HOMOAROMATICS AS INTERMEDIATES IN THE SUBSTITUTION REACTIONS OF 1,2,4,5-TETRAZINES WITH AMMONIA AND HYDRAZINE

Promotor: dr.H.C.van der Plas, hoogleraar in de organische scheikunde

ANDA COUNOTTE-POTMAN

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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 29 mei 1981
des namiddags te vier uur in de aula
van de Landbouwhogeschool te Wageningen.

STELLINGEN

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Dit proefschrift

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10a Aangezien chemische en biologische research gepaard kan gaan met de vorming van nieuwe verbindingen, waarvan de teratogene effecten niet bekend zijn, verdient het aanbeveling vrouwelijke onderzoekers in de tweede en derde maand van hun zwangerschap toe te staan met verlof te gaan.

10b Het in 10a bedoelde verlof dient onbetaald te zijn.

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Aan Guillaume

Aan mijn ouders

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CONTENTS

The following publications form part of this thesis.

- S_N(ANRORC) mechanism XX. Degenerate ring transformations in reactions of 1,2,4,5-tetrazines with hydrazine
  A.Counotte-Potman and H.C.van der Plas
  J.Heterocyclic Chem., 15, 445 (1978).

- A new synthesis of 6-(alkyl)amino-3-aryl(alkyl)-1,2,4,5-tetrazines
  A.Counotte-Potman and H.C.van der Plas
  J.Heterocyclic Chem., (1981), in press.

- 1,6-Dihydro-1,2,4,5-tetrazine, a neutral homoaromatic system
  A.Counotte-Potman, H.C.van der Plas and A.van Veldhuizen
  J.Org.Chem., (1981), in press.

- ^{13}C NMR investigations of the anionic homoaromatic σ-adducts formed between liquid ammonia and 1,2,4,5-tetrazines
  A.Counotte-Potman, H.C.van der Plas and A.van Veldhuizen
  J.Org.Chem., submitted.

- The occurrence of the S_N(ANRORC) mechanism in the hydrazination of 1,2,4,5-tetrazines
  A.Counotte-Potman, H.C.van der Plas, A.van Veldhuizen and C.A.Landheer
  J.Org.Chem., submitted.

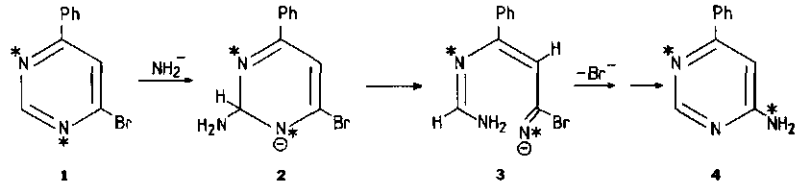
- The crystal structure of homoaromatic 6-ethyl-3-phenyl-1,6-dihydro-1,2,4,5-tetrazine
  C.H.Stam, A.Counotte-Potman and H.C.van der Plas
  J.Org.Chem., in preparation.

1 INTRODUCTION

1.1 THE S_N(ANRORC) MECHANISM

Investigation of the behaviour of aza- and polyazaaromatics towards nitrogen-containing nucleophiles continues to remain a major topic at the Laboratory of Organic Chemistry in Wageningen. A great variety of different reaction pathways has been discovered in recent years, depending on the structure of the substrate and the nature of the attacking nucleophile. For some review articles see references 1-6.

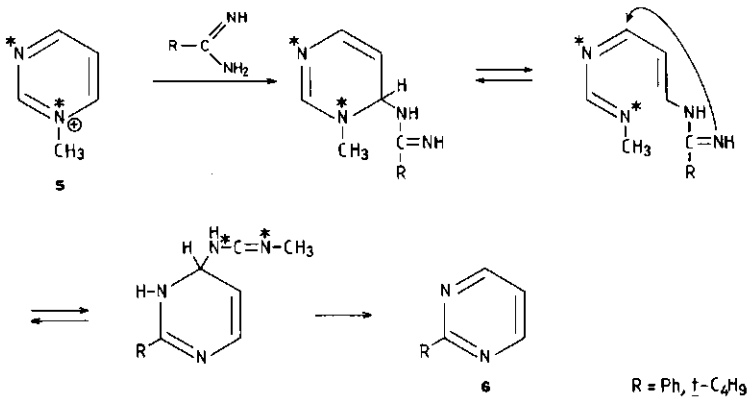
In the early seventies a new mechanism for nucleophilic substitution was discovered[7], the S_N(ANRORC) mechanism[8,9]. A reaction exemplifying this mechanism is given in scheme 1.1 and shows the conversion of 4-bromo-6-phenylpyrimidine (1)[7] into the corresponding 4-amino compound 4 on treatment with potassium amide. The process is described by a sequence of reactions, involving Addition of the Nucleophile to position 2, resulting in 2-amino-4-bromo-6-phenyl-1,2-dihydropyrimidinide (2). Ring Opening subsequently forms the open-chain intermediate 3, which undergoes Ring Closure to 4. This mechanism was substantiated by ^{15}N-labelling.



