σ-ADDUCTS OF PYRIMIDINES AND PTERIDINES

AN NMR STUDY

CENTRALE LANDBOUWCATALOGUS
0000 0086 9764

Dit proefschrift met stellingen van

JACOB PIERRE GEERTS

doctorandus in de chemie, geboren te Amsterdam op 30 maart 1946,
is goedgekeurd door de promotor dr.H.C.van der Plas, hoogleraar
in de organische scheikunde.

De Rector Magnificus van de Landbouwhogeschool,

H.C.van der Plas

Wageningen, 10 november 1977

MN08201,708

J.P. GEERTS

σ-ADDUCTS OF PYRIMIDINES AND PTERIDINES

AN NMR 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 20 januari 1978
des namiddags te vier uur in de aula
van de Landbouwhogeschool te Wageningen

ISN = 104052-04

BIBLIOTHEEK
DER
LANDBOUWHOGESCHOOL
WAGENINGEN

NN08201, 708.

STELLINGEN

1. De opvatting dat in het ^{13}C NMR spectrum van chinazoline koolstofatoom 2 bij lagere magnetische veldsterkte resoneert dan koolstofatoom 4 is een in de literatuur wijd verbreid misverstand.

   R.J.Pugmire, D.M.Grant, M.J.Robins en R.K.Robins, J.Amer.Chem.Soc., 91, 6381 (1969).
   J.B.Stothers, Carbon-13 NMR Spectroscopy, Academic Press, New York, London, 1972, p 262.
   G.C.Levy en G.L.Nelson, Carbon-13 NMR for Organic Chemists, Wiley-Interscience, New York, 1972, p 100.
   E.Breitmaier en W.Voelter, Carbon-13 NMR Spectroscopy, Verlag Chemie, Weinheim, 1974, p 188.

2. De reactiviteit van pyridine-1-oxide ten opzichte van cyanide, actieve methyleen verbindingen en andere nucleofielen wordt door Koyama et al. ten onrechte aangevoerd ter rationalisering van het door deze onderzoekers voorgestelde mechanisme met betrekking tot de reactie van pyridine-1-oxide met formamide.

   T.Koyama, T.Nanba, T.Hirota, S.Ohmori en M.Yamato, Chem.Pharm.Bull., 25, 964 (1977).

3. De wijze waarop Mattern het ANRORC mechanisme toepast op de reactie van 2-amino-3,5-halogeenpyridinen met hydroxiden en alkoxiden is fundamenteel onjuist.

   G.Mattern, Helv.Chim.Acta, 60, 2062 (1977).

4. De chemical shift die Collins en Tomkins toekennen aan het enolisch proton van ethyl 5-hydroxy-7a-methyl-1-oxo-*cis*-3a, 6,7,7a-tetrahydro-1*H*-indeen-4-carboxylaat is weinig waarschijnlijk; een uitgebreidere bewijsvoering is daarom wenselijk.

   D.J.Collins en C.W.Tomkins, Aust.J.Chem., 30, 443 (1977).

5. De door Krueger et al. weergegeven massaspectra in "bargraph" representatie zijn niet in alle gevallen in overeenstemming met de feitelijke meetresultaten.

O.Becker, N.Fürstenau, W.Knippelberg en F.R.Krueger, Org.Mass. Spectrom., 12, 461 (1977).

6. De Nederlandse consument beschikt over te weinig adequate informatie om zelf zijn voedselpakket verantwoord samen te stellen.

7. Voor de behandeling van obesitas is meer nodig dan een "energie-beperkt" voedingsvoorschrift.

8. Het beleidsvoornemen van de Directie Landbouwkundig Onderzoek om de onderzoekcapaciteit gericht op de produktieverhoging van landbouwgewassen te beperken, gaat voorbij aan de uit de daling van het areaal cultuurgrond voortvloeiende noodzaak tot intensivering van de akkerbouw die wordt voorzien in de nota Landbouwverkenningen.

Meerjarenvisie 1977-1981 voor het Landbouwkundig en visserij-onderzoek, Den Haag, 1977.
Landbouwverkenningen, Den Haag, 1977.

9. De overheid zou een belangrijke bijdrage kunnen leveren tot het behoud van de klassieke automobiel door de "60 dagen kaart" faciliteit uit te breiden tot automobielen met een minimum leeftijd van 10 jaar.

J.P.Geerts
σ-Adducts of pyrimidines and pteridines, an NMR study

aan Anneke

aan mijn ouders

VOORWOORD

Op deze plaats wil ik graag allen bedanken die hebben bijgedragen aan de voltooiing van dit proefschrift. Dit onderzoek, dat werd uitgevoerd op het Laboratorium voor Organische Chemie te Wageningen, werd mogelijk gemaakt door de medewerking van velen binnen en buiten deze afdeling.
In het bijzonder wil ik prof.dr.H.C.van der Plas bedanken voor zijn niet aflatend enthusiasme, de vrijheid die hij mij gelaten heeft bij de opzet van dit onderzoek, de vele stimulerende discussies die ik met hem had, en zijn kritische en snelle beoordeling van het manuscript.
Direct of indirect werd in de beschreven experimenten geparticipeerd door Willem Combé, Hugo Jongejan, Cees Landheer, Gerrit Lelyveld, Pim Melger, Bep van Veldhuizen en Eef Vleeming. Mies Snell is erg aardig geweest door dit proefschrift te willen typen. De fraaie tekeningen werden vervaardigd door Sander Schuchhard. Bert van Amersfoort heeft het typewerk voor de publikaties verricht.
Tot slot wil ik alle leden van de vakgroep Organische Chemie bedanken voor hun bijdrage aan de voortreffelijke sfeer, die het werken op het Laboratorium tot een waar genoegen heeft gemaakt.

CONTENTS

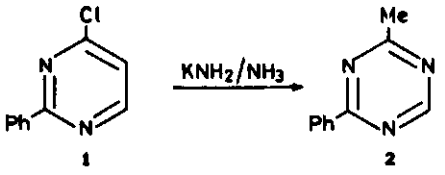
The following chapters have been published in the literature:

Chapter 2	Recl.Trav.Chim.(Pays-Bas) 92, 1232 (1973)
Chapter 3	Recl.Trav.Chim.(Pays-Bas) 93, 231 (1974)
Chapter 4	Org.Magn.Reson., 7, 86 (1975)
Chapter 6	Org.Magn.Reson., 8, 607 (1976)

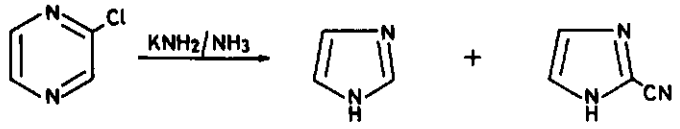
Chapter 5 is submitted to the Journal of Organic Chemistry

1.1 GENERAL

Since 1960 there is strong interest in the behaviour of aza- and diaza-aromatics towards strong nucleophiles[1,2] at the Laboratory of Organic Chemistry in Wageningen. It has been found that depending on the nucleophilicity of the reagents used, nucleophilic substitution or ring interconversions can occur. It appeared that of the strong bases applied, the alkali-amide-ammonia system has unique properties in performing ring transformation reactions in diazaaromatic systems[3-8]. To illustrate this we will take just two examples from the extensive data available i.e. the conversion of 4-chloro-2-phenylpyrimidine (1) in 2-phenyl-4-methyl-s-triazine (2) and the ring contraction of chloropyrazine (3) in the imidazoles 4 and 5.

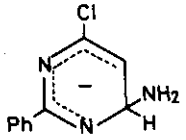


1 2



3 4 5

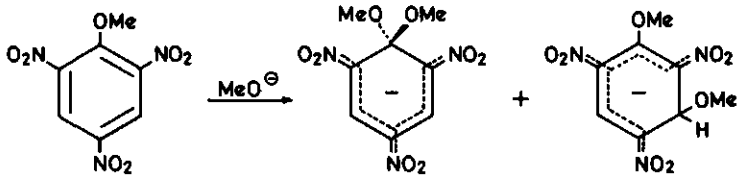
The first reaction step, common to these conversions is the attack of the nucleophilic amide ion on a ring carbon atom, yielding a stable* 1:1 anionic σ-adduct. For example in the conversion of 1 into 2 the σ-complex 6 is involved.



6

*The term stable is meant to include those complexes which, although not isolable, can be observed for short periods of time in solution at low temperature

These intermediate σ-adducts are structurally closely related to the well-known Meisenheimer complexes formed when the methoxide ion is reacted with the strongly electrondeficient 2,4,6-trinitroanisole (7)[9,10].



7 8 9

The acetal complex 8 is formed by attack of the methoxide ion on C-1 as determined by ^{1}H-NMR spectroscopy[11]. Servis made the important observation that, if concentrated sodium methoxide solution was added to a solution of 2,4,6-trinitroanisole in dimethyl sulphoxide (DMSO), the NMR spectrum initially produced was that of the methine adduct 9. With time the spectrum gradually changed to that of the thermodynamically more stable C-1 adduct 8[12].

It is suggested that the formation of 9 is kinetically favoured, but under equilibrium conditions 9 rearranges into 8, due to the greater thermodynamic stability of the latter. One of the primary reasons for greater thermodynamic stability of the acetal complex 8 compared to the methine complex 9 may be steric relief between the 1-methoxyl group and the *ortho* nitro groups on adduct formation, since a hybridization change of C-1 ($sp^2 \rightarrow sp^3$) makes that both geminal methoxyl groups in 8 lie outside the plane of the ring. In 9 steric compression between the 1-alkoxyl group of the parent and the adjacent nitro groups is *not* relieved. Such compression may even be increased, as enhanced conjugative interactions in 9 might hinder rotation of the nitro groups out of the ring plane.

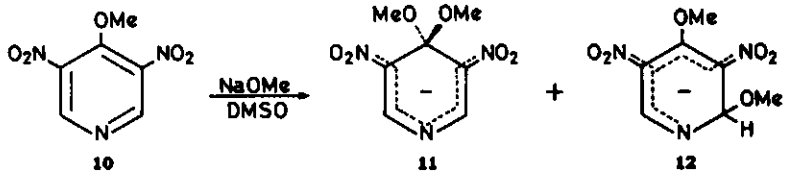
An extensive amount of work has been done on these species, as reflected in the large amount of substrate-nucleophile combinations that have been examined. Among the substrates tested are the picrylethers, trinitrobenzene[11], picrylchloride[13], 3,5-dinitro-1-chlorobenzene[13], 3,5-dinitrobenzonitrile[14], 3,5-dinitro-4-X-methylbenzoate (X=OCH_3, Cl)[15] and 1-N,N-dimethylamino-2,4,6-trinitrobenzene[16]. A variety of nucleophiles has been employed, e.g. cyanide

ion[17], N-methylanilide[18], ethylmercaptide[19] and the ambident phenoxide ion[20]. Spirocomplexes derived from glycol-2,4,6-trinitrophenylether[21] and from N,N'-dimethyl-N-picrylethylenediamine[22] have also been reported. The subject of Meisenheimer complexes[23] and of anionic σ-complexes in general[24] has been reviewed extensively.

Aza analogues of Meisenheimer complexes have been prepared from substrates in which one or more $=CNO_2$-entities have been replaced by the =N-(aza) group. The main properties associated with the aza group may be briefly summarized as follows.

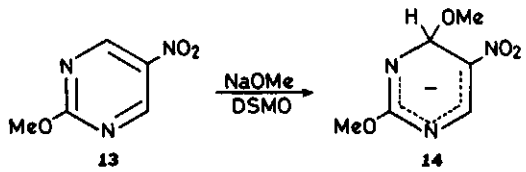
- The polar effect of this group is qualitatively of the same type as that of the exocyclic nitro group in that both withdraw electrons from the ring by the inductive and the conjugative mechanisms.
- The steric requirements of a =N-system however, in contrast to those of the relatively bulky nitro group do not exceed those of an aromatic =CH-group.

Action of sodium methoxide on 3,5-dinitro-4-methoxypyridine (10) in DMSO solution leads to the formation of sodium 4-aza-1,1-dimethoxy-2,6-dinitrocyclohexadienate (11), and the thermodynamically less stable 4-aza-1,3-dimethoxy-2,6-dinitrocyclohexadienate (12).



10 11 12

The replacement of a nitro group by an aza group at the position *para* to the reactive center results in a decrease in the stability of the Meisenheimer compound 11, and in an increase in its rate of formation[25,26]. The lower thermodynamic stability of the methine complexes 9 and 12 compared with that of the acetal complexes 8 and 11 has been ascribed to adverse steric interactions between the methoxyl group attached to an sp^2 carbon atom and the *ortho* nitro groups (see above). As ring nitrogen atoms are sterically less demanding than nitro groups, such differential effects are less pronounced in the nitropyrimidine series. Therefore, when 2-methoxy-5-nitropyrimidine (13) is reacted with methoxide ion in DMSO, predominant formation of methine complex 14 has been observed[27].



13 14

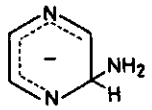
1.3 STRUCTURAL CHARACTERIZATION OF σ-COMPLEXES

The structure of Meisenheimer complexes has fascinated chemists since the late 19th century, but a major breakthrough in the structural characterization of anionic σ-complexes occurred in 1964 when a report of the PMR spectrum of the Meisenheimer adduct 8 was published[28]. The NMR technique proved to be very successful as appears from the fact that only two years later enough PMR spectral data concerning σ-adducts were available for a short review[29]. Coupled with evidence from visible and infrared spectroscopy, structures were assigned to a wide variety of such complexes. Extensive reviews concerning σ-adducts between nitroarenes and nitrohetarenes and a variety of nucleophiles appeared a few years afterwards[23,24]. Structure and stability of σ-complexes, as well as electronic and PMR spectra are qualitatively correlated by simple HMO techniques[30,31,32]. More detailed HMO treatments[33] and Pariser-Parr-Pople-type SCF calculations with configuration interaction[34] provide a more complete description of electronic structure. The value of NMR spectroscopy for the structure elucidation of σ-complexes is due to the fact that the ring carbon to which the nucleophile adds, undergoes a change in hybridization from sp^2 in the parent compound to sp^3 in the adduct. This results in an upfield shift of 3-4 ppm for a proton bonded to that sp^3 ring carbon atom. The remaining ring protons attached to sp^2 carbon atoms are shielded due to the increased negative charge in the ring. An additional upfield shift may be expected from the rescinding of the aromatic ring current upon σ-complex formation.
The diagnostic character of ^{13}C-NMR spectroscopy is even greater. This is demonstrated by the large upfield shift of about 90 ppm that is found for the ring carbon atom to which the nucleophile has added and further by the ^{13}C-H coupling constant. If the newly formed tetrahedral center carries a proton, the J(C-H) decreases from about 180 Hz to 150 Hz upon adduct formation. The distribution of the electronic charge brought into the ring is reflected to a great extent by the chemical shift of the remaining ring

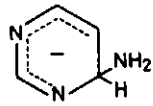
carbon atoms.

1.4 σ-ADDUCTS BETWEEN AZAAROMATICS AND AMIDE ION

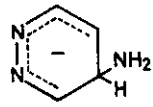
The first direct observation of a 1:1 anionic σ-complex involving an amide ion as nucleophile was reported in 1972. In that year the structure of complexes 15-17 between the three parent diazines and amide ion was revealed by ^{1}H-NMR spectroscopy[35].



15

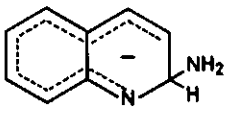


16

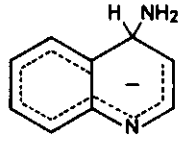


17

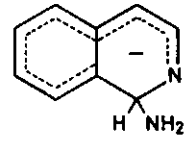
In the presence of a slight excess of amide ions adduct formation is indicated by the usual upfield shifts (2.2-4.5 ppm). Alongside this effect a triplet splitting pattern is found for the NMR signal from the proton bonded to the tetrahedral center due to spin-coupling with the amine protons. With a greater excess of amide ions, however, proton exchange within the amino group occurs and this spin-coupling is not found. These adducts have been found to be stable in solution for several days at -70°C.
Interestingly, a stable σ-complex between amide ion and pyridine has not been found, presumably because of the insufficient activation power of one aza entity. However, pyridine derivatives with a fused benzo ring e.g. quinoline and isoquinoline are easily converted into the σ-adducts 18, 19 and 20 respectively, when they are dissolved in KNH_2/NH_3[36]. The benzo ring provides clearly an extra activation towards complex formation.



