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Reactions of pyridines, pyrimidines and 1,3,5-triazines with nucleophilic reagents

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ABSTRACT. Literature data published since 1971 on the addition of nucleophiles to the C=N bond of the most studied π-deficient six-membered heterocycles, viz. pyridine, pyrimidine and 1,3,5-triazine leading to their transformation have been examined and correlated. Possible applications and proposed mechanisms for the considered processes have been discussed.

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I. Introduction

Nitrogen atoms of the pyridine type in six-membered nitrogen-containing aromatic compounds redistribute the electron density such that the carbon atoms in the heterocycle are depleted of electrons.[1,2] The maximum deficiency of negative charge is formed in the positions *ortho* and *para* to the hetero atom.[2] The angle between the valence bonds of nitrogen and carbon in heterocycles of such type differ from 120°.[3] The above mentioned reasons facilitate the addition of nucleophilic reagents at the C=N bonds of these rings. Among the considered compounds the uncondensed azines lie in the series 1,3,5-triazine > pyrimidine > pyridine in reactivity towards nucleophiles in accordance with the decrease in π-deficiency.[1]

In several cases the addition of nucleophiles to these heterocycles leads to transformations of the latter.

Conversions of heterocycles known up to 1971 have been collated in a review.[4] Separate problems on recyclisation under the action of certain nucleophilic reagents have been considered in reviews for pyridines,[7,13] pyrimidines[5,6,10,12] and other azines.[8,9,11]

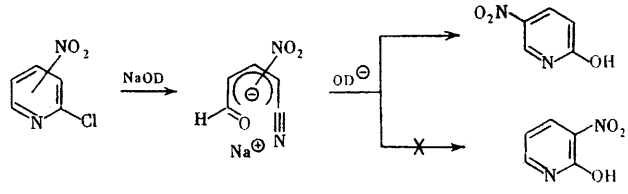
A large number of studies has been published in the chemical literature in the last decade on such transformations the analysis and correlation of which for uncondensed pyridines, pyrimidines and 1,3,5-triazines is the subject of the present review.

II. Recyclisation of pyridines, pyrimidines and 1,3,5-triazines under the action of water, alkali, amines, and strong acids

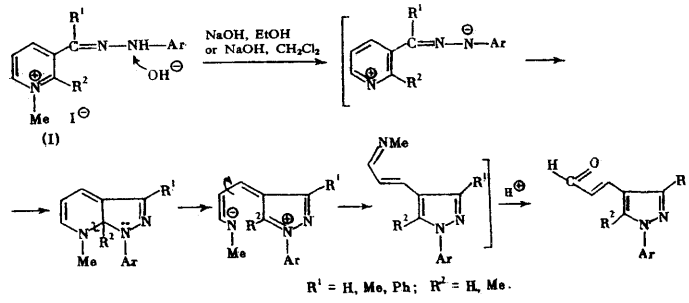
Pyridines, having only one nitrogen atom, are the most 'aromatic' among the compared heterocycles and are least inclined to interact with nucleophiles. In order to facilitate addition of nucleophilic reagents at the C=N bond of the pyridine ring their quaternary salts are usually used.[3,7,13] An analogous method is frequently applied in the case of pyrimidine compounds characterising high reactivity towards nucleophiles. The three nitrogen atoms of 1,3,5-triazines show such high overall electron-accepting action that these molecules are sufficiently activated for reaction with nucleophiles without quaternisation.

The products of cleaving pyridinium salts by nucleophiles are derivatives of glutaconic aldehyde which are used in organic synthesis for cyclisation into derivatives of pyridine and other heterocycles.[13]

Derivatives of glutaconic aldehyde are formed on heating 2-chloropyridines having a nitro group in the 3 or 5 positions with alkali. However these cyclise once more into a pyridine compound but only a 5-nitropyridine derivative.[14]

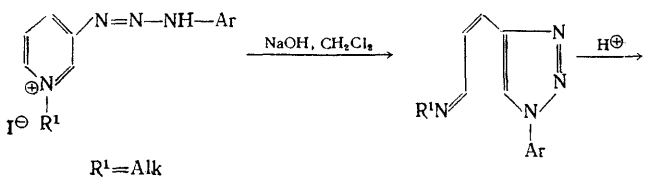


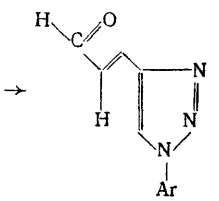
3-Arylhydrazonomethyl-1-methylpyridinium iodides (I) are converted into acroleylpyrazoles in the presence of base. According to the proposed mechanism, under the action of base a negative charge arises on the nitrogen atom of the hydrazone fragment in (I) and this aids intramolecular cyclisation. Rupture of the pyridine ring then occurs and a pyrazole derivative is formed.[15,16]



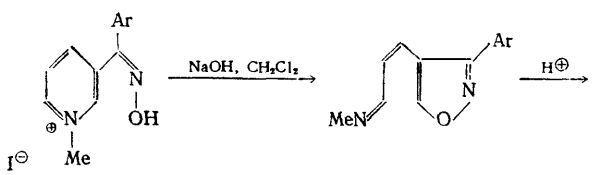
As might have been expected from the conversion scheme electron-donating substituents R^1 in (I) reduce the yield of pyrazole derivative. A substituent R^2 in (I) also shows a negative effect on the course of the reaction due to steric hindrance when forming the intermediate bicyclic compound.

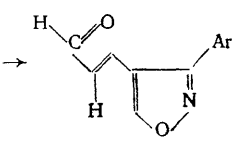
If the $R^1-C=$ fragment in the pyridine salt (I) is replaced by nitrogen then the 3-(3′-aryl-1′-triazenyl)-1-methylpyridinium salt is converted under the above conditions by an analogous scheme into a 1,2,3-triazole derivative.[16,17]



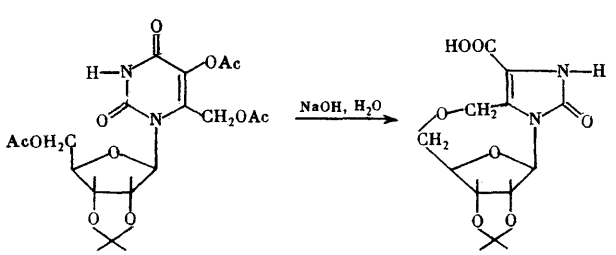


Derivatives of isoxazole are formed by a similar reaction from oximes of 3-benzoyl-1-methylpyridinium iodides in 10% yield.[16,17]





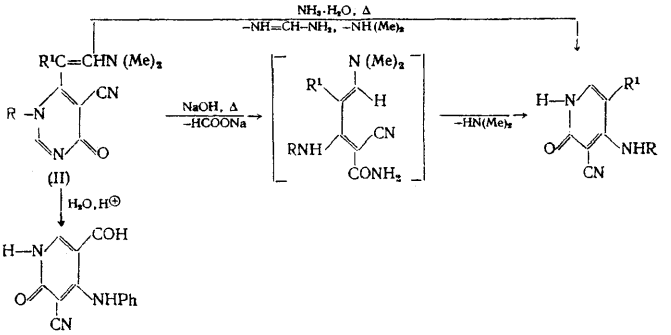
Uracil compounds are converted by alkali into imidazolones which are used in nucleic acid chemistry.[18]



Similar conversions of the pyrimidine nucleus into imidazolones occur in aqueous solutions of amines or alkali and also in the case of pyrimido[4,5*e*]1,2,4-triazines.[19,20]

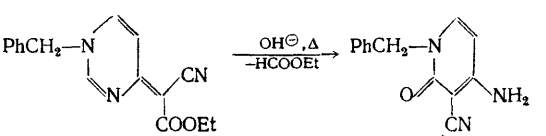
1,6-Disubstituted 5-cyano-4-oxo-1,4-dihydropyrimidines (II) are decomposed on boiling in dilute alkali with fission of the C(2)—N(1) and C(2)—N(3) bonds with separation of formic acid salts. Cyclisation of the resulting intermediate occurs through the dimethylaminovinyl fragment with cleavage of dimethylamine.[21–24] A similar conversion of (II) (R = $PhCH_2$, R^1 = H) occurs on boiling with aqueous ammonia with cleavage of formamidine.[25]

In the case of hydrolysis of (II) (R = Ph, R^1 = H) with acid the recyclisation product was 3-cyano-5-formyl-2-oxo-4-phenylamino-1,2-dihydropyridine.[26]

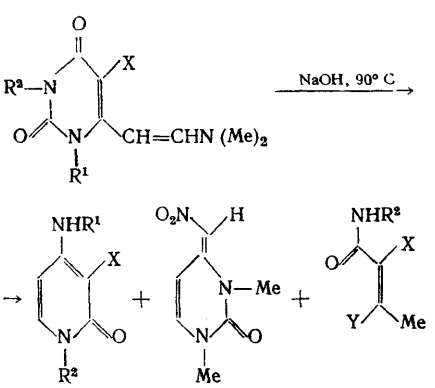


R^1, R = $-(CH_2)_n-$, n = 2,3; R = $PhCH_2$, Ar, cyclohexyl, R^1 = H.

Alkaline hydrolysis of 1-benzyl-4-(ethoxycarbonylcyanomethylene)-1,4-dihydropyrimidine also led to a 2-pyridone derivative.[27]

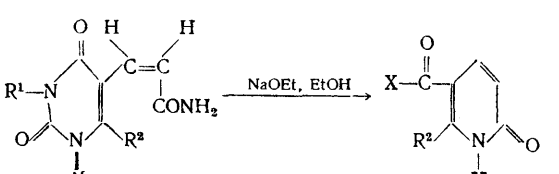


6-Dimethylaminovinylated derivatives of uracil are converted on heating in alkali into 2-pyridone derivatives with the formation of pyrimidines and acyclic compounds as side products.[28,29]



X=NO_2, CN; Y=R^1NH, OH;
R^1=Me, Ph, $PhCH_2$; R^2=Me, $C_6H_{11}Ar$

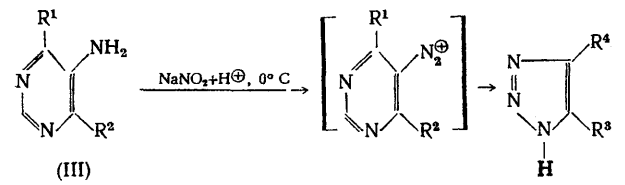
5-(2′-Carbamoylvinyl)uracils with sodium ethoxide in ethanol form 5-carbamoylpyrid-2-ones the ratio of which depends on the amount of water added to the reaction mixture.[30]



R^1R^2=H, Alk; X=R^1NH, OEt.

