CINE AND DIRECT AMINATIONS OF 5- AND 6-HALOGENOPYRIMIDINES A MECHANISTIC STUDY

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CINE AND DIRECT AMINATIONS OF 5- AND 6-HALOGENOPYRIMIDINES A MECHANISTIC STUDY

proefschrift
ter verkrijging van de graad
van doctor in de landbouwwetenschappen,
op gezag van de rector magnificus,
dr.H.C.van der Plas,
hoogleraar in de organische scheikunde,
in het openbaar te verdedigen
op vrijdag 6 oktober 1978
des namiddags te vier uur in de aula
van de Landbouwhogeschool te Wageningen.

ISN 104272-03

Aan mijn ouders

Aan Ellen

STELLINGEN

I

De vorming van 5-(7-) nitroindolen bij inwerking van alcoholische loog op 6-(8-) nitroindolizinen kan op een andere manier verlopen dan beschreven wordt door Kost et.al.

A.N.Kost, R.S.Sagitullen en S.P.Gromov, Heterocycles 7, 997 (1977).

II

Het mechanisme van het ontstaan van 1,3-dicrotyl-1,2,3,4-tetrahydro-6-methyl-2,4-dioxopyrimidine bij de reactie van 2,4-dicrotoxy-6-methylpyrimidine met p-tolueensulfonzuur zoals voorgesteld door Kato et.al. is aan bedenkingen onderhevig.

T.Kato, N.Oda en I.Ito, Chem.Pharm.Bull. 25, 215 (1977).

III

De aanwezigheid van 2-5% van een M+2 piek in het massaspectrum van 1,2,4,5-tetrazines kan behalve door het voorkomen van een dihydro-1,2,4,5-tetrazine als verontreiniging ook verklaard worden door middel van processen die zich in de massaspectrometer afspelen.

A.D.Counotte-Potman en H.C.van der Plas, J.Het.Chem. 15, 445 (1978).
G.R.Waller, "Biochemical Applications of Mass Spectrometry" Wiley-Interscience, 1972, blz. 521.

IV

De door Buchan et.al. gegeven verklaring voor de vorming van 8-phenacyl-2-phenyl-8-azaindolizin-7(8H)-on en 8-phenacyl-2-phenyl-8-azaindolizin-5(8H)-on uit 4-methoxy-2-methylpyrimidine onder invloed van phenacyl bromide is aanvechtbaar.

R.Buchan, M.Fraser en C.Sand, J.Org.Chem. 42, 2448 (1977).

V

De door Friedman gegeven behandeling van de thermodynamica van de processen die optreden bij het mengen van twee vloeistoffen die waterstofbruggen kunnen vormen is te eenvoudig.

N.Friedman, J.Chem.Ed. 54, 248 (1977).

VI

Tegen de structuur van het door Crook en Sykes voorgestelde openketen intermediair bij de omlegging van 5-cyaan-3,4-dihydro-2,6-diphenyl-4-iminopyrimidine onder invloed van het dicyaanmethanide anion zijn bezwaren aan te voeren.

S.Crook en P.Sykes, J.Chem.Soc. Perkin I, 1977, 1791.

VII

De toename van het aantal wetenschappelijke tijdschriften is niet bevorderlijk voor een efficiënte verspreiding van de informatie die deze bevatten.

VIII

Pogingen het benzineverbruik te verminderen worden nadelig beinvloed door de weigering van de verzekeringsmaatschappijen in vele gebieden van Nederland fietsen te verzekeren.

IX

Het valt te betreuren dat toename aan persoonlijke vrijheid veelal gepaard gaat met afname aan persoonlijk fatsoen.

C.A.H.Rasmussen Wageningen, 6 oktober 1978

Cine and direct aminations of 5- and 6-halogenopyrimidines.
A mechanistic study.

VOORWOORD

Gaarne wil ik op deze plaats mijn dank betuigen aan allen die op enigerlei wijze hebben bijgedragen aan het tot stand komen van dit proefschrift.
Een aantal personen wil ik graag met name noemen.
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Veel dank ben ik verschuldigd aan Cees Landheer en Willem Combé voor de talloze massaspectrometrische gegevens, aan Hugo Jongejan voor de microanalyses, aan Bep van Veldhuizen voor opname en interpretatie van de PMR spectra, alsmede aan Pim Melger en Gerrit Lelyveld voor de chromatografische adviezen.
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CONTENTS

Chapters 2 and 3 have been published in the literature

Chapter 2 Recl.Trav.Chim.(Pays-Bas) 93, 231 (1974)
Chapter 3 Recl.Trav.Chim.(Pays-Bas) 96, 101 (1977)

Chapters 4 and 5 are in the press

Chapter 4 Recueil des Travaux Chimiques (Pays-Bas)
Chapter 5 Journal of Heterocyclic Chemistry

Chapters 6 and 7 are submitted for publication

Chapter 6 Recueil des Travaux Chimiques (Pays-Bas)
Chapter 7 Tetrahedron Letters

1 INTRODUCTION

1.1 GENERAL

Investigation of the behaviour of aza- and polyazaaromatics towards nitrogen containing nucleophiles continues to remain a major research topic at the Laboratory of Organic Chemistry in Wageningen. A great variety of different reaction pathways has been discovered in recent years, depending on the structure of the substrate and the nature of the attacking nucleophile[1-4]. In general the reactions can be divided into two main classes.

(i) Reactions which lead to a product containing a *different* aromatic ring than the starting material. A ring transformation has occurred.

(ii) Reactions which give a product having the *same* heterocyclic ring as the original substrate. A nucleophilic substitution has taken place.

Both classes have been found to occur frequently. This introduction will deal with the various mechanisms, according to which nucleophilic substitutions can take place in halogen containing azaaromatics, with primary emphasis on the use of the amide ion as reagent.

1.2 NUCLEOPHILIC SUBSTITUTION

Dependent on the location of the introduced amino functions in the reaction product the following substitution patterns can be discerned.

(i) Direct substitution. The amino group is found on the same carbon atom that bore the halogen in the starting material.

(ii) Cine substitution. The newly introduced moiety is located on the carbon atom adjacent to the one bearing the halogen in the original substrate.

(iii) Tele substitution. In this case the carbon atom bearing the amino function is separated from the atom originally carrying the halogen by one or more ring atoms.

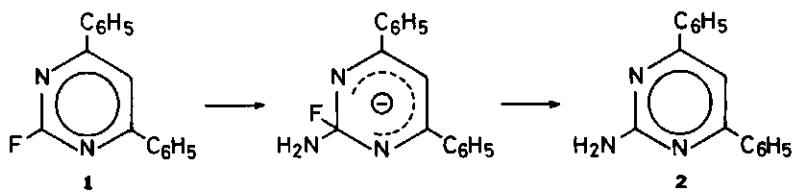
A survey of the reaction mechanisms observed to date in the direct, cine and tele substitutions involved is given in the following sections.

1.2.1 *Mechanisms of direct substitution*

Four different types of mechanisms have been observed in direct nucleophilic substitutions of halogenoazaaromatics.

1.2.1.1 *The $S_N(AE)$ mechanism*

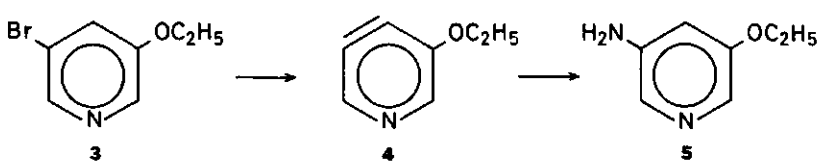
This process is initiated by addition of an amide ion to the heterocyclic ring on the halogen-bearing carbon atom. A halide ion is subsequently expelled. This mechanism is exemplified in the amination of 4,6-dipheny1-2-fluoropyridine (1) by potassium amide in liquid ammonia, giving 2[5].



Scheme 1.1

1.2.1.2 *The $S_N(EA)$ mechanism*

In this case hydrogen halide is initially eliminated by the strong base potassium amide to give a hetaryne intermediate which then undergoes addition of ammonia. The amination of 3-bromo-5-ethoxypyridine (3) into the corresponding 3-amino derivative 5 proceeds *via* 4, the unilateral addition of ammonia to 4 being dictated by the -I effect of the ethoxy group[6].

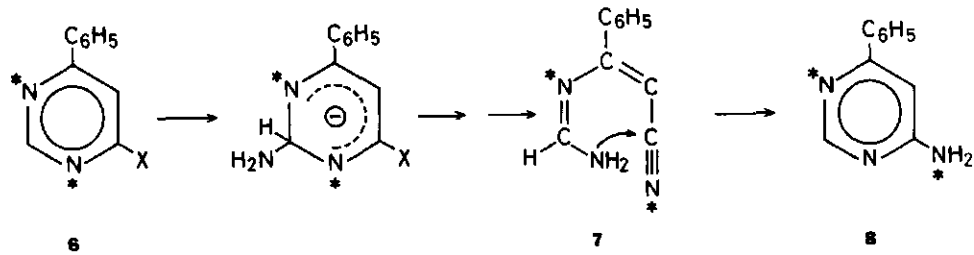


Scheme 1.2

1.2.1.3 *The $S_N(ANRORC)$ mechanism:*

The reactions of 4-halogeno-6-phenyl-[1(3)-^{15}N]pyrimidines (6), X = F, Cl, Br, with potassium amide have indicated that the resulting amino derivative 8 contains

^{15}N-label in the amino group. This process is explained by addition of the amide ion to C-2, after which a ring opening takes place to give an open-chain intermediate 7, followed by recyclization as shown to 8.

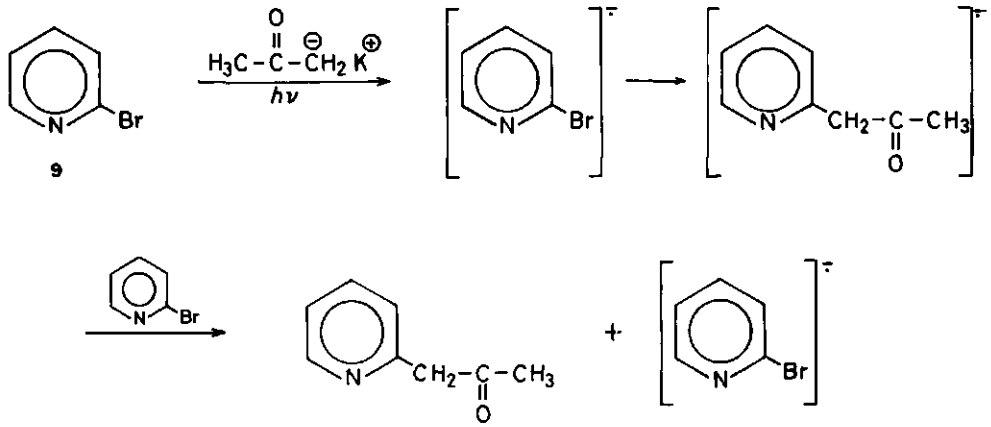


Scheme 1.3

This process is called an S_N(ANRORC) mechanism (Addition of Nucleophile, Ring Opening and Ring Closure)[7,8]. It has also been observed in the aminations of 2-halogeno-4-phenylpyrimidines by potassium amide in liquid ammonia[9,10].
An interesting and important aspect of this type of nucleophilic substitution mechanism is that although externally the ring systems of starting material and reaction product are the same the latter does not contain the same individual atoms within the ring as the original substrate. In actual fact a ring transformation has occurred. This sort of process in which the *type* of heterocyclic system remains unchanged is referred to as a degenerate ring transformation.

1.2.1.4 The $S_{RN}1$ mechanism

This process is initiated by formation of a radical anion of the halogenated heterocycle. This electron transfer can occur by photostimulation[11] or by generating solvated electrons in liquid ammonia by the addition of potassium[12].
The unstable radical anion loses the halide ion and the resulting radical combines with the nucleophile. The newly formed radical anion then transfers an electron to another substrate molecule in a chain-propagating process.
To date examples of this mechanism occurring in reactions of halogen containing azaaromatics are few but 2-bromopyridine (9) has been shown to undergo direct substitution *via* this mechanism with ketone enolates in potassium amide in liquid ammonia[11] as shown for the reaction with potassioacetone[13].



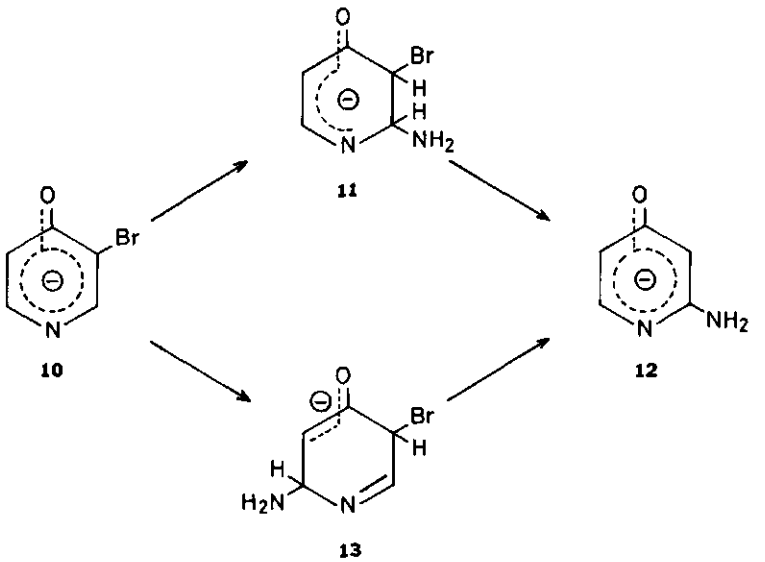
Scheme 1.4

1.2.2 Mechanisms of cine substitution

Prior to the work described in this thesis two types of mechanisms of cine substitutions had been observed.

1.2.2.1 The $S_N(AE)^{cine}$ mechanism:

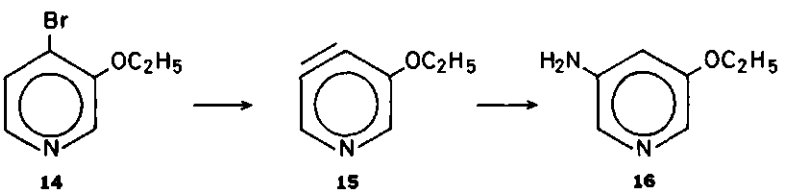
In this case addition of amide ion takes place to the carbon atom *adjacent* to the one bearing the halogen. This addition is followed by protonation and loss of hydrogen halide. This pathway has been proposed for the conversion by potassium amide in liquid ammonia of the anion of 3-bromo-pyrid-4-one (10) into the anion of 2-amino-pyrid-4-one (12), *via* addition of amide ion to C-2, yielding 11[14]. Conclusive proof is lacking however in that the competitive route of addition of amide ion to C-6 gives 13, which ultimately leads to the same product 12[15].



Scheme 1.5

1.2.2.2 The $S_N(EA)^{cine}$ mechanism:

This mechanism has been shown to occur in the amination of 4-bromo-5-ethoxy-pyridine (14) by potassium amide[6]. Elimination of hydrogen bromide affords 15, after which addition of ammonia yields exclusively the cine substitution product 3-amino-5-ethoxypyridine (16).



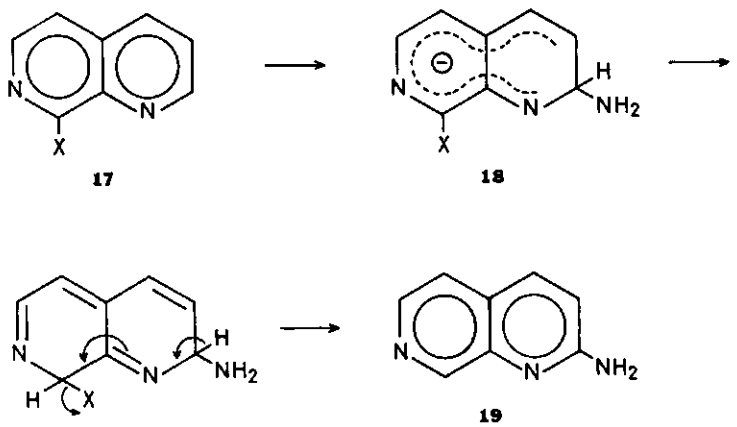
Scheme 1.6

1.2.3 Mechanisms of tele substitution

Three mechanisms have been reported for tele substitution reactions.

1.2.3.1 The $S_N(AE)^{tele}$ mechanism:

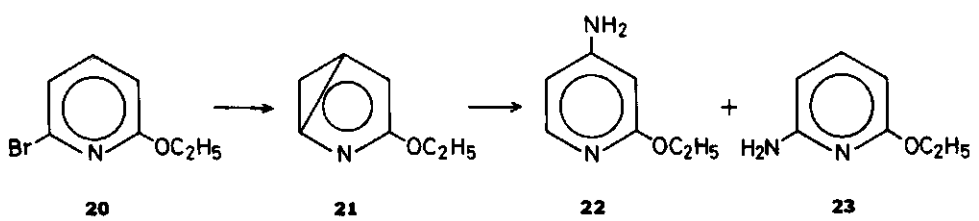
Several examples of this type of mechanism are available. Essential in this process is that the addition takes place to a carbon atom separated by one or more ring atoms from the carbon to which the halogen is attached. The formation of 2-amino-1,7-naphthyridine (19) alongside 8-amino-1,7-naphthyridine on treatment of 8-halogeno-1,7-naphthyridine (17) (X=Br, Cl) with potassium amide exemplifies this pathway[16,17]. Addition of amide ion to C-2 of 17 gives the σ-adduct 18, after which protonation and loss of hydrogen halide affords 19.



Scheme 1.7

1.2.3.2 The $S_N(EA)^{tele}$ mechanism:

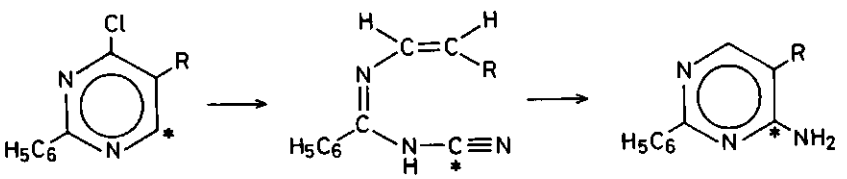
This process has been observed in the amination of 2-bromo-6-ethoxypyridine (20) which yields 4-amino-6-ethoxypyridine (22) alongside 2-amino-6-ethoxypyridine (23). The *meta* didehydropyridine (21) is postulated as intermediate[18,19].



Scheme 1.8

1.2.3.3 The $S_N(ANRORC)^{tele}$ mechanism:

There is only one example of this mechanism reported in the literature to date, *i.e.* the conversion of ^{14}C-labelled 5-substituted 4-chloro-2-phenylpyrimidines (24) into the ^{14}C-labelled 5-substituted 6-amino-2-phenylpyrimidines (26). The benzamidine intermediate 25 has been isolated and has been found to contain the ^{14}C-label in the cyano group[20].



24 **25** **26**

Scheme 1.9

1.2.4 Summary

A summary of the complex picture of nucleophilic substitution of halogen containing azaaromatics described in the preceding sections, is shown in the following table.