Scheme 1.1

The amide ion is the nucleophile in many conversions involving the S_N(ANRORC) mechanism and in the overall reaction *one* nitrogen atom of the heteroaromatic ring is replaced by the nitrogen atom of the nucleophile[8]. These reactions are classified as degenerate ring transformations[5,10]. The term degenerate ring transformation is used for a reaction sequence in which the ring system in the product is the same type of heterocyclic ring as originally present in the starting material[5].

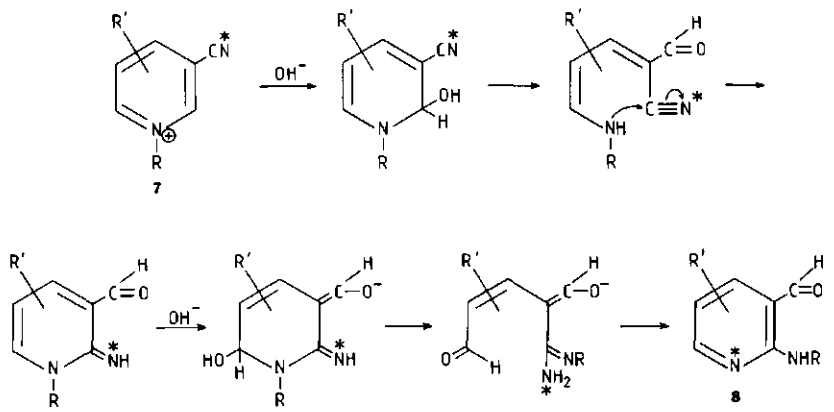
At the start of the study described in this thesis only two degenerate ring transformations involving *more* than one atom, had been described[10]. The reaction of 1-methylpyrimidinium iodide (5) with benzamidine gives 2-phenylpyrimidine (6), with the *three* atom N_1- C_2- N_3 fragment of 6 originating from the amidine. The reaction sequence is shown in scheme 1.2. In the reaction of 5 with O-methylisourea, yielding 2-aminopyrimidine, the N_2- C_2 fragment also originates from the nucleophile[10].



Scheme 1.2

Other remarkable examples of degenerate ring transformations have recently been reported in the literature. N-aminopyrimidinium salts react with hydroxylamine, forming pyrimidine N-oxides[11]. 3-Cyanopyrimidinium salts (7) undergo a double rearrangement with hydroxide ion to give 2-alkylamino-3-formylpyridines (8)[12] as visualized in scheme 1.3. This reaction can be described as an initial addition of hydroxide ion at position 2, followed by ring opening and cyclization by attack of the amino lone pair on the carbon atom of the cyano group. A renewed

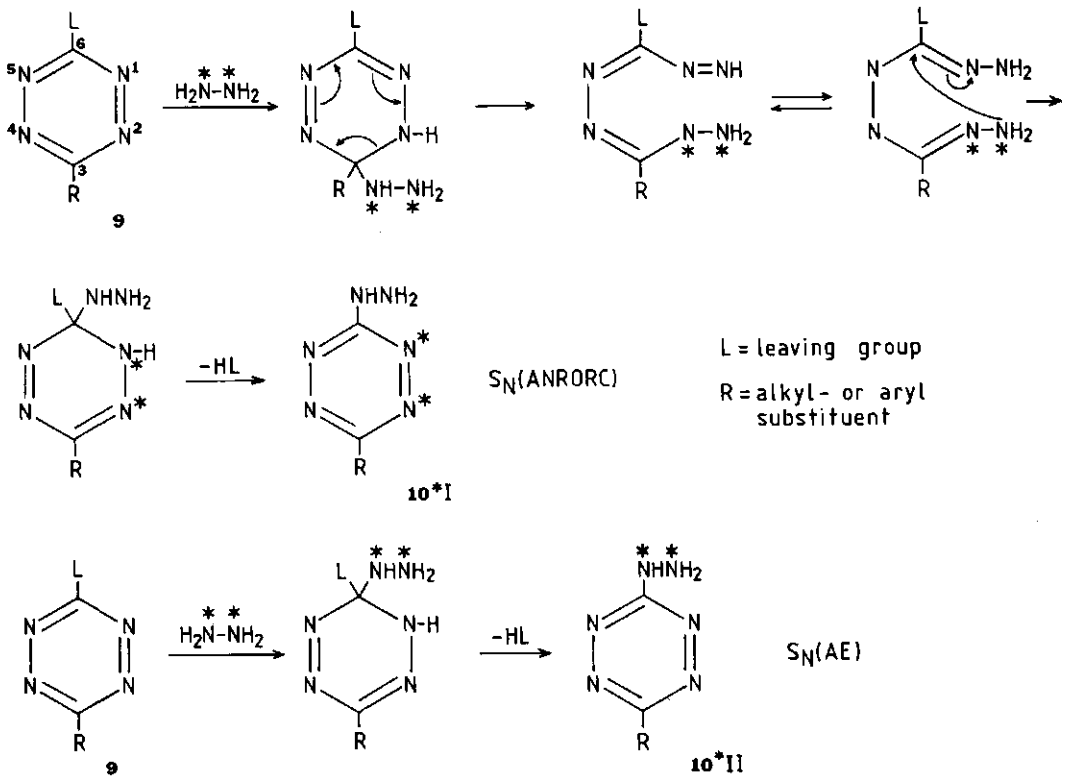
addition of hydroxide ion at position 6, ring opening and ring closure subsequently gives the reaction product 8.