Unsubstituted pyrimidine is converted into 5-ethyl-2-methylpyridine on heating with aqueous methylamine in a sealed tube.[31]

4,6-Disubstituted 5-aminopyrimidines containing no labile hydrogen atoms in the 4 and 6 positions form 4,5-disubstituted 1,2,3-triazoles on treatment with nitrous acid.[32–35]

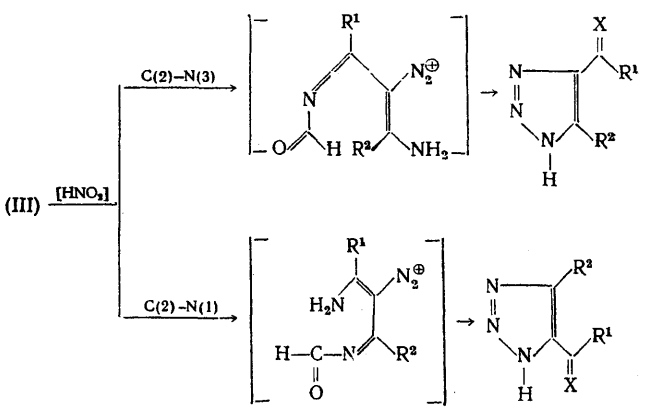


(III)

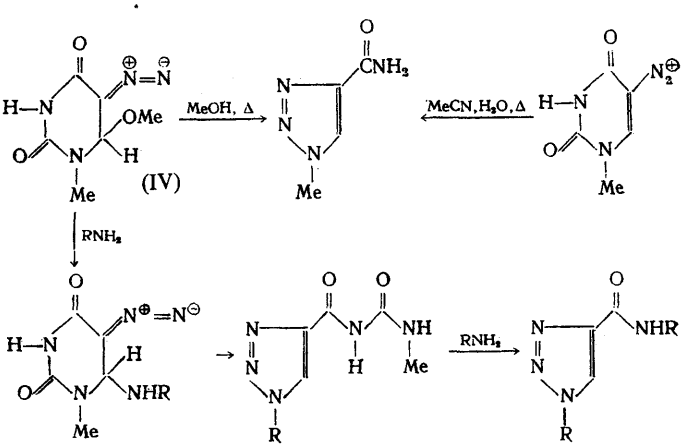
R^1=OMe, $N(Me)_2$, OEt; R^2=SAlk, SAr, SHetar, $N(Me)_2$, Cl, OMe, OEt; R^3=R^2, CN, $C(=Y)R^2$, where Y=NH, O;

R^4=COOMe, COOEt, CN, $C(=O)SR$.

It is presumed that diazonium salts are formed initially which are subjected to covalent hydration at position 2 of the pyrimidine ring. The presence of a methyl group in the second position of (III) had no effect on the course of hydration. Then either the C(2)–N(1) or the C(2)–N(3) bond in the pyrimidine ring may break. The obtained intermediates are cyclised into 1,2,3-triazole derivatives.[32–35]



Diazonium salts of the uracil series are converted on heating in methanol or aqueous acetonitrile by fission of the N(1)–C(2) bond of the pyrimidine nucleus into 4-carbamoyl-1-methyl-1,2,3-triazole.[36,37]

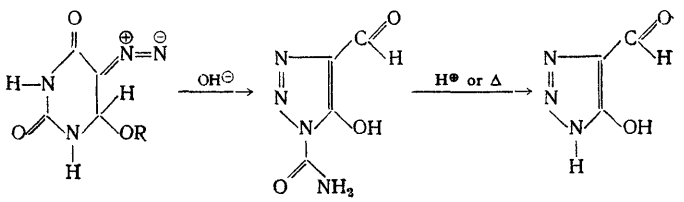


(IV)

R=Alk, $-CH_2CH=CH_2$, $-(CH_2)_3N(Me)_2$.

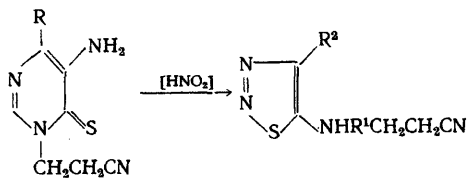
Compound (IV) forms 1,2,3-triazoles by reaction with various primary amines.[38,39] Possibly primary amines initially replace the alkoxy residue of (IV) and then fission of the C(6)–N(1) bond occurs with closing of the five-membered 1,2,3-triazole ring and inclusion in it of the amino group nitrogen. Similar reactions take place for 3-methyl and 1-desmethyl derivatives of (IV).

Alkaline hydrolysis of 5-diazouracils leads to 1,2,3-triazoles in 60–90% yield.[40]



Conversions of 5-diazouracils into compounds of the 1,2,3-triazole series are used in nucleic acid chemistry.[37,41]

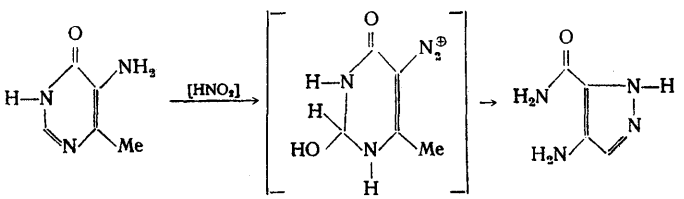
4-Substituted 5-amino-1-(β-cyanoethyl)-1,6-dihydropyrimidine-6-thiones, in contrast to 6-alkylthio derivatives are converted by diazotisation into 5-amino-1,2,3,thiadiazoles.[34,35,42]



R=Cl (a), OMe (b)

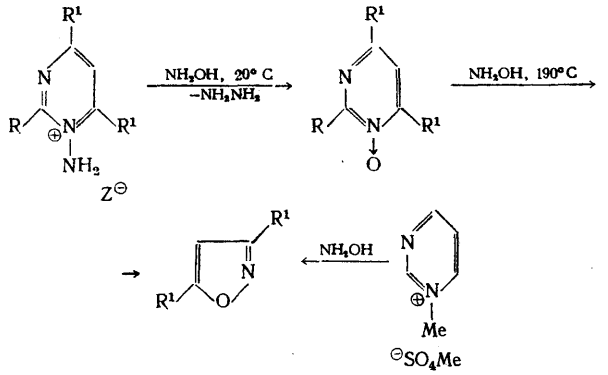
R^1=CN, R^2=CHO (a), R^1=COH, H; R^2=COOMe (b)

In the case of 5-amino-4-methyl-6-oxo-1,6-dihydropyrimidine, the acyclic intermediate formed under conditions of diazotisation is cyclised to a pyrazole derivative owing to the presence of the methyl group.[34,35]

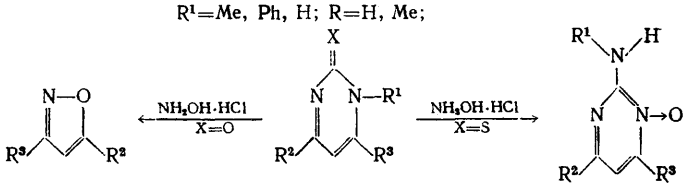


N-Dinitrophenylpyridinium salts give pyridine *N*-oxide on interaction with hydroxylamine through a glutaconic aldehyde derivative.[7,13]

Interaction of pyrimidine compounds with hydroxylamine usually leads to an isoxazole derivative or pyrimidine *N*-oxide.[43–45]

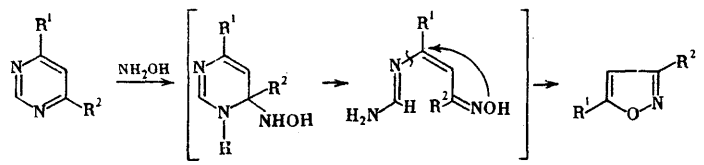


R^1=Me, Ph, H; R=H, Me;

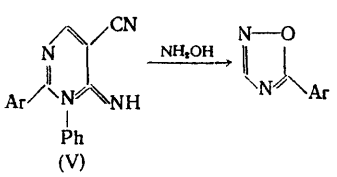


R^1, R^2, R^3=Me, Ph, Ar.

It is assumed that in these reactions hydroxylamine is added at the 1,6-position of the pyrimidine nucleus after which the ring breaks. The intermediate cyclises to an isoxazole compound containing the C(4)–C(5)–C(6) fragment of the initial pyrimidine.[43]

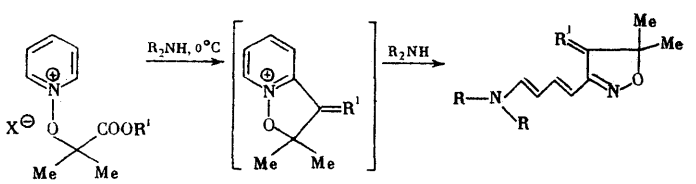


Pyrimidine compound (V) is converted under the action of hydroxylamine into a 1,2,4-oxadiazole derivative.[10,46]



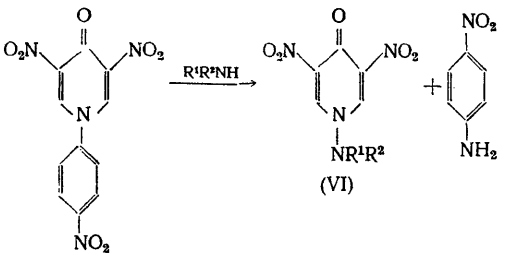
(V)

Alkoxypyridinium salts are recyclised in methanol with amines into isoxazole derivatives.[47] The isolation of the bicyclic intermediate from the reaction mixture confirmed the proposed scheme.[47]



R^1 = OEt(a), Ph(b), R^1 = O(a), Ph, OH(b) R^1 = O(a), Ph, OH(b)

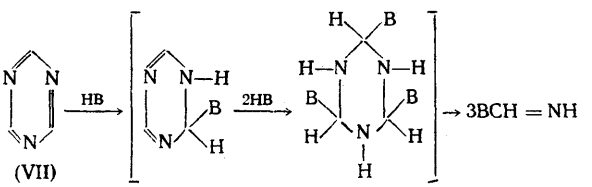
When 3,5-dinitro-1-(4-nitrophenyl)pyrid-4-one reacts with amines recyclisation occurs with the formation of 4-nitroaniline and the corresponding 1-amino substituted pyridone (VI).[48] This reaction (55–100% yield) is used for replacing amino groups in amino acids. The free amino acid is obtained by reacting (VI) with stronger bases. Racemisation of the amino acid was not observed.[49]



(VI)

R^1, R^2 = $-(CH_2)_5-$; R^1 = H, R^2 = Alk, amino acid.

