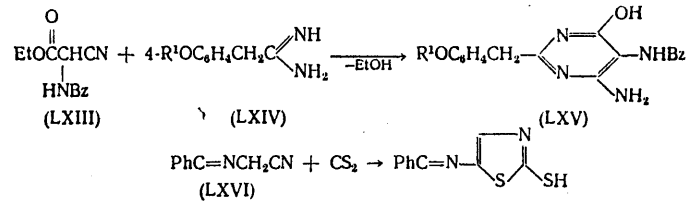
R^1 = H, Alk, Alk-cyclo, alkenyl,Ph, C_6H_4MeO-4; R^2 = H, Me; R^3 = H, Me, Ph, Ar, C(O)C_5H_{11}; R^4 = H, Bz.

Nitrilotriacetonitrile (VI) can add on 3 moles of hydroxylamine directly.[208] In the presence of sodamide, dicyanomethylamines (LVIII) add on primary amines to give 2,5-diiminopiperazines (LIX) and (LX).[208] The α-aminonitriles (LXI) add on azide ions to give tetrazoles (LXII).[209]

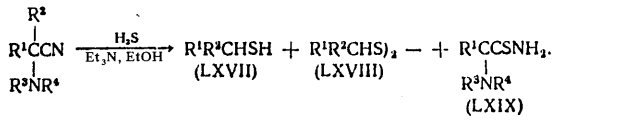


R^1 = H, Et.

The *N*-benzyl protecting group excludes the amino group of compound (LXIII) from the reaction with amidines (LXIV), which results in the formation of pyrimidines (LXV).[210] In a similar manner carbon disulphide does not affect the benzylidenamino group in the aminoacetonitrile derivative (LXVI).[164]

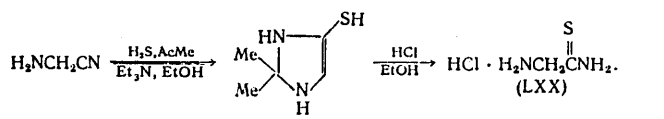


In the examples given α-aminonitriles undergo reactions that are typical for nitriles in general.[211,212] On the other hand, addition of carbon disulphide to α-aminonitriles usually gives a mixture of thiols (LXVII), disulphides (LXVIII), and α-aminothioamides (LXIX).[26,56,120] In this case the latter component is only stabilised when R^1 = H; R^2, R^3, R^4 = Ph, H, iso-Pr; $C_6H_3(MeO)_2$-3, 4, H, Me; $C_6H_3(MeO)_2$-3, 4, Me, Me; Ph, Me, Me; $C_6H_3(MeO)_2$-3, 4, H, Ph; Ph, H, H; t-Bu(O)C, R^3 + R^4 = Phth



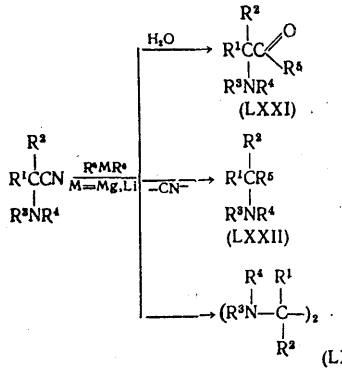
The reaction of α-aminonitriles with hydrogen sulphide followed by oxidation of the initially formed thiols so that disulphides (LXVIII) can be obtained deliberately is reported in a patent.[213]

The synthesis of 2-aminothioacetamide hydrochloride (LXX) was successfully carried out in two stages.[214]



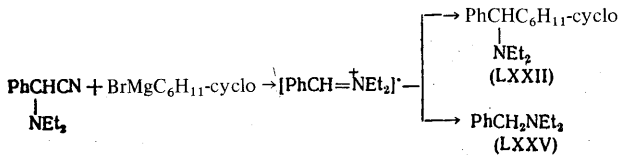
The reactions of α-aminonitriles with organometallic compounds also occur in a unique manner. Thus, for example, in the reaction of α-aminonitriles with Grignard reagents and lithium alkyls, products

with a "normal" structure—α-aminoketones (LXXI)—have been detected.[77,215] However, a more typical course for the reaction of α-aminonitriles with organometallic compounds is replacement of the cyano group by the radical R^5, resulting in the formation of amines (LXXII).[77,216,217] In two studies[218,219] the formation of diamines (LXXIII) has been recorded in the reaction between α-aminonitriles and Grignard reagents.



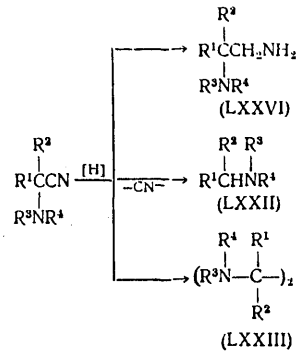
The general mechanisms of the reaction between α-aminonitriles and organometallic compounds has been discussed in a review.[220] They are determined by the nature of the α-aminonitriles themselves and the reagents. Thus, for example, it was observed that an increase in the degree of substitution of α-aminonitriles and the size of the substituents R^3 and R^4 leads to a change in the ratio of aminoketones (LXXI) to amines (LXXII) in favour of the former;[219] the sole products of the reaction between *N*-acetyl-α-aminonitriles and Grignard reagents and alkyllithium are compounds (LXXI).[77] Derivatives of aminoacetonitrile that are not substituted on the carbon atom react with alkylmagnesium halides to give mainly substitution products (LXXII).[77] In general, replacement of the Grignard reagent by alkyllithium [77] and dialkylmagnesium[215] assists in the formation of products (LXXI) derived from addition on the cyano group.

In one study[218] using a deuterium label it was possible to determine the mechanism of the reaction of α-aminonitriles (LXXIV) with cyclohexylmagnesium bromide, which gave a compound of the type (LXXII) and a reduction product (LXXV)



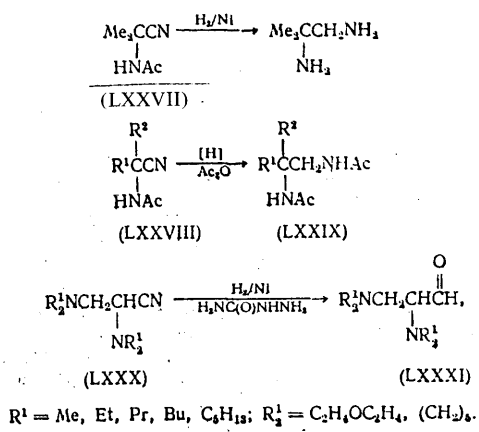
The other group of reactions of the cyano group that is closely related to that just considered is made up by the reactions of α-aminonitriles with reducing agents. Thus, for example, when α-aminonitriles are reduced with sodium in a water–ether emulsion[221,222] and boiling toluene,[223] with hydrogen on Raney nickel, platinum, and palladium,[224] and also with lithium aluminium hydride,[225] the same by-products (LXXII) and (LXXIII) are formed as in the reaction with organometallic compounds. In general, these reducing agents can in principle be regarded as a special case of "organometallic" compounds in which hydrogen or aluminium plays the role of the metal and H· represents the "organic" radical.