Scheme 1.3

During the last ten years a number of ring transformations have been described[1-6,13,14], in which the ring systems in starting material and product are different. Recent examples are the conversions of 1-alkylpyrimidinium salts into 2-alkylaminopyridines and N-alkylpyridinium salts into alkylanilines under the influence of hydroxide ion[14] and the reaction of 5-nitropyrimidine with ketones in which all hetero atoms are lost and replaced by carbon atoms[15].
The investigation into the occurrence of the S_N(ANRORC) mechanism, during the reaction of a diaza nucleophile - namely hydrazine - with a *vicinal* diaza substrate - for example 6-L-1,2,4,5-tetrazine (9)[16-18] - is the central theme of the study in this thesis. If this mechanism is operative the *two* atom N_1- N_2 fragment of the 1,2,4,5-tetrazine ring of the resulting 6-hydrazino-1,2,4,5-tetrazine (10 I) will be replaced by the two nitrogens of hydrazine as visualized in scheme 1.4. The alternative pathway of the S_N(AE)[19] - Addition Elimination mechanism (leading to 10 II) is also depicted.
These two pathways can easily be distinguished by use of ^{15}N double labelled hydrazine as indicated by an asterix in scheme 1.4. If the substitution takes place according to the S_N(ANRORC) mechanism the label will be incorporated in the 1,2,4,5-tetrazine ring (10^{*}I), while in a reaction *via* the S_N(AE) mechanism

the label will be located in the exocyclic hydrazino group ($10^{*}II$).



Scheme 1.4

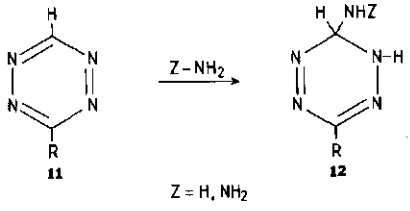
In scheme 1.4 the symbol L represents the leaving groups. These will also include hydrogen, because we are also interested in a possible occurrence of a Chichibabin hydrazination[20] of 1,2,4,5-tetrazines. The only example of this kind of reaction is the displacement of hydrogen by hydrazide ion in some pyridine derivatives[21].

1.2 σ-ADDUCTS

The first step in the reaction sequence of nucleophiles with electron deficient aromatics is the addition of the nucleophile, forming a covalently bonded σ- or Meisenheimer complex[22]. The formation of these σ-complexes can be detected by NMR spectroscopy[22].

When the amide ion or ammonia reacts with azaaromatics the formation of the σ- adduct is characterized by a large upfield shift of the hydrogen or carbon atom to which addition takes place in both ^{1}H NMR[23,24] and ^{13}C NMR[25]. This is due to a rehybridization of the carbon atom from sp^2 to sp^3. The magnitude of the upfield shift is independent of the charge, in that a negatively charged and a neutral σ-adduct show approximately the same upfield shift[25,26].

As part of the study of the S_N(ANRORC) mechanism we are interested whether a σ-adduct 12 is formed upon addition of hydrazine to 1,2,4,5-tetrazine (11); or - as a model study for this reaction - whether a σ-adduct is formed upon addition of ammonia to 1,2,4,5-tetrazine (11).