18



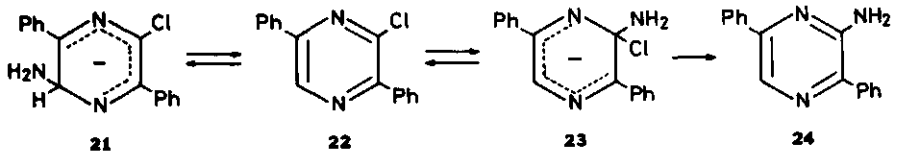
19



20

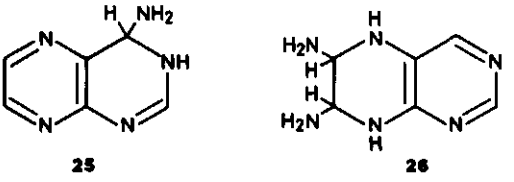
Investigations in our laboratory revealed that anionic σ-complexes are generally found in reactions of *halogen* containing azaaromatics with an amide ion. Of special interest is that initially the ring carbon bearing the

halogen substituent is *not* attacked by the amide ion. This would lead to a short-lived σ-complex not discernable by NMR spectroscopy, because it readily loses a halide ion in a direct substitution process. Instead, attack takes place on a ring carbon atom positioned next to the aza group, leading to a stable σ-complex, which can be observed by NMR spectroscopy for a long period of time. In the amination of 2-chloro-3,6-diphenylpyrazine (22) for instance a stable σ-complex 21 between the substrate and amide ion has been unequivocally identified. However, results obtained with 5-D labelled starting material make it clear that the precursor of the amino compound 24 ultimately formed[37] is not the σ-complex 21, but 23.

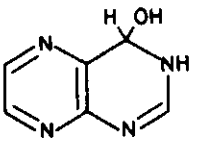


1.5 UNCHARGED NUCLEOPHILES

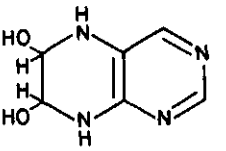
Uncharged nucleophiles require a considerable activation of the substrate to yield σ-complexes. Examples are the tetraazanaphthalenes e.g. pyrazinopyrazines and pteridines which form covalent addition complexes with the relatively weak nucleophiles water, methanol and amines[38-40]. Recently ^{1}H-NMR spectra of the 3,4-monoadduct 25 as well as the 6,7-diadduct 26 between ammonia and pteridine were reported[41,42].



Defective ^{13}C-NMR spectroscopic data have been published concerning the mono and dihydrates 27 and 28 of pteridine[43].



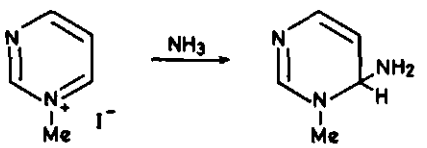
27



28

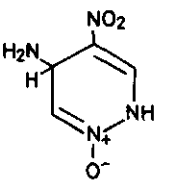
However, ^{13}C-NMR spectroscopic data found for the ammonia adducts 25 and 26, enabled us to interprete the ^{13}C-NMR spectra of the hydrates 27 and 28 more completely[44].

It has been established by ^{1}H-NMR spectroscopy that N-alkyl pyrimidinium salts form σ-complexes with ammonia. Thus,when 1-methylpyrimidinium iodide (29) is dissolved in liquid ammonia, covalent amination of the N-1 – C-6 bond results[45]. These findings have been confirmed by ^{13}C-NMR spectroscopy[46].



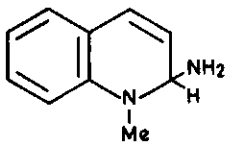
29 30

In the pyridazine series activation by quaternization alone, appears insufficient for adduct formation with ammonia. It was established by ^{1}H and ^{13}C-NMR spectroscopy that for instance pyridazine-1-oxide shows no reaction with liquid ammonia, but when activation is enhanced by the introduction of a nitro group at position 4 covalent complexation takes place[47,48], yielding the σ-adduct 31, in which the nucleophile has attacked C-5.

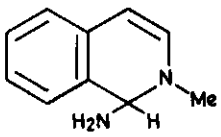


31

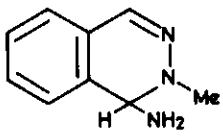
Covalent amination is also reported in quaternized azaaromatics containing a fused benzo ring (quinoline, isoquinoline, phthalazine, quinoxaline and triazanaphthalene). These cations are converted into the aminodihydro- and tetrahydro derivatives 32-36 in liquid ammonia.



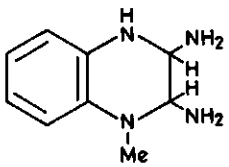
32



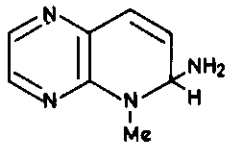
33



34



35



36

Comparison of the extent of covalent amination and hydration reveals that for the cations considered here, amination in liquid ammonia is complete, but hydration in water is insignificant[49].

1.6 PURPOSE OF THE INVESTIGATION

The aim of this investigation is to extend our knowledge of the mechanistic implications that play a role in ring interconversions. The structure of addition complexes and open-chain compounds, as well as the mechanisms according to which transitions of these intermediates can occur, were studied. Since in many cases these intermediates are unstable we applied ^{1}H- and ^{13}C-NMR spectroscopy to establish directly in the reaction mixture which intermediates are formed and how they emerge and disappear.

In chapter 2 ^{1}H-NMR experiments are described in which the existence of a 1:1 σ-adduct between amide ion and 2-substituted 4-chloropyrimidines is proved, and it is suggested that the formation of this addition complex is the first step in the ring transformation leading to 2-substituted 4-methyl-s-triazines.

In chapter 3 the formation of σ-complexes in reactions of 5-bromo-4-

substituted pyrimidines is described.

The ^{13}C-NMR technique has proven to be very valuable in identifying reaction intermediates. This is shown in chapter 4 in which the ^{13}C-NMR spectral characteristics of 2-substituted pyrimidines and their 4-chloro derivatives and their σ-adducts with amide ion are described and interpreted.

In chapter 5 a ^{1}H- and ^{13}C-NMR investigation is described of the ring transformation of 4-chloro-2-dimethylaminopyrimidine with KNH_2/NH_3 into 2-dimethylamino-4-methyl-s-triazine. Special attention has been paid to the intermediates which are formed after the σ-complex has been obtained.

In chapter 6 ^{13}C-NMR spectroscopic data concerning the tetraazaaromatic bicyclic system pteridine and a number of its derivatives are collected. A method has been developed to discern spectroscopically between 6- and 7-substituted derivatives using ^{13}C-NMR substituent effects. Furthermore covalent complexes between pteridine and derivatives and NH_3 as well as H_2O were analysed by ^{13}C-NMR spectroscopy.

1.7 REFERENCES

1. H.J.den Hertog and H.C.van der Plas, Adv.Heterocycl.Chem., 4, 121 (1965).
2. H.J.den Hertog and H.C.van der Plas, in H.G.Viehe:"Chemistry of Acetylenes" Dekker (New York), (1969), p.1149.
3. H.J.den Hertog, H.C.van der Plas, M.J.Pieterse and J.W.Streef, Recl.Trav.Chim.(Pays-Bas), 84, 1569 (1965).
4. H.C.van der Plas, B.Haase, B.Zuurdeeg and M.C.Vollering, Recl.Trav.Chim.(Pays-Bas), 85, 1101 (1966).
5. H.C.van der Plas and B.Zuurdeeg, Recl.Trav.Chim.(Pays-Bas), 88, 426 (1969).
6. H.C.van der Plas, B.Zuurdeeg and H.W.van Meeteren, Recl.Trav.Chim. (Pays-Bas), 88, 1156 (1969).
7. P.J.Lont, H.C.van der Plas and A.Koudijs, Recl.Trav.Chim.(Pays-Bas), 90, 207 (1971).
8. H.C.van der Plas, Lectures in Heterocyclic Chemistry, vol.II, Ed.R.N.Castle and L.B.Townsend, Utah (1974).
9. C.J.Jackson and F.H.Gazzolo, Amer.Chem.J., 23, 376 (1900).
10. J.Meisenheimer, Justus Liebigs Ann.Chem., 323, 205 (1902).
11. M.R.Crampton and V.Gold, J.Chem.Soc., 4293 (1964).

12. K.L.Servis, J.Amer.Chem.Soc., 87, 5495 (1965).
13. L.Syper and J.Barycki, Tetrahedron, 28, 2233 (1972).
14. F.Terrier, F.Millot and M.P.Simonnin, Tetrahedron Lett., 2933 (1971).
15. M.R.Crampton, M.A.El Ghariani and H.A.Khan, J.Chem.Soc. (D), Chem. Commun., 834 (1971).
16. M.R.Crampton and V.Gold, J.Chem.Soc.(B), 893 (1966).
17. L.H.Gan and A.R.Norris, Can.J.Chem., 52, 8 (1974).
18. E.Buncel, H.Jarrell, H.W.Leung and J.G.K.Webb, J.Org.Chem., 39, 272 (1974).
19. G.Biggi and F.Pietra, J.Chem.Soc., Perkin Trans I, 1980 (1973).
20. E.Buncel and J.G.K.Webb, J.Amer.Chem.Soc., 95, 8470 (1973).
21. J.Murto, Suomen Kemistilehti B, 38, 255 (1965).
22. C.F.Bernasconi and C.L.Gehriger, J.Amer.Chem.Soc., 96, 1092 (1974).
23. M.R.Crampton, Adv.Phys.Org.Chem., 7, 211 (1969).
24. M.J.Strauss, Chem.Rev., 70, 667 (1970).
25. G.Illuminati and F.Stegel, Tetrahedron Lett., 4169 (1968).
26. P.Bemporad, G.Illuminati and F.Stegel, J.Amer.Chem.Soc., 91, 6742 (1969).
27. M.E.C.Biffin, J.Miller, A.G.Moritz and D.B.Paul, Aust.J.Chem., 22, 2561 (1969).
28. M.R.Crampton and V.Gold, J.Chem.Soc., 4293 (1964).
29. R.Foster and C.A.Fyffe, Rev.Pure Appl.Chem., 16, 61 (1966).
30. R.Destro, C.Gramaccioli and M.Simonetta, Acta Crystallogr., 24, 1369 (1968).
31. T.Abe, Bull.Chem.Soc.Jap., 37, 508 (1964).
32. T.Abe, Bull.Chem.Soc.Jap., 39, 627 (1966).
33. P.Caveng, P.B.Fisher, E.Heilbronner, A.L.Miller and H.Zollinger, Helv.Chim.Acta, 50, 848 (1967).
34. H.Hosoya, S.Hosoya and S.Nagakura, Theor.Chim.Acta., 12, 117 (1968).
35. J.A.Zoltewicz and L.S.Helmick, J.Amer.Chem.Soc., 94, 682 (1972).
36. J.A.Zoltewicz, L.S.Helmick, T.M.Oestreich, R.W.King and P.E.Kandetzki, J.Org.Chem., 38, 1947 (1973).
37. P.J.Lont, H.C.van der Plas and A.van Veldhuizen, Recl.Trav.Chim. (Pays-Bas), 92, 708 (1973).
38. D.D.Perrin, J.Chem.Soc., 645 (1962).
39. A.Albert and H.Mizuno, J.Chem.Soc. (B), 2423 (1971).
40. A.Albert and K.Ohta, J.Chem.Soc. (C), 2357 (1971).
41. A.Nagel, H.C.van der Plas and A.van Veldhuizen. Recl.Trav.Chim.(Pays-Bas), 94, 45 (1975).
42. B.E.Evans, J.Chem.Soc., Perkin Trans I, 357 (1974).

43. U.Ewers, H.Günther and L.Jaenicke, Angew.Chem.internat.Edit., 14, 354 (1975).
44. J.P.Geerts, A.Nagel and H.C.van der Plas, Org.Magn.Reson., 8, 607 (1976).
45. E.A.Oostveen, H.C.van der Plas and H.Jongejan, Recl.Trav.Chim.(Pays-Bas), 93, 114 (1974).
46. J.P.Geerts, H.C.van der Plas and A.van Veldhuizen, Org.Magn.Reson., 7 86 (1975).
47. D.E.Klinge and H.C.van der Plas, Recl.Trav.Chim.(Pays-Bas), 94, 233 (1975).
48. D.E.Klinge, H.C.van der Plas and A.van Veldhuizen, Recl.Trav.Chim. (Pays-Bas), 95, 21 (1976).
49. J.A.Zoltewicz, T.M.Oestreich, J.K.O'Halloran and L.S.Helmick, J.Org.Chem., 38, 1949 (1973).

2 NMR evidence for the occurrence of σ-addition complexes in reactions of 4-chloropyrimidines with potassium amide in liquid ammonia

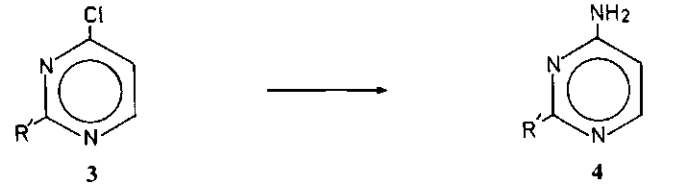
J.P.Geerts, H.C.van der Plas and A.van Veldhuizen

2.1 INTRODUCTION

Several years ago it was found in this laboratory that the 4-chloro derivatives of 2-methyl-, 2-ethyl-, 2-phenyl-, 2-N-methylanilino-, 2-N,N-dimethylamino-, 2-morpholino- and 2-piperidinopyrimidine (1) are converted into the corresponding 2-substituted 4-methyl-*s*-triazines (2) when treated with potassium amide in liquid ammonia at -33° [1,2,3].
By means of tracer experiments, using 4-chloro-2-phenylpyrimidine-4-^{14}C, evidence was presented[4] that in these ring transformations the initial attack of the amide ion takes place on position 6 and not on position 4, which carries the chlorine atom. No intermediates could ever be isolated, but it was established[3] that in these ring transformations an ethynyl derivative must be present as an intermediate.

1 2

R = CH_3, C_2H_5, C_6H_5, $N(CH_3)C_6H_5$, $N(CH_3)_2$,



3 4

R′ = $NHCH_3$, NHC_6H_5, $CH_2C_6H_5$

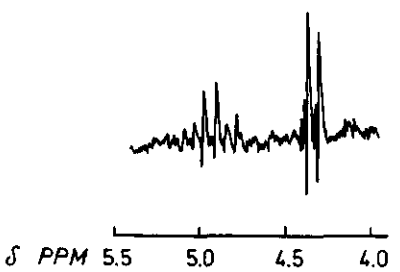
Interestingly, it was further found[2], that when the substituent present in position 2 of the pyrimidine nucleus bears an acidic hydrogen atom α to the aromatic ring i.e. (3), instead of *s*-triazines, the corresponding 4-amino 2-substituted pyrimidine compounds (4) are the sole reaction products.

2.2 RESULTS AND DISCUSSION

We now wish to present additional evidence that the ring transformation reaction leading to the 4-methyl-2-substituted *s*-triazines can proceed via initial attack of the nucleophilic amide ion on position 6.
When the 4-chloropyrimidine (1) is dissolved in a solution of 2 equivalents of potassium amide in liquid ammonia and this solution is examined by NMR spectroscopy at -38°, the NMR spectrum has changed in two ways with respect to the spectrum of the starting material measured in $CDCl_3$, CCl_4 or $(CD_3)_2CO$[5] (see Table):

i the signals of the two aromatic hydrogen atoms H-5 and H-6 undergo an upfield shift of 2.35-2.89 ppm and 3.41-3.65 ppm respectively;

ii the H-6 doublet (J = 5.5 Hz) observed in these solvents is found to be split further in the potassium amide - liquid ammonia system into a triplet (J = 7.5 Hz).



NMR-signals of the H_5 and H_6 protons in adduct 5 (R = C_6H_5).

These two effects i.e. the large upfield shift of both the H-5 and H-6 proton and the doublet-triplet splitting pattern of H-6 strongly indicate the existence of a 1:1 σ- complex (5), formed by addition of the amide ion to position 6. Although adduct formation between aromatics or heteroaromatics with nucleophiles has been known for a long time[6,7], only very recently the existence of adducts of unsubstituted diazines with potassium amide

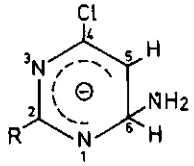
Table

Chemical shifts (δ) of the protons in adduct (5), compared with those of the corresponding parent compound (1).