At the same time there have been reports about the reduction of α-aminonitriles with hydrogen on Raney nickel,[58,224] platinum, and palladium,[224] lithium aluminium hydride,[70,142] and also diborane and diisopropylbutylaluminium [70] giving exclusively "normal" products—ethylenediamines (LXXVI). As hydrogen is evolved it reduces α-aminonitriles to compounds of the type (LXXVI) only when R^1 and R^2 = Ar.[221] Otherwise the formation of products (LXXII) from the reductive elimination of the cyano group (LXXII) [221–223] and their dimers (LXXIII) occurs. Hydrogenation of α-aminonitriles on Raney nickel, platinum, and palladium [224] also generally gives a mixture of compounds such as (LXXVI) and (LXXIII). When the reaction is carried out in an alcoholic solution of ammonia, the formation of dimers of the type (LXXIII) is inhibited.[226] When treated with sodium borohydride [227,228] and hydrogen on palladium oxide in 0.5 *N* hydrochloric acid,[54] α-aminonitriles are selectively converted to products of the type (LXXII) derived from the reductive elimination of the cyano group.



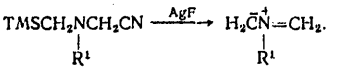
In the reaction of α-aminonitriles with lithium aluminium hydride, an excess of reducing agent[218] assists the formation of diamines of the type (LXXVI), the presence of aluminium chloride [229] favours the formation of amines (LXXII), and the formation of dimers such as (LXXIII) is assisted by an excess of initial α-aminonitrile [225] and a high reaction temperature.[230] The course of the reaction is also related to steric factors.[231]

Reduction of the cyano group in α-aminonitriles may be accompanied by side reactions. Thus, for example, the hydrogenation of *N*-acetyl-α-aminonitriles (LXXVII) on Raney nickel takes place concurrently with removal of the protecting group.[232] Reduction of the acetyl derivative (LXXVIII) in acetic anhydride, on the other hand, gives the diacylated product (LXXIX).[233] An exception to the general pattern of reactions of α-aminonitriles with reducing agents is the hydrogenation of compounds (LXXX) on Raney nickel in the presence of semicarbazide to give α-aminoaldehydes (LXXXI).[234]



R^1 = Me, Et, Pr, Bu, C_6H_{13}; R^1_2 = $C_2H_4OC_2H_4$, $(CH_2)_5$.

Treatment of *N*-trimethylsilyl-α-aminonitriles with silver fluoride results in elimination of the trimethylsilyl and cyano groups with formation of azomethine ylides (LXXXIII).[235,236]



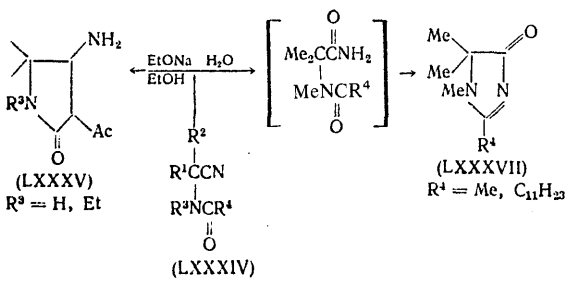
(LXXXII) (LXXXIII)

3. Reactions of the amino and cyano groups

(a) α-Aminonitriles in the synthesis of heterocycles

Usually both nitrogen atoms of the initial molecule are retained when α-aminonitriles undergo heterocyclisation, while one of them can be converted to an exocyclic amino functional group. This nitrogen atom always originates from the cyano group in α-aminonitriles.

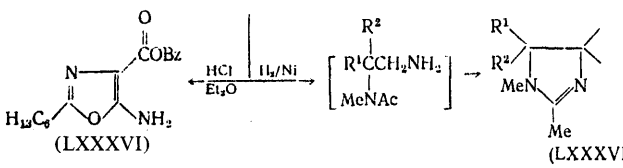
α-Aminonitriles that contain not less than one double bond in the amino functional group will undergo heterocyclisation. Thus, for example, *N*-acylated α-aminonitriles (LXXXIV) can, depending on the conditions, cyclise to pyrrolidones (LXXXV),[237] the oxazole (LXXXVI),[238] imidazolinones (LXXXVII),[38,238] or imidazolines (LXXXVIII).[58]



(LXXXV) R^3 = H, Et

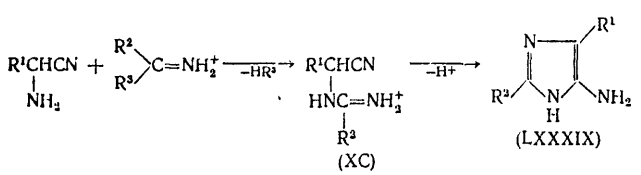
(LXXXIV)

(LXXXVII) R^4 = Me, $C_{11}H_{23}$



(LXXXVI) (LXXXVIII)

The reactions of primary α-aminonitriles with immonium salts are widely used for the synthesis of 5(4)-aminoimidazoles (LXXXIX). The reaction of α-aminonitriles with amidines,[90,149,239] imidates,[240–244] and thioimidates [242,245,246] is accompanied by elimination of ammonia, alcohols, and mercaptans respectively. In one study[242] an intermediate of the type (XC) was isolated in a pure state

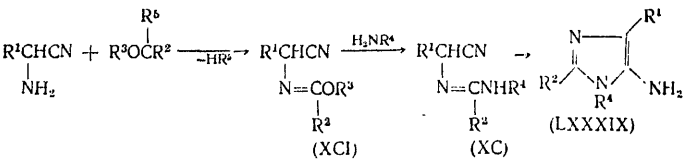


(XC) (LXXXIX)

R^1 = H, Ph, C_6H_3OMe-4, COEt, COPr-iso, COBz, COPh, COC_6H_4Cl-4, CNH_2, CONHMe, CNHEt, CNHPh, CN; R^2 = H, Alk, C_6H_{11}-cyclo, Bz, glycosyl, CH_2OPh, C_2H_4Ph, COEt, Ar, Het, OMe, SH, SMe, SBz, SPh; R^3 = NH_2, OAlk, SMe, SBz.

However, it should be noted that only condensation of α-aminonitriles with thioimidates achieved a satisfactory yield of imidazoles (LXXXIX).

"Linear imidates" (XCI), obtained from primary α-aminonitriles and imidates under mild conditions or from α-aminonitriles and ortho esters, when treated with primary amines are also converted to amidines of the type (XC) and then cyclise to aminoimidazoles such as (LXXXIX).[93,168,169,247,248]



(XCI) (XC) (LXXXIX)

C O O O NH

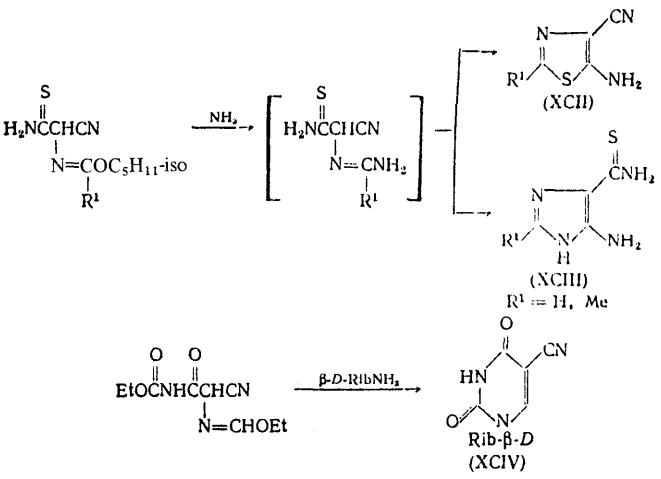
R^1=CPh, COEt, CNH_2, CNHMe, $C(=NH)NH_2$, CN; R^2=H, Me, $CH_2CH(OH)CH_2OH$, Bz; R^3=Me, Et, Bu-iso C_5H_{11}; R^4 = H, Alk, C_6H_{11}-cyclo, CHCOEt, *D*-ribofuranosyl, galactosyl, xylopyranosyl, phosphoribosyl



NH_2, NHMe, NMe_2;

R^5 = NH_2; OR^3.

