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Zelinskii Institute of Organic Chemistry,
Academy of Sciences of the USSR

CYCLISATION REACTIONS BASED ON ACRYLONITRILE

P. F. Butskus

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Both acrylonitrile itself and the cyanoethylated compounds synthesised with its help[1-4] are widely employed for obtaining both simple and complex ring systems. Almost all the investigations in this field have been published during the past fifteen years. The starting materials for these reactions are in most cases readily available.

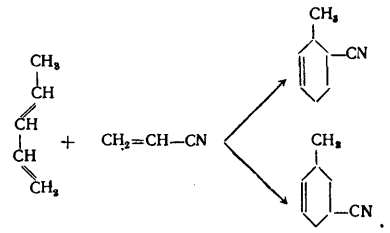
The use of acrylonitrile and cyanoethylated compounds in reactions involving ring formation is of interest from the point of view of both theory and preparative work, as it enables various cyclic systems to be synthesised, including those containing the cyanoethyl group, that either cannot be obtained by other methods or else can be so obtained only in poor yields.

1. ACRYLONITRILE IN DIENE SYNTHESIS

Acrylonitrile acts as a dienophile in reactions involving the Diels-Alder diene synthesis.

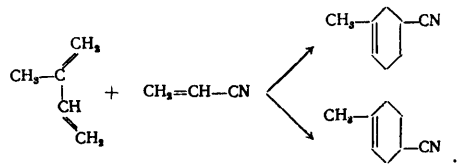
Condensation of butadiene with acrylonitrile results in the formation of cyclohex-3-enyl cyanide[1,3,5-12], although under some conditions it is assumed that 2-vinyldihydropyridine is formed as well[12].

Two structural isomers can theoretically be formed in condensations of 1-substituted dienes with acrylonitrile. It was considered for a long time that such reactions yield exclusively the *ortho*-isomer. In 1947, however, Frank *et al.*[13] demonstrated the presence of a small quantity of the *meta*-isomer in the mixture of adducts obtained by the condensation of penta-1,3-diene with acrylonitrile. The structural orientation of diene synthesis was subsequently studied in detail by Nazarov and his coworkers[14,15], who showed that the condensation of 1-substituted dienes with acrylonitrile yields a mixture of the two possible adducts containing 85–95% of the *ortho*-isomer and 5–15% of the *meta*-isomer. For example, in the case of penta-1,3-diene the reaction proceeds as follows:

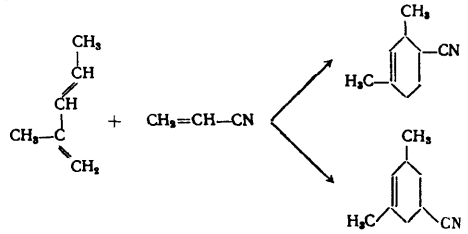


Other workers have also investigated[5,16-21] the interaction of penta-1,3-diene with acrylonitrile.

In the condensation of 2-substituted dienes with acrylonitrile, the orienting effect of the substituent in the diene molecule results in preferential formation of *para*-adducts[14,15]. In the case of isoprene[16,17,22-24] the process takes place according to the scheme

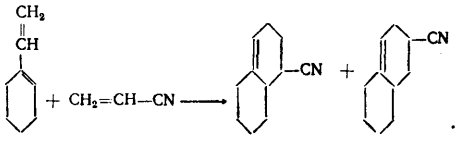


The interaction of 1,2-dimethylbutadiene (3-methylpenta-1,3-diene) with acrylonitile gives mainly 2,3-dimethylcyclohex-3-enyl cyanide and a small quantity of 4,5-dimethylcyclohex-3-enyl cyanide[14]. Reaction of 1,3-dimethylbutadiene (2-methylpenta-1,3-diene) with acrylonitrile produces mainly 2,4-dimethylcyclohex-3-enyl cyanide and also a small amount of the "symmetrical" isomer[15]:

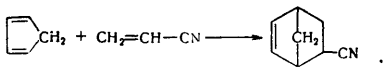


Heating diethyl *trans–trans*-muconate with acrylonitrile in the presence of quinol at 160°–170° for 30 h gives a 64%

yield of diethyl 2-cyanocyclohex-5-ene-1,4-dicarboxylate[25,26]. The reaction of vinylcyclohexene with acrylonitrile can be represented as follows[14]:



Cyclopentadiene[1,9,27,28], tetraphenylcyclopentadiene[29], and cyclohexa-1,3-diene[27,28] give the corresponding bicyclic systems with acrylonitrile, for example:



Interaction of acrylonitrile with 1,1-bicyclohexenyl results in the formation of 9-cyanododecahydrophenanthrene[30].

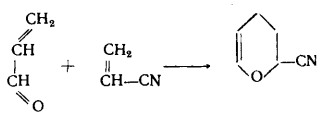
Anthracene is not cyanoethylated by acrylonitrile, but forms a diene synthesis adduct with it[31-34].