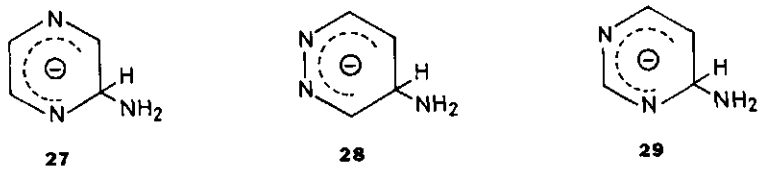
Table 1.1

Mechanism	Type of substitution		
	Direct	Cine	Tele
$S_N(AE)$	+	(+)	+
$S_N(EA)$	+	+	+
$S_N(ANRORC)$	+		+
$S_{RN}1$	+		

1.3 THE FORMATION OF σ-ADDUCTS

Addition of an amide ion to the heterocyclic ring is an important step in many

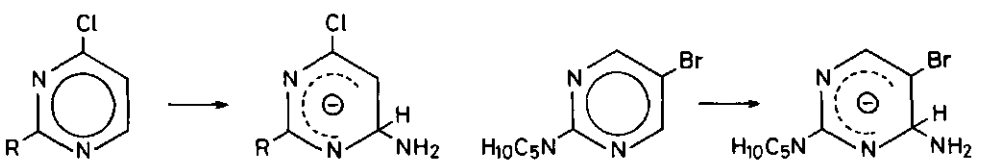
of the processes described in the previous sections. Although adduct formation between heteroaromatics and nucleophiles has been known for some time[21] the existence of the 1:1 σ-adducts 27-29 formed between an amide ion and non substituted diazines was only recently proven by PMR spectroscopy[22].



27 28 29

Scheme 1.10

Since then numerous examples have been reported for various substituted and non-substituted azaaromatics[16,17,23,24]. In the pyrimidine series it has been shown that 2-substituted 4-chloropyrimidines 30[25] and 5-bromo-2-piperidino-pyrimidine (32)[26] form 1:1 σ-adducts, 31 and 33 respectively, by addition of amide ion to C-6. The existence of these adducts can be discerned with PMR



30 31 32 33

Scheme 1.11

spectroscopy by the large upfield shift (2.2-4.5) ppm undergone by the proton bonded to the carbon atom to which addition takes place. This is due to the hybridisation change of that carbon from sp^2 to sp^3. A second effect, a triplet splitting pattern of the proton, due to coupling with the amine protons is found to be dependent on the amide ion concentration.

1.4 PURPOSE AND SCOPE OF THE INVESTIGATION

Bearing in mind the possibility of pyrimidine derivatives forming anionic 1:1 σ-adducts with amide ions and of amination reactions of halogen containing pyrimidines by potassium amide in liquid ammonia proceeding *via* a ring opening

process it was decided to launch an investigation in depth into the cine amination of 4-substituted 5-halogenopyrimidines by this reagent. In this thesis the results of this work will be described.

Chapter 2 deals with the results of a PMR investigation of solutions of 4-substituted 5-bromopyrimidines in liquid ammonia containing potassium amide[27].

Chapter 3 describes investigations into the mechanism of the cine amination of 5-bromo-4-*t*-butylpyrimidine[28].

In Chapter 4 some aspects of this mechanism are emphasized by a study on the reaction pattern of 4-*t*-butyl-5-chloropyrimidine, 5-bromo-2,4-di-*t*-butylpyrimidine and 5-chloro-2,4-di-*t*-butylpyrimidine with this reagent[29].

The effect of the nature of the substituent on C-4 of 4-substituted 5-bromopyrimidines on the amination mechanism is discussed in Chapter 5[30].

In Chapter 6 it is shown that a number of factors influencing the cine amination are also valid for the direct amination of 4-substituted 6-halogenopyrimidines[31].

Chapter 7 reports on the mechanism of the aminodemethoxylation of dimethoxypyrimidines by potassium amide in liquid ammonia[32].

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13. It should be emphasized that this process is essentially different from those described in the preceding and following sections in that, although it takes place in the potassium amide in liquid ammonia medium the function of the amide ion is to *generate* the nucleophile.
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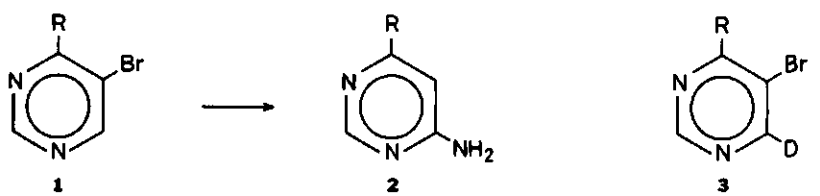
2 PMR studies on the formation of adducts between 4-substituted 5-bromopyrimidines and potassium amide in liquid ammonia

J.P.Geerts, C.A.H.Rasmussen, H.C.van der Plas and A.van Veldhuizen

2.1 INTRODUCTION

Previous investigations in this laboratory[1,2] have shown that the 4-substituted 5-bromopyrimidines (1a-1c, 1f) are converted into the corresponding 6-amino derivatives 2 on treatment with potassium amide in liquid ammonia at -33°.



R = a) C_6H_5 b) t-Bu c) OCH_3 d) $H_3CNC_6H_5$ e) $NHCH_3$ f) CH_3

R = a) C_6H_5 b) t-Bu

Scheme 2.1

Occurrence of a 5,6-didehydropyrimidine intermediate in the formation of 2 was suggested on the basis of experiments with the 6-deuterium-labelled pyrimidines 3. It was shown that with these compounds in this basic medium no deuterium-hydrogen exchange takes place and that no deuterium is present in the resulting 6-aminopyrimidines 2a, 2b[2,3]. These results exclude a mechanism in which an initial addition of an amide ion at position 6 is followed by an internal 6,5-hydride shift with simultaneous loss of a bromide ion. Recent PMR studies on substituted azaaromatics[4-7] led us to investigate the reaction of 1 in greater detail. Strong evidence can now be presented for the occurrence of a stable σ-complex 4, formed by addition of an amide ion to the C-6 atom of the pyrimidine nucleus.

2.2 RESULTS AND DISCUSSION

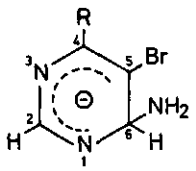
On dissolving the pyrimidines 1a-1d in liquid ammonia, containing two equivalents of potassium amide, and examining the resulting mixtures by PMR spectrometry shortly after preparation, signals are observed arising from:

(i) the solvent

(ii) the 1:1 σ-adduct 4

(iii) in some cases the reaction product 2

Absorptions from unreacted starting materials are not detected in any of the experiments.



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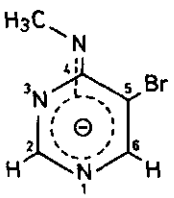

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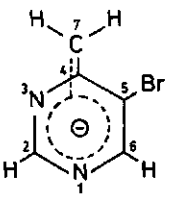

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Scheme 2.2

The assignment of the signals to the complexes 4 is based on comparing their spectra with those of the starting substances 1a-1d, measured in deuteriochloroform. Two marked differences appear:

(i) The H-2 and H-6 signals undergo a considerable shielding, as indicated by an upfield shift of 1.88-2.38 ppm and 3.69-4.28 ppm respectively (see Table 2.1)

(ii) The H-6 signal is split into a triplet, due to coupling with the protons of the attached amino group (J_{HCNH} = 7.5 Hz).

A typical example showing these features is given in the spectrum of 4b (fig. 2.1).

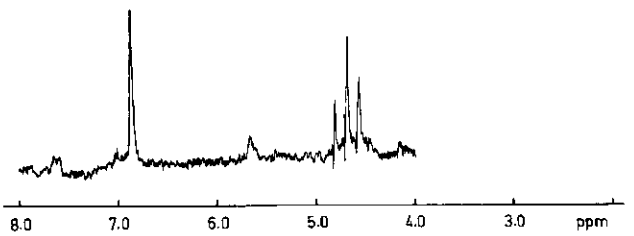

Fig. 2.1

These results are consistent with those published in the literature[4-6] and are summarized in Table 2.1.
In order to establish firmly that adduct formation occurs at C-6 and not at C-2, spectra of 1a, 1b, containing 50% of deuterium at C-6 were measured. A 50% intensity decrease of the triplet signal is observed, conclusively proving that the amino group is actually attached to C-6.

Table 2.1 PMR chemical shifts of the species 1a-1f,4a-4d,4f,5,6

	$CDCl_3$[a]			KNH_2/NH_3		
	H-2	H-6		H-2	H-6	°C
1a	9.23(s)	8.98(s)	4a	6.96(s)	4.79(t)	-50
1b	9.25(s)	8.95(s)	4b	6.87(s)	4.67(t)	-40
1c	8.68(s)	8.59(s)	4c	6.80(s)	4.85(t)	-40
1d	8.79(s)	8.34(s)	4d	6.83(s)	4.65(t)	-60
1e	8.58(s)	8.31(s)	5	7.64(s)	7.38(s)	-50
1f	8.98(s)	8.73(s)	6	7.08(s)	6.77(s)	-55
			4f	6.80(s)	4.69(t)	-55

[a] All spectra measured in $CDCl_3$ were taken at 27°.
s = singlet, t = triplet

The immediate conversion of the 5-bromopyrimidines 1a-1d into the σ-adducts 4 in liquid ammonia containing potassium amide provides us with a new explanation for the lack of deuterium-hydrogen exchange in 3. Originally it was assumed that the anion formed by abstraction of the deuteron from 3 is *de*stabilized by Coulomb repulsion between the adjacent C and N sp^2 orbitals, each containing

an electron pair[2,8]. In fact however, the D-6 is attached to a carbon atom with sp^3 hybridization instead of sp^2, due to complex formation in this medium, thus considerably decreasing its acidity[6].

The PMR spectrum of 1e in liquid ammonia containing potassium amide is completely different from those of 1a-1d, since it shows only absorptions of the solvent and the ionized substrate 5 (Scheme 2.2). The easy formation of this species is due to the presence of an acidic proton in the position α to the pyrimidine nucleus[5]. No trace of the complex 4e is observed. The H-2 and H-6 ring protons are shielded by 0.94 and 0.93 ppm respectively, compared with the H-2 and H-6 protons of the starting substance in deuteriochloroform (see Table 2.1). Despite the lack of a "PMR visible" adduct however, 1e reacts slowly with potassium amide to give 2e[9]. The PMR spectrum of a solution of 5-bromo-4-methylpyrimidine (1f) in liquid ammonia, containing two equivalents of potassium amide (Fig.2.2), is very interesting in that it shows signals which are ascribed to both the anion 6, resulting from proton abstraction from the methyl group, and the σ-complex 4f. The ratio in which both species are present is 3:1 respectively.

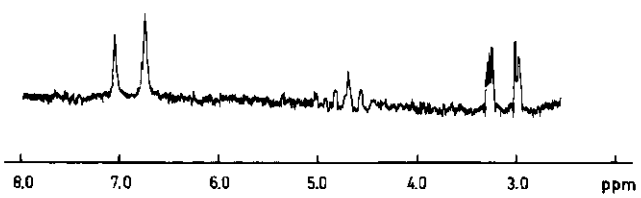

Fig. 2.2

The methylene group, appearing as a methyl singlet in the spectrum of 1f in deuteriochloroform, is split into an AB pair of doublets at δ = 3.30 and δ = 3.02 ppm (J = 2.3 Hz), the coupling being caused by the rescinding of free rotation round the C-4 — C-7 bond and the resulting difference in chemical environment of the methylene protons. The lower field component shows a further splitting into a pair of doublets, presumably through coupling with a ring proton (J = 1.1 Hz). These observations, combined with the changes in chemical shift of the ring protons - 1.90 ppm for H-2 and 1.96 ppm for H-6 - clearly establish that a charge-delocalized anion is formed. A virtually identical pattern is obtained on measurement of the spectrum of 4-methylpyrimidine and the results are consistent with earlier reports on 2-methylpyridine in the literature[7].

The remaining signals, *i.e.* a weak but distinct triplet (J = 7.5 Hz) at δ = 4.69 ppm and a singlet at δ = 6.80 ppm, the latter being partially obscured by the H-6 absorption of the anion 6, are assigned to H-6 and H-2 respectively of the complex 4f. Increase of the excess of potassium amide causes a collapse of the triplet into a singlet. This is due to a fast proton exchange in the amino group, leading to spin decoupling[10,11]. The signal of the methyl group lies in the range of the absorption of the solvent.

Additional evidence for formation of the complex 4f at C-6 is furnished by the PMR spectrum of a solution of 5-bromo-6-deuterio-4-(trideuteriomethyl)pyrimidine[12] containing 90% of D at position 6. Two phenomena are observed:

(i) as expected the H-6 triplet signal virtually disappears

(ii) the concentration ratio of anion to σ-complex changes from 3:1 for the hydrogen-containing compounds 6 and 4f into 1:2 for the deuterium-containing analogues. This dramatic increase in σ-complex formation may be ascribed to a deuterium isotope effect, making deuteron abstraction from the deuterated methyl group less easy and thereby favouring the competitive formation of the σ-adduct.

2.3 EXPERIMENTAL DATA

Melting points are uncorrected. IR spectra were recorded with a Hitachi, model EPI-G.3. Mass spectra were recorded on an AEI MS-902 instrument. PMR spectra in deuteriochloroform were obtained with a JEOL JNM C-60H spectrometer using tetramethylsilane (TMS, δ = 0) as internal standard. The amount of deuterium present in starting materials and recovered products was established by PMR spectroscopy, the content in position 6 being determined by comparing the integrated peak area of the H-6 signal with that of the H-2 signal, used as internal standard.

2.3.1 Preparation of starting materials

5-Bromo-4-phenylpyrimidine (1a)[13], *5-bromo-4-t-butylpyrimidine* (1b)[13], *5-bromo-4-methylpyrimidine* (1f)[13] and *5-bromo-4-methoxypyrimidine* (1c)[3] were prepared by procedures given in the literature.

5-Bromo-6-deuterio-4-phenylpyrimidine (3a), *5-bromo-6-deuterio-4-t-butylpyrimidine* (3b) and *5-bromo-6-deuterio-4-(trideuteriomethyl)pyrimidine* (1f, R = CD_3, H_6 = D) were prepared by procedures described for the non-deuterated compounds (cf. ref. 12, 13 and ref. 2, note d).

5-Bromo-4-(N-methylanilino)pyrimidine (1d)

550 mg (5.1 mmol) of freshly distilled *N*-methylaniline were added to a solution of 500 mg (2.5 mmol) of 5-bromo-4-chloropyrimidine[14] in 8 ml of ethanol (abs). After standing overnight at room temperature the mixture was kept at 0-5° for 24 h. The resultant precipitate was filtered off, yielding 440 mg (64%) of crude product. Recrystallisation from ethanol (abs) gave m.p. 88-89°.
$C_{11}H_{10}BrN_3$(264.13); calcd. C 50.01, H 3.82; found C 49.8, H 3.9.

5-Bromo-4-(N-methylamino)pyrimidine (1e)

1.0 g (5 mmol) of 5-bromo-4-chloropyrimidine[14] in 2 ml of ethanol was added drop by drop over 30 min to 5 ml of 30% solution of methylamine in ethanol, maintaining the temperature at 0°. After standing overnight, ether was added, the resultant precipitate was filtered off and the filtrate was evaporated to dryness. The residue was recrystallized from petroleum ether (60-80°), yielding 0.75 g (80%) of 1e, m.p. 128-129°.
$C_5H_6BrN_3$(188.04); calcd. C 31.93, H 3.22; found C 31.7, H 3.2.

2.3.2 *General procedure for measuring the PMR spectra in liquid ammonia containing potassium amide*

10 ml of dry liquid ammonia were condensed in a 50 ml three-neck round-bottomed flask, equipped with a Dry Ice/acetone condenser. 10 mmol of potassium and a few crystals of ferric nitrate catalyst were added. After stirring for 30 min at -33° 5 mmol of substrate 1a-1f were introduced at the appropriate reaction temperature (see Table 2.1). A sample was taken and measured after 5 min. For this purpose the spectrometer was equipped with a JES-VT-3 variable temperature controller. Spectra were obtained at temperatures between -40 and -60° (see Table 2.1). Trimethylamine was used as an internal standard (δ = 2.13 ppm).

2.4 REFERENCES

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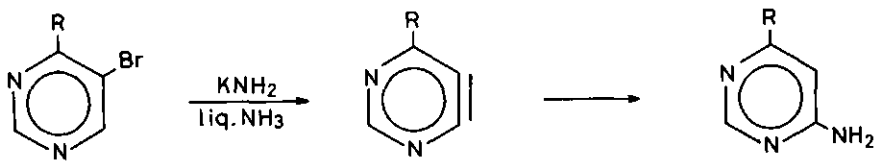
3 A reinvestigation of the mechanism of the amination of 5-bromo-4-*t*-butylpyrimidine. On the occurrence of an S_N(ANRORC) mechanism

C.A.H.Rasmussen and H.C.van der Plas

3.1 INTRODUCTION

The conversion of 4-substituted 5-bromopyrimidines into the corresponding 6-amino derivatives on treatment with potassium amide in liquid ammonia has in the past been studied extensively in this laboratory[1-3]. The results obtained from these studies were interpreted as indicating that the cine substitution proceeds *via* a mechanism involving a 4-substituted 5,6-didehydropyrimidine intermediate (Scheme 3.1).



Scheme 3.1

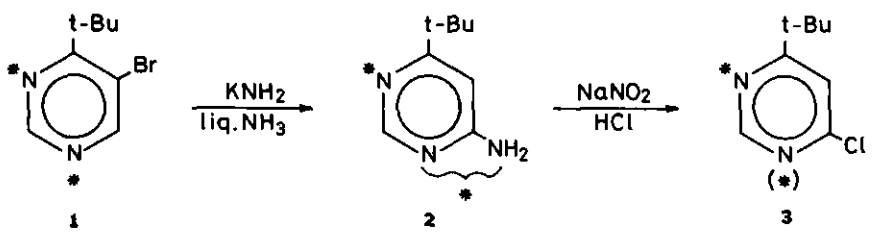
During the course of these investigations a reaction route involving an internal hydride shift from C-6 to C-5 following addition of an amide ion to C-6 was ruled out on the basis of results obtained when 5-bromo-4-*t*-butyl-6-deuteriopyrimidine was utilised as starting material, since the isolated 6-aminopyrimidine was found to contain no deuterium[3].

The discovery of the occurrence of an S_N(ANRORC) mechanism (Addition of Nucleophile, Ring Opening and Ring Closure) in the aminations of 4-substituted 6-halogeno-[4,5] and 4-substituted 2-halogeno-pyrimidines[6,7] with potassium amide in liquid ammonia induced us to reinvestigate this cine substitution reaction. For this purpose we prepared ^{15}N-labelled 5-bromo-4-*t*-butylpyrimidine. Coincident with this research the results of PMR studies on σ-adduct formation between 5-bromopyrimidines and potassium amide in liquid ammonia[8] also gave rise to doubt as to the validity of the "hetaryne mechanism" in the conversion to the

6-amino compound.

3.2 RESULTS AND DISCUSSION

^{15}N-labelled 5-bromo-4-*t*-butylpyrimidine (1) was synthesized as described previously for the unlabelled compound, utilising ^{15}N-labelled thiourea as starting material. On treating 1 with potassium amide in liquid ammonia for 24 hours at -33^{o} a reaction mixture was obtained consisting of 60% of unreacted starting material 1, 33% of ^{15}N-enriched 6-amino-4-*t*-butylpyrimidine (2) and a trace of 4-*t*-butylpyrimidine[9]. The reaction mixture was conveniently separated by column chromatography. In the case where 2 has been formed by an S_N(ANRORC) mechanism, part of the original ^{15}N-enrichment should be present in the extranuclear amino function. In order to investigate this, 2 was diazotised by using sodium nitrite in concentrated hydrochloric acid, yielding 4-*t*-butyl-6-chloro-[x-^{15}N]pyrimidine (3)(Scheme 3.2).



Scheme 3.2

The diazotization procedure[10] was preferred to the more conventional two-step process of an acidic hydrolysis of 2 to the corresponding 6-oxo compound and subsequent conversion of the latter to 3, because of the small amounts of 2 available. Comparison of the ^{15}N-enrichment of 1, 2 and 3 by mass spectrometry gave the amount of ^{15}N present in the amino group of 2, from which the percentage of S_N(ANRORC) mechanism in the reaction could be calculated. The results are shown in Table 3.1.