When there are other reactive groups in addition to the cyano group in the "linear imidate" molecule, alternative pathways of cyclisation are possible, leading, for example, to thiazoles (XCII) or imidazoles (XCIII) [249] and pyrimidinediones (XCIV).[250]



(XCII)

(XCIII)

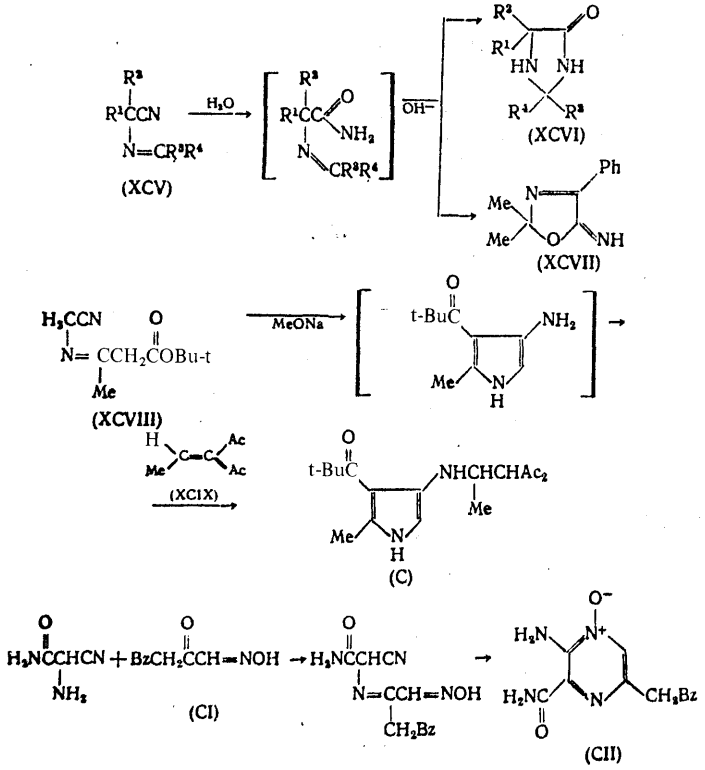
R^1 = H, Me

Rib-β-*D*

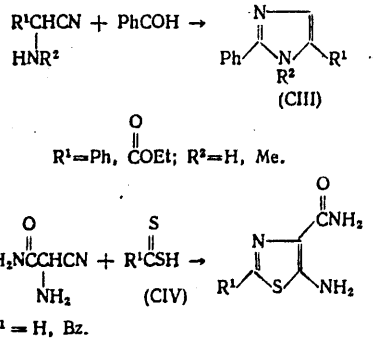
(XCIV)

In aqueous alkali solutions azomethines (XCV) are cyclised either to imidazolones (XCVI) or to oxazolimine (XCVII).[164] The first stage in the reaction of azomethine (XCVIII) with the olefin (XCIX) in the presence of sodium methoxide, which gives pyrrole (C) in the end, is apparently intramolecular attack by the methylene group on to the carbon atom of the cyano group in compound (XCVIII).[163] The α-hydroxyiminoketone (CI) can undergo cyclisation with a primary α-aminonitrile in the absence of water to give the

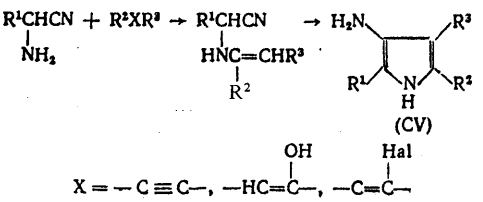
2-aminopyrazine-1-oxide (CII).[251]



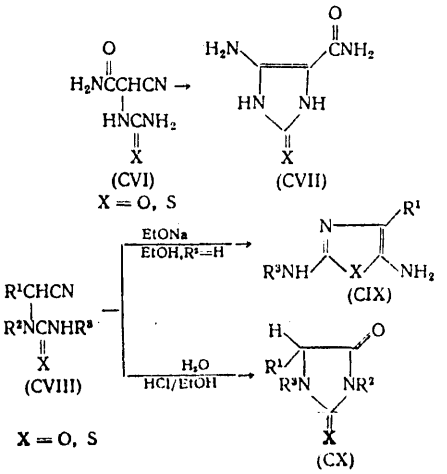
The synthesis of imidazoles (CIII) from secondary α-aminonitriles and benzaldehyde occurs in a different manner.[164] Dithiocarboxylic acids (CIV) constitute another group of condensation agents for α-aminonitriles.[149]



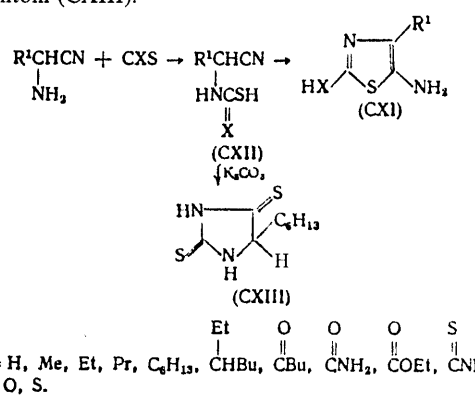
When α-aminonitriles are reacted with acetylenes or olefins that can undergo *cis*-elimination of water or hydrogen halides, 3-aminopyrroles (CV) are formed as final products.[252]



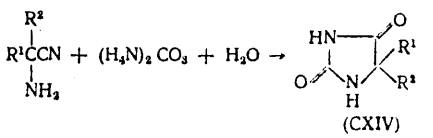
Heterocumulenes constitute a large group of reagents that react with both the amino group and cyano group of α-aminonitriles. A feature of these reagents is that they convert α-aminonitriles directly to aromatic five-membered heterocycles. Thus, for example, the monosubstituted urea and thiourea (CVI), which are obtained from 2-amino-2-cyanoacetamide and potassium cyanate and thiocyanate respectively, are cyclised to 2-oxo- [253] and 2-thio-5-aminoimidazole-4-carboxamides [254] (CVII) respectively. In turn, *N*,*N*-disubstituted ureas and thioureas (CVIII) in an ethanol solution of sodium ethoxide are cyclised to 5-aminooxazoles [160] and 5-aminothiazoles [148] (CIX). On the other hand, in the presence of hydrogen chloride compounds (CVIII) are converted to the hydantoin[160] and thiohydantoin [161] (CX).