In contrast to pyridines and pyrimidines unsubstituted 1,3,5-triazine (VII) is able to add up to three molecules of nucleophile with the formation of an adduct which is decomposed into three molecules of amine by the following scheme.[50]

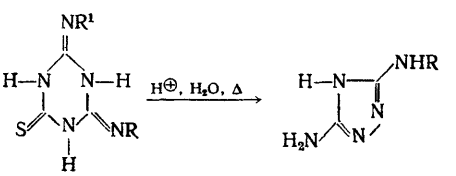


(VII)

HB – nucleophile

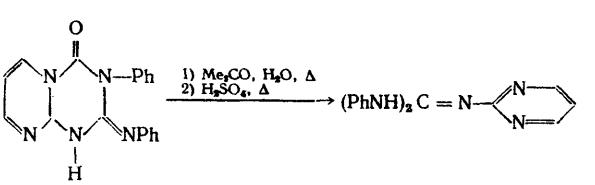
The ability of (VII) to be decomposed into three fragments by the action of nucleophiles is used in various syntheses for introducing a methylenimine group.[51–56]

Unsymmetrically substituted 1,3,5-triazines may be recyclised in a more complex manner under the action of nucleophilic reagents.[57]



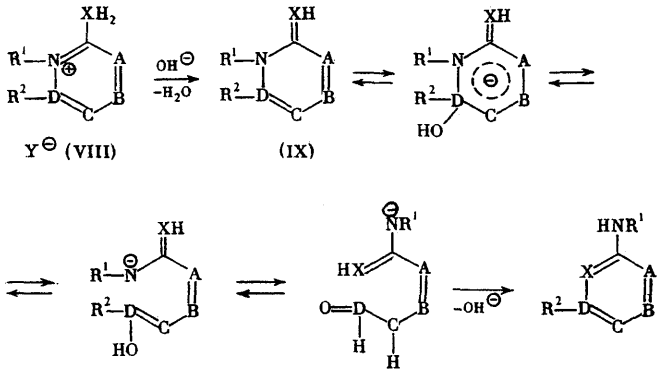
R = H, Ph; R^1 = H, NH.

Condensed pyrimido[1.2a]1,3,5-triazines are split in a stepwise manner. Initially the pyrimidine ring is cleaved on boiling in aqueous acetone and a 2-acroleylamino-1,3,5-triazine derivative is obtained. Boiling in sulphuric acid causes opening of the 1,3,5-triazine ring and splitting away of the acroleylamino residue. Subsequent cyclisation leads to a pyrimidine derivative.[58]



III. The Dimroth and Kost–Sagitullin reactions

Rearrangements are often observed in the reaction of nucleophiles with electron-deficient nitrogen-containing rings. A general mechanism for this is given in the scheme.[59,60]



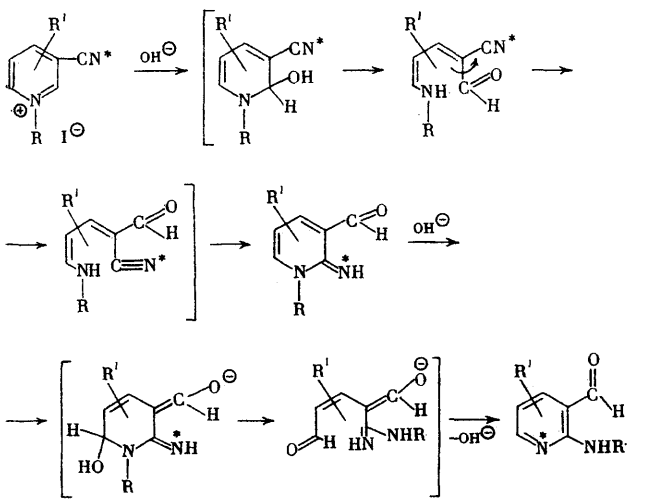
$Y^{\ominus}$ (VIII) (IX)

X, A, B, C, D = N or CH.

A quaternary salt of the heterocycle (VIII), its anhydro base or imino form (IX) adds nucleophile (hydroxyl ion, amine or hydroxylamine) and is converted into a new heterocyclic system. If a new C–N bond is formed as a result of recyclisation the reaction is called a Dimroth rearrangement.[61] If a new C–C bond is formed on recyclisation and the obtained heterocycle contains one atom of nitrogen less than the initial (VIII) such a rearrangement is called a Kost–Sagitullin rearrangement.[8,60] The presence of labile exocyclic α-atoms of hydrogen is one of the conditions for these reactions.[59]

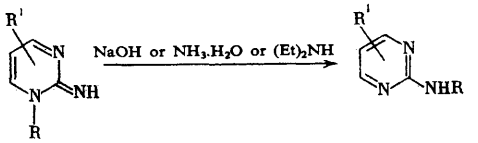
The Kost–Sagitullin rearrangement is characteristic of pyridinium and pyrimidinium salts[9] and the Dimroth reaction is a feature of pyrimidines and 1,3,5-triazines[61] but is rarely met in pyridines.[62]

1-Alkyl-3-cyanopyridinium iodides are converted in alkaline solution first into derivatives of 1-alkyl-2-aminopyridine which are recyclised once more into 2-alkylaminopyridines. To detect the indicated conversions it was helpful to introduce ^{15}N into the cyano group of the initial pyridine and study the subsequent behaviour of the label.[62]



R = Me, R^1 = H(a); R = Et, R^1 = 5-Me(b); N* – ^{15}N-labelled atom.

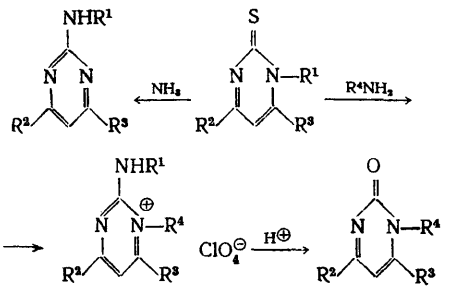
The Dimroth rearrangement for pyrimidines usually takes place in protic solvents in the presence of base. 1-Substituted 2-amino-1,2-dihydropyrimidines take part in it particularly readily[61] and are converted into 2-alkylaminopyrimidines.



R = Alk, CH_2COOEt; R^1 = Alk, Hal, NO_2, $N(Et)_2$.

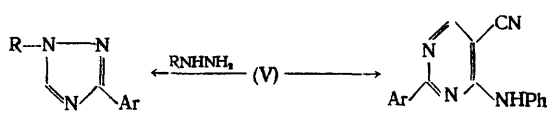
The reaction does not take place in aprotic solvents, a change of protic solvent may influence the course of the rearrangement.

1,4,6-Trisubstituted 2(1H)-pyrimidinethiones react with ammonia in a sealed tube by a type of Dimroth rearrangement. The presence of perchlorate anion is necessary for the analogous rearrangement with primary amines. The resulting salts are readily hydrolysed by acid to 2-pyridones.[63]



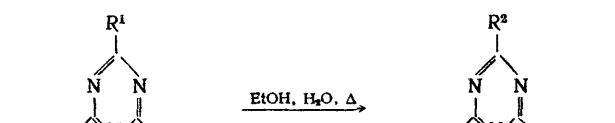
R^1, R^3 = Me, Ar, Ph; R^2 = Me; R^4 = Alk.

Reaction of pyrimidines (V) with guanidine, ethylenediamine or thiosemicarbazide gives 2-aryl-5-cyano-4-phenylaminopyrimidines, the products of Dimroth rearrangement.[10,46] When a bulky substituent is present in the nucleophile recyclisation leads to a 1,2,4-triazole derivative.[10,46]



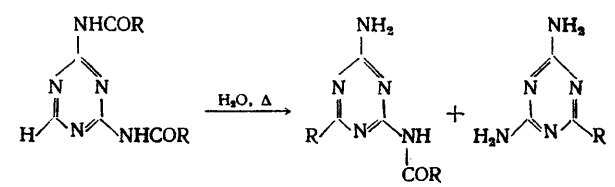
R = Ar, Ph, H

2,4-Diacylamino-1,3,5-triazines undergo a Dimroth rearrangement on heating in aqueous alcoholic solution.[64,65]



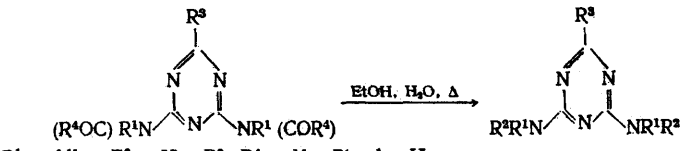
R^1 = H, Me; R^2 = Ph, Ar.

Two products are formed in the case of aliphatic *N*-acyl residues[66] and the processes proceed more rapidly than for the corresponding aromatic acyl derivatives.



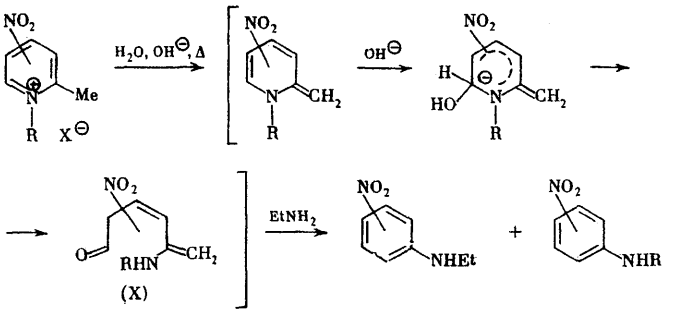
R = Alk

2,4-Di-(*N*-alkyl, *N*-acylamino-1,3,5-triazines undergo a double Dimroth rearrangement on boiling in aqueous alcohol.[67] The reaction proceeds twenty times more slowly with *N*-alkylated *N*-acylaminotriazines than with *N*-unalkylated compounds.



R^1 = Alk; R^2 = H; R^3, R^4 = Me, Ph, Ar, H.

The simplest example of a Kost–Sagitullin rearrangement is the recyclisation of pyridines[68] and their quaternary derivatives[69–74] on heating in aqueous solutions of ammonium salts and alkali to give substituted alkylanilines.



Recyclisation is assisted by electron-accepting substituents in positions 3 and 5 of the pyridine ring,[69–72] by the presence in the α-position to nitrogen of groups capable of deprotonation with the formation of anhydro bases and by the presence of amine as cyclising agent in the reaction mixture.

If the substituents in the amine and at nitrogen of the pyridinium ring are different then transamination at the stage of the acyclic intermediate (X) and the formation of several recyclisation products is possible.