9-Anthraldehyde[35], 9-cyanoanthracene[36], and 9-nitroanthracene react similarly[37]. Diene synthesis products have been obtained also by the interaction of acrylonitrile with chloroprene[6,11,38], bromoprene[6], fluoroprene[39], 2-methoxy-,[40] 2-ethoxy-,[11,40] 2-cyano-,[41] 1-phenyl-,[42,43] 2-phenyl-,[44] and 1-*p*-nitrophenyl-butadienes[45], and with the following di- and tri-substituted butadienes: 2-chloro--3-methyl[46], 1,1-dimethyl[47], 2,3-dimethyl[5], 1,4-bisdimethylamino[48], 1,1,2-trimethyl[49], 1,1,3-trimethyl[49-51], 1,2,3-trimethyl[52], and 2-isopropyl-1,1-dimethyl[49,53]. The reaction of acrylonitrile with the following compounds has also been investigated: hexa-2,4-diene[5,54], hexachlorocyclopentadiene[55], 6,6-dimethyl-[9,56] and 6,6-diphenyl--fulvenes[57], alloocimene[58,59], myrcene[58,60], α- and β--pyronens[61], L-pimaric acid[62], some unsaturated aliphatic acids and their esters[63,64], cyclooctatetraene[65], bicycloheptadiene[66], 1,3-diphenyl-[67] and 1,3-di-1-naphthylisobenzofurans[68], and other compounds containing a system of conjugated double bonds[1,3,5,8,9,65,69-73].

In the case of the condensation of 2-isopropyl-1,1-dimethylbutadiene with acrylonitrile the normal product of diene synthesis is accompanied by the corresponding adduct of the isomeric 2-isopropyl-1,3-dimethylbutadiene[53]. When 1,1-dimethylbutadiene is heated with acrylonitrile in a solvent at 200° for 4 h, the adduct corresponding to 1,3-dimethylbutadiene is obtained in ~ 20% yield[47].

cis-1-Cyanobutadiene does not react with acrylonitrile; the *trans*-isomer apparently gives an adduct, but the latter has now been isolated in a pure form[74].

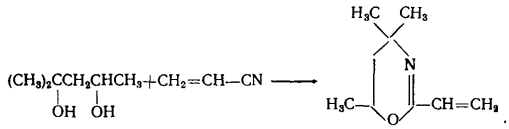
The reaction of acrylonitrile with acrolein also constitutes a diene synthesis[75]:



Experiments on the preparation of Diels-Alder reaction products from acrylonitrile and 3,5-dimethylpyrazole, 2,4-dimethylthiazole, and *N*-methylimidazole[76], as well as tetramethylfuran[77], had no success[76]. Attempts to carry out a diene synthesis between acrylonitrile as the diene and quinone as the dienophile were likewise unsuccessful[78].

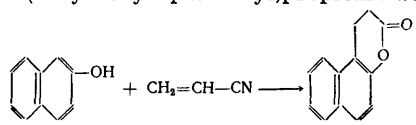
2. ACRYLONITRILE IN OTHER REACTIONS INVOLVING RING FORMATION

Acrylonitrile reacts with several glycols in the presence of concentrated sulphuric acid to give heterocycles containing a vinyl group in the side chain[79-82], for example:

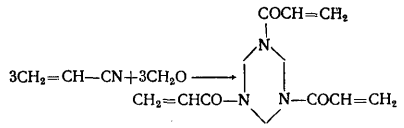


With mercapto-alcohols acrylonitrile similarly forms thiazolines and dihydrothiazines[83].

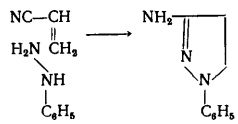
Condensation of acrylonitrile with 2-naphthol in the presence of zinc chloride and hydrogen chloride yielded the lactone of 3-(2-hydroxynaphth-1-yl)propionic acid[84]:



Formaldehyde (and also trioxymethylene) form 1,3,5-triacryloylhexahydro-1,3,5-triazine with acrylonitrile in the presence of concentrated sulphuric acid[1,3,85-87]:

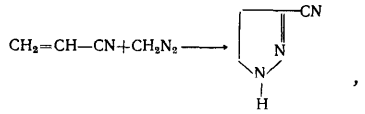


Duffin and Kendall[88] obtained from acrylonitrile and phenylhydrazine a 74% yield of 3-amino-1-phenylpyrazoline:

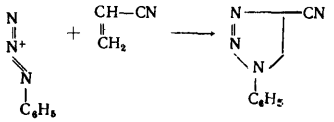


This reaction also takes place with other arylhydrazines.

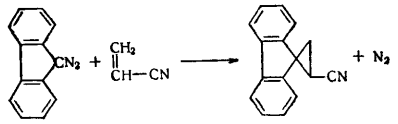
Although some investigators[89] were unable to isolate the reaction products from acrylonitrile and diazomethane in a pure form, Gurvich and Terent'ev[90] obtained a 94% yield of 3-cyanopyrazoline from these starting materials:



and from acrylonitrile and diazoacetic ester they obtained ethyl 5-cyanopyrazoline-3-carboxylate. They also showed that acrylonitrile reacts with phenyl azide at room temperature to form 4-cyano-1-phenyltriazoline in 91% yield:



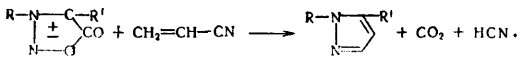
With 9-diazofluorene nitrogen is evolved and a three-membered ring is formed[91,92]:



Interaction between acrylonitrile and diazoacetone is supposed to involve the formation of a pyrazoline ring[93].

