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.

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Aan mijn ouders

Aan Ellen

hn 8201 736

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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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.

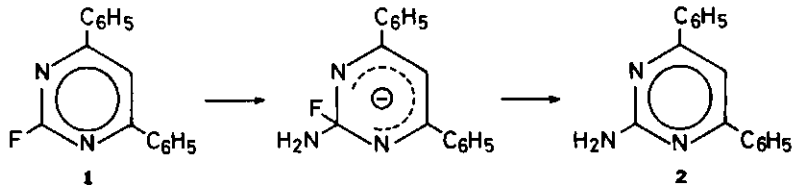
A survey of the reaction mechanisms observed to date in the direct, cine and tele substitutions involved is given in the following sections.

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*

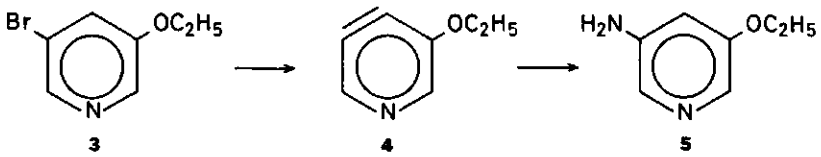
This process is initiated by addition of an amide ion to the heterocyclic ring on the halogen-bearing carbon atom. A halide ion is subsequently expelled. This mechanism is exemplified in the amination of 4,6-diphenyl-2-fluoropyridine (1) by potassium amide in liquid ammonia, giving 2[5].



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].

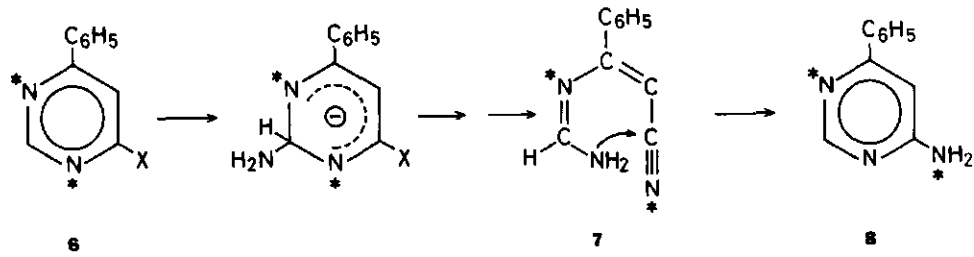


Scheme 1.2

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.

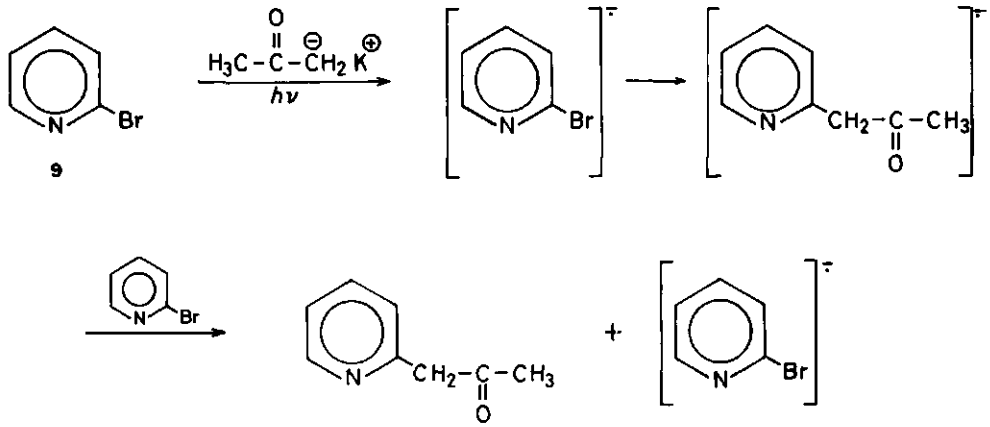


Scheme 1.3

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].