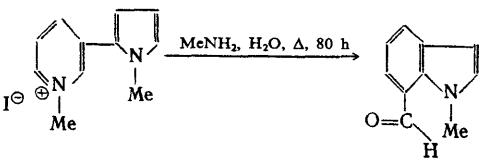
The presence of groups with labile hydrogen atoms at positions 2 and 6 of the pyridine leads to the formation of two anhydro bases (XI) and (XII) and as a result two isomeric anilines (XIII) and (XIV) are generated in the presence of methylamine.[70,72,73]

The ratio of (XIII) and (XIV) is determined by the degree of preference of attack of hydroxyl ion on the initial pyridine at the position *para* to the nitro group compared to the formation of *ortho* isomer (XII). However transamination of the acyclic intermediate (XI) is hindered. Consequently *para* isomer (XIV) predominates in the transamination products (except when R = Me).[75]

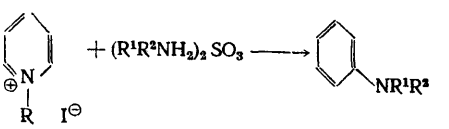
When the chain length of the *N*-alkyl substituent in the pyridinium salts reaches C_{12}, in the author's opinion, micelle formation takes place in the aqueous solution in which the pyridine bases are disposed on the micelle surface.[76,77] As a result the approach of water molecules to the recyclisable product and ring opening are facilitated and the approach of amine is hindered and transamination practically does not occur.

The Kost–Sagitullin rearrangement is also used for introducing an aromatic residue into other heterocycles[78–81] and the preparation of aromatic amines.[8,82–88]

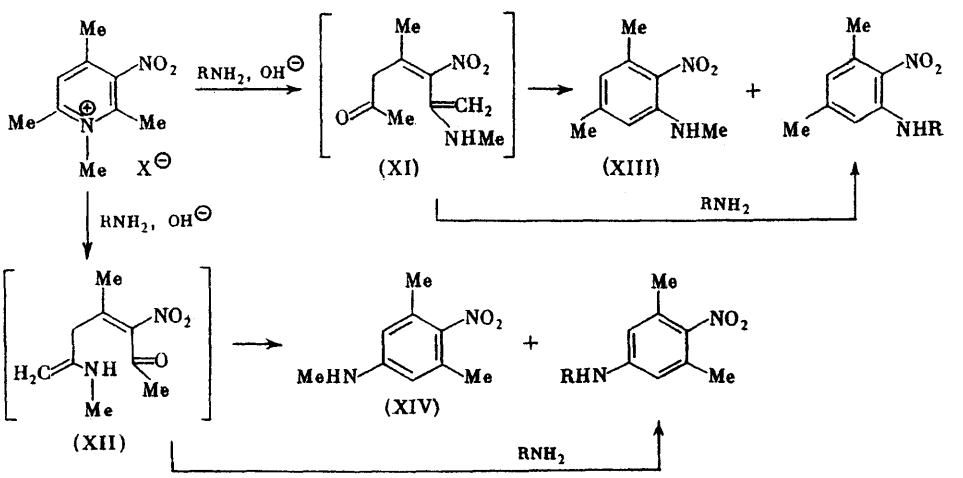
Thus heating nicotine methiodide at 150 °C with methylamine leads to recyclisation to 7-formyl-1-methylindole.[79]



Alkylpyridinium salts form arylamines under the conditions of the Kost–Sagitullin reaction.[82]

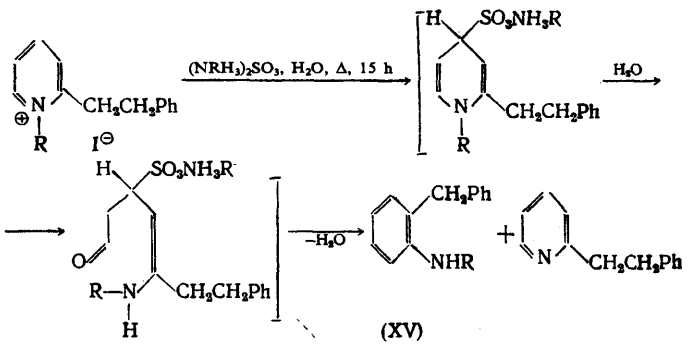


R, R^1, R^2 = Alk.

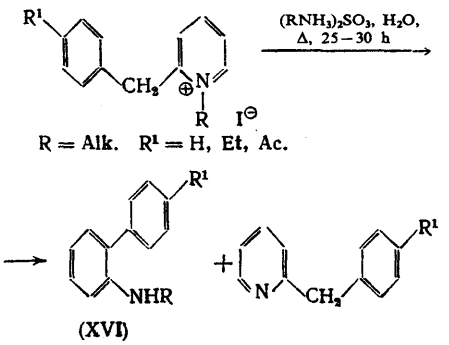


R = Alk

Similarly 2-(2-phenylethyl)pyridinium salts form *ortho*-alkylaminodiphenylmethanes (XV).[83,84]



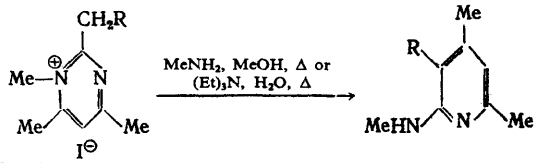
Benzylpyridinium salts form 2-aminobiphenyls (XVI).[85,86]



N-Dealkylation products are formed in these reactions together with (XV) and (XVI).[83–86]

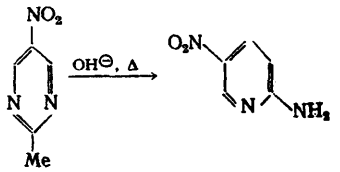
Transamination may occur at the ring opening stage if the R substituent in the pyridinium salt and in the alkylamine sulphite are different. Yields of biphenyl recyclisation products (XVI) are reduced with increasing volume of the *N*-alkyl group, or with the introduction of substituents into the α and β positions of the pyridine nucleus which hinders the addition of sulphite anion, or by introducing electron-donating residues into the phenyl nucleus impeding intramolecular cyclisation of intermediates.

Pyrimidinium salts readily add nucleophiles under conditions of the Kost–Sagitullin reaction and are converted into α-aminopyridine derivatives.[89]

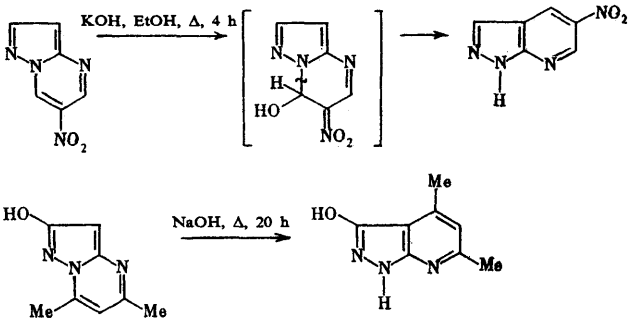


R = Ph, COOEt

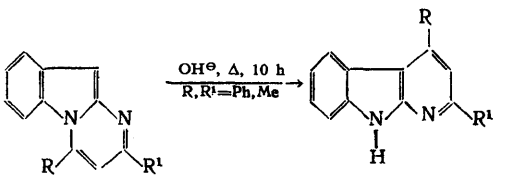
A nitro group in the pyrimidine ring facilitates these reactions and recyclisation of 2-methyl-4-nitropyrimidine is possible without obtaining the quaternary salt.[90]



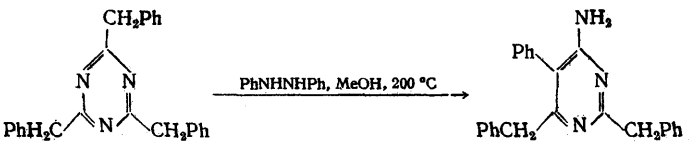
Condensed systems such as pyrazolo[1,2a]pyrimidines are recyclised into pyrazolo[3,4b]pyridines on heating with alkali. The presence of a nitro group in the starting material facilitates the reaction.[91]



Pyrimido[1,2a]indoles are converted into α-carbolines on boiling in alkali.[92]

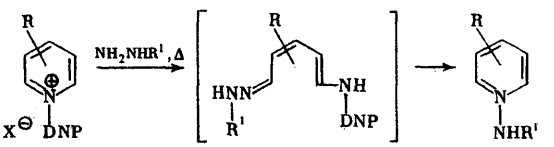


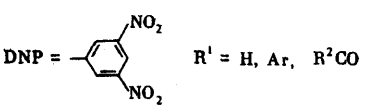
The Kost–Sagitullin rearrangement recalls the conversion of 2,4,6-tribenzyl-1,3,5-triazine into a pyrimidine derivative on heating with hydrazobenzene in methanol.[93]



IV. Recyclisations during hydrazinolysis

The interaction of pyridines, activated by donating-accepting substituents or transformed into quaternary salts, with hydrazine[7,13] proceeds with recyclisation of the pyridinium ring into an *N*-aminopyridinium ring.



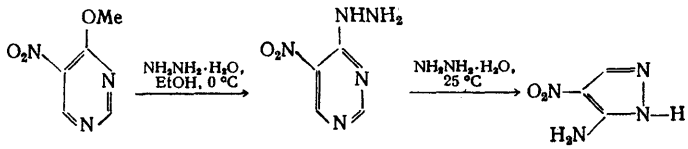


Many studies have been devoted to the hydrazinolysis of pyrimidine derivatives[35,90,94–104] mainly to pyrazoles[90,94–104] and to 1,2,4-triazoles.[35,95,102]

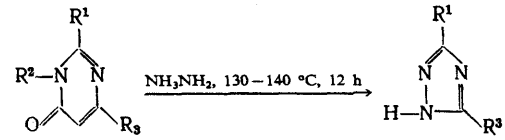
If there are substituents in the pyrimidine ring capable of interacting with hydrazine then at low temperature (<0 °C) hydrazinopyrimidines are formed.[94,96,99,101] and on increasing the temperature (occasionally to room)[99] and using an excess of

hydrazine, addition of one further molecule of hydrazine to the pyrimidine[96,99,101] and recyclisation were observed.