Substituent in position 2	δ_{H_5} in (KNH_2/NH_3)*	δ_{H_5} in solvent indicated by a, b or c	$\Delta\delta H_5$	δ_{H_6} in (KNH_2/NH_3)*	δ_{H_6} in solvent indicated by a, b or c	$\Delta\delta H_6$
phenyl	4.30 (d)	7.19[a]	2.89	4.90 (d-t)	8.55[a]	3.65
morpholino	4.02 (d)	6.37[a]	2.35	4.70 (d-t)	8.20[a]	3.50
piperidino	3.97 (d)	6.48[b]	2.51	4.72 (d-t)	8.20[b]	3.48
dimethylamino	3.97 (d)	6.45[c]	2.48	4.75 (d-t)	8.17[c]	3.42
N-methylanilino	4.20 (d)	6.58[c]	2.38	4.75 (d-t)	8.16[c]	3.41
methylamino	5.52 (d)	6.55[c]	1.03	7.67 (d)	8.19[c]	0.52
anilino	5.51 (d)	6.86[b]	1.35	7.86 (d)	8.40[b]	0.54

[a] Measured in CCl_4.
[b] Measured in hexadeuteroacetone.
[c] Measured in $CDCl_3$.
d = doublet.
d-t = doublet-triplet.
* The chemical shifts have been measured against trimethylamine as internal standard having δ = 2.13 ppm.

in liquid ammonia has been proved[8,9].



5

In contrast, the NMR spectrum of a solution of a 4-chloro-2-substituted pyrimidine (3) in liquid ammonia containing 2 equivalents of potassium amide, does *not* show the characteristic doublet-triplet splitting pattern of H-6.

An upfield shift is observed for both the H-5 and H-6 doublets (shifts ∿ 1.2 ppm and ∿ 0.5 ppm respectively (see Table)). This seems to be reasonably explained by the formation of a negatively charged pyrimidine nucleus, generated by the abstraction of the acidic hydrogen from the substituent present in the 2-position[10]. The magnitude of these upfield shifts is in agreement with those observed for solutions of 2-methylpyridine, 2-aminopyridine and pyridone-2 in potassium amide - liquid ammonia[11]. This result unambiguously indicates that in this solution a long lived σ-complex such as (5) does not exist. Considering the mechanism of the formation of the 4-amino derivative (4) we propose that an addition of the amide ion to position 4 of the anion takes place leading to a dianionic 1:1 adduct. That addition of an amide ion to an anionic compound can take place is in agreement with the well-known fact that ionisation of a group α to the aromatic ring (e.g. - NH_2, - CH_3) considerably hinders[12] the addition of the amide ion, but does not exclude it[10a]. Assuming that the substitution reaction occurs *via* an $S_N(AE)$-mechanism and since the NMR-spectrum of these solutions only shows the peaks of the anionic starting material and not those of such a dianionic 1:1 adduct, it suggests that the formation of that adduct may well be rate-determining.

2.3 REFERENCES

1. H.C.van der Plas, B.Haase, B.Zuurdeeg and M.C.Vollering, Recl.Trav.Chim. Pays-Bas 85, 1101 (1966).
2. H.C.van der Plas and B.Zuurdeeg, Recl.Trav.Chim.Pays-Bas 88, 426 (1969).
3. H.C.van der Plas, B.Zuurdeeg and H.W.van Meeteren, Recl.Trav.Chim. Pays-Bas 88, 1156 (1969).
4. H.W.van Meeteren and H.C.van der Plas, Recl.Trav.Chim.Pays-Bas 86, 15 (1967).
5. The NMR-spectra of the starting material have been measured in these solvents since the solubility of the initial compound in pure liquid ammonia is too low to take a reference spectrum. It is known[8] that the change of chemical shift when changing the solvent from chloroform to liquid ammonia is in general small. The spectra were obtained with a Jeol JNM C 60 H spectrometer, equipped with a JES-VT-3 variable temperature controller at -38^{o}.
6. M.R.Crampton and V.Gold, J.Chem.Soc., 4293 (1964); J.Chem.Soc.(B), 893 (1966).
7. See for review articles M.J.Strauss, Chem.Rev. 70, 667 (1970) and M.R.Crampton, Adv.Phys.Org.Chem. 7, 211 (1969).
8. P.J.Lont, H.C.van der Plas and A.van Veldhuizen, Recl.Trav.Chim.Pays-Bas 92, 708 (1973).
9. J.A.Zoltewicz and L.S.Helmick, J.Amer.Chem.Soc. 94, 682 (1972).
10. a T.Birchall and W.Jolly, J.Amer.Chem.Soc. 88, 5439 (1966);
    b T.Birchall and W.Jolly, J.Amer.Chem.Soc. 87, 3007 (1965).
11. J.A.Zoltewicz and L.S.Helmick, J.Org.Chem. 38, 658 (1973).
12. F.W.Bergstrom, J.Amer.Chem.Soc. 53, 3027 (1931); F.W.Bergstrom, J.Org.Chem. 3, 233 (1938).

3 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

3.1 INTRODUCTION

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

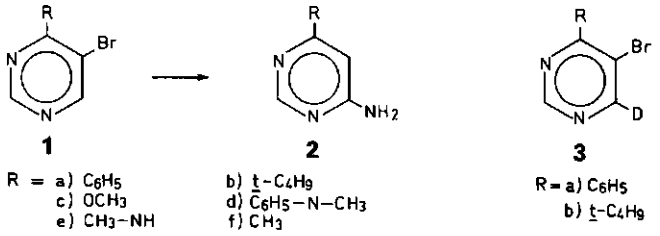


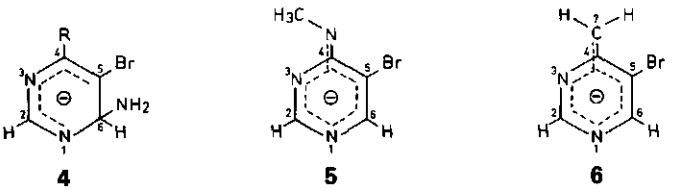
Fig. 1

Occurrence of a 5,6-didehydropyrimidine intermediate in the formation of 2 was suggested on the basis of experiments with the 6-D-labelled pyrimidines 3. It was shown that with these compounds in this basic medium no D/H 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.

3.2 RESULTS AND DISCUSSION

Recent PMR-studies on substituted azaaromatics[4,5,6,7] 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. On dissolving the pyrimidines 1a-1d in liquid ammonia, containing 2 equivalents of KNH_2, 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 and (iii) in some cases the reaction product 2. Absorptions from unreacted

starting materials are not detected in any of the experiments.



4 **5** **6**

Fig. 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 $CDCl_3$. 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).

(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.3).

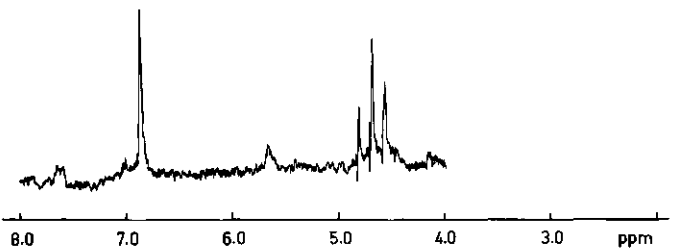


Fig. 3

These results are consistent with those published in the literature[4-6] and are summarized in the Table.

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

	$CDCl_3$*			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

* All spectra measured in $CDCl_3$ were taken at 27°C.
s = singlet, t = triplet.

The immediate conversion of the 5-bromopyrimidines 1a-1d into the σ-adducts 4 in KNH_2/liquid ammonia provides us with a new explanation for the lack of D/H 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 KNH_2/liquid ammonia is completely different from those of 1a-1d, since it shows only absorptions of the solvent and the ionized substrate 5. 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 $CDCl_3$ (see Table). Despite the lack of a "PMR-visible" adduct, however, 1e reacts slowly with KNH_2 to give 2e*.

The PMR-spectrum of a solution of 5-bromo-4-methylpyrimidine (1f) in liquid ammonia, containing two equivalents of potassium amide (Fig.4), 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.

* On allowing the reaction to proceed to completion one product could be isolated. PMR and mass-spectroscopic data on this substance are fully consistent with the structure 2e.

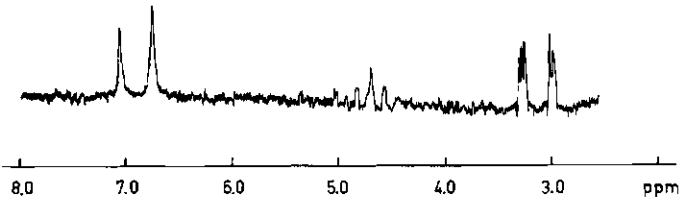


Fig. 4

The methylene group, appearing as a methyl singlet in the spectrum of 1f in $CDCl_3$, 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[9,10]. The CH_3 signal 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 containing 90% of D at position 6 in KNH_2/liquid ammonia**. Two phenomena are observed. First, as expected, the H-6 triplet signal virtually disappears. Secondly the concentration ratio of anion to σ-complex changes from 3:1 for the hydrogencontaining compounds 6 and 4f into 1:2 for

** Oxidation of 5-bromo-6-hydrazino-4-methylpyrimidine by silver acetate in D_2O did not give 5-bromo-6-deuterio-4-methylpyrimidine[11] but 5-bromo-6-deuterio-4-(trideuteriomethyl)pyrimidine.

the deuteriumcontaining 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.

3.3 EXPERIMENTAL

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 $CDCl_3$ were obtained with a JEOL JNM C-60H spectrometer using tetramethylsilane (TMS, δ= 0) as an 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.

3.3.1 Starting materials

5-Bromo-4-phenylpyrimidine (1a)[11], *5-bromo-4-*tert*-butylpyrimidine* (1b)[11], *5-bromo-4-methylpyrimidine* (1f)[11] 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-*tert*-butylpyrimidine* (3b) and *5-bromo-6-deuterio-4-(trideuteriomethyl)pyrimidine* (1f, R=CD_3H_6=D) were prepared by procedures described for the non-deuterated compounds (cf. note**; ref. 11 and ref.2, note d).

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

550 mg (5.1 mmoles) of freshly distilled *N*-methylaniline were added to a solution of 500 mg (2.5 mmoles) of 5-bromo-4-chloropyrimidine[12] in 8 ml of ethanol (abs). After standing overnight at room temperature the mixture was kept at 0-5°C 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.
$C_{11}H_{10}BrN_3$(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 mmoles) of 5-bromo-4-chloropyrimidine[12] in 2 ml of ethanol was added drop by drop over 30 min to 5 ml of a 30% solution of methylamine in ethanol, maintaining the temperature at 0°C. 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°C), yielding 0.75 g (80%) of 1e, m.p. 128-129°C.
$C_5H_6BrN_3$(188.04); calcd. C 31.93, H 3.22; found C 31.7, H 3.2.

3.3.2 General procedure for measuring the PMR-spectra in KNH_2/liquid NH_3

10 ml of dry liquid NH_3 were condensed in a 50 ml three-neck round-bottomed flask, equipped with a Dry Ice/acetone condenser. 10 mmoles of potassium and a few crystals of $Fe(NO_3)_3 \cdot 9H_2O$ catalyst were added. After stirring for 30 min at -33°C 5 mmoles of substrate 1a-1f were introduced at the appropriate reaction temperature (see Table). 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°C (see Table). Trimethylamine was used as an internal standard (δ = 2.13 ppm).

3.4 REFERENCES

1. H.C.van der Plas and G.Geurtsen, Tetrahedron Letters, 2093 (1964).
2. H.C.van der Plas, P.Smit and A.Koudijs, Tetrahedron Letters, 9 (1968).
3. Cf. note 5 in H.C.van der Plas and A.Koudijs, Recl.Trav.Chim.(Pays-Bas) 89, 129 (1970).
4. P.J.Lont, H.C.van der Plas and A.van Veldhuizen, Recl.Trav.Chim. (Pays-Bas) 92, 708 (1973).
5. J.P.Geerts, H.C.van der Plas and A.van Veldhuizen, Recl.Trav.Chim. (Pays-Bas) 92, 1232 (1973).
6. J.A.Zoltewicz, L.S.Helmick, T.M.Oestreich, R.W.King and P.E.Kandetzki, J.Org.Chem. 38, 1947 (1973).
7. J.A.Zoltewicz and L.S.Helmick, J.Org.Chem. 38, 658 (1973).
8. W.Adam, A.Grimison and R.Hoffmann, J.Amer.Chem.Soc. 91, 2590 (1969).
9. R.A.Ogg, Jr., Discuss.Faraday Soc. 17, 215 (1954).

10. D.R.Cluther and T.J.Swift, J.Amer.Chem.Soc. 90, 601 (1968).
11. H.C.van der Plas, Recl.Trav.Chim.(Pays-Bas) 84, 1101 (1965).
12. J.Chesterfield, J.F.W.McOmie and E.R.Sayer, J.Chem.Soc., 3478 (1955).

4 Carbon-13 nuclear magnetic resonance investigation on σ-adduct formation of pyrimidine and some of its derivatives with potassium amide in liquid ammonia

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

4.1 INTRODUCTION

The existence of σ-addition complexes between 6-membered diazaaromatics and amide ions in liquid ammonia has been established by means of ^{1}H NMR spectroscopy, both in this laboratory[1-3] and by others[4].
These spectroscopic results unequivocally show that the addition of an amide ion always takes place in a position adjacent to the nitrogen. Very interestingly, in halogeno-diazaaromatics, in which the halogen atom is present in a position adjacent to the nitrogen, the amide ion adds to the carbon atom *not* bearing the halogen atom, i.e. position 6 in 4-halogeno-pyrimidines, position 5 in 2-chloropyrazines. Since σ-adduct formation between 4-halogenopyrimidines and the amide ion plays an important role in pyrimidine ring interconversions and nucleophilic substitutions, it is of great interest to compare the results obtained by ^{1}H NMR spectroscopy with the relatively new technique of ^{13}C NMR spectroscopy. To our knowledge no data concerning ^{13}C NMR spectroscopy of σ-adducts, either in the benzene or in the heteroaromatic field of chemistry, have yet been published.

4.2 RESULTS AND DISCUSSION

4.2.1 Parent compounds

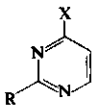
Before measuring the ^{13}C NMR spectra in KNH_2/NH_3, the ^{13}C spectra of the following parent compounds were recorded, using deuterochloroform as solvent: (i) 2-substituted pyrimidines (1f) to (1j), (3c), (3d); (ii) 4-chloropyrimidine (11); (iii) 4-chloro-2-substituted pyrimidines (1a) to (1e), (3a), (3b). All data are collected in the Table.
The C-5 ^{13}C resonance in 1a to 1d, and 3a and 3b is found to be more shielded than that of 4-chloropyrimidine (11) in contrast to the resonances of the carbons at positions 4 and 6. This is apparent because of the electron - donating capability of the substituted amino group, enhancing the electron density at C-5, located *para* to the substituent. The same effect of the amino substituent is observed on comparing the ^{13}C spectra of the nonhalo-

genated compounds (1f to 1i, 3c and 3d) with that of pyrimidine (1k). The data are consistent with those measured in 2-substituted pyridines[5]. Distinction between ^{13}C resonances of C-6 on the one hand and C-2 and C-4 on the other in the 2-substituted 4-chloro starting materials (1a to 1e, 3a and 3b), was achieved by recording the spectra of these compounds nonproton decoupled, and also by comparison of the proton decoupled spectra of 1a to 1e, 3a and 3b (see Table) with those of the 2-substituted pyrimidines (1f to 1j, 3c and 3d), in which assignment between C-2 and C-4,6 is easily made on account of the peak intensities, as well as the nonproton decoupled spectra.

In order to distinguish further between the very close lying ^{13}C absorptions of C-2 and C-4 in the 2-substituted 4-chloropyrimidines (1a to 1e, 3a and 3b), measured in $CDCl_3$, we investigated the substituent additivity relationship. The shielding effects exerted by the substituents R in position 2 on C-2 and C-4 of the pyrimidine ring were determined by comparing the spectra of the 2-substituted pyrimidines (1f to 1j, 3c and 3d) with the data for pyrimidine (1k) itself. The substituent effect of the chloro atom in position 4 on C-2 and C-4 was obtained by comparing 4-chloropyrimidine (11) with pyrimidine (1k). The combined shielding increments allowed us to calculate the shieldings of C-2 and C-4 of the 4-chloro-2-substituted pyrimidines. These calculated shifts showed good agreement with the measured shifts. For the C-2 absorptions they only differ by 0.1 ppm, except for 4-chloro-2-phenylpyrimidine (1e) where a deviation of 1.1 ppm is found. The values calculated for the C-4 absorptions exhibit a somewhat larger difference (0.2 to 0.8 ppm) compared with the experimentally determined figures. These reasonable agreements make the C-2 and C-4 assignments quite reliable.