Table 3.1 Percentages of the excess of ^{15}N in the pyrimidines 1, 2 and 3[a,b]

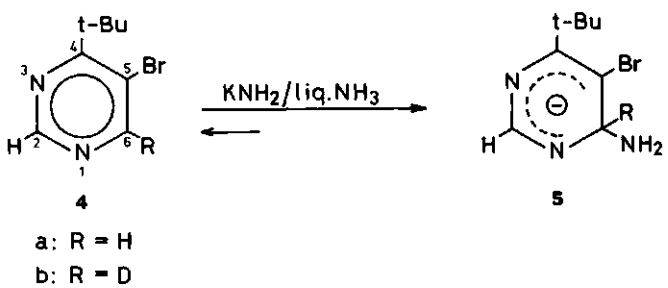
Compound	% excess ^{15}N
5-bromo-4-*t*-butyl-[1(3)-^{15}N]pyrimidine (1)	7.3
6-amino-4-*t*-butyl-[x-^{15}N]pyrimidine (2)	7.3
4-*t*-butyl-6-chloro-[x-^{15}N]pyrimidine (3)	5.5

[a] All experiments were carried out in duplicate

[b] Accuracy ± 0.2%

The decrease in the excess of ^{15}N from 7.3% in 2 to 5.5% in 3 indicates that 1.8/3.65 x 100% = 49% of 2 is formed by a mechanism involving an open-chain intermediate [S_N(ANRORC)].

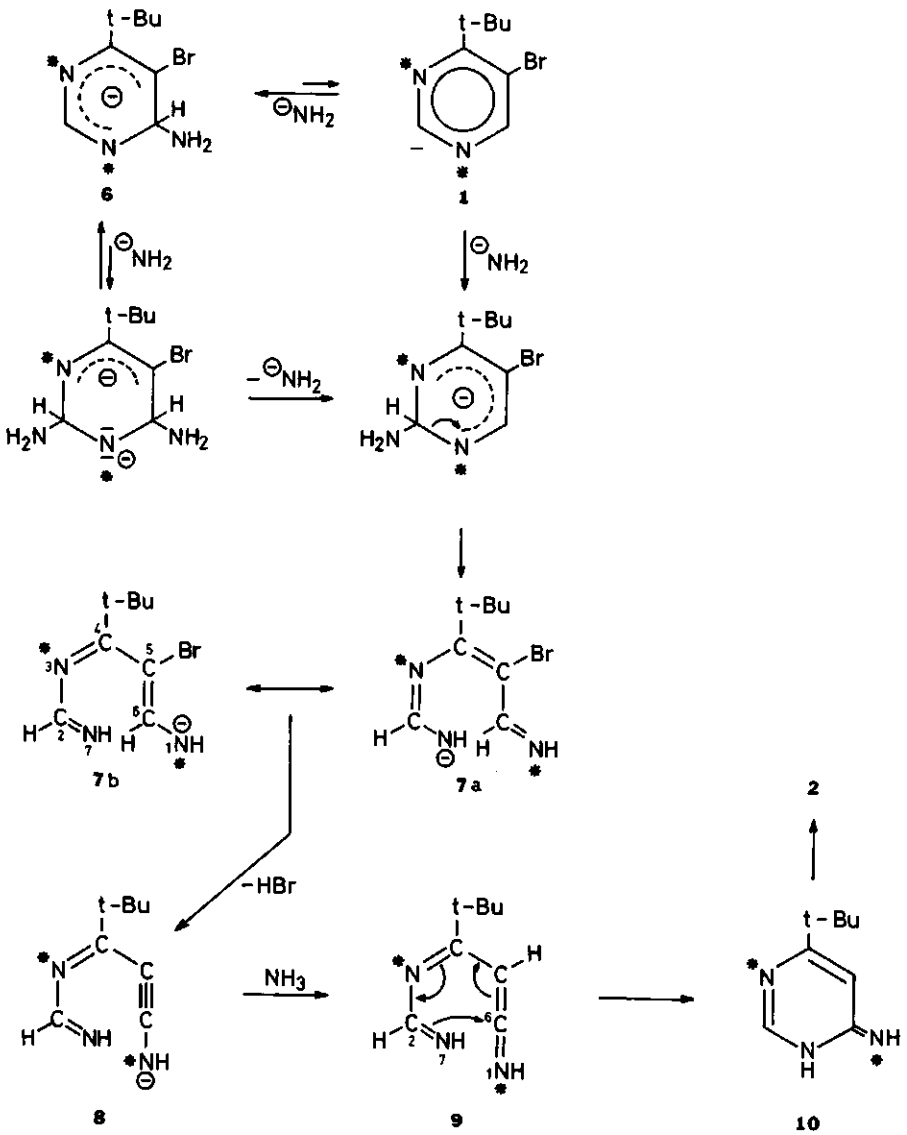
As mentioned in the introduction, the formation of σ-adducts between 5-bromopyrimidines and potassium amide in liquid ammonia has been extensively studied by PMR spectroscopy[8]. It was proved conclusively that on dissolving 4 in liquid ammonia, containing two equivalents of potassium amide, immediate formation of the stable σ-adduct 5 takes place (Scheme 3.3).



Scheme 3.3

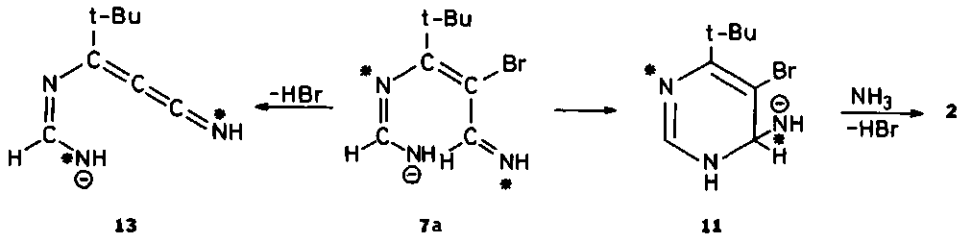
The existence of this species 5 lends no support to the "hetaryne mechanism" shown in Scheme 3.1. As no signals of unreacted 4 are visible in the PMR spectra alongside those of 5 it is clear that the concentration of 4 - if present at all - is below the minimum required for PMR visibility.

The explanation of the mechanism for the reaction is complicated further by the fact that the σ-adduct 6 cannot give rise to 2 containing ^{15}N on the extranuclear amino function. If cleavage of the N-1 — C-6 bond should take place an anionic open-chain compound is formed that on recyclisation yields either the original



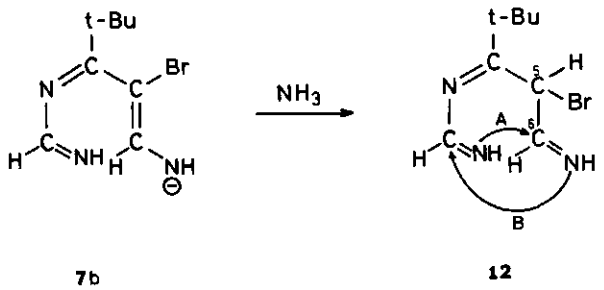
Scheme 3.4

adduct 6 or 2-amino-4-*t*-butylpyrimidine, which compound is not formed in the reaction. Amination *via* the σ-adduct 6 can never lead to the observed distribution of ^{15}N over the ring nitrogen atoms *and* the exocyclic amino function.
The following mechanism, depicted in Scheme 3.4, can account for the facts observed. Attack of an amide ion takes place on C-2 of either the σ-adduct 6, yielding a dianion as intermediate, or of the starting material 1, leading to a monoadduct. Formation of the latter by direct addition of the amide ion to C-2 of 6 with *simultaneous expulsion* of an amide ion from C-6 cannot be excluded either. After the addition cleavage of the N-1 — C-2 bond takes place. The resonance stabilised open-chain intermediate 7a ⟷ 7b then loses hydrogen bromide, giving *N*-(3-amino-1-*t*-butyl-2-propynylidene) formamidine (8). Proton abstraction from the solvent gives the ketenimine 9, that subsequently cyclises to 10. Prototropy then yields 2 with isotopic nitrogen outside the pyrimidine nucleus.
The initial step of this mechanism, attack of amide ion on C-2, is also observed in the reactions of 4-substituted 6-halogenopyrimidines with potassium amide in liquid ammonia[4,5] . The available data are insufficient to distinguish which of the two possible species, the σ-adduct 6 or the starting material 1 actually undergoes the addition. In both cases, however, we have a potential explanation for the comparatively slow reaction rate, as is evident from the 60% recovery of starting material after 24 hours. An attack of an amide ion on the negatively charged σ-adduct 6 is retarded due to electrostatic repulsion. In the case of addition to the starting material 1 the reaction will be slowed down, due to the at best low concentration of 1.
Once the addition at C-2 has taken place the ring opening must occur rapidly, since the PMR data[8] show no indication at all of the existence of any species besides 6. Essential for the remainder of the process is the fact that hydrogen bromide must be extruded from 7a ⟷ 7b *before* recyclisation takes place. An alternative mechanism, shown in Scheme 3.5, in which cyclisation from 7a to 11 by an attack of the anionic nitrogen on the imino function occurs first, *followed* by elimination of hydrogen bromide can be rejected on the following grounds. Barring the position of the isotopic nitrogen atoms, 11 is identical with the original σ-adduct 6. If this process should occur to any great extent, then, on quenching of the reaction after the 24 hour run and examining the ^{15}N content of the *retrieved starting material* 1, a decrease should be observed. This is not the case, as the recovered 1 containg the full original excess of 7.3% of ^{15}N.



Scheme 3.5

A similar cyclisation from 7b can also be ruled out, since this would yield 2-amino-4-*t*-butylpyrimidine which is not formed. A mechanism (Scheme 3.6) in which 7a ⟷ 7b extracts a proton from the solvent before the elimination of hydrogen bromide, yielding 12 can be rejected on similar grounds.



Scheme 3.6

The resulting acyclic diimine 12 can, due to the possibility of free rotation round the C-5 — C-6 bond, be expected to cyclise in two ways, as indicated by A and B, yielding a mixture of the 2-amino- and 6-amino-pyrimidines. It has been reported in the literature[11] that the ring contraction of 2,3-dihydro-5-methyl-6-phenyl-4*H*-1,2-diazepin-4-one into a mixture of 2-amino-3-hydroxy-4-methyl-5-phenylpyrimidine and 6-amino-3-hydroxy-4-methyl-5-phenylpyrimidine through the action of base, occurs *via* a similar diimine. Again, the complete absence of 2-amino-4-*t*-butylpyrimidine in our case eliminates this reaction pathway.

All the evidence collected so far points to the reaction route shown in Scheme 3.4.

Ynamine formation by elimination of hydrogen halide from alkenes is known[12]. The final cyclisation reaction following the addition of a proton from the solvent to C-5 in 8 can be expected to proceed only in the direction indicated, due to the difference in electrophilic character between C-2 and C-6 combined with the inflexibility of the ketenimine structure and the consequently greater distance between N-1 and C-2 as compared with that between N-7 and C-6. For similar reasons we consider it less likely that the elimination of hydrogen bromide will take place from 7a. The resulting cumulene 13 (Scheme 3.5) seems less attractive for cyclisation, due to the increased distance between the atoms involved.

We have already mentioned[3] the absence of deuterium in 6-amino-4-*t*-butylpyrimidine obtained when 5-bromo-4-*t*-butyl-6-deuteriopyrimidine (4b) was utilised as the substrate. In view of our results with the ^{15}N-labelled 5-bromopyrimidine 1 we reverted to these studies. In contrast to the earlier work however, the focal point of attention was not the deuterium distribution in the 6-amino reaction product, but in the starting material retrieved after the reaction. Compound 4b was utilised containing different amounts of deuterium at C-6. On examination of the retrieved starting material after 24 hours reaction time, it was discovered that in all runs the deuterium content was raised in comparison with the original content. As shown in Table 3.2, the increase was least when the original content was highest.

Table 3.2 Percentage of deuterium contents in 5-bromo-4-t-butyl-6-deuteriopyrimidine (4b)[a,b]

Run	% in 4b before reaction	% in 4b recovered after reaction	increase in %
1	26.7	32.1	5.4
2	50.7	54.6	3.9
3	76.1	79.2	3.1

[a] All experiments were carried out in duplicate

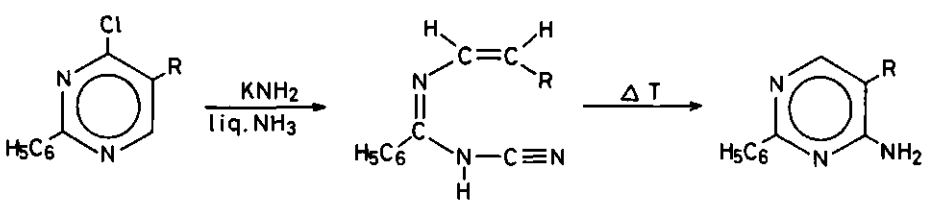
[b] Accuracy $\pm$ 0.2%

At the same time, it was observed that the amount of 6-amino-4-*t*-butylpyrimidine formed during the reaction decreased markedly with a rising deuterium content in 4b. These results indicate the existence of an isotope effect in the reaction. The deuterium-labelled compound 4b undergoes amination at a slower rate than the

non-labelled substrate. An isotope effect k_H/k_D of around 2 is indicated (see Experimental Data). This isotope effect makes it clear that in the reaction process a rate-determining step is involved with abstraction of hydrogen from C-6 being preferred to abstraction of deuterium. It is not possible to determine from the available data whether this isotope effect is operative in that part of the reaction that proceeds *via* the S_N(ANRORC) mechanism, in the part proceeding *via* a mechanism not involving a ring opening or in both. In the S_N(ANRORC) process the conversion of 7b to 8 would be rate-determining.

Regarding the 51% of the reaction that does not proceed *via* a ring opening process it now seems highly unlikely that a "hetaryne mechanism" is involved. The most plausible pathway is addition of an amide ion to 1, yielding the σ-adduct 6, followed by protonation and loss of hydrogen bromide, similar to the conversion of 11 into 2 as shown in Scheme 3.5. In this process again, an isotope effect could be operative.

Summarizing, it is proved conclusively that the conversion of 5-bromo-4-*t*-butylpyrimidine (4a) into 6-amino-4-*t*-butylpyrimidine shows the first example of an S_N(ANRORC) process in which the nucleophile is introduced into a *different* position than the one vacated by the expelled halide ion. We refer to this mechanism as an $S_N(ANRORC)^{cine}$ process.



14 **15** **16**

Scheme 3.7

A somewhat similar pathway has been recorded in the tele-amination of 5-substituted 4-chloro-2-pnenylpyrymidines 14 into 5-substituted 6-amino-2-phenylpyrimidines 16[13] as determined by ^{14}C-labelling (Scheme 3.7). This reaction also occurs *via* a ring opening, as has been proved by isolation of the open-chain compound *N*-(2-R-vinyl)-*N*-cyanobenzamidine 15. We propose to refer to this mechanism as an $S_N(ANRORC)^{tele}$ process.

The accumulated results prove that the hitherto accepted theory that the described conversion proceeds *via* a "hetaryne mechanism" is incorrect. In this light caution

should be taken regarding the aminations of other 4-substituted 5-bromopyrimidines with potassium amide in liquid ammonia currently accepted as involving a hetaryne intermediate[1,2,14]. Extensive further research into these and similar processes[15] is indicated.

3.3 EXPERIMENTAL DATA

Melting points are uncorrected. The excess of ^{15}N in compounds 1, 2 and 3 was measured by comparison of the M+1 and M intensities on an AEI MS-902 mass spectrometer. Deuterium contents in 4b were obtained by the same procedure. The PMR measurements have been described in a previous paper[8]. IR spectra were recorded on a Hitachi, model EPI-G3.
All samples taken for excess ^{15}N measurements were additionally purified by gas chromatography on a Becker Unigraph-F type 407 instrument. Samples were collected after passing through a stainless steel column 100 cm in length and with an internal diameter of 3 mm, filled with 2.4 g of ABS + 20% OV-17. Typical retention times at an oven temperature of 158° and F_o(nitrogen) 30 ml per minute are 1: 2.1 min; 2: 4.8 min and 3: 0.9 min. Column chromatography was carried out over Merck silica gel 60 (70-230 mesh ASTM).

3.3.1 Preparation of starting materials and reference compounds

^{15}N-labelled thiourea[16,17] and *ethyl 4,4-dimethyl-3-oxovalerate*[18] were prepared as described in the literature.
5-Bromo-4-t-butyl-[1(3)-^{15}N]pyrimidine (1)[19] and its precursors *4-t-butyl-2-thioxo-[1(3)-^{15}N] pyrimid-6-one*[20], *4-t-butyl-[1(3)-^{15}N] pyrimid-6-one*[19], *5-bromo-4-t-butyl-[1(3)-^{15}N] pyrimid-6-one*[19], *5-bromo-4-t-butyl-6-chloro [1(3)-^{15}N]-pyrimidine*[19] and *5-bromo-4-t-butyl-6-hydrazino-[1(3)-^{15}N] pyrimidine*[19] were prepared according to procedures described for the unlabelled compounds.
The reference compounds *4-amino-6-t-butylpyrimidine* and *4-t-butyl-6-chloro-pyrimidine* were prepared as described in the literature[19], as was *5-bromo-4-t-butyl-6-deuteriopyrimidine* (4b)(cf. ref.3, note d).

3.3.2 Amination of 5-bromo-4-t-butyl-[1(3)-^{15}N] pyrimidine (1) with potassium amide in liquid ammonia

Twenty-five ml of extra-dry liquid ammonia were distilled from potassium. 156 mg of potassium (4 mmol) were added, along with a few crystals of ferric

nitrate catalyst. After stirring for 30 min, a solution of 215 mg of 5-bromo-4-*t*-butyl-[1(3)-^{15}N]pyrimidine (1)(1 mmol) in 2½ ml of absolute ether was run in. The resulting mixture was stirred at -33° for 24 h when 500 mg of ammonium chloride were added, after which the ammonia was evaporated. The residue was extracted with 2 x 80 ml of boiling chloroform. After filtration and evaporation of the solvent the oily residue was dissolved in 2 ml of chloroform. Column chromatography of this solution with chloroform as eluent over silica gel gave the unreacted starting material 1 and on changing the eluent to methanol, 2 was obtained. Evaporation of the chloroform gave 120-135 mg of 1; evaporation of the methanol 45-55 mg of 2, m.p. 166-170° (lit.170-171°)[19]. An IR spectrum was identical with that of an authentic sample of 2.

3.3.3 Conversion of 6-amino-4-t-butyl-[x-^{15}N] pyrimidine (2) into 4-t-butyl-6-chloro-[x-^{15}N] pyrimidine (3)[10]

Fifty mg of 6-amino-4-*t*-butyl-[x-^{15}N]pyrimidine (2) (0.33 mmol) were dissolved in 0.5 ml of concentrated hydrochloric acid. A solution of 230 mg of sodium nitrite (3.34 mmol) in 1 ml of water was added dropwise over a period of 20 min, with stirring, maintaining the temperature of the mixture at -10 to -15°. The reaction mixture was stirred for 2½ h during which the temperature was allowed to rise to room temperature. N_2 was evolved. Following dilution by the addition of 5 ml of water and adjustment of the pH to 7 through the careful addition of concentrated sodium hydroxide solution, the mixture was extracted with 2 x 30 ml of ether. The ethereal solution was dried over anhydrous magnesium sulphate, the latter was filtered off and the ether was evaporated slowly *in vacuo*, maintaining the bath temperature below 30°. 5-10 mg of 3 were obtained (9-17%). An IR spectrum was identical with that of an authentic specimen.

3.3.4 Calculation of the isotope effect k_H/k_D

On reacting 215 mg of 4a, 50 mg of 6-amino-4-*t*-butylpyrimidine (2) were obtained, whereas from 215 mg of 4b, containing 76.1% of deuterium only 22 mg of 2 could be isolated. The isotope effect k_H/k_D was calculated as follows. From 215 mg of starting material 4b containing 26.7% of deuterium 137 mg of 4b containing 32.1% of deuterium was retrieved after the reaction. From these data, utilizing the formula $k_H/k_D = \ln(H/H_o)/\ln(D/D_o)$ the value of 1.9 was obtained.