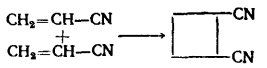
According to Pietra's results[94] the action of acrylonitrile on benzamidine results in the formation of 3,4,5,6-tetrahydro-4-imino-2-phenylpyrimidine. The reaction between acrylonitrile and diazonium salts can be used in the synthesis of 3-arylpiperidines[95] and 3,4-diarylpiperidines[96]; with benzonitrile oxide acrylonitrile gives isoxazoline derivatives[97]. Reaction of acrylonitrile with 2-amino-4-hydroxypteridines in aqueous pyridine yields the corresponding tricyclic systems[98]. Acrylonitrile has been used as starting material for the synthesis of *N*-substituted derivatives of 4-hydroxpiperidine[99] and the betel nut alkaloid arecoline[100,101]. The interaction of acrylonitrile with tetrafluoroethylene[102-104] and with allenes[69,105-109] has also been investigated, derivatives of cyclobutane and Δ9-octahydronaphthalene being obtained in the latter case. Acrylonitrile[110-113] and its addition product with hydrogen chloride[114-120] have also been used to obtain other cyclic systems.

On being heated with acrylonitrile, sydnones undergo cleavage with evolution of CO_2 and HCN and formation of pyrazole derivatives[121]:



Thus 3-phenylsydnone and excess of acrylonitrile yielded on heating 1-phenylpyrazole in ~ 80% yield. The reaction evidently takes place *via* the intermediate formation of nitriles of substituted pyrazolinecarboxylic acids.

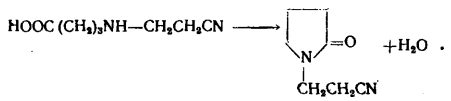
When a benzene solution of acrylonitrile is heated at 280° for 2 h, a 5% yield is obtained of a mixture of *cis*- and *trans*-1,2-dicyanocyclobutane[122]:



Pyridine can be detected in the residue from the distillation of technical acrylonitrile. However, attempts to dimerise acrylonitrile with the aim of preparing pyridine and its derivatives proved unsuccessful[78].

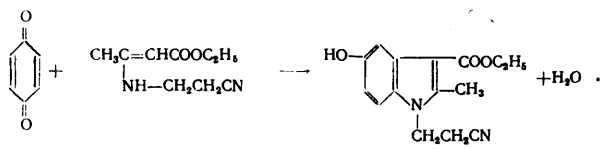
3. CYCLISATION OF CYANOETHYLATED COMPOUNDS PRESERVING THE 2-CYANOETHYL GROUP

Heating *N*-(2′-cyanoethyl)-4-aminobutyric acid leads to the formation of *N*-(2′-cyanoethyl)pyrrolid-2-one[123]:



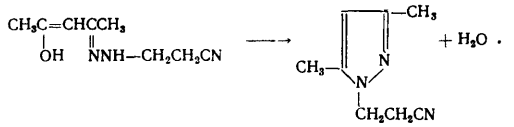
Similarly, the cyanoethylation products of glutamic acid[124,125] and of δ- and ε-amino-acids[126] yield the corresponding *N*-cyanoethylated lactams.

Ethyl *N*-(2′-cyanoethyl)-3-aminocrotonate forms with *p*-benzoquinone ethyl 1-(2′-cyanoethyl)-5-hydroxy-2-methylindole-3-carboxylate[127]:

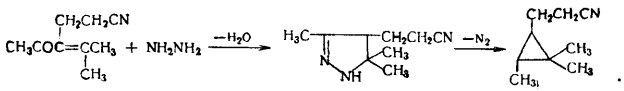


Reaction of cyanoethylated phenylhydrazine with cyclopentanone, cyclohexanone, and cycloheptanone yielded *N*-cyanoethylated indole with five-, six-, and seven-membered rings respectively fused in the 2,3-position[128].

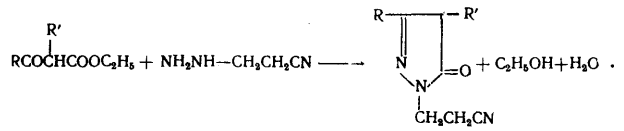
The monohydrazone obtained from monocyanoethylated hydrazine and acetylacetone cyclises into *N*-cyanoethylated 3,5-dimethylpyrazole[76]:



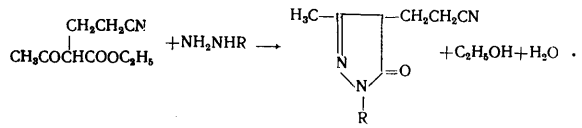
The action of monocyanoethylated hydrazine on mesityl oxide and other αβ-unsaturated ketones gives the corresponding *N*-cyanoethylated pyrazolines[129]. Monocyanoethylation products of mesityl oxide are readily converted by hydrazine hydrate to 4-(2′-cyanoethyl)-3,5,5-trimethylpyrazoline, which under the conditions of a Woolf–Kishner reaction yields 1-(2′-cyanoethyl)-2,2,3-trimethylcyclopropane[130]:



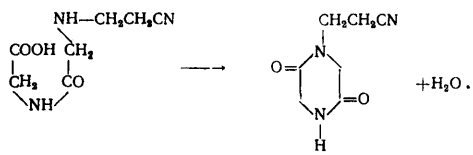
Kost *et al.*[131] have shown that the interaction of monocyanoethylhydrazine with esters of various β-keto-acids gives good yields (65–95%) of the corresponding 1-(2′-cyanoethyl)-3,4-dialkylpyrazol-5-ones:



The patent literature[132,133] contains an indication that it is possible to obtain 1-(2′-cyanoethyl)-3-methyl- and 1-(2′-cyanoethyl)-3-phenyl-pyrazol-5-ones by this method. Pyrazolones having the β-cyanoethyl group in position 4 are synthesised from monocyanoethylated acetoacetic ester and the corresponding hydrazines[131]:

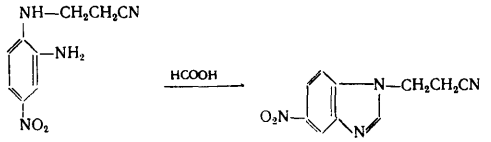


Cyclisation of *N*-2-cyanoethylglycylglycine in ethylene glycol gives 1-(2′-cyanoethyl)-2,5-dioxopiperazine[134]:

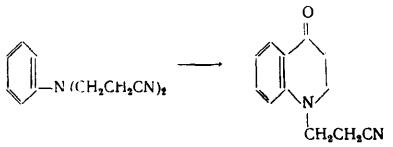


The same cyclic product is obtained under similar conditions from *NN*-di-(2-cyanoethyl)glycylglycine[134]. Esters of *N*-2-cyanoethyl-α-amino-acids on being heated form 1,4-di-(2′-cyanoethyl)-2,5-dioxopiperazines[134,135]. Attempts to prepare the latter by heating certain *N*-mono-2-cyanoethyl- and *NN*-di-(2-cyanoethyl)-α-amino-acids in ethylene glycol were unsuccessful, since under these conditions decyanoethylation takes place as well cyclisation[134]. Several derivatives of *C*-cyanoethylated 2,5-dioxopiperazine also can be obtained by reductive cyclisation[136].

2-(2′-Cyanoethyl)amino-5-nitroaniline reacts with acetic anhydride or formic acid to give the corresponding *N*-2-cyanoethylbenzoimidazole derivatives[137], for example:



When *NN*-biscyanoethylated aromatic amines are heated in chlorobenzene in the presence of aluminium chloride and a small amount of concentrated hydrochloric acid, 1-(2′-cyanoethyl)-1,2,3,4-tetrahydro-4-oxoquinolines are obtained together with other cyclisation products[138-141], for example:

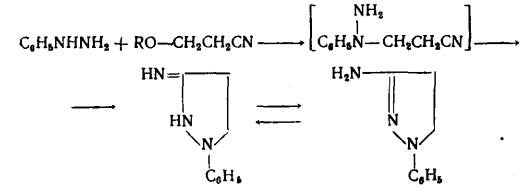


Other compounds which have been used to obtain various cyanoethylated cyclic systems are 3-aminopropionitrile[137,142-146], cyanoethylhydrazine[146], di-2-cyanoethylamine[142], *N*-2-cyanoethylanthranilic acid[147], tetra-2-cyanoethyl-*p*-phenylenediamine[140], *N*-2-cyanoethyl-*N*-phenylthiourea[3], *NN*-biscyanoethylated monoamides of dibasic acids and of some of their derivatives[148,149], *N*-2-cyanoethylisatin[150], and other cyanoethylated compounds[151]. According to the patent literature[152,153], several cyclic tetramers, pentamers, hexamers, and heptamers can be obtained from *Si*-cyanoethylated compounds.

4. CYCLISATION OF CYANOETHYLATED COMPOUNDS INVOLVING THE 2-CYANOETHYL GROUP

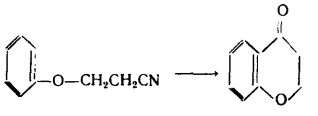
(*a*) *O*-Cyanoethylated Compounds

Kost and Ershov[118] have shown that ethylene cyanohydrin and 3-alkoxypropionitriles react with phenylhydrazine in the presence of sodium ethoxide to form 3-amino-1-phenylpyrazoline:



3-Alkoxypropionitriles have been empolyed for the synthesis of lactones[154], oxalactones[155], pyrimidines[156-164], and thiazolines[165]. The reaction between acrylonitrile and salicylaldehyde gives both the cyanoethylation product and cyclisation products (3-cyano-4-hydroxychroman and 3-cyanobenzopyran)[166,167].

Chromanone and its derivatives have been obtained by the cyclisation of 3-aryloxpropionitriles[166,169-171], for example:



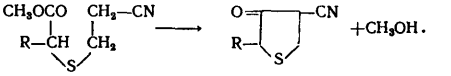
2-Cyanoethyl ethers of 2-naphthol and its derivatives are cyclised in a similar manner[169,172]. The yield of chromanone is 87.5%. The cyclisation of 3-aryloxypropionitriles to chromanones can be effected *via* an intermediate stage of hydrolysis[173,174]. Cyclisation of bis-2-cyanoethyl ethers of dihydric phenols[166,175] and of the bis-2-carboxyethyl ethers[176] obtained from them yields the corresponding bicyclic and tricyclic systems.

Ring formation also takes place when resorcinol reacts with 2-cyanoethyl *p*-toluenesulphonate[177].

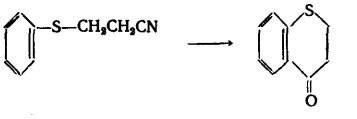
Attempts to synthesise dehydromorpholines from 2-cyanoethyl ethers of acetylenic alcohols, *via* a stage of keto-amide formation and subsequent treatment with sodium hypobromite, were unsuccessful. Dehydromorpholines can be obtained from these starting materials by forming successively the corresponding keto-esters, hydrazone-hydrazides, keto-azides, and finally the keto-urethanes, which are hydrolysed with calcium hydroxide[178].