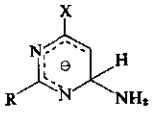
4.2.2 Adducts

When compounds 1a to 1k were dissolved in liquid ammonia containing two equivalents of KNH_2, ^{13}C spectra of these solutions showed in all cases the presence of the σ-adduct (2); no trace of compound 1 could be detected. Neglecting the signals arising from the substituents in position 2, the spectra of the adducts 2a to 2k show a very uniform pattern, in that the shieldings of the corresponding carbon atoms in the class of compounds 1a to 1e and 1f to 1k only differ by a few ppm.



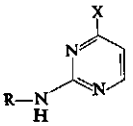
(1)

(a): R = $N(CH_3)_2$; X = Cl
(b): R = $N(CH_3)C_6H_5$; X = Cl
(c): R =  X = Cl
(d): R =  X = Cl
(e): R = C_6H_5; X = Cl
(f): R = $N(CH_3)_2$; X = H



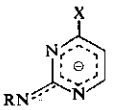
(2)

(g): R = $N(CH_3)C_6H_5$; X = H
(h): R =  X = H
(i): R =  X = H
(j): R = C_6H_5; X = H
(k): R = H; X = H
(l): R = H; X = Cl



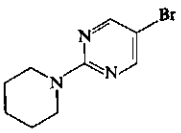
(3)

(a): R = CH_3; X = Cl
(b): R = C_6H_5; X = Cl

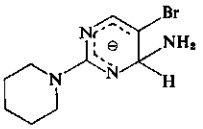


(4)

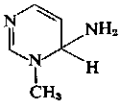
(c): R = CH_3; X = H
(d): R = C_6H_5; X = H



(5)



(6)



(7)

All carbon atoms are shifted upfield compared with the shieldings of corresponding atoms of the parent compounds 1 in chloroform. This upfield shift has the order C-6 > C-5 > C-4 > C-2. The enormous upfield shift of C-6 (91 to 94 ppm) is striking and must be ascribed to rehybridisation of C-6 ($sp^2 \rightarrow sp^3$) on adduct formation. This value is in excellent agreement with the shielding difference of ∿ 90 ppm resulting from the rehybridisation change $sp^2 \rightarrow sp^3$ estimated by comparing the chemical shifts of the α-carbon atoms in styrene and in toluene[6-8]. This supports well the formation of σ-adduct 2 from the pyrimidine (1) and the amide ion, as originally established from the ^{1}H NMR data of the adducts 2a to 2e[2]. In accordance with these

data is the change of J(C-6 — H) upon rehybridisation. In $CDCl_3$ for 4-chloro-2-phenylpyrimidine (1e) we find J(C-6 - H)= 180 Hz, while in the adduct 2e a value of J(C-6 — H)= 150 Hz is observed. For pyrimidine itself these values are 182 Hz[9] and 147 Hz, respectively. To establish finally that the resonances from C-5 and C-6 in the σ-adduct (2) have been assigned correctly, a selective decoupling experiment was performed with the σ-adduct of 4-chloro-2-phenylpyrimidine and the amide ion. On irradiation of νH-6, the doublet arising from C-6 at δ = 66.8 ppm collapses into a singlet, while the same happens with the doublet from C-5 at δ = 88.9 ppm on irradiation of νH-5. These changes in the splitting pattern indicate that the signal at higher field originates from C-6. Because of the great similarity of the spectra of adducts 2 this finding is assumed to be valid for all adducts measured.

When compounds 3a to 3d were dissolved in KNH_2/NH_3, a ^{13}C spectrum quite different from σ-adduct 2 was obtained. Comparing the ^{13}C resonances of the anions 4a to 4d with those of the starting materials, C-2 was now somewhat deshielded ($\sim$ 4 to 5 ppm), C-4 (in 4a) and C-5 shielded (C-5 > C-4) and the resonance from C-6 nearly unchanged. Thus the large upfield shift of C-6, as observed in the adduct 2, is not found. These data are consistent with the formation of anion 4 and confirm results obtained earlier[2]. The relatively large upfield shift of C-5 reflects the enhancement of charge in the pyrimidine nucleus, brought about by the anionic amino group in position 2, strongly affecting the *para* related carbon atom C-5. Comparing the C-5 data for 4a, 4c R = CH_3 with those for 4b, 4d R = C_6H_5 the latter absorb at lower field, reflecting the better capability of the phenyl group to accommodate charge compared with the methyl group. In contrast to 4d, in which C-4 and C-6 are equivalent, 4c shows discrete signals for these carbon atoms (157.9 and 157.5 ppm), indicating that due to the partial double bond character of the C-2 — methylamino bond brought about by the N—H ionisation, the rotation round this bond has become considerably hindered. This has been confirmed by ^1H NMR spectroscopy. Under the same circumstances 4c shows, besides a triplet for H-5, a multiplet for H-4 and H-6 resulting from an ABX system formed by H-4, H-6 and H-5.

That the hindered rotation of a ring substituent can remove the equivalence of *meta* oriented ring protons, is in accordance with results obtained on α,α, 2,4,6-pentachlorotoluene[10].

The ^{13}C spectrum of 5-bromo-2-piperidinopyrimidine (5) has also been studied.

It was observed that the 5-bromo substituent has a *shielding* effect on C-5, in contrast to the *deshielding* of C-4 brought about by the 4-chloro substituent in the 4-chloro-2-substituted pyrimidines, but in accordance with the substituent effect of the bromo substituent in the benzene series[11]. In a solution of KNH_2/NH_3 compound 5 forms the σ-adduct 6 shown by the considerable shielding of C-6. Furthermore the data of the σ-adduct 6 are fully consistent with those of the σ-adducts 2a to 2k. These results are in agreement with those found earlier with ^1H NMR spectroscopy. Finally, the addition of ammonia to the quaternary salt *N*-methylpyrimidinium methyl sulphate was established by ^{13}C NMR spectroscopy. Interestingly, the chemical shifts of the tetrahedral carbon atom C-6 in the *anionic* σ-adduct of pyrimidine with the amide ion 2k and in the *neutral* σ-adduct 7 only differ by 0.4 ppm, indicating that the electron density on these carbon atoms is essentially identical.

TABLE

	C-2		C-4		C-5		C-6	
	Compound 1	Adduct 2	Compound 1	Adduct 2	Compound 1	Adduct 2	Compound 1	Adduct 2
(a)	162·3	161·2	161·1	147·8	108·3	86·2	158·7	67·3
(b)	161·9	159·3	161·0	146·4	110·2	88·1	158·8	67·1
(c)	161·6	160·0	161·2	147·7	108·3	86·0	158·8	67·1
(d)	161·7	160·1	161·4	147·4	109·6	86·8	158·9	66·8
(e)	165·6	158·2	161·6	147·4	119·3	88·9	158·3	66·8
(f)	162·6	162·2	157·6	141·5	109·0	94·2	157·6	64·7
(g)	162·3	160·6	157·7	140·9	110·8	96·5	157·7	64·7
(h)	162·0	161·2	157·7	141·5	109·2	94·3	157·7	64·6
(i)	162·1	161·0	157·8	141·3	110·3	94·8	157·8	64·4
(j)	165·0	158·5	157·3	141·2	119·1	97·0	157·3	63·2
(k)	159·6[a]	156·7	157·6[a]	140·5	122·5[a]	98·0	157·6[a]	62·5
(l)	159·1	—	161·4	—	122·3	—	158·3	—
	Compound 5	Adduct 6	Compound 5	Adduct 6	Compound 5	Adduct 6	Compound 5	Adduct 6
	160·2	159·5	158·0	141·5	105·0	95·6	158·0	70·3
		7		7		7		7
		150·3		134·8		108·2		62·9
	Compound 3	Anion 4	Compound 3	Anion 4	Compound 3	Anion 4	Compound 3	Anion 4
(a)	163·0	166·1	161·1	158·4	109·7	96·3	159·3	159·4
(b)	160·3	[b]	161·6	[b]	112·2	100·3	159·1	159·5
(c)	163·4	167·1	158·1	157·9	110·3	98·7	158·1	157·5
(d)	160·7	165·3	158·1	158·1	112·5	103·0	158·1	158·1

[a] Measured as neat liquid, taken from Ref.6, p.240.

[b] Because of the low solubility in KNH_2/NH_3 of 3b no signals of C-2 and C-4 could be detected. The greater intensity, due to the shorter relaxation time, of C-5 and C-6 and the stronger NOE influence make the signals from *these* carbon atoms easily discernible.

4.3 EXPERIMENTAL

All carbon spectra were obtained with a Varian XL-100-15 spectrometer operating at 25.2 MHz. The spectrometer was equipped with a Varian Fourier transform unit. The pulse separation was chosen as 20s, because of the slow relaxation of the substituted carbon atoms in position 2.
The spectral width was 5000 Hz (1.25 Hz/point). For most of the spectra proton noise decoupling was utilised. In $CDCl_3$ solutions, ^{13}C chemical shifts were measured from internal TMS, while in ammonia solutions ^{13}C chemical shifts were measured from internal $(CH_3)_3N$ and were converted to the TMS scale by adding 47.5 ppm. The $CDCl_3$ solvent was used as field-frequency lock; in the case of liquid ammonia as solvent field-frequency lock was based on the ^{19}F NMR signal of a capillary of hexafluorobenzene positioned along the longitudinal axis of the 12 mm (o.d.) sample tubes employed. The probe temperature when measuring samples in liquid ammonia was $-50^{o}C$.
The technique of preparation of the solutions in liquid ammonia have been described earlier[1].
Compounds 1a to 1f, 1h, 1j to 1l, and 3a to 3d were prepared according to procedures given in the literature[12].
5-Bromo-2-piperidinopyrimidine (5) was synthesised from 2-piperidinopyrimidine by bromination according to the method described for the bromination of 4,6-dimethyl-2-piperidinopyrimidine[13]. Yield 96%; m.p. 57 to $58^{o}C$.
2-Morpholinopyrimidine (1i) was prepared from 2-chloropyrimidine and morpholine according to the procedure given for the preparation of 4,6-dimethyl-2-morpholinopyrimidine[14]. Yield 80%, (145^{o}/21 mm Hg).
2-Methylanilinopyrimidine (1g). 2-Chloropyrimidine was heated at $100^{o}C$ with an excess of freshly distilled *N*-methylaniline for 2 h. The dark brown reaction mixture was poured into 1 N HCl. This solution was neutralised (pH=7) and extracted with ether. The residue obtained after evaporation of the solvent was distilled *in vacuo* to remove the excess of *N*-methylaniline.The resulting residue was again distilled *in vacuo* to give the 2-methylanilinopyrimidine. Yield 65%, (166^{o}/14 mm Hg).

4.4 REFERENCES

1. J.P.Geerts, C.A.H.Rasmussen, H.C.van der Plas and A.van Veldhuizen, Rec.Trav.Chim. 93, 231 (1974).
2. J.P.Geerts, H.C.van der Plas and A.van Veldhuizen, Rec.Trav.Chim. 92, 1232 (1973).
3. P.J.Lont, H.C.van der Plas and A.van Veldhuizen, Rec.Trav.Chim. 92, 708 (1973).
4. J.A.Zoltewicz and L.S.Helmick, J.Amer.Chem.Soc. 94, 682 (1972).
5. H.L.Retcofsky and R.A.Friedel, J.Phys.Chem. 72, 2619 (1968).
6. J.B.Stothers, in A.T.Blomquist and H.Wasserman (Ed.), Organic Chemistry. Vol. 24, Carbon-13 NMR Spectroscopy, Academic Press, New York, 1972, p. 211.
7. R.Waack, M.A.Doran, E.B.Baker and G.A.Olah, J.Amer.Chem.Soc. 88, 1272 (1966).
8. R.Waack, L.D.McKeever and M.A.Doran, Chem.Commun., 117 (1969).
9. G.S.Reddy, R.T.Hobgood Jr and J.H.Goldstein, J.Amer.Chem.Soc. 84, 336 (1962).
10. B.J.Fuhr, B.W.Goodwin, H.M.Hutton and T.Schaefer, Can.J.Chem. 48, 1558 (1970).
11. G.C.Levy and G.L.Nelson, Carbon-13 Nuclear Magnetic Resonance for Organic Chemists, Wiley-Interscience, New York, 1972, p. 81.
12. D.J.Brown in A.Weissberger (Ed.), The Chemistry of Heterocyclic Compounds, Vol. 16, The Pyrimidines, Interscience, New York, 1962.
13. T.Nishiwaki, Tetrahedron 22, 2401 (1966).
14. D.Brown and J.Lyall, Australian J.Chem. 17, 794 (1964).

5 ^{13}C and ^{1}H Nuclear Magnetic Resonance Investigations on the Mechanism of the Ring Transformation Reaction of Pyrimidines into s-Triazines

J.P.Geerts and H.C.van der Plas

5.1 INTRODUCTION

Several papers have been published yet concerning σ-adduct formation between the nucleophilic amide ion and the parent diazines[1], as well as some of their derivatives, containing a leaving group (Cl, Br, SCH_3, SO_2CH_3)[2-6]. The results of these studies show that in the absence of a leaving group, the σ-complex is stable and does not undergo a subsequent reaction[1,3], but that in the presence of such a leaving group however, further reactions beyond the stage of the σ-adduct can occur[2-6].

A reaction which has attracted our interest for several years is the ring transformation of 2-substituted 4-chloropyrimidines into 2-substituted 4-methyl-s-triazines by potassium amide in liquid ammonia[7]. ^{1}H and ^{13}C-NMR spectroscopy indicated that the first step in this ring interconversion is the formation of a 1:1 anionic σ-complex 2a in which the amide ion is thus not attached to C-4, the carbon bearing the halogen substituent, but to C-6[3,4]. More examples of this unexpected addition behaviour have been found with other diazines[2,6].

We have investigated by ^{13}C-NMR spectroscopy two reactions in particular i.e. the ring transformation of 4-chloro-2-dimethylaminopyrimidine (1a) into 2-dimethylamino-4-methyl-s-triazine (5a)(yield 80% with potassium amide) and of the hitherto unknown conversion of 4-chloro-2-dimethylamino-5-phenyl-pyrimidine (1b) into 4-benzyl-2-dimethylamino-s-triazine (5b)(yield 60% with potassium amide),specially aiming to obtain information about intermediates beyond the stage of the σ-adducts.

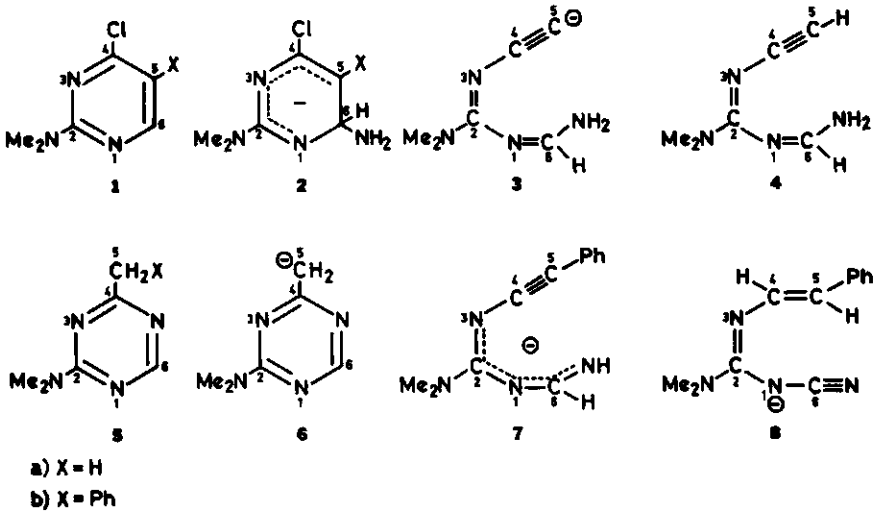
5.2 RESULTS AND DISCUSSION

4-chloro-2-dimethylaminopyrimidine (1a)

From the results of our studies we reached the conclusion that the conversion of 1a into 5a occurs by the following reaction sequence
1a → 2a → 3 → 4 → 5a (see Scheme 1).

Table Summary of the ^{13}C chemical shifts of the starting materials 1a, 1b and intermediates and end-products, obtained in the reaction of 1a, 1b with KNH_2/NH_3

	C-2	C-4	C-5	C-6	$(CH_3)_2N$	solvent
1a	162.3	161.1	108.3	158.7	37.1	$CDCl_3$
1b	161.1	159.1	121.3	158.9	37.1	$CDCl_3$
2a	161.2	147.8	86.2	67.3	37.9	NH_3 liq.
2b	160.3	144.4	95.6	70.8	38.3	NH_3 liq.
3	168.4	113.3	118.5	166.0	39.6	NH_3 liq.
5a	163.7	175.8	25.4	166.0	36.1	NH_3 liq.
5b	164.4	176.6	45.5	165.6	36.1	$CDCl_3$
6	162.4	163.1	66.8	161.7	35.8	NH_3 liq.
	165.9	105.0	59.7	165.1	37.6	NH_3 liq.
7	167.6	104.8	59.4	168.0	37.6	NH_3 liq.
8	162.1	141.7	108.8	124.6	38.3	NH_3 liq.