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9. Dehalogenation under influence of strong nucleophiles is not uncommon. Cf. for example debromination in the reaction of o-bromoanisole with lithium diethylamide in diethyl ether, E.R.Biehl, S.M.Smith, S.Lapis and P.C.Reeves, J.Org.Chem. 37, 3529 (1972).
10. Conversion of a primary amino group into a chloro function through diazotization has been observed regularly in pyrimidine chemistry. See D.J.Brown, "The Pyrimidines", Wiley Interscience, New York, 1962, its supplement 1, 1970 and references cited therein. In general however, the 2-amino group reacts more readily than an amino group in the 4-position. It has recently been observed that 4-aminopyrimidine derivatives where the amino group is thus both α and γ to a potential or actual sp^2 nitrogen atom resist diazotization. Cf. R.N.Butler, Chem.Rev. 75, 241 (1975). The reaction reported in this paper thus constitutes an exception to this observation.
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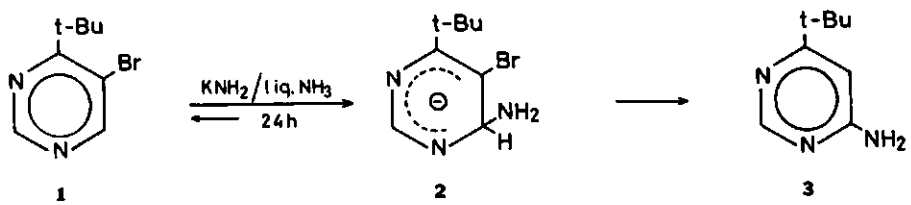
21. Precautions should be taken to exclude all traces of water; these lead to several by-products, for example 4-*t*-butylpyrimid-6-one.

4 Aspects of the amination of 4-*t*-butyl-5-halogenopyrimidines by potassium amide in liquid ammonia

C.A.H.Rasmussen and H.C.van der Plas

4.1 INTRODUCTION

In the course of investigations into the reactions of halogenoazaaromatics with nitrogen containing nucleophiles we recently published a study on the cine substitution of 5-bromo-4-*t*-butylpyrimidine (1) by potassium amide in liquid ammonia[1] (Scheme 4.1).



Scheme 4.1

It was proven by means of ^{15}N-labelling that two mechanisms are operative in this process. 51% of 1 reacts *via* the "PMR visible"[2] σ-adduct 2, which by protonation and subsequent loss of hydrogen bromide yields 3. The remaining 49% is converted into 3 *via* an S_N(ANRORC) mechanism, which mechanism describes the pathway in which a ring nitrogen ends up on the exocyclic amino function. This latter process is initiated by an attack of amide ion on C-2 of 1. Cleavage of the N-1 — C-2 bond occurs in the C-2 σ-adduct after which hydrogen bromide is eliminated from the resulting open-chain intermediate *before* cyclisation. In accordance with these findings a deuterium isotope effect of about 1.9 was observed in the cine substitution reaction.

In view of these results we decided to modify the substrate in an attempt to emphasize and clarify some aspects of the amination. The reaction of 4-*t*-butyl-5-chloropyrimidine (11a) was studied in order to determine the influence of the halogen substituent. Bearing furthermore in mind that introduction of a bulky

group at C-2 can be expected to hinder the access of amide ion to that position and consequently disfavour an S_N(ANRORC) mechanism an investigation was undertaken into the amination of 5-bromo-2,4-di-*t*-butylpyrimidine (11b) and 5-chloro-2,4-di-*t*-butylpyrimidine (11c). The *t*-butyl group was chosen as blocking group since previous experiences with the phenyl group in this laboratory have shown that this substituent is not always effective as such[3,4].

4.2 RESULTS AND DISCUSSION

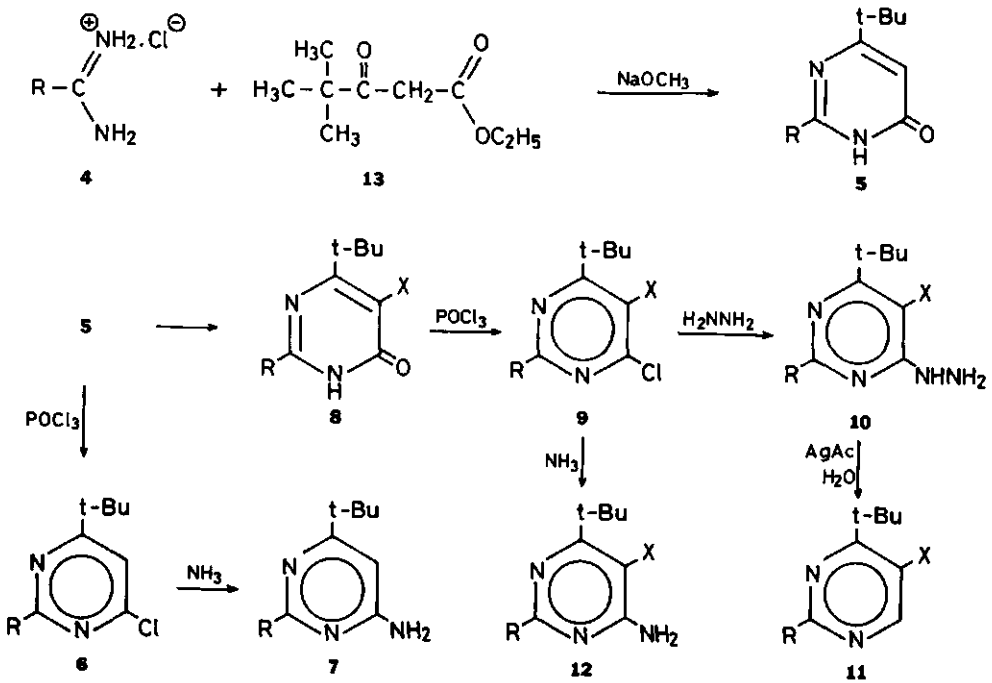
4.2.1 The reaction of 4-t-butyl-5-chloropyrimidine (11a) with potassium amide in liquid ammonia

4-*t*-Butyl-5-chloropyrimidine (11a) was synthesized according to the route shown in Scheme 4.2 (See Experimental Data, section 4.3).
It was found that the rate of amination of 11a was lower compared with that of the 5-bromo analogue, as appeared from the fact that 35% of the starting material could still be retrieved after treatment of 11a with potassium amide in liquid ammonia for 72 hours. Only 15% of the expected cine substitution product 6-amino-4-*t*-butylpyrimidine (7a) was found however. The main product was 6-amino-4-*t*-butyl-5-chloropyrimidine (12a)(30%), identified *via* an independent synthesis from 9a, as shown in Scheme 4.2. Small amounts of 4-*t*-butylpyrimidine and 4-*t*-butylpyrimid-6-one (5a) were also found.

Table 4.1 PMR chemical shifts of solutions of 4-t-butyl-5-halogenopyrimidines (1,11a) and 2,4-di-t-butyl-5-halogenopyrimidines (11b,11c) in deuterated chloroform and in potassium amide in liquid ammonia

Compound	$CDCl_3$		KNH_2/NH_3	
	H-2	H-6	H-2	H-6
1[a]	9.25	8.95	6.87	4.67
11a	8.93	8.51	6.92	4.68
11b	--	8.59	--	4.90
11c	--	8.42	--	4.76

[a] viz.reference 2



4 - 7 : a) R = H
b) R = t-Bu

8 - 12 : a) R = H, X = Cl
b) R = t-Bu, X = Br
c) R = t-Bu, X = Cl

Scheme 4.2

It was established by PMR spectroscopy that the H-6 in 11a undergoes a characteristic upfield shift of 3.83 ppm when replacing deuterated chloroform as solvent by liquid ammonia containing potassium amide (see Table 4.1). This indicates that in this latter system an anionic 1:1 σ-adduct is present on C-6 (14a, Scheme 4.3).

The amination was subsequently carried out with $\left[1(3)\text{-}^{15}N\right]$-labelled 11a containing 6.3% of excess ^{15}N scrambled over the N-1 and N-3 atoms in order to establish whether a degenerate ring transformation *via* an S_N(ANRORC) mechanism is involved in the formation of 7a and 12a. The obtained products, $\left[x\text{-}^{15}N\right]$ 7a and $\left[x\text{-}^{15}N\right]$ 12a were converted into 4-*t*-butyl-6-chloro-$\left[x\text{-}^{15}N\right]$ pyrimidine and 4-*t*-butyl-5,6-dichloro-$\left[x\text{-}^{15}N\right]$ pyrimidine respectively through diazotization in hydrochloric acid[1]. All compounds were examined for their ^{15}N contents by mass spectrometry. The results are summarized in Table 4.2 and they unequivocally show that there is complete retention of ^{15}N excess in *all* compounds.

Table 4.2 Excess of ^{15}N in the pyrimidines involved in the reaction of 4-t-butyl-5-chloro-$\left[1(3)\text{-}^{15}N\right]$ pyrimidine with potassium amide in liquid ammonia[a,b]

pyrimidine	% excess ^{15}N
4-*t*-butyl-5-chloro-$\left[1(3)\text{-}^{15}N\right]$ pyrimidine	6.3
6-amino-4-*t*-butyl-5-chloro-$\left[x\text{-}^{15}N\right]$ pyrimidine	6.3
6-amino-4-*t*-butyl-$\left[x\text{-}^{15}N\right]$ pyrimidine	6.4
4-*t*-butyl-5,6-dichloro-$\left[x\text{-}^{15}N\right]$ pyrimidine	6.2
4-*t*-butyl-6-chloro-$\left[x\text{-}^{15}N\right]$ pyrimidine	6.4
4-*t*-butyl-5-chloro-$\left[x\text{-}^{15}N\right]$ pyrimidine[c]	6.5

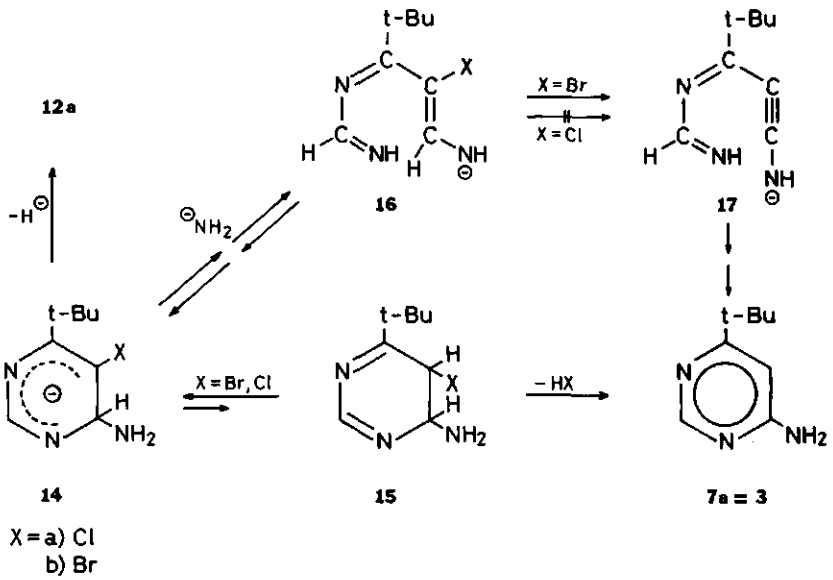
[a] all experiments were carried out in duplicate

[b] accuracy ± 0.2%

[c] starting material retrieved after the reaction

These results imply that the S_N(ANRORC) mechanism is *not* operative in the amination of 11a. Both products 12a and 7a can be formed from the intermediate 14a (Scheme 4.3), the Chichibabin type amination product 12a by loss of a hydride ion from 14a[5,6] and 7a by protonation of 14a and subsequent loss of hydrogen chloride from 15a *via* an E2 or an ElcB elimination. Elimination of hydrogen chloride can be expected to be slower than that of hydrogen bromide[7].

This may explain the slower reaction rate in the formation of 7a from 11a compared with that of 7a from 1.



Scheme 4.3

14a may well undergo a ring opening following an attack by an amide ion on C-2, as has been shown in the reaction of 1 with potassium amide. The resulting open-chain intermediate 16a formed by such a process can *only* recyclise to the original species by an intramolecular attack on C-2 (Scheme 4.3). The other theoretical possibility for recyclisation, an intramolecular attack on C-6, leads to an adduct identical to 14a, except for the ^{15}N distribution in the labelled compound. If this process were operative a decrease in ^{15}N-enrichment in the starting material retrieved after quenching the reaction would be observed, which is not the case (Table 4.2). Loss of hydrogen chloride from 16a - in analogy to the loss of hydrogen bromide from 16b - would ultimately lead to 7a in which ^{15}N is located on the exocyclic amino function, *contrary* to our observations. The non-occurrence of hydrogen chloride elimination can possibly be explained by the fact that the rate of elimination in the formation of acetylenes from haloalkenes is I > Br > Cl > F[8].

4.2.2 The reaction of 5-bromo-2,4-di-t-butylpyrimidine (11b) *and 5-chloro-2,4-di-t-butylpyrimidine* (11c) *with potassium amide in liquid ammonia*

The compounds 11b[9] and 11c were prepared according to Scheme 4.2, as was the reference compound 6-amino-2,4-di-*t*-butylpyrimidine (7b). The product pattern of the 5-bromo compound 11b versus the 5-chloro compound 11c was found to be virtually identical to that of 1 versus 11a, except for a slightly lower reaction rate, 72 hours being used as reaction time for 11b and 11c. Thus 11b yielded 60% of 6-amino-2,4-di-*t*-butylpyrimidine (7b), 32% of unreacted starting material and some dehalogenated product; 11c gives 45% of 6-amino-5-chloro-2,4-di-*t*- butylpyrimidine (12c) (identified by independent synthesis as shown in Scheme 4.2) , 30% of retrieved starting material, 5% of 7b and a trace of 2,4-di-*t*- butylpyrimidine. Some tar is also obtained.

The PMR spectra of solutions of 11b and 11c in liquid ammonia containing potassium amide again showed the existence of a 1:1 σ-adduct with an amide ion attached to C-6 (Table 4.1). The aminations were subsequently studied by utilizing ^{15}N-labelled potassium amide in ^{15}N-labelled ammonia, a technique recently described[10]. It was discovered after conversion of the amino compounds into the corresponding chloro derivatives by diazotization in hydrochloric acid that *no* ^{15}N had been incorporated into the pyrimidine ring during the formation of 7b from 11b and of 12c from 11c. The small amount of 7b formed from 11c precluded formation of the chloro compound 6b, but in view of the results mentioned above the possibility of the occurrence of an S_N(ANRORC) process is virtually non-existent, because of the combined effects of the chloro atom at C-5 (section 4.2.1) and accessibility to C-2. The measured excess of ^{15}N values are shown in Table 4.3. They represent clear proof that the occurrence of an S_N(ANRORC) process in the conversion of the 4-*t*-butyl-5-halogenopyrimidines 11b and 11c is dependent on the accessibility of C-2 to the amide ion.

Table 4.3 Excess of ^{15}N in the pyrimidines 6b,7b,9c and 12c[a,b]

Starting material	pyrimidine	% excess ^{15}N
11b	7b	4.0
	6b	0
11c	12c	3.9
	9c	0

[a] all experiments were carried out in duplicate
[b] accuracy ± 0.2%

Although it has been proved by ^{15}N-labelling that in 1, without a substituent at C-2, addition of an amide ion at C-2 can take place, no PMR proof for the existence of a 1:1 σ-adduct at C-2 was ever obtained. Therefore full attention was now focussed on attempts to prove the existence of σ-adducts on C-2 of the pyrimidine ring by PMR spectroscopy. Since the formation of 1:1 σ-adducts at C-6 occurs easily, we hoped that if an unreactive bulky group was attached to C-4 and C-6, hindering adduct formation at these positions, the amide ion could be forced to add at C-2. Unfortunately attempts to prepare 5-bromo-4,6-di-*t*-butylpyrimidine by bromination with bromine in glacial acetic acid, bromine with silica gel[11] or by the use of *N*-bromosuccinimide all failed. *t*-Butylation of 5-bromo-4-*t*-butylpyrimidine by the method of Minisci[9] was also unsuccessful. 5-Bromo-4,6-diphenylpyrimidine could not be prepared either. The non halogen containing compound 4,6-di-*t*-butylpyrimidine was found to be insoluble in the potassium amide in liquid ammonia system, thus precluding PMR measurements. Fortunately, however, 4,6-diphenylpyrimidine gives a clear adduct[12]. The H-2 and H-5 signals, visible at δ = 9.33 and δ = 8.08 in deuteriochloroform undergo an upfield shift to δ = 4.68 and δ = 6.10 respectively in liquid ammonia containing potassium amide. The signal at δ = 4.68 is split up into a *triplet*. The data agree with the existence of a σ-adduct at C-2.

4.3 EXPERIMENTAL DATA

Melting points are uncorrected. ^{15}N contents were determined on an AEI MS-902 mass spectrometer by measuring the intensities of the M+1 and M peaks. PMR spectra were recorded on a JEOL C-60 spectrometer equipped with a JES-VT-3 variable temperature controller or on a Hitachi-Perkin Elmer R-24B spectrometer. TMS was used as internal standard for the spectra taken in deuteriochloroform. Preparative gas chromatography was performed on a Becker Research Gas Chromatograph, type 3810 with Cycloprep 2400. Column chromatography was carried out over Merck Silica gel 60 (70-230 mesh ASTM).

4.3.1 Preparation of starting materials and reference compounds

Ethyl-4,4-dimethyl-3-oxovalerate (13)[13], *4-t-butylpyrimid-6-one* (5a)[14] and its [*1(3)-*^{15}N]*-labelled analogue*, *pivalamidine hydrochloride* (4b)[15,16], *4,5-di-t-butylpyrimidine*[17] and *4,6-diphenylpyrimidine*[18] were prepared according to established procedures. Other [*1(3)-*^{15}N]*- labelled pyrimidines* were synthesized according to the processes described below for the corresponding unlabelled

compounds.

4-t-butyl-5-chloropyrimid-6-one (8a)

2.4 g of chlorine were passed through a solution of 3.9 g (25.6 mmol) of 4-*t*-butylpyrimid-6-one (5a) in 65 ml of freshly distilled acetic acid. The solution was cooled at 0° for 15 min and the solvent was evaporated. 12 ml of water were added, the precipitate was filtered off and dried *in vacuo* to yield 2.4 g (50%) of 8a. Crystallisation from petroleum ether (60-80°) gave m.p. 152-154°; M^+(m/e) 186/188. PMR: δ = 1.40 (s,9H), δ = 8.10 (s,1H).
$C_8H_{11}ClN_2O$(186.64); calcd. C 51.48, H 5.94; found C 51.6, H 6.2.

4-t-butyl-5,6-dichloropyrimidine (9a)

2.7 g (14.5 mmol) of 8a were refluxed with 30 ml of phosphoryl chloride for 3 h. The excess of phosphoryl chloride was distilled off *in vacuo* , the residue was poured onto crushed ice and, after neutralisation with ammonia, extracted with ether. The ethereal extract was dried over anhydrous magnesium sulphate, filtered and evaporated. The semi-solid product was purified by distillation *in vacuo*. 9a was collected at 109-110°/15 mm, to give 2.6 g of 9a (88%) which solidified on standing, m.p. 45-47°.
$C_8H_{10}Cl_2N_2$(205.09);calcd. C 46.85, H 4.91; found C 47.1, H 5.0.

6-amino-4-t-butyl-5-chloropyrimidine (12a)

98 mg (0.48 mmol) of 9a were heated in a sealed tube at 130° for 24 h with 8 ml of ethanolic ammonia saturated at 0°. After evaporation of the solvent the residue was extracted with 50 ml of boiling toluene. The toluene was distilled off *in vacuo* and the product was purified by column chromatography (silica gel, ethyl acetate) to give 48 mg (54%) of 12a, m.p. 148-150°; M^+(m/e) 185/187.
$C_8H_{12}ClN_3$(185.66); calcd. C 51.75, H 6.52; found C 51.9, H 6.8.