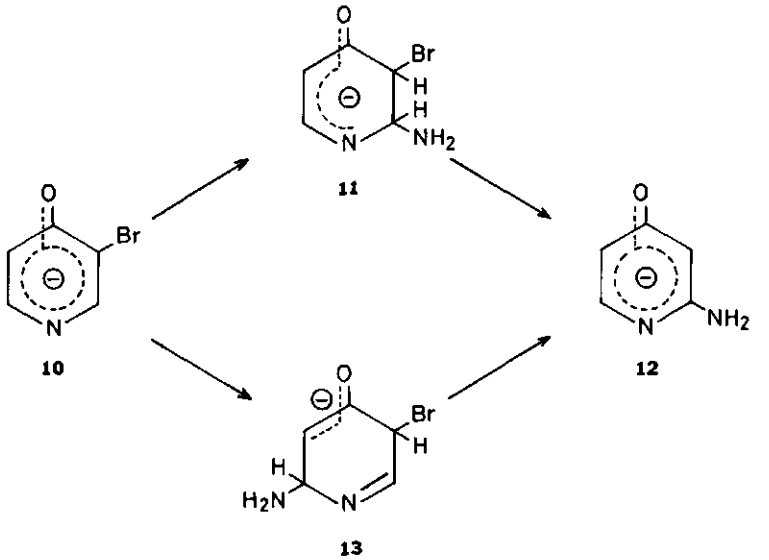
Scheme 1.4

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:

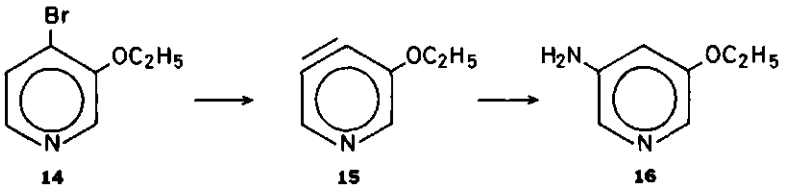
In this case addition of amide ion takes place to the carbon atom *adjacent* to the one bearing the halogen. This addition is followed by protonation and loss of hydrogen halide. This pathway has been proposed for the conversion by potassium amide in liquid ammonia of the anion of 3-bromo-pyrid-4-one (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).



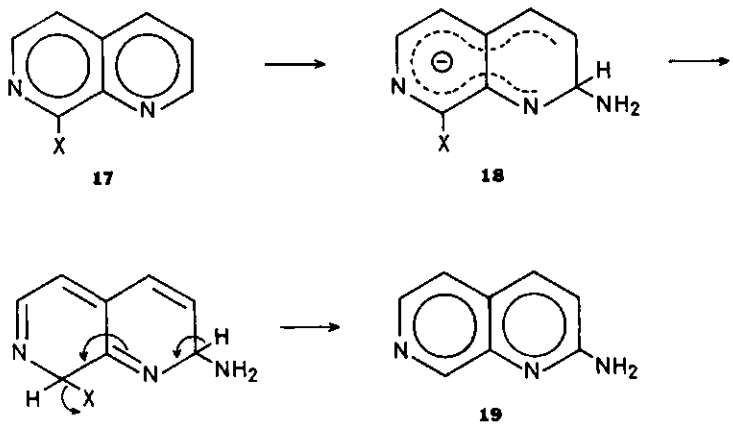
Scheme 1.6

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:

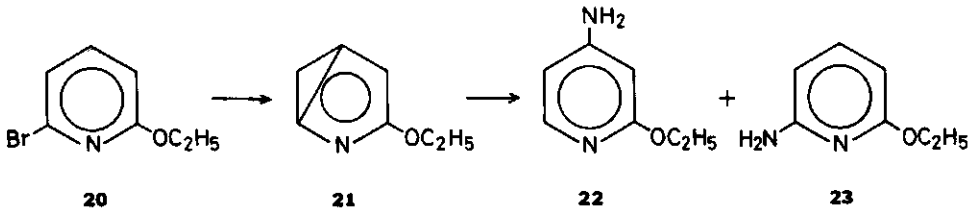
Several examples of this type of mechanism are available. Essential in this process is that the addition takes place to a carbon atom separated by one or more ring atoms from the carbon to which the halogen is attached. The formation of 2-amino-1,7-naphthyridine (19) alongside 8-amino-1,7-naphthyridine 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:

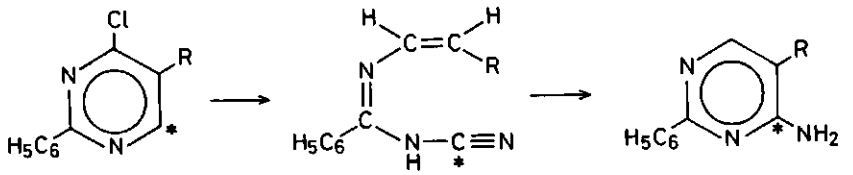
This process has been observed in the amination of 2-bromo-6-ethoxypyridine (20) which yields 4-amino-6-ethoxypyridine (22) alongside 2-amino-6-ethoxypyridine (23). The *meta* didehydropyridine (21) is postulated as intermediate[18,19].