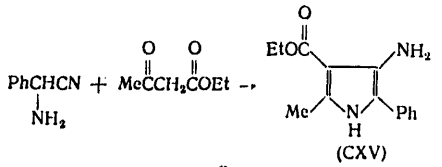
When treated with carbon disulphide[149,159,197,242] and carbon oxysulphide,[255] primary α-aminonitriles are converted to 2-mercapto- and 2-hydroxy-5-aminothiazoles (CXI). In the presence of potassium carbonate a dithiocarbamate of the type (CXII) is cyclised to the dithiohydantoin (CXIII).[256]



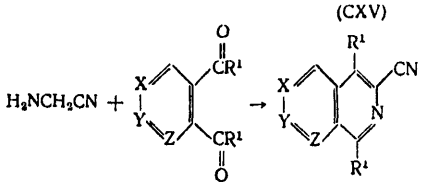
Hydantoins (CXIV) are the final products in the Bucherer–Bergs reaction.[103,157]



Condensation of 2-phenyl-2-aminoacetonitrile with ethyl acetoacetate gives the aminopyrrole (CXV).[257] The reaction of aminoacetonitrile with *o*-dicarbonyl compounds (CXVI), giving condensed pyridines (CXVII), occurs in a different manner.[258–261]



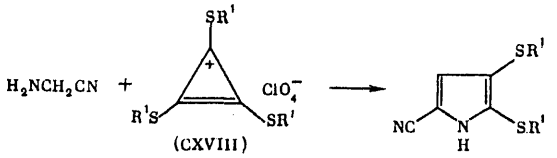
(CXV)



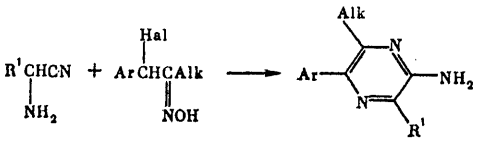
(CXVI) (CXVII)

X, Y, Z = CH, N.

Other bifunctional reagents such as cyclopropenyl cations (CXVIII) [262] and oximes (CXIX) [263] have also been used for the heterocyclisation of α-aminonitriles.



(CXVIII)



(CXIX)

V. Physicochemical properties of α-aminonitriles

Stretching vibrations from the cyano group of α-aminonitriles appear in the region 2210–2250 cm^{-1} in their IR spectra.[98,101,117,128,150,153] When hydroxyl or acetyl groups are present in the α-aminonitrile molecule, the intensity of this band is considerably reduced.[211] Thus, IR spectroscopy is not always a reliable method for confirming the structure of α-aminonitriles; in this respect a more promising method could be mass spectroscopy.[111]

The ^1H and ^{13}C NMR spectra,[20,136,138,140] microwave[3] and EPR [264] spectra of α-aminonitriles have been reported. In one study[265] information about the acid-base properties of aminoacetonitrile is given. It was shown that the experimental pK_a value (5.17) was in good agreement with the results of quantum-chemical calculations of the atomic charges.

VI. Biological activity of α-aminonitriles

At the present time the biological and biochemical properties of α-aminonitriles have been studied quite widely. It has been found, for example, that aminoacetonitrile inhibits different enzymes, including monoamino oxidase,[266–268] dimethylase,[269–271] glycine decarboxylase[272,273] and nitrilase.[258,274] Aminoacetonitrile also has an effect on the contraction of muscles[275–277] and the mechanical properties of bones[278–280] and it inhibits the introduction of gallium into tissues.[281]

In 1983 the first report was published on the antitumour activity of 2-amino-2-phenylacetonitrile derivatives.[66] Three compounds of this series proved to be highly effective towards carcinoma and seminoma in a clinical experiment.

A number of α-aminonitriles exhibit fungicidal[282] and herbicidal[144,154,283] activity.

References

1. D Jones *General Organic Chemistry* (Translated into Russian), Izd. Khimiya, Moscow, 1983, p. 233
2. V I Ivanskii *Khimiya Geterotsiklicheskikh Soedinenii* (The Chemistry of Heterocyclic Compounds), Izd. Vys. Shkola, Moscow, 1978, p. 147
3. J C Guillemin, J M Denis, M Bogey, J L Destombes *Tetrahedron Lett.*, 1986, **27**(10) 1147
4. S L Miller, G Schlesinger *Adv. Space Res.*, 1983, **3**(9) 47
5. C A Buehler, D E Pearson *Organic Syntheses* (Translated into Russian), Part 2, Izd. Mir, Moscow, 1973
6. P J Irurre, E R Herbera, B F Sanchez, et al. *Afinidad*, 1985, **42**(397) 270
7. P Van Deale *Meded. Vlaam. Chem. Ver.*, 1961, **23** 163; *Chem. Abs.*, 1962, **57** 16365
8. J-P Fleury, A Baysang, D Clerin *Bull. Soc. Chim. Fr.*, 1969, (11) 4108
9. K Takahashi *Senryo to Yakugin*, 1985, **30**(5) 128; *Chem. Abs.*, 1985, **100** 87191
10. A Strecker *Ann. Chem. Pharm.*, 1850, **75** 27
11. K V Vapiro, G L Mishchenko *Imennye Reaktsii v Organicheskoi Khimii* (Name Reactions in Organic Chemistry), Izd. Khimiya, Moscow, 1976, p. 495
12. H T Bucherer, W Steiner *J. Prakt. Chem.*, 1934, **140** 291
13. K Takahashi, H Saitoh, K Ogura, H Iida *Heterocycles*, 1986, **24**(10) 2905
14. H Distler, H Schlecht, BRD P. 2625935; *Chem. Abs.*, 1978, **88** 105785
15. M P Dave, J Patel, N A Laugalia, K A Thaker *J. Inst. Chem. (India)*, 1985, **57**(3) 113
16. F Seel, A Dessauer, G Simon, U Z Eder *Z. Naturforsch.*, 1982, **37B**(12) 1540
17. R Walther, R Hübner *J. Prakt. Chem.*, 1916, **93** 119
18. R P Iyer, R K Ratham, S P Kulkarni, M S Sonaselth *J. Heterocycl. Chem.*, 1986, **24**(4) 991
19. T E Koballa, E E Schmitz *Res. Discl.*, 1985, **253** 265; *Chem. Abs.*, 1985, **103** 37084
20. K Weinges, K P Klotz, H Droste *Chem. Ber.*, 1980, **113**(2) 710
21. M Mussim, I Beker, M Ungar, Israel P. 59048; *Chem. Abs.*, 1985, **102** 149784
22. W J Stepek, M M Nigro, S. African ZA P. 8402266; *Chem. Abs.*, 1986, **105** 148198
23. S Chuberek, French P. 1521741; *Chem. Abs.*, 1969, **71** 12611
24. J C Menendez, G G Trigo, M M Sollhuber *Tetrahedron Lett.*, 1986, **27**(28) 3285
25. K W Saunders, W H Montgomery, J C French, US P. 3167580; *Chem. Abs.*, 1965, **62** 13052
26. A Spaltenstein, T P Holler, P B Hopkins *J. Org. Chem.*, 1987, **52** 2977
27. T A Baer US P. 4517130; *Chem. Abs.*, 1985, **103** 104732
28. J L Boucher, L Stella *Tetrahedron*, 1985, **41**(5) 875
29. U H Pandya, R R Astik, K A Thaker *J. Inst. Chem. (India)*, 1979, **51** 127
30. A Commeyras, J Taillades, L Mion, et al., French P. 2405924; *Chem. Abs.*, 1979, **91** 140371