4-t-butyl-5-chloro-6-hydrazinopyrimidine (10a)

2.6 g (12.5 mmol) of 9a were refluxed for 3 h with 3.8 ml of hydrazine hydrate in 110 ml of ethanol. After evaporation of the solvent the crude product was crystallized from ethanol/water 1:1 to give 1.9 g (76%) of 10a, m.p. 108-109°.
$C_8H_{13}ClN_4$(200.67); calcd. 47.88, H 6.53; found C 48.2, H 6.5.

4-t-butyl-5-chloropyrimidine (11a)

1.8 g (8.8 mmol) of 10a was refluxed for 3 h with vigorous stirring with 9 g of freshly prepared silver acetate in 30 ml of water. The reaction mixture was extracted repeatedly with ether. The ethereal extract was dried over anhydrous magnesium sulphate, filtered and evaporated at atmospheric pressure. The oily residue was distilled *in vacuo* to give 0.69 g (46%) of 11a, b.p. 84-85°/15 mm, M^+(m/e) 170/172. PMR: δ = 1.60 (s,9H), δ = 8.51 (s,1H), δ = 8.93 (s,1H). $C_8H_{11}ClN_2$(170.64); calcd. C 56.30, H 6.50; found C 56.3, H 6.5.

2,4-di-t-butylpyrimid-6-one (5b)[19]

A solution of 15.7 g (91 mmol) of ethyl-4,4-dimethyl-3-oxovalerate (13) in 20 ml of methanol was added drop by drop with stirring at 0° to a solution of 3.9 g (169 mmol) of sodium in 75 ml of methanol. Maintaining the temperature at 0°, 10.5 g (78 mmol) of pivalamidine hydrochloride (4b) was added in small portions, after which stirring was continued for 2 h. After standing overnight the precipitate was filtered off and washed with cold methanol. The filtrate was concentrated to half volume, diluted with 125 ml of water, treated with decolourising carbon, filtered and acidified to pH 4 with acetic acid. The resulting precipitate was filtered off and extracted with 200 ml of boiling petroleum ether (60-80°). Filtration and evaporation of the solvent gave 8.5 g (53%) of 5b, m.p. 164-165°, M^+(m/e) 208. PMR: δ = 1.29 (s,9H), δ = 1.45 (s, 9H), δ = 6.29 (s,1H). $C_{12}H_{20}N_2O$(208.30); calcd. C 69.19, H 9.68; found C 69.0, H 9.6.

5-bromo-2,4-di-t-butylpyrimid-6-one (8b)

Method a) 3 g (14.4 mmol) of 5b were dissolved in 15 ml of distilled acetic acid. After addition of a solution of 0.55 ml of bromine in 5 ml of distilled acetic acid the reaction mixture was kept at room temperature for 24 h. The precipitate was filtered off and recrystallized twice from ethanol to give 2.4 g (58%) of 8b, m.p. 187-188°.

Method b)[20] 3 g (14.4 mmol) of 5b were refluxed for 2 h with stirring with 2.8 g (15.8 mmol) of *N*-bromosuccinimide in 25 ml of chloroform. The precipitate was filtered off and the solvent evaporated. The residue was treated with 50 ml of boiling water, filtered, dried and crystallized from ethanol to give 3.4 g (82%) of 8b, m.p. 187-188°; M^+(m/e) 286/288. PMR: δ = 1.43 (s), δ = 1.50 (s). $C_{12}H_{19}BrN_2O$(287.20); calcd. C 50.18, H 6.67; found C 50.0, H 6.7.

5-chloro-2,4-di-t-butylpyrimid-6-one (8c)

15 g (72 mmol) of 5b and 21 g (157 mmol) of *N*-chlorosuccinimide were refluxed in 125 ml of chloroform for 24 h. The precipitate was filtered off, the solvent evaporated and the residue treated with 500 ml of boiling water. The crude product was filtered off and crystallized from ethanol to give 12.8 g (73%) of 8c, m.p. 181-182°. PMR: δ = 1.39 (s), δ = 1.43 (s).

$C_{12}H_{19}ClN_2O$(242.75); calcd. C 59.37, H 7.89; found C 59.3, H 8.1.

5-bromo-6-chloro-2,4-di-t-butylpyrimidine (9b)

Prepared from 2.6 g (9.1 mmol) of 8b and 15 ml of phosphoryl chloride (see procedure described for 9a). 2.6 g (92%) of 9b were obtained as a pale yellow oil which could be used without purification. An analytical sample was obtained by column chromatography (silica gel, chloroform) to give M^+(m/e) 304/306/308. PMR: δ = 1.35 (s), δ = 1.49 (s).

$C_{12}H_{18}BrClN_2$(305.65); calcd. C 47.15, H 5.94; found C 47.2, H 5.8.

2,4-di-t-butyl-5,6-dichloropyrimidine (9c)

Prepared from 10 g (41.2 mmol) of 8c and 50 ml of phosphoryl chloride (see procedure described for 9a). The crude product was purified by distillation *in vacuo* to give 9.0 g (84%) of 9c, b.p. 140°/15 mm.

$C_{12}H_{18}Cl_2N_2$(261.19); calcd. C 55.18, H 6.95; found C 55.2, H 7.0.

6-amino-5-chloro-2,4-di-t-butylpyrimidine (12c)

1.2 g (4.6 mmol) of 9c were heated for 20 h at 130° with 10 ml of ethanolic ammonia saturated at 0° in two sealed tubes. After evaporation of the solvent the residue was extracted with 120 ml of petroleum ether (60-80°). Evaporation of the petroleum ether gave 945 mg (85%) of crude product, m.p. 68-72°. An analytical sample was obtained by column chromatography (silica gel, chloroform) to give m.p. 70-72°.

$C_{12}H_{20}ClN_3$(241.76); calcd. C 59.61, H 8.34; found C 59.7, H 8.3.

5-bromo-2,4-di-t-butyl-6-hydrazinopyrimidine (10b)

Prepared from 4 g (13.1 mmol) of 9b and 4.0 ml of hydrazine hydrate (see procedure described for 10a). The crude product was extracted with boiling petroleum

ether (60-80°). Evaporation of the solvent gave 3.8 g (96%) of 10b. Crystallisation from ethanol gave m.p. 94-96°.
$C_{12}H_{21}BrN_4$(301.24); calcd. C 47.84, H 7.03; found C 48.1, H 6.8.

5-chloro-2,4-di-t-butyl-6-hydrazinopyrimidine (10c)

Prepared from 5 g (19.1 mmol) of 9c and 5.5 ml of hydrazine hydrate (see procedure described for 10b). Yield 4.5 g (91%) of 10c, m.p. 70-72° from ethanol.
$C_{12}H_{21}ClN_4$(256.78); calcd. C 56.13, H 8.24; found C 56.0, H 8.0.

5-bromo-2,4-di-t-butylpyrimidine (11b)

Prepared from 1.3 g (4.3 mmol) of 10b (see procedure described for 11a). After evaporation of the ether a crude product was obtained which was purified by column chromatography (silica gel, petroleum ether (60-80°) - benzene 1:1). 560 mg (48%) of 11b were obtained as an almost colourless oil; M^+(m/e) 270/272.
PMR: δ = 1.38 (s,9H), δ = 1.48 (s,9H), δ = 8.59 (s,1H).
$C_{12}H_{19}BrN_2$(271.20); calcd. C 53.14, H 7.06; found C 53.0, H 7.0.

5-chloro-2,4-di-t-butylpyrimidine (11c)

Prepared from 2.5 g (9.7 mmol) of 10c (see procedure described for 11a). After purification twice by column chromatography (silica gel, cyclohexane-benzene 1:1), 920 mg (42%) of 11c were obtained as a pale yellow oil; M^+(m/e) 226/228.
PMR: δ = 1.38 (s,9H), δ = 1.47 (s,9H), δ = 8.42 (s,1H).
$C_{12}H_{19}ClN_2$(226.75); calcd. C 63.56, H 8.45; found C 63.6, H 8.7.

6-chloro-2,4-di-t-butylpyrimidine (6b)

Prepared from 4.5 g (21.6 mmol) of 5b and 65 ml of phosphoryl chloride (see procedure described for 9a). After evaporation of the ether the crude product was purified by preparative gas chromatography at 200° over a copper column, 200 cm in length and with an outer diameter of 10 mm, filled with 51.8 g chrom. sorb. W-AW 30/60 mesh + 30% OV-17. 6b was obtained as a colourless liquid[21]. Yield 2.6 g (53%); M^+(m/e) 226/228. PMR: δ = 1.30 (s,9H), δ = 1.36 (s,9H), δ = 6.96 (s,1H).
$C_{12}H_{19}ClN_2$(226.75); calcd. C 63.56, H 8.45; found C 63.4, H 8.5.

6-amino-2,4-di-t-butylpyrimidine (7b)

300 mg (1.32 mmol) of 6-chloro-2,4-di-*t*-butylpyrimidine (6b) were heated at 150° for 24 h with 21 ml of ethanolic ammonia saturated at 0° in three sealed tubes. After evaporation of the solvent the residue was dissolved in 50 ml of chloroform and extracted with a saturated solution of sodium carbonate. The chloroform was evaporated and the crude product was purified by column chromatography (silica gel, chloroform) to give 156 mg (57%) of 7b, m.p. 88-90°.
$C_{12}H_{21}N_3$(207.31); calcd. C 69.52, H 10.21; found C 69.3, H 10.2.

4.3.2 Amination procedures

Amination of 11a *by potassium amide in liquid ammonia*

The amination of 11a was carried out by the procedure described in a previous paper[1]. The products were separated by column chromatography (silica gel). Unreacted starting material 11a and 6-amino-4-*t*-butyl-5-chloropyrimidine (8a) were obtained first by elution with chloroform, after which 6-amino-4-*t*-butylpyrimidine (7a) was isolated by elution with ethyl acetate or methanol.

Amination of 11b *and* 11c *by* ^{15}*N-labelled potassium amide in* ^{15}*N-labelled ammonia*[10]

The amination was carried out on one half-scale of the procedure described in reference 1, *i.e.* with 12.5 ml of ammonia, 2 mmol of potassium and 0.5 mmol of substrate. An excess of 4.0% of ^{15}N was used. Work-up procedures were identical to those of the reaction of 5-bromo-4-*t*-butylpyrimidine (1)[1] for substrate 11b and to those of 11a, described above, for substrate 11c.

4.3.3 Conversion of the 6-amino derivatives 7a, 7b, 12a and 12c *into the corresponding 6-chloropyrimidines*

The compounds were diazotized according to the procedure reported for the conversion of 7a[1]. Yields: 4-*t*-butyl-5,6-dichloropyrimidine (9a) from 12a: 30%; 6-chloro-2,4-di-*t*-butylpyrimidine (6b) from 7b: 35%; 2,4-di-*t*-butyl-5,6-dichloropyrimidine (9c) from 12c: 15%.

4.4 REFERENCES

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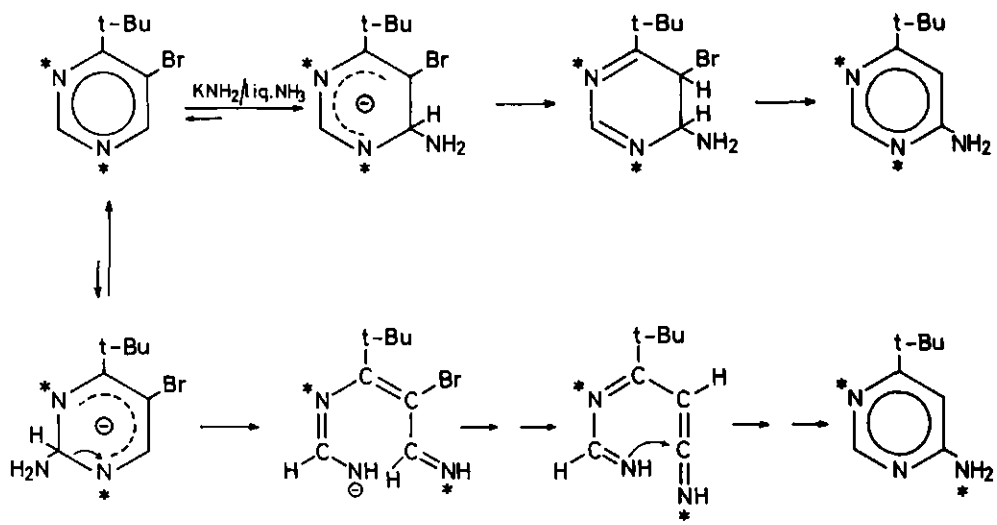
5 Investigations into the cine amination of 4-substituted 5-bromopyrimidines by potassium amide in liquid ammonia

C.A.H.Rasmussen, H.C.van der Plas, P.Grotenhuis and A.Koudijs

5.1 INTRODUCTION

Recently a detailed investigation into the mechanism of the cine substitution of 5-bromo-4-*t*-butylpyrimidine (1a) was published[1]. ^{15}N-labelling experiments proved that the reaction proceeds *via* two different mechanisms, as summarized in Scheme 5.1.



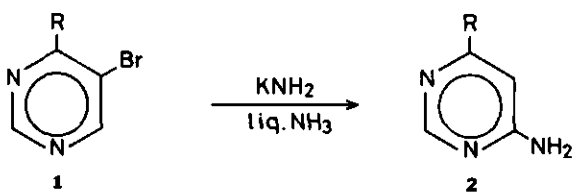
Scheme 5.1

49% of the 6-amino-4-*t*-butylpyrimidine (2a) is formed *via* a mechanism involving an Attack of the Nucleophile on C-2, followed by Ring Opening, loss of hydrogen bromide and Ring Closure (S_N(ANRORC)). The remainder is derived from the 1:1 σ-adduct[2] on C-6 by protonation and subsequent loss of hydrogen bromide. As shown in Scheme 5.1, using 5-bromo-4-*t*-butyl-[1(3)-^{15}N] pyrimidine as the substrate, the label is completely retained within the ring in the latter pathway

and partially located on the exocyclic amino group in the S_N(ANRORC) process. More recently the open-chain mechanism received additional support by the observation that introduction of a *t*-butyl group at C-2 effectively blocks this pathway in the cine substitution of 5-bromo-2,4-di-*t*-butylpyrimidine[3]. It was therefore of interest to extend the investigations to 5-bromopyrimidines 1 with other substituents than a *t*-butyl group at C-4. A number of these compounds are known to undergo the cine substitution on treatment with potassium amide[4,5]. A mechanism involving a hetaryne was tentatively proposed. PMR investigations[2] had since then given rise to doubts as to the validity of this mechanism so an investigation in greater detail was started with the prime objective to ascertain whether the substituent on C-4 influences the reaction mechanism to any great extent.

5.2 RESULTS AND DISCUSSION

Treatment of the 5-bromopyrimidines 1a-1i with four equivalents of potassium amide in liquid ammonia at -33° slowly gave the corresponding 6-aminopyrimidines 2a-2i as major reaction products (Scheme 5.2).



1 2

R = a) t-Bu e) CH_3 i) OH
b) C_6H_5 f) $NHCH_3$
c) OCH_3 g) NHC_6H_5
d) NC_5H_{10} h) NH_2

Scheme 5.2

The reaction times, identified products and yields are summarized in Table 5.1. A varying amount of unidentifiable tar is also obtained in some cases, especially with substrates 1d and 1e. In order to establish whether an S_N(ANRORC) mechanism is operative in these conversions the reactions were studied with two different ^{15}N-labelling techniques. The substrates 1a-1c and 1h were enriched with ^{15}N in the pyrimidine ring, the label being scrambled over the N-1 and N-3

Table 5.1 Reaction conditions and products obtained on treatment of 4-R-5-bromopyrimidines 1 with potassium amide in liquid ammonia

4-R-5-bromo pyrimidine 1		mmoles of substrate employed	reaction time (hours)	composition of reaction mixture (%)				
				retrieved starting material 1	4-R-6-amino-pyrimidine 2	4-R-pyrimidine	4-R-5-bromo-6-amino-pyrimidine	4-R-2-amino-pyrimidine
1a[a]	R = t-Bu	1	24	60	33	trace[b]	-	-
1b	R = C_6H_5	3	24	45	25	6-10[b]	8[d]	-
1c	R = OCH_3	1	24	21	75	-[c,d]	1-2[d]	-
1d	R = NC_5H_{10}	0.5	48	10	40	1-2[b]	trace[b]	4-6[d]
1e	R = CH_3	0.5	72	10	50	1-2[b]	-	-
1f	R = NCH_3 H	0.5	48	30	48	-	-	-
1g	R = NC_6H_5 H	0.5	72	10	67	3-4[b]	-	-
1h	R = NH_2	1	24	60	30	trace[b,d]	-	-
1i	R = OH	1	24	55	35	-	-	-

[a] viz reference 1
[b] identified by mass spectrometry
[c] identified as 4-aminopyrimidine, see text
[d] identified by independent synthesis

atoms, and treated with unlabelled reagent (method A). Compounds 1d-1g were reacted with ^{15}N-labelled potassium amide in ^{15}N-labelled ammonia (method B)[3,6] If ring opening takes place ^{15}N will be present in the amino group of the products 2a-2c and 2h and will have been incorporated into the pyrimidine ring of 2d-2g. In order to establish this fact the obtained 6-aminopyrimidines 2a-2h were subsequently converted into the 6-halogeno derivatives. Acidic hydrolysis of compound 2b followed by treatment with phosphoryl bromide afforded 6-bromo-4-phenylpyrimidine[7]. Products 2a[1] and 2c-2g were diazotized in concentrated hydrochloric acid to yield the corresponding 6-chloropyrimidines. Both procedures have been reported as cited. A modification of the diazotization reaction, involving the use of cuprous chloride, enabled us to obtain some 4,6-dichloropyrimidine from 2h. The excess of ^{15}N contents in the 6-amino- and 6-halogenopyrimidines and, when appropriate, the starting materials, were determined by mass spectrometry, by comparing the intensities of the M+1 and M peaks. An S_N(ANRORC) mechanism is indicated if a *decrease* in ^{15}N-enrichment is observed in the 6-halogenopyrimidines obtained from 2a-2c and 2h and if *any* excess of ^{15}N is found in the compounds formed from 2d-2g. The values obtained are shown in Table 5.2.

Table 5.2 % of excess of ^{15}N in the pyrimidines involved in the cine-substitution of (1a-1h)[a,b] and % of S_N(ANRORC) mechanism in the formation of 2a-2h

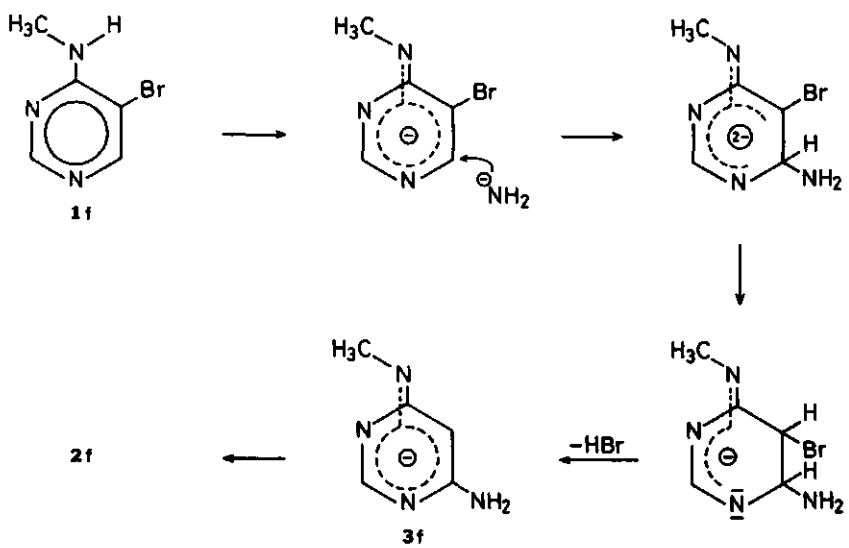
Reaction method	% excess ^{15}N			% S_N(ANRORC)
	starting material 1	4-R-6-amino-pyrimidine 2	4-R-6-halogeno-pyrimidine	
A	1a[c]	7.3	7.3	5.5	49
A	1b	8.8	8.8	6.5	52
A	1c	7.9	7.8	6.8	26
B	1d	-	3.9	1.1	28
B	1e	-	4.1	0	0
B	1f	-	4.0	0	0
B	1g	-	4.0	0	0
A	1h	7.9	7.7	7.7[d]	0

[a] accuracy ± 0.2%
[b] all experiments were carried out in duplicate
[c] viz. reference 1
[d] measured as 4,6-dichloropyrimidine, see text

No product suitable for mass spectrometric analysis could be obtained from 2i however, so the investigation of 1i unfortunately had to be abandoned[8].
It is evident from the results in Table 5.2 that there is a remarkable difference between the compounds 1a-1d compared to 1e-1h. We will therefore discuss the results of both groups separately.