(*b*) *S*-Cyanoethylated Compounds

The patent literature mentions[179] the formation of 5-substituted derivatives of 3-cyano-4-oxothiolane by the cyclisation, under the influence of sodium ethoxide, of esters of *S*-cyanoethylated α-mercapto-carboxylic acids:



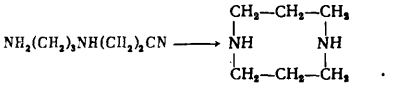
The cyclisation of 3-arylthiopropionitriles is represented as follows[169,172]:



3-Alkyl-6-oxo-2-thiotetrahydro-1,3-thiazines were obtained from cyanoethylated *N*-alkylated dithiocarbamic acids[180] and their hydrolysis products[181].

(*c*) *N*-Cyanoethylated Compounds

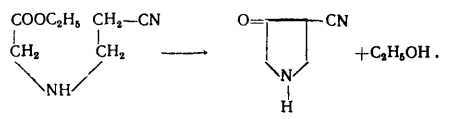
Several *N*-cyanoethylated compounds undergo cyclisation on reduction. Thus an 82% yield of 1,5-diazacyclooctane is obtained when *N*-2-cyanoethyltrimethylenediamine is reduced with sodium in butanol[182]:



When di-(2-cyanoethyl)methylamine is hydrogenated in the presence of nickel and ammonia, 1-methyl-1,5-diazacyclooctane is formed as a side-product[183]. Hydrogenation of 3-acylaminopropionitriles yields acyl derivatives of trimethylenediamine, which on distillation cyclise to form a tetrahydropyrimidine ring[3]. Ring formation takes place in the reduction of *N*-2-cyanoethylsuccinimide[3].

Some *N*-cyanoethylated compounds cyclise under the influence of strongly alkaline reagents. Thus di-(2-cyanoethyl)amine is converted to 3-cyano-4-oxopiperidine by the action of metallic sodium[185]. The biscyanoethylation product of methylamine is cyclised in a similar way[186].

In 1952 Cocker *et al.* [187] reported that heating the ethyl ester of *N*-2-cyanoethylglycine in benzene in the presence of sodium ethoxide leads to the formation of 3-cyano-4-oxopyrrolidine:



However, these workers did not investigate the structure of the reaction product, but confined themselves merely to the analytical data. Nevertheless, 1,4-di-(2′-cyanoethyl)--2,5-dioxopiperazine [135], which is obtained when the same ester is heated in the absence of solvent and alkaline reagent, has the same melting point and gives the same analysis as the 3-cyano-4-oxopyrrolidine obtained by the Irish workers.

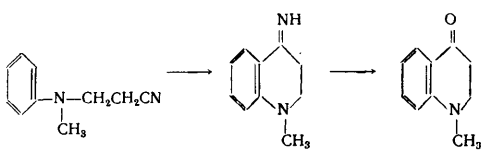
The ethyl ester of *N*-2-cyanoethylsarcosine cyclises in a similar way in the presence of alkaline reagents, forming 3-cyano-1-methyl-4-oxopyrrolidine [186].

Kost and Ershov [118] have shown that 3-dialkylaminopropionitriles react with phenylhydrazine in the presence of sodium ethoxide to form 3-amino-1-phenylpyrazoline. *p*-Tolylhydrazine reacts similarly to phenylhydrazine [188].

According to Pietra [94] *N*-2-cyanoethyl-*N*-phenylhydrazine under the influence of heat or dilute alkalis cyclises into the corresponding amine, whose structure was confirmed by its hydrolysis to 3-oxo-1-phenylpyrazolidine. *N*-2-Cyanoethyl-*NN′*-diphenylhydrazine does not give the corresponding pyrazolidine under similar conditions. Other workers showed later [189] that *N*-2-cyanoethyl-*N′*-phenylhydrazine can be cyclised to 3-amino-2-phenylpyrazoline or 3-amino--2-phenylpyrazole depending on the conditions.

According to the patent literature [190], the nitrosation of 3-arylaminopropionitriles followed by their reduction with zinc in acetic acid gives 1-arylpyrazolidine derivatives.

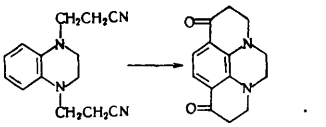
Several quinoline derivatives have been obtained by the cyclisation of *N*-monocyanoethylated aromatic amines in the presence of aluminium chloride. In particular, the cyclisation of *N*-2-cyanoethyl-*N*-methylaniline yielded 1-methyl-4-oxo-1,2,3,4-tetrahydroquinoline [1,3,168,191]:



Heating *NN*-biscyanoethylated aromatic amines in chlorobenzene in the presence of aluminium chloride and a small amount of concentrated hydrochloric acid results in the formation of 1-(2′-cyanoethyl)-4-oxo-1,2,3,4-tetrahydroquinolines or 1,6-dioxojulolidines [138-141,192-194].

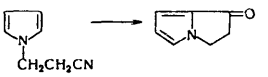
Ring formation has been effected with the products of the *NN*-biscyanoethylation of aniline, *m*- and *p*-chloroanilines, *p*-bromoaniline, *m*- and *p*-toluidines, *p*-anisidine (in this case the reaction is sometimes accompanied by demethylation), *p*-aminobiphenyl, and 2-naphthylamine, and also with the tetrakiscyanoethylation product of *p*-phenylenediamine.