31. D M Stout, L A Black, W L Matier *J. Org. Chem.*, 1983, **48**(26) 5369
32. *3rd Symposium on the Syntheses of Organic Compounds* (Translated into Russian), Izd. Inostr. Lit., Moscow, 1952
33. T Honda, T Dosono, H Ohashi, K Aoki, Japanese P. Appl. 7 203 606; *Chem. Abs.*, 1972, **76** 176 426
34. F Becke, J Gnad, J Jung, BRD P. 2 044 642; *Chem. Abs.*, 1972, **76** 152 634
35. K Wakabayashi, M Itoh, Y Imai, J Oya, Japanese P. Appl. 7 106 615; *Chem. Abs.*, 1971, **75** 48 474
36. R A Firestone, D F Reinhold, M Sletziger, J M Chermerda, BRD P. 1 493 965; *Chem. Abs.*, 1971, **74** 141 326
37. A N Ghandhi, French P. 1 575 104; *Chem. Abs.*, 1970, **73** 14 241
38. V Machacek, G Svobodova, V Sterba *Coll. Czech. Chem. Commun.*, 1987, **52**(1) 140
39. S Chabereck, BRD P. 1 902 934; *Chem. Abs.*, 1970, **72**, 121 160
40. Y Senda, N Kajitani, Japanese P. Appl. 7 205 242; *Chem. Abs.*, 1972, **76** 112 746
41. W R Grace, B. P. 1 163 684; *Chem. Abs.*, 1970, **72**, 21 354
42. C P Morgan, J J Gadfrey, French P. 1 561 020; *Chem. Abs.*, 1970, **72** 54 811
43. K E Davis, K S Shim, BRD P. 1 805 404; *Chem. Abs.*, 1969, **71** 170 146
44. C E Greco, W Stamm, BRD P. 1 815 110; *Chem. Abs.*, 1969, **71** 101 351
45. R N Mesiah, French P. 1 532 168; *Chem. Abs.*, 1969, **71** 49 340
46. J Z Harper, D A Daniels, French P. 1 513 031; *Chem. Abs.*, 1969, **70** 87 078
47. J J Singer, M Weisberg, US P. 3 061 628; *Chem. Abs.*, 1963, **58** 7836
48. R W Foreman, G K Meloy, French P. 1 501 552; *Chem. Abs.*, 1969, **70** 3322
49. D A Daniels, J L Harper, T R Steadman, US P. 347 387; *Chem. Abs.*, 1970, **72** 21 348
50. A B Silaev, V M Svetlaeva, A P Teren'tev *Vestnik MGU Ser. Fiz-Mat i Estest. Nauk*, 1955, **10**(10) 115
51. A B Silaev, V M Svetlaeva, A P Terent'ev *Vestnik MGU Ser. Fiz-Mat i Estest. Nauk*, 1955, **10**(12) 109
52. W Glund, W Klempt, F Brodkorb, German P. 656 349; *Chem. Abs.*, 1938, **32** 3423
53. F Osama, K Wada, W Mihara, Japanese P. Appl. 7 414 423; *Chem. Abs.*, 1974, **80** 145 485
54. R Kuhn, W Kirschenlohr *Angew. Chem.*, 1955, **67** 786
55. K Takahashi, K Suenobu, K Ogura, H Iida *Chem. Lett.*, 1985, 1487
56. K Takahashi, A Tachiki, K Ogura, H Iida *Heterocycles*, 1986, **24**(10) 2835
57. R Iwata, T Ido, T Takahashi, et al *Appl. Radiat. Isol.*, 1987, **38**(2) 97 102
58. A Kozakowska, W Kula, T Tkaczynsky *Acta Pol. Pharm.*, 1974, **31**(5) 595; *Chem. Abs.*, 1975, **83** 28 153
59. K Mai, G Patil *Tetrahedron Lett.*, 1984, **25**(41) 4583
60. K Mai, G Patil *Org. Prep. Proced. Int.*, 1985, **17**(3) 183
61. K Weinges, H Blackholm *Chem. Ber.*, 1980, **113**(9) 3098
62. A Gvozhakova, J Schnittova *Acta Fac. Rerum Natur. Univ. Comenianae Chim.*, 1966, **11** 59
63. J S Sandhu, P S Sethi, M J Suresh *Ind. Chem. Soc.*, 1971, **48**(1) 91
64. Y Murao, T Ochiai, T Nakanome, Japanese P. Appl. 7 946 717; *Chem. Abs.*, **1979, 91** 57 536
65. S Harusawa, Y Hamada, T Shioiri *Tetrahedron Lett.*, 1979, 4663 H A Niepper, F Köhler, Swiss P. 637 828; *Chem. Abs.*, 1983,
66. **100**, 96 704
67. P Geneste, J-M Kamenka, P Dessapt *Bull. Soc. Chim. Fr.*, 1980, (3–4), Pt. 2 187
68. K Mai, G Patil *Synth. Commun.*, 1985, **15**(2) 157
69. S Waki, S Nakata, H Dandan, Japanese P. Appl. 7 988 220; *Chem. Abs.*, 1979, **91** 210 929
70. W L Matier, D A Owens, W T Cromer *J. Med. Chem.*, 1973, **16**(8) 901
71. B. P. 482 352; *Chem. Abs.*, 1938, **32** 6668
72. F Reinhold, U Heinrich, German P. 673 590; *Chem. Abs.*, 1939, **33** 6347
73. A Kotelko, B Zajczkowska *Acta Pol. Pharm.*, 1962, **19** 223; *Chem. Abs.*, 1963, **59** 7370
74. H Distler, K L Hock, Europ. P. Appl. 45 496; *Chem. Abs.*, 1982, 97 38 510
75. German P. 669 808; *Chem. Abs.*, 1939, **33** 5415
76. L A Yanovskaya, B I Kozyrkin, V F Kucherov, USSR P. 191 526; *Byul. Izobret.*, 1967, (4) 28
77. J Yoshimura, Y Ogo, T Sato *Bull. Chem. Soc. Jpn.*, 1965, **38**(11) 1809
78. E E Vittal, A S Gibin, A V Dombrovskii *Zhur. Obshch. Khim.*, 1975, **45**(8) 1872
79. J Gardent *C. R. Seances Acad. Sci.*, 1963, **256** 3140
80. D H R Barton, A Billion, J Boivin *Tetrahedron Lett.*, 1985, **26**(9) 1229
81. E C Evers, W O Freitag, J N Keith, et al. *J. Amer. Chem. Soc.*, 1959, **81**(17) 4493
82. D A Evans, G L Caroll, L K Truesdale *J. Org. Chem.*, 1974, **39**(7) 914
83. J W Zubrick, B I Dunbar, H D Durst *Tetrahedron Lett.*, 1975, (1) 71
84. B Uznanshi, W J Stec *Synthesis*, 1978, (2) 154
85. F Brunnmueler, M Kroner, BRD P. 3 242 193; *Chem. Abs.*, 1984, **101** 210 589
86. A I Ayi, R Guedj *J. Fluor. Chem.*, 1984, **24**(2) 137
87. Y Murao, T Ochiai, T Nakanome, Japanese P. Appl. 7 946 716; *Chem. Abs.*, 1979, **91** 57 537
88. V P Chekhun, E N Zvonkova, R P Evstigneeva, USSR P. 438 257; *Byul. Izobret.*, 1976, (7) 201
89. M L Dhanani, N K Undavia, K A Thaker *J. Inst. Chem. (India)*, 1974, (46), Pt. 6 187
90. J-M Bourgeois *Helv. Chim. Acta*, 1975, **59**, Fasc. 2 363
91. F Becke, P Pässler, BRD P. 1 950 280; *Chem. Abs.*, 1971, **75** 6346
92. F Becke, P Pässler, *Annalen*, 1970, **733** 27
93. K H X Mai, G Patil, US P. 4 551 537; *Chem. Abs.*, 1986, **104** 168 194
94. K H X Mai, G Patil, US P. 4 551 537; *Chem. Abs.*, 1986, **104** 168 195
95. K Mai, G Patil *Synth. Commun.*, 1984, **14**(14) 1299
96. J W Apsimon, R P Seguin *Tetrahedron*, 1979, **35** 2797
97. K Horst, W Sager *Angew. Chem.*, 1987, **99**(6) 595
98. J Morrison *Asymmetric Synthesis. Analytical Methods* (Translated into Russian), Izd. Mir, Moscow, 1987, p. 21
99. S S Naim, N H Khan, A A Siddiqui *Ind. J. Chem. Sec. B*, 1980, **19**(7) 622
100. Y Yamasaki, T Maekawa, T Ishihara, T Ando *Chem. Lett.*, 1985, (9) 1387