(i) 4-R-5-BROMOPYRIMIDINES 1e-1h

None of these compounds 1e-1h are transformed into the 6-amino derivatives 2e-2h *via* an S_N(ANRORC) process. They all have one characteristic in common however, *i.e.* that the substituents on C-4 possess an acidic hydrogen atom in a position adjacent to the pyrimidine ring. In the strongly basic potassium amide in liquid ammonia system this hydrogen atom can easily be abstracted to form an anion, the charge of which can be delocalized over the pyrimidine ring as exemplified in Scheme 5-3 for compound 1f. Evidence for the existence of the anions of 1e and 1f had already been obtained from PMR studies[2]. The pyrimidines 1g and 1h are insufficiently soluble in the potassium amide in liquid ammonia system to enable PMR measurements to be carried out[9]. Since an essential step of the S_N(ANRORC) process is addition of an amide ion to C-2 of the pyrimidine ring, the data indicate that this route is apparently blocked by formation of an anion.



Scheme 5.3

Delocalisation of the negative charge leads to an enhanced electron density on the nitrogen atoms adjacent to C-2, thus causing a repulsion of an attack on that position by a negatively charged entity. Compounds 2e-2h are formed *via* the process shown in Scheme 5.3 for the reaction of 1f. The final step from 3f probably takes place on quenching the reaction by the addition of ammonium chloride or nitrate.

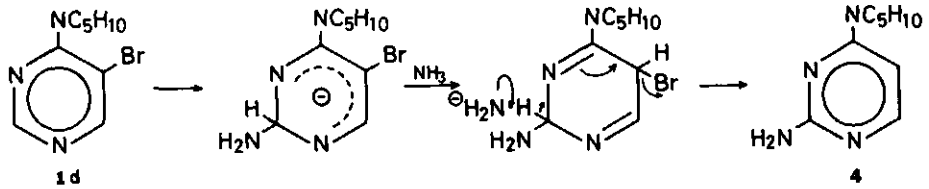
(ii) 4-R-5-BROMOPYRIMIDINES 1a-1d

The remaining four pyrimidines 1a-1d all undergo a nucleophilic cine substitution *via* , to a certain extent, an open-chain intermediate. Compounds 1a-1c have been found to give a 1:1 σ-adduct on C-6, as proven by PMR measurements. Compound 1d is only slightly soluble in the reaction mixture, which makes it impossible to prove the existence of the σ-adduct, but it seems reasonable to assume that 1d also forms a similar adduct[10,11]. Since the S_N(ANRORC) process is initiated by addition to C-2 it is proposed that the attack of amide ion at C-2 occurs on the neutral substrate and not on the anionic σ-adduct at C-6. This possibility has been advanced earlier for the amination of 1a in order to explain the low reaction rate[1].

Apart from the general pattern described above there are some interesting aspects of the conversion of 1b-1d arising from the products formed alongside 2b-2d (see Table 5.1).

The reaction of 1d is of special interest because of the formation of 2-amino-4-piperidinopyrimidine (4). This is the *only* example to date of the occurrence of a tele amination in the 5-halogenopyrimidine series[12]. The structure of 4 was proven by independent synthesis. 2,4-Dichloropyrimidine on treatment with piperidine yields 2-chloro-4-piperidinopyrimidine as the major product, as confirmed by reduction of the latter to 4-piperidinopyrimidine. Aminolysis of 2-chloro-4-piperidinopyrimidine with ethanolic ammonia gave 2-amino-4-piperidinopyrimidine. Compound 4 obtained from the reaction of 1d with ^{15}N-labelled potassium amide was found to contain 3.7% of excess of ^{15}N. After diazotization however, the isolated 2-chloro-4-piperidinopyrimidine contained no excess of ^{15}N at all, implying that an S_N(ANRORC) process is *not* involved in the formation of 4 from 1d. In our earlier study on 1a[1] we proved that the σ-adduct on C-6 cannot be involved in an S_N(ANRORC) process by cleavage of the N-1 — C-6 bond since this would lead to the formation of 2-amino-4-*t*-butylpyrimidine, which is not found in the reaction mixture of 1a. The fact that *no* ^{15}N is built into 4 in the reaction of 1d is

further evidence that the σ-adduct at C-6 is not involved in a ring opening reaction since a process as described above would lead to incorporation of ^{15}N in the pyrimidine ring of 4. The formation of 4 is excellent additional proof of attack occurring at C-2 in the reaction of 1d with potassium amide. The mechanism proposed for the formation of 4 is depicted in Scheme 5.4



Scheme 5.4

When 1c is treated with potassium amide in liquid ammonia the dehalogenated product, 4-methoxypyrimidine, is not observed but a small amount of 4-aminopyrimidine is detected. Control experiments have shown that 4-methoxypyrimidine is completely converted into 4-aminopyrimidine under the conditions employed for the reaction of 1c[13].

The reaction of 1b deserves further attention due to the formation of an unusually high percentage of dehalogenated starting material 4-phenylpyrimidine[14]. This product cannot be formed by dehalogenation of the starting material as such, since it was observed recently that 4-phenylpyrimidine is converted into a mixture of 2-amino-4-phenyl- and 6-amino-4-phenylpyrimidine by potassium amide in liquid ammonia[15]. Since no 2-amino-4-phenylpyrimidine is detected in the reaction mixture of 1b 4-phenylpyrimidine cannot be present either and is presumably formed on quenching the reaction by addition of ammonium salts.

The possibility of dehalogenation at C-5 of the pyrimidine occurring under the reaction conditions studied raised the question as to whether 6-amino-4-phenylpyrimidine (2b) could be obtained by dehalogenation of 6-amino-5-bromo-4-phenylpyrimidine, a side product in the reaction of 1b. This idea can be rejected on the following grounds. When 6-amino-5-bromo-4-phenylpyrimidine is reacted with potassium amide under identical conditions as 1b, 46% of starting material, 30% of 2b and 9% of a third product is obtained, to which, based on mass m/e 264/266 the structure of 5-bromo-2,4-diamino-6-phenylpyrimidine was tentatively assigned. However, careful investigation of the reaction mixture of 1b by mass spectrometry showed that no trace of this compound with mass m/e 264/266 was

present. This implies that 6-amino-5-bromo-4-phenylpyrimidine is excluded as precursor of 2b and that it is likely that just like 4-phenylpyrimidine, it is formed on quenching.

5.3 EXPERIMENTAL DATA

Melting points are uncorrected. Mass spectra were recorded and excesses of ^{15}N were measured on an AEI MS-902 mass spectrometer. Column chromatography was carried out over Merck silica gel 60 (70-230 mesh ASTM). PMR spectra were recorded in deuteriochloroform on a Hitachi-Perkin Elmer R-24B spectrometer.

5.3.1 Preparation of starting materials and reference compounds

The following pyrimidines were prepared according to established procedures: *5-bromo-4-t-butyl-* $\left[1(3)-^{15}N\right]$ *pyrimidine* (1a)[1], *5-bromo-4-methylpyrimidine* (1e)[16] *5-bromo-4-N-methylaminopyrimidine* (1f)[2], *6-amino-4-t-butylpyrimidine* (2a)[16], *6-amino-4-phenylpyrimidine* (2b)[16], *6-amino-4-methoxypyrimidine* (2c)[17], *6-amino-4-piperidinopyrimidine* (2d)[18], *6-amino-4-methylpyrimidine* (2e)[16], *6-amino-4-N-methylaminopyrimidine* (2f)[18], *6-amino-4-anilinopyrimidine* (2g)[18], *4,6-diaminopyrimidine* (2h)[19], *6-amino-pyrimid-4-one* (2i)[19], *4-t-butyl-6-chloropyrimidine*[16], *6-bromo-4-phenylpyrimidine*[7], *6-chloro-4-methoxypyrimidine*[20], *6-chloro-4-piperidinopyrimidine*[18], *6-chloro-4-methylpyrimidine*[16], *6-chloro-4-N-methylaminopyrimidine*[21], *4-anilino-6-chloropyrimidine*[22], *4,6-dichloropyrimidine*[23], *4-methoxypyrimidine*[24], *4-aminopyrimidine*[19], *5-bromo-4-chloropyrimidine*[25], *5-bromo-6-chloro-4-phenylpyrimidine*[16] and *2,4-dichloropyrimidine*[26]. *5-bromo-4-phenyl-*$\left[1(3)-^{15}N\right]$ *pyrimidine*[16], *5-bromo-4-methoxy-* $\left[1(3)-^{15}N\right]$ *-pyrimidine*[27], *4-amino-5-bromo-* $\left[1(3)-^{15}N\right]$ *pyrimidine*[25] and *5-bromo-* $\left[1(3)-^{15}N\right]$ *-pyrimid-4-one*[25] were synthesized as described for the respective unlabelled compounds 1b, 1c, 1h and 1i.

5-bromo-4-piperidinopyrimidine (1d)

A solution of 2.0 g (23.5 mmol) of piperidine in 4 ml of ethanol (abs) was added at 0° with stirring to a solution of 1.5 g (7.7 mmol) of 5-bromo-4-chloropyrimidine[25] in 6 ml of ethanol (abs). After 72 h at 0° the precipitate was filtered off and the filtrate evaporated. The residue was extracted with 60 ml of ether. The ethereal extract was dried over anhydrous magnesium sulphate, filtered and evaporated. The residual oil was purified by distillation *in vacuo* to give 1.0 g (54%) of 1d, b.p. 164°/18 mm, M^+ (m/e) 241/243; PMR : δ = 8.43 (s, 1H), δ = 8.30

(s,1H), δ = 3.60 (m,4H), δ = 1.66 (m,6H). Picrate, m.p. 148-149°(from ethanol). $C_{15}H_{15}BrN_6O_7$(picrate, 471.23); calcd. C 38.23, H 3,21; found C 38.3, H 3.1.

4-anilino-5-bromopyrimidine (1g)

A solution of 1.5 g (16 mmol) of freshly distilled aniline in 6 ml of ethanol (abs) was added at 0° with stirring to a solution of 1.5 g (7.7 mmol) of 5-bromo-4-chloropyrimidine[25] in 12 ml of ethanol (abs). After 72 h at 0° the solvent was evaporated and the residue was extracted with 80 ml of ether. The precipitate was filtered off and the filtrate was evaporated to dryness to give 1.8 g (94%) of 1g as a pale yellow oil that slowly solidified on standing, m.p. 68-70°, M^+ (m/e) 249/251.
$C_{10}H_8BrN_3$(250.10): calcd. C 48.02, H 3.23; found C 47.9, C 3.0.

6-amino-5-bromo-4-phenylpyrimidine

190 mg (0.7 mmol) of 5-bromo-6-chloro-4-phenylpyrimidine[16] were heated in a sealed tube at 140° for 24 h with 10 ml of ethanolic ammonia saturated at 0°. After evaporation of the solvent the residue was extracted with 40 ml of cold chloroform. The chloroform was evaporated to give 164 g (94%) of 6-amino-5-bromo-4-phenylpyrimidine. An analytical sample was obtained by column chromatography (silica gel, chloroform) to give m.p. 179-180°.
$C_{10}H_8BrN_3$(250.10): calcd. C 48.02, H 3.23; found C 48.2, H 3.4.

6-amino-5-bromo-4-methoxypyrimidine

350 mg (2.8 mmol) of 6-amino-4-methoxypyrymidine (2c)[17] were refluxed for 3 h with 540 mg (3.0 mmol) of *N*-bromo-succinimide in 15 ml of carbon tetrachloride. The precipitate was filtered off and the filtrate evaporated to dryness. The residue was crystallized from water to give 194 mg (25%) of crude product, m.p. 155-160°. An analytical sample was obtained by column chromatography (silica gel, chloroform) to give m.p. 158-160°.
$C_5H_6BrN_3O$(204.04): calcd. C 29.43, H 2.96; found C 29.1, H 2.8.

2-chloro-4-piperidinopyrimidine

1.3 g (10.1 mmol) of 2,4-dichloropyrimidine[26] was refluxed for 1 h with 1.8 g (21.2 mmol) of piperidine in 50 ml of chloroform. After evaporation of the solvent the residue was extracted with 100 ml of ether. The ether was evaporated

and the product obtained was purified by column chromatography (silica gel, chloroform) to give 1.2 g (61%) of 2-chloro-4-piperidinopyrimidine, m.p. 79-80°. $C_9H_{12}ClN_3$(197.67): calcd. C 54.68, H 6.12; found C 54.8, H 6.4.

4-piperidinopyrimidine

A mixture of 200 mg (1.0 mmol) of 2-chloro-4-piperidinopyrimidine, 40 mg of magnesium oxide, 40 mg of palladium-charcoal catalyst and 50 ml of methanol was shaken with hydrogen for 1 h. The solvent was evaporated after filtration and the residue was purified by column chromatography (silica gel, chloroform) to give 60 mg (37%) of 4-piperidinopyrimidine, m.p. 46-48°. PMR: δ = 8.49 (s,1H), δ = 8.07 (d,1H), δ = 6.43 (d,1H), δ = 3.57 (m,4H), δ = 1.64 (m,6H); $J_{5,6}$ = 6 Hz. $C_9H_{13}N_3$(163.22): calcd. C 66.23, H 8.03; found C 66.0, H 8.4.

2-amino-4-piperidinopyrimidine (4)

200 mg (1.0 mmol) of 2-chloro-4-piperidinopyrimidine were heated in a sealed tube at 140° for 24 h with 10 ml of ethanolic ammonia saturated at 0°. After evaporation of the solvent the residue was treated with a saturated solution of sodium bicarbonate and extracted with 150 ml of chloroform. The chloroform was dried over anhydrous magnesium sulphate, filtered and evaporated. The product was purified by column chromatography (silica gel, ethyl acetate) to give 156 mg (88%) of 4, m.p. 133-134°. PMR: δ = 7.82 (d,1H), δ = 5.95 (d,1H), δ = 3.56 (m,4H), δ = 1.65 (m,6H); $J_{5,6}$ = 6 Hz.
$C_9H_{14}N_4$(178.23): calcd. C 60.65, H 7.92; found C 60.4, H 8.0.

5.3.2 Amination procedures

The procedures for the amination reactions have been reported in previous papers. For method A (substrates 1a, 1b, 1c and 1h) see reference 1, for method B (substrates 1d-1g) see references 3 and 6. The amination of 4-methoxypyrimidine was carried out by method A.

5.3.3 Conversion of 4-R-6-aminopyrimidines into 4-R-6-halogenopyrimidines

The conversion of 6-amino-4-phenylpyrimidine (2b) into 6-bromo-4-phenylpyrimidine is described in the literature[7]. The 4-R-6-aminopyrimidines 2c-2g were diazotized into the corresponding 6-chloropyrimidines as described for the conversion of 2a[1]. A similar procedure was followed for the diazotization of 2-amino-4-piperidino-

pyrimidine (4) into 2-chloro-4-piperidinopyrimidine. Purifications, when necessary, were carried out by column chromatography over silica gel, using chloroform, ethyl acetate or mixtures of these as eluent.

Diazotization of 4,6-diaminopyrimidine (2h)

45 mg (0.4 mmol) of 4,6-diaminopyrimidine (2h) were dissolved in 2 ml of concentrated hydrochloric acid. A solution of 0.5 g (7.3 mmol) of sodium nitrite in 2 ml of water was added dropwise with stirring, maintaining the temperature at -15 — -20°. After the addition 5 ml of a solution of freshly prepared cuprous chloride in concentrated hydrochloric acid were added at -10°. The stirring was continued at room temperature for 2 h after which the reaction mixture was neutralized with concentrated ammonia and extracted with 50 ml of ether. The ethereal extract was dried over anhydrous magnesium sulphate, filtered and evaporated to yield 1-2 mg of 4,6-dichloropyrimidine.

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shows signals that can only be ascribed to a similar adduct at C-6. Viz. reference 9.

11. The PMR spectrum of 1e, besides showing the signals of the anion (Section i), also shows the presence of a σ-adduct on C-6 in the reaction mixture, albeit in a smaller amount (3:1). Viz.ref.2.
12. Recently strong indications have been obtained that a similar tele amination occurs on treatment of 5-bromo-4-*N*,*N*-dimethylaminopyrimidine with potassium amide in liquid ammonia. This substrate was not investigated in detail owing to very poor reproducibility of the reaction. Considerable amounts of tar are obtained.
13. This amino-demethoxylation has also been observed in this laboratory with other 4-methoxy derivatives, *i.e.* the formation of 4-amino-5-chloropyrimidine from 5-chloro-4-methoxypyrimidine, of 4-amino-6-methoxypyrimidine (2c) from 4,6-dimethoxypyrimidine and of 4-amino-5-bromo-6-methoxypyrimidine from 5-bromo-4,6-dimethoxypyrimidine.
14. Considerable dehalogenation has also been observed on treatment of 5-bromo-6-halogeno-4-phenylpyrimidines with potassium amide in liquid ammonia. Viz. J.de Valk and H.C.van der Plas, Recl.Trav.Chim.(Pays-Bas) 92, 145 (1973); J.de Valk, H.C.van der Plas and J.W.A.de Bode, Recl.Trav.Chim.(Pays-Bas) 92, 442 (1973).
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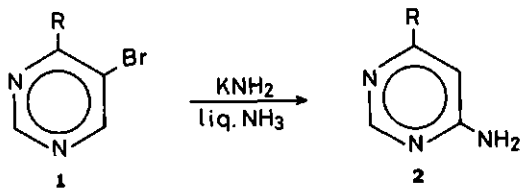
6 Factors influencing the occurrence of S_N(ANRORC) mechanism in the amino-dehalogenation of 4-substituted 6-halogenopyrimidines by potassium amide in liquid ammonia

C.A.H.Rasmussen and H.C.van der Plas

6.1 INTRODUCTION

Recent investigations in depth into the cine substitution of 4-substituted 5-bromopyrimidines 1 by potassium amide in liquid ammonia (Scheme 6.1) have shown that this conversion can take place *via* an S_N(ANRORC) mechanism involving an open-chain intermediate[1,2].



Scheme 6.1

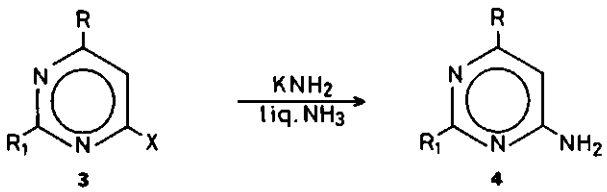
In this process a ring nitrogen atom of 1 is located on the exocyclic amino function of the cine substitution product 2, as was determined by ^{15}N-labelling experiments. It was also shown that this reaction route is blocked, either when a bulky *t*-butyl group is introduced at C-2 of the pyrimidine ring[3], or when the substituent at C-4 contains an acidic hydrogen atom in the α-position to the ring[2]. The former of these two factors was interpreted as conclusive proof that in this S_N(ANRORC) process an attack of an amide ion on C-2 of the pyrimidine ring is a crucial step of the mechanism.