Scheme 1

Evidence for this mechanism is based on the following data. Addition of 1a to 2 equivalents of potassium amide in liquid ammonia gives the σ-adduct 2a (see Table). Surprisingly we observed that when the excess of potassium amide is raised to 4 equivalents and the reaction time is prolonged, the ^{13}C-NMR spectrum of the resulting reaction mixture is completely different from that of the σ-complex 2a. The new spectral data have been assigned to the intermediary aminoethynyldiazabutadiene anion 3 (see Table). Two sharp signals at δ = 113.3 and δ = 118.5 have been attributed to the acetylenic carbons C-4 and C-5, and two signals at δ = 168.4 (JC-H = 157 Hz) and δ = 166.0 - being broadened - to C-2 and C-6 respectively. The broadening observed for the resonances of C-2 and C-6 may well find its cause in E-Z isomerism around the N-1 - C-6 double bond.

In order to assign C-4 and C-5 in 3 correctly, we acquired ^{13}C-NMR spectral information on the chemical shifts of acetylide anions. It was found by dissolving 3-methoxypropyn ($\overset{1}{H}\overset{2}{C} \equiv \overset{3}{C} - CH_2OCH_3$) in liquid ammonia containing two equivalents of potassium amide, that in the acetylide anion thus formed, the ^{13}C-NMR signals of C-1 and C-2 are shifted downfield 75.7 ppm and 28.2 ppm with respect to the parent compound measured in $CDCl_3$ (74.8 ppm → 150.5 ppm for C-1 and 79.9 ppm → 108.1 ppm for C-2). Distinction between C-1 and C-2 in the acetylide form could be made on the basis of the triplet splitting (^2JC-H = 5.6 Hz) found for C-2 when wide band proton noise decoupling was *not* utilized. A deshielding effect upon anion formation is also found

in a number of organolithium compounds, in which the metallated acetylenic carbons are shifted donwfield with respect to the parent acetylenes[8,9]. Furthermore we compared the ^{13}C-NMR spectrum of ethoxyethyn (δ C-1 = 23.2 and δ C-2 = 89.4[10]) - in this compound the ^{13}C-NMR shifts of the acetylenic carbons are strongly subjected to the +M and -I effects due to the neighbouring oxygen atom - with that of its anion generated in KNH_2/NH_3. In this medium C-1 and C-2 are found to resonate at δ = 116.2 and δ = 72.5 respectively (downfield shifts of 93.0 ppm and 16.9 ppm with respect to the parent compound). These data clearly show that the assignments proposed for C-4 and C-5 in 3 are quite reliable.

Also the ^{1}H-NMR spectrum of a solution, obtained by reaction of 1a with 4 equivalents of KNH_2/NH_3 for 30 min confirms the formation of intermediate 3. Besides the sharp singlet at δ = 2.62 of the dimethylamino substituent, a very broad absorption band around δ = 8 belonging to H-6 is found. Intermediate 3 is found to be stable for at least 5 h under the reaction conditions. Under these conditions no indication for the formation of the ultimate reaction product 2-dimethylamino-4-methyl-s-triazine (5a) could be obtained. However, when the reaction mixture was quenched with ammonium chloride, the ^{13}C-NMR spectrum of that solution had drastically changed and resonance signals appeared that must be ascribed to the presence of the triazine 5a (see Table). Apparently, by the addition of ammonium chloride intermediate 3 is converted to its conjugate acid 4 which easily undergoes the cyclisation into 5a. We have not obtained any evidence for the occurrence of the reverse reaction 5a → 3. In fact when 5a is dissolved in KNH_2/NH_3 anion 6 is formed, as is convincingly shown by the *triplet* splitting found for the side chain carbon C-5. (^1JC-H = 153 Hz) and the considerable downfield shift (27.2 ppm) observed on comparison of the chemical shift of this signal with that of the ^{13}C-NMR signal from the methyl group of 5a, obtained in $CDCl_3$ solution. This downfield shift, together with the value for the ^1JC-H typical for a sp^2 carbon indicates that in species 6 the negative charge is partly delocalized over the s-triazine ring.

4-chloro-2-dimethylamino-5-phenylpyrimidine (1b)

As we have seen the negative charge on C-5 in 3 plays a vital role in the stability of this species, since not 3, but its conjugate acid 4 is found to be able to undergo cyclisation. Therefore we became interested in the influence of a substituent in position 5 of the pyrimidine ring. For that

purpose we chose the phenyl group. Reaction of 4-chloro-2-dimethylamino-5-phenylpyrimidine (1b) with potassium amide in liquid ammonia gave 4-benzyl-2-dimethylamino-s-triazine (5b) (yield 60%), together with only a small amount of 4-amino-2-dimethylamino-5-phenylpyrimidine. The presence of the phenyl group is found to increase substrate reactivity. Therefore, in order to detect intermediate stages, it was necessary to lower the reaction temperature to -60°C. Even at this low temperature we could not avoid that two or more intermediate species were simultaneously present in the reaction mixture, making characterisation of the reaction intermediates by ^{13}C-NMR very troublesome. However, by varying the excess of KNH_2 employed we were able to control the progress of the reaction to some extent. Taking samples at short intervals the rather complex spectra could be analysed, and the rise and fall of three intermediates be monitored.

It was found that when 1 equivalent of KNH_2 is employed first the σ-adduct 2b appears (see Figure). The ^{13}C-NMR chemical shifts of this adduct agree well with those recorded for 2a (see Table). When 1b is reacted with two equivalents of KNH_2 at -60°, the ^{13}C-NMR spectrum of a sample of the reaction mixture shows signals that arise from the anionic (phenylethynyl)amino-diazabutadiene 7. Under those conditions only a small number of weak signals of σ-adduct 2b are observed (see Figure).

Of particular interest is the fact that each of the carbon atoms 2,4,5 and 6 of intermediate 7 show a pair of singlets in approximate 1:2 ratio, indicating the existence of two isomers. In these isomers different values for the C-6 - H-6 coupling constants are found. JC-6 - H = 169.2 Hz and 162.1 Hz for the major and minor signals respectively. Based upon the relatively large chemical shift differences found between the resonance pairs from C-2 and C-6 ($\Delta\delta$ = 1.7 and $\Delta\delta$ = 2.9 resp.) E-Z isomerism around the N-1 - C-6 double bond is proposed, just as has been described for intermediate 3. Which resonance signals belong to the E- or Z-isomer was not determined. C-5 resonates at a somewhat higher field (δ = 59.7) compared with the corresponding nucleus in phenylacetylene (δ = 84.8). The electron donating effect however, exerted by the partly negatively charged N-3 readily accounts for this upfield shift.

In contrast to 1a, the reaction of 1b with KNH_2 does not stop at the stage of 7 : in the presence of a fourfold amount of KNH_2 a new intermediate arises, which we assigned structure 8 (see Figure and Table). From the proton coupled ^{13}C-NMR spectra the presence of two C-H entities can be easily seen; their absorptions at δ = 141.7 and 108.8 ppm are attributed to C-4 and C-5 (JC-H = 152 Hz and 150 Hz respectively). The signal at δ = 124.6

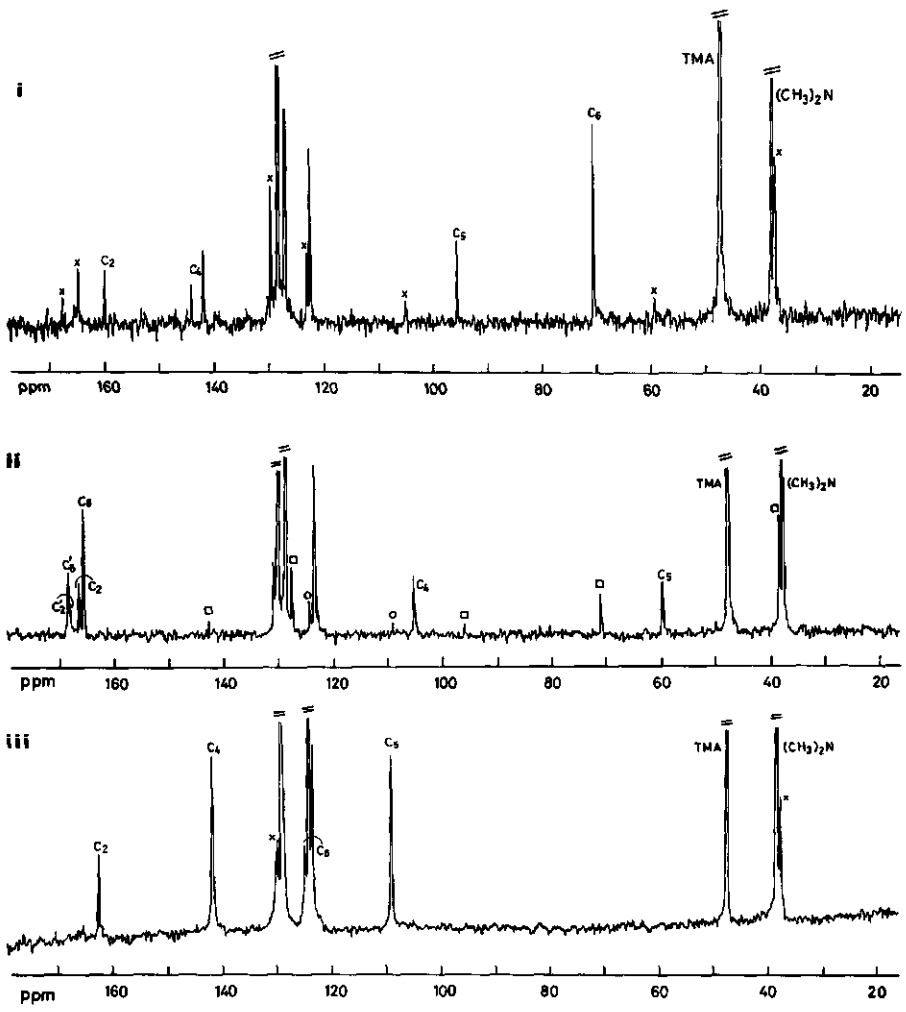
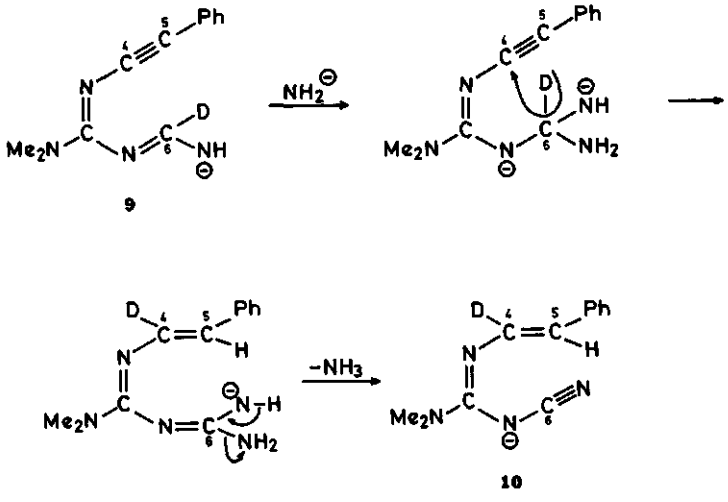


FIGURE: ^{13}C-NMR spectra at 25.2 MHz of reaction intermediates 2b, 7 and 8, taken in liq. NH_3.
(i) signals mainly from 2b; x refers to signals from 7
(ii) signals mainly from 7 ; □ and ○ refer to signals from 2b and 8 respectively
(iii) signals mainly from 8 ; x refers to signals from 7

belongs to the nitrile carbon C-6, thus the signal at δ = 162.1 must originate from C-2. The ^{1}H-NMR spectrum showed an AB pattern, chemical shifts were found at δ = 8.38 and δ = 5.82, showing a coupling constant J = 13.3 Hz. Since interproton coupling is known[11] to have its origin in the indirect intramolecular interaction of nuclear moments through *sigma* bonds, the assumption seems justified that the negative π-charge in intermediate 8 does not affect the value of the JH,H to a significant extent, compared with the uncharged conjugate acid of 8. Comparing the value of the coupling constant of 13.3 Hz with those published for both *cis* and *trans* isomers of uncharged 1,2-disubstituted olefines[12,13], containing methoxy- or amino groups - coupling constants for *cis* isomers range from 6-9 Hz and for *trans* isomers from 12-14 Hz - intermediate species 8 is assumed to possess a *trans* substituted double bond[14].

The formation of 8 takes place from 7. This rearrangement involves an intramolecular redox reaction in which reduction of the triple bond of 7 to a double bond occurs simultaneously with oxidation of the amino substituted C-6. This reaction reminds of the self oxidation-reduction process which aldehydes can undergo in the presence of strong bases. The conversion 7 → 8 can be described to occur by a reversible addition of the amide ion to the C-6 - N-1 double bond. The resulting tetrahedral charged complex can act as a hydride donor and transfers the hydride ion in a six-membered cyclic transition state to C-4. After protonation at C-5 and loss of ammonia 8 is formed (see Scheme 2).



Scheme 2

In order to prove this hypothesis, we synthesized 4-chloro-6-deutero-2-dimethylamino-5-phenylpyrimidine. This substrate was reacted with 2 equivalents of KNH_2, at first to the level of the open-chain compound 9. ^{13}C-NMR spectroscopy of a sample of the reaction mixture showed all resonance signals of 7, except the one, originating from C-6. This is because carbon-deuterium multiplets are very weak, or lost in the noise of ^{13}C-NMR spectra, since they lack nuclear Overhauser effects[15].

Increasing the excess of potassium amide to fourfold, the signals of 10 appear at the expense of 9, but now the resonance signal of C-4 is missing, indicating the presence of deuterium at that position. Supporting evidence for the presence of deuterium at position 4 is obtained by ^{1}H-NMR spectroscopy, showing the absence of the resonance signal from H-4; H-5 now appears as a singlet.

All the data support the proposal of the internal disproportionation type mechanism as a reasonable pathway for the formation of 8 from 7. ^{13}C-NMR spectroscopy of a sample of a reaction mixture containing 8 that has been quenched with ammonium chloride revealed that no cyclisation takes place at this level of the reaction (contrary to what has been found for 3 upon quenching). Only if the solvent ammonia has been evaporated, the s-triazine 5b is formed as is found in the chloroform extract of the resulting residue. The question why 7 undergoes an internal disproportionation into 8 and 3 does *not* , may be explained by the fact that, although the first step in this conversion i.e. addition of the amide ion to C-6 can occur in both species (see Scheme 2), the subsequent hydride transfer to C-4 is prevented by the negative charge present in the acetylene group of 3.

5.3 EXPERIMENTAL

5.3.1 Spectra

^{13}C and ^{1}H-NMR spectra were obtained with a Varian XL-100-15 spectrometer, equipped with a Varian 620/L 16K computer, operating at 25.2 MHz in the FT Mode and at 100.1 MHz in the CW Mode respectively.

In $CDCl_3$ solution the deuterium resonance of the solvent was used as an internal field-frequency lock signal. In the case of liquid ammonia as solvent, field-frequency lock was obtained from the ^{19}F NMR signal of a capillary of hexafluorobenzene positioned along the longitudinal axis of the 12 mm (o.d.) sample tubes employed. Spectra were taken at ambient temperature, but when measuring liquid ammonia samples the probe temperature was -50^{o}.

In $CDCl_3$ solutions ^{13}C and ^{1}H chemical shifts were measured from internal TMS. In NH_3 solutions ^{13}C and ^{1}H chemical shifts were measured from internal trimethylamine and they were converted to the TMS scale by adding 47.5 and 2.13 ppm respectively. Typical ^{13}C spectral parameters were as follows: spectral width 5120 Hz (1.25 Hz/point) acquisition time 0.8 s, pulse delay 1.2 s, pulse width 10 μs. All samples were run as approximately 1 molar solutions in NH_3. The IR spectra were recorded with a Hitachi, model EPI-G. 3. Mass spectra were obtained with an AEI-MS-902 instrument.

5.3.2 Preparation of starting materials

4-chloro-2-dimethylaminopyrimidine (1a) was prepared according to ref.7.