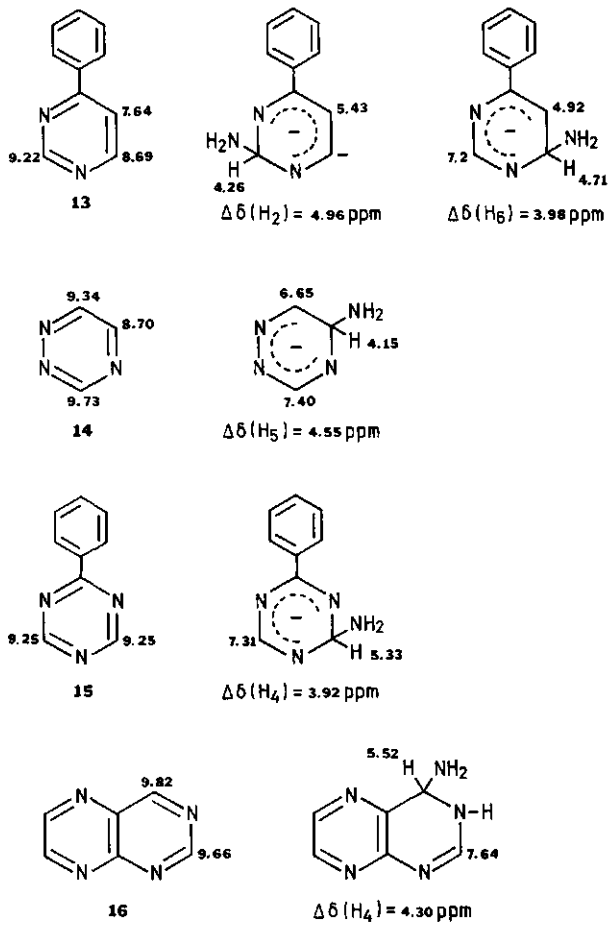


Scheme 1.5

A survey of the upfield shifts of the hydrogens attached to the sp^3 carbon atoms in several adducts is presented in scheme 1.6.

Upfield shifts (Δδ) result from addition of amide ion to C_2 or C_6 of 4-phenylpyrimidine (13)[27], to C_5 in 1,2,4-triazine (14)[28] and to C_4 of 2-phenyl-1,3,5-triazine (15)[29]. Addition of ammonia to C_4 of pteridine (16)[30] causes a similar shift. The magnitude of the upfield shift in these adducts is between 4 and 5 ppm, compared with the starting materials in usual NMR solvents.

The covalent hydrazination of 1-methylpyrimidinium iodide (17) has been described recently[31]. This is the only example - proven by means of NMR spectroscopy - of a σ-adduct formed between an azaaromatic compound and hydrazine.

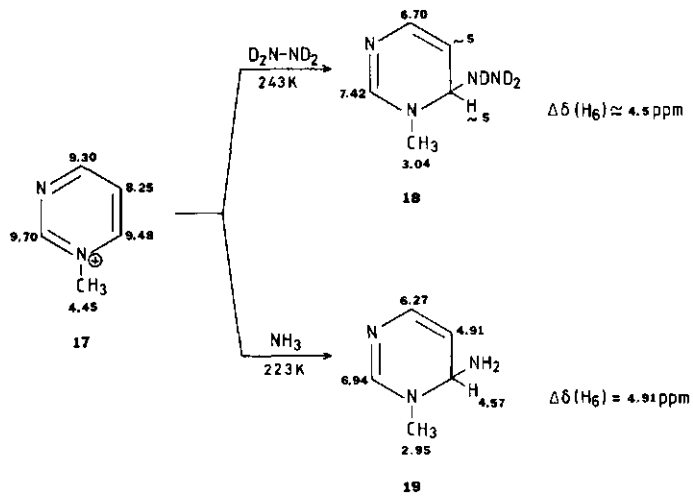


Scheme 1.6

Comparison of the ^{1}H chemical shift data of the σ-adduct 18 with those of the product of covalent amination 19[26] and with those of 17 itself (Scheme 1.7), reveals that with both nucleophiles the attack takes place at C_6 and that the upfield shifts in both σ-adducts 18 and 19 are similar. This indicates that in general an upfield shift of 4-5 ppm can be expected upon addition of nucleophiles to azaaromatics[32].

On dissolving 1,2,4,5-tetrazines in liquid ammonia or hydrazine, however, the expected Δδ value of 4-5 ppm was not found. A very unusual upfield shift was observed instead[33,34].

On comparison with several model compounds it became obvious that the explanation for this anomaly can be found in the concept of homoaromaticity[34].



Scheme 1.7

1.3 HOMOAROMATICITY

Homoaromaticity as a concept was introduced by Winstein[35] in 1959. He defined[36] a species to be homoaromatic if the σ-backbone is interrupted either by removing the σ-bond entirely or by interposition of one or more methylene groups. The σ-skeleton may be interrupted on one, two or three sides giving rise to a monohomo-, bishomo- or trishomoaromatic species. As for aromaticity the criteria for homoaromaticity are: a) the compound must obey the Hückel rule and possess (4n+2) π electrons; b) delocalization energy due to cyclic electron delocalization must exist; c) the compounds must be able to sustain an induced ring current.

The overlap between the two ends of the conjugated system to form a (4n+2) cyclic array is brought about by homoallylic participation[37,38] of the cyclopropane ring, which is visualized in figure 1.1. The overlap is of a type intermediate between σ and π . Overlap becomes restricted to single lobes, the boundaries of which are limited to that surface of the molecule opposite to the bridged atom.

