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RING DEGENERATE TRANSFORMATIONS OF AZINES

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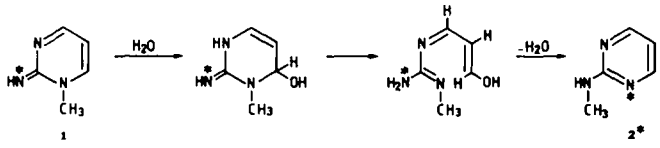
CONTENTS

DEFINITION OF RING DEGENERATE TRANSFORMATIONS; LIMITATIONS AND SCOPE

Ring transformations of carbocyclic and heterocyclic compounds have attracted the interest of many organic chemists for many decades. This interest is due to the fact that these sometimes complicated bond reorganization processes challenge chemists to unravel the mechanism of these reactions and to apply these ring transformations as synthetic tools. Nowadays, ring transformations of heterocyclic compounds have been found to be very useful for synthesizing heterocycles (and non-heterocyclic compounds) which are otherwise difficult to obtain or even inaccessible.

Ring transformations of heterocycles have been the subject of several monographs and review articles.[1a,b] It is my intention to discuss in this Tetrahedron Report a special class of ring transformations, namely the so-called ring degenerate transformations.[2] A ring degenerate transformation can be defined as a transformation reaction in which substrate and product contain the *same* heterocyclic ring, but differ in the respect that in the product the heterocyclic ring system does not contain the same carbon or hetero atom(s) as in the starting material, due to incorporation of the carbon or hetero atom of the reagent or side-chain into the ring system. In this Report I confine myself to the chemistry of the nitrogen-containing six-membered aromatics, the azines.

An important and well-studied class of degenerate ring transformations are the amidine rearrangements (Dimroth rearrangements) in azines[3–5] as exemplified in the base-assisted conversion of 1-methyl-2-[^{15}N]iminopyrimidine (**1**) into the 2-(methylamino)[^{15}N]pyrimidine (**2**).[6]



Scheme 1.

Amidine rearragnements are usually initiated by attack of the nucleophile (water, alcohol, amine, hydrazine) to a position of the ring, being adjacent to the nitrogen and unsubstituted. After ring opening, ring closure can take place, liberating the nucleophilic species. Thus, in amidine rearrangements the nucleophile primarily serves as a reagent to induce, after addition, ring opening; no incorporation of the nucleophile in the newly formed ring takes place. Although amidine rearrangements certainly form an important part of ring degenerate transformations, in this report the chemistry of amidine rearrangements is not included, since this subject has been excellently reviewed. I want to discuss mainly those rearrangements in which the nucleophile not only acts as a reagent to induce opening of the heterocyclic ring system, but is also incorporated in the ring system during ring closure.

Following this line, ring degenerate transformations of azines can be divided into two main types of reactions.

A. Ring degenerate transformations being involved in nucleophile displacement of a nucleophugic group, attached to a ring carbon atom.

B. Ring degenerate transformations involving the replacement of one or more hetero atoms, being part of a heterocyclic ring system.

In an early stage of our work on ring degenerate transformations we published an article in *Accounts of Chemical Research*[7] describing the first results of studies on these rearrangements. Since that time new examples of these reactions have become available and it seems therefore appropriate to present a more extensive and in-depth description of these A- and B-type ring degenerate transformations.

A. RING DEGENERATE TRANSFORMATIONS OF AZINES DURING DISPLACEMENT OF A NUCLEOPHUGIC GROUP, ATTACHED TO A RING CARBON ATOM

A.1. INTRODUCTION

As will be shown in the next paragraphs, ring degenerate transformations very often occur in nucleophilic displacement reactions with substituted pyrimidines. Therefore first the chemistry related to ring degenerate transformations of pyrimidines will be discussed and subsequently those of other azines. The discovery of the occurrence of ring degenerate transformations in pyrimidines and other azines is mainly based on the results of studies with use of ^{15}N-labelled substrates and/or ^{15}N-labelled reagents. For a better understanding of the course of the rearrangement reactions it is necessary to develop some kind of notation which makes it possible to differentiate between the different types of ^{15}N-labelling in substrates and products. In Scheme 2 the following notations are used. These notations are explained with use of the pyrimidine ring system, but it is evident that these notations can, *mutatis mutandis*, also be used in other heterocyclic ring systems.

For the mono ^{15}N-labelled compounds:

*Structure A** represents a *mono*-labelled compound in which the ^{15}N-label is located on one of the ring nitrogens. These compounds show in the mass spectrum an enhanced M + 1 peak.

Structure B(*) represents a mixture of *mono*-labelled compounds. x% of the molecules is labelled on N-1 and (100 − x)% of the molecules on N-3. The compound is characterized by an enhanced M + 1 peak.

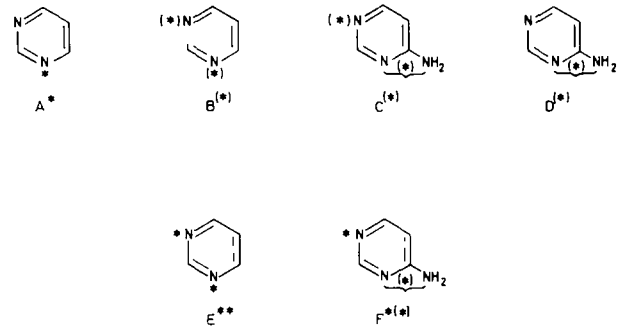
Structure C(*) represents a mixture of *mono*-labelled compounds in which x% of the molecules is ^{15}N-labelled on one ring nitrogen and (100 − x)% of the molecules contain the ^{15}N-label on either the other ring nitrogen atom or the exocyclic nitrogen.

Structure D(*) represents a *mono*-labelled compound in which x% of the molecules is labelled on ring nitrogen and (100 − x)% on the exocyclic amino group. The compound shows in the mass spectrometer an enhanced M + 1 peak.

For the double-^{15}N-labelled compounds:

*Structure E*** represents a *double*-labelled compound in which both nitrogen atoms are ^{15}N-labelled. These compounds are characterized by an enhanced M + 2 peak.

Structure F(*)* represents a *double*-labelled compound in which one ^{15}N-label is present on one ring nitrogen and the other ^{15}N-label is divided over the ring nitrogen and the exocyclic nitrogen. The compounds show in the mass spectrometer an enhanced M + 2 peak.

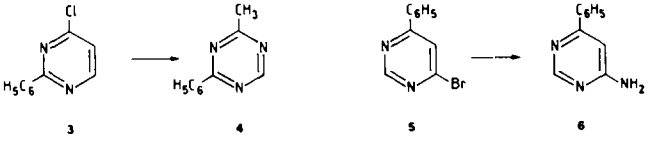


Scheme 2.

A.1.a. *Ring degenerate transformations of diazines*

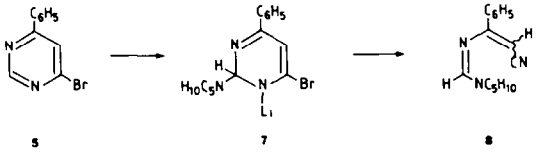
A.1.a.1. *Pyrimidines*

A.1.a.1.a. *History of the discovery of the* S_N(ANRORC) *mechanism.* In our study of the occurrence of ring transformations induced by nucleophiles we found in our laboratory many years ago that 4-chloro-2-phenylpyrimidine (**3**), when reacted with KNH_2–NH_3 at −40°, gave in reasonable yield 4-methyl-2-phenyl-1,3,5-triazine (**4**),[8–10] but that 6-bromo-4-phenylpyrimidine (**5**), when subjected to treatment with the same reagent at −75° for 30 min, did not undergo a ring transformation reaction but yielded 6-amino-4-phenylpyrimidine (**6**).[11]



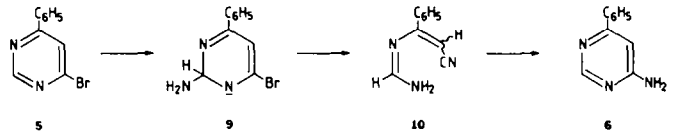
Scheme 3.

Interestingly enough, when compound **5** was reacted with lithiumpiperidide in piperidine/ether, only a trace of 6-piperidino-4-phenylpyrimidine was found; the main product was, surprisingly, a *Z*/*E* mixture of an open-chain compound, i.e. 2-aza-4-cyano-3-phenyl-1-piperidino-1,3-butadiene (**8**).[12] Apparently, instead of a piperidino-debromination at position 4, a nucleophilic addition of lithiumpiperidide at C-2 has taken place, yielding **7**, which by ring-opening yields **8**. The apparent



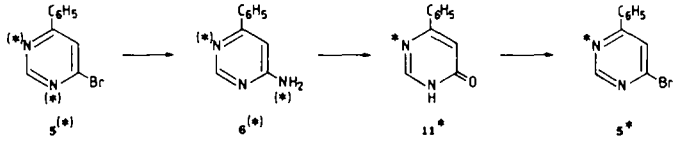
Scheme 4.

inconsistency observed in the course of the amination of **5** with KNH_2–NH_3 and with lithiumpiperidide–piperidine induced us to reinvestigate the reaction of **5** with KNH_2–NH_3 with the view in mind that **5** might react similarly with KNH_2–NH_3 as with lithiumpiperidide–piperidine: thus first addition at C-2 of the amide ion, yielding the C-2 anionic σ-adduct **9**, followed by ring-opening into 1-amino-2-aza-4-cyano-3-phenyl-1,3-butadiene (**10**). Unlike **8**, this open-chain intermediate **10** can undergo a subsequent cyclization into **6**. To prove the occurrence of this alternative pathway for the



Scheme 5.

amino-debromination of **5** into **6**, we carried out the amination with the mono ^{15}N-labelled 6-bromo-4-phenyl [1(3)-^{15}N]pyrimidine [**5**$^{(*)}$]; in this compound the ^{15}N-label was equally scrambled over N-1 and N-3. If **5**$^{(*)}$ would indeed react according to the route given in Scheme 5 it would lead to compound **6**$^{(*)}$, in which 50% of the molecules are ^{15}N-labelled on the N-3 in the pyrimidine ring and 50% ^{15}N-labelled on the exocyclic nitrogen of the amino group. Conversion of **6**$^{(*)}$ with hydrochloric acid into 4-phenylpyrimidin-6-one (**11***) and replacement of the oxo group in **11*** by a bromo atom would give 6-bromo-4-phenylpyrimidine **5***, containing exactly half of the ^{15}N-enrichment present in the starting material **5**$^{(*)}$.



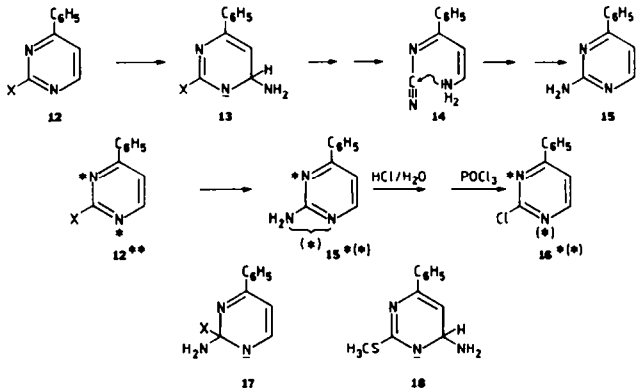
Scheme 6.

We found that if the starting material **5**$^{(*)}$ contained 6% of ^{15}N-enrichment, the 6-bromocompound **5***, obtained from **6**$^{(*)}$ → **11*** → **5***, contained 3.5% ^{15}N-enrichment indicating that 2.5/3.0 = 83% of the molecules have been aminated accordimg to the route involving Addition of the Nucleophile, Ring Opening, and Ring Closure.[11] We refer to nucleophilic substitutions involving this reaction sequence as reactions which occur according to the S_N(ANRORC) mechanism. The conversion of **5**(**5***) into **6**(**6***) is a clear example of a ring degenerate transformation: substrate and product contain the same pyrimidine ring system; however, in the product one of the nitrogens of the ring is not the same one as originally present in the substrate; it has originated from the amide ion. This study also shows that the occurrence of A-type ring degenerate transformations can be nicely demonstrated by using either ^{15}N-enriched substrates or ^{15}N-enriched reagents.

A.1.a.1.b. 4-*Phenylpyrimidines, containing a nucleophugic group at position* 2. Treatment of 2-X-4-phenylpyrimidine (**12**), containing at position 2 a nucleophugic group [X = F,Cl,Br,I,SCH_3,SO_2CH_3,SCN,CN,$^+N(CH_3)_3$] with KNH_2–NH_3 at temperatures between −75° and −33° (depending on the substituent) gave in good yields the corresponding 2-amino-4-phenylpyrimidine (**15**). When the amination was carried out with the *double*-labelled 2-X-4-phenyl-[1,3-^{15}N]pyrimidine (**12****), **15***$^{(*)}$ was obtained, indicating that the amino group has been enriched with nitrogen-15.[13] [15] This result shows that in the formation of **15***$^{(*)}$ a ring degenerate transformation has taken place. The degree of ^{15}N-labelling on the exocyclic nitrogen of the amino group in **15***$^{(*)}$ was established by measuring the ^{15}N content in **15***$^{(*)}$ and in 2-chloro-4-phenylpyrimidine (**16***$^{(*)}$), obtained after converting **15***$^{(*)}$ into the corresponding 4-phenylpyrimidin-2-one and subsequent replacement of the oxo group by a chloro atom on treatment with phosphorylchloride. As seen in Table 1, a considerable decrease of the M + 2/M ratio was found for nearly all substrates **12****, providing unequivocal evidence that all compounds **12** react—although to a different degree—according to an S_N(ANRORC) process, involving an initial addition of the amide ion to C-6, yielding **13** and ring-opening into open-chain intermediate **14**. The open-chain intermediate is stable[13,14] since it is probably present in the anionic form due to the strong

basic medium and does not tend to cyclise. Sound evidence for the stability of open-chain intermediates in a strong basic medium has been found in the Chichibabin amination of phenylpyrimidines (see paragraph A.1.a.1.e) as well as purines (see paragraph A.1.a.3). Addition of an ammonium salt, the appropriate reagent to neutralize the amide ion before work-up, will also neutralize the anionic open-chain species and it is suggested that in this neutral species cyclization takes place.

The molecules that do not react according to the S_N(ANRORC) process will probably undergo an S_N(AE) type substitution, involving the C-2 adduct **17**.



Scheme 7.

Additional evidence for the occurrence of the S_N(ANRORC) mechanism in the amination of **12** came from the following experimental data.

a. Measurement of the ^{1}H-NMR spectrum of 2-thiomethyl-4-phenylpyrimidine (**12**, X = SCH_3) in KNH_2–NH_3 clearly showed[15] the formation of C-6 σ-adduct **18**, as proved by the fact that H-6 has undergone an upfield shift of about 3.8 ppm on adduct formation [H-6 in **12** (X = SCH_3) at δ 8.50, H-6 in the C-6 adduct **18** at δ 4.74] due to the $sp^2 \rightarrow sp^3$ change[13–16].

b. The intermediate (3-amino-1-phenylallylidene) cyanamide (**14**) could be isolated (~ 50% yield) when the amination of 2-X-4-phenylpyrimidine (**12**, X = Br) was carried out for a short period of time (at −75°). This intermediate could be converted with KNH_2–NH_3 into 2-amino-4-phenylpyrimidine (**15**).

Thus, in summary, amination of 2-X-4-phenylpyrimidine (**12**) by KNH_2–NH_3 leads to a ring degenerate transformation, in which convincing evidence is found for the initial σ-adduct formation at C-6, i.e. **13** (X = SCH_3), and for the open-chain intermediary compound **14**.

The question can be raised why the incoming amide ion does not add at C-2, being highly activated, but prefers in most cases to add preferentially to the isomeric C-6 position. There is ample evidence that in electron-deficient carboaromatics and heteroaromatics attack on a carbon carrying a hydrogen is often more rapid than attack on a carbon being substituted by a nucleophugic group.[16j,17] Several factors are suggested to be of importance in determining the mode of addition (i.e. steric hindrance of approach reagent,[18,19] stabilization by charge delocalization in the isomeric adducts).[20,21] However, the relative importance of these, in many cases interdependent factors is not well understood. Based on

Table 1. Percentage of ^{15}N-enrichment in compounds **12**** and **16***(*)** (calculated from $\Delta M + 2/M$) and the percentage of **12**** which react according to the S_N(ANRORC) mechanism

X	Compd **12****(%)	Compd **16***(*)**(%)	% S_N(ANRORC) mechanism
F	6.0	1.1	82
Cl	6.0	0.7	90
Br	6.0	0.7	88
I	6.0	1.6	73
SCH_3	6.0	0.5	91
SO_2CH_3	6.0	1.6	73
SCN	6.0	0.6	34
CN	6.0	5.7	5
$N^+(CH_3)_2$	6.0	5.4	10

Table 2. Yields, obtained in the amination of 2-X-4-phenylpyrimidine, % S_N(ANRORC) mechanism, non-resonance constants F and resonance constants R of substituent X

Substituent X	a % S_N(ANRORC)/100	b yield (%)/100	a × b	F	R
SCH_3	0.91	0.72	0.65	0.332	−0.186
SO_2CH_3	0.73	0.68	0.50		
CN	0.05	0.56	0.03	0.847	0.184
$N^+(CH_3)_3$	0.10	0.62	0.06	1.460	0.00
Cl	0.90	0.59	0.53	0.690	−0.161
Br	0.88	0.67	0.59	0.727	−0.176
F	0.80	0.78	0.62	0.708	−0.336
I	0.73	0.50	0.37	0.672	−0.197
H	0.92	0.60	0.55	0.000	0.00

the limited set of data available in Table 1 we tried to establish whether a correlation could be established between the field, inductive and resonance effects of the substituents and the fraction of compounds **12** which took part in the ANRORC-process (X_{ANRORC}). For the field, inductive and resonance effects of the substituents the Swain non-resonance constants F and resonance constants R were used[22] (Table 2) and the value X_{ANRORC} was calculated from %(ANRORC)/100 × %(yield)/100. In Table 2 the results obtained with the 2-sulphonylmethyl compound **12**(X = SO_2CH_3) are not included since this group has been proven[13] to be deprotonated in this strong basic medium and the F and R values of the conjugate base are unknown. Also, the F and R values of the sulphonylphenyl and the thiocyanato group are unknown; therefore also these values were not included.

Based on the set of data given in Table 2 we were able to establish a correlation between X_{ANRORC} and the F and R effects of the substituent at the position 2 in **12**, as presented in equation 1.

$$X_{ANRORC} = -0.34F - 1.04R + 0.55. \quad (1)$$

The average correlation coefficient is 0.95. The square of the correlation coefficient is 0.90, which means that on the average 90% of the variation can be predicted on basis of equation 1. A surprisingly satisfactory correlation. Equation 1 predicts that in case both F and R are zero, 4-phenylpyrimidine (**12**, X = H) should undergo an ANRORC-process having an X_{ANRORC} value of 0.55. As one will see later in paragraph A.1.a.1.e, amination of 4-phenylpyrimidine gives 2-amino-4-phenylpyrimidine in 60% yield and its formation occurs for 92% according to the ANRORC-process. The value for X_{ANRORC}, being calculated from these data, is 0.92 × 0.60 = 0.552, a remarkable agreement with the predicted value from equation 1 for F and R = 0.

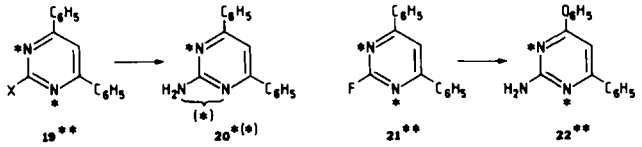
All these results show that equation 1 gives a rather reliable and quantitative description of the influence of substituents on the amide-induced amination of 2-X-4-phenylpyrimidine according to the S_N(ANRORC)-process. Concerning the influence of the various halogeno atoms on the ANRORC-process, it is now apparent that the resonance effects R, more than the non-resonance effects F, direct the nucleophilic amide ion to the *meta* position on C-6 fluorine (R = −0.336) is about twice as strong an electron donor as bromine (R = −0.176) and chlorine (R = −0.161), suggesting that the 2-fluorocompound is less easily inclined to addition of the nucleophilic amide ion at C-6 than the 2-chloro- or 2-bromocompound. This tendency is indeed observed in the somewhat lower percentages of the S_N(ANRORC)-mechanism for the fluoro- in comparison with the chloro- and bromocompound **12**** (X = Cl,Br) (Table 1).