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.

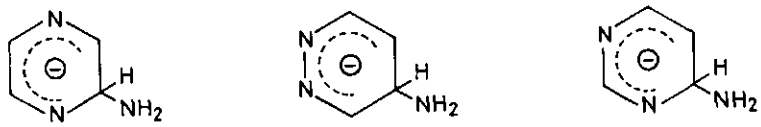
Table 1.1

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

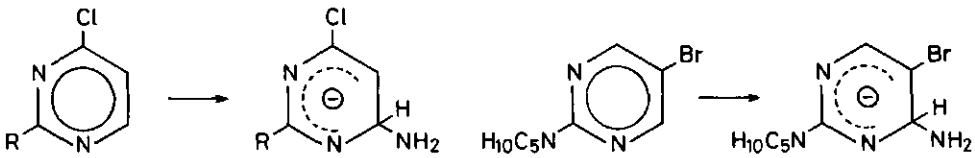
of the processes described in the previous sections. Although adduct formation between heteroaromatics and nucleophiles has been known for some time[21] the existence of the 1:1 σ-adducts 27-29 formed between an amide ion and non substituted diazines was only recently proven by PMR spectroscopy[22].



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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12. R.A.Rossi and J.F.Bunnett, J.Amer.Chem.Soc. 94, 683 (1972).

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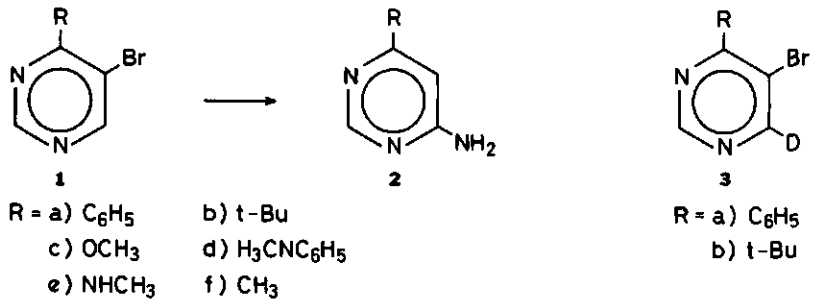
2 PMR studies on the formation of adducts between 4-substituted 5-bromopyrimidines and potassium amide in liquid ammonia

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°.



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

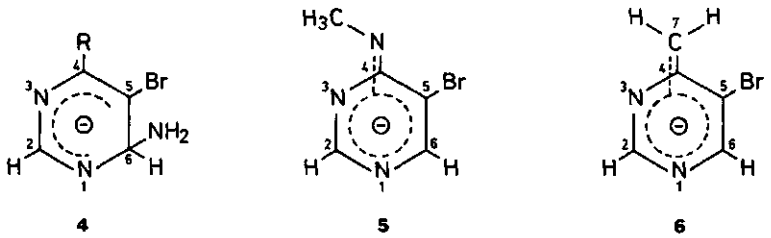
On dissolving the pyrimidines 1a-1d in liquid ammonia, containing two equivalents of potassium amide, and examining the resulting mixtures by PMR spectrometry shortly after preparation, signals are observed arising from:

(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.



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).

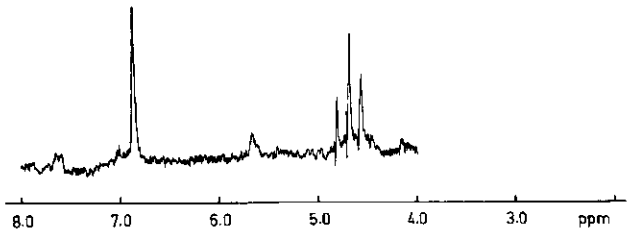


Fig. 2.1

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	^oC
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.

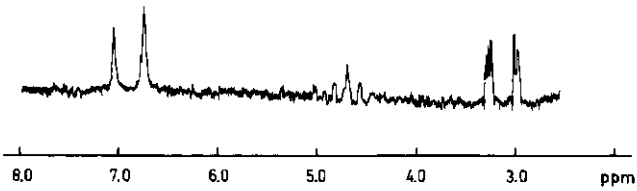


Fig. 2.2

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).