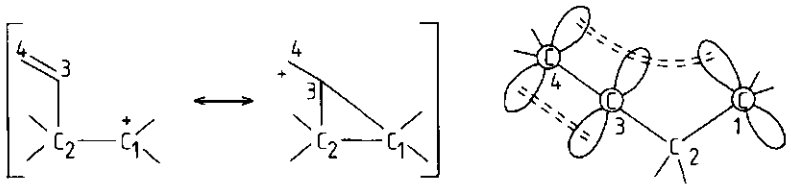
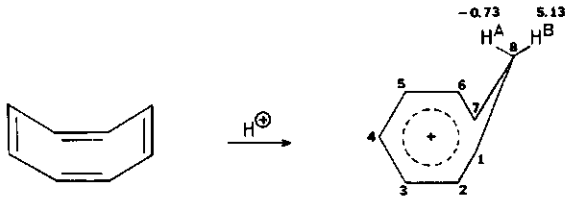


Fig.1.1 Homoallylic participation

The net level of homoaromatic delocalization will be linked directly to the resultant overlap integral. Homoaromatic interactions occur because of stabilizing π interactions but only at the expense of the energy required to distort the σ-framework.

The compound examined most thoroughly is the homotropylium cation (21), obtained upon deprotonation of cyclooctatetraene (20)[39].



Scheme 1.8 **20** **21**

Experimental evidence proving homoaromaticity in 21 is provided by the following observations:

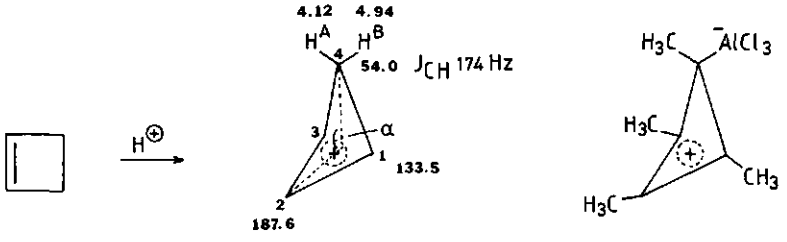
a) The great difference in chemical shift[37] between H^A (the hydrogen above the aromatic ring, which is in the shielding regio) and H^B (the hydrogen in the exoposition, which is in the deshielding regio) due to the ring current. A comparison with the ^1H NMR data of several model compounds reveals[37] that none of these species offers a better description of the observed phenomena.

b) The ^{13}C chemical shift values which give a measure of the delocalization of charge[40], related - of course - to the electron delocalization.

c) The diamagnetic susceptibility exaltation Λ[41], which is a measure of the extra anisotropy due to the ring current of aromatic molecules. A Λ of 20 was measured[42] for the homotropylium cation, which - on subtraction of the contribution of the cyclopropane ring (Λ = 5) - is comparable with the Λ of the tropylium cation (Λ = 16).

d) The UV spectrum from which the 1,7 resonance integral is calculated. The π-bond order calculated from β_{17} is 0.56[43].

It is also possible to optimize the conformation of the homoaromatic molecule by theoretical calculations[44]. The last few years these theoretical calculations are the main field of interest in the literature concerning homoaromaticity. Only crystal structural data however will give a quantitative estimate of the amount of orbital overlap and the importance of homoaromatic contribution. This subject is the major theme in a recent review article on homoaromaticity[45]. An example of a calculated structure[47] which is in good agreement with the X-ray structure[48] is found for the smallest homoaromatic compound, the homocyclopropenium cation (23), formed on protonation of cyclobutene (22). The X-ray structure was determined for the aluminiumtrichloride complex of tetramethylcyclobutadiene (24)(see Table 1.1).



22 23 24

Scheme 1.9

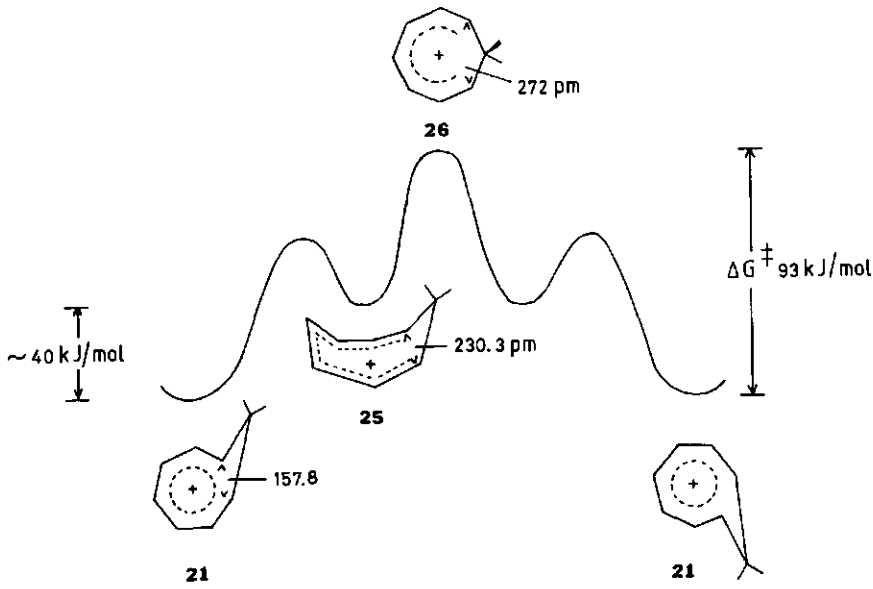
Table 1.1 Calculated and X-ray structure of the homocyclopropenium cation