The ring degenerate transformation was also found to occur when position 6 is substituted by the phenyl group: 2-X-4,6-diphenyl[1,3-^{15}N]pyrimidine (**19****, X = ClBr) reacts for about 70% into the 2-amino compound **20***(*) according to the S_N(ANRORC)-process.[23] This percentage is about 20% lower than the one found for 2-X-4-phenylpyrimidine (**12**, X = Cl,Br) indicating some steric interference of the incoming nucleophile with the phenyl group at position 4(6); it is evident that the bulkiness of the phenyl group is not effective enough to prevent addition at C-6 in **19** (X = Cl,Br). In the light of these results it is quite remarkable that amination of 2-fluoro-4,6-diphenyl-[1,3-^{15}N]-pyrimidine (**21****) does *not* involve an S_N(ANRORC)-process at all;[23] in the 2-amino compound **22**** *all* ^{15}N is present on the nitrogens of the pyrimidine ring indicating the exclusive occurrence of an S_N(AE)-process. A straightforward explanation cannot be given. However, since we have seen that compound **12** (X = F) is less inclined to undergo the S_N(ANRORC)-process than **12** (X = Cl,Br),

Table 3. Percentage of ^{15}N-excess in compounds **23(*)a–d**, **24(*)** and **25(*)** (calculated from $\Delta M + 1/M$) and the percentage of these compounds which react with KNH_2–NH_3, according to the S_N(ANRORC) mechanism

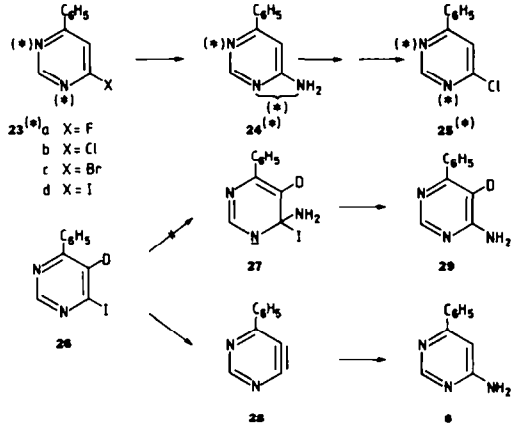
Compd **23(*)**	%	Compd **24(*)**,%	Compd **25(*)**,%	% S_N(ANRORC) mechanism
a (X = F)	7.4	7.4	4.7	70
b (X = Cl)	6.0	6.1	3.2	90
c (X = Br)	6.0	6.0	3.5	80
d (X = I)	7.4	7.4	6.9	13

introduction of the phenyl group at C-6 apparently influences the delicate balance between addition at C-6 and C-2 in favour of C-2.



Scheme 8.

A.1.a.1.c. 4- *or* 5-*Substituted pyrimidines containing a nucleophugic group at position* 6. The occurrence of a ring degenerate transformation observed in the amino-debromination of 6-bromo-4-phenylpyrimidine (5) (Section A.1.a.1.a) was also found[24] to occur to a great extent (> 70%) during amination of 6-fluoro- [**23(*)a**] and 6-chloro-4-phenyl-[1(3)-^{15}N]-pyrimidine [**23(*)b**], see Table 3. In contrast, the amino-deiodination of the 6-iodocompound **23(*)d** takes place to only a small extent (< 13%, see Table 3) according to the S_N(ANRORC)-process. The method used to establish these results is the same as discussed in Section A.1.a.1.a. The results show that the 6-fluoro-, 6-chloro- and 6-bromocompounds **23** react very similarly with KNH_2–NH_3 as the corresponding 2-

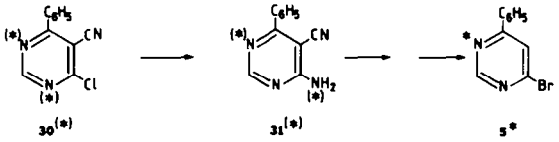


Scheme 9.

halogenocompounds **12**. It was observed that 5-deutero-6-iodo-4-phenylpyrimidine (**26**) on amination does not give 6-amino-5-deutero-4-phenylpyrimidine (**29**) but the undeuterated 6-amino compound **6**.[24] This result excludes the intermediacy of σ-adduct **27** and suggests the transient intermediate species 4-phenyl-5,6-didehydropyrimidine (**28**), being exclusively attacked by the amide ion at position 6. All these observations clearly show that for all four 6-halogeno-4-phenylpyrimidines **23** addition at C-6 is not the main process: in case of the 6-fluoro-, chloro- and bromocompound **23a–c** the initial addition takes place at C-2 and for the 6-iodocompound **23d** the initial deprotonation at C-5 is most preferred. That the 2-iodocompound **12**** (X = I) gives a much higher % S_N(ANRORC) mechanism (73%) than the 6-iodocompound (**23(*)d**, 13%) is probably due to the fact that with **12** (X = I) competitive didehydro formation cannot take place. This example shows how delicate the balance is

between proton abstraction at C-5, leading to **28** and addition at C-2, yielding **27**. When position 6 is occupied by a phenyl group the percentage of the molecules, which react according to the S_N(ANRORC)-mechanism is considerably decreased: 4-chloro-2,6-diphenylpyrimidine (45%), 4-bromo-2,6-diphenylpyrimidine (0%), 4-fluoro-2,6-diphenylpyrimidine (0%).[25,26] This result is mainly caused by steric interference of the phenyl group at 4(6) with the incoming amide ion.

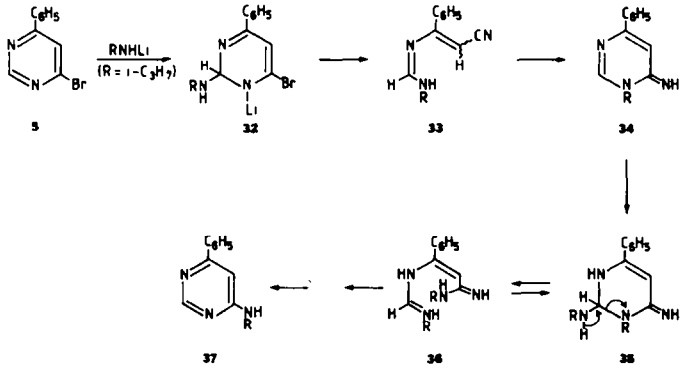
As can be expected, introduction of an electron withdrawing substituent at position 5 of the pyrimidine ring in **23** facilitates the addition at C-2 and therefore may increase the percentage of molecules that undergo the S_N(ANRORC)-mechanism. This result has been found indeed.[27] 6-Chloro-5-cyano-4-phenyl-[1(3)-^{15}N]-pyrimidine (**30**$^{(*)}$, $\%^{15}N = 7.4\%$) gave on amination with KNH_2–NH_3 the 6-amino compound **31**$^{(*)}$ ($\%^{15}N = 7.4\%$) in which exactly half of the ^{15}N-labelling was found to be present on the exocyclic amino nitrogen, as proved by its conversion into the 6-bromocompound **5*** ($\%\ ^{15}N = 3.7\%$). Thus, the conversion **30** → **31** is again a beautiful example of a ring degenerate transformation!



Scheme 10.

It has been proved using the technique of ^{15}N-labelling that amino-dechlorination of 4-chloro-6-phenylpyrimidine-1-oxide by KNH_2–NH_3 does not involve a ring-opening, ring-closure process,[28,29] but follows an initial addition of the amide ion at C-4 and elimination of the chloride ion $S_N(AE)^{ipso}$. No ^{1}H-NMR spectrum of a solution of this compound in KNH_2–NH_3 was measured; therefore no indication for an initial C-2 adduct formation or deprotonation at C-2 could be obtained.

Reaction of 6-bromo-4-phenylpyrimidine (**5**) with lithium isopropylamide in isopropylamine at 20° gave 6-(isopropylamino)-4-phenylpyrimidine (**37**) in 70% yield.[30] A seemingly simple conversion, but actually found to occur by a complicated series of steps, involving two ring degenerate transformations. When the reaction was carried out at −75° instead of 20°, a mixture of the 2-aza-4-cyano-1-isopropylamino-3-phenyl-1,3-butadiene (**33**) and the isomeric 6-imino-1-isopropyl-4-phenyl-1,6-dihydropyrimidine (**34**) [ratio **33**:**34** ~ 10:1] was isolated. The iminopyrimidine **34** gives a fast Dimroth rearrangement into **37** by lithium isopropylamide at 20°. Thus, the conversion of **5** into **37** involves two series of ANRORC-reactions (**5** → **32** → **33** → **34** and **34** → **35** → **36** → **37**), both reaction series being initiated by a nucleophilic addition at C-2.



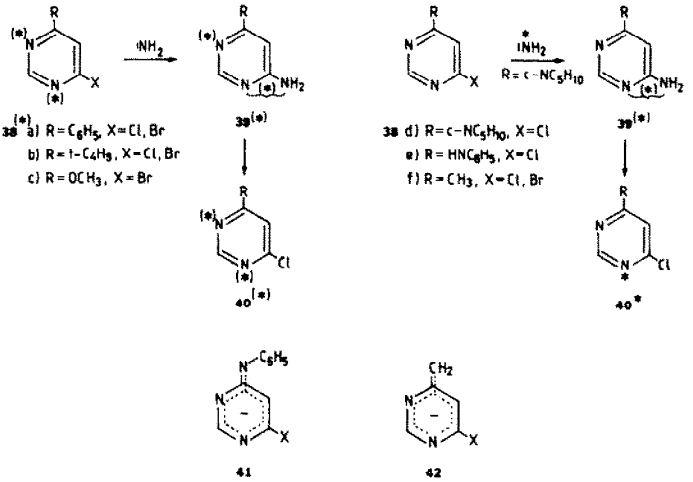
Scheme 11.

An extensive study has been published[31] concerning the influence of C-4 substituents in 4-R-6-X-pyrimidines (**38**, R = C_6H_5, *t*Bu, OCH_3, *c*-NC_5H_{10}, NHC_6H_5, CH_3, X = Cl,Br) on the occurrence of ring degenerate transformations during amination with KNH_2–NH_3. For this purpose the reaction of ^{15}N-labelled mono-labelled substrates **38**$^{(*)}$ with unlabelled potassium amide as well as that of unlabelled **38** with ^{15}N-labelled potassium amide was used. For the determination of the partition of ^{15}N over the ring nitrogen and/or the amino group in the 6-amino compound obtained, i.e. **39**$^{(*)}$ from

Table 4. Percentage of ^{15}N-enrichment (measured by ΔMH/M) in **38**$^{(*)}$, **39**$^{(*)}$ and **40**$^{(*)}$ and the percentage of **38**, which react according to the S_N(ANRORC) mechanism.

Starting material	React. temp	% ^{15}N-enrichment Start. mat. **38**	**39**$^{(*)}$	**40**$^{(*)}$	% S_N(ANRORC)
38*a, X = Br	−75°	6.0	6.0	3.5	83
38*a, X = Cl	−75°	6.0	6.1	3.2	93
38*b, X = Br	−75°	7.8	7.9	4.8	77
38*b, X = Br	−33°	7.8	7.8	6.5	33
38*c, X = Br	−33°	10.3	10.0	8.4	31
38d, X = Cl	−33°	0.0	4.3	0.9	21
38e, X = Cl	−33°	0.0	4.3	0	0
38f, X = Br	−33°	0.0	4.1	0	0
38f, X = Cl	−33°	0.0	3.8	0	0

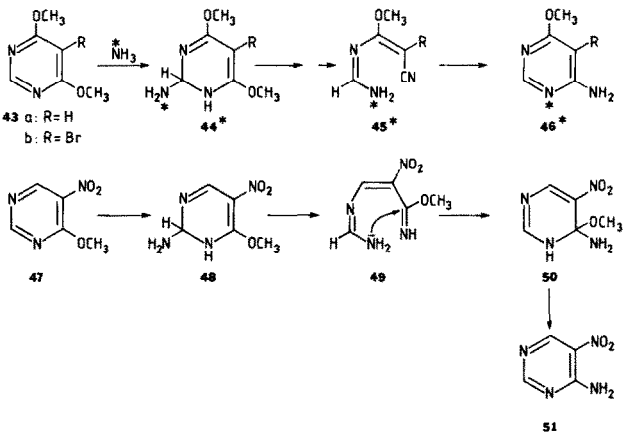
38$^{(*)}$, or **39**$^{(*)}$ from **38**, the 6-amino compounds were converted into the corresponding 6-chloropyrimidines **40**$^{(*)}$ (or **40***). The results of these labelling studies are summarized in Table 4 and clearly show that the pyrimidines **38**$^{(*)}$**a, b, c** and **38d** undergo—to a different degree—a ring degenerate transformation, being initiated by addition at C-2. In the amination of the compounds **38e** and **38f** the



Scheme 12.

ANRORC-process is not operative. This is due to formation of the negatively charged species **41** and **42** respectively, leading to enhancement of the electron density at N-1 and N-3 and consequently to a disfavoured addition at the adjacent C-2 position. Deprotonation of substituents, containing an acidic hydrogen, has actually been observed by ^1H-NMR spectroscopy in pyrimidines,[16c,d] pyridines,[32-35] pyrazines,[32,33] pyridazines,[32] naphthyridines[36,37] and purines.[32,38] The amination of **38**$^{(*)}$**b** (X = Br) has been studied at different temperatures. A considerable temperature effect has been observed (Table 4): at −75° addition at C-2 becomes more favoured than at −33°. At low temperature (−75°) we probably deal with the formation of the kinetically favoured C-2 adduct,[39] whereas at −33° the thermodynamically more stable C-6 adduct is formed.

4,6-Dimethoxypyrimidine (**43a**) and its 5-bromo derivative (**43b**) when reacted with KNH_2–NH_3 at −33° gave the corresponding 4-methoxy-6-aminopyrimidines **46a** and **46b** respectively;[39] both compounds are entirely formed by a ring-opening and ring-closure process, as was proved by using ^{15}N-labelled potassium amide and finding that the 6-amino compounds **46*a, b** contain all the ^{15}N-label inside the ring! The amination follows the same reaction pathway as given for **5** → **6**, involving initial addition of the amide ion at C-2, yielding **44***, and formation of the open-chain aminocyanoazabutadiene **45***.



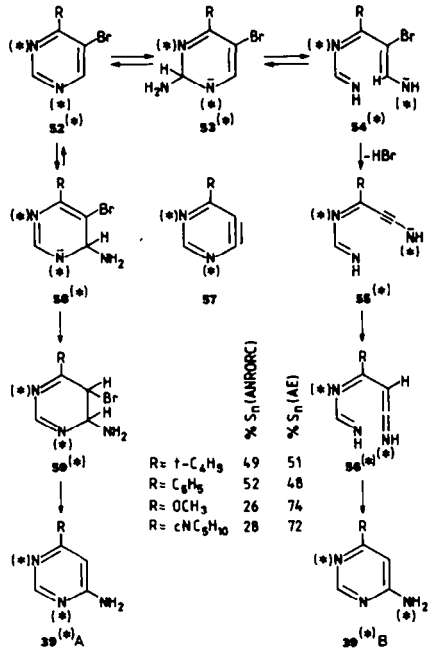
Scheme 13.

It has been found very recently that a solution of 4-methoxy-5-nitropyrimidine (**47**) in liquid NH_3 (thus containing no KNH_2), when allowed to stand for 5 min at room temp, gives 4-amino-5-nitropyrimidine (**51**).[40] It has been established by NMR spectroscopy that **47** easily gives the C-2 adduct **48** at low temperature, suggesting that conversion of **47** into **51** would follow the route presented in Scheme 13; thus first addition of ammonia into **48**, ring-opening into the nitroiminoester **49**, and an easy cyclisation into **50**. No ^{15}N-labelling studies on this mechanistic proposal have been performed, but it seems very plausible that this proposal is correct.

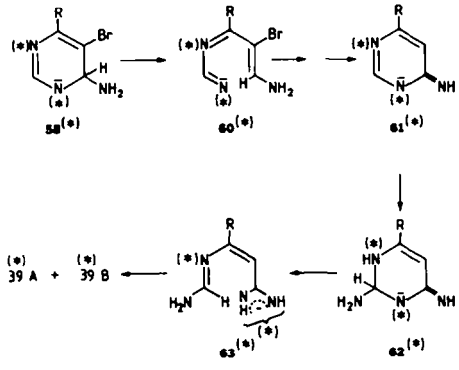
A.1.a.1.d. *4-Substituted 5-halogenopyrimidines.* The 4-substituted 5-bromopyrimidines (**52**, R = *t*Bu, C_6H_5, OCH_3, *c*-NC_5H_{10}) were reported[41–43] to give with KNH_2–NH_3 the 6-amino product **39**. This cine-amination process was suggested to involve the intermediacy of a 5,6-didehydropyrimidine (**57**).[43–47] However, it was proved that this intermediate is not formed: using as substrate the mono-labelled [1(3)-^{15}N]-5-bromopyrimidine **52**$^{(*)}$ it was found[41] that the 6-amino product contained a part of the ^{15}N-label *in* the 6-amino group (i.e. **39**$^{(*)}$**B**), indicating that the molecules of **52**$^{(*)}$ have partly undergone a ring degenerate transformation; to which extent depends strongly on the substituent *R* in **52**$^{(*)}$. To explain the rearrangement reaction of **52**$^{(*)}$ into **39**$^{(*)}$**B** an initial attack of the amide ion on C-2 has been postulated yielding **53**$^{(*)}$, followed by ring-opening into **54**$^{(*)}$ through cleavage of the N(1)—C(2) bond. The bromo atom is supposed[41] to split off in the short-lived species **54**$^{(*)}$ by a base-induced elimination of hydrogen bromide to give the N-(3-amino-1-*t*-butyl-2-propynylidene) formamidine (**55**$^{(*)}$). Cyclization via the ketenimine **56**$^{(*)}$ yields **39**$^{(*)}$**B**, having the isotopic nitrogen partly outside the pyrimidine nucleus. One refers to this process as an S_N(ANRORC)^{cine} reaction. The degree of ANRORC-rearrangement (Scheme 14) was established in the usual way, i.e. conversion of the 6-amino product **39**$^{(*)}$ into the corresponding 6-chlorocompound and measurements of the ^{15}N-enrichments in starting materials, 6-amino products and 6-chlorocompounds.

In an attempt to detect the C-2 adduct **53** by ^1H-NMR spectroscopy a solution of **52** (X = *t*Bu,C_6H_5,OCH_3, $C_6H_5NCH_3$) in KNH_2–NH_3 was measured.[16c] Interestingly enough the solution only displayed the characteristic signals of the C-6 adduct **58**; no indication for the presence of C-2 adduct **53** was found.[27] This result is surprising in view of the fact that **58** can only account for the formation of the 6-amino product **39**$^{(*)}$**A** in which only one of the ring nitrogens is ^{15}N-labelled and not of the formation of **39**$^{(*)}$**B**. Apparently the formation of **53*** is less favoured than that of **58*** and its concentration is below the minimum required for ^1H-NMR visibility.

It can be questioned that **39**$^{(*)}$**A** and **39**$^{(*)}$**B** are not formed from two different σ-adducts [**53**$^{(*)}$ → **39**$^{(*)}$**B** and **58**$^{(*)}$ → **39**$^{(*)}$**A**] but from a common intermediate, i.e. **58**$^{(*)}$. The argument is as follows: ring-opening would lead to the formation of **60**$^{(*)}$ from which similarly to the pathway discussed in Scheme 14, the anionic iminocompound **61*** is obtained, having both ring nitrogens ^{15}N-labelled. This iminopyrimidine **61*** could then undergo a very fast Dimroth-like rearrangement, via **62**$^{(*)}$ into the open-chain species **63**$^{(*)}$. Scrambling occurs in the amidino moiety of **63**$^{(*)}$, ring closure would then give a mixture of about equal amounts of **39**$^{(*)}$**A** and **39**$^{(*)}$**B**, what has been found indeed for R = *t*-butyl and



Scheme 14.



Scheme 15.

C_6H_5. There are, however, a few objections to the mechanism as presented:

The low percentage of S_N(ANRORC) mechanism found[42] for the methoxy- and the piperidinogroup (26 and 28% respectively) is conflicting with the occurrence of a scrambling process.

The addition of ammonia across the C(2)—N(3) bond in anionic **61**$^{(*)}$ must be much faster than the conversion of **61**$^{(*)}$ into the very stable anion of a 6-aminopyrimidine derivative. This seems highly unlikely.