Heating 1,4-biscyanoethyl-1,2,3,4-tetrahydroquinoxaline in chlorobenzene in the presence of aluminium chloride and concentrated hydrochloric acid at 140°–160° gives a 63% yield of a dioxodiazadecahydropyrene [195]:



N-2-Cyanoethylindoline has also been subjected to the action of aluminium chloride and concentrated hydrochloric acid [196,197].

N-2-Cyanoethylpyrrole is cyclised under the influence of hydrogen chloride and zinc chloride [198]:

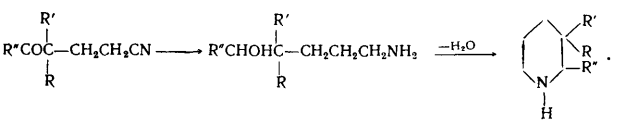


The cyclisation of 1-(2′-cyanoethyl)-1,2,3,4-tetrahydroquinoline [193,199] and of *N*-2-cyanoethylcarbazole [199,200] has also been investigated. Heating *N*-2-cyanoethylanthranilic acid with acetic anhydride in the presence of potassium acetate did not result in ring formation [147].

In some cases the cyclisation of *N*-cyanoethylated compounds passes through an intermediate stage involving hydrolysis, esterification, reduction, or the formation of imino-ethers. Products of the hydrolysis of *N*-cyanoethylated aromatic amines [191-193,201-203] *N*-cyanoethylated anthranilic acid [147,203], *N*-2-cyanoethylindoline [196], 1-(2′-cyanoethyl)-1,2,3,4-tetrahydroquinoline [193], *N*-2--cyanoethylphenoxazine [204], *N*-2-cyanoethylphenothiazine [205,206] and its derivatives [206,207], *N*-2-cyanoethylphenoselenazine [208], and 1-(2′-cyanoethyl)-2-chlorophenoselenazine [208] have undergone such cyclisation. Ring formation has been carried out also with products of the esterification of di-(2-cyanoethyl)methylamine [100,101], *N*-2-cyanoethylanthranilic acid [209], and *N*-2-cyanoethylphenothiazine derivatives [207], and reduction products of 3-aminopropionitrile and its *N*-substituted derivatives [210,211], and also some imino-ether products [212,213]. Other cases and examples of the application of *N*-cyanoethylated compounds for the synthesis of cyclic systems have also been studied [3,212,214-222].

(*d*) *C*-Cyanoethylated Compounds

The principal method for obtaining ring systems from *C*-cyanoethylated compounds is reductive cyclisation. Reduction of the monocyanoethylation product of benzyl cyanide by Vyshnegradskii's procedure gives a 59% yield of 3-phenylpiperidine [96]. Products of the monocyanoethylation of nitrocyclohexane [223] and of the biscyanoethylation of benzyl cyanide [224,225] have also been cyclised. Terent'ev and Gurvich [226-229] showed that homologues of piperidine are formed by the reduction of monocyanoethylated ketones under the conditions of the Vyshnegradskii reaction:



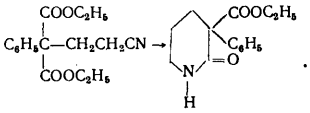
Acetone, diisopropyl ketone, and isopropyl phenyl ketone were used as starting materials. Appreciable quantities

of the corresponding amino-alcohols could be isolated in addition to the piperidine homologues. Reductive cyclisation of monocyanoethylated cylohexanone with metallic sodium in butyl alcohol results in the formation of *trans*--decahydroquinoline. Ketonic cleavage of the cyanoethylation products of acetoacetic ester and its homologues followed by cyclisation under the conditions of the Vyshnegradskii reaction yielded the corresponding piperidines [230].

Kost *et al.* [231] prepared a series of 2-oxopiperidines by the reaction of monocyanoethylated ketones with formic acid and sodium formate. Yur'ev *et al.* [232] used the same method to convert 2-(4'-cyano-2,2-dimethyl-1-oxobutyl)-selenole† to 3,3-dimethyl-6-oxo-2-(selenol-2'-yl)piperidine. The reduction of monocyanoethylated cyclohexanone under these conditions gives *trans*-octahydro-2-oxoquinoline in 72% yield [231].

Catalytic hydrogenation of succinonitrile (the product resulting from the cyanoethylation of hydrocyanic acid) produces pyrrolidine [233,234]. 2-Oxopyrrolidine also has been obtained from this dinitrile [235]. Reductive cyclisation of 2-ethoxycarbonyl-2-phenylglutaronitrile over palladised charcoal (in absolute ethyl alcohol in the cold) yields 3-ethoxycarbonyl-3-phenylpiperidine [116,117].

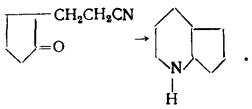
Hydrogenation of the cyanoethylation product of phenylmalonic ester in acetic acid over platinum oxide gives a 70% yield of ethyl 2-oxo-3-phenylnipecotate [236]:



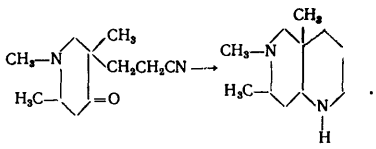
2-(2'-Cyanoethyl)-2-phenylcyclohexanone, on hydrogenation in the presence of the same catalyst in absolute ethyl alcohol, is converted into decahydro-10-phenylquinoline [115].