101. A J Cowper, R R Astik,, K A Thaker *J. Inst. Chem. (India)*, 1981, **53**, Pt. 4 195
102. J Huang, D F Bushey, M D Graves, et al. *J. Heterocycl. Chem.*, 1987, **24** 1
103. C Pedragal, G G Trigo, M Espada, et al. *J. Heterocycl. Chem.*, 1984, **21** 1527
104. J Kant, F D Popp, B C Uff *J. Heterocycl. Chem.*, 1985, **22** 1065
105. P Potier *Rev. Latinoamer. Quim.*, 1978, **9** 47
106. M Lounasmaa, A Koskinen *Tetrahedron Lett.*, 1982, **23** 349
107. A Koskinen, M Lounasmaa *Tetrahedron*, 1983, **39**(9) 1627
108. Y Nomura, T Shimura, Y Takeuchi *Bull. Chem. Soc. Jpn.*, 1964, **37**(6) 892
109. J Taillades, A Commeyras *Tetrahedron*, 1974, **30**(1) 127
110. M Bejaud, L Mion, J Taillades, A Commeyras *Tetrahedron*, 1975, **31**(5) 403
111. J S Sandhu, S Mohan, G Schroll *Acta Chem. Scand.*, 1971, **25**, Fasc.2 590
112. J C Guillemin, J M Denis *Chem. Commun.*, 1985, 951
113. L A Yanovskaya, Kh Shakhidayatov, E P Prokof'ev, et al. *Tetrahedron*, 1968, **24**(13) 4677
114. F L Logemann, G Shaw *Chem. Ind.*, 1980, (13) 541
115. V D Domkin, A A Kur'yanovich *Zhur. Obshch. Khim.*, 1976, **12**(4) 908
116. K Kadir, G Shaw, G Wright *J. Chem. Soc., Perkin Trans. I*, 1980, (12) 2728
117. P S Khokhlov, V A Kashemirov, A D Mikityuk, et al. *Zhur. Obshch. Khim.*, 1984, **54**(11) 2641
118. T Brown, G Shaw, G J Durant *J. Chem. Soc., Perkin Trans. I*, 1980, (10) 2310
119. E Catalucci, BRD P. 2 700 733; *Chem. Abs.*, 1977, **87** 117 596
120. G Duguay, J P Guemas, J C Meslin, et al. *J. Heterocycl. Chem.*, 1980, **17** 767
121. C M Darling, C P Chen *J. Pharm Sci.*, 1978, **67**(6) 860
122. N F Tullar, US P.2 393 723; *Chem. Abs.*, 1946, **40** 2465
123. M Fields, D E Waltz, S Rothchild *J. Amer. Chem. Soc.*, 1951, **73** 1000
124. H J F Weiss, B. P. 583 307; *Chem. Abs.*, 1947, **41** 2747
125. Y Otsuka, Japanese P. Appl. 7 441 317; *Chem. Abs.*, 1974, **81** 169 159
126. Kh Shakhidayatov *Zhur. Obshch. Khim.*, 1973, **9**(7) 1373
127. O W Bauer, J W Teter, US P. 2 552 026; *Chem. Abs.*, 1951, **45** 9074
128. K Kawashiro, H Yoshida, S Marimoto *Bull. Chem. Soc. Jpn.*, 1977, **50**(1) 2956
129. E C Taylor, J H Sun *Synthesis*, 1986, (10) 801
130. Yu M Kosyrev, N P Novoselov, N I Kirichenko, et al., USSR P. 232 233; *Byul. Izobret.*, 1969, (1) 21
131. L de Vries *J. Org. Chem.*, 1971, **36**(22) 3442
132. Japanese P. 95 952; *Chem. Abs.*, 1982, **97** 162 405
133. M Inone, S Enomoto *Bull. Chem. Soc. Jpn.*, 1982, **55**(1) 33
134. R Ciabatti, Europ. P. Appl. 97 839; *Chem. Abs.*, 1984, **101** 68 534
135. J C Jochims *Chem. Ber.*, 1963, **96** 980
136. K Weinges, F Kromm *Liebigs Ann. Chem.*, 1985, (1) 90
137. R Sarges, H R Howard, P R Kelbaugh *J. Org. Chem.*, 1982, **47**(21) 4081
138. K Weinges, G Brune, H Droste *Liebigs Ann. Chem.*, 1980, (1) 212
139. P K Subramanian, R W Woodward *Synth. Commun.*, 1986, **16**(3) 337
140. K Weinges, H Brachmann, P Stahrecker, et al. *Liebigs Ann. Chem.*, 1985, (3) 566
141. T A Hylton, F L Shenton, US P. 4 072 698; *Chem. Abs.*, 1978, **88** 152 276
142. H F Kung, C C Yu, J Billings, et al. *J. Med. Chem.*, 1985, **28**(9) 1280
143. M Acs, E Fogassy, F Faigl *Tetrahedron*, 1985, **41**(12) 2465
144. N Kametaka, N Nagato, K Hirimeto, et al., BRD P. Appl. 3 531 084; *Chem. Abs.*, 1986, **105** 173 046
145. M Makossa, J Winiarsky *Bull. Soc. Chim. Belg.*, 1987, **49**(4) 303
146. Y Tanaka, K Sakai, T Kouno, et al., Europ. P. 171 768; *Chem. Abs.*, 1986, **104** 163 736
147. M Lim, R S Klein *Tetrahedron Lett.*, 1981, **22**(1) 25
148. A H Cook, J Heilbron, E Smith *J. Chem. Soc.*, 1949 1440
149. M Yu Kolobov, V A Bakulev, V S Mokrushin, A T Lebedev *Khim. Geterotsikl. Soedin.*, 1987, (11) 1503
150. J F Mooze, US P 4 260 624; *Chem. Abs.*, 1981, **95** 25 080
151. T Winkler, W Lutz, H Kristinson *Liebigs Ann. Chem.*, 1985, (2) 433
152. R P Kreher, J Pfister *Chem.-Ztg.*, 1984, **108**(9) 275
153. M W Willard *J. Org. Chem.*, 1982, **47**(5) 886
154. J Schapira, J Pecheur, R Jacquier, BRD P. Appl. 3 001 433; *Chem. Abs.*, 1981, **94** 65 307
155. B V Suvorov, L A Krichevskii, V M Kagasov, et al. *Khimicheskie Sintezy na Osnove Odnouglerodnykh Molekul* (Chemical Syntheses Based on Single-carbon Molecules), Moscow, 1987
156. Kamaluddin, H Janagawa, F Egami, J Iudia *Biochem. Biophys.*, 1981, **18**(3) 215
157. T Irijura, K Nishino, S Suzue, et al., Japanese P. 10 206; *Chem. Abs.*, 1968, **68** 30 062
158. A F McKay, G Y Paris, D L Garmaise *J. Amer. Chem. Soc.*, 1958, **80** 6276
159. A H Cook, I M Heilbron, A L Levy *J. Chem. Soc.*, 1947, 1598
160. A H Cook, G D Hunter *J. Chem. Soc.*, 1952, 3785
161. A F McKay, C Podesva, M-E Kreling *J. Chem. Soc.*, 1962, **27** 2884
162. E R Young, BRD P. Appl. 2 940 037; *Chem. Abs.*, 1980, **93** 132 092
163. J R Ross, J W Sowell *J. Heterocycl. Chem.*, 1985, **22** 817
164. A C Davis, A L Levy *J. Chem. Soc.*, 1951, 3749
165. D L Leussing, N V Ryghavan *J. Amer. Chem. Soc.*, 1980, **102**(17) 5635
166. R S Hosmane *Tetrahedron Lett.*, 1984, **25**(4) 363
167. R S Hosmane, F N Burnett, M S Albert *J. Org. Chem.*, 1984, **49**(7) 1212
168. L A Pavlova, Yu A Davidovich, S V Rogozhin *Uspekhi Khim.*, 1986, **55**(11) 1803 [*Russ. Chem. Rev.*, 1986(11)]
169. T Brown, G Shaw *J. Chem. Soc., Perkin Trans. I*, 1983, (4) 809
170. B Ruiner, C Tapiro, J L Imbach *J. Carbohydrates, Nucleosides, Nucleotides*, 1976, **9**(1–2) 1
171. J L Montero, A Dhainaut, J L Imbach *J. Heterocycl. Chem.*, 1978, **15**(6) 929
172. D H Robinson, Europ. P. Appl. 66 909; *Chem. Abs.*, 1983, **98** 143 429
173. A Edenhofer *Helv. Chim. Acta*, 1975, **58**, Fasc. 7 2192
174. T Teitei *Austral. J. Chem.*, 1983, **36**(11) 2307
175. D Ranganathan, S Ranganathan, S Bamezai *Tetrahedron Lett.*, 1982, **23**(27) 2789
176. C J Barnett, US P.4 199 525; *Chem. Abs.*, 1980, **93** 94 970