compound	bond length[a]			α[b]
	1-2	1-3	1-4	
23	140.2	173.9	150.2	149.3
24	138.7	177.5	151.0	148.5

a bond length in pm

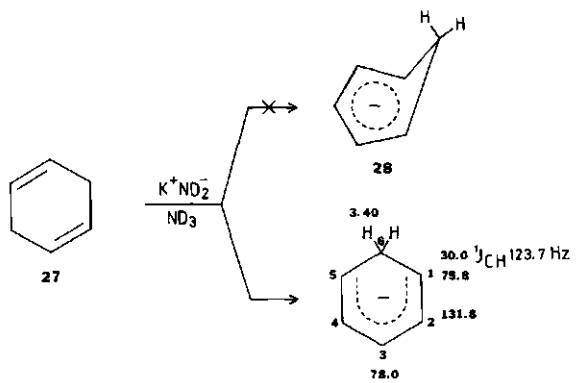
b see scheme 1.9

New ab initio calculations have been carried out recently[49] for the homotropylium cation (21). This compound had already been found to exist in two forms, one with the CH_2 group pointing upwards, the other with the CH_2 group downwards. Deuteration instead of protonation (see scheme 1.8) showed that the interchange between these two forms is a ring inversion[50] with $\Delta G^{\ddagger}$ = 93 kJ/mol.



Scheme 1.10

This ring inversion was originally visualized as proceeding through a planar form, the classical cyclooctatrienyl cation (26)[43]. It became evident from the new calculations of Haddon[49], that this energy profile contains an extra species, a non-planar cyclooctatrienyl cation (25), which lies 40 kJ/mol higher in energy than the homotropylium ion. The ring inversion is accompanied by an enlargement of the 1,7 interatomic distance - the calculated values of which are given in scheme 1.10 - and consequently the methylene bridge is flattened. The *negatively* charged counterpart of the homotropylium cation is the homocyclopentadienyl anion (28). Considerable effort has been undertaken to prove the existence of this species, but without success. A recent study[51] definitively proves that on proton abstraction from 1,3- and 1,4-cyclohexadienes (27) a *planar nonhomoaromatic cyclohexadienyl anion (29)* is formed. This was concluded from NMR spectroscopic evidence in ND_3 containing $K^+ND_2^-$.

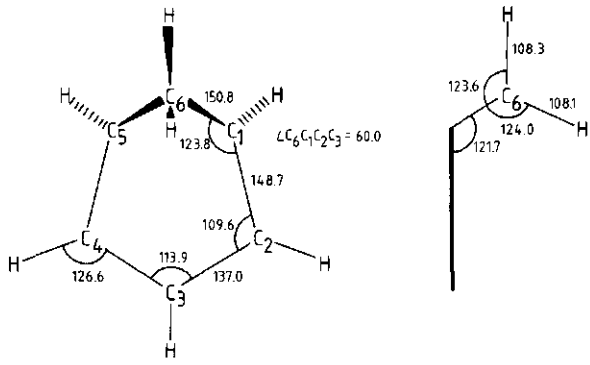


Scheme 1.11

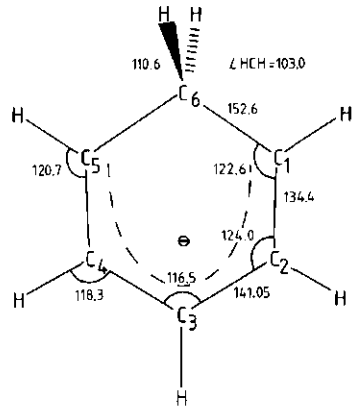
Coupling constants between ^{13}C and ^{1}H nuclei are very sensitive to angular distortion. In the homotropylium cation $^{1}J_{C_8H}$ is found to be 159 Hz[37]. The coupling constant found for 29 ($^{1}J_{C_6H}$ = 123.7 Hz) however, is comparable with that of the benzenium cation (122 Hz) and that of an sp^3 carbon atom in 27 (126 Hz). According to ^{13}C NMR the negative charge in 29 is localized on C_1, C_3 and C_5, this is in agreement with the π-electron populations calculated by Birch et al.[52].

The STO-3G optimized structure of 29 actually reveals that the ring is planar[52], the STO-3G structure of 28 reveals that this structure also corresponds to a

local minimum, but this lies 142 kJ/mol above that of 29.