4-chloro-2-dimethylamino-5-phenylpyrimidine (1b)

2-ethylthio-5-phenyl-4-pyrimidone[16] (14.8 g) was heated with dimethylammonium acetate[17] (65 ml) at 160° for 2.5 h. The mixture was left overnight and filtered under suction. The white crystals (13 g, crude 2-dimethylamino-5-phenyl-4-pyrimidone) were twice thoroughly washed with water, dried and subsequently refluxed with freshly distilled phosphorusoxychloride (75 ml) for 2 hours. The excess of phosphorusoxychloride was evaporated and the residue was treated with ice water. The resulting mixture was carefully neutralized with aqueous ammonia ($0° < t < 5°$) and extracted three times with ether. After evaporation of the solvent the residue was distilled *in vacuo* . The fraction boiling between 130 and 135°(0.4 mm Hg) was collected. Yield 11.9 g. Anal.Calcd. for $C_{12}H_{12}ClN_3$: C, 61.7; H,5.2. Found: C, 61.8; H, 5.1.

4-chloro-6-deutero-2-dimethylamino-5-phenylpyrimidine

4,6-dichloro-2-dimethylamino-5-phenylpyrimidine (4.5 g) and hydrazine hydrate (100%)(17 ml) are refluxed in ethanol (40 ml) for 0.5 h. On cooling 3.75 g of 4-chloro-2-dimethylamino-6-hydrazino-5-phenylpyrimidine separate out as white needles (m.p. 127-128° from ethanol). This compound is refluxed in a small volume of CD_3OD, yielding after evaporation of the solvent the hydrazino deuterated starting material. 1.6 g are dissolved in $CDCl_3$ (30 ml) containing CD_3NO_2 (7 ml) as a D-donor and reacted at 40° in an inert atmosphere (N_2) with MnO_2/C [18] (30 g) that is added portion-wise over 2 h. The reaction mixture is kept at 40° for another 0.5 h and then filtered under suction. The residue is washed well with chloroform. The oil obtained after evaporation of the filtrate is purified twice by column chromatography over silica with $CHCl_3$ and benzene-ethylacetate (4:1) respectively as eluent.

Yield 0.5 g. The deuterium content at position 6 was about 90% as determined by ^{1}H-NMR using the signal from the dimethylamino group as an internal standard.

4,6-dichloro-2-dimethylamino-5-phenylpyrimidine

To a boiling mixture of N,N-dimethylguanidine . HCl (24.6 g) in methanol (abs.) (150 ml) containing sodium methoxide (21.6 g) was added under stirring diethyl phenylmalonate (47.2 g). After 4 h reaction time, the mixture is left overnight at ambient temperature. The white precipitate is filtered off and the filtrate is acidified with acetic acid. The resulting voluminous paste is washed with water and dried at 80° over phosphoruspentoxide *in vacuo*. This crude 4,6-dihydroxy-2-dimethylamino-5-phenylpyrimidine is treated with phosphorusoxychloride (360 ml) as described before (See the preparation of 4-chloro-2-dimethylamino-5-phenylpyrimidine).
After evaporation of the excess of phosphorusoxychloride and neutralization, the precipitate is collected and extracted with ether. Evaporation of the solvent afforded a colourless oil, that solidified upon standing. Recrystallization from aqueous ethanol yielded 17.7 g, m.p. 80-81°(lit.[19] 81-82°)(overall yield 33%). Anal.Calcd. for $C_{12}H_{11}Cl_2N_3$: C, 53.7; H, 4.2. Found: C, 53.6; H, 4.4.

5.3.3 Reaction of 1b with potassium amide into 4-benzyl-2-dimethylamino-s-triazine (5b)

20 ml of dry liquid ammonia were condensed in a 50 ml three-neck round-bottomed flask, equipped with a Dry-Ice/acetone condenser. 390 mg potassium and a few crystals of $Fe(NO_3)_3$. 9 H_2O catalyst were added. After stirring for 30 min at reflux temperature 0.58 g 4-chloro-2-dimethylamino-5-phenylpyrimidine (1b) was added at -60°. After 4 h the reaction was quenched with ammonium chloride and the ammonia was evaporated. The residue was extracted with ether and the extract evaporated to dryness. Separation from the by-product 4-amino-2-dimethylamino-5-phenylpyrimidine(yield 0.037 g (7%), m.p. 119-120°; Anal.Calcd. for $C_{12}H_{14}N_4$: C, 67.3; H, 6.6. Found: C, 67.2; H, 6.8) was performed by column chromatography (silica), yield 0.32 g, oil, picrate m.p. 143-144°. Anal.(picrate) Calcd. for $C_{18}H_{17}N_7O_7$: C, 48.8; H, 3.9. Found: C, 48.8; H, 4.0.

5.4 REFERENCES

1. J.A.Zoltewicz and L.S.Helmick, J.Amer.Chem.Soc., 94, 682 (1972).
2. A.P.Kroon, H.C.van der Plas and G.van Garderen, Recl.Trav.Chim. (Pays-Bas), 93, 325 (1974).
3. J.P.Geerts, H.C.van der Plas and A.van Veldhuizen, Org.Magn.Reson., 7, 86 (1975).
4. J.P.Geerts, H.C.van der Plas and A.van Veldhuizen, Recl.Trav.Chim. (Pays-Bas), 92, 1232 (1973).
5. J.P.Geerts, C.A.H.Rasmussen and A.van Veldhuizen, Recl.Trav.Chim. (Pays-Bas), 93, 231 (1974).
6. P.J.Lont, H.C.van der Plas and A.van Veldhuizen, Recl.Trav.Chim. (Pays-Bas), 92, 708 (1973).
7. H.C.van der Plas and B.Zuurdeeg, Recl.Trav.Chim.(Pays-Bas), 88, 426 (1969).
8. R.Waack, M.A.Doran, E.B.Baker and G.A.Olah, J.Amer.Chem.Soc., 88, 1272 (1966).
9. A.J.Jones, D.M.Grant, J.G.Russell and G.Fraenkel, J.Phys.Chem., 73, 1624 (1969).
10. G.C.Levy and G.L.Nelson, Carbon-13 Nuclear Magnetic Resonance for Organic Chemists, Wiley-Interscience, New York, 1972, p.74.
11. N.F.Ramsey, Phys.Rev., 91, 303 (1953); N.F.Ramsey and E.M.Purcel, Phys.Rev., 85, 143 (1952).
12. G.J.Martin and M.L.Martin, in: Progress in NMR Spectroscopy, 8, 163 (1972).
13. N.F.Chamberlain, The Practise of NMR Spectroscopy, Plenum Press, New York-London (1974).
14. In previous work from this Laboratory a *cis* configuration was assigned to the cognate 1-cyano-2,5-diphenyl-1,3-diazapenta-2,4-diene. See:H.W.van Meeteren and H.C.van der Plas, Recl.Trav.Chim.(Pays-Bas), 90, 105 (1971).
15. E.Breitmaier and W.Voelter, C-13 NMR Spectroscopy, p. 99, Verlag Chemie, Weinheim/Bergstr., 1974.
16. H.L.Wheeler and H.S.Bristol, Am.Chem.J., 33, 448 (1905).
17. W.V.Curran and R.B.Angier, J.Org.Chem., 28, 2672 (1963).
18. Prepared in D_2O according to: L.A.Carpino, J.Org.Chem., 35, 3971 (1970).
19. B.Stelander and H.G.Viehe, Angew.Chem., 89, 182 (1977).

6 ^{13}C NMR-data of pteridine,some of its derivatives and their covalent σ-adducts with ammonia and water

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

6.1 INTRODUCTION

Carbon-13 NMR has been reported to be a useful tool in elucidating the structure of naturally occurring pteridines. Recently ^{13}C NMR spectral data of the biologically important folic acid[1] and the reduced forms, i.e. 7,8-dihydro- and 5,6,7,8-tetrahydrofolate[2] were reported. However, the low solubility in common organic solvents, caused by the substitution of one or more hydrogen atoms of the parent compound, i.e. pteridine (1a), by hydroxyl and/or amino groups, necessitates the use of acids or dilute mineral alkali as solvents. In these solvents protonation or anion formation occurs, affecting the ^{13}C NMR chemical shifts of several pteridines (e.g.lumazine, leucopterin, xanthopterin) considerably[3]. Assignment of these ^{13}C NMR signals was achieved by the usual techniques and by relating the ^{13}C NMR-spectra with previously recorded[4,5] ^{1}H NMR-spectra of these molecules. However so far no straightforward interpretation of the pteridine ring system has been made[1,6,7]. Our recent interest in the chemistry of pteridines, especially the behaviour of these substrates towards nucleophiles, induced us to investigate in detail the ^{13}C NMR-spectrum of pteridine (1a) and some of its derivatives, dissolved in $CDCl_3$, and of several covalent amination products, obtained by dissolving the appropriate pteridine in liquid ammonia.

6.2 RESULTS AND DISCUSSION

6.2.1 Pteridine

The four *intense* signals of the ^{13}C NMR-spectrum of pteridine (1a) dissolved in $CDCl_3$, found at 148.4, 153.0, 159.5 and 164.1 ppm, (Table I) are associated with one bond ^{13}C-^{1}H coupling constants of 188, 186, 206 and 186 Hz, respectively. The signal at 159.5 ppm having the largest coupling constant ^{1}J(CH) = 206 Hz is assigned to C-2 since it is known that substitution on carbon by electronegative atoms causes a significant enhancement of the s character of the C-H bond, leading to an increase in the ^{1}J(CH) coupling constant[8].

This large value for the ^{13}C– ^{1}H coupling constant is found in many related compounds, containing the same structure element N–CH–N, e.g. pyrimidine $^{1}J(C\text{-}2,H)$ = 206 Hz[9] , 1,3,5-triazine $^{1}J(CH)$ = 207 Hz[10] , purine $^{1}J(C\text{-}2,H)$ = 207 Hz[11], quinazoline $^{1}J(C\text{-}2,H)$ = 204 Hz[12] . Now that the position of the NMR resonance of C-2 is known, the position of the ^{1}H NMR-signal of H-2 in the ^{1}H NMR-spectrum of 1a can be established, using the selective heteronuclear decoupling technique. Because of the fact that H-6 and H-7 give rise to a pair of doublets, the remaining singlet must be ascribed to H-4. Irradiation at the H-4 frequency showed that the carbon resonance at 164.1 ppm arises from C-4.

It is of interest that, in contrast to pyrimidine, C-2 resonates at a *higher* field than C-4. In order to assign the ^{13}C NMR-signals at 148.4 and 153.0 ppm, we measured the ^{13}C NMR-spectrum of 7-methylpteridine (1c), the structure of which has been firmly established[13](see Table I). Comparison of the resonances of 1a and 1c and taking into account the literature data on the α- and β-substituent effects (+9.2 and 0.0 ppm, respectively) found in methylpyrazine[14] allowed us to assign the remaining resonances at 148.4 and 153.0 ppm to C-6 and C-7, respectively. The assignments of the signals of C-9 and C-10 were based on those already established for similar systems such as quinoxaline, quinazoline and purine[6].

By using heteronuclear double resonance ^{13}C NMR spectral assignments presented in this paper were found to be in sound agreement with the interpretation of the ^{1}H NMR-spectrum of pteridine[15] which was firmly based on a study with deuterium labelled pteridines.

6.2.2 Pteridine derivatives

Of the recorded monosubstituted compounds (1b-1g), it is noteworthy that in 2-chloropteridine (1b) the chloro atom is found to shift the *meta* oriented C-4 more downfield (2.0 ppm) than C-2 (1.8 ppm). The same effect was found in the ^{13}C NMR-spectrum of 2-chloropyrimidine[12] (downfield shifts of 2.7 and 2.4 ppm for C-4 and C-2, respectively).

^{13}C NMR spectroscopy - unlike ^{1}H NMR spectroscopy - can be successfully applied in establishing the position of the phenyl group in the pteridine ring (C-6 or C-7) obtained when a 4,5-diaminopyrimidine derivative is condensed with phenylglyoxal in ethanol. This structure assignment is essentially based on the well known fact that the phenyl group shifts the carbon

TABLE 1. SUMMARY OF THE ^{13}C CHEMICAL SHIFTS[a]

Pteridine		C-2	C-4	C-6	C-7	C-9	C-10
Parent	(1a)	159·5	164·1	148·4	153·0	154·4	135·3
2-Chloro	(1b)	161.3	166.1	148·0	153·3	155·2	133·9
7-Methyl	(1c)	159·2	162·9	149·0	163·2	153·7	133·1
2-Methylthio	(1d)	174·8	163·0	145·6	152·0	154·4	133·0
2-Phenyl	(1e)	164.9	163.6	146·7	152·4	154·4	133·8
4-Phenyl	(1f)	158·5	169·0	146·6	151·6	154·9	133·6
7-Phenyl	(1g)	159·4	162·7	146·2	158·9	153·6	133·4
2-Chloro-4-methyl	(1h)	160·4	177·3	146·6	152·9	154·5	133·4
2-Chloro-4-phenyl	(1i)	160·9	171·4	146·6	152·1	156·2	[b]
6,7-Dimethyl	(1j)	158·1	161·8	157·4	163·1	153·0	132·9
4,7-Diphenyl	(1k)	158·9	168·1	144·7	157·8	154·5	[b]
2-Methylthio-4-phenyl	(1l)	174·2	168·2	144·4	151·1	155·4	[b]
4-*t*-Bu-2-chloro-6-phenyl	(1m)	159·4	184·5	151·2	149·7	154·2	[b]
4-*t*-Bu-2-chloro-7-phenyl	(1n)	160·4	184·1	142·5	157·8	154·2	[b]
4-*t*-Bu-2-methoxy-6-phenyl	(1o)	164·0	184·6	148·6	148·4	154·8	[b]
4-*t*-Bu-2-methoxy-7-phenyl	(1p)	164·6	184·2	139·5	157·3	155·7	[b]
2-Chloro-4,7-diphenyl	(1q)	161·2	170·2	144·6	158·3	156·0	[b]
4,6-Diphenyl-2-methylthio	(1r)	173·4	167·2	151·2	149·1	154·2	[b]
4,7-Diphenyl-2-methylthio	(1s)	174·0	167·2	142·6	157·7	154·9	[b]
4,6,7-Triphenyl	(1t)	158·5	167·6	155·0	159·8	153·1	[b]

[a] All samples were measured for $CDCl_3$ solutions.
[b] Could not be detected because of signal overlap by the phenyl group.

atom to which it has been attached about 5 ppm downfield, and the adjacent carbon atom about 2 ppm upfield. Consequently in a 6-phenyl isomer the signals of C-6 and C-7 must approach each other relative to the corresponding signals in 1a, while in a 7-phenyl isomer they must move apart. This is clearly demonstrated by comparison of the data of the 2,4-disubstituted 6-phenylpteridines (1m, 1o and 1r), and the corresponding 7-phenylpteridines (1n, 1p and 1s) where there is a striking difference in the region of the absorptions of C-6 and C-7. As a corollary ^1H selective decoupling completely clarifies the ^1H NMR-spectrum of these 6- (or 7-)phenylpteridines.

6.2.3 Ammonia adducts

It has been demonstrated by several investigators using both UV and ^1H NMR spectroscopy[16,17] that pteridine forms with ammonia a 1:1 σ-adduct (2a) and a 2:1 σ- adduct[18](3a). Until now no ^{13}C NMR spectral data on these covalent adducts have been published. To obtain a ^{13}C NMR-spectrum of the covalent 3,4-monoadduct (2a) (see Table 2) proved to be difficult. During the time between its preparation and the acquisition of the last free induction decay a considerable quantity of precipitate was formed. This results in the spectra being difficult to analyse because of the relatively bad signal to noise ratio. ^{13}C NMR spectral data of 3a and some of its derivatives have also been obtained (see Table 2). The general picture of the spectrum of

this 2:1 σ- adduct totally differs from that found for the parent pteridine (1a) as seen by the appearance of strong signals at 60.9 and 62.8 ppm in the sp^3 carbon region resulting from C-6 and C-7.

Furthermore, the spectrum exhibits the typical pattern of a pyrimidine derivative in that C-2 now resonates at *lower* field than C-4. Because of the saturation of the pyrazine ring upon diadduct formation, the electron attracting N-atoms of the pyrazine ring have adopted the electron releasing character of an amino group, as indicated by the upfield shift found for the resonances of the pyrimidine fragment of the molecule. This phenomenon is clearly illustrated by the resemblance found when one compares the spectrum of 3a with that of the structurally closely related 4,5-diamino-pyrimidine (4) (see Table 2).

Again the difference in magnitude of the ^1J (C-2,H) and the ^1J (C-4,H) (198 and 176 Hz, respectively) makes it possible to differentiate between the signals from C-2 and C-4.