The amino-dehalogenation of 6-halogeno-4-phenylpyrimidines by potassium amide in liquid ammonia has also been proven to occur *via* an S_N(ANRORC) process initiated by addition of an amide ion to C-2[4,5]. We decided to determine whether the factors influencing the cine substitution of 1 are also of importance for the replacement

of the halogeno atom by an amino group in 4-substituted 6-halogenopyrimidines.

6.2 RESULTS AND DISCUSSION

Treatment of the 4-substituted 6-halogenopyrimidines 3a-3g with four equivalents of potassium amide in liquid ammonia at -33° for one hour gives the corresponding 6-amino derivatives 4a-4g in 80-100% yield (Scheme 6.2).



3 **4**

	R	R_1	X		R	R_1
a)	C_6H_5	H	Br, Cl	a)	C_6H_5	H
b)	t-Bu	H	Br, Cl	b)	t-Bu	H
c)	OCH_3	H	Br, Cl	c)	OCH_3	H
d)	NC_5H_{10}	H	Cl	d)	NC_5H_{10}	H
e)	HNC_6H_5	H	Cl	e)	HNC_6H_5	H
f)	CH_3	H	Br, Cl	f)	CH_3	H
g)	t-Bu	t-Bu	Br, Cl	g)	t-Bu	t-Bu

Scheme 6.2

In order to determine whether a ring-opening is involved in these amino-dehalogenations the compounds 3a-3g were investigated with ^{15}N-labelling experiments. In the early stages of the investigation we incorporated the ^{15}N-label into the pyrimidine ring of the starting material (3a*, X=Br, Cl; 3b*, X=Br, Cl; 3c*, X=Br)[6] in such a way that the ^{15}N was scrambled over the N-1 and N-3 atoms and carried out the reaction with unlabelled potassium amide (method A)[1,5]. In a more advanced phase of the study the experiments were performed by treating unlabelled substrate (3c, X=Cl; 3d-3g) with ^{15}N-enriched potassium amide in ^{15}N-labelled ammonia (method B)[2,7]. Both techniques have been described as cited. 6-Amino-4-phenylpyrimidine (4a*), obtained from 3a* was converted into 6-bromo-4-phenylpyrimidine as described in the literature[4]. The other 6-amino derivatives 4b*-4g* were converted into the corresponding 6-chloropyrimidines through diazotization in concentrated hydrochloric acid[1]. The ^{15}N-enrichments in the starting materials 3 - when appropriate - , the 6-amino compounds 4* and the 6-halogenopyrimidines obtained from 4* were determined by mass spectro -

metry, by measuring the intensities of the M+1 and M peaks. The results of these measurements and the percentages to which an S_N(ANRORC) mechanism is operative in the amino-dehalogenations are summarized in Table 6.1.

A striking parallel is observed when the results are compared with the data obtained in the earlier study of the 5-bromopyrimidine series[2]. From the results shown in the Table the 6-halogenopyrimidines 3 can be categorized in two different groups

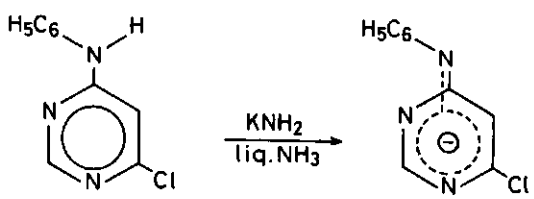
i) the pyrimidines that react to a certain extent *via* an S_N(ANRORC) mechanism, 3a-3d.

ii) those that do not react with a ring-opening, 3e-3g.

In the latter category two essentially different classes of substrate can be discerned.

i) Those that feature the presence of an effective blocking group at C-2, 6-bromo-2,4-di-*t*-butylpyrimidine (3g, X=Br) and 6-chloro-2,4-di-*t*-butylpyrimidine (3g, X=Cl). This group effectively screens off C-2 from the attacking amide ion, thus hindering this essential step for the occurrence of an S_N(ANRORC) process.

ii) The substrates that contain an acidic hydrogen atom in the α-position to the pyrimidine nucleus on the substituent at C-4, *i.e.* 6-chloro-4-anilinopyrimidine (3e), 6-bromo-4-methylpyrimidine (3f, X=Br) and 6-chloro-4-methylpyrimidine (3f, X=Cl). In the strongly basic potassium amide in liquid ammonia medium this hydrogen atom will easily be abstracted to form a charge-delocalized anion, as exemplified in Scheme 6.3 for 3e.



3e

Scheme 6.3

This leads to enhancement of electron density on the N-1 and N-3 atoms, which will disfavour addition of a negatively charged species on the adjacent C-2 position, thus rendering an S_N(ANRORC) mechanism inoperative. Similar observations were made in the 5-bromo series[2], where the existence of anions could actually be proven by PMR spectroscopy[8].

Table 6.1 Reaction method employed, excess of ^{15}N values measured[a,b] and percentages of S_N(ANRORC) mechanism operative in the reaction of 4-substituted 6-halogenopyrimidines 3 with potassium amide in liquid ammonia

Starting material 3		Reaction method	Reaction temperature in °C	% excess ^{15}N			% S_N(ANRORC)
				starting material 3	2-R_1-4-R-6-amino-pyrimidine 4	2-R_1-4-R-6-halogeno-pyrimidine	
3a* [c]	Br	A	-75	6.0	6.0	3.5	83
	Cl	A	-75	6.0	6.1	3.2	93
3b*	Br	A	-75	7.8	7.9	4.8	77
	Br	A	-33	7.8	7.8	6.5	33
	Cl	A	-33	7.9	7.8	3.7	100
3c*	Br	A	-33	10.3	10.0	8.4	31
3c	Cl	B	-33	-	3.9	3.9	100
3d	Cl	B	-33	-	4.3	0.9	21
3e	Cl	B	-33	-	4.2	0	0
3f	Br	B	-33	-	4.1	0	0
	Cl	B	-33	-	3.8	0	0
3g	Br	B	-33	-	3.9	0	0
	Cl	B	-33	-	4.0	0	0

[a] all experiments were carried out in duplicate

[b] accuracy ± 0.2%

[c] viz references 4,5

3 h while a constant stream of nitrogen was led through the mixture into a Carius tube containing 20 ml of methanol and cooled at -65°. 3 g (18 mmol) of diethylmalonate were added and the sealed tube was kept at room temperature for 7 days. The precipitate, ^{15}N-malondiamide, was collected, washed with a little cold methanol and dried. Yield 1.64 g (86%), m.p. 169-172° (lit.[21] 169-170°).

4,6-dibromopyrimidine

3 g (26.8 mmol) of pyrimi-4,6-dione were heated at 125° for 4 h with 15 mg of phosphorylbromide and 5 g of phosphorus pentabromide. The reaction mixture was treated with crushed ice and extracted with 5x50 ml of ether. The ethereal extracts were collected, dried over anhydrous magnesium sulphate and evaporated. The residue was purified twice by sublimation *in vacuo* to give 1.2 g (19%) of 4,6-dibromopyrimidine, m.p. 45-49°(lit.[22] 48-50°).

6-bromo-4-methoxypyrimidine (3c, X=Br)

1.5 g (6.3 mmol) of 4,6-dibromopyrimidine was dissolved in 20 ml of methanol. A solution of 0.16 g (7 mmol) of sodium in 10 ml of methanol was added drop by drop with stirring. The solvent was evaporated after standing at room temperature for 1 h and the residue was sublimated *in vacuo* , to give 1.0 g (84%) of crude product, m.p. 50-55°. An analytical sample was obtained by preparative thick layer chromatography over silica gel, using chloroform as eluent, to give m.p. 53-55°.
$C_5H_5BrN_2O$(189.02); calcd. C 31.77, H 2.67; found C 32.0, H 2.7.

6-bromo-4-methylpyrimidine (3f, X=Br)

5 g (46 mmol) of 4-methylpyrimid-6-one[16] were heated with 25 g of phosphoryl bromide for 3 h at 100°. The reaction mixture was poured on crushed ice, neutralized by careful addition of concentrated ammonia and extracted with 6x100 ml of ether. The collected ethereal extracts were dried over anhydrous magnesium sulphate, filtered and evaporated. The residue was purified by distillation *in vacuo*. The product was collected at 105-110°/18 mm and solidified immediately to give m.p. 29-31°. Yield 2.8 g (35%). It slowly decomposed on standing.
$C_5H_5BrN_2$(173.02); calcd. C 34.71, H 2.91; found C 34.5, H 2.7.

6-bromo-2,4-di-t-butylpyrimidine (3g, X=Br)

Prepared from 1.3 g (6.3 mmol) of 2,4-di-*t*-butylpyrimid-6-one[3] and 13 g of phosphoryl bromide (see procedure described above for 3f, X=Br). After evaporation of the ether the product was purified by preparative gas chromatography at 200° over a copper column, 200 cm in length and with an outer diameter of 10 mm, filled with 51.8 g chrom.sorb. W-AW 30/60 mesh + 30% OV-17. 680 mg (40%) of 3g were obtained, m.p. 32-33°; M^+(m/e) 270/272.
$C_{12}H_{19}BrN_2$(271.20); calcd. C 53.14, H 7.06; found C 53.0, H 7.3.

6.3.2 Amination of 4-substituted 6-halogenopyrimidines 3

The amination of 3a (X=Cl , Br) has been reported in the literature *i.e.* at -75° for 1 h[5]. 3b (X=Br) was aminated at -75° and at -33° for 1 h. All other aminations were carried out at -33° for 1 h. The aminations of 3b and 3c (X=Br) (Method A) were performed as described for the reaction of 5-bromo-4-*t*-butyl-[1(3)-^{15}N] pyrimidine[1]. The procedure used for the aminations of 3c (X=Cl) and 3d-3g was the same as described for the conversion of 5-bromo-2,4-di-*t*-butylpyrimidine[3] (Method B).

6.3.3 Conversion of 4-substituted 6-aminopyrimidines 4 *into 4-substituted 6-halogenopyrimidines*

6-Amino-4-phenylpyrimidine (4a) was converted into 6-bromo-4-phenylpyrimidine as reported[4]. All other 6-aminopyrimidines 4b-4g were diazotized in concentrated hydrochloric acid as described for 6-amino-4-*t*-butyl-[x-^{15}N] pyrimidine[1], to give the corresponding 6-chloro derivatives. Purification, when necessary, was achieved by column chromatography (silica gel), chloroform or mixtures of chloroform and ethyl acetate being used as eluent.

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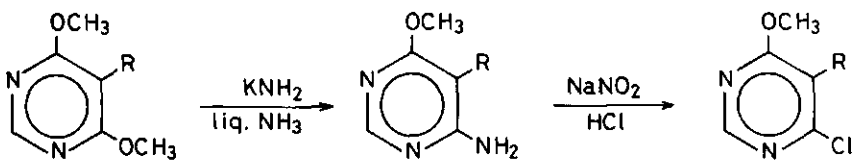
7 An S_N(ANRORC) mechanism in the amino-demethoxylation of 4,6-dimethoxypyrimidines

C.A.H.Rasmussen and H.C.van der Plas

7.1 RESULTS AND DISCUSSION

During a recent investigation of the cine amination of 4-substituted 5-bromopyrimidines by potassium amide in liquid ammonia[1] it was observed that 5-bromo-4,6-dimethoxypyrimidine (1a)[2] undergoes an amino-demethoxylation to 4-amino-5-bromo-6-methoxypyrimidine (2a)[1] on treatment with this reagent at -33° for 24 hours. A similar replacement was observed with 4,6-dimethoxypyrimidine (1b)[3],



1
a) R = Br
b) R = H

2

3

Scheme 7.1

yielding 4-amino-6-methoxypyrimidine (2b)[3]. The amino compounds 2a and 2b could be diazotized into the corresponding 4-chloropyrimidines 3a[2] and 3b[4] by the action of sodium nitrite in concentrated hydrochloric acid. All products were identified by comparison with authentic samples obtained as cited.

In view of observations that the amino-dehalogenation of 4-halogenopyrimidines by potassium amide in liquid ammonia frequently occurs *via* a mechanism involving an open-chain intermediate[5,6] - the S_N(ANRORC) mechanism - we studied both replacement reactions with ^{15}N-labelled potassium amide in liquid ammonia. The 4-aminopyrimidines 2a*[7] and 2b* and the corresponding 4-chloropyrimidines 3a* and 3b* were examined for their ^{15}N contents by mass spectrometry, comparing the intensities of the M+1 and M peaks. The results are collected in Table 7.1.

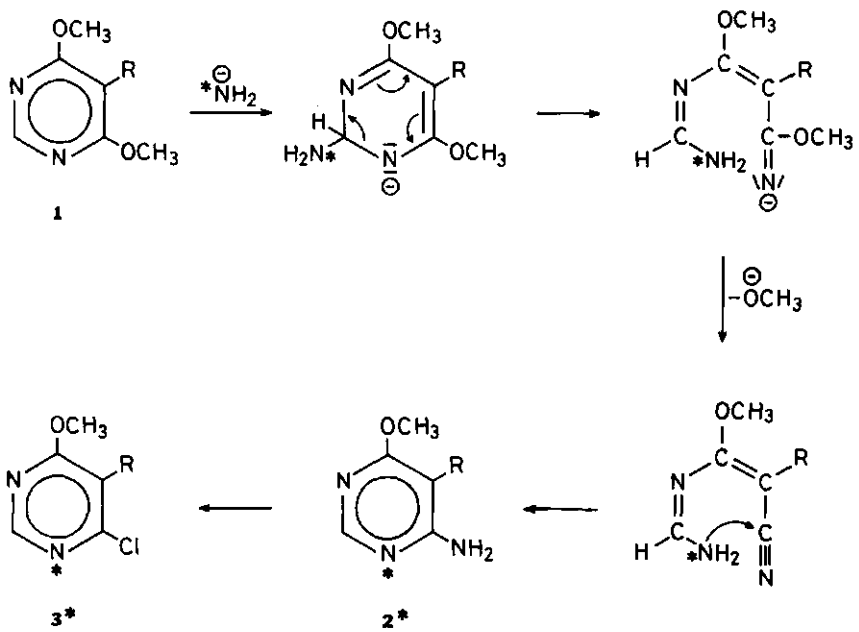
Table 7.1 Percentages of the excess of ^{15}N in the pyrimidines $2a^*$, $2b^*$, $3a^*$ and $3b^*$ [a,b] and the percentage of S_N(ANRORC) mechanism in the amino-demethoxylation of 1a and 1b

	% Excess ^{15}N			% S_N(ANRORC)
$2a^*$:	3.9	$3a^*$:	3.9	100
$2b^*$:	3.4	$3b^*$:	3.5	100

[a] All experiments were carried out in duplicate

[b] Accuracy ± 0.2%

The complete retention of the excess of ^{15}N in the 4-chloro derivatives $3a^*$ and $3b^*$ implies that the ^{15}N label is present in the pyrimidine ring and that the amino-demethoxylation of 1a and 1b has *completely* taken place *via* an open-chain intermediate. These results constitute the first examples of an S_N(ANRORC) process occurring on replacement of a methoxy function by an amino group. The pathway shown in Scheme 7.2, is proposed for the reaction.



Scheme 7.2

An addition of a nucleophile to C-2 of 4,6-diethoxypyrimidine has been proposed earlier in the hydrazinolysis of 4,6-diethoxypyrimidine, yielding 3-methyl-1,2,4-triazole[8].

7.2 REFERENCES

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8 DISCUSSION

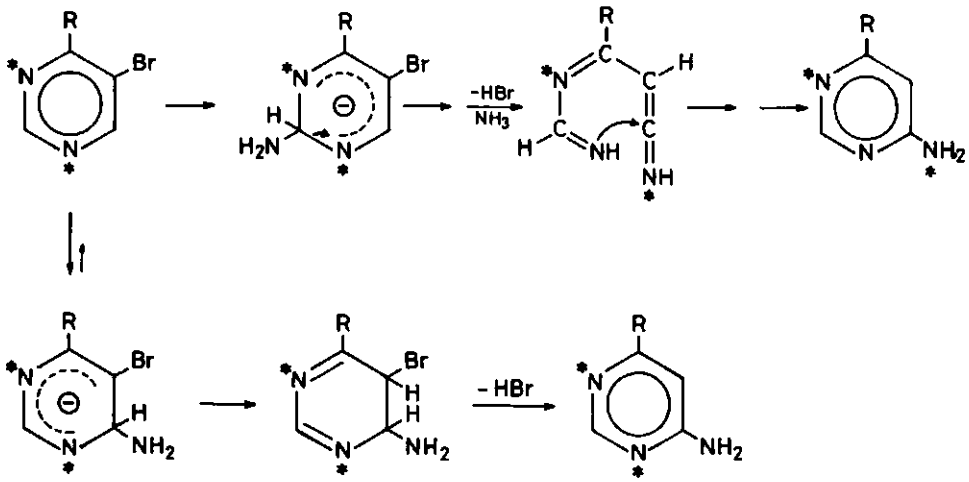
8.1 DISCUSSION

The investigations described in this thesis primarily concern the cine amination of 4-substituted 5-bromopyrimidines into the corresponding 4-substituted 6-amino-pyrimidines by potassium amide in liquid ammonia. The data accumulated on this reaction prior to this study have been interpreted as suggesting a mechanism in which loss of hydrogen bromide from the substrate leads to formation of a 5,6-pyrimidyne, to which addition of ammonia takes place. The exclusive location of the amino group on C-6 was ascribed to the directing influence of the ring nitrogen atoms[1-3].

It has become clear from our work however that this relatively simple mechanism is erroneous and that more intricate mechanistic pathways are involved[4-7]. Indications for this complexity were initially obtained from PMR investigations into solutions of 4-substituted 5-bromopyrimidines in liquid ammonia containing potassium amide[4]. Dependent on the nature of the substituents two possible processes can occur. If the substituent at C-4 contains an acidic proton in the α-position to the pyrimidine nucleus, as in 4-*N*-methylamino- and 4-methyl-5-bromopyrimidine this proton will be abstracted in the strongly basic medium and a charge-delocalized anion will be formed. In the absence of such an acidic proton a 1:1 anionic σ-adduct is formed at C-6 between the substrate and an amide ion, as shown for the 4-*t*-butyl-, 4-phenyl-, 4-methoxy- and 4-*N*-methylanilino-5-bromo compounds. A similar pattern has been observed for 2-substituted 4-chloropyrimidines[8,9]. The formation of the adducts at C-6 (C-4) is consistent with results obtained for the parent diazines[10]. The exclusive addition to this position is supported by calculations based on the Frontier Orbital Theory of Fukui[11,12].

A significant fact is that, regardless of whether an anion or a σ-adduct is formed on dissolving the 5-bromopyrimidines in liquid ammonia containing potassium amide, the reaction into the corresponding 6-amino derivatives slowly takes place. Extensive ^{15}N-labelling studies have shown however that a dramatic difference in the mechanisms of the formation of the 6-aminopyrimidines exists, dependent on the presence or absence of the acidic proton on the C-4 substituent[5,7].

In the latter case, *i.e.* for the *t*-butyl, phenyl, methoxyl and piperidino substituents the reaction proceeds to a differing degree (49, 52, 26 and 28% respectively) *via* a pathway in which a ring nitrogen atom of the starting material is finally located in the amino function of the reaction product. In the former instance, as shown for the conversions of 4-methyl-, 4-*N*-methylamino-, 4-anilino- and 4-amino-5-bromopyrimidine, this mechanism is not operative.
Let us consider some of the important steps in this ring opening process.