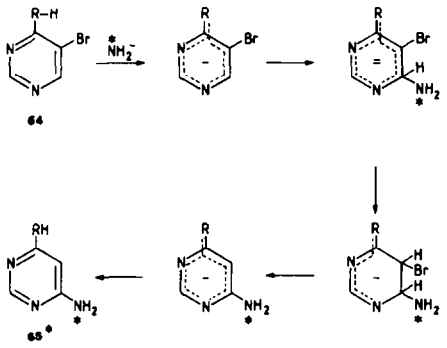
The fact that 5-bromo-4-piperidinopyrimidine (**52**, R = piperidino) in reaction with KNH_2–NH_3 was found[42] to give beside **39** (R = *c*-NC_5H_{10}) the tele amination product 2-amino-4-piperidinopyrimidine being *exclusively ring-labelled*. The formation of the last-mentioned product strongly suggests the intermediacy of C-2 adduct **53** (R = *c*-NC_5H_{10}).

The importance of an unsubstituted C-2 position for the ring-opening process in **52** during amination was substantiated in the reaction of 2,4-di-*t*-butyl-5-bromopyrimidine with ^{15}N-labelled KNH_2–NH_3: in the 6-amino-2,4-di-*t*-butylpyrimidine obtained no ^{15}N-label was incorporated in the pyrimidine ring.[48]

Changing the halogeno atom in position 5 of the pyrimidine ring from bromo to chloro is also of decisive influence on the occurrence of the S_N(ANRORC)^{cine} process. Reacting 5-chloro-4-*t*-butyl [1(3)-

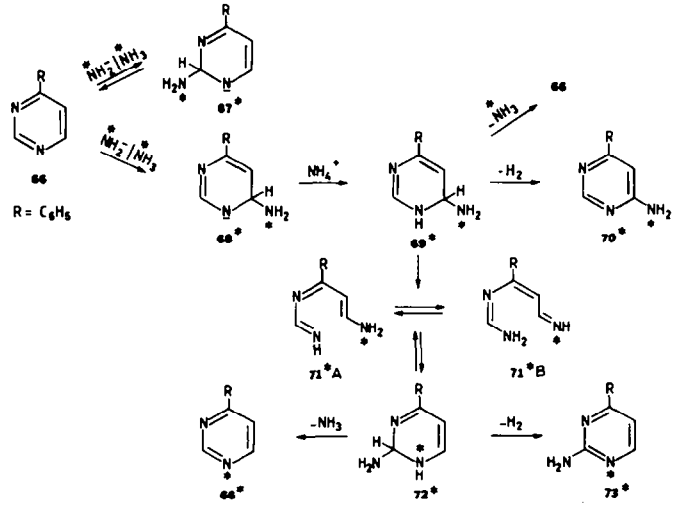
^{15}N] pyrimidine (**52**$^{(*)}$, replace Br by Cl) with KNH_2–NH_3, *no* ^{15}N-label was found to be present on the exocyclic amino group. This result is explained by the fact that the rate of elimination of HCl from **54*** (replace Br by Cl) to form the acetylenic bond in **55**$^{(*)}$ is lower than elimination of HBr from the bromo intermediate **54**$^{(*)}$.[49] It was observed that compound **64** (RH = CH_3,$NHCH_3$,HNC_6H_5,NH_2), when reacted with ^{15}N-labelled KNH_2–NH_3, gave—very slowly—the 6-aminopyrimidines **65*** being exclusively labelled at the amino group. These results are explained as follows: above mentioned substituents contain a labile hydrogen and therefore are easily deprotonated in the strong basic medium. The negatively charged species do not undergo addition at C-2, but prefer addition at C-6, although slowly. See also Section A.1.a.1.c concerning the amination of 4-R-6-halogenopyrimidines (R = NHC_6H_5,CH_3). The formation of an anionic group at C-4 has been proved by NMR spectroscopy for **64** (R = CH_2,NCH_3).

The cine-amination process can be described as follows:



Scheme 16.

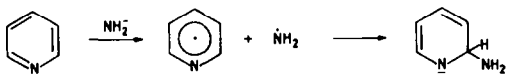
A.1.a.1.e. *Chichibabin amination of 4-phenylpyrimidine.* ^{15}N-*labelling studies.* Treatment of one equivalent of 4-phenylpyrimidine (**66**) with KNH_2–NH_3 for 70 hr gives rise to the formation of two isomeric products, i.e. 2-amino-4-phenylpyrimidine (**73**, 60%) and 6-amino-4-phenylpyrimidine (**70**, 15%). It was found[50] that when this amination was carried out with ^{15}N-labelled KNH_2–NH_3 the 2-amino compound contains the ^{15}N-label almost exclusively *in* the pyrimidine ring, i.e. **73*** and that in the 6-amino compound the ^{15}N-label is located on the amino group, i.e. **70***. These results indicate that in the formation of **73*** a degenerate ring transformation has taken place leading to incorporation of ^{15}N-label in the ring. Ninety-two percent of **66** reacts according to the S_N(ANRORC) process into **73**.



Scheme 17.

A detailed study of σ-adduct formation in this Chichibabin amination process by ^{1}H- and ^{13}C-NMR spectroscopy showed[50] that a solution of **66** in KNH_2–NH_3 contains two σ-adducts, i.e. the C-2 adduct **67** and the C-6 adduct **68**; the ratio **67**/**68** 20 min after dissolving **66** in KNH_2/NH_3 is about 20:80. On standing this ratio changes; the amount of C-2 adduct diminishes and is finally absent. Apparently, we are dealing with the kinetically favoured formation of the C-2 adduct, which slowly converts *via* **66** into the more stable C-6-adduct **68**. This C-6 anionic adduct is stable, even for days. However, when ammonium chloride was added, immediately hydrogen gas evolves and the formation of 6-amino *and* 2-amino product is observed.[51] These observations show that the 2-amino compound **73** is formed from the 6-amino-σ-adduct **68**. Furthermore the profound effect of the ammonium ion on the proceeding of the reaction indicates that the formation of the amino products does not take place from the anionic σ-adduct **68** but from the neutral **69**, being obtained after neutralization of **68** by the ammonium ion, being a strong acid in this medium. The species **69** can either give **70**, with exocyclic ^{15}N-labelling on the amino group in case the reaction is carried out with ^{15}N-labelled KNH_2–NH_3 or undergoes a ring-opening into the acyclic intermediate **71A** ⇄ **71B**. Recyclization gives 2-amino-4-phenyl-1,2-dihydropyrimidine (**72**) and subsequently 2-amino-4-phenylpyrimidine (**73**) by loss of hydrogen. Since intermediate **72** can also undergo aromatization by loss of ammonia, it can be expected that when the reaction is carried out with ^{15}N-labelled KNH_2–NH_3 the recovered 4-phenylpyrimidine should contain ^{15}N-label in the ring. This has been found indeed, **66*** could be isolated. Attempts to register by ^{1}H-NMR spectroscopy the acyclic intermediate **71** failed.

Inhibition of the S_N(ANRORC) *mechanism.* It has been suggested[52,53] that in the amination of azines in an apolar solvent, like *o*-xylene, at 80–140°—the classical conditions for a Chichibabin amination—a radical anion, formed by an electron transfer from the nucleophile to the heterocycle, would be involved, prior to the σ-adduct formation. Supporting evidence was obtained from the fact that amination does not occur in the presence of radical scavengers, like nitrobenzene, azobenzene and oxygen.



Scheme 18.

Since the pyrimidine ring is very electron deficient it was investigated to see whether this electron transfer process would also occur when **66** was aminated with KNH_2–NH_3 at low temperature in the presence of a radical scavenger like azobenzene. Intriguing effects are found.[51] If azobenzene is added after quenching of the reaction with ammonium chloride the main product is still 2-amino-4-phenylpyrimidine. By addition of azobenzene before quenching with ammonium chloride, however, the product mixture is changed dramatically. The main product is now 6-amino-4-phenylpyrimidine (75%). Carrying out the reaction in the presence of ^{15}N-labelled KNH_2–NH_3 *no* incorporation of ^{15}N-label in any of the amino compounds was found! No explanation is offered.

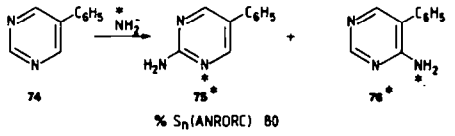
Amination in m-*xylene as solvent.* As mentioned before the Chichibabin amination of azines is usually carried out in apolar solvents.[53] The amination of **66** was also studied in *m*-xylene, especially with the view in mind whether in this solvent a degenerate ring transformation would take place.[51] Reaction of **66** with ^{15}N-labelled KNH_2–NH_3 in *m*-xylene at 90° showed the formation of the 6-amino compound (**70**, 35%) and 2-amino-4-phenylpyrimidine (**73**, 55%), both compounds having the ^{15}N-label in the exocyclic amino group; this result leads to the conclusion that an addition–elimination [S_N(AE)] process accounts for virtually all products.

The results obtained on the amination in liquid ammonia and in *m*-xylene are rationalized as follows: in *m*-xylene as solvent the rate-determining step is considered to be the initial nucleophilic attack on C-2 as well as C-6. Due to lack of solvating power of the solvent, these adducts are not highly stable and react immediately further into the respective amino products. Thus isomerization of C-2 adduct **67** into C-6 adduct **68** is not possible. In liquid ammonia **68** is the more stable adduct and ring-opening of **68** becomes the rate-determining step. This allows **67** to isomerize into **68**, leading finally to incorporation of ^{15}N-label inside the ring.

It has been established[54] that amination of 5-phenylpyrimidine (**74**) by KNH_2–NH_3 also leads to a ring degenerate transformation as evidenced by the fact that with ^{15}N-labelled KNH_2–NH_3 a

considerable incorporation of ^{15}N-label into the pyrimidine ring of the 2-amino product **75*** was found; in the isomeric 6-amino product **76** no ^{15}N-incorporation into the ring was established. The incorporation of ^{15}N-label into the pyrimidine ring of **75** follows the same pathway as formulated for 4-phenylpyrimidine (**66**) (ANRORC process).

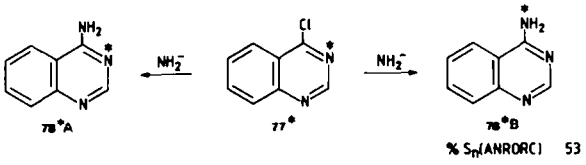
The Chichibabin amination of 4-*t*-butylpyrimidine was found[51] to occur to only a very limited extent according to an ANRORC-process.



Scheme 19.

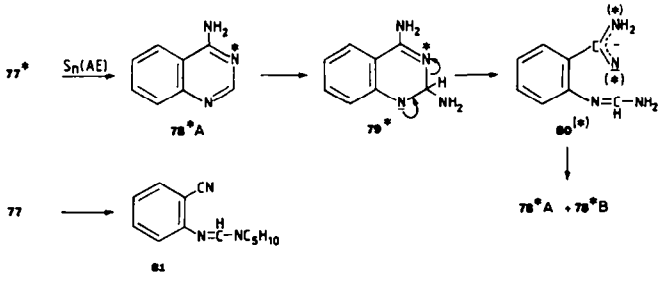
A.1.a.2. *Quinazolines.*

A.1.a.2.a. *Quinazolines, containing a nucleophugic group at position* 4. Amide-induced replacement of the chloro atom in 4-chloroquinazoline (**77**) was found to take place for 53% according to the S_N(ANRORC) mechanism.[55] This result was concluded from the fact that the amino group in 4-aminoquinazoline (**78***) obtained from [3-^{15}N]-4-chloroquinazoline (**77***) contained 53% of the ^{15}N-enrichment of **77***, i.e. **78*B**. The remaining 47% of the ^{15}N-enrichment in **78*** is present in the ring, i.e. **78*A**. Thus in quinazoline **77*** addition of the amide ion at C-2 [S_N(ANRORC)] leading to **78*B** and at C-4 [S_N(AE)] is highly competitive. The suggestion can be made[55] that the approximately equal



Scheme 20.

distribution of the ^{15}N-label over the ring nitrogen and amino nitrogen in the 4-amino compound **78*** (the actual ratio = 47:53) is due to a scrambling process in **80**$^{(*)}$, proposed as intermediate in an alternative mechanism (Scheme 21). Compound **78*A**, being obtained from **77*** by an S_N(AE) process, should undergo an addition of the amide ion to C-2, yielding **79***; ring-opening gives **80**$^{(*)}$ in which the ^{15}N is scrambled over both nitrogens in the amidino moiety. Ring-closure leads to a mixture of **78*A** and **78*B** (ratio 50:50). However, this suggestion seems highly unlikely, based on the consideration that **78*A** undergoes preferentially deprotonation of the amino group, making addition at C-2, yielding **79***, very unfavourable.



Scheme 21.

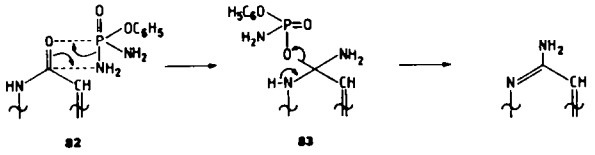
This was also experimentally verified:

An independently prepared specimen of **78*A** (^{15}N-enrichment 4.6%), when subjected to treatment with KNH_2–NH_3 under the same condition as used for **77***, does not show any decrease of ^{15}N-enrichment in the quinazoline ring, proving that scrambling indeed does not occur.

Reaction of 4-chloroquinazoline (**77**) with lithium piperidide–piperidine gives as main product *o*-(piperidinomethylene) iminobenzonitrile (**81**), demonstrating again the susceptibility of the C-2 position in 4-chloroquinazoline for nucleophilic attack.[55]

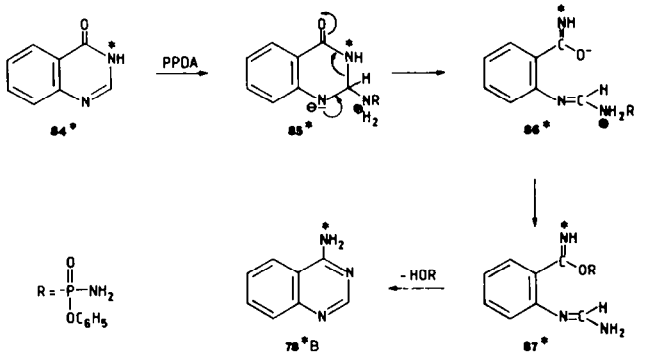
It was found[56] that 4-chloroquinazoline not only partly undergoes an S_N(ANRORC) replacement by a strong nucleophile, like an amide ion, but also by the weaker nucleophilic ammonia, the degree of S_N(ANRORC) participation, however, being lower (19% with ammonia, 53% with amide ion).

The replacement of an oxo group in an azinone by an amino group using as reagent phenylphosphorodiamidate (PPDA) at enhanced temperature is reported[57,58] to be a useful method for introducing amino groups; the oxo-amino exchange is proposed to involve intermediate **83**, obtained via a four-centre type transition state **82**.



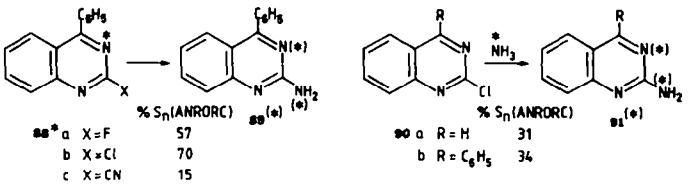
Scheme 22.

However, the amino-deoxogenation in quinazolin-4-one using PPDA at 235° is certainly more complicated than described in the scheme above, since it is found[59] that 4-aminoquinazoline obtained from [3-^{15}N] quinazolin-4-one (**84***) is a mixture of **78*B**, labelled in the amino group, and the ring-labelled **78*A**. A complication in this labelling study is that under the conditions of the reaction the amino group in 4-aminoquinazoline undergoes exchange with the amino group of the reagent, also via a ring-opening, ring-closure sequence. However, the exchange reaction occurs to a considerably lower extent than the amino-deoxogenation. The conclusion of this study was that the replacement of the oxo group by an amino group must partly involve the addition of the weak nucleophilic nitrogen of PPDA at C-2, yielding **85***, ring-opening into **86***, from which by an intramolecular N → O migration of the phenylphosphoroimidate group intermediate **87*** is obtained; cyclization yields **78*B**.



Scheme 23.

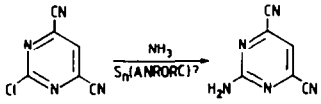
A.1.a.2.b. *Quinazolines containing at position* 2 *a nucleophugic group.* Because addition of nucleophiles to the C(4)—N(3) azomethine bond in quinazoline takes place more easily than addition at C-2 one can expect that the 2-halogenoquinazolines are probably more inclined to undergo an S_N(ANRORC) process than the 4-halogenoquinazolines. This has been found indeed. Amination of 2-chloro-4-phenyl-[3-^{15}N] quinazoline (**88*b**) with KNH_2–NH_3 gave 2-amino-4-phenylquinazoline (**89**$^{(*)}$), being exocyclic labelled for 70%.[56] So, despite the presence of a substituent at position 4, ring degenerate transformation takes place. Extension of these amination studies to the 2-fluoro- (**88*a**) and 2-cyano-4-phenylquinazoline (**88*c**) shows[56] that the reactivity order in this S_N(ANRORC) process is Cl > F > CN. This result is in qualitative agreement with the reactivity order found for amination of 2-Cl-, 2-F- and 2-CN-4-phenylpyrimidine (see Table 1).



Scheme 24.

The occurrence of an S_N(ANRORC) process has also been established in reactions of 2-chloroquinazoline (**90a**) and its 4-phenyl derivative (**90b**) with ^{15}N-labelled ethanolic ammonia at 160°, although, as expected, the extent in which this process takes place in the formation of the 2-aminoquinazoline **91**(*) is considerably lower than in the KNH_2–NH_3 system.[56] These results also show that the presence of the phenyl substituent on the position of the initial nucleophilic addition, i.e. C-4, does not influence the course of the reaction at all. The "blocking" effect of the phenyl group can apparently be neglected.

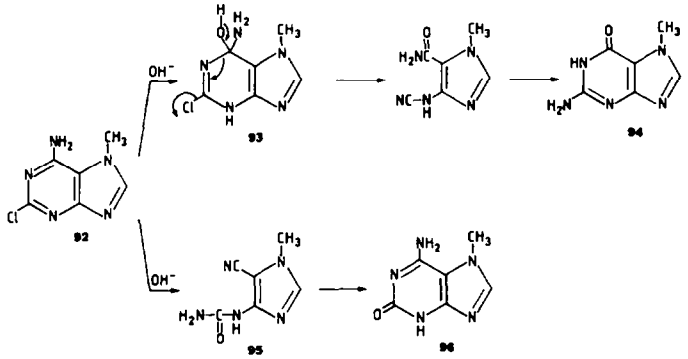
These results warrant us that the aminolysis of highly activated pyrimidines with aqueous or ethanolic ammonia—usually described to occur by the classical $S_N(AE)^{ipso}$ reaction—can take place according to the less conventional S_N(ANRORC) mechanism. As illustration: the conversion of 2-chloro-4,6-dicyanopyrimidine into 2-amino-4,6-dicyanopyrimidine by ammonia will at least partly occur by an S_N(ANRORC) process.[59a] The reaction needs to be investigated with ^{15}N-ammonia to establish the real pathway.



Scheme 24(a).

Comparison of the percentages of the ANRORC-reactions in the aminolysis of 2-chloroquinazoline and 4-chloroquinazoline with ethanolic ammonia (31%, resp. 19%) confirms the greater and easier accessibility of nucleophiles to addition of the azomethine C(4)—N(3) bond in quinazolines.[60]

A.1.a.3. *Purines.* The first ring degenerate transformation in heterocyclic chemistry was found in 1898, when Fisher discovered[61] that treatment of 6-amino-2-chloro-7-methylpurine (**92**) with base does not yield the expected 7-methylisoguanine (**96**) but 7-methylguanine (**94**). In a later reinvestigation[62] of this reaction it was shown that besides **94**, **96** is also formed, indicating that not one but two substitutions have taken place. The formation of **94** involves the intermediacy of the C-6 adduct **93** and the formation of an imidazole derivative obtained from **92** by a base-induced 1,4-dehydrochlorination. The hydroxy-dechlorination of **92** into **96** involves the (non-isolable) imidazole **95**, in which the urea side-chain adds across the nitrile group, leading to an intramolecular cyclization.

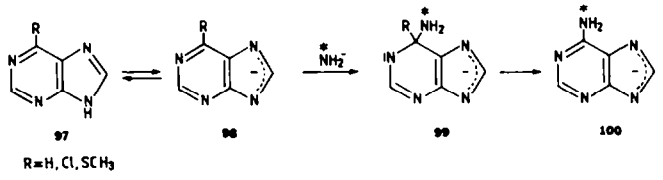


Scheme 25.