Hydrogenation of 4-ethoxycarbonyl-4-(pyrid-2'-yl)-butyronitrile in acid medium in the presence of platinum gives 1-ethoxycarbonylquinolizidine and 2-oxo-3-(piperid--2'-yl)piperidine [237]. 2-(Pyrid-2'-yl)propionitrile gives a 43% yield of indolizidine under similar conditions.

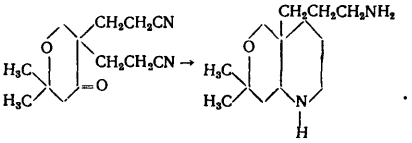
Nickel is often used as a catalyst in reductive cyclisations. That of cyanoethylated nitro-compounds in the presence of Raney nickel yields substituted pyrrolidines and oxopyrrolidines [238,239]. The product obtained by the monocyanoethylation of cyclopentanone gives a 76% yield of 2,3-cyclopentanopiperidine [240]:



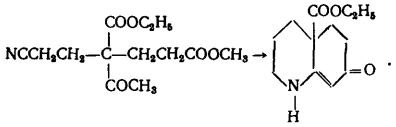
Products of the monocyanoethylation of several substituted cyclopentanones undergo analogous ring formation [241]. Nazarov *et al.* [242] showed that decahydroquinolines are obtained by reduction in the presence of Raney nickel of mono- and bis-cyanoethylated cyclohexanone. They established that the products of the monocyanoethylation of 1,2,5-trimethyl-, 2,5-dimethyl-1-ethyl-, and 1,2,3,6--tetramethyl-4-oxopiperidines on hydrogenation in the presence of nickel in an autoclave at 100° undergo cyclisation to form bicyclic compounds containing two nitrogen heteroatoms and an angular methyl group, for example:



The products of the monocyanoethylation of 2,4-dimethylcyclopentanone and 2,4-dimethylcyclopentanone are cyclised in a similar manner. Under the same conditions monocyanoethylated decahydro-1,2-dimethyl-4-oxoquinoline gives an 81% yield of a tricyclic compound containing two nitrogen heteroatoms and a fused ring in the angular position. The same workers report that reduction of the biscyanoethylation product of 2,2-dimethyl-4-oxotetrahydropyran gives a 66% yield of a bicyclic compound containing a pyran and a piperidine ring fused together:



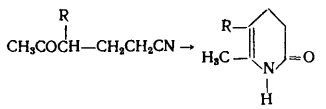
The octahydroquinoline system, with a fully reduced piperidine ring, is obtained from the following cyanoketo--ester [243]:



The same system is formed by reducing the monocyanoethylation product of isophorone in the presence of nickel [244]. This method has been used to obtain the corresponding piperidines from products of the cyanoethylation of aldehydes [245], ketones [246-248], derivatives of benzyl cyanide [249], malonic ester [250], acetoacetic ester and its homologues [248,251-253], and also esters of other keto-acids [248-251]. Products of the cyanoethylation of malonic ester [254-256], its acetamido [257-259], dodecyl [247], and phenoxy [256] derivatives, and also other cyanoethylated esters [260] have yielded the corresponding 2-oxopiperidines.

The reductive cyclisation of *C*-cyanoethylated compounds has also been carried out with iron in hydrochloric acid, zinc dust in the presence of ammonium chloride [239], and lithium aluminium hydride [261].

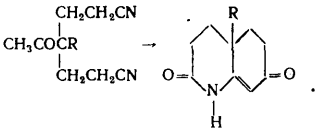
Shusherina *et al.* [262] have shown that cyclisation of the monocyanoethylation products of ethyl methyl, butyl methyl, isobutyl methyl, and methyl pentyl ketones under the influence of hydrogen chloride gives 25–60% yields of 5,6-dialkyl-3,4-dihydropyrid-2-ones:



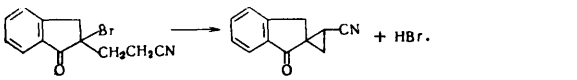
Products of the biscyanoethylation of ethyl methyl ketone, benzyl methyl ketone, and acetoacetic ester, as well as

† "Selenophen" in the original paper (Ed. of Translation).

triscyanoethylated acetone, on being heated with 40–80% sulphuric acid form the corresponding octahydro-2,7-dioxoquinolines in yields of 42–68% [263]:



Under the influence of bases 2-bromo-2-cyanoethylindanone gives a cyano-ketone having the following structure [264]:

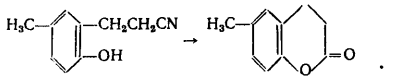


The latter compound is also formed directly from acrylonitrile and 2-bromoindanone.

Ziegler cyclisation of *o*-di(2-cyanoethyl)benzene yields the bicyclic benzocycloheptane system. Whereas American workers [265] obtained the corresponding cyano-ketone by this reaction, Chizhov [266] was able to stop the process at the stage of the formation of 6-cyano-7-iminobenzocycloheptane.

The biscyanoethylation product of fluorene yielded corresponding spirocompounds [267].