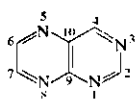
The results of our investigations clearly show that a restrictive condition with respect to diadduct formation in liquid ammonia is that positions 6 and 7 of the pteridine derivative must be unsubstituted[17]. Therefore, of all pteridines listed in Table 1, only a limited number gave the 6,7-di-amino adducts (3a-3g) (see Table 2).

TABLE 2. SUMMARY OF THE ^{13}C CHEMICAL SHIFTS OF ADDUCTS OF PTERIDINES

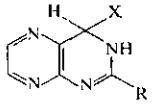
	Solvent	C-2	C-4	C-6[a]	C-7[a]	C-9	C-10
3a	NH_3	148·9	135·8	60·9	62·8	150·5	125·3
3b	NH_3	153·4	136·1	61·2	63·0	150·6	124·1
3c	NH_3	148·7	143·7	61·0	62·3	151·1	121·3
3d	NH_3	157·9	136·4	60·9	62·9	151·1	122·0
3e	NH_3	148·0	136·3	60·7	62·8	152·5	124·4
3f	NH_3	147·3	145·9	60·8	62·4	151·6	120·7
3g	NH_3	148·3	144·7	61·0	62·5	153·2	120·4
3h	H_2O	148·3	135·7	73·5	75·0	150·1	124·7
3h$^{\ominus}$	1 N HCl	144·1	123·8	73·1	75·4	153·8	125·2
2a	NH_3	151·5	61·4	144·2	140·4	[b]	[b]
2b	NH_3	158·5	69·6	142·5	135·9	155·2	140·6
2c	H_2O	151·9	73·9	145·8	142·0	[b]	[b]

	Solvent	C-2	C-4	C-5	C-6
4	D_2O	149·5	155·3	126·6	139·1
4$^{\ominus}$	1 N HCl	144·0	157·6	127·6	124·8

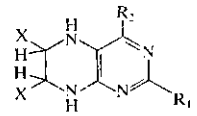
[a] Signals may be interchanged.
[b] Signals did not exceed signal-to-noise level.



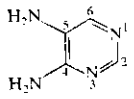
1a



2a R = H, X = NH_2
2b R = Cl, X = NH_2
2c R = H, X = OH



3a $R_1 = R_2 = H$, X = NH_2
3b $R_1 = C_6H_5$, $R_2 = H$, X = NH_2
3c $R_1 = H$, $R_2 = C_6H_5$, X = NH_2
3d $R_1 = SCH_3$, $R_2 = H$, X = NH_2
3e $R_1 = OCH_3$, $R_2 = H$, X = NH_2
3f $R_1 = Cl$, $R_2 = CH_3$, X = NH_2
3g $R_1 = Cl$, $R_2 = C_6H_5$, X = NH_2
3h $R_1 = R_2 = H$, X = OH



4

All the assignments based on the ^{13}C NMR-spectra are fully consistent with results obtained earlier by ^{1}H NMR spectroscopy[16-18].

6.2.4 Hydrates

After studying the ^{13}C NMR-spectra of covalent adducts of ammonia and pteridine, we became interested in comparing these spectral data with those of the corresponding complexes of pteridine and water[7]. The knowledge acquired from the study on the ammonia adducts 2a and 3a allowed straightforward interpretation of the ^{13}C NMR-spectra of the mono- and dihydrate of pteridine 2c and 3h. When 1a is dissolved in water at pH =6.8 and the ^{13}C NMR-spectrum of the solution is recorded without delay, signals of smaller intensity belonging to 4-hydroxy-3,4-dihydropteridine (2c) are found in addition to those of the parent compound (1a). The spectrum of this monohydrate closely resembles that of the 3,4-monoammonia adduct (2a) of pteridine. Only the chemical shift of the sp^3 hybridized C-4 reflects the difference between O- and N-substitution to a considerable extent.
The ^{13}C NMR-spectrum of this solution taken after a prolonged period of time (7 h) reveals a number of additional peaks, two of which are found in the sp^3 carbon region, indicating the formation of the dihydrate (3h). A sample consisting almost entirely of the dihydrate (3h) could be prepared by dissolving 1a in 1 N HCl solution[19] and by neutralizing the solution (pH 7),

after standing for 60 min. The spectrum of this solution closely resembled that of the diammonia adduct (3a).
The 1 N HCl solution of pteridine did not show signals belonging to the parent compound. The three signals at high field indicate that in this solution cations of the mono and dihydrate ($2c^{\oplus}$, $3h^{\oplus}$) have been formed. Interestingly, the low field part of the ^{13}C NMR-spectra of the dihydrate cation ($3h^{\oplus}$) and the cation of 4,5-diaminopyrimidine ($4^{\oplus}$), both recorded for a 1 N HCl solution, are virtually the same.

6.3 EXPERIMENTAL

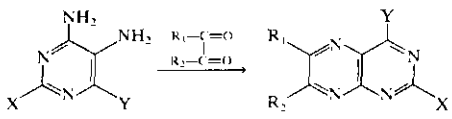
^{13}C-spectra were measured on a Varian XL-100-15 spectrometer operating at 25.2 MHz, equipped with a pulse unit and a 620 L-16K on line computer system. In $CDCl_3$ solution the deuterium resonance of the solvent was used as an internal field-frequency lock signal. In the case of liquid ammonia or water as solvent, field-frequency lock was obtained from the ^{19}F NMR-signal of a capillary of hexafluorobenzene positioned along the longitudinal axis of the 12 mm (o.d.) sample tubes employed. Spectra were taken at ambient temperature, but when measuring liquid ammonia samples the probe temperature was $-50^{o}C$.
In $CDCl_3$ solution ^{13}C NMR chemical shifts were measured from internal TMS. In NH_3 and H_2O solution ^{13}C NMR chemical shifts were measured from internal trimethylamine and internal dioxane respectively, and they were converted to the TMS scale by adding 47.5 and 67.4 ppm respectively. Typical spectral parameters were as follows: spectral width 5120 Hz (1.25 Hz/point) acquisition time 0.8 s, pulse delay 1.2 s, pulse width 10 μs. For most of the samples sufficient signal-to-noise ratio was obtained after accumulating and transforming 2000-4000 free induction decays.

6.3.1 Synthesis of the recorded pteridines

The following compounds were prepared according to procedures given in the literature, pteridine[20](1a), 2-chloropteridine[17](1b), 7-methylpteridine[13](1c), 2-methylthiopteridine[13](1d), 2-phenylpteridine[21](1e), 4-phenylpteridine[22] (1f), 2-chloro-4-phenylpteridine[17](1i), 6,7-dimethylpteridine[13](1j), 2-methylthio-4-phenylpteridine[23](1l), 4,6-diphenyl-2-methylthiopteridine[23](1r) and 4,7-diphenyl-2-methylthiopteridine[23] (1s).

The following pteridines (see Table 3) were obtained by condensation of the appropriate 4,5-diaminopyrimidine derivative and glyoxal[24], phenylglyoxal or benzil. With the two former compounds the condensation reaction proceeded smoothly in boiling ethanol. The preparation of 4,6,7-triphenylpteridine (1t) was carried out in boiling 2-ethoxyethanol. 4-*t*-Bu-2-chloro-6-phenylpteridine (1m) was not isolated. TLC and ^{13}C NMR revealed its formation in a minute amount in addition to the major isomer (1n) (ratio 1:10). Dechloromethoxylation of this mixture afforded the isomeric 4-*t*-Bu-2-methoxy-6- and 7-phenylpteridines (1o and 1p), which were measured as a mixture.

Table 3



Starting pyrimidine	Pteridine derivative	m.p.(°C)	Yield %
X = Y = H	X = Y = R_1 = H, R_2 = C_6H_5 (1g)	158–160	95
X = Cl, Y = CH_3	X = Cl, Y = CH_3, R_1 = R_2 = H (1h)	155–157	80
X = H, Y = C_6H_5	X = R_1 = H, Y = R_2 = C_6H_5 (1k)	154–155	92
X = Cl, Y = *t*-Bu	X = Cl, Y = *t*-Bu, R_1 = H, R_2 = C_6H_5 (1n)	174–176	60
—	X = OCH_3, Y = *t*-Bu, R_1 = H, R_2 = C_6H_5 (1p)	142–144	75
X = Cl, Y = C_6H_5	X = Cl, R_1 = H, Y = R_2 = C_6H_5 (1q)	198–199	72
X = H, Y = C_6H_5	X = H, Y = R_1 = R_2 = C_6H_5 (1t)	174–175	86

6.3.2 General procedure for measuring the ^{13}C NMR-spectra in liquid ammonia

The procedure followed was reported previously[17]. In this study the formation of the 6,7-diamino-5,6,7,8-tetrahydropteridines was accelerated by preparing a solution of the appropriate pteridine derivative in liquid ammonia at room temperature in a suitable all glass vessel. The cooled solution was siphoned over into a ^{13}C NMR tube.

6.4 REFERENCES

1. J.A.Lyon, P.D.Ellis and R.B.Dunlap, Biochemistry 12, 2425 (1973).
2. W.Frick, R.Weber and M.Viscontini, Helv.Chim.Acta 57, 2658 (1974).
3. G.Müller and W.von Philipsborn, Helv.Chim.Acta 56, 2680 (1973).
4. A.Dieffenbacher and W.von Philipsborn, Helv.Chim.Acta 52, 743 (1969).
5. R.Wagner and W.von Philipsborn, Helv.Chim.Acta 53, 299 (1970).

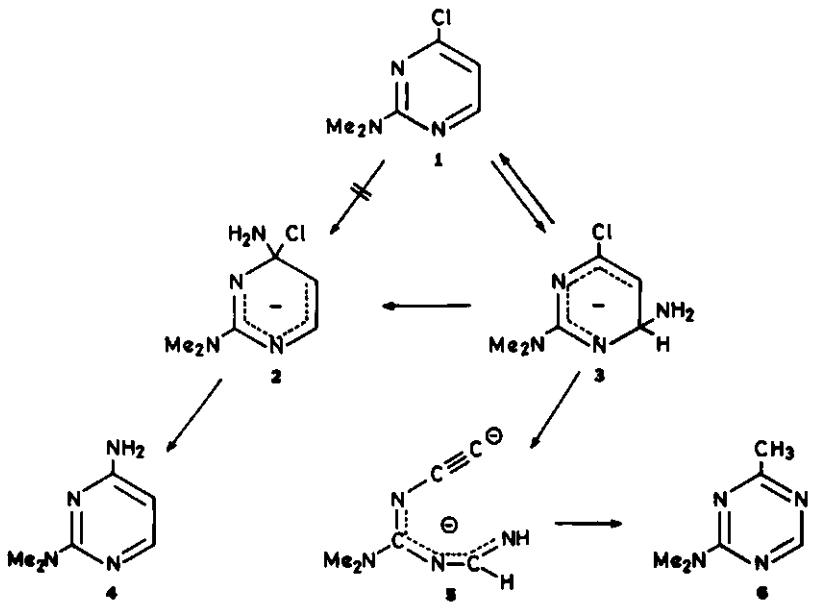
6. U.Ewers, H.Günther and L.Jaenicke, Chem.Ber. 106, 3951 (1973).
7. U.Ewers, H.Günther and L.Jaenicke, Angew.Chem.Int.Ed.Engl. 14, 354 (1975).
8. G.C.Levy and G.L.Nelson, Carbon-13 Nuclear Magnetic Resonance for Organic Chemists, Wiley-Interscience, New York, 1972, p.25.
9. K.Tori and T.Nakagawa, J.Phys.Chem. 68, 3163 (1964).
10. S.Braun and G.Freij, Org.Magn.Reson. 7, 194 (1975).
11. J.M.Read Jr and J.H.Goldstein, J.Am.Chem.Soc. 87, 3440 (1965).
12. Measured in this laboratory.
13. Compare assignments made by UV spectroscopy: A.Albert, D.J.Brown and H.C.S.Wood, J.Chem.Soc., 3832 (1954); A.Albert, D.J.Brown and G.W.H. Cheeseman, J.Chem.Soc., 1620 (1954).
14. C.J.Turner and G.W.H.Cheeseman, Org.Magn.Reson. 6, 663 (1974).
15. S.Matsuura and T.Goto, J.Chem.Soc., 1773 (1963); J.Chem.Soc., 623 (1965).
16. B.E.Evans, J.Chem.Soc.Perkin Trans 1, 357 (1974).
17. A.Nagel, H.C.van der Plas and A.van Veldhuizen, Rec.Trav.Chim.Pays-Bas 94, 45 (1975).
18. A.Albert and K.Ohta, J.Chem.Soc. C, 2357 (1971).
19. J.Clark, J.Chem.Soc.C, 313 (1968).
20. A.Albert and H.Yamamoto, J.Chem.Soc., C, 2289 (1968).
21. J.Clark, P.N.T.Murdoch and D.L.Roberts, J.Chem.Soc., C, 1408 (1969).
22. J.Clark and P.N.T.Murdoch, J.Chem.Soc., C, 1883 (1969).
23. A.Nagel and H.C.van der Plas, Chem.Pharm.Bull. 23, 217 (1975).
24. H.Raudnitz, J.Chem.Soc., 763 (1948).

7 General discussion

As already pointed out in the Introduction there is a vast amount of literature concerning Meisenheimer complexes[1-4], but only a few reports are available covering the subject of the formation of anionic σ-adducts between pyrimidines and amide ion. Our ^{1}H-NMR results establishing unequivocally that the addition of the amide ion to the substituted pyrimidines, mentioned in this thesis, takes place at C-4,6 and not C-2, are consistent with the results obtained by Zoltewicz and coworkers[5], who studied the ^{1}H-NMR spectra of addition complexes between the parent diazines and KNH_2 in liquid NH_3. An explanation for this exclusive addition at C-4,6 could be provided by application of the Frontier Orbital Theory (FOT) of Fukui[6]. This theory predicts the reactivity of a certain position in a molecule on the basis of the Frontier Orbital Density (Fr^{OD}) at that position. In a nucleophilic process the frontier orbitals are the LUMO of the substrate and the HOMO of the nucleophile. The extent to which the incoming electron pair of the attacking nucleophile can be accommodated at a certain position of the substrate is quantified by the Fr^{OD}. The theory gives no information concerning the transition state, and a high reactivity as determined by the FOT at a certain position does not guarantee that the reaction actually occurs at that position. Application of the FOT is only valid if the reaction under study is "Orbital Controlled" as pointed out by Klopman[7].
It can be shown that this is indeed the case for the above-mentioned reaction. The frontier orbitals were calculated by the SCF-PPP method, using the parameter set of Fisher Hjalmars et al.[8-18]. Interestingly these calculations revealed that the Fr^{OD}'s in the LUMO of pyrimidine are zero at C-2 and C-5[19]. Therefore the C-2 and C-5 positions are less accessible for nucleophilic attack. Based upon symmetry considerations the assumption seems justified that the Fr^{OD} values for 4,6-diphenylpyrimidine will follow the same order as those calculated for the parent pyrimidine. Contrary to these predictions, it is found that when 4,6-diphenylpyrimidine is dissolved in potassium amide in liquid ammonia, the ^{1}H-NMR spectrum shows besides the absorptions of the phenyl groups, only two singlet signals, one at δ = 4.60 (H-2) and the other at δ = 6.05 (H-5). It indicates that a *symmetrical* σ-adduct has been formed, in which the amide ion has attacked position 2 of the substrate. This experiment shows the limitations of the Frontier Orbital Theory.

The results described in this thesis clearly show that in 4-chloro-2-dimethylaminopyrimidine (1) addition of the amide ion takes place at position 6 and *not* at position 4, although this position is more electron-deficient than position 6, due to the presence of the chloro substituent. This addition results in a σ-adduct 3, which is stable in KNH_2/NH_3. Addition to C-4 would give rise to the formation of the unstable *gem* amino-chloro σ-complex 2, that will be short-lived because of the good leaving group character of the chloro substituent.

The interesting question arises if the 4-amino-2-dimethylaminopyrimidine (4), found as a minor component in the reaction of 1 with KNH_2/NH_3 together with the main product 4-methyl-2-dimethylamino-s-triazine (6), is formed via a short-lived σ-adduct 2 or by a nucleophilic attack at C-4 in the σ-adduct 3. (see Scheme 1)



Scheme 1

In connection with this it is worth mentioning[20] that the ratio in which 4 and 6 are formed from 1 is strongly dependent on the alkali metal employed to produce the amide reagent (see Table).

Table. Product distribution in the reaction of 1 → 4 + 6 in percentage of total amount of product formed, depending on the alkali metal employed.

M	4(%)	6(%)
Li	74	26
Na	25	75
K	9	91
Cs	2	98

Yields of 4 + 6 vary from 80-100%

From the data listed in the table, it can be seen that with $LiNH_2$ as a nucleophile the 4-aminopyrimidine (4) is formed as the main product in the reaction.