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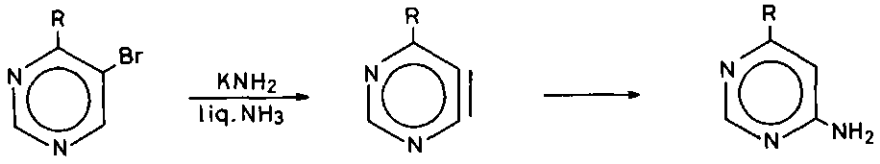
3 A reinvestigation of the mechanism of the amination of 5-bromo-4-*t*-butylpyrimidine. On the occurrence of an S_N(ANRORC) mechanism

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).



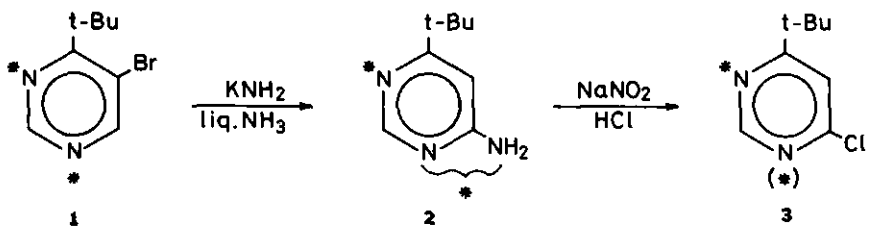
Scheme 3.1

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° 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

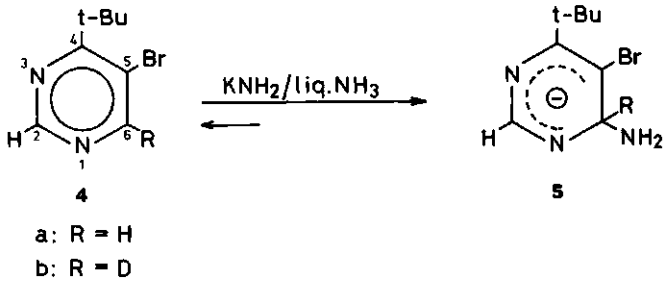
The diazotization procedure[10] was preferred to the more conventional two-step process of an acidic hydrolysis of 2 to the corresponding 6-oxo compound and subsequent conversion of the latter to 3, because of the small amounts of 2 available. Comparison of the ^{15}N-enrichment of 1, 2 and 3 by mass 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

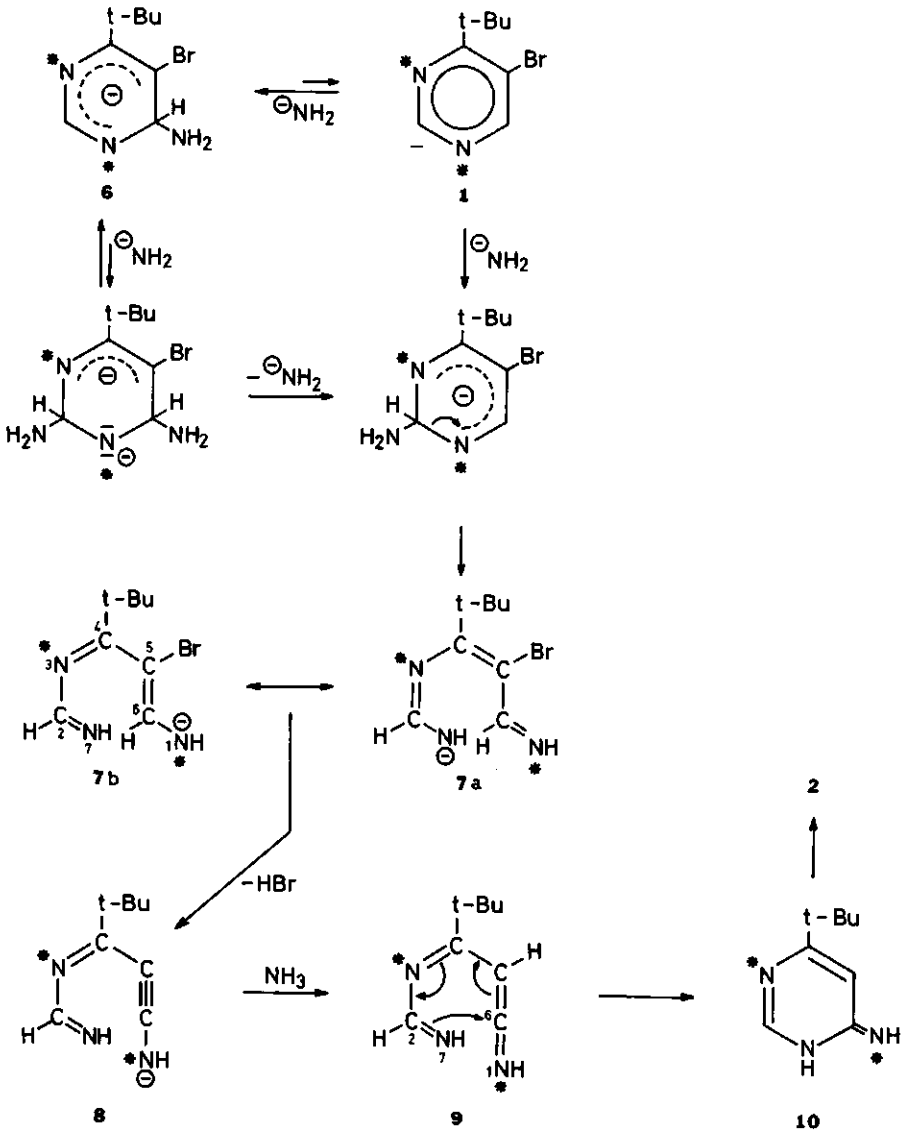
[a] All experiments were carried out in duplicate
[b] Accuracy ± 0.2%