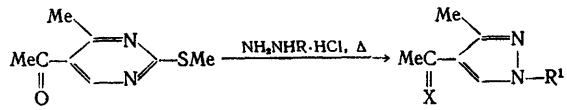
4-Methoxy-5-nitropyrimidine forms 4-hydrazino-5-nitropyrimidine with hydrazine hydrate in alcohol at 0 °C, which at room temperature and with an excess of hydrazine is converted into 3-amino-4-nitropyrazole.[96]



Analogous reactions proceed above 100 °C in the absence of the nitro group.[102]



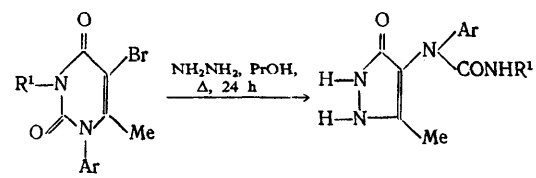
Heating 5-acetyl-4-methyl-2-methylthiopyrimidine with hydrazine hydrochlorides leads to pyrazole derivatives.[101]



R = H, Me, Ph, , $CONH_2$, $CSNH_2$;

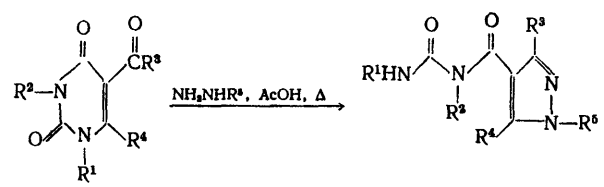
X = O, NH_2; R^1 = R, H

On heating 1,3-disubstituted 1-aryl-5-bromo-6-methyluracils with hydrazine in isopropanol they recyclise into 4-substituted 3-pyrazolones.[97,98]



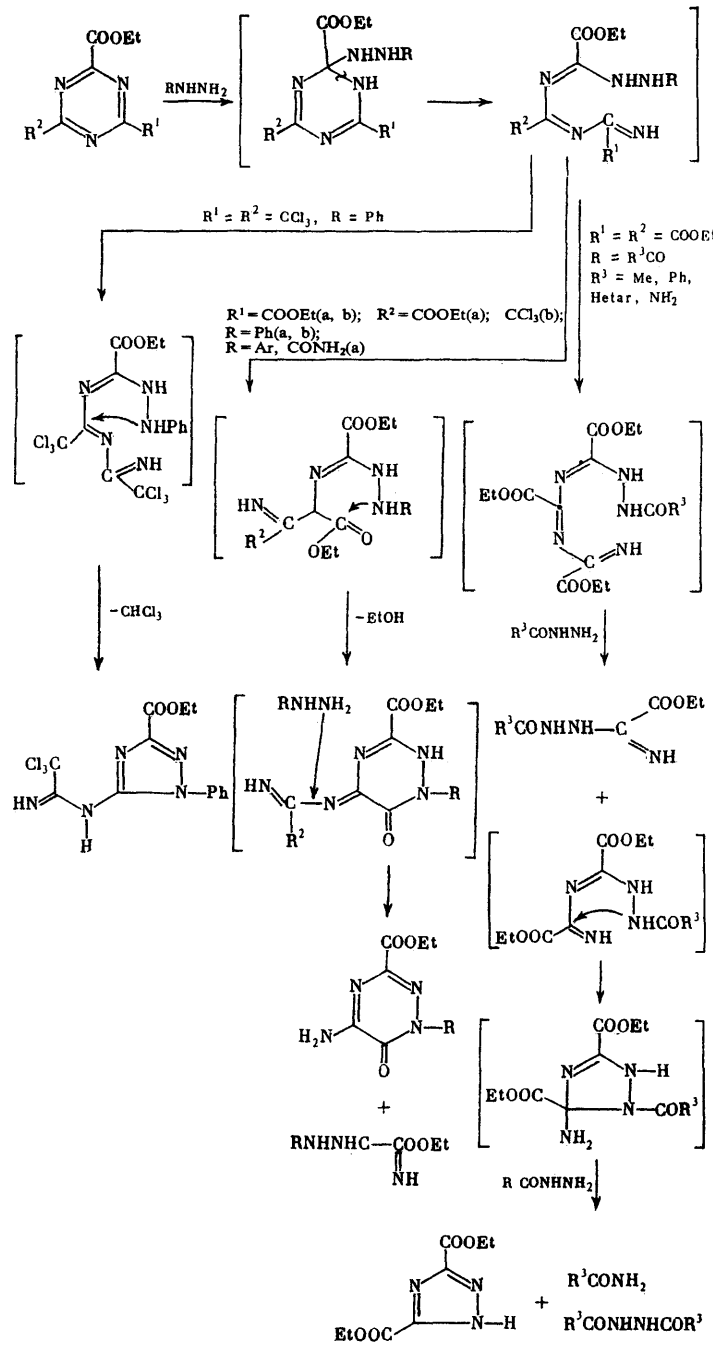
R^1 = Alk, $-CH_2-CH=CH_2$.

Hydrazinolysis of uracil derivatives in acetic acid also leads to pyrazoles.[99,100]



R^1, R^4 = H, Me, Et; R^2, R^3, R^5 = H, Me.

By reaction with aryl-, acylhydrazines, semicarbazide or thiosemicarbazide 2,4,6-triethoxycarbonyl-1,3,5-triazines are converted into derivatives of 1,2,4-triazine or 1,2,4-triazole depending on the nucleophilicity of the hydrazine derivative nitrogen atoms. Acyclic products were also isolated from the reaction mixture the formation of which is in agreement with the proposed scheme.[105–109] The conversion of 1,3,5-triazines containing both trichloromethyl and ethoxycarbonyl groups goes by a similar scheme under the action of phenylhydrazine.[109] On reducing the nucleophilicity of the hydrazine (isoniazide) the reactions with 1,3,5-triazines containing ethoxycarbonyl and trichloromethyl groups did not go.



V. Reactions with alkali metal amides in liquid ammonia

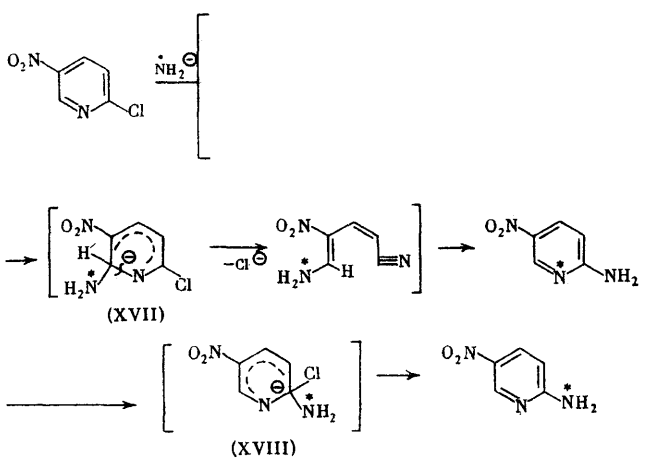
The reaction of nitrogen-containing heterocycles with potassium amide in liquid ammonia has been studied principally by van der Plas.[110,111,113,115–131] Depending on the structure of the

starting material and the concentration of potassium amide conversions may proceed both by an S_N(AE) and by an S_N(ANRORC) mechanism.

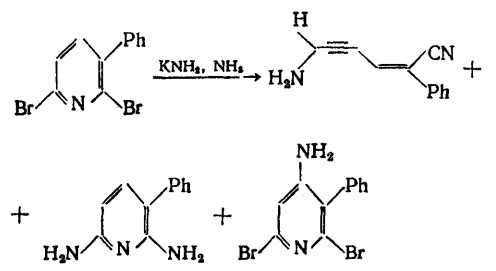
If the reaction is accompanied by recyclisation then the product may be both the initial ('degenerate recyclisation')[6] and a transformed heterocycle. Degenerate recyclisations were detected with an ^{15}N label in the potassium amide or in the heterocycle.[104,115–119,126,131]

The reaction of pyridine with potassium amide in liquid ammonia may proceed by an S_N(AE) mechanism (Chichibabin amination)[132] or with recyclisation of the pyridine nucleus.[110–115] In both cases the process starts with the formation of a σ complex of pyridine with amide anion. Electron-accepting substituents in the pyridine molecule facilitate the formation of a σ complex, opening of the ring and subsequent recyclisation.

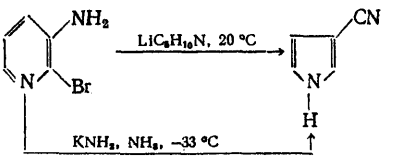
2-Chloro-5-nitropyridine forms two σ complexes (XVII) and (XVIII) with amide anion, the nitro group in the *ortho* position enables breaking of the C(2)–N(1) bond and the resulting intermediate is cyclised to 2-amino-5-nitropyridine. The second σ complex (XVIII) splits off chloride anion and is also converted into 2-amino-5-nitropyridine.[110] To discriminate between the resulting pyridines was possible with the aid of potassium amide labelled with ^{15}N. Steric hindrance occurred in the formation of σ complex (XVIII) consequently 75% σ complex (XVII) was formed.



It was possible to form three products under the same conditions from 2,6-dibromo-3-phenylpyridine, viz. an acyclic compound, 2,6-diamino-3-phenylpyridine [(S_N(ANRORC) mechanism] and 4-amino-2,6-dibromo-3-phenylpyridine [S_N(AE) mechanism].[111]

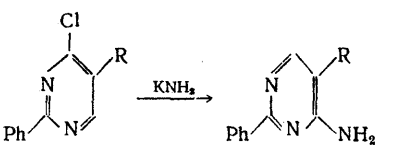


3-Amino-2-bromopyridine is converted into 3-cyanopyrrole with potassium amide in liquid ammonia at −33 °C or with lithium piperidinide at 20 °C.[114]



In pyrimidines as in pyridines the interaction with potassium amide in liquid ammonia may occur with a 'degenerate recyclisation'.[115–127] The course of the reaction is principally determined by the structure of the initial pyrimidine.

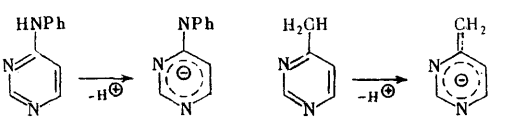
5-Substituted 4-chloro-2-phenylpyrimidines form σ complexes with amide anion at positions 4 and 6, position 2 is sterically hindered. On breaking the pyrimidine ring bonds C(4)–C(5) and C(5)–C(6) respectively were severed.[120]



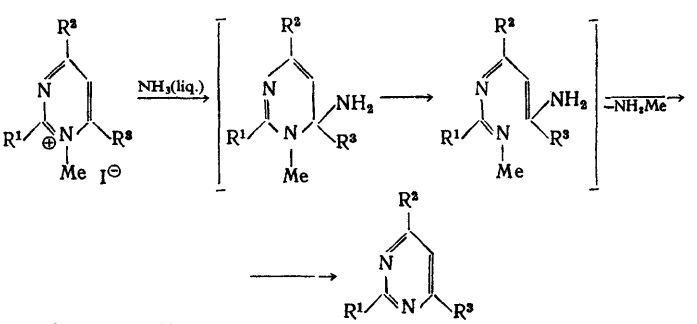
R = OMe, SMe, Ph, OEt.