The conversion of **92** into **94** can undoubtedly be considered as a ring degenerate transformation and in fact is the first example of a nucleophilic displacement according to the S_N(ANRORC) mechanism. Although the conversion of **92** → **96** also involves an Addition Nucleophile Ring-Opening and Ring-Closure sequence, it is evident that this conversion cannot be classified as a ring degenerate transformation. Very recently, more examples of nucleophilic displacements, involving an ANRORC mechanism, but not leading to a ring degenerate transformation, have been reported.[63]

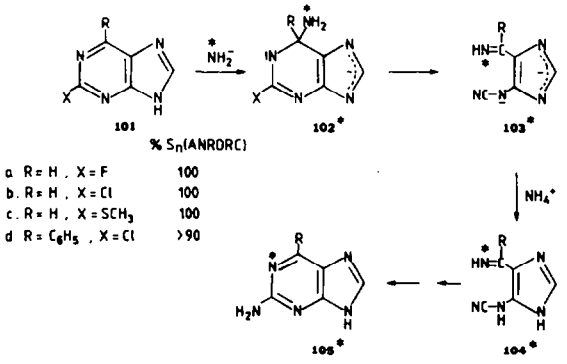
Extensive investigations of amide-induced aminations of purine and its derivatives have been carried out in order to establish whether these aminations would involve a ring degenerate transformation. It was found[38] that the parent substance purine (**97**, R = H) as well as its 2-methyl- and 8-methyl derivative undergo with KNH_2–NH_3 an exclusive amination at C-6. However, using ^{15}N-labelled potassium amide, *no* incorporation of the nitrogen-15 label in the ring took place. Thus, from **97** (R = H) adenine (**100***) is formed, having the ^{15}N-label exclusively on the amino nitrogen. As proved by NMR spectroscopy the reaction follows a pathway in which first the anion of purine is formed, i.e. **98** followed by addition of the amide ion at C-6 yielding the dianionic species **99**. The aromatization step takes place after neutralization with ammonium chloride.

Also the aminolysis of 6-chloro- and 6-(methylthio) purine into adenine (**100**) using ^{15}N-labelled KNH_2–NH_3 does not lead to incorporation of ^{15}N into the pyrimidine ring of **100**. All the results show that in the anion of purine and its 6-substituted derivatives, i.e. **98**, position 6 is the most reactive one for addition of the amide ion;[64] however, the dianionic σ-adduct **99** formed does not tend to undergo a ring-opening reaction.



Scheme 26.

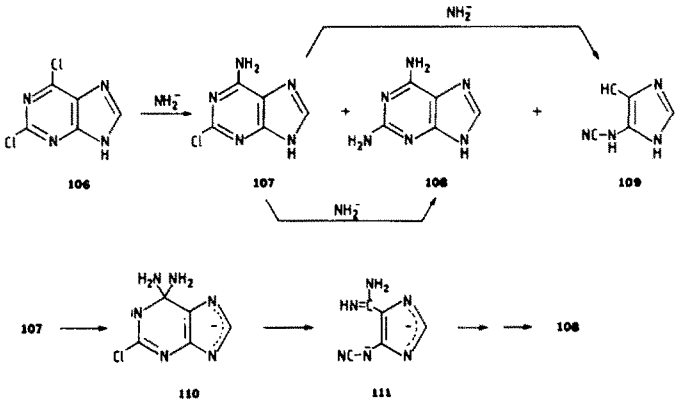
Amination of 2-fluoro (**101a**), 2-chloro (**101b**), 2-(methylthio) purine (**101c**) and 2-chloro-6-phenylpurine (**101d**) with ^{15}N-labelled KNH_2–NH_3 gives 2-aminopurine (**105***), containing *all* ^{15}N in the pyrimidine ring in the case of R = H and more than 90% in the case of R = C_6H_5.[65] This amination reaction is initiated by addition of the amide ion at C-6 yielding **102***, which, due to the presence of a group at C-2 with considerable leaving group character, is able to undergo ring-opening into **103***. After addition of ammonium chloride before work-up neutralization of **103*** into **104*** takes place, which by an internal cyclization of the iminomethylene and the aminocyano group gives **105***, with all the ^{15}N incorporated inside the ring. Supporting evidence for this mechanism, came from the fact that it was possible (i) to prove the formation of the short-lived C-6 σ-adduct **102** by ^1H-NMR spectroscopy, (ii) to isolate the rather unstable imidazole derivative **104** (R = H) and (iii) to prove by IR spectroscopy the presence of the conjugated N—CN group.



Scheme 27.

That position 6 in a purinyl anion is indeed the most vulnerable position for nucleophilic attack of the amide ion can further be shown[65] by the fact that if this position is occupied by a substituent, such as in 6-methylpurine, 6,8-di-*t*-butylpurine, 6-*t*-butyl-8-(methylthio) purine and in adenine, no reaction takes place. The effective blocking effect of the 6-*t*-butyl group is certainly due to its bulkiness and that of the 6-methyl and the 6-amino group by the easy formation of their conjugate bases, being highly inactivated for nucleophilic attack.

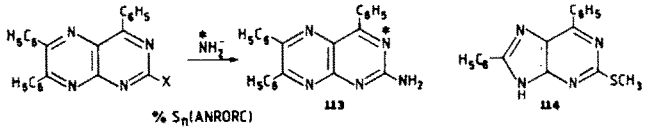
Amination of 2,6-dichloropurine (**106**) with KNH_2–NH_3 leads to the formation of three products: 2-chloroadenine (**107**), 2,6-diaminopurine (**108**) and 4-cyano-5-cyanoaminoimidazole (**109**).[66] The last two compounds originate from **107** as subsequent reaction products.



Scheme 28.

It seems highly unlikely that **108** is formed by an $S_N(AE)^{ipso}$ reaction at C-2, in view of the fact that amination at C-2 in purines seems to involve in general an initial attack at C-6. It is postulated that in the formation of **108** first initial addition takes place at C-6. In the σ-adduct **110** the pyrimidine ring is opened to give the imidazole **111**; cyclization yields **108**. Addition of an amino group to a position being already occupied by an amino group is not unprecedented. The amide-induced ring transformations of 4-amino-2-bromoquinoline into 4-amino-2-methylquinazoline[67] and of 4-amino-2-bromo-1,5-naphthyridine into 4-amino-2-methyl-1,3,5-triazanaphthalene[68] are good examples of a reaction in which addition of the amide ion to the C-4 position in quinoline, being occupied by an amino group, has to take place in order to understand the course of the reaction.

A.1.b.4. *Pteridines.* There are only a few reports on the occurrence of ring degenerate transformations during aminolysis of pteridines. It was found[69–72] that 2-X-4,6,7-triphenylpteridines (**112 a–c**) on treatment with KNH_2–NH_3 undergo two different conversions: aminolysis to 2-amino-4,6,7-triphenylpteridine (**113**) and in the case of X = SCH_3 an additional ring contraction into 2-(thiomethyl)-6,8-diphenylpurine (**114**). The formation of **113** involves a ring degenerate transformation since reaction of **112** with ^{15}N-labelled KNH_2–NH_3 leads to incorporation of ^{15}N into the pyrimidine ring. The percentage of S_N(ANRORC) mechanism depends on the nature of the substituent. The reactivity order is Cl > SCH_3 > F. The percentage of molecules of **112** that undergo this ring degenerate transformation is also strongly dependent on the potassium amide concentration: 1 mmol of **112c** dissolved in 25 ml of liquid ammonia with 4 eq. of potassium amide react for 50% according to the S_N(ANRORC) mechanism, but with 10 eq. of potassium amide this percentage is 85%.[69]



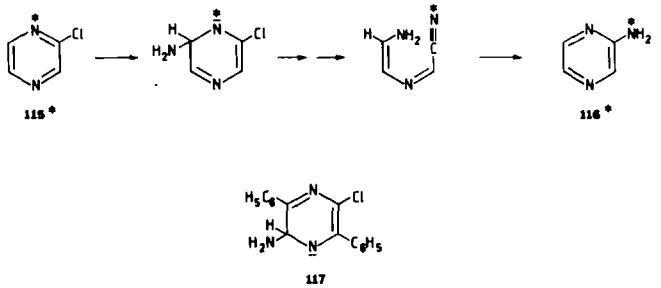
% S_N(ANRORC)

112 a X = F 40
b X = Cl 100
c X = SCH_3 50–85

Scheme 29.

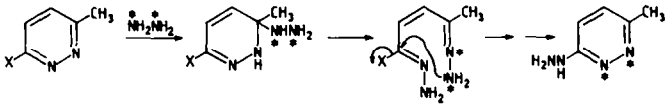
These results clearly evidence that qualitative comparison of the reactivity of compounds with different nucleophugicities is only allowed if one is assured that the concentration of potassium amide, used in these studies, is nearly the same.

A.1.a.5. *Pyrazines and pyridazines.* The occurrence of a ring degenerate transformation has also been established in the amination of 2-chloropyrazine (**115**). Reaction of 2-chloro-[1-^{15}N]-pyrazine (**115***) with KNH_2–NH_3 gave 2-aminopyrazine (**116***), being exclusively ^{15}N-labelled on the amino group.[73,74] This rearrangement can be described according to the same ANRORC-mechanism as presented for the amination of 4-bromo-6-phenylpyrimidine (**5**) (see Section A.1.a.1). That in the pyrazine ring system the amide ion preferentially attacks on a carbon position not carrying the chloro atom, has been firmly established in the covalent amination of 2-chloro-3,6-diphenylpyrazine, yielding the anion σ-adduct **117**.[75] Extensive studies on the amination of 2-chloroquinoxaline have shown that in the formation of 2-aminoquinoxaline no ring-opening has been involved.[76]



Scheme 29(a).

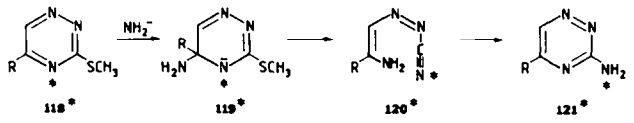
In the pyridazine series it has been shown that in the reaction of 3-X-6-methylpyridazines (X = Cl,Br) with double ^{15}N-labelled hydrazine a part of the ^{15}N-label (20–30%) is incorporated into the ring of the product 3-hydrazino-6-methylpyridazine.[77] This ring degenerate transformation can be described as pictured below, involving an initial addition of the nucleophilic hydrazine at C-6. For a more thorough discussion on ring transformations of *ortho* diazines with hydrazine, we refer to Section A.1.c.



Scheme 29(b).

A.1.b. *Ring degenerate transformation of triazines*

A.1.b.1. 1,2,4-*Triazines and benzo*-1,2,4-*triazines.* Studies on the amination of 3-X-1,2,4-triazines have shown that they easily undergo ring degenerate transformations, provided that these compounds contain at C-3 a nucleophugic group with a negative resonance factor (see Table 5). When 3-(methylthio)-1,2,4-triazine (**118*a**), being enriched with ^{15}N-label at position 4, is aminated into 3-amino-1,2,4-triazine (**121*a**), 93% of the ^{15}N-label is located on the *exocyclic* amino group.[78]



		% S_N(ANRORC)
a	R = H	93
b	R = C_6H_5	100
c	R = t-C_4H_9	95

Scheme 30.

The mechanism involves the intermediacy of the C-5 σ-adduct **119*** and its existence has been firmly proven by ^{1}H- and ^{13}C-NMR spectroscopy.[79] The open-chain compound 1-cyano-4-amino-1,2-diaza-1,3-butadiene (**120***) could not be isolated, despite many efforts.

When 5-phenyl- (**118*b**) and 5-*t*-butyl-3-(methylthio)-[4-^{15}N]-1,2,4-triazine (**118*c**) was reacted with KNH_2–NH_3, the 3-amino compounds obtained, i.e. **121*b** and **121*c** respectively, contained the ^{15}N-label for more than 95% on the exocyclic amino group.[80] Apparently the presence of the phenyl or *t*-butyl group at C-5 has no effect at all on the covalent addition at C-5. This is a remarkable result, especially for the *t*-butyl group, bearing in mind its bulkiness and electron-donating character, which should prevent or at least retard the addition to C-5, and therefore should favour the competitive *ipso* nucleophilic displacement at C-3 ($S_N(AE)^{ipso}$ mechanism).[81]

The high susceptibility of C-5 in 1,2,4-triazine for nucleophilic addition can further be nicely demonstrated by the fact that the parent 1,2,4-triazine undergoes covalent addition at C-5 with liquid ammonia,[162] while pyrimidine, pyrazine and pyridazine need the strong nucleophilic amide ion to give covalent adducts.[16j,82] Studies on the amination of 3-X-5-phenyl-1,2,4-triazines (**122a**) with different substituents at position 3 (X = F,Cl,Br,I,SO_2CH_3,$N^+(CH_3)_3$) into the corresponding 3-amino-5-phenyl-1,2,4-triazines (**123a**), using either ^{15}N-labelled substrates **122*a** with unlabelled KNH_2–NH_3 or unlabelled substrates **122a** with ^{15}N-labelled KNH_2–NH_3, gave the results as being summarized in Table 5.[80,83] These results show that the 1,2,4-triazines **122a** undergo—although to a different degree—the ring degenerate transformations according to the S_N(ANRORC) mechanism and that the reactivity order is $SCH_3 > Cl \sim Br > I > SO_2CH_3 > N^+(CH_3)_3 > F$.

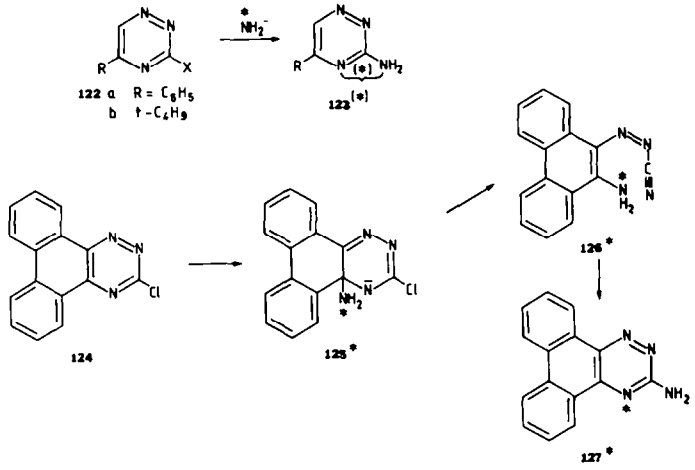
Comparison of this reactivity order with that found in 2-X-4-phenylpyrimidines ($SCH_3 \sim Br \sim Cl > F > SO_2CH_3 \sim I > N^+(CH_3)_3$, see Table 1) shows important differences. Especially the fluoro substituent, which in the pyrimidine series has about the same reactivity order as the chloro or bromo atom, shows in the 1,2,4-triazine series a low activity for addition at C-5. A sufficient explanation was not offered. However, one factor has to be mentioned which probably makes comparison of the reactions of 5-phenyl-3-X-1,2,4-triazines (**122a**) with those of the 2-X-4-phenyl-pyrimidines rather troublesome, namely the fact that the yields obtained in the 1,2,4-triazine series (see Table 5) are considerably lower than the ones obtained with the pyrimidines, due to the occurrence of side-reactions, i.e. ring contraction, dehalogenation, ring degenerate transformation. Some of these reactions are initiated by addition at C-5 of nucleophilic species, being formed during the amination reaction by degradation of the starting material.[83] Thus, the percentage of the molecules that undergo addition at C-5 is certainly higher than can be derived from the percentage of the molecules that undergo the S_N(ANRORC) type amination.

Also the presence of a *t*-butyl group at position 5 does not prevent amination at C-3 in 3-X-5-*t*-butyl-1,2,4-triazine [**122b**, X = Cl,SO_2CH_3,$N^+(CH_3)_3$] according to the S_N(ANRORC) process. Using either ^{15}N-labelled substrates or ^{15}N-labelled potassium amide it could be proved that a considerable percentage of the compounds (X = Cl,SO_2CH_3) undergo amination with ring-opening (X = Cl, 95%; X = SO_2CH_3, 54%), and that for X = $N^+(CH_3)_3$ this percentage is much smaller ($\pm$ 13%). An elegant experiment also demonstrating the easy accessibility of C-5 in the 1,2,4-triazine ring is found in the amination of 3-chlorophenanthro-1,2,4-triazine (**124**).[84] On treatment of ^{15}N-labelled KNH_2 it was established that 75% of the ^{15}N-labelling being found in the 3-amino compound **127*** was present *inside* the ring. This result can only be explained if addition takes place at the C-5a-position in **124**, yielding σ-adduct **125*** from which the ring-opened intermediate **126*** is formed. Addition of an amide ion to a

Table 5. Yields obtained in the amination of 3-X-5-phenyl-1,2,4-triazines (**122a**) and % S_N(ANRORC) mechanism in these aminations involved

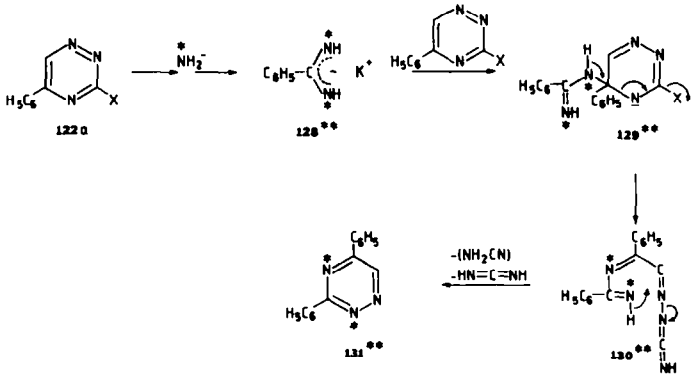
Substituent X	Yield (a)	S_N(ANRORC) (b)	a × b
SCH_3	72%	100%	0.71
F	54%	18%	0.10
Cl	40%	96%	0.38
Br	29%	93%	0.28
I	31%	63%	0.20
SO_2CH_3	65%	33%	0.22
$N^+(CH_3)_3$	42%	34%	0.14

junction carbon is unusual, certainly in the light of the results of the amination of 3-chlorobenzo-1,2,4-triazine[83] and 2-chloroquinoxaline[76] showing that with ^{15}N-labelled KNH_2–NH_3 the amino products obtained from these compounds contain the ^{15}N-label *exclusively* on the nitrogen of the amino group; no incorporation of nitrogen-15 into the pyrazine ring or 1,2,4-triazine ring was observed.



Scheme 31.

As already mentioned before, amination of **122a** (X = Cl,Br,I) gave besides the 3-amino compounds **123a** several by-products. It is certainly beyond the scope of this review to discuss the formation of all these by-products, however with exception of one, namely the formation of 3,5-diphenyl-1,2,4-triazine (**131**).[83] Evidence has been presented that the formation of **131** is due to the fact that in this strong basic medium **122a** partly decomposes into the potassium salt of benzamidine (**128**). Interestingly enough, when the reaction was carried out with ^{15}N-labelled potassium amide *both* nitrogens of benzamidine **128**** were found to be ^{15}N-labelled. Also in **131** two nitrogens are labelled, i.e. **131****. This ring transformation is a very interesting and quite unusual one, since it presents the rare case of incorporation of *two* nitrogen atoms, derived from the potassium amide, into the 1,2,4-triazine ring system. The benzamidine anion **128**** plays a role in the formation of **131**** from **122a**, following a reaction pathway involving a nucleophilic attack of the benzamidine anion to C-5 in **122a** yielding **129****, ring-opening into the peculiar open-chain species **130**** and ring-closure into **131**** by loss of carbodiimide (or aminocyan).



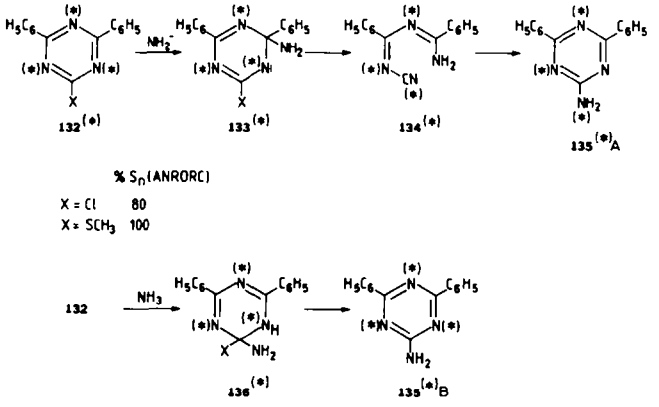
Scheme 32.