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).



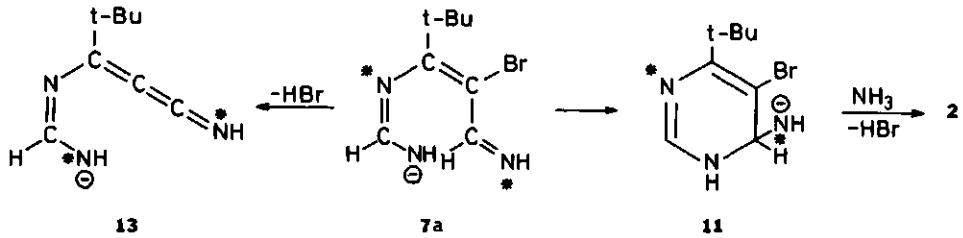
Scheme 3.3

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



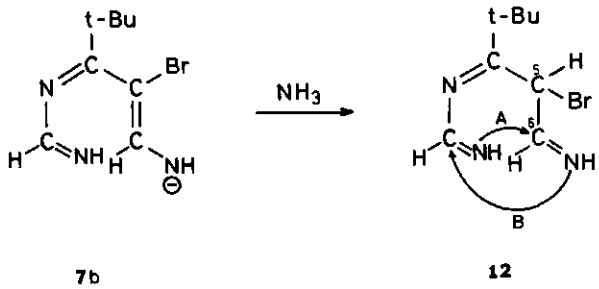
Scheme 3.4

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

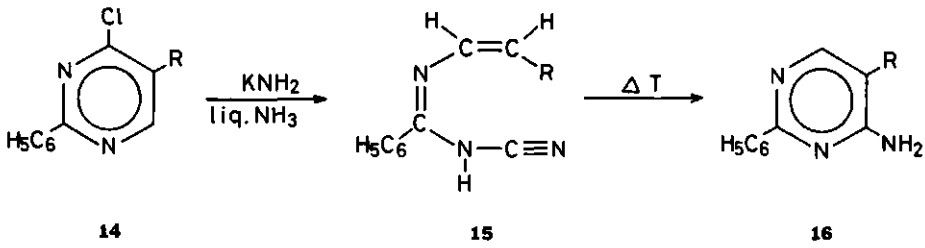
[b] Accuracy $\pm$ 0.2%

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.



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.

3.4 REFERENCES

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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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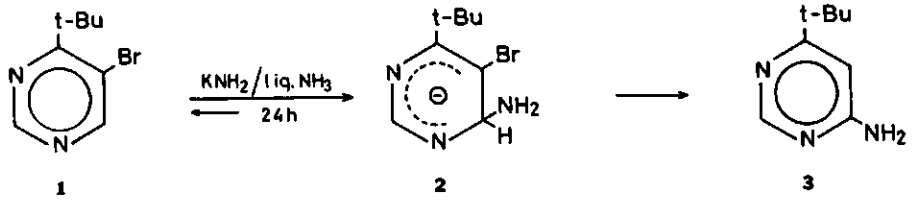
21. Precautions should be taken to exclude all traces of water; these lead to several by-products, for example 4-*t*-butylpyrimid-6-one.