In order that the interaction of pyrimidines with amide anion should go by an S_N(ANRORC) mechanism it is necessary to observe the following conditions.[120–123] There must be the possibility of forming a σ complex able to open the pyrimidine ring. With unsubstituted pyrimidines a σ complex is formed at position 2. In substituted pyrimidines several σ complexes may be formed.[120,122,123] For 2-fluoro substituted pyrimidimes the splitting away of fluoride ion occurs after the formation of σ complex with amide anion at position 2 and the reaction goes by the S_N(AE) mechanism.[123]

Substituents at positions 4 and 6 of the pyrimidine nucleus must not have an acidic proton capable of forming stable anions of type (XIX) and (XX) hindering attack of the nucleophile.[121]



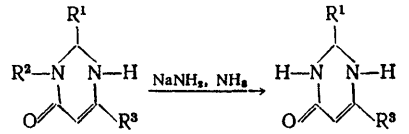
Dealkylation of *N*-alkylpyrimidinium salts in liquid ammonia may occur at an S_N(ANRORC) mechanism.[79,124]



R¹, R², R³ = H, Me.

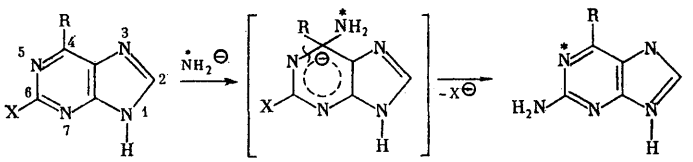
6-Ethoxy-1,3-diethyl-4-oxo-3,4-dihydropyrimidinium tetrafluoroborate is dealkylated in liquid ammonia to 3-ethyl-6-ethylamino-4-oxo-3,4-dihydropyrimidine.[125]

The interaction of 4,6-disubstituted 3-alkyl-2-pyrimidones with sodium amide in liquid ammonia also leads to dealkylation at nitrogen.[102]



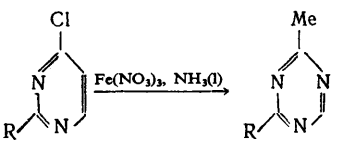
R^1 = iso-Pr, Ph; R^2 = H, Me, Et; R^3 = Me, Et.

The reaction of 2-substituted purines with potassium or sodium amides in liquid ammonia is accompanied by the formation of a complex at position 6 with subsequent conversion of the pyrimidine nucleus.[126,127] If position 6 in the purine is occupied by a methyl group amination goes by an S_N(AE) mechanism.



X = Hal, SMe; R = H, Me.

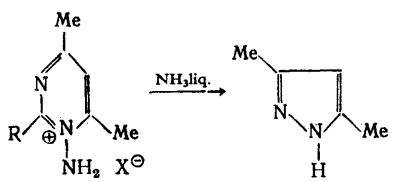
!,3,5-Triazines[128] and five-membered nitrogen-containing rings[129] may be obtained by the recyclisation of pyrimidines in liquid ammonia.



R = Alk; Ph, N(Me)$_2$

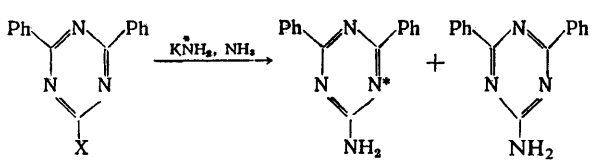
It was established by ^{14}C labelling that the C(5)–C(6) bond in the pyrimidine ring was severed.[128]

N-Aminopyrimidinium salts were converted into liquid ammonia into 3,5-disubstituted pyrazole.[129]



R = H, Me.

The interaction of substituted 1,3,5-triazines with potassium amide in liquid ammonia may be accompanied by a 'degenerate recyclisation'. Whether the amination reaction has an S_N(ANRORC) or S_N(AE) mechanism depends on the potassium amide concentration and the nature of the leaving group.[130,131]



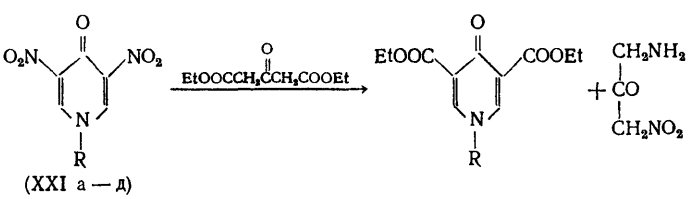
X = H, Cl, SMe.

VI. Conversions with CH-acids and ambident nucleophiles

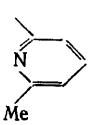
It was considered previously that the general mechanism for the reaction of nitrogen-containing π-deficient heterocycles with anions of CH-acids or ambident nucleophiles consisted of addition of anion to the heterocycle with the formation of a Meisenheimer complex, opening of the heterocycle and closure of a new ring with replacement of a portion of the ring atoms by a residue of the ambident nucleophile or CH-acids [S_N(ANRORC) mechanism]. The formation of a Meisenheimer complex is facilitated if the heterocycle is activated by an electron-accepting substituent.

Recent work has shown that the formation of bridge structures is occasionally possible for ambident nucleophiles on reaction with a heterocycle. In some cases these structures have been successfully established.[11,134,135,151,159,161,169] To establish non-cyclic intermediates and σ adducts is more difficult since they are unstable and their further conversion by ring opening and rapid recyclisation are thermodynamically favourable.

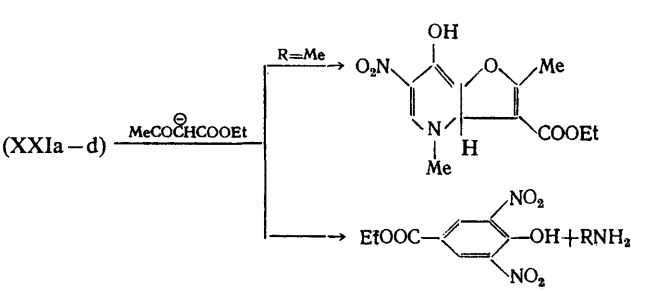
1-Substituted 3,5-dinitro-4-oxo-1,4-dihydropyridines (XXIa–e) with acetonedicarboxylic acid diethyl ester form 1-substituted 3,5-diethoxycarbonyl-4-oxo-1,4-dihydropyridines (58–85% yield) and 3-amino-1-nitropropan-2-one.[133,134]



(XXI а — д)

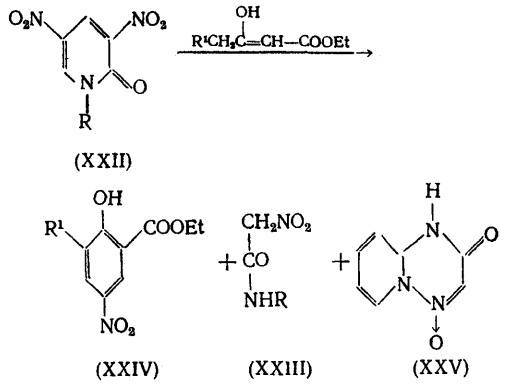
R = Me (a), 3-Py (b), 4-Py (c),  (d), H (e).

The interaction of (XXIa–d) with the sodium derivative of acetoacetic acid ester in alcohol depends on substituent R at the nitrogen atom in (XXIa–d). The reaction product is a furano-[2,3b]pyridine for the electron-donating R = Me (XXIa). In the case of electron-accepting substituents (XXIb–d) the reaction product was 4-hydroxy-3,5-dinitrobenzoic acid ethyl ester.[134]



The interaction of 1-substituted 3,5-dinitro-2-oxopyridines (XXII) with the sodium derivative of acetoacetic ester (R^1 = H) or acetonedicarboxylic acid ethyl ester (R^1 = COOEt) depending on the character of the substituents R and R_1 leads to *N*-substituted

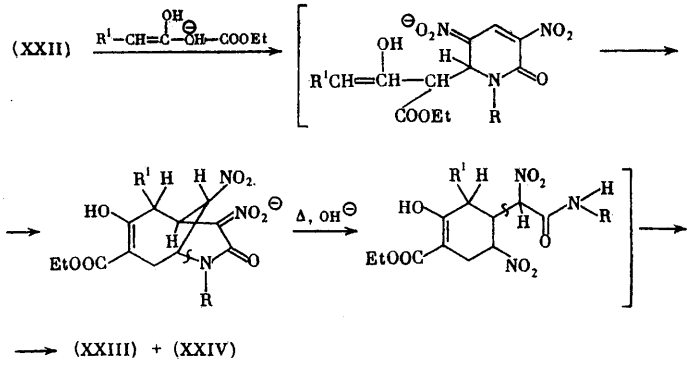
α-nitroacetamide (XXIII), a derivative of 5-nitrobenzoic acid ethyl ester (XXIV) and bicyclic derivatives (XXV).[133–137]



(XXII) (XXIV) (XXIII) (XXV)

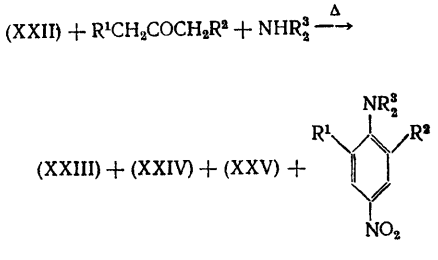
R = Me, CH_2Ar, CH_2Hetar, H, OMe, 2-Py; R^1 = H, COOEt.

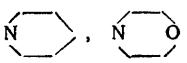
Conversion of pyrid-2-ones (XXII) to *para*-nitrophenols (XXIV) may go through an anionic σ adduct and then through a bicyclic derivative according to the scheme.[134–137]



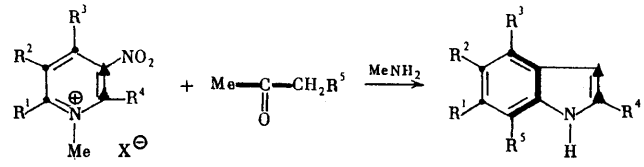
(XXII) → (XXIII) + (XXIV)

On reacting pyrid-2-one (XXII) with ketones in the presence of amines condensation of amine with ketone and further reaction of the resulting activated enamine with pyridone (XXII) may occur. Consequently *N*-substituted *para*-nitroaniline is present in the reaction products in addition to *para*-nitrophenol (XXIV).[137]

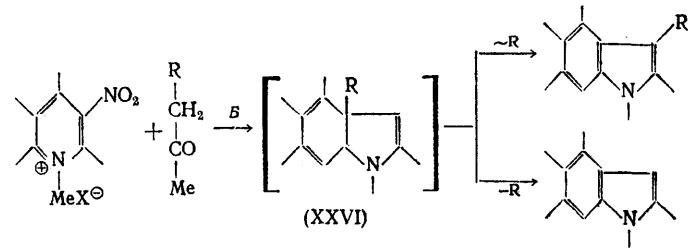


R^1, R^2 = H, Me, COOEt; NR^3_2 = 

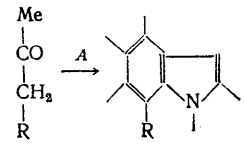
It was discovered recently tht 3-nitropyridinium salts are converted into indole derivatives on reaction with ketones in the presence of amines.[138,139] A specially developed spectroscopic procedure made it possible to establish the structure of the products formed and to suggest structural rules for the construction of the indole molecules ('diazine' process).[140]