177. D B Luten, Jr. *J. Org. Chem.*, 1939, **3** 588
178. A Goldberg, W Kelly, US P. 2493578; *Chem. Abs.*, 1950, **44** 3535
179. A A Goldberg, W Kelly, B. P. 593753; *Chem. Abs.*, 1948, **42** 2289
180. T Hamamoto, K Harada, Europ. P. Appl. 53400; *Chem. Abs.*, 1982, **97** 181771
181. M Nakai, K Harada, Y Mori, US P. 4269982; *Chem. Abs.*, 1981, **95** 62231
182. N V Konstantinova, USSR P. 956476; *Byul. Izobret.*, 1982, (33) 103
183. Yu M Shafran, V A Bakulev, V S Mokrushin, S G Alekseev *Khim. Geterotsikl. Khim.*, 1984, (9) 1266
184. Yu M Shafran, V A Bakulev, V S Mokrushin, P N Kondrat'ev, USSR P.1055741; *Byul. Izobret.*, 1983, (43) 79
185. V A Bakulev, V S Mokrushin *Khim. Geterotsikl. Soedin.*, 1986, (8) 1011
186. K Vaughan, R J La France, Y Tang, D L Hooper *Can. J. Chem.*, 1985, **63**(9) 2455
187. D L Hooper, H W Manning, R J La France, K Vaughan, *Can. J. Chem.*, 1986, **64**(2) 250
188. A M Pinchuk, L N Markovskii, E S Levchenko, V I Shevchenko *Zhur. Obshch. Khim.*, 1967, **37**(4) 852
189. A M Pinchuk, L N Markovskii, I M Kozinskaya *Zhur. Obshch. Khim.*, 1968, **38**(5) 1008
190. P L de Benneville, US P. 2743291; *Chem. Abs.*, 1956, **50** 16826
191. J Denkstein, V Kadarabek *Coll. Czech. Chem. Commun.*, 1966, **31**(7) 2915
192. M W Harman, US P. 2649470; *Chem. Abs.*, 1954, **48** 7629
193. K Yamashita, K Koen, J Nagaoka, Japanese P. Appl. 7514813; *Chem. Abs.*, 1976, **84** 135142
194. T Mitsui, Japanese P. Appl. 59130246; *Chem. Abs.*, 1984, **101** 192477
195. Yuasa Battery Co., Japanese P. Appl. 81118047; *Chem. Abs.*, 1982, **96** 35722
196. K Nakayasu, B Furaya, Y Hasaki, US P. 4299978; *Chem. Abs.*, 1982, **96** 104768
197. A H Cook, S F Cox, *J. Chem. Soc.*, 1949, 2337
198. E Tolksdorf, BRD P. 2717371; *Chem. Abs.*, 1979, **90** 138201
199. Japanese P. 57158743; *Chem. Abs.*, 1983, **98** 107779
200. A Commeyras, J Taillades, J Brugidou, et al., French P. 2565225; *Chem. Abs.*, 1986, **105** 153543
201. C B Warren, R D Minard, C N Matthews *J. Org. Chem.*, 1974, **39**(23) 3375
202. N K Undavia, M L Dhanani, K A Thaker *J. Inst. Chem. (India)*, 1978, **50**(1) 41
203. W H J Boesten, BRD P. 2637204; *Chem. Abs.*, 1977, **87** 39839
204. M E D Hillman, US P. 3560551; *Chem. Abs.*, 1971, **74** 87447
205. D Giraud-Clenet, J Anatol *C. R. Seances Acad. Sci., Ser. C*, 1966, **262**(2) 224
206. D W Wooley, J W B Hershey, H A Jodlowski *J. Org. Chem.*, 1963, **28**(8) 2012
207. D F Ewig, D G Neilson *J Chem. Soc., Sec. C*, 1966, (4) 390
208. N R Barot, J A Elvidge *J. Chem. Soc., Perkin Trans. I*, 1972, (7) 1009
209. J L Kraus *Synth. Commun.*, 1986, **16**(7) 827
210. RG Melik-Ogadzhanyan, R G Mirzoyan, A A Aroyan *Arm. Khim. Zhur.*, 1975, **28**(1) 53
211. Z Rappoport (Editor) *The Chemistry of the Cyano Group*, Interscience, London–New York–Sydney–Toronto, 1970
212. E N Zilberman *The Reactions of Nitriles* (Translated into Russian), Izd. Khimiya, Moscow, 1972
213. A C W Curran, R Crossley, US P. 3907899; *Chem. Abs.*, 1976, **84** 30643
214. M Paventi, J T Edward *Can. J. Chem.*, 1987, **65**(2) 282
215. Z Welwart *Compt. Rend.*, 1960, **250** 1870
216. H Ahlbrecht, H Dollinger *Synthesis*, 1985, (8) 743
217. Z E Overman, R M Burk *Tetrahedron Lett.*, 1984, **25**(16) 1635
218. J Sansoulet, C Tackx, Z Welwart *Compt. Rend.*, 1960, **250** 4370
219. T Thomson, T S Stevens *J. Chem. Soc.*, 1932, 2607
220. R Epsztein, N Le Goff *Tetrahedron*, 1985, **41**(22) 5349
221. W McMeeking, T S Stevens *J. Chem. Soc.*, 1933, 347
222. H Thies, H Schönenberger, P H Qasba *Arch. Pharm.*, 1969, **302**(11) 803; *Chem. Abs.*, 1970, **72** 42998
223. H Thies, H Schönenberger, P H Qasba *Tetrahedron Lett.*, 1965, (3) 163
224. E Münch, O. Schlichting, German P. 561156; *Chem. Abs.*, 1933, **27** 995
225. Z Welwart *International Congress on Aluminium*, Vol.1, Paris, 1955, p. 97; *Chem. Abs.*, 1958, **52** 19926
226. A Kotelko *Acta Pol. Pharm.*, 1962, **19** 109; *Chem. Abs.*, 1963, **59** 1482
227. S Yamada, H Akimoto, Japanese P. Appl. 7419243; *Chem. Abs.*, 1965, **82** 97816
228. S Yamada, H Akimoto *Tetrahedron Lett.*, 1969, (36) 3105
229. G Le Ny, Z Welwart *Compt. Rend.*, 1957, **245** 434
230. Z Welwart *Compt. Rend.*, 1951, **233** 1121
231. Z Welwart *Compt. Rend.*, 1954, **238** 2536
232. R Granger, H Orzalesi, Y Robbe *Trav. Soc. Pharm. Montpellier*, 1967, **27**(1) 15; *Chem. Abs.*, 1968, **68** 77818
233. H Reihlen, G Hessling, G Hühn, E Weinbrenner *Liebigs Ann. Chem.*, 1932, **493** 20
234. A Gaiffe, A Padovani *Compt. Rend., Ser. C*, 1969, **269**(2) 144
235. A Padwa, Y Y Chen, U Chiacehio, W Dont *Tetrahedron*, 1985, **41**(17), 3529
236. T Otohiko, U Kazumori, K Shuji, Y Kiyotaka *Bull. Chem. Soc. Jpn.*, 1980, **59** 1809
237. T Kato, M Sato *Yakugaku Zasshi*, 1972, **92**(12) 1515; *Chem. Abs.*, 1973, **78** 97451
238. P Verschave, J Vekemans, G Hoornaert *Tetrahedron*, 1984, **40**(12) 2395
239. J A Gauthier, I Z Jirkovsky, US P. 4492697; *Chem. Abs.*, 1985, **102** 132054
240. N J Cusack, G Shaw, F I Zogemann *J. Chem. Soc., Perkin Trans. I*, 1980, (10) 2316
241. B G Christensen, J Hannah, D H Shih, US P. 4189493; *Chem. Abs.*, 1980, **93** 8012
242. M H Elnagdi, S M Sherif, R M Mohareb *Heterocycles*, 1987, **26**(2) 497
243. E Gomez, C Evendafio, A McKillop *Tetrahedron*, 1986, **42** 2634
244. C Avendano, T Ramos, E Gomez-Molinero *J. Heterocycl. Chem.*, 1985, **22** 537
245. J Heyes, N Ward, B. P. 1373347
246. C J Rose, A T Ainsworth, B. P. 1421787
247. T C McKenzie, S M Rolfe *J. Heterocycl. Chem.* 1987, **24** 859
248. C K Chu, S Y Cutler *J. Heterocycl. Chem.*, 1986, **24**(2) 289
249. G Shaw, D N Butler *J. Chem. Soc.*, 1959, 4040
250. N J Cusack, G Shaw *Chem. Commun.*, 1970, (17) 1114
251. O W Lever, B R Vessal *J. Heterocycl. Chem.*, 1985, **22** 5