Scheme 8.1

The mechanism described above is initiated by an essential attack of an amide ion on C-2, followed by a ring opening through cleavage of the N-1 — C-2 bond. The short-lived open-chain intermediate loses hydrogen bromide after which recyclisation to C-6 and prototropy give the reaction product. The top half of Scheme 8.1 depicts the process for 4-substituted 5-bromo-[1(3)-^{15}N] pyrimidines and shows the ^{15}N distribution. These reactions constitute the first examples of an S_N(ANRORC) mechanism (Addition of Nucleophile, Ring Opening and Ring Closure) in a cine substitution. This type of process is designated as an S_N(ANRORC)^{cine} mechanism.
The importance of the addition of the amide ion to C-2 is significantly emphasized by the observation that the S_N(ANRORC)^{cine} process no longer occurs when this position is blocked by the introduction of a bulky *t*-butyl group. This effect is demonstrated in the reaction of 5-bromo-2,4-di-*t*-butylpyrimidine with potassium amide in liquid ammonia[6]. Further evidence is obtained from the direct aminations of 4-substituted 6-bromo and 4-substituted 6-chloropyrimidines with this reagent[13].

The S_N(ANRORC) process involved in the conversion of 4-X-6-phenylpyrimidines[14,15] (X=F,Cl,Br) is also postulated as being initiated by addition of an amide ion to C-2 and this suggestion is elegantly confirmed by the absence of a ring opening mechanism in the aminations of 6-bromo-2,4-di-*t*-butyl- and 6-chloro-2,4-di-*t*-butylpyrimidine[13].

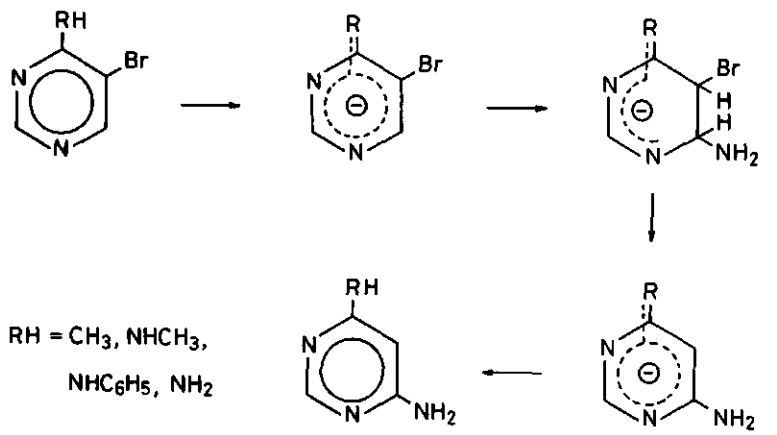
A second vital step in the S_N(ANRORC)^{cine} mechanism is the elimination of hydrogen bromide from the open-chain intermediate. The observation of a deuterium isotope effect of 1.9 on use of 5-bromo-4-*t*-butyl-6-deuteriopyrimidine as substrate has shown that this step may be rate-determining. It must be emphasized however that an elimination of hydrogen bromide is also an important step in that part of the amination that does *not* proceed *via* the S_N(ANRORC)^{cine} process. The lower half of Scheme 8.1 shows that in this case protonation of the PMR visible[4] σ-adduct on C-6 is followed by elimination of hydrogen bromide to give the 6-amino derivative with retention of the ^{15}N label in the pyrimidine ring.

This facet of the conversion is emphasized on comparison of the reactions of some 5-chloropyrimidines with their 5-bromo analogues. The effect of a relatively small change in leaving group character between bromide and chloride ions[16] has a surprisingly great influence on the amination patterns of the fairly unreactive[17,18] 5-halogenopyrimidines by potassium amide in liquid ammonia. On treatment of 4-*t*-butyl-5-chloro- and 5-chloro-2,4-di-*t*-butylpyrimidine with this reagent the cine substitution is found to be a minor pathway. A Chichibabin reaction now dominates in which loss of hydride ion from the PMR visible σ-adduct at C-6 yields the corresponding (2,)4-(di) substituted 6-amino-5-chloropyrimidines[6]. No S_N(ANRORC)^{cine} processes are involved and the fact that the side product 6-amino-4-*t*-butylpyrimidine obtained from 4-*t*-butyl-5-chloropyrimidine is also formed without a ring opening is of special significance.

The preference to retain the 5-chloro substituent is also observed in the reaction of 5-chloro-4-phenylpyrimidine, which forms a σ-adduct at C-6 but gives little or no reaction product, and of 5-chloro-4-methoxypyrimidine, in which replacement of the methoxyl group at the more reactive C-4 position occurs[17] to give 4-amino-5-chloropyrimidine.

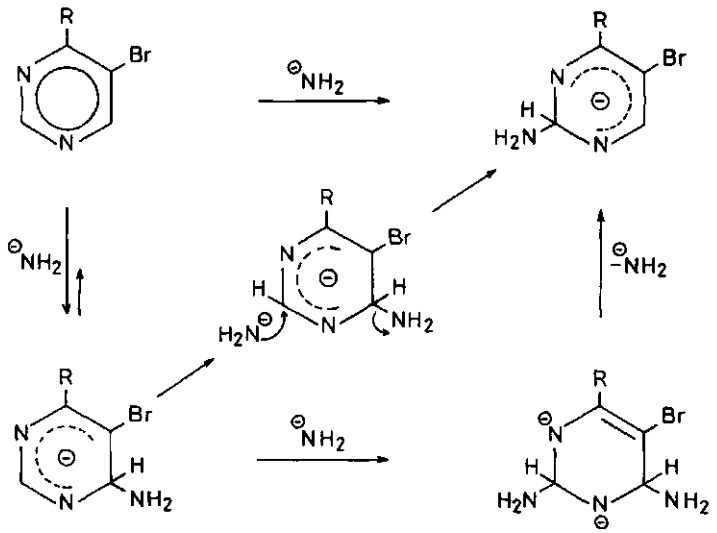
One question regarding the addition of the amide ion to C-2 in the S_N(ANRORC) mechanism remains. Does the attack take place on the PMR visible σ-adduct at C-6 or on the neutral starting material? This problem is as yet unresolved but certain indications may be obtained from the reaction mechanisms of the 5-bromopyrimidines containing a substituent on C-4 with an acidic proton in the α-position to the heterocyclic ring. As stated earlier in this discussion these

compounds are present in the reaction medium as anions. The resulting negative charge leads to an enhancement of the electron density on the ring nitrogen atoms. Addition of an amide ion to a negatively charged aromatic ring has been shown to be disfavoured[19,20] but not excluded[21]. In these 5-bromopyrimidines it seems reasonable to assume that such an addition will preferentially take place at C-6 and not at C-2. This is very elegantly born out by the observation that none of these substrates studied, *i.e.* 4-methyl-, 4-*N*-methylamino-, 4-anilino- and 4-amino-5-bromopyrimidine, are converted into the cine substitution products *via* an $S_N(ANRORC)^{cine}$ mechanism[7]. A process as shown in Scheme 8.2, in which proton abstraction from the C-4 substituent is followed by an Addition-Elimination sequence ($S_N(AE)^{cine}$) is indicated.



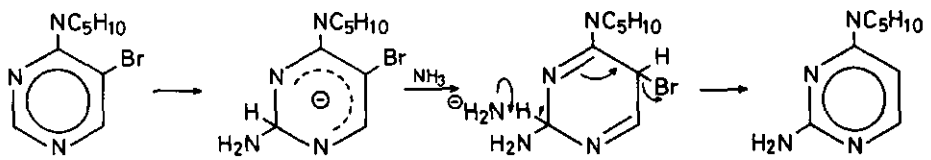
Scheme 8.2

If however the $S_N(ANRORC)^{cine}$ process in the conversion of the 5-bromopyrimidines largely present as σ-adduct on C-6 in the reaction medium, were to be initiated by an attack on C-2 *of that adduct* this addition should be susceptible to similar electrostatic repulsion influences. This essential step would be strongly disfavoured. Considering that the C-6 σ-adduct is the *only* species visible by PMR spectroscopy, it seems reasonable to assume that a di-adduct with a double negative charge is not formed as such. Addition probably either takes place at C-2 of the neutral substrate, present in, at best, low concentration, or at C-2 of the 1:1 C-6 adduct with *simultaneous expulsion* of an amide ion from C-6. Whichever alternative actually occurs, it is followed by immediate ring opening. Scheme 8.3 summarizes these considerations.



Scheme 8.3

The conversion of 5-bromo-4-piperidinopyrimidine is of special interest. This reaction constitutes the *only* example amongst the aminations studied of a tele substitution occurring alongside the cine amination. 2-Amino-4-piperidinopyrimidine is obtained as minor reaction product. ^{15}N-labelling experiments have shown that this compound is not formed by an $S_N(ANRORC)^{tele}$ process but *via* an $S_N(AE)^{tele}$ mechanism as depicted in Scheme 8.4. Here again addition to C-2 occurs[7].



Scheme 8.4

On considering the entire pattern of the cine aminations described above it becomes clear that we can now extend Table 1.1 summarizing the picture of nucleophilic substitutions of halogenoazaaromatics presented in the introduction. Incorporating the now definitely established occurrence of the $S_N(AE)^{cine}$ and $S_N(ANRORC)^{cine}$ mechanisms it now reads as follows:

Table 8.1

Mechanism	Type of substitution		
	Direct	Cine	Tele
$S_N(AE)$	+	+	+
$S_N(EA)$	+	+	+
$S_N(ANRORC)$	+	+	+
$S_{RN}1$	+		

A number of the considerations described above for the cine amination processes are also of importance in the direct substitution of 4-substituted 6-X-pyrimidines (X=Cl,Br). Free access to C-2 of the pyrimidine ring being essential to the occurrence of an S_N(ANRORC) mechanism in this type of amination has already been commented on. In addition the same rules regarding the presence or absence of an acidic proton on the C-4 substituent are shown to apply[13].
One very new, but extra interesting aspect has emerged from the studies on these direct aminations, namely that the reaction mechanism can be dependent on the reaction temperature. On treatment of 6-bromo-4-*t*-butylpyrimidine with potassium amide in liquid ammonia at -33° an S_N(ANRORC) mechanism is shown to be operative to the extent of 33%. At -75° however this percentage has increased to 77.
Finally it should be noted that reactions involving ring opening processes and open-chain intermediates may be more widespread than hitherto assumed. The amino-demethoxylations by potassium amide in liquid ammonia of 5-bromo-4,6-dimethoxy- and 4,6-dimethoxypyrimidine into the corresponding 4-amino-6-methoxy derivatives have been proven to take place exclusively *via* an S_N(ANRORC) mechanism[22], thus providing an interesting extension of the processes in which this type of mechanism is known to occur.

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SUMMARY

This thesis describes investigations into the mechanistic aspects of the cine amination of 4-substituted 5-halogenopyrimidines and the direct amination of 4-substituted 6-halogenopyrimidines by potassium amide in liquid ammonia.

PMR spectra of some 4-R-5-bromopyrimidines (R=C_6H_5, *t*-Bu, OCH_3, $H_3CNC_6H_5$, $HNCH_3$, CH_3) in liquid ammonia containing potassium amide are reported. Evidence is presented for the formation of stable 1:1 σ-adducts by addition of an amide ion to C-6 of the pyrimidine ring in the cases of R=C_6H_5, *t*-Bu, OCH_3 and $H_3CNC_6H_5$. When R=$HNCH_3$ deprotonation of the substituent occurs. In the case of R=CH_3 deprotonation is observed alongside adduct formation, the ratio of anion to σ-complex changing from 3:1 when R=CH_3 to 1:2 for R=CD_3. This increase in σ-complex formation is ascribed to a deuterium isotope effect.

Evidence is presented that the cine substitution of 5-bromo-4-*t*-butyl-[1(3)-^{15}N]-pyrimidine by potassium amide in liquid ammonia takes place to a considerable extent *via* an $S_N(ANRORC)^{cine}$ mechanism. This process involves an addition of an amide ion to C-2 of the pyrimidine ring, ring opening, loss of hydrogen bromide and subsequent ring closure. A deuterium isotope effect of about 2 is observed, indicating that hydrogen (deuterium) loss is a rate-determining step in the cine amination.
No $S_N(ANRORC)^{cine}$ mechanism, but an $S_N(AE)^{cine}$ process is observed when the C-2 atom is inaccessible to the attacking amide ion, as in the cine amination of 5-bromo-2,4-di-*t*-butylpyrimidine.
Treatment of 4-*t*-butyl-5-chloro- and 5-chloro-2,4-di-*t*-butylpyrimidine with potassium amide in liquid ammonia yields only minor quantities of the cine substitution product. The 6-amino-5-chloro derivatives are obtained as main products. It is proved that no $S_N(ANRORC)$ processes are involved in this Chichibabin reaction, the amination products being formed *via* an $S_N(AE)$ mechanism.

The nature of the substituent at C-4 in 4-R-5-bromopyrimidines influences the mechanism of the cine amination. An $S_N(ANRORC)^{cine}$ pathway is observed when

R=*t*-Bu, C_6H_5, OCH_3 or a piperidino group. If the substituent possesses an acidic proton α to the pyrimidine ring (R=CH_3, $HNCH_3$, HNC_6H_5 and NH_2) deprotonation occurs and the resulting anions are converted into the corresponding 6-amino derivatives *via* an $S_N(AE)^{cine}$ process.
When R=piperidino a small amount of 2-amino-4-piperidinopyrimidine is obtained *via* an $S_N(AE)^{tele}$ route.

The occurrence of an S_N(ANRORC) mechanism in the direct substitutions of 4-R-6-X-pyrimidines (X=Br or Cl) is dependent on the same characteristic structural requirements as shown for the cine amination, unhindered access of the amide ion to C-2 and absence of an acidic proton α to the heterocyclic ring on the substituent at C-4. Ring opening is observed when R=*t*-Bu, C_6H_5, OCH_3 and piperidino. An S_N(AE) process is indicated when R=CH_3 (X=Br or Cl), when R=HNC_6H_5 (X=Cl) and in the reactions of 2,4-di-*t*-butyl-6-X-pyrimidines (X=Br or Cl). It is shown that the temperature can influence the percentage of the reaction that takes place *via* an S_N(ANRORC) process considerably.

The amino-demethoxylation of 5-bromo-4,6-dimethoxypyrimidine and 4,6-dimethoxypyrimidine by potassium amide is shown to occur entirely *via* an S_N(ANRORC) mechanism to give the corresponding 6-amino derivatives.

SAMENVATTING

In dit proefschrift worden onderzoekingen beschreven naar de mechanistische aspecten van de cine aminering van 4-gesubstitueerde 5-halogeenpyrimidinen en de directe aminering van 4-gesubstitueerde 6-halogeenpyrimidinen door kalium amide in vloeibare ammoniak.

De PMR spectra van een aantal 4-R-5-broompyrimidinen (R=C_6H_5, *t*-Bu, OCH_3, $H_3CNC_6H_5$, $HNCH_3$, CH_3) in vloeibare ammoniak dat kalium amide bevat worden beschreven. Het bewijs wordt geleverd dat wanneer R=C_6H_5, *t*-Bu, OCH_3 en $H_3CNC_6H_5$ een stabiel 1:1 σ-adduct wordt gevormd door additie van een amide ion aan C-6 van de pyrimidine ring. In het geval R=$HNCH_3$ vindt deprotonering van de substituent plaats. Bij R=CH_3 wordt deprotonering waargenomen naast vorming van een adduct, en het blijkt dat de verhouding anion : σ-complex zich wijzigt van 3:1 indien R=CH_3 naar 1:2 indien R=CD_3. Deze toename in de mate van σ-complex vorming wordt toegeschreven aan een deuterium isotoop effect.

Bewezen wordt dat de cine substitutie van 5-broom-4-*t*-butyl-$\left[1(3)\text{-}^{15}N\right]$pyrimidine door inwerking van kalium amide in vloeibare ammoniak voor een aanzienlijk gedeelte plaatsvindt *via* een $S_N(ANRORC)^{cine}$ mechanisme. Dit proces omvat een additie van een amide ion aan C-2 van de pyrimidine ring, het opengaan van de ring en verlies van broomwaterstof, gevolgd door ringsluiting. Een deuterium isotoop effect van ongeveer 2 wordt waargenomen, een aanwijzing dat afsplitsing van een proton (deuteron) een snelheidsbepalende stap in de cine aminering is.
Wanneer het C-2 atoom niet toegankelijk is voor het aanvallend amide ion dan wordt niet een $S_N(ANRORC)^{cine}$ mechanisme maar een $S_N(AE)^{cine}$ proces waargenomen, zoals bij de cine aminering van 5-broom-2,4-di-*t*-butylpyrimidine.
Bij inwerking van kalium amide in vloeibare ammoniak op 4-*t*-butyl-5-chloor- en 5-chloor-2,4-di-*t*-butylpyrimidine worden slechts geringe hoeveelheden van het cine substitutieproduct verkregen. De 6-amino-5-chloor derivaten worden als hoofdproducten geisoleerd. Het bewijs wordt geleverd dat er geen $S_N(ANRORC)$ processen optreden bij deze Chichibabin reactie maar dat de amineringen plaatsvinden

via een $S_N(AE)$ mechanisme.

De aard van de substituent op C-4 in 4-R-5-broompyrimidinen is van invloed op het mechanisme van de cine aminering. Een $S_N(ANRORC)^{cine}$ proces wordt waargenomen indien R=*t*-Bu, C_6H_5, OCH_3 of een piperidino groep. Wanneer de substituent een zuur proton bevat α ten opzichte van de pyrimidine ring (R=CH_3, $HNCH_3$, HNC_6H_5 en NH_2), dan treedt deprotonering op en de resulterende anionen worden *via* een $S_N(AE)^{cine}$ proces omgezet in de overeenkomstige 6-amino derivaten. In het geval waarin R=piperidino wordt een kleine hoeveelheid 2-amino-4-piperidinopyrimidine verkregen *via* een $S_N(AE)^{tele}$ mechanisme.

Het optreden van een $S_N(ANRORC)$ mechanisme bij de directe substituties van 4-R-6-X-pyrimidines (X=Br of Cl) is afhankelijk van dezelfde karakteristieke structurele vereisten gevonden voor de cine aminering : onbelemmerde toegankelijkheid tot C-2 voor het amide ion en afwezigheid van een zuur proton α ten opzichte van de heterocyclische ring in de substituent op C-4. Ring opening wordt waargenomen indien R=*t*-Bu, C_6H_5, OCH_3 en piperidino. Een $S_N(AE)$ proces treedt op wanneer R=CH_3 (X=Br, Cl), R=HNC_6H_5 (X=Cl) en bij de reacties van 2,4-di-*t*-butyl-6-X-pyrimidines (X=Br, Cl). Het blijkt dat de temperatuur het percentage van de reactie dat volgens een $S_N(ANRORC)$ proces verloopt in belangrijke mate kan beinvloeden.

De amino-demethoxylering van 5-broom-4,6-dimethoxypyrimidine en 4,6-dimethoxypyrimidine blijkt geheel volgens een $S_N(ANRORC)$ mechanisme te verlopen, waarbij de overeenkomstige 6-amino derivaten worden verkregen.

CURRICULUM VITAE

Na het behalen van het eindexamen Gymnasium β aan Het Nederlandsch Lyceum te Den Haag in 1963 werd in september van dat jaar begonnen met de studie in de scheikunde aan de Rijksuniversiteit te Leiden.
Het candidaatsexamen, letter f, werd behaald in september 1968 waarna de studie werd voortgezet onder leiding van Prof.Dr.E.Havinga (hoofdvak,organische chemie), Dr.W.L.Groeneveld (anorganische chemie) en Dr.H.W.Joustra (fysische chemie).
Het doctoraal examen werd afgelegd in juni 1971.
In de periode van januari 1965 tot juli 1971 heb ik als student-assistent meegewerkt aan een aantal chemische practica.
Van januari 1972 tot mei 1978 ben ik als wetenschappelijk medewerker verbonden geweest aan het Laboratorium voor Organische Chemie van de Landbouwhogeschool te Wageningen, alwaar het in dit proefschrift beschreven onderzoek werd verricht. Daarnaast verleende ik assistentie op practica voor studenten in diverse studiefasen.