The reaction seemingly begins with condensation of ketone or ketimine with the pyridinium salt and the formation of a bicyclic derivative in which the C(3)–C(4) and C(6)–N(1) bonds of the pyridinium nucleus are broken. A three carbon fragment of the ketone is introduced between the fragments of the pyridine ring. The proposed scheme was confirmed by the detection by chromatomass spectrometry of the two different directions (A and B) for the process linked with the orientation of the ketone on reaction with the pyridinium salt.[141]



(XXVI)

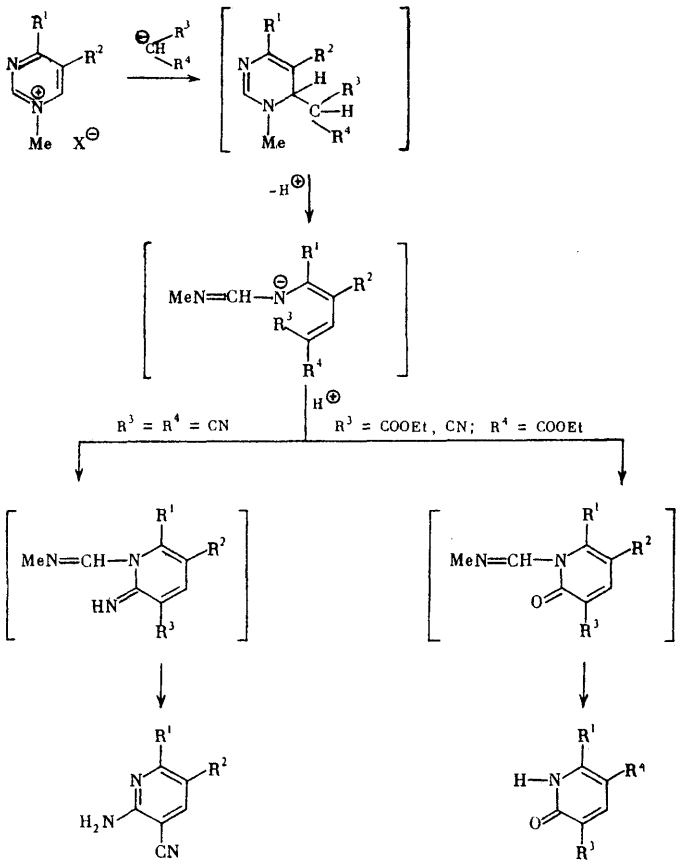


Route A leads to an indole of normal structure. In the case of route B intermediate (XXVI) may be aromatised by migration of R or by its elimination.

The use of prepared ketimines (in place of a mixture of ketone and amine) and polar aprotic solvents in the reaction improves yields (up to 80%) and simplifies the isolation process of the indole.[142,143]

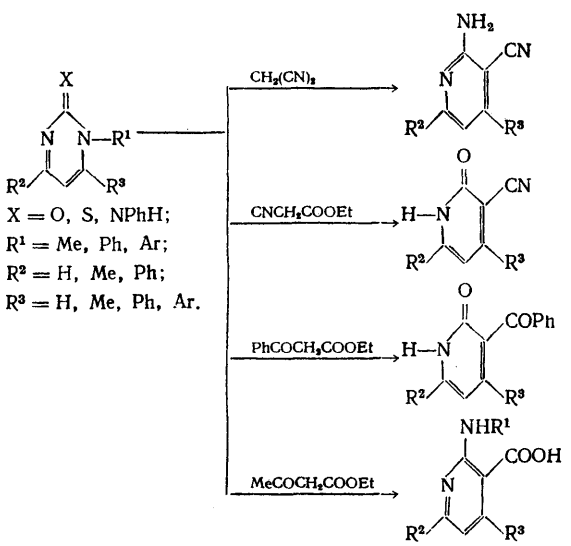
Many recyclisations of the pyrimidine ring on reaction with CH-acids and ambident nucleophiles are known.[144–172] To facilitate these reactions the pyrimidine derivatives are usually converted to quaternary salts,[145] and are then converted into substituted pyridines on reaction with the sodium derivatives of malonic ester, malondinitrile or cyanoacetic ester by replacement of the N(1)–C(2) fragment of the pyrimidinium system by a two-carbon fragment of the CH-acid. In the case of cyanoacetic ester closing of the acyclic intermediate as shown in the scheme goes through the ester and not

through the cyano group.[145]



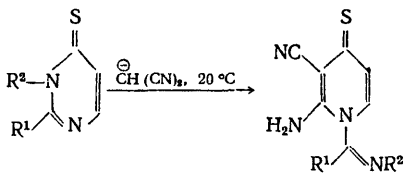
R^1, R^2 = H, Ph

The interaction of 2,4,6-trisubstituted 2,3-dihydropyrimidines with compounds having an active methylene group at room temperature in the presence of sodium ethoxide leads to pyridines.[146] In this the C(6)–N(1) bond in the initial pyrimidine is broken and yields of the pyridine derivative are determined by steric hindrance in the formation of a σ complex with the CH-acid at position 6 of the pyrimidine ring.



X = O, S, NPhH;
R^1 = Me, Ph, Ar;
R^2 = H, Me, Ph;
R^3 = H, Me, Ph, Ar.

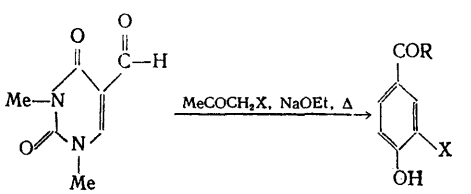
Interaction of 2,3-disubstituted 4-thio-3,4-dihydropyrimidines with malondinitrile in the presence of sodium ethoxide also goes with the formation of pyridine derivatives. Because of steric factors the CH-acid is added at C(4) of the pyrimidine nucleus and the C(4)–N(3) bond of the pyrimidine ring is broken.[147]



Three atoms of the pyrimidine ring may be replaced by three atoms of the nucleophilic reagent.[144,148–153]

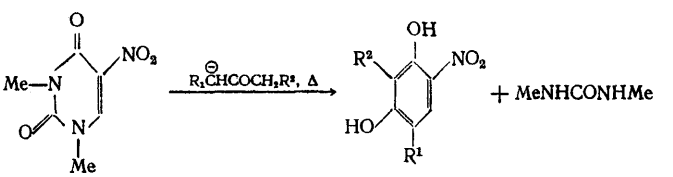
If the N(1)–C(2)–N(3) fragment of the pyrimidine nucleus is replaced by a C–C–C or C–C–N residue from an ambident nucleophile then benzene derivatives are formed in the first case[144,148–152] and pyridine derivatives in the second.[144,148,151,153]

On boiling 5-formyl-1,3-dimethyluracil with CH-acids in alcoholic sodium ethoxide derivatives of *p*-hydroxybenzoic acid are formed.[148,149,152]



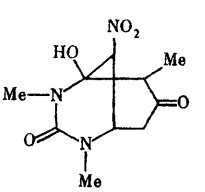
X = COMe, $CONH_2$, Ph, COOEt; R = OEt, NHMe.

1,3-Dimethyl-5-nitrouracil with ketones in boiling alcoholic alkali is recyclised to nitroresorcinol derivatives.[150]



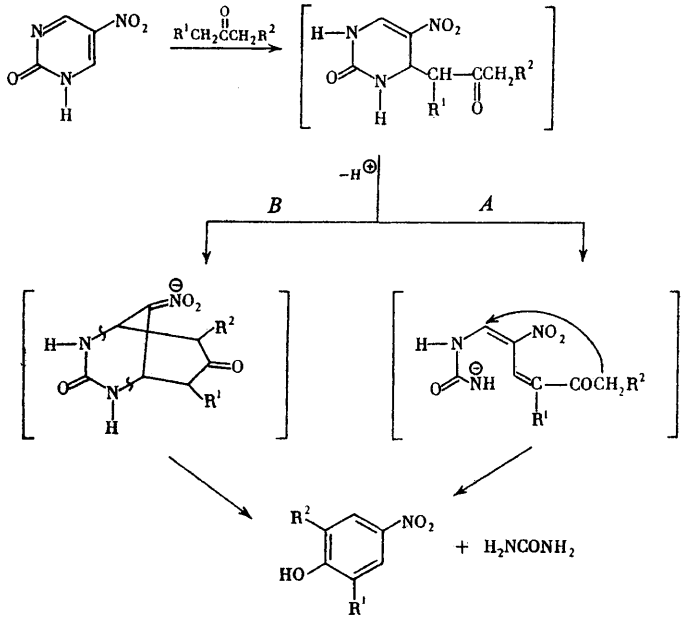
R^1 = COOEt, H, Me; R_2 = H

With unsymmetrically substituted ketones (R_1 = Me, R^2 = H) a mixture of two final products is formed because of the possibility of forming σ complexes at the different CH-groups.[150] A bicyclic product was isolated from the reaction mixture in the case of butanone.

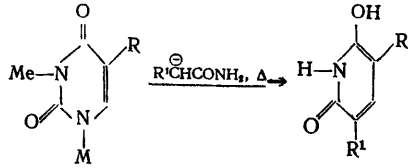


Similar bicyclic structures were successfully established in the reaction of ketones with 5-nitro-2-oxo-1,2-dihydropyrimidines. The final products of this reaction were *para*-nitrophenol derivatives.[151] Conversion of the pyrimidinium nucleus into benzene occurs in two directions, an S_N(ANRORC) (route *A*) and through

the formation of a bicyclic structure with subsequent splitting away of a urea derivative (route *B*).[151]

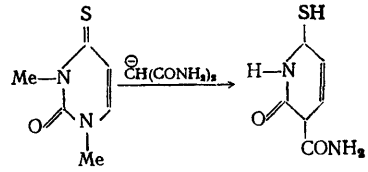


Reaction of 1,3-dimethyluracils with α-substituted acetamides in alcoholic sodium ethoxide leads to pyridine derivatives.[148,149,152,153]

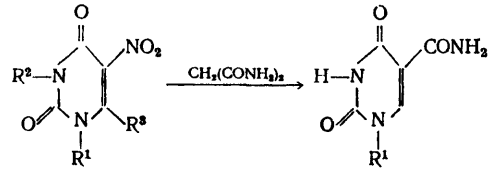


R = H, Me, CN, F, C(=O)H; $R^1 = CONH_2$, **CN**, COMe, Ph.