It was established that the amino-deoxogenation of 5-phenyl-[4-^{15}N]-1,2,4-triazin-3-one (**122*a**, X = OH) into the 3-amino compound **123*** by reaction with phenylphosphorodiamidate occurs for only a small percentage (± 10%) according to the S_N(ANRORC) process.[80] The remaining ± 90% probably reacts according to the route described before, involving transition state **82**. The corres-

ponding conversion of 5-*t*-butyl-[4-^{15}N]-1,2,4-triazin-3-one into 5-*t*-butyl-3-amino-1,2,4-triazine by the same reagent phenylphosphorodiamidate does not involve a ring-opening reaction at all.[80]

A.1.b.2. 1,3,5-*Triazines.*

A.1.b.2.a. 1,3,5-*Triazines, containing a leaving group at carbon.* 2-X-4,6-Diphenyl-1,3,5-triazine (**132**, X = Cl,SCH_3) can be converted with good yields into 2-amino-4,6-diphenyl-1,3,5-triazine (**135**) by treatment with KNH_2–NH_3.[85] When this amination was carried out with ^{15}N-labelled substrate **132**$^{(*)}$, the greater part of the ^{15}N-label was found to be present on the exocyclic nitrogen of the amino group in the 2-amino compound, i.e. **135**$^{(*)}$**A**; 80% of the 2-chlorocompound (**132**$^{(*)}$, X = Cl) and 100% of the 2-(methylthio) derivative (**132**$^{(*)}$, X = SCH_3) undergo the ring-opening, ring-closure sequence (**132**$^{(*)}$ → **133**$^{(*)}$ → **134**$^{(*)}$ → **135**$^{(*)}$**A**) during the amination. These results again show the striking fact that the carbon atoms to which the phenyl groups are attached are more favoured for attack by the amide ion than the carbon, being substituted by the chloro or methylthio group.



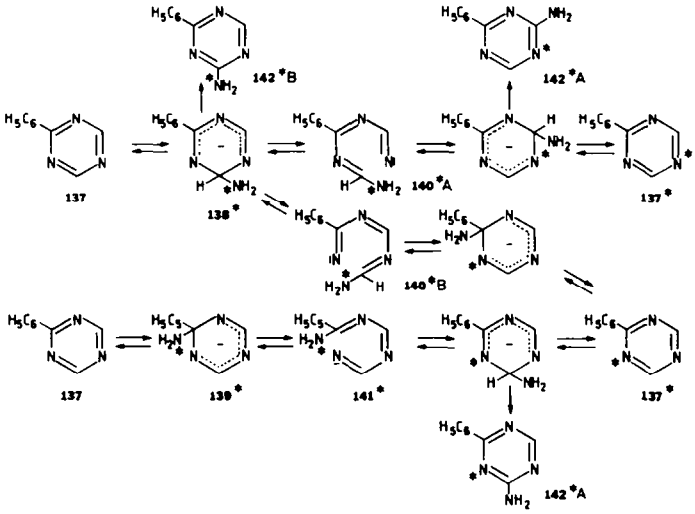
Scheme 33.

The percentage of **132**$^{(*)}$ (X = Cl) that undergoes this ring degenerate transformation during the amination is strongly dependent of the substrate/potassium amide ratio used: with 33 eq. of KNH_2 the % S_N(ANRORC) mechanism amounted to 91%, with 6 eq. KNH_2 it was 80%, with 2 eq. KNH_2 it decreased to the low percentage of 6% and with liquid ammonia, not containing potassium amide, the % S_N(ANRORC) was 0%. Thus, with a decreasing amount of potassium amide the percentage of **132** (X = Cl) that undergoes the ring degenerate transformation also decreases. The competitive $S_N(AE)^{ipso}$ process leading to **135*B** is the only reaction which takes place when no KNH_2 is present. Apparently in the amination of the highly electron-deficient 1,3,5-triazines a competition is involved between the strong nucleophilic amide ion, aminating **132*** (X = Cl) via the σ-adduct **133** and open-chain compound **134** [S_N(ANRORC) process] and the weak nucleophile ammonia, which reacts with **132*** (X = Cl) by an S_N(AE) process, involving the C-2 adduct **136***.

A.1.b.2.b. *Chichibabin amination of* 1,3,5-*triazines.* Chichibabin amination of phenyl-1,3,5-triazine (**137**) by KNH_2–NH_3 at low temperature was found to involve a ring degenerate transformation[86] (see for corresponding results in the pyrimidine series, Section A.1.a.1.e). The formation of 4-amino-2-phenyl-1,3,5-triazine (**142**) occurs very slowly (reaction time 70 hr) and in low yield (10%) and even addition of potassium nitrate does not show a perceptible increase in the rate of formation of **142**. The ^{1}H-NMR spectrum of a solution of **137** in KNH_2–NH_3 displays the resonance signals of σ-adduct **138**. By reacting **137** with ^{15}N-labelled KNH_2–NH_3, 55% of the ^{15}N-enrichment in the amino compound was incorporated into the triazine ring, i.e. formation of **142***. This process of ^{15}N-incorporation may be initiated by ring-opening of the covalent anionic σ-adduct **138**, although an alternative possibility, i.e. ring-opening of the σ-adduct **139***, cannot be excluded. The results obtained do not provide information on the relative importance of these two routes, but there is enough experimental evidence that ring carbon atoms substituted by a phenyl group but adjacent to the ring nitrogen are vulnerable to nucleophilic attack and can undergo addition.

Since the formation of σ-adduct **138** is rapid and the formation of the amino-1,3,5-triazine **142** slow,

it is possible that equilibria are involved between **137**, its σ-adducts **138** (and possibly **139**) and the open-chain amidines **140** and **141**. If this equilibrium substrate $\rightleftarrows$ σ-adducts $\rightleftarrows$ amidines indeed exists one can expect that quenching of the reaction of **137** with ^{15}N-labelled KNH_2–NH_3 before it comes to completion may lead to incorporation of nitrogen-15 in the starting material. This has been found indeed. After 40 hr reaction time about 50% of ^{15}N was incorporated in recovered starting material, i.e. **137***.



Scheme 34.

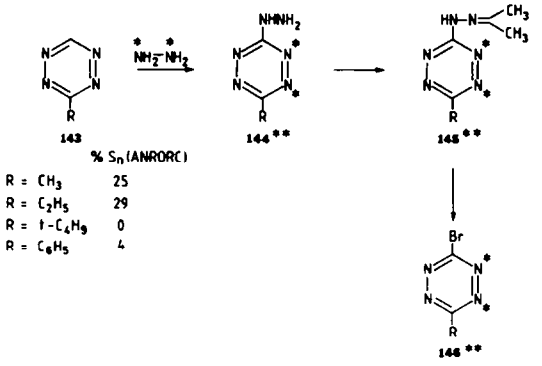
4,6-Diphenyl-1,3,5-triazine (**132**, X = H) undergoes in a very low rate Chichibabin amination by KNH_2–NH_3 into the 2-amino compound **135** in good yield. When the mono-labelled **132**$^{(*)}$ (X = H) was subjected to the Chichibabin amination and the incorporation of the ^{15}N-label in the amino group of **135** was determined, all ^{15}N-label was found to be present on the amino nitrogen, excluding a ring-opening, ring-closure process.[85] A remarkable contrast to the results obtained in the amination of phenyl-1,3,5-triazine (**137**). Since **132** (X = H) easily gives σ-adduct **136** (X = H) it is apparently not the addition reaction, but the ring-opening which does not occur.

A.1.c. *Ring degenerate transformation of* 1,2,4,5-*tetrazines*

Hydrazination of 3-alkyl(aryl)-1,2,4,5-tetrazines (**143**), using 3 eq. of hydrazine hydrate in ethanol at room temp gives in low yield the 3-alkyl(aryl)-6-hydrazino-1,2,4,5-tetrazine (**144**). When the hydrazination of **143** (R = CH_3,C_2H_5) was carried out with ^{15}N-double-labelled hydrazine, a small incorporation (25–30%) of the ^{15}N-label was found[87] in the tetrazine ring of **144****; no ^{15}N-incorporation was observed in **144**** for R = *t*-butyl and only 4% in **144**** for R = C_6H_5. Since the hydrazino compounds **144**** are somewhat unstable and difficult to purify, the method to establish the ^{15}N distribution over ring nitrogens and nitrogens in the hydrazino group involved first derivatization into its acetone-hydrazones **145**** and subsequent conversion into the 6-bromocompounds **146**** by oxidation with bromine in acetic acid. The percentage of ^{15}N-enrichment in the double-labelled molecules was determined by quantitative mass spectrometry, comparing the M + 2 peak of those double-labelled compounds with those of unlabelled reference compounds.

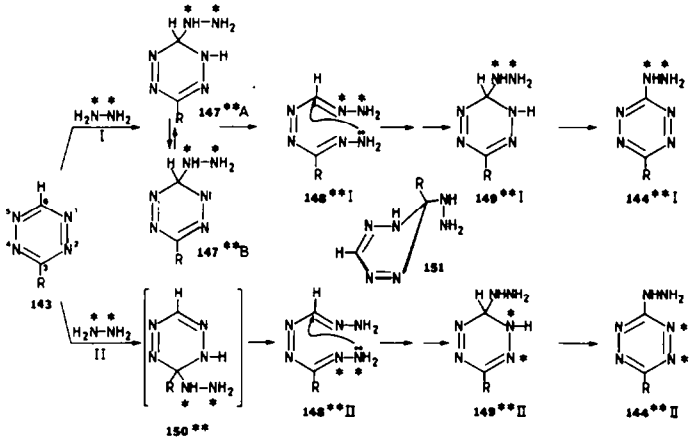
^1H- and ^{13}C-NMR spectroscopy of a solution of **143** in hydrazine hydrate in deuteromethanol at −40° shows clearly the presence of C-6 adduct **147** as evidenced by the large upfield shift of H-6 ($\Delta\delta$ between 8.25 and 8.92 ppm) and C-6 ($\Delta\delta$ = 59–62 ppm), accompanied by the decrease of $J_{C6\text{-}H}$ from 213–215 Hz in **143** to 159–160 Hz in **147**.[87] Evidence was presented that at the pH of the solution adduct **147** was present in its anionic form **147B**.[87] The large upfield shift found for H-6 was proved to be due to the homoaromatic structure of the adduct.[88–91] On warming of these solutions the anionic homoaromatic σ-adducts **147** are converted into open-chain intermediates as evidenced by both ^1H- and ^{13}C-NMR spectroscopy. These intermediates are formulated as **148**.

From the results of the spectroscopic studies on the ^{15}N-labelling distribution in product **144** it is postulated that **148****I undergoes preferentially or exclusively ring-closure by a nucleophilic



Scheme 35.

addition of the nitrogen of the hydrazino group on C-6 and not on C-3, carrying group R. This exclusive mode of addition is due to the fact that if addition on C-3 would take place, it should lead to the homoaromatic species **151** featuring two large groups (R and the hydrazino group) on the methylene bridge; this seems highly unlikely. The fact that the *t*-butyl compound **143** (R = *t*Bu) does not undergo hydrazination with ^{15}N-incorporation supports this hypothesis strongly. Thus, from **148**I** only cyclization into **149**I** occurs; it leads to the 6-hydrazinocompound **144**I**, being labelled on the exocyclic nitrogen.

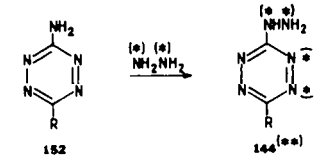


Scheme 36.

The fact that during hydrazination of **143** (R = CH_3,C_2H_5) ^{15}N-incorporation took place, at least to some extent, requires the intermediacy of the C-3 adduct **150****, which via **148**II** and **149**II** gave the 6-hydrazinocompound **144**II** being ^{15}N-labelled in the tetrazine ring.

All data available show that both routes I and II involve an additional ring-opening, ring-closure sequence. They differ, however, considerably, since route II leads to a ring degenerate product, i.e. **144**II**, while route I gives product **144**I**, in which no ^{15}N was incorporated. The reaction sequence described in route I is very interesting, since it is one of the few examples in which it could be proven that the nucleophilic substitution occurs with ring-opening and the ring-closure but leading to a tetrazine without ^{15}N-incorporation into the ring.[92] Thus, no evidence for an S_N(AE) process has been found. Which factor(s) determine(s) why the ring is first opened before product formation takes place is not well understood; more examples of this type of ANRORC reactions have to be found before a more concise picture of this interesting phenomenon could be obtained.

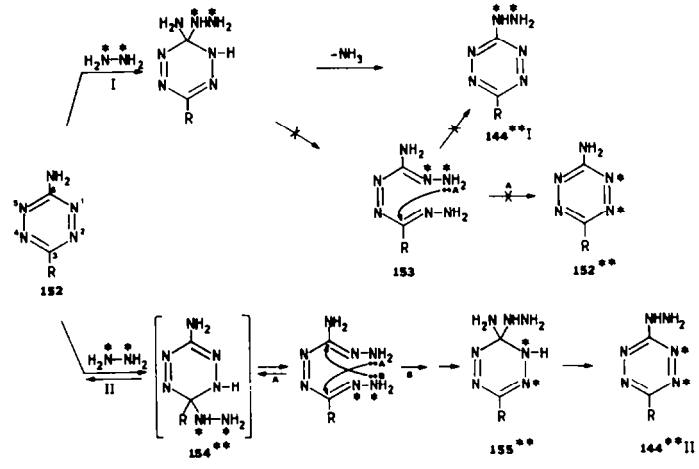
The complexity of the reaction between 1,2,4,5-tetrazines and hydrazine can further be illustrated on the hydrazino-deamination in 3-alkyl(aryl)-6-amino-1,2,4,5-tetrazines (**152**).[87] Treatment of **152** (H,CH_3,C_2H_5) with double-labelled hydrazine gives the 6-hydrazino compound **144(**)**, having a *partial* incorporation of ^{15}N-label in the tetrazine ring.



	% S_N(ANRORC)
R = H	22
R = CH_3	25
R = C_2H_5	18
R = t-C_4H_9	0
R = C_6H_5	0

Scheme 37.

A very careful ^{1}H- and ^{13}C-NMR spectroscopic analysis of the reaction mixture obtained between **152** (R = CH_3) and hydrazine in several stages during the reaction showed the appearance and disappearance of signals which, combined with the results of the ^{15}N-labelling, make it possible to propose the following mechanism for the hydrazino-deamination.[87]



Scheme 38.

In contrast to the route given for the formation of **144**I** from **143**, it is very likely that compound **144**I**, obtained from **152**, is not formed in an ANRORC-process, but according to the $S_N(AE)^{ipso}$ mechanism. The reason to exclude the ANRORC-mechanism is that it should involve the intermediacy of **153**, from which besides **144**I**, starting material **152**** (R = CH_3) with incorporation of ^{15}N-label should be obtained. This is not found.

The formation of ring-labelled **144**II** (R = CH_3) involves as intermediate the homoaromatic species **154** (R = CH_3) and **155** (R = CH_3). The fact that in the hydrazination of **152** (R = *t*-Bu, C_6H_5) no ANRORC-process is involved supports the proposed mechanism, since with the *t*-butyl or phenyl group at position 3 the addition into **154** is prevented due to the steric requirements involved in the homoaromatic species.

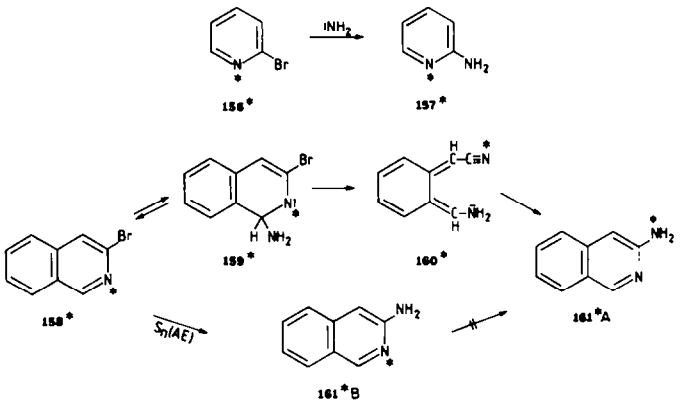
It has been reported[87] that also 3-methyl-6-X-1,2,4,5-tetrazines (X = Cl,Br) and 3-ethyl-6-bromo-1,2,4,5-tetrazine react with hydrazine into the corresponding 6-hydrazinocompounds for only a small percentage (2–20%) according to the S_N(ANRORC)-process.

A.1.d. *Ring degenerate transformations of isoquinolines*

Amination of 2-bromo[^{15}N]-pyridine (**156***) with KNH_2–NH_3 has been reported to yield 2-amino-[^{15}N]-pyridine (**157***) being exclusively labelled in the pyridine ring.[93] The fact that no ^{15}N-label is incorporated in the nitrogen of the amino group shows that in this amination no ring degenerate transformation has been involved; an $S_N(AE)^{ipso}$ process[2] seems the most reasonable pathway.

However, 3-bromo-[^{15}N]-isoquinoline (**158***), when subjected to treatment with KNH_2–NH_3

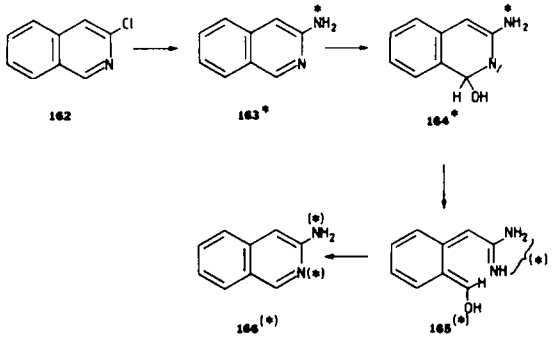
gave in good yield 3-aminoisoquinoline (**161**) containing 53% of its ^{15}N-enrichment on the exocyclic nitrogen, i.e. **161*A**, and 45% inside the ring, i.e. **161*B**.[94] In the formation of **161*A** the covalent σ-adduct **159*** and the open-chain intermediate **160*** are involved. The ratio 55:45 for the ^{15}N-distribution over the exocyclic and ring nitrogen in **161** suggests that a scrambling process in **161*B** [formed from **158*** by an $S_N(AE)$ process] might also explain the observed distribution (see the discussion mentioned in Sections A.1.a.1.d and A.1.a.2.a). Control experiments with labelled 3-aminoisoquinolines show that this compound does not undergo scrambling under the conditions of the amination.[94]



Scheme 39.

That 2-bromopyridine does not, and 3-bromoisoquinoline undergoes (partly) an S_N(ANRORC) process can be easily understood in the light of covalent amination studies of the parent azines with KNH_2–NH_3: pyridine does not form a σ-adduct,[82] but isoquinoline easily gives an adduct at C-1.[95] Therefore the intermediacy of σ-adduct **159*** in the formation of **161*A** seems very plausible.

Extension of this work to aminate **158*** with ethanolic ammonia has shown[94] that under the conditions applied (130°, a week, $CuSO_4$) about 25% of the molecules of **158*** undergo amination involving a ring-opening reaction. It is of interest that one of the first reports on ring-opening reactions during aminolysis concerned the reaction of 3-chloroisoquinoline (**162**) with labelled aqueous ammonia (44 hr, 155–180°).[96] In the 3-aminoisoquinoline (**166**$^{(*)}$) formed there is an about equal distribution of the ^{15}N-label over the ring nitrogen and the exocyclic nitrogen. This result has been explained by a ring-opening in the primarily formed 3-aminoisoquinoline (**163***) that under the severe conditions of the reaction undergoes covalent hydration into **164*** and subsequent ring-opening into the formamidine derivative **165**$^{(*)}$, in which both nitrogens are scrambled. It has been argued that a combination of an S_N(ANRORC) and S_N(AE) process could also explain the results of the ^{15}N-labelling experiment very easily.



Scheme 40.

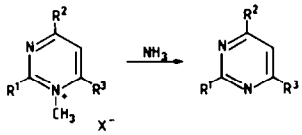
B. RING DEGENERATE TRANSFORMATIONS OF AZINES, INVOLVING THE REPLACEMENT OF ONE OR MORE ATOMS OF THE HETEROCYCLIC RING BY ONE OR MORE ATOMS OF A NUCLEOPHILE

All reactions discussed in Section A were carried out with azines, containing one or more nitrogen atoms and being substituted by a group or atom with considerable nucleophugicity. As we have seen, they are found to be accessible for nucleophilic attack on a carbon atom by strong nucleophilic reagents, being more than one atom away from the one occupied by the leaving group. The ring degenerate transformations which will be discussed in Section B deal with azines in which no substituent with good nucleophugicity is present and in which the electron deficiency is enhanced by ring nitrogen quaternization or by introduction of strong electron acceptors. These azines are very apt to react with weak nucleophiles. The presentation follows the same line as used in Section A. First, the chemistry of ring degenerate transformations of appropriately substituted pyrimidines will be discussed, since these systems can easily undergo B-type transformations. Then follows a discussion on ring degenerate transformations with pyridines and triazines.