252. T Giorgio, P Gianbattista, US P. 4 198 502; *Chem. Abs.*, 1980, **93** 220 579
253. L H Smith Jr, P Yates *J. Amer. Chem. Soc.*, 1954, **76** 6080
254. G Weitzel, F Schneider, H Guglielmi, J Sander *J. Physiol. Chem.*, 1966, **346** 208
255. A H Cook, G D Hunter *J. Chem. Soc.*, 1949, 1443
256. A D Ainley, A Sexton *Biochem. J.*, 1948, **43** 468
257. G Tarzia, G Pansone, US P. 4 212 806; *Chem. Abs.*, 1981, **94** 83 936
258. A M Macadam, C J Knowles *Biotechnol. Lett.*, 1985, **7**(12) 865
259. S Mataka, K Takahashi, M Tashiro *J. Heterocycl. Chem.*, 1983, **20**(4) 971
260. S Mataka, K Takahashi, M Tashiro, Y Tsuda *Synthesis*, 1980, (10) 842
261. S Mataka, K Takahashi, Y Tsuda, M Tashiro *Heterocycles*, 1980, **14**(6) 789
262. S Yoneda, H Hirai, Z Yoshida *Heterocycles*, 1981, **15**(2) 865
263. C J Barnett, T L Emmick, R C Hoying, US P. 4 211 870; *Chem. Abs.*, 1980 **93** 220 777
264. D Griller, D C Nouhebel, J C Walton *J. Chem. Soc., Perkin Trans. II*, 1983, (9) 1373
265. R D Hancock, B S Nakani, F Marsicano *Inorg. Chem.*, 1983, **22**(18) 2531
266. I R Rowland, B G Lake, J C Philips, S D Gandolli *Mutant Res.*, 1980, **72**(1) 63
267. N Seiler, B Knoedyen, G Buik, S Sarhau, F Bolkenius *Adv. Polym. Res.*, 1983, **4** 135
268. B G Lake, I R Rowland, R A Harris, et al. *Adv. Exp. Med. Biol.*, 1982, **136**, Pt. B 1143
269. T Kawanishi, Y Ohno, A Takahashi, et al., *Arch. Toxicol.*, 1984, **56**(1) 7
270. G Diaz, I Maric, H M Goday, J A Castro *Arch. Toxicol.*, 1981, **47**(3) 159
271. C Stephen, B J Neuburger, M F Argus *Cancer Lett.*, 1980, **9**(2) 161
272. G Walker, G Sarogini, D Y Oliver *Biochem. Biophys. Res. Commun.*, 1982, **107**(3) 856
273. J Behavides, N Croci, M S Benedetti *Biochem. Pharmacol.*, 1983, **32**(2) 287
274. A M Macadam, C J Knowles *Biotechnol. Lett.*, 1985, **7**(12) 865 865
275. K Minami, K Shika *Yakugaku Zasshi*, 1984, **26**(3) 882; *Chem. Abs.*, 1985, **102** 91 189
276. W Schmidt *Z. Wiss, Ernst-Moritz-Arndt-Univ. Greifaw. Med. Reihe*, 1983, **32**(1–2) 27; *Chem. Abs.*, 1984, **101** 49 894
277. H G Vogel *Arzneim. Forsch.*, 1984, **34**(2) 213
278. S Oshima *Tsurumi Shigaku*, 1982, **8**(3) 345; *Chem. Abs.*, 1983, **98** 29 173
279. W Schmidt, D Wendler *Folia Morphol.*, 1982, **30**(2) 146
280. D Wendler, W Schmidt, W Gabler *Anat. Arz.*, 1980, **147**(5) 413; *Chem. Abs.*, 1982, **96** 81 093
281. S Kojima, Y Hamo, T Sasaki, A Kubodera *Fur. J. Nucl. Med.*, 1983, **98** 212 186
282. O Kirino, T Oishi, N Kameda, et al., BRD P. 2 442 239; *Chem. Abs.*, 1975, **83** 27 636
283. K Bauer, H Bieringer, G Frisch, et al., BRD P. Appl. 2 948 095; *Chem. Abs.*, 1982, **96** 7068