A 2-hydroxy-6-mercaptonicotinamide is formed from 1,3-dimethyl-6-thiouracil by an analogous reaction.[153]

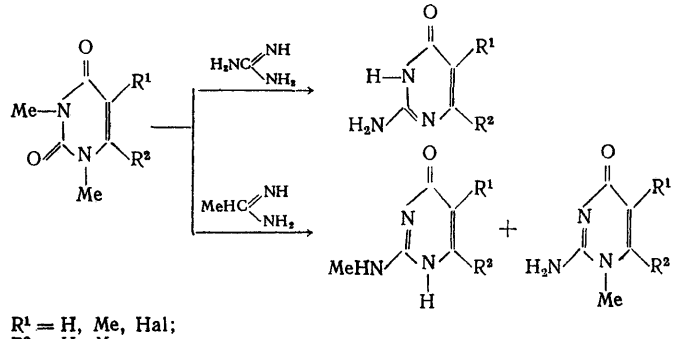


Reaction of 5-nitrouracils with malondiamide in alcoholic sodium ethoxide leads to 5-carboxamidouracils.[154,155] In this case the C–C–N residue of the nucleophile replaces C(5)–C(4)–N(3) of the pyrimidine ring. The reaction does not take place when the substituents at the uracil nitrogen atoms $R^1 = R^2 = H$ since the anionic form of the initial uracil is not able to add nucleophile.

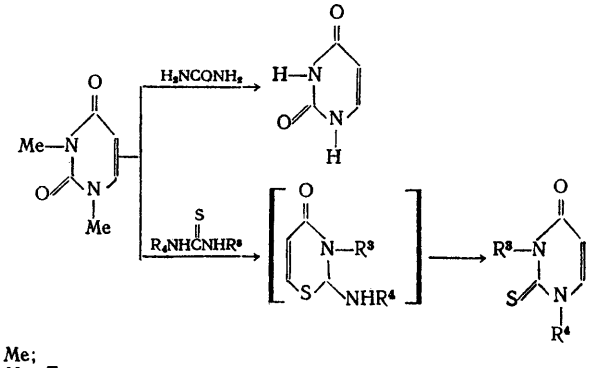


R^1, R^3 = H, Me, C_6H_{11}; R^3 = H, Me.

A 'degenerate recyclisation' occurs when the N(1)–C(2)–N(3) fragment of the pyrimidine is replaced by the N–C–N fragment of the nucleophile. Derivatives of guanidine, urea and thiourea are used as nucleophiles. Similar conversions of pyrimidine bases are used in nucleic acid chemistry.[144,148,149,156,157]



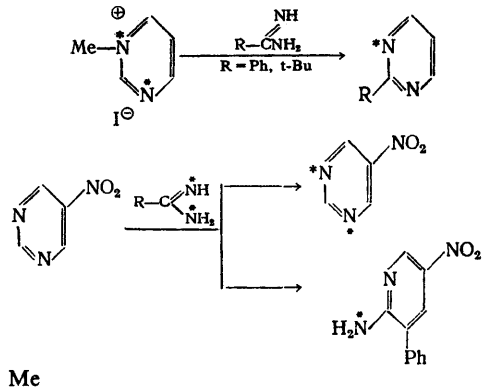
R^1 = H, Me, Hal;
R^2 = H, Me



R^3 = H, Me;
R^4 = H, Me, F.

6-Methyluracil derivatives (R^2 = Me) do not react with ureas due to the impossibility of forming a Meisenheimer complex at position 6. Electron-accepting substituents at position 5 of the pyrimidine facilitate the reaction.[157]

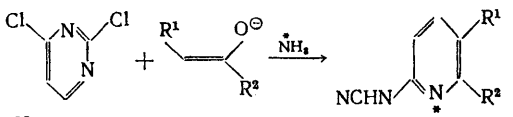
Recyclisation of quaternary salts or pyrimidines activated by a nitro group goes ambiguously with the formation of pyrimidines and pyridine (demonstrated by ^{15}N NMR).[158–161]



R = Ph, t-Bu, Me

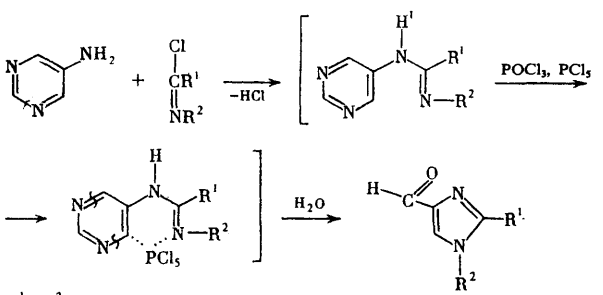
Reaction of 2,4-dichloropyrimidine with the potassium enolates of ketones in liquid ammonia leads to recyclisation to 2-cyano-pyridine. The N(1)–C(2)–N(3) fragment of the pyrimidine nucleus is

replaced by the C–C fragment of the ketone and a nitrogen from the ammonia (demonstrated by ^{15}N NMR).[162]



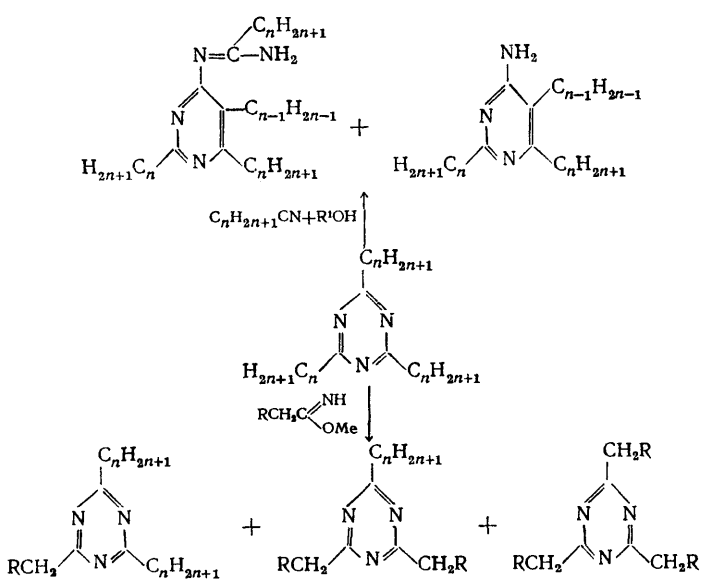
R^1, R^2 = Alk, H.

The conversions of pyrimidines considered above by reaction with ambident nucleophiles occur with the formation of six-membered heterocycles. Reaction of 5-aminopyrimidine with imidoyl chlorides in the presence of phosphorus oxychloride or pentachloride leads to 1,2-disubstituted 5-formylimidazole.[163] Phosphorus oxychloride or pentachloride is necessary to activate the nitrogen atoms, initially the side chain nitrogen is activated and then that in the pyrimidine ring.[163]



R^1, R^2 = H, Alk, Ph

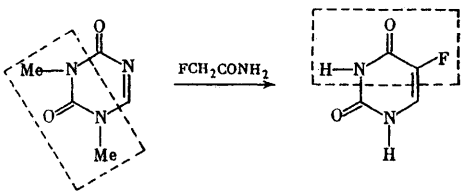
The reaction of 2,4,6-trialkyl-1,3,5-triazines with nitriles in alcohol at 100–150 °C under pressure is seemingly effected by conversion of nitrile into iminoether which replaces a portion of the triazine molecule. The reaction product may react with a further molecule of imidate and it is possible to obtain a completely transalkylated triazine.[164] A reaction was also possible under the same conditions in which pyrimidine derivatives are formed.[165]



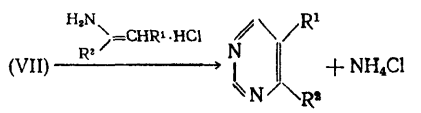
n = 1, 2; R = Me, Ph, Ar, Hetar; R^1 = H, Me, Et.

A similar process was evidently observed in the reaction of 2,4,5-trisubstituted 1,3,5-triazines with ammonia and nitriles in the presence of catalyst.[166]

With 1,3-dimethyl-5-azauracil fluoroacetic acid amide replaces the N–C–N fragment of the 1,3,5-triazine by a C–C–N fragment of the nucleophile with the formation of 5-fluorouracil. The reaction goes by an S_N(ANRORC) mechanism.[167]

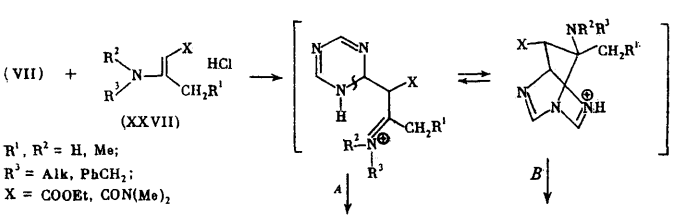


Heating 1,3,5-triazine (VII) in acetonitrile with an activated enamine hydrochloride leads to a 4,5-disubstituted pyrimidine.[168]

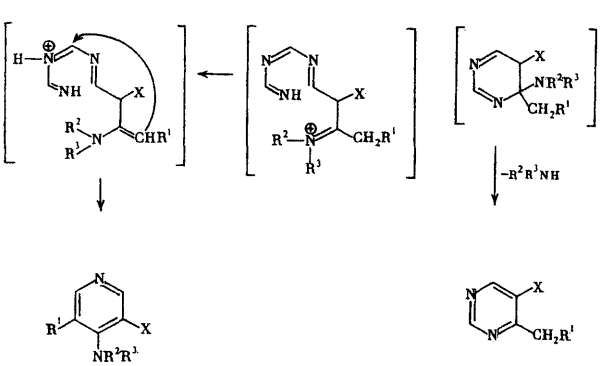


R^1 = Alk; R^2 = COOEt, MeCO.

However on boiling (VII) in acetonitrile with enaminoketone (XXVII) pyrimidine derivatives constitute a reaction by-product (5–10% yield). The formation of 4-aminopyridines containing electron-accepting substituents is the main direction (30–45% yield).[169] The ability of (XXVII) to insert three of its carbon atoms into the pyridine ring is unusual. An *N*-phenyl substituent in (XXVII) impedes the reaction.



R^1, R^2 = H, Me;
R^3 = Alk, $PhCH_2$;
X = COOEt, $CON(Me)_2$



It was proposed that (VII) is protonated by the action of (XXVII) hydrochloride, its nucleus is activated towards nucleophilic attack by the β carbon atom of (XXVII) and simultaneously towards recyclisation into a bicyclic adduct. An equilibrium mixture of intermediates is present in the mixture at the first stage of the reaction of (VII) and (XXVII). One of them is converted by route *A* [S_N(ANRORC) mechanism] into a pyridine derivative and the other proceeds by a reverse Diels–Alder reaction by route *B* with the formation of a pyrimidine derivative.[169]

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