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

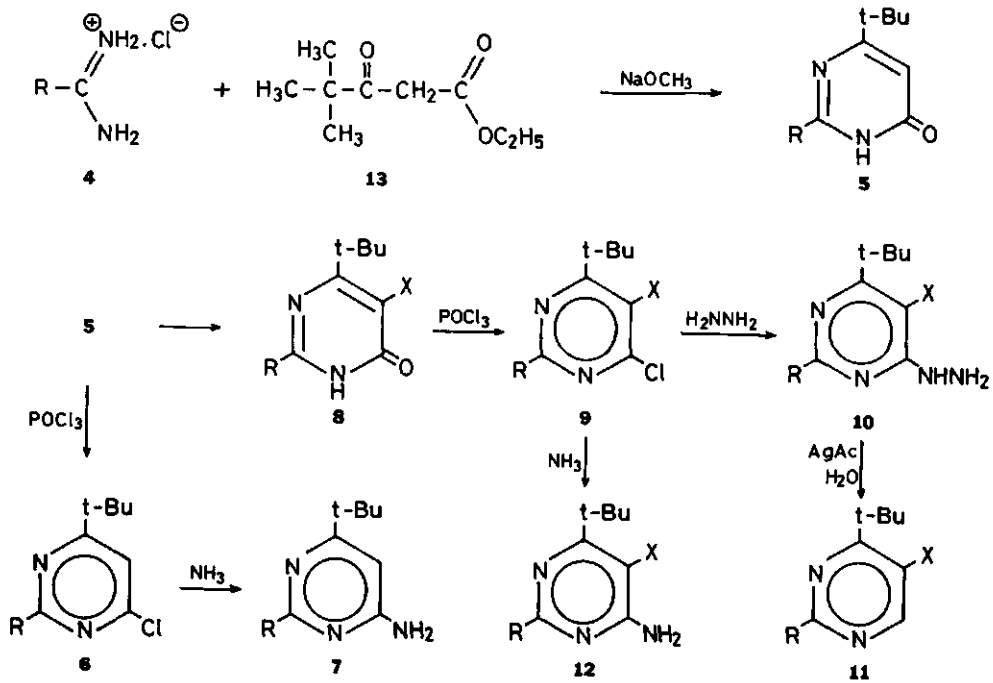
4.2.1 The reaction of 4-t-butyl-5-chloropyrimidine (11a) *with potassium amide in liquid ammonia*

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 $\left[1(3)-^{15}N\right]$-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, $\left[x-^{15}N\right]$ 7a and $\left[x-^{15}N\right]$ 12a were converted into 4-*t*-butyl-6-chloro-$\left[x-^{15}N\right]$ pyrimidine and 4-*t*-butyl-5,6-dichloro-$\left[x-^{15}N\right]$ 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-$\left[1(3)-^{15}N\right]$ pyrimidine with potassium amide in liquid ammonia[a,b]

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

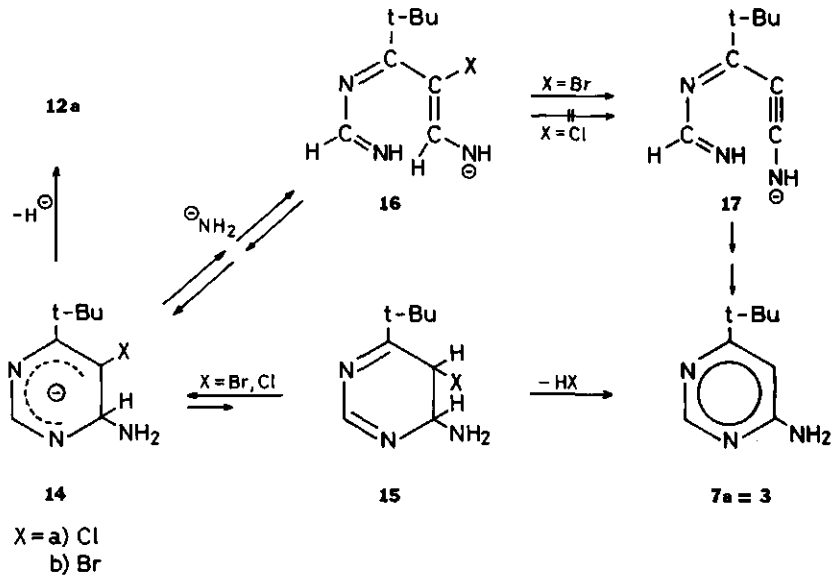
[a] all experiments were carried out in duplicate

[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%