28



29

Fig. 1.2 STO-3G optimized structures for the homocyclopentadienyl anion (28) and the cyclohexadienyl anion (29)

A homoaromatic system can be described by an interaction between the conjugated system and the methylene group. Olah et al.[51,53] explain the absence of the expected homoaromaticity of the cyclohexadienyl anion by the stabilizing interaction of $\pi^*(CH_2)$ with the HOMO of the pentadienyl fragment (as in figure 1.3), which makes the puckering to a homoaromatic structure unnecessary. In contrast cations have a low lying HOMO and the interaction with $\pi^*(CH_2)$ will be negligible and the unfavourable interaction with the filled $\pi(CH_2)$ will dominate. In these cases puckering to the homoaromatic conformation will be favourable, since the

overlap with the $\pi(CH_2)$ will decrease.

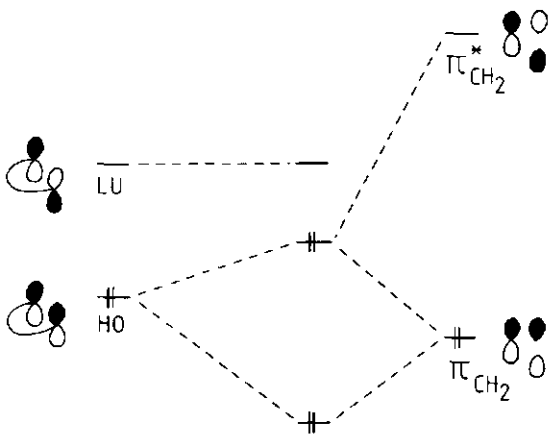
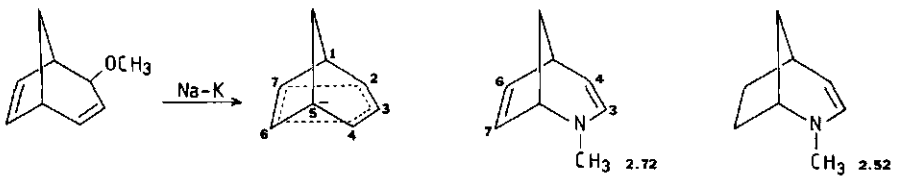


Fig.1.3 Interaction of linear (4n+2) π-electron systems with a methylene group

An example of a negatively charged 6π electron species which has homoaromatic properties is the *bis*homocyclopentadienide anion (31)[57], prepared from Na-K treatment of the bicyclic diene 30. Comparison with the unsubstituted bicyclic diene showed that the most significant difference is the upfield shift of H_6 and H_7, due to delocalization of negative charge to C_6 and C_7.



30 31 32 33

Scheme 1.12

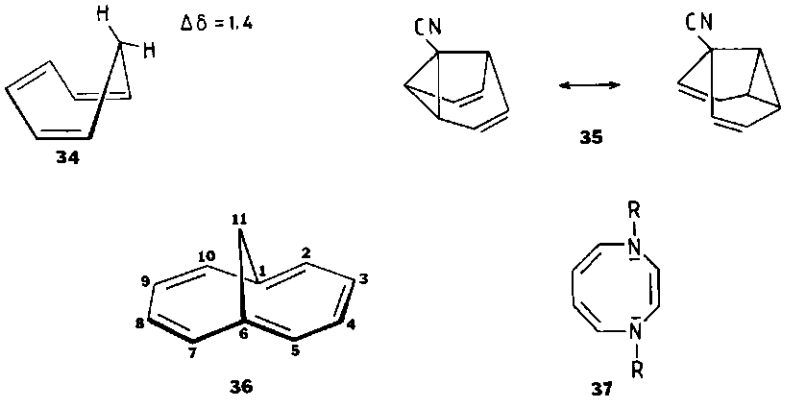
A *neutral* heterocyclic analogon of 31 in which the lone pair of the nitrogen atom contributes to the 6π electron system has also been described[58]. Comparison of the UV spectrum of N-methyl-2-azabicyclo [3,2,1] octa-3,6-diene (32) (λ_{max} 242 (2470), 272 (1350)) with that of the partially saturated 33 (248 (1950)) gives a strong indication of the non-bonded interaction between the two chromophores. The downfield shift of 0.2 ppm of the methyl group in 32 as compared with 33 also indicates that there is a transfer of lone pair density, due to a contribution of the nitrogen lone pairs to the delocalized system. The question remains however whether a homoaromatic *contribution* is involved or actual homoaromaticity.

Although neutral homoaromaticity is elusive probably because systems designed to produce neutral homoaromatic stabilization are somewhat antiaromatic[56], a few examples of possible homoaromatic contributions are found in the literature. None of them however has a very pronounced homoaromatic character. Paquette has devised a theoretical criterion for homoaromaticity based on a vector analysis of overlap calculated from a knowledge of the particular molecular geometry (X-ray analysis) of the species[59].

MINDO/3 calculations have shown[60] that in 1,4- and 1,2-dihydropyridine there is a homoaromatic stabilization due to a contribution of the nitrogen lone pair to the HOMO. These calculated structures are hardly puckered however and show a great distance between the termini of the π-system, so that they cannot be regarded as real homoaromatic species.