B.1. RING DEGENERATE TRANSFORMATIONS OF PYRIMIDINES AND BENZO DERIVATIVES

B.1.a. *Ring degenerate transformations involving a one atom replacement*

B.1.a.1. *Ring degenerate transformations involving the replacement of a ring nitrogen by the nitrogen of liquid ammonia.* When 1-methylpyrimidiniummethylsulphate (**167a**, $X^- = CH_3OSO_3^-$) is dissolved in liquid ammonia at $-33°$ and allowed to react for 1 hr, pyrimidine (**168a**) is formed (yield 55–60%).[97] This demethylation reaction proved to be a general reaction since 1,2-dimethylpyrimidinium iodide (**167b**, $X^- = I^-$),[97] 1,4,6-trimethylpyrimidinium iodide (**167c**, $X^- = I^-$),[97] 1,2,4,6-tetramethylpyrimidinium iodide (**167d**, $X^- = I^-$)[97] and 1-methyl-4-phenylpyrimidinium iodide (**167e**, $X^- = I^-$)[51] are also found to be demethylated into the corresponding pyrimidine derivative. Dealkylation also occurs with aqueous ammonia.[98]

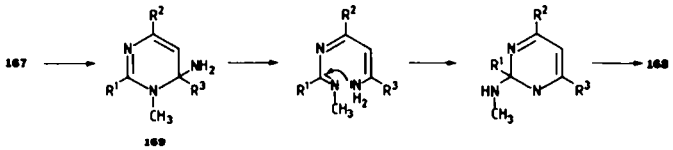


a $R^1 = R^2 = R^3 = H$
b $R^1 = CH_3$, $R^2 = R^3 = H$
c $R^1 = H$, $R^2 = R^3 = CH_3$
d $R^1 = R^2 = R^3 = CH_3$
e $R^1 = R^3 = H$, $R^2 = C_6H_5$

Scheme 41.

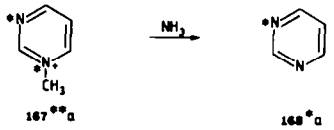
The very mild conditions which can be applied to achieve the demethylation are in remarkable contrast to the drastic conditions used for the dealkylation of pyridinium salts by hard and soft nucleophiles. This difference in reaction conditions suggested that in liquid-ammonia-induced demethylation another mechanism is operative than the S_N2-type displacement in the demethylation of pyridinium salts.[99–100]

It was considered that the demethylation started by initial addition of ammonia to C-6, yielding the σ-covalent adduct **169**. An electrocyclisation of **169** into the 6-amino-1,3-diazatriene and subsequent cyclisation, due to a nucleophilic attack of the nitrogen of the amino group on the electron-deficient carbon in the azomethine bond, would lead to 1,2-dihydro-2-(methylamino)pyrimidine that by loss of methylamine would form **168**.



Scheme 42.

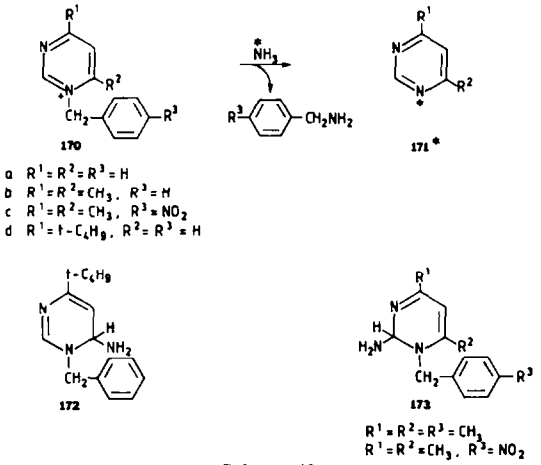
The mechanism proposed was proved to be correct. When the double-labelled pyrimidinium salt **167**a**—prepared from [1,3-^{15}N]-pyrimidine with dimethylsulphate—was reacted with liquid ammonia, pyrimidine contained ^{15}N nearly exclusively on one of the nitrogens, i.e. **168*a**.[97] Evidence



Scheme 42 (a).

that the initial addition of the ammonia indeed takes place at position 6 and not at position 2—an alternative way to explain the demethylation reaction—has been obtained by ^{1}H-NMR spectroscopy (see Table 6).[97] The ^{1}H-NMR spectrum of a solution of **167a** in liquid ammonia displays the resonance signals at much higher field than the ones obtained in a solution of **167a** in D_2O. The hydrogen of position 6 is most upfield shifted (about 4.6–4.8 ppm), reflecting the $sp^2 \rightarrow sp^3$ rehybridisation. In addition, a change in the multiplicity pattern as well as in the magnitude of the coupling constant is observed which fully supports the intermediacy of **169**. Similar observations were made with the pyrimidinium salts **167b** and **167c**.

It has recently been reported that also the N-benzyl salts of pyrimidine (**170a**), 4,6-dimethylpyrimidine (**170b, c**) and 4-*t*-butylpyrimidine (**170d**) undergo debenzylation in liquid ammonia.[101] When reacting **170b** with ^{15}N-labelled ammonia 4,6-dimethylpyrimidine obtained contained ^{15}N, indicating that an ANRORC mechanism is involved in the benzylamine–ammonia exchange. ^{1}H-NMR spectroscopy undoubtedly showed that **170d** undergoes an initial addition at C-6, i.e. **172**, but that **170b, c** surprisingly gives the C-2 adduct **173**.[101] The ring-opening and ring-closure takes place according to the same process, as pictured for the conversions **167** → **168**.

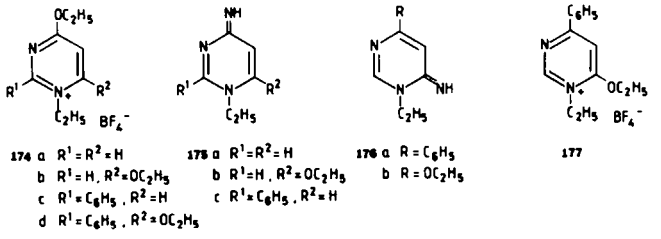


Scheme 43.

Table 6. Chemical shifts (δ) of the ring H-atoms of the N-alkylpyrimidinium salts **167a–c**, **174a–b** and **183** (R = H)

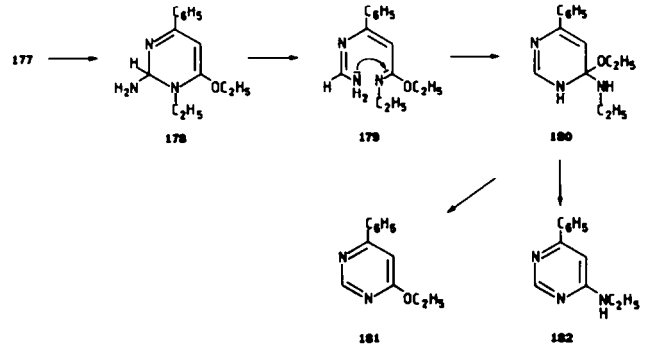
Compound	Solvent	H(2)	H(4)	H(5)	H(6)
167a ($X^- = CH_3OSO_3^-$)	D_2O	9.60	9.39	8.17	9.21
	NH_3	6.94	6.27	4.91	4.57
167b ($X^- = I^-$)	D_2O	—	9.0	8.01	9.2
	NH_3	—	6.15	4.84	4.42
167c ($X^- = I^-$)	D_2O	9.34	—	8.00	—
	NH_3	6.82	—	4.48	—
174a	acetone-d_6	9.36	—	7.45	8.90
	NH_3	5.37	—	4.57	6.84
174b	acetone-d_6	9.05	—	6.92	—
	NH_3	5.26	—	4.10	—
183 (R = H)	acetone-d_6	9.50	—	6.14	—
	NH_3	5.20	—	4.12	—

The 4-ethoxy-1-ethylpyrimidinium salts **174a** and **174b**, when subjected to treatment with liquid ammonia at −33°, gave a reaction different from the one found with the N-methylpyrimidinium salts **167**. *No* N-deethylation is observed, only replacement of the ethoxy group by an amino group at position C-4 and/or C-6. From **174a** 1,4-dihydro-1-ethyl-4-iminopyrimidine (**175a**, 68%) is obtained and from **174b** a mixture of the 1,4-dihydro-6-ethoxy-1-ethyl-4-iminopyrimidine (**175b**, 55%) and 1,6-dihydro-4-ethoxy-1-ethyl-6-iminopyrimidine (**176b**, unspecified yield) respectively is formed. It was proved, using ^{15}N-labelled ammonia, that the amino-deethoxylation reaction does *not* involve ring opening.[102]



Scheme 44.

4-Ethoxy-1-ethyl-2-phenylpyrimidinium tetrafluorobrate (**174c**) shows with liquid ammonia a more complex behaviour: besides amino-deethoxylation into **175c**, N-deethylation into 4-ethoxy-2-phenylpyrimidine occurs. When the N-deethylation reaction was investigated with ^{15}N-labelled ammonia, it was found that the 4-ethoxy-2-phenylpyrimidine contained the same excess of ^{15}N as present in the labelled ammonia. Thus, the deethylation occurs via a ring-opening/ring-closure mechanism and presents another example of a ring degenerate transformation. Interestingly, from 6-ethoxy-1-ethyl-4-phenylpyrimidinium tetrafluoroborate (**177**)—being isomeric with **174c**—three different products are obtained. One product is **176a**, formed by amino-deethoxylation, the second product is 4-ethoxy-6-phenylpyrimidine (**181**) and the third product is 4-(ethylamino)-6-phenylpyrimidine (**182**). It is assumed that the N-deethylation of **177** into **181** and the formation of the 4-(ethylamino)-pyrimidine derivative **182** proceed *via* the common intermediate **180**. Its formation occurs by a subsequent series of reactions involving addition at C-2, ring-opening of the covalent σ-adduct **178** into the diazahexatriene **179** by cleavage of the N(1)—C(2) bond and recyclisation by addition of the amino group to the iminoester moiety. Loss of ethylamine or ethanol from **180** yields **181** and **182** respectively. It is evident that the formation of both compounds can be considered as ring degenerate transformation. The formation of a product with a 4(6)-ethylamino substituent, accompanied by an N-deethylation product, is also observed with 4,6-diethoxy-1-ethyl-2-phenylpyrimidinium tetrafluoroborate (**174d**), 4,6-diethoxy-2-phenylpyrimidine and 4-(ethylamino)-6-ethoxy-2-phenylpyrimidine being obtained.[102] It is evident that the formation of both compounds can be assumed to be formed by the same mechanism as pictured below.



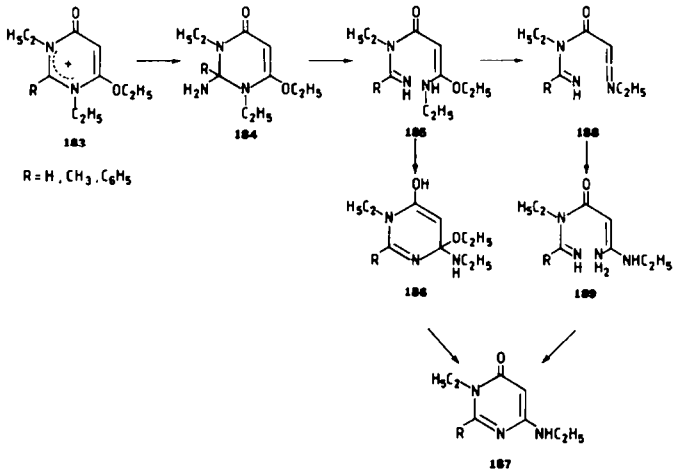
Scheme 45.

Measurement of the ^1H- and ^{13}C-NMR spectra of solutions of **174a** and **174b** in liquid ammonia (Tables 6 and 7) support the initial addition of the liquid ammonia at C-2.[102]

Table 7. Chemical shifts (ppm) and coupling constants of the ring carbon atoms of **174a, b** and **183** (R = H) in acetone-d_6 and in liquid ammonia

Compound	Solvent	C(2)	C(4)	C(5)	C(6)	^1J C(2)H	^1J C(5)H	^1J C(6)H
174a	acetone-d_6	156.2	172.8	111.9	151.4	210	180	192
	NH_3	78.3	162.1	83.1	144.4	165	170	172
174b	acetone-d_6	154.9	174.7	91.2	165.2	216	178	—
	NH_3	81.0	164.2	62.8	160.8	163	170	—
183 (R = H)	acetone-d_6	154.7	161	91.8	161	214	174	—
	NH_3	79.1	166.1	69.8	161.8	160	170	—

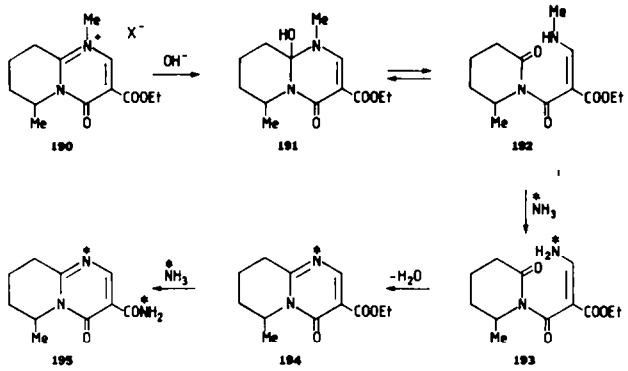
Ring degenerate transformations have also been observed when the 6-ethoxy-4-oxopyrimidinium tetrafluoroborates (**183**, R = H, CH_3, C_6H_5) are reacted with liquid ammonia, the 1,6-dihydro-1-ethyl-4(ethylamino)-6-oxopyrimidines (**187**) being obtained.[102] The C-2 adducts **184** are primarily formed (see Tables 6 and 7) and undergo an N(1)—C(2) bond fission into the open-chain intermediates **185**. Ring closure gives the 1,4-dihydropyrimidines **186**, which by loss of ethanol yield **187**. No indication for the formation of 1,6-dihydro-1-ethyl-4-ethoxy-6-oxopyrimidine has been obtained, making the intermediacy of **186** less attractive. The intermediacy of the ketenimine **188** seems more attractive, although ketenimines usually undergo addition of alcohols in basic solution.[103] In case **188** would have been formed, it gives with ammonia the addition products **189**, yielding on cyclisation **187**.



Scheme 46.

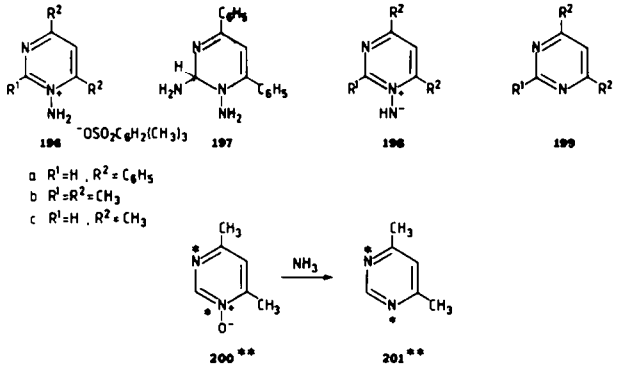
Demethylation by a ring degenerate transformation has also been reported to occur during treatment of the N-methyl quaternary salt of tetrahydro 4H-pyrido-[1,2,-a]-pyrimidine-4-one **190** with aqueous ammonia. Reaction of **190** with ^{15}N-labelled ammonia showed incorporation of ^{15}N-label into the pyrimidine ring.[104,105] This result has been explained by an initial addition of the hydroxide ion at the bridgehead carbon yielding the pseudobase **191**. By ring-opening the amino-ketone tautomer **192** is obtained, being in equilibrium with the pseudobase. Methylamino–amino exchange, initiated by a Michael addition of the ammonia at the β-position towards the carbethoxygroup yields **193**, that after cyclization is converted into **194**. Amino–ethoxy exchange in the ester group of **194** leads to the formation of the ^{15}N-labelled carboxamide group in **195**.

N-Aminopyrimidinium salts were found to undergo N-deamination when dissolved in liquid ammonia. Treatment of N-amino-4,6-diphenylpyrimidinium mesitylene sulphonate (**196a**) with liquid ammonia gave a quantitative deamination into 4,6-diphenylpyrimidine (**199a**). When the reaction was carried out with ^{15}N-labelled liquid ammonia (containing 9.9% of excess of ^{15}N) **199a** contained 2.7% of enrichment of ^{15}N, indicating that about 27% of the molecules of **196a** have been deaminated according to the ANRORC mechanism.[106] The remaining 73% of **196a** will react by an S_N2 nucleophilic attack of ammonia on the N-amino group, with concomitant fission of the N^+—N bond.



Scheme 47.

An attempt to detect by ^{1}H-NMR spectroscopy an intermediate species in the deamination failed due to low solubility of **196a** in liquid ammonia. Therefore no experimental evidence is available to demonstrate whether ammonia adds to C-2 or C-6 before ring-opening. However, since 4,6-diphenylpyrimidine in KNH_2–NH_3 easily undergoes addition at C-2,[107] it may (prudently) be suggested that also **196a** preferentially undergoes addition at C-2, yielding **197**. There is sufficient evidence to show that the competitive deprotonation of the amino group in the N-aminopyrimidinium salts can easily occur in a basic medium;[108,109] therefore **196** can (partly) exist in the pyrimidinio amide form **198**. Recent SCP-PPP calculations have shown that in the pyrimidinio amide form C-2 is more favoured for nucleophilic attack than C-6.[110]



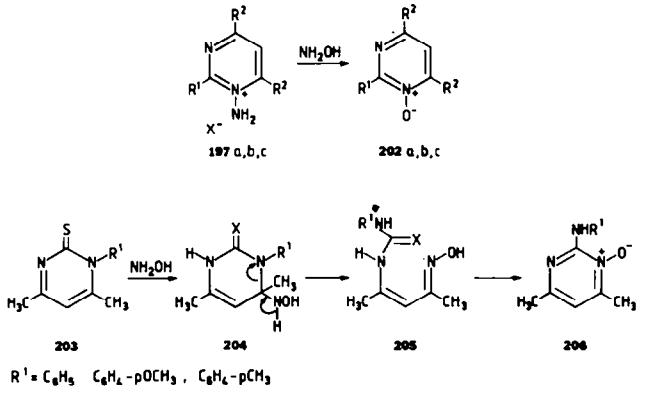
Scheme 48.

The reaction of N-amino-2,4,6-trimethylpyrimidinium mesitylene sulphonate (**196b**) with liquid ammonia shows it is more complex.[106] Deamination into 2,4,6-trimethylpyrimidine (**199b**, 40%) is the main reaction pathway, but also ring contraction into 3,5-dimethyl-1,2,4-triazole (12%) takes place. It was established by carrying out experiments with $^{15}NH_3$, that the deamination occurs to the extent of ~ 80% by an S_N2 type nucleophilic attack on the N-amino group and for only 20% according to the ANRORC process. Treatment of N-amino-4,6-dimethylpyrimidinium salt **196c** with liquid ammonia leaves no trace of the deamination product **199c**.

Attempts to achieve deoxygenation of 4,6-dimethylpyrimidine-N-oxide (**200**) by treatment with liquid ammonia at −33° and at 70° were unsuccessful. Heating, however, with liquid ammonia at 160°(!) for 2 hr resulted in the formation of **201**.[111] The deoxygenation does not involve an ANRORC mechanism: 4,6-dimethylpyrimidine (**201****) obtained from double-labelled [1,3-^{15}N]-pyrimidine-N-oxide (**200****) has the same percentage of ^{15}N-enrichment as present in starting material.[111]

B.1.a.2. *Ring degenerate transformations involving the replacement of one ring nitrogen by the nitrogen of* RNH_2 (R = alkyl(aryl),OH,NH_2). A ring degenerate transformation, being of preparative value for the synthetic organic chemist, is the conversion of the N-aminopyrimidinium salts **196a, b, c** into the pyrimidine N-oxides (**202a, b, c**) by a reaction with hydroxylamine. These reactions occur in

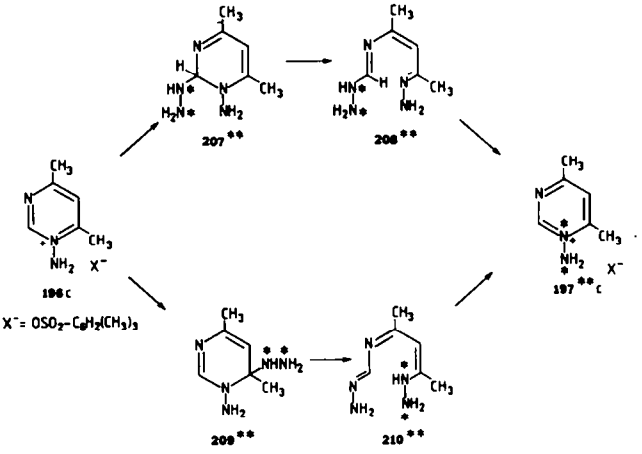
reasonable to high yields (**196a** → **202a**, 35%; **196b** → **202b**, 90%; **196c** → **202c**, 85%).[112] This method of formation of pyrimidine N-oxides is a valuable addition to the more classical oxidation method with peracids, since the yields obtained are usually higher, and the method opens the possibility of preparing pyrimidine N-oxides containing substituents, which are sensitive to oxidation. This conversion can be explained by either an initial nucleophilic attack at C-2 and/or C-6.