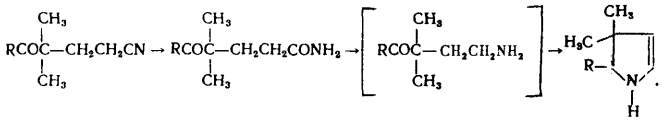
Cyclisation of the *C*-cyanoethylation products of monohydric and polyhydric phenols leads to the formation of dihydrocoumarin and its derivatives [1,3,84,114,119,120,268-272], for example:



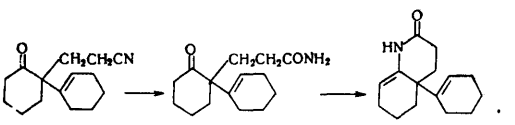
9-Cyanoethylfluoren-9-ol undergoes an analogous cyclisation [273].

Hydrolysis of the monocyanoethylation product of benzyl cyanide gives the corresponding acid, isolated as the anhydride [274], while products of the biscyanoethylation of the same nitrile [225,274,275], and of cyanoacetic and malonic acids [276], yield the corresponding acid imides on acid hydrolysis.

In some cases the cyclisation of *C*-cyanoethylated compounds passes through an intermediate stage of hydrolysis. Thus hydrolysis of the monocyanoethylation products of diisopropyl ketone and isobutyrophenone to the amides by Radzishevskii's method followed by Hofmann rearrangement leads to the formation of 4,4-dimethyl-5-isopropyl-2--pyrroline (yield 70%) and 4,4-dimethyl-5-phenyl-2-pyrroline (yield 58%) [277]:

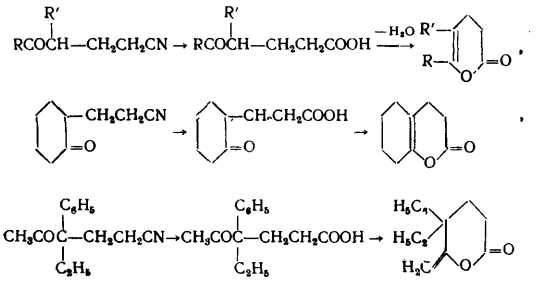


The corresponding amide could not be isolated in the case of monocyanoethylated butyrophenone. Hydrolysis with hydrogen peroxide gave an oil, which on vacuum distillation was converted to an unsaturated lactam [278]. A cyclic system having the following structure [279] has been synthesised from 2-cyanoethyl-2-cyclohexenylcyclohexanone, the corresponding amide being obtained as an intermediate stage:



Hydrolysis of the mono- and bis-cyanoethylation products of some nitro-compounds with concentrated hydrochloric acid gives γ-lactones [280]. Saturated δ-lactones can be obtained from monocyanoethylated aldehydes by reaction of the latter with organomagnesium compounds followed by alkaline hydrolysis [281,282].

A convenient method for the synthesis of unsaturated δ-lactones is saponification of monocyanoethylated ketones to δ-keto-acids with subsequent lactonisation of the latter [244,278,283-296]:



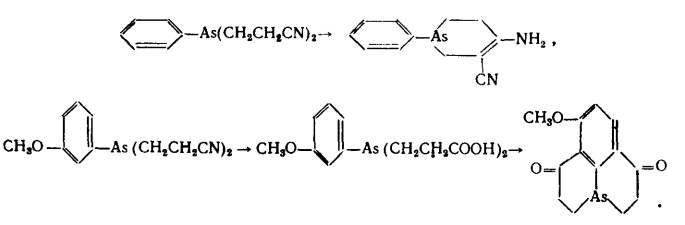
The following have been used as the initial ketones: acetone, ethyl methyl, methyl propyl, butyl methyl, methyl pentyl, isopropyl methyl, and diisopropyl ketones, acetophenone, cyclopentanone, cyclohexanone, α- and β-tetralones, indanone, methyl *p*-tolyl and benzyl methyl ketones, propiophenone, isophorone, and other ketones. The yields of δ-keto-acids are 75–100%. Lactonisation usually takes place when the δ-keto-acids are heated with acetyl chloride or acetic anhydride. The above method can be used for the synthesis of steroids and allied substances [295,296].

Other work has also been published on the cyclisation of *C*-cyanoethylated compounds passing through an intermediate hydrolysis stage [225,273,275,276,297-312].

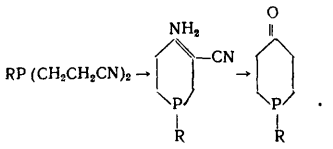
In some cases cyclisation passes through an intermediate esterification stage [222,267,299,300,304,313-325]. Other cases are also known of the employment of *C*-cyanoethylated compounds for the synthesis of cyclic systems [1,3,222,230,248,274,282,326-344].

(*e*) *As*- and *P*-Cyanoethylated Compounds

Among products of the mono- and bis-cyanoethylation of arsines, cyclic systems have been obtained containing an arsenic atom in the ring [345,346], for example:



Several cyclic compounds have been synthesised from biscyanoethylated phosphines[345]:



Other attempts to cyclise cyanoethylation products of arsines[192,347] and phosphines[347] were unsuccessful.

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Fresh work has been published very recently on the use both of acrylonitrile itself and of cyanoethylated compounds synthesised with its aid, to obtain simple and complex ring systems[348-369].

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Kapsukas Vilna State University

MICROBIOLOGICAL REACTIONS OF STEROIDS

L. M. Kogan

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I. INTRODUCTION

Hardly anyone has to be convinced nowadays of the importance of microorganisms for the development and sustenance of life on earth. Nor do chemists have to be told of the significance of microbiological processes in present-day industry. The mere mention of antibiotics is sufficient.