The reaction is found to proceed slowly; when a reaction mixture containing 1 in the presence of 4 equivalents of $LiNH_2$ is examined by ^{13}C-NMR shortly after preparation, *only* signals resulting from the C-6 σ-complex 3 are observed. Reexamination of this solution after a prolonged period of time shows almost exclusively the signals of the *anionic* form of 4-amino-2-dimethylaminopyrimidine (4). No other intermediates could be detected. These data make it clear that the 4-aminopyrimidine (4) must originate from the C-6 σ-adduct 3, in which the amide ion has attacked position 4, presumably under simultaneous expulsion of the amino group at C-6, yielding 2. That this process is slow is due to the negative charge in species 3, the actual substrate being attacked. It is assumed that the same process is valid in the case of KNH_2 as a nucleophile in the formation of 4.

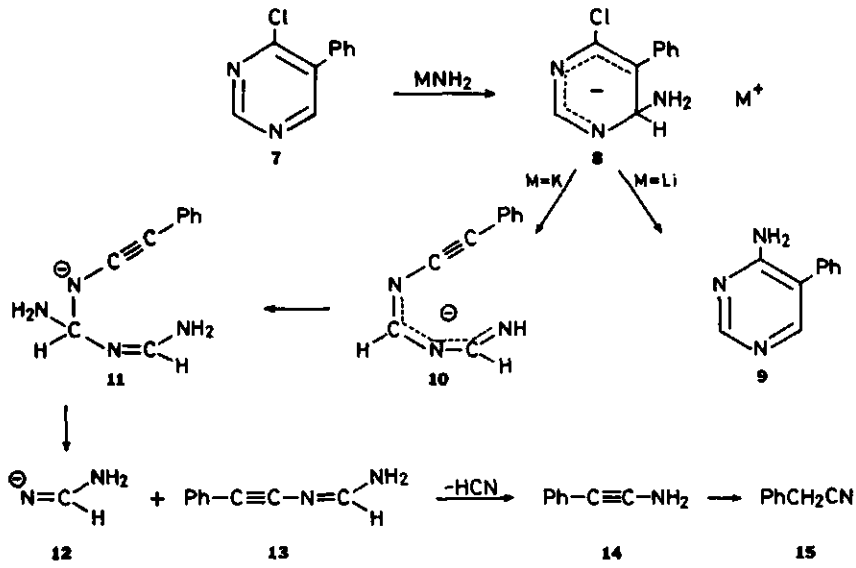
The following comments can be made concerning the ring opening process leading to the s-triazine 6. It is found that although the σ-adduct 3 is formed instantaneously in KNH_2/NH_3 the process of ring opening is much slower, as indicated by the observation that after treatment of a solution of the σ-adduct 3 with ammonium chloride the parent compound 1 is completely retrieved. However, addition of ammonium chloride to a solution in which the open-chain 5 is present, leads to the formation of the triazine 6. Based upon these data it is suggested that the ring opening process 3 → 5 is rate determining.

The results found in chapter 5 concerning the mechanism of the ring trans-

formation of 4-chloro-2-dimethylamino-5-phenylpyrimidine into 4-benzyl-2-dimethylamino-s-triazine, induced us to reexamine data found earlier in our laboratory[21], on the reaction of 4-chloro-5-phenylpyrimidine (7) with KNH_2/NH_3. It has been established that in this reaction not a benzyl-s-triazine is formed - as expected - but benzylcyanide (15) in 47% yield, besides a small amount of 4-amino-5-phenylpyrimidine. Tracer experiments with the aim to establish from which ring carbon atom (C-4 or C-6) the carbon atom of the benzyl group in 15 originates revealed that the benzylcyanide, obtained from 4-chloro-5-phenylpyrimidine-6 ^{14}C, was *non*-radioactive.

We reinvestigated this reaction by means of ^{13}C-NMR spectroscopy. It appeared that when the substrate 7 is reacted with two equivalents of potassium amide at -60° a rather complicated ^{13}C-NMR spectrum is obtained, resulting presumably from a mixture of several intermediate species. When lithiumamide is used as a nucleophile however, only ^{13}C-NMR signals from the σ-adduct 8 are observed at δ = 153.6 (C-2), δ = 142.4 (C-4), δ = 98.9 (C-5) and δ = 69.3 (C-6). The coupling constants found $^{J}C\text{-}H$ = 185 Hz for C-2 and $^{J}C\text{-}H$ = 155 Hz for C-6 agree excellently with the proposed structure [compare the corresponding values found in the pyrimidine C-6 adduct (170 and 147 Hz respectively)]. After working up of the reaction mixture, we could establish by GLC that besides some starting material 7 a large amount of 4-amino-5-phenylpyrimidine (9) is found. No benzylcyanide could be detected. Based upon the results of our extensive studies on the reaction course established for 4-chloro-2-dimethylamino-5-phenylpyrimidine (see Chapter 5) we propose now the following mechanism for the formation of benzylcyanide from 7 by the potassium amide-liquid ammonia system (see Scheme 2).

At first the σ-complex 8 is formed between 7 and the amide ion. The next step depends on the nature of the alkali metal ion. With lithiumamide no ring opening occurs, and 4-amino-5-phenylpyrimidine (9) is formed. With potassium amide, however, fission of the C-5 - C-6 bond takes place resulting in the formation of the (phenylethynyl)aminodiazabutadiene species 10. Since C-2 in 10 is unsubstituted and consequently vulnerable to attack by the amide ion, addition takes place at C-2, yielding the tetrahedral complex 11. This splits off the formamidine anion 12 to give 13. Loss of hydrogen cyanide results in the formation of the ynamine 14 which isomerizes instantaneously into the benzylcyanide (15). This reaction course is consistent with the ^{14}C labelling experiment mentioned before, in that the label is lost in the fragmentation step of the open-chain species 11 (see Scheme 2).



Scheme 2

REFERENCES

1. M.J.Strauss, Chem.Rev., 70, 667 (1970).
2. M.R.Crampton, Adv.Phys.Org.Chem., 7, 211 (1969).
3. E.Buncel, A.R.Norris and K.E.Russell, Quart.Rev.(London), 22, 123 (1968).
4. G.Illuminati, Adv.Heterocycl.Chem., 3, 285 (1964).
5. J.A.Zoltewicz and L.S.Helmick, J.Amer.Chem.Soc., 94, 682 (1972).
6. K.Fukui, Theory of Orientation and Stereoselection, Springer-Verlag, Heidelberg (1975).
7. G.Klopman, J.Amer.Chem.Soc., 90, 223 (1968).
8. B.Roos and P.N.Skancke, Acta Chem.Scand., 21, 233 (1967).
9. B.Roos, Acta Chem.Scand., 21, 2318 (1967).
10. I.Fisher-Hjalmars and M.Sundbom, Acta Chem.Scand., 22, 607 (1968).
11. a. B.Grabe, Acta Chem.Scand., 22, 2237 (1968).
    b. B.Grabe, Acta Chem.Scand., A 28, 315 (1974).
12. H.Jensen and P.N.Skancke, Acta Chem.Scand., 22, 2899 (1968).
13. G.Höjer, Acta Chem.Scand., 23, 2589 (1969).
14. O.Gropen and P.N.Skancke, Acta Chem.Scand., 23, 2685 (1969).
15. A.Skancke and P.N.Skancke, Acta Chem.Scand., 24, 23 (1970).
16. P.G.Seybold and I.Fisher-Hjalmars, Acta Chem.Scand., 24, 1373 (1970).
17. O.Gropen and P.N.Skancke, Acta Chem.Scand., 24, 1768 (1970).

18. E.M.Farbrot and P.N.Skancke, Acta Chem.Scand., 24, 3645 (1970).
19. R.J.Platenkamp, J.P.Geerts and H.C.van der Plas, unpublished results.
20. J.P.Geerts and H.C.van der Plas, unpublished results.
21. A.L.Alons, H.W.van Meeteren and H.C.van der Plas, unpublished results.

SUMMARY

This thesis deals with the results obtained by an NMR investigation on anionic σ-adducts that are formed between a number of pyrimidines and potassium amide in liquid ammonia and the covalent addition complexes that are formed between a number of pteridines and liquid ammonia or water.

^{1}H-NMR spectra of some 5-bromo-4-R-pyrimidines (R = Ph, *t*Bu, OMe, PhMeN, MeNH, Me) in KNH_2/liquid NH_3 are described. Evidence is presented for the formation of stable σ-adducts by attack of an amide ion to C-6 of the pyrimidinering in the cases of R = Ph, *t*Bu, OMe, PhMeN. When the substituent in position 4 contains an acidic hydrogen atom α to the aromatic nucleus (R = MeNH, Me), deprotonation occurs and in the case of R = CH_3 also adduct formation has been observed. The ratio of anion to σ-complex is found to change from 3:1 to 1:2 for R = CD_3 compared with R = CH_3. This dramatic increase in σ-complex formation has been ascribed to a deuterium isotope effect.

^{1}H and/or ^{13}C-NMR spectral information is presented concerning the σ-addition complexes between amide ion and some 2-R-pyrimidines, 4-chloro-2-R-pyrimidines (R = Me_2N, PhMeN, piperidino, morpholino, Ph), 5-bromo-2-piperidinopyrimidine and pyrimidine itself.
It was proven that in the ring interconversion that occurs when 4-chloro-2-R-pyrimidines are treated with potassium amide in liquid ammonia in first instance a 1:1 anionic σ-complex is formed in which the amide ion has attacked position 6 of the substrate. Furthermore it was established for R = Me_2N that the next step of this reaction is fission of the pyrimidine ring between C-5 and C-6 yielding the 6-amino-3,5-diaza-4-dimethylamino-3,5-hexadiene-1-yne anion. This species appeared to be stable under the reaction conditions. However, when the reaction was quenched by the addition of ammonium chloride cyclization took place to give the final reaction product 2-dimethylamino-4-methyl-s-triazine. For comparison we examined the influence of a phenyl group substituted in position 5. By means of ^{13}C-NMR spectroscopy it was established that when 4-chloro-2-dimethylamino-5-phenylpyrimidine is reacted with KNH_2/NH_3, the final product 4-benzyl-2-dimethylamino-s-triazine is formed *via* addition of the amide ion to position 6. This addition is followed by a ring fission process yielding the 6-amino-3,5-diaza-4-dimethylamino-1-

phenyl-3,5-haxadiene-1-yne anion. Interestingly it was further observed, that in this species a hydride ion is transferred from C-6 to C-2. This hydride shift could be unequivocally established using 4-chloro-6-deutero-2-dimethylamino-5-phenylpyrimidine as starting material. The 5-cyano-3,5-diaza-4-dimethylamino-1-phenyl-1,3-pentadiene anion formed in this internal disproportionation mechanism cyclizes into the 4-benzyl-2-dimethylamino-s-triazine that is ultimately formed upon work up.

^{13}C-NMR spectral data of the biologically important pteridine and nineteen of its derivatives (containing one or more Cl, MeS, Me, *t*Bu or Ph substituents) are reported. The ^{13}C-NMR spectrum of the title compound has been assigned conclusively. ^{13}C-NMR substituent effects are shown to be very useful in discerning between 6- and 7-substituted pteridines. Additionally, the ^{13}C-NMR spectra of several covalent amination products, i.e. the 3,4-dihydro-4-amino- and the 5,6,7,8-tetrahydro-6,7-diaminopteridine derivatives have been recorded. The ^{13}C-NMR spectra of the corresponding covalent hydrates are also reported.

SAMENVATTING

In dit proefschrift worden de resultaten beschreven van een NMR onderzoek aan σ-adducten tussen een aantal pyrimidines en kaliumamide in vloeibare ammoniak en aan de covalente complexen tussen een aantal pteridines en vloeibare ammoniak of water.

De ^1H NMR spectra van een aantal 5-broom-4-R-pyrimidines (R = C_6H_5, tC_4H_9, OCH_3, $C_6H_5NCH_3$, CH_3NH, CH_3) in KNH_2/NH_3 worden beschreven. Het bewijs wordt geleverd dat indien R = C_6H_5, tC_4H_9, OCH_3, $C_6H_5NCH_3$ een stabiel σ-adduct wordt gevormd door aanval van een amide ion op C-6 van de pyrimidinering. Indien de substituent op positie 4 een zuur proton bezit, α ten opzichte van de aromaatkern, (R = CH_3NH, CH_3) treedt deprotonering op. In het geval R = CH_3 wordt ook de vorming van een adduct waargenomen. Het blijkt dat de verhouding anion : σ-complex zich wijzigt van 3:1 voor R = CH_3 tot 1:2 voor R = CD_3. Deze dramatische verschuiving wordt toegeschreven aan een deuterium isotoop effect.

Hiernaast werden ^1H en/of ^{13}C NMR spectrale gegevens verzameld aangaande de σ-complexen tussen amide ion en een aantal 2-R-pyrimidines, 4-chloro-2-R-pyrimidines (R = $(CH_3)_2N$, $C_6H_5NCH_3$, piperidino, morfolino, C_6H_5), 5-broom-2-piperidinopyrimidine en pyrimidine zelf. Bewezen werd dat als eerste stap in de ringverandering die optreedt wanneer 4-chloor-2-R-pyrimidines behandeld worden met KNH_2/NH_3 een 1:1 σ-complex wordt gevormd, waarin het amide ion zich gehecht heeft aan positie 6. Vervolgens werd vastgesteld voor R = $(CH_3)_2N$ dat in de volgende reactiestap het 6-amino-3,5-diaza-4-dimethylamino-3,5-hexadieen-1-yn anion wordt gevormd *via* opening van de pyrimidinering tussen C-5 en C-6. Dit intermediair blijkt stabiel te zijn onder de reactieomstandigheden. Echter indien de reactie wordt geblust met ammonium chloride, treedt cyclisatie op tot het eindproduct 2-dimethylamino-4-methyl-s-triazine. Ter vergelijking werd de invloed van een fenylsubstituent op C-5 onderzocht. Met behulp van ^{13}C NMR spectroscopie werd vastgesteld dat het 4-benzyl-2-dimethylamino-s-triazine dat als eindproduct in de reactie van 4-chloor-2-dimethylamino-5-phenylpyrimidine met KNH_2/NH_3 ontstaat, wordt gevormd via additie van het amide ion aan positie 6. Deze additie wordt gevolgd door een ringopening proces waarbij het 6-amino-3,5-

diaza-4-dimethylamino-1-phenyl-3,5-hexadieen-1-yn anion ontstaat. In deze intermediaire verbinding werd een 6,2 hydride verschuiving waargenomen. Het optreden van deze hydride verhuizing kon bewezen worden door uit te gaan van 4-chloor-6-deutero-2-dimethylamino-5-phenylpyrimidine. Het 5-cyano-3,5-diaza-4-dimethylamino-1-phenyl-1,3-pentadieen anion, dat in deze interne disproportionerings reactie wordt gevormd, cycliseert tot het uiteindelijke reactieproduct 4-benzyl-2-dimethylamino-s-triazine bij opwerken.

Vervolgens worden ^{13}NMR gegevens gerapporteerd aangaande het biologisch belangrijke pteridine en negentien derivaten hiervan, die één of meer Cl, CH_3S, CH_3, tC_4H_9 of C_6H_5 substituenten bevatten. Het ^{13}C NMR spectrum van de titelverbinding wordt volledig toegekend. De bruikbaarheid van ^{13}C NMR substituent effecten om onderscheid te maken tussen 6- en 7-gesubstitueerde pteridines wordt aangetoond. Hiernevens worden de ^{13}C NMR spectra van verscheidene covalente amineringsproducten te weten de 3,4-dihydro-4-amino- en de 5,6,7,8-tetrahydro-6,7-diaminopteridine derivaten geïnterpreteerd, evenals ^{13}C NMR spectra van de corresponderende covalente hydraten.

CURRICULUM VITAE

Na in 1965 het eindexamen gymnasium β te hebben afgelegd aan het Buitenveldert Lyceum te Amsterdam, begon ik in september van dat jaar met mijn academische studie in de scheikunde aan de Universiteit van Amsterdam.
Het kandidaatsexamen S 2 werd afgelegd in oktober 1968. Onder leiding van de hoogleraren dr.Th.J.de Boer (fysisch organische chemie), dr.E.C.Slater (biochemie) en dr.H.O.Huisman (synthetisch organische chemie) bereidde ik mij voor op het doctoraalexamen, dat in november 1971 werd afgelegd.
Vanaf december 1971 ben ik als wetenschappelijk medewerker werkzaam op het Laboratorium voor Organische Chemie van de Landbouwhogeschool te Wageningen, alwaar ik onder leiding van Prof.dr.H.C.van der Plas het in dit proefschrift beschreven onderzoek verrichtte.