Scheme 49.

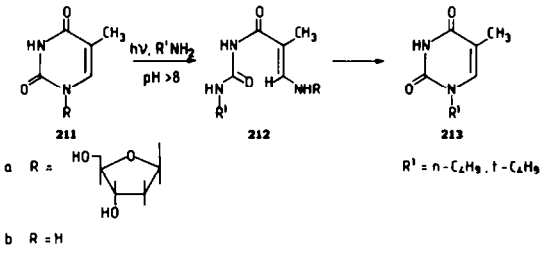
A similar type of rearrangement has been reported[113] when the 4,6-dimethyl-1-aryl-2(1H)-pyrimidinethiones (**203**) are treated with hydroxylamine hydrochloride in the presence of sodium hydroxide, the 2-anilino-4,6-dimethylpyrimidine-1-oxides (**206**) being obtained. The mechanism being proposed involves formation of C-4 adduct **204** and the open-chain intermediate **205**. The reaction was also found to occur with different aryl or alkyl(aryl) substituents at positions 1, 4 and 6.

It is interesting that reaction of **196c** with double-labelled hydrazine has been proved to lead to incorporation of ^{15}N into the pyrimidine ring, i.e. formation of **197**c**. This ring degenerate transformation can only be explained[114] by a mechanism involving the intermediacy of the C-2-adduct **207**** and/or C-6 adduct **209**** and the ring-opened products **208**** and/or **210****.



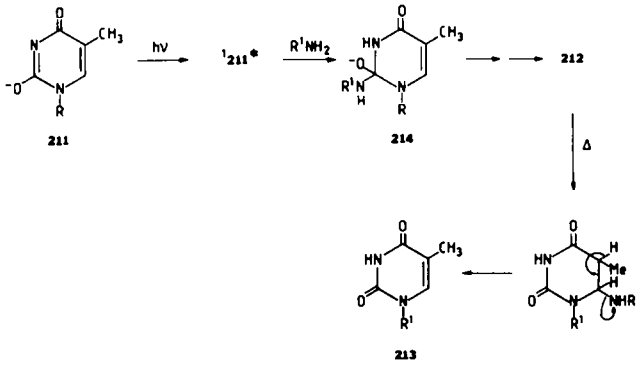
Scheme 50.

Interesting examples of ring degenerate transformations were reported to occur when an aqueous solution of thymidine (**211a**) or thymine (**211b**) was irradiated (> 254 nm) in the presence of primary alkylamines at ambient temperatures, the thymines **213** being formed in reasonable yields.[115,116] The urea derivatives **212** are the primarily formed photoproducts; they have been isolated when the photoreaction was carried out at low temp (0–5°) in the presence of *n*-butyl- and *t*-butylamine. Brief heating of **212** in water at about 70° or acid treatment immediately gave **213**.



Scheme 51.

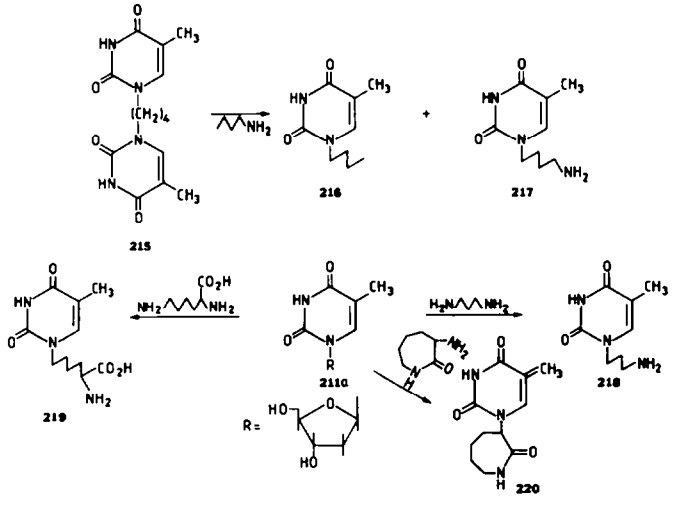
When this photoreaction was carried out in acetone no ring transformation but an intermolecular cycloaddition yielding a dimer took place, suggesting that not the triplet state but the singlet state is responsible for the photo-induced degenerate ring transformation reaction.[115] Moreover, since the photoreaction only occurs in aqueous solvent at a pH > 8 it suggests that an ionized form of the photo-excited species is involved in this photoreaction. The reaction **211** → **213** can be described as follows:



Scheme 52.

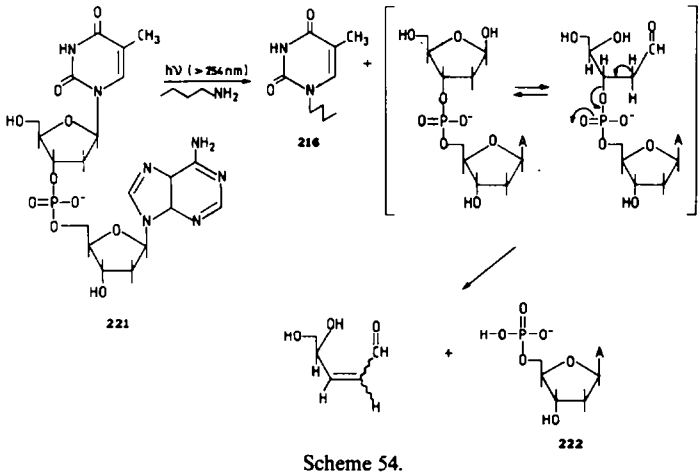
In the photo-excited anionic singlet [1] **211*** addition takes place at C-2, yielding **214**—and not at C-6, as has been proposed previously—followed by ring-opening into **212**. Although nucleophilic addition at C-2 is less documented than addition at C-6, there is sufficient evidence available that C-2 addition in the ground state of 4-oxopyrimidinium salts (see also Section B.1.a.1, p. 263) can easily occur.

This photo-stimulated nitrogen exchange is successfully employed for the synthesis of a variety of N(1)-substituted thymines. Examples are the conversion of **215** into the mixture of both thymines **216** and **217** by reaction with butylamine, and the conversion of **211a** into the N(1)-substituted thymines **218**, **219** and **220** by photoirradiation in 1,3-diaminopropane, lysine and aminocaprolactam respectively.[115]



Scheme 53.

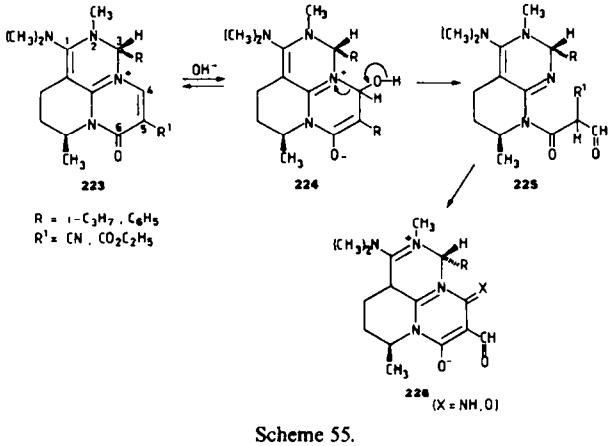
An extension of this photoconversion has shown[117] that dAdo, dGuo and dCyt do not give any detectable photoadduct when they are reacted with *n*-butylamine under the same conditions as used for **211a, b**. When a mixture of **211a** and dAdo was irradiated in the presence of *n*-butylamine, the photoaddition took place selectively in **211a**, suggesting that the photoreaction occurs preferentially with thymidines (and thymines). The nucleotide TpdA **221**, containing both the thymidine and adenosine ring systems, when irradiated in water with *n*-butylamine at 0° and subsequently heated at 90°, gives 1-*n*-butylthymine (**216**) and dAMP (**222**). The production of both products can easily be explained by the route given below.



Scheme 54.

Above mentioned results seem to indicate that by irradiation in alkylamines, DNA (single-stranded) can undergo a remarkable modification: a selective release of thymine from DNA, accompanied with strand scission. This has been experimentally verified. Irradiation of calf thymus DNA (10.6 mg/100 ml aq. distil.) with 5 ml of *n*-butylamine for about 2.5 hr gives in about 21% yield the open-chain photoproduct, which after heating at 70° gives in 17% yield 1-*n*-butylthymine (**216**).[117]

B.1.a.3. *Ring degenerate transformations involving the replacement of one ring carbon atom by a side-chain carbon.* An interesting ring degenerate transformation has been reported to occur when the 2,3a,6a-triazaphenalenium salt (**223**) is treated with aqueous alkali, resulting in the formation of the stable betaine **226**.[118–120] In this ring transformation the carbon atom of the cyano- or carbethoxy group at position 5 is incorporated at position 4 of the ring system and the carbon atom at C-4 is present in the formyl group of **226**. The transformation involves addition at C-4, i.e. **224**, and formation of the dicarbonyl compound **225**. Position 4 in **223** is the most favoured position for nucleophilic addition since treatment of **223** with bisulphite or cyanide anions leads to the formation of the stable betaines **224** (R = Ph, R′ = CO_2Et and replace OH by SO_3 or CN). The addition of the nucleophile at C-4 is calculated to take place most favourably from the opposite side of the phenyl group at C-3.

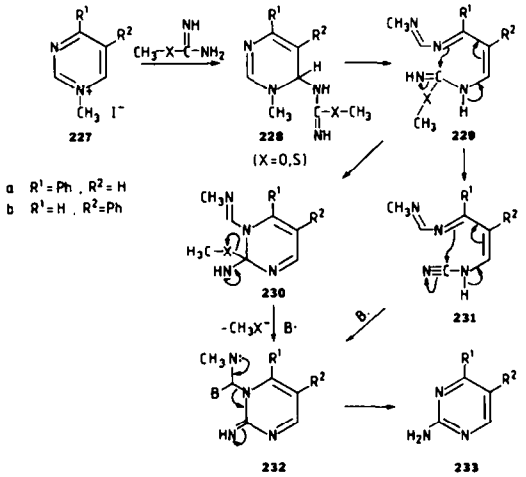


Scheme 55.

B.1.b. *Ring degenerate transformations involving a two-atom moiety replacement*

Reaction of 1-methyl-4-phenylpyrimidinium iodide (**227a**) and the 1-methyl-5-phenylpyrimidinium salt (**227b**) with S-methylisothiourea in basic medium has been reported to afford the 2-amino-4-phenyl (**233a**, 70%) and 2-amino-5-phenylpyrimidine (**233b**, 40%) respectively.[121] Both 2-amino compounds are formed by an overall displacement of the C(2)—N(1) fragment of the pyrimidine ring by the N—C fragment of S-methylisothiourea. No detectable amounts (by GLC) of 2-(methylthio) 4- or 5-phenylpyrimidines were found.

This ring degenerate transformation can be described to involve as initial step an attack of the nucleophilic centre in the reagent at position 6 of **227**, yielding σ-adduct **228** (X = S); subsequent ring-opening gives the diamidine **229**. It is suggested that the formation of **233** from **229** takes place via **230** and **232**, but an alternative pathway via **231** and **232** can certainly not be excluded. Reason to suggest the amidino-N-cyano compound **231** as intermediate is the fact that both 2-amino compounds **233a** and **233b** can also be obtained (yields 60 and 35% respectively) when the 1-methylpyrimidinium salts **227a** and **227b** are reacted with cyanamide.[121]



Scheme 56.

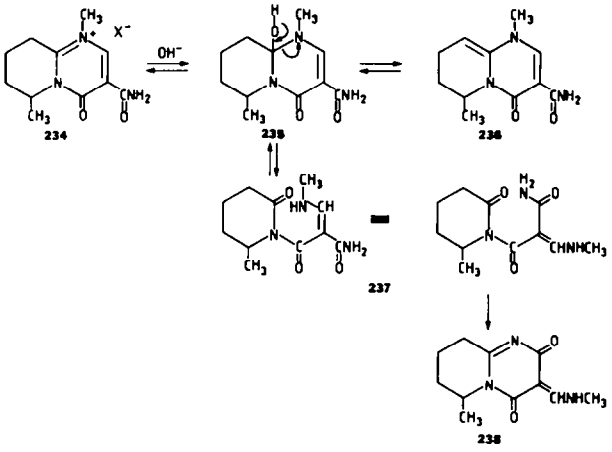
A two-atom replacement leading to compounds **233a** and **233b** has also been found when instead of S-methylisothiourea, S-methylisourea was used as reagent, the yields of both 2-aminopyrimidines were much lower however (**233a**: 35%; **233b**: 15%). Attempts to prepare **233** by reaction of **227** with the more basic guanidine failed.

An interesting ring degenerate transformation also involving a two-atom replacement has been recently observed[105] when the 1-methyl salt of 4-oxo-tetrahydro-4H-pyrido-[1,2-a]-pyrimidine-3-carboxamide **234** or the enamine **236** is heated in an aqueous solution of sodium bicarbonate, both compounds giving in nearly quantitative yield the same product, i.e. 3-methylaminomethylene-hexahydropyrido-[1,2-a]-pyrimidine-2,4-dione (**238**). The reaction involves addition of the nucleophile at C-9a, giving **235**, that by a base-induced ring-opening yields the aminoketone (**237**). Ring-closure due to an intramolecular cyclization between the aminocarbonyl moiety and the ring carbonyl group leads to incorporation of the exocyclic carbon and nitrogen of the carboxamido group and replaces the N(1)—C(2) fragment of **234** or **236**.

B.1.c. *Ring degenerate transformations involving a three-atom moiety replacement*

Reaction of N-methylpyrimidinium iodide (**239**) with benzamidine in basic medium affords 2-phenylpyrimidine (**243**, R = C_6H_5) in 45% yield; with pivalamidine the yield on 2-*t*-butylpyrimidine (**243**, R = *t*-C_4H_9) is much lower (10%).[121] When the phenylation reaction was carried out with [1,3-^{15}N]-pyrimidinium iodide (**239****) it was found that **243** (R = C_6H_5) was not ^{15}N-labelled, providing sound evidence that the N(1)—C(2)—N(3) fragment of the pyrimidine ring has been replaced by the N—C—N moiety of the amidine.[121]

The results of these experiments have been explained by an addition of the 1,3-ambident



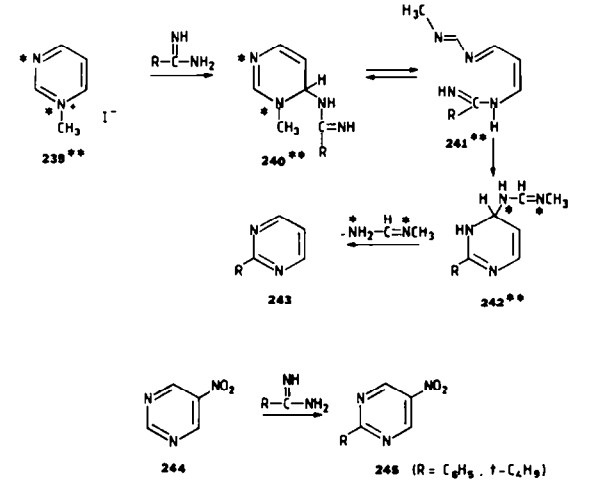
Scheme 57.

nucleophile amidine at C-6 leading to **240****, ring-opening into **241**** and ring-closure into the 1,6-dihydro compound **242****. Loss of double-labelled formamidine yields unlabelled **243**.

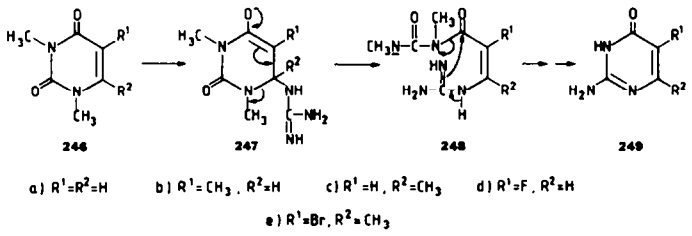
Very recently a ring degenerate transformation also involving a three-atom replacement has also been observed when 5-nitropyrimidine (**244**) is reacted with phenyl- or pivalamidine, affording the 2-substituted 5-nitropyrimidines (**245**, R = C_6H_5, t-C_4H_9).[122] The conversion of **244** into **245** can be described according to the same mechanism as presented for the formation of **243** from **239**. Attempts to prepare 2-benzyl-5-nitropyrimidine (**245**, R = $CH_2C_6H_5$) by this route failed; the reaction leads to the formation of a pyridine derivative.[123]

Other interesting examples of three-atom N—C—N replacements have been reported[124,125] in reactions of 1,3-dimethyluracils (**246a–e**) with several 1,3-ambident nucleophiles. With guanidine in reasonable-to-good yields the isocytosines (**249a–e**) were obtained. The ease of the reaction depends on the electronic nature of the substituent at C-5 and C-6 as well as the steric environment at C-6. For example, the 5-fluoro compound **246d** reacts more easily into **249d** than the 5-methyl derivative **246b** into **249b**. A similar difference in reactivity has been demonstrated between **246c** and **246e**. The reaction can be plausibly formulated to occur via the intermediacy of the C-6 adduct **247** and the open-chain intermediate **248** and has close similarity to the mechanism given for the conversion of **239** into **243**.

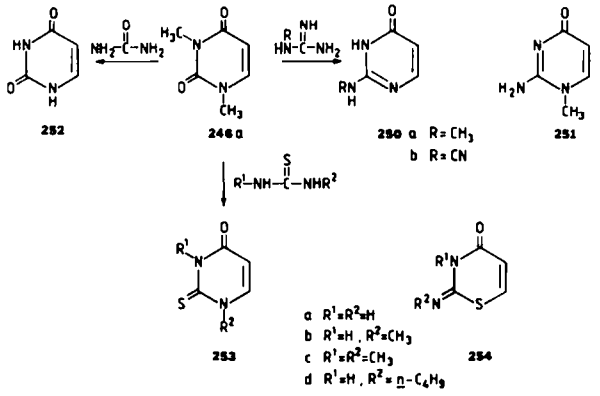
The generality and practicality of these pyrimidine-to-pyrimidine transformations can be demonstrated by the good-yield conversions of **246a** with a series of other 1,3-ambident nucleophiles (methylguanidine, cyanoguanidine, urea, thiourea, 1-butylthiourea, 1-methylthiourea) **246a** → **250a**



Scheme 58.



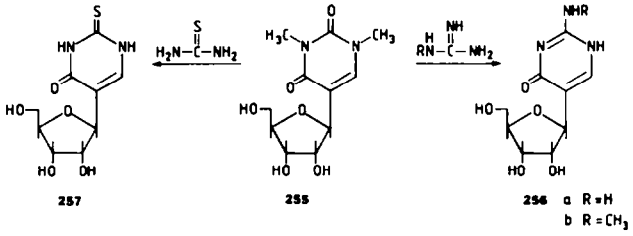
Scheme 59.



Scheme 60.

(+**251**); **246a** → **250b**; **246a** → **252**; **246a** → **253a, b, c, d** (probably via the 1,3-thiazine intermediate **254**).[125]

An interesting and useful application of these ring degenerate transformations has been found in the preparation of the anti-leukemic C-nucleoside 5(β-D-ribofuranosyl) isocytosine (pseudoisocytodine) **256a** from 1,3-dimethylpseudouridine (**255**) by a reaction with guanidine. In a similar way N-methylpseudoisocytidine (**256b**) and 2-thiopseudouridine (**257**) has been obtained.[125]

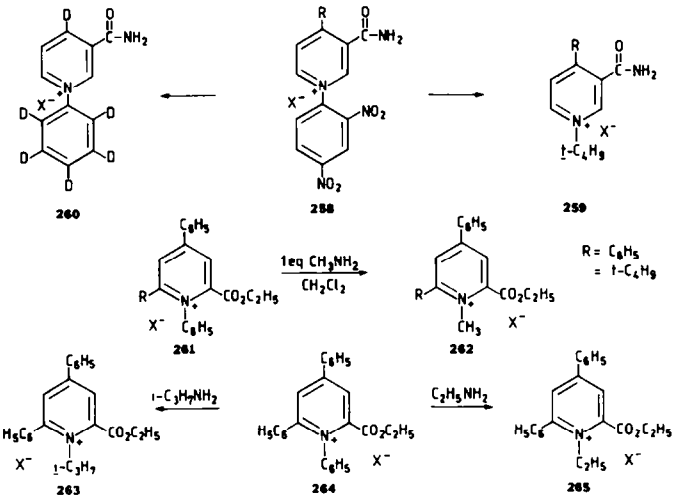


Scheme 61.

B.2. RING DEGENERATE TRANSFORMATIONS OF PYRIDINES

B.2.a. *Ring degenerate transformations involving a one-atom replacement*

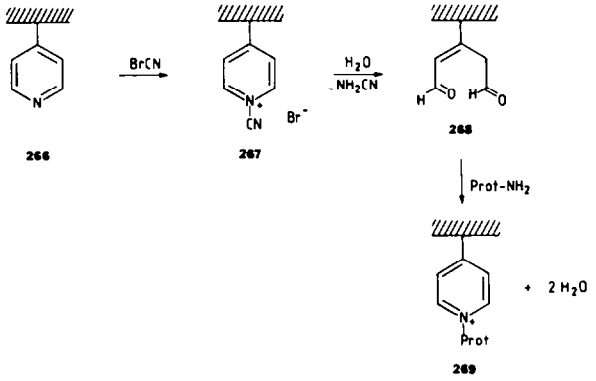
The earliest described ring degenerate transformations in pyridines are the so-called Zincke exchange reactions, which occur when 1-(2,4-dinitrophenyl) pyridinium salts are reacted with R—NH_2 (R = alkyl, aryl), the 1-R-pyridinium salts and 2,4-dinitroaniline being obtained.[126–129] This method has considerable preparative value:[130] with heterocyclic amines, with more complex amines (tryptamine, 7-aminocholestrol,[131] etc.), with hydrazines[132–134] and hydroxylamine[133] N-substituted pyridinium salts can be obtained. Recent examples of these Zincke-type conversions are the conversions of 3-aminocarbonyl-1-(2,4-dinitrophenyl) pyridinium salt (**258**, R = H) into 3-aminocarbonyl-1-*t*-butylpyridinium salt (**259**, R = H) by an exchange reaction with *t*-butyl-amine[135] and the preparation of 1-(pentadeuterophenyl)-3-aminocarbonyl-4-deuteropyridinium salt (**260**) from 3-aminocarbonyl-1-(2,4-dinitrophenyl)-4-deuteropyridium salt (**258**, R = D) with pentadeuteroaniline.[136]



Scheme 62.

It has been reported that 1-phenyl-2(ethoxycarbonyl) pyridinium salts (**261**) undergo a ring degenerate transformation according to the ANRORC mechanism in reaction with primary amines.[137] When a solution of **261** (R = C_6H_5, *t*-C_4H_9) in CH_2Cl_2 is reacted with 1 eq. of methylamine at room temp in good yield the corresponding N-methylpyridinium salts **262** are obtained. Similar reactions were reported with ethylamine and i-propylamine, **264** → **263** and **264** → **265**. When the reactions are carried out in boiling ethanol besides the N^+-phenyl → N^+-alkyl exchange deethoxycarbonylation takes place. With *t*-butylamine no N^+-phenyl → N^+-*t*-butyl exchange was observed; only deethoxycarbonylation was found.

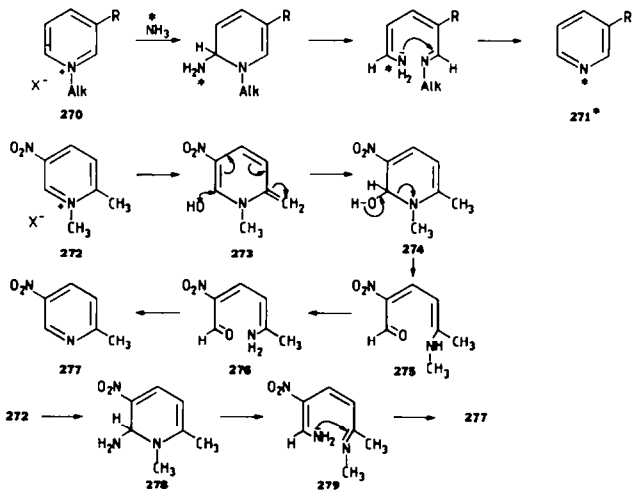
Another interesting application of the Zincke ring degenerate transformation in pyridinium salts is the protein immobilization to pyridine-containing polymers.[138] By reacting pyridine polymers (**266**) with cyanogen bromide into **267** the pyridine ring is highly activated for nucleophilic ring-opening[138a] into a polyaldehyde (**268**) that in the presence of a protein recyclizes into a pyridine ring, leading to a polymeric system, in which the protein is present in immobilized form.



Scheme 63.

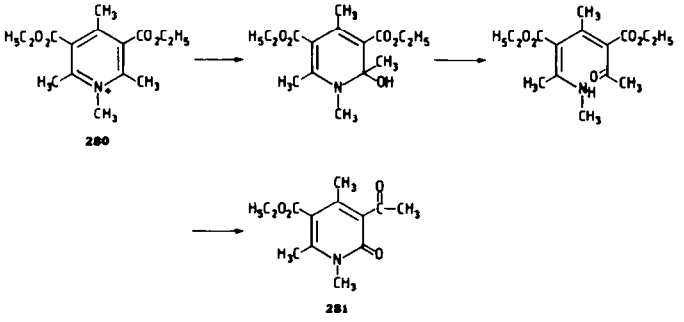
Replacement of the quaternary nitrogen in pyridinium salts by a nitrogen of liquid ammonia has been found[136,139,140] when 1-alkyl-3-pyridinium salts **270** (R = NO_2,SO_2,Me,$CONH_2$,CF_3,CN) react with liquid ammonia, the "dealkylated" product **271** being obtained after evaporating the ammonia. It has been proved that this reaction—in analogy to the demethylation and debenzylation reactions with N-methyl(benzyl)pyrimidinium salts (see Section B.1.a.1)—occurs by a ring-opening/ring-closure sequence: reaction of **270** (Alk = CH_3, R = $CONH_2$) with liquid ammonia, being ^{15}N-labelled, leads to incorporation of ^{15}N into the pyridine ring.[136] The reaction can be explained by a mechanism involving an initial addition of the ammonia either at C-2 or at C-6. By ^1H-NMR spectroscopy it has been convincingly shown that the initial addition only took place at C-6.

A demethylation reaction involving ring-opening has been found when the 1,2-dimethyl-5-nitropyridinium salt (**272**) is treated with aqueous ammonia,[141,142] 2-methyl-5-nitropyridine (**277**) being obtained. The reaction has been described to occur by addition of the hydroxide anion to the conjugate base (**273**), after which a base-induced ring-opening of **274** in **275** occurs. It has been postulated that in this open-chain intermediate **275** the amino–methylamino exchange takes place, yielding **276**. It cannot be excluded, however, that besides the hydroxide anion ammonia will add to C-6 in **272**, yielding **278**. Ring-opening gives then **279**, which on reclosure yields **277**.



Scheme 64.

An interesting group of ring degenerate transformations concerns the exchange of the carbon atom of a cyano or carbethoxy side-chain by a ring carbon of the pyridine ring. A good example of this rearrangement is the alkaline-induced conversion of 1,2,4,6-tetramethyl-3,5-diethoxycarbonyl-pyridinium salt (**280**) into 1,4,6-trimethyl-3-acetyl-5-ethoxycarbonyl-2-pyridone (**281**).[143,144] The reaction involves addition of the base at C-2, ring-opening and ring-closure involving the carbethoxy group.

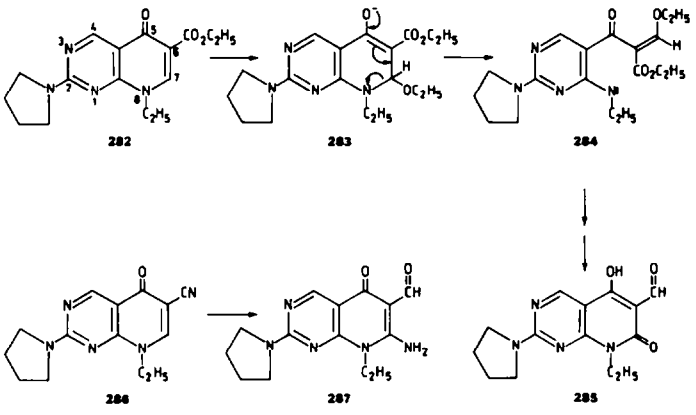


Scheme 65.

Other examples of side-chain participation in a ring degenerate transformation are observed when the pyrido [2,3-d] pyrimidines **282** and **286** are treated with sodium ethanolate in DMSO. From **282** the 6-formyl-7-oxo derivative **285** and from **286** the 6-formyl-7-amino compound **287** are obtained.[145] These ring degenerate transformations involve initial addition of the base at C-7, as exemplified in the formation of **283** and subsequent ring-opening into **284**.

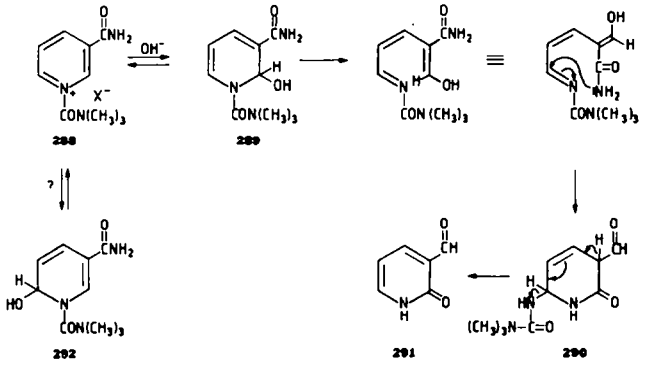
B.2.b. *Ring degenerate transformations involving a two-atom moiety replacement*

C—N exchange in a pyridinium salt by the C—N portion of a side-chain substituent has been found to be an attractive method to induce ring degenerate transformations. A good example of that synthetic



Scheme 66.

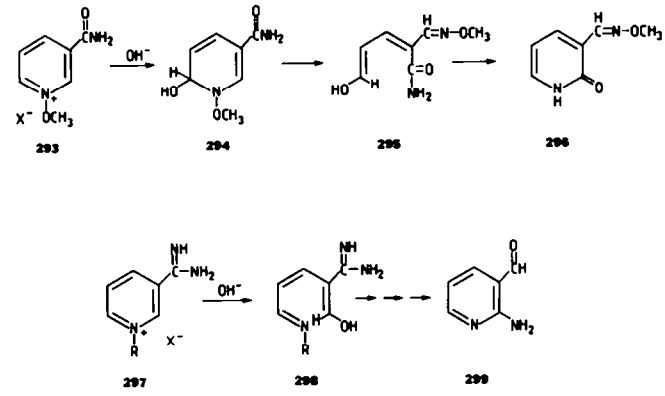
principle is the base-induced transformation of the 1,3-di(aminocarbonyl)pyridinium salt (**288**) into the 3-formylpyridone-2 (**291**).[146] The reaction must involve the C-2 adduct **289**, followed by ring-opening and ring-closure into the dihydropyridine **290**. It cannot be excluded that **288** would first be converted at low temperature into the kinetically favoured C-6 adduct **292**; however, this C-6 adduct cannot be considered as intermediate in the formation of **291**.



Scheme 67.

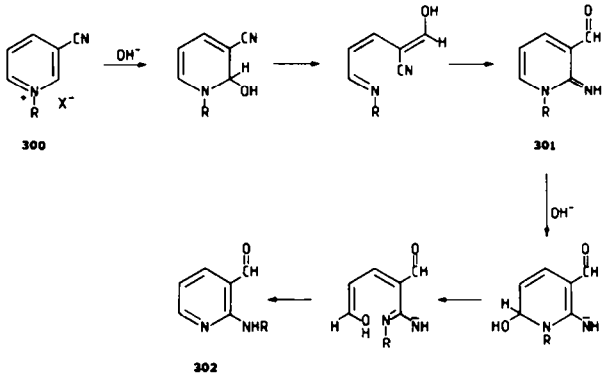
A quite similar ring degenerate transformation is observed, when the N-methoxypyridinium salt **293** is treated with a base, the methoxyoxime of 3-formyl-2-pyridone (**296**) being obtained.[147] In order to explain the results it is evident that in this conversion the C-6 adduct **294**, and not the C-2 adduct, undergoes the ring-opening reaction. No spectroscopic measurements on adduct formation of both compounds **287** and **293** at various temperatures have been carried out, by which possibly information could be obtained whether the addition is kinetically or thermodynamically controlled. Therefore it is difficult to explain the difference in the course of the transformation of **288** and **293**. A very similar two-atom replacement has been reported to occur during base treatment of the pyridiniumformamidine (**297**) into 3-formyl-2-aminopyridine (**299**).[148] It is evident that this degenerate ring transformation can only occur via the intermediacy of a C-2 adduct and the open-chain compound **298**.

An intriguing, more complicated rearrangement, also involving the overall replacement of a C(2)—N moiety of the pyridine ring by a side-chain carbon–nitrogen, has been reported[149–153] when the 3-cyanopyridinium salt (**300**, R = CH_3) is reacted with a base. The product obtained is 2-(methylamino)-3-formylpyridine (**302**, R = CH_3) and involves a six-step rearrangement reaction, involving first an initial reaction of the hydroxide ion at C-2 in **300**, ring-opening and ring-closure into **301** and a subsequent Dimroth rearrangement of **301** into **302**, initiated by addition of the hydroxide ion at C-6 in **301**. The corresponding 2- or 4-cyano-1-methylpyridinium salts do not give the ring transformation but only give in alkaline medium the corresponding amide. When **300** (R = CH_3) is



Scheme 68.

reacted with an alkylamine 2-(alkylamino)-3-formylpyridine (**301**, R = alkyl) is obtained.[153] The methylamine–alkylamine exchange has been proposed to take place in one of the open-chain intermediates. Accordingly, 3-cyanopyridine ethiodide (**300**, R = C_2H_5) with aqueous methylamine leads to elimination of the ethylamino group with formation of **302** (R = CH_3).[153]



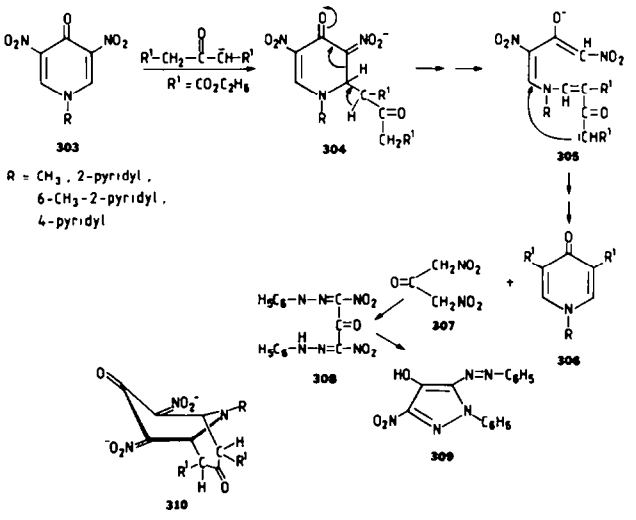
Scheme 69.

B.2.c. *Ring degenerate transformations involving a three-atom moiety replacement*

Ring degenerate transformations, involving a three-atom moiety replacement in the pyridine ring, are very scarce, but it has recently been found that the 3,5-dinitro-4-pyridones (**303**) when reacted with diethylsodio-3-oxopentanedioate, give in good yields 3,5-di(ethoxycarbonyl)-4-pyridones (**306**, R' = $CO_2C_2H_5$).[154] 1,3-Dinitroacetone (**307**) was formed as by-product as was proved by conversion of **307** into **308** by a reaction with phenyldiazonium chloride, that on heating cyclizes into the pyrazole derivative **309**. The transformation can be described to involve a series of steps, first the formation of the C-2 adduct **304** and subsequent ring-opening into **305**. Intermediate **305**, still containing an acidic hydrogen on the carbon adjacent to the carbonyl group, undergoes cyclization by carbanionic attack on the carbon adjacent to the NR-group with elimination of **307**. However, it cannot be excluded that the reaction involves as intermediate the bicyclic adduct **310** formed by addition of both nucleophilic carbon centres adjacent to the keto group to C-2 and C-6 in **303**. Examples of bicyclic adduct formation with nitroarenes have been reported.[16j,155]

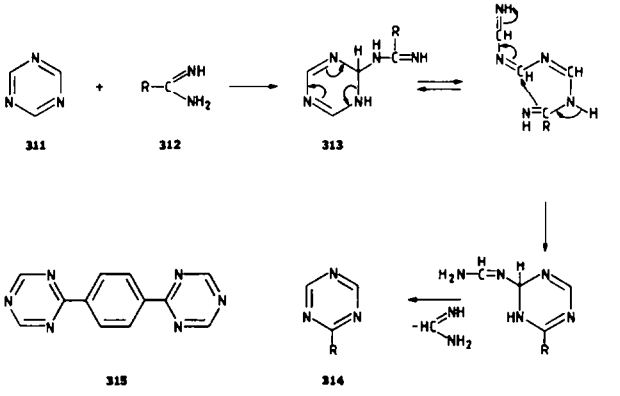
B.3. RING DEGENERATE TRANSFORMATION OF TRIAZINES

Reaction of 1,3,5-triazine (**311**) with a number of amidines (**312**, R = $CH_2C_6H_5$,CCl_3,CH_3S, CH_3O,NH_2,NHC_6H_5,$NHC_{12}H_{25}$) gives in reasonable-to-good yields the mono-substituted 1,3,5-

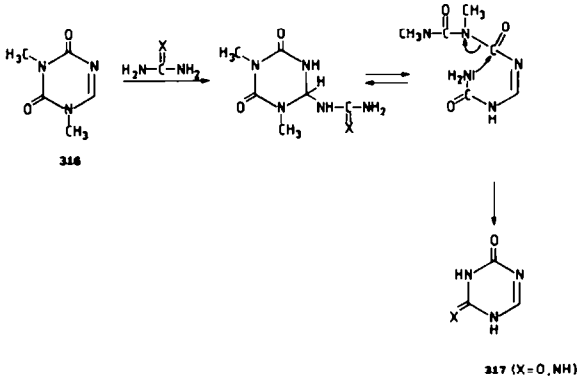


Scheme 70.

triazines (**314**).[156] This reaction offers an efficient and broadly applicable method for the preparation of mono-substituted 1,3,5-triazines. As by-product in the reaction formamidine is obtained. Thus, in the reaction an overall replacement of the N—C—N portion of the 1,3,5-triazine ring by the N—C—N moiety of the amidine took place and occurs according to an ANRORC-process, involving the initial C-2 adduct **313**, ring-opening and ring-closure.



Scheme 71.



Scheme 72.

Extension of this reaction using terephthalamidine as reagent gave[156] the interesting compound *p*-phenylene di[1,3,5-triazin-2-yl] (**315**). The addition of benzamidine to a 1,2,4-triazine derivative leading to an overall replacement of the N(2)—C(3)—N(4) moiety of the 1,2,4-triazine ring by the N—C—N amidine has already been discussed in Section A.1.b.1 and concerns the degenerate ring transformation of 3-halogeno-5-phenyl-1,2,4-triazine (**122a**) into 3,5-diphenyl-1,2,4-triazine (**131**).

Treatment of dimethyl-5-azauracil (**316**) with guanidine HCl in ethanolic sodium ethanolate gave 5-azacytosine (**317**, X = NH); with urea 5-azauracil (**317**, X = O) was obtained.[157] Both reactions have strong similarity with the ring degenerate transformation, reported in reactions of 1,3-dimethyluracils with the 1,3-ambident nucleophiles guanidine and urea (see Section B.1.c).

Acknowledgement—It is a pleasure for me to thank all my co-workers, who have been involved in these studies. Their names are recorded in the references. It is due to their efforts and experimental skills that we are able to get a better understanding of this field of ring degenerate transformations in azaheterocycles. I am especially indebted to Dr. A. Counotte-Potman, who assisted me in collecting the literature data for this review and was stimulating in critical discussions.

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