Other neutral species, possessing at least some homoaromatic character are: cycloheptatriene (34)[61] and 1-cyanosemibullvalene (35)[62]. A controversy exists in the literature [45,63] about the homoaromaticity of the methano bridged annulenes, for example 1,6-methano[10] annulene (36).

The parent [10] annulenes do not show aromatic properties[64] and in the isoelectronic diaza [8] annulenes (37) the aromaticity depends on the substituents R present on the nitrogen atoms[65]. In contrast the ^{1}H NMR spectrum of the bridged [10] annulene derivatives does indicate the presence of a diamagnetic ring current. The transannular resonance integral was estimated at about 40% of that of neighbouring p_z orbitals in benzene[63] and the 1,6 distance in the 11,11-dimethyl derivative of 36 was only 180 pm[66]. The corresponding bridged [9] annulene anion[67] and [11] annulene cation[68] have also been described. In the latter the 1,6 distance was found to be 230 pm, by means of X-ray diffraction analysis[69]. It was obvious from the ^{13}C NMR data, that this compound can be regarded as a substituted homotropylium cation[68].



Scheme 1.13

Compared with naphthalene these bridged annulenes possess transannular overlap and lack the 9,10 σ-bond, which is replaced by a sp^3 carbon atom. From this point of view they can be regarded as homoaromatic species.
Thus far no real homoaromatic compounds possessing heteroatoms in the aromatic ring have been described. The examples mentioned above[58,60] only show a homoaromatic contribution.

1.4 PURPOSE OF THE INVESTIGATION

The central theme in this study is the investigation of the reactivity of 1,2,4,5-tetrazines towards hydrazine with the aim to establish whether in these reactions an S_N(ANRORC) mechanism occurs. A study on the reaction of ammonia with 1,2,4,5-tetrazines and on the character of 1,6-dihydro-1,2,4,5-tetrazines was also included in the course of our research.

Chapter 2 describes the one-pot oxidation of the covalent amination products of 3-aryl(alkyl)-1,2,4,5-tetrazines.

Chapter 3 reports on a ^{1}H-NMR study of 1,6-dihydro-1,2,4,5-tetrazines as model compounds for the σ-adduct of ammonia or hydrazine to 1,2,4,5-tetrazine. A new homoaromatic system is discovered.

Chapter 4 comprises a ^{13}C NMR investigation of the σ-adducts formed between ammonia and 1,2,4,5-tetrazines. Evidence is presented that these σ-adducts are anionic homoaromatic species in liquid ammonia.

Chapter 5 describes the hydrazinolysis reactions of 6-amino- and 6-bromo-3-methyl-1,2,4,5-tetrazine. ^{15}N-labelled hydrazine is used to establish the reaction mechanism.

Chapter 6 presents the finally complete reaction mechanism of hydrazine with 1,2,4,5-tetrazines. Both ^{15}N-labelling and ^{1}H- and ^{13}C NMR spectroscopy are used to elucidate the reaction mechanism. Evidence is compiled showing that at least part of the molecules react *via* the S_N(ANRORC) mechanism.

Chapter 7 reports on the crystal structure of 6-ethyl-3-phenyl-1,6-dihydro-1,2,4,5-tetrazine, which is elucidated by means of X-ray structural analysis.

Chapter 8 contains a general discussion of the work described in this thesis.

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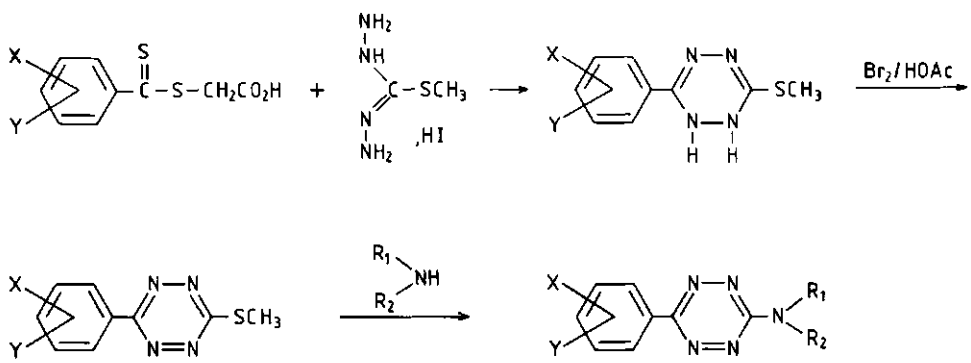
2 A NEW SYNTHESIS OF 6-(ALKYL)AMINO-3-ARYL(ALKYL) -1,2,4,5-TETRAZINES

2.1 INTRODUCTION

There is strong interest in the synthesis of 6-(substituted)amino-3-aryl-1,2,4,5-tetrazines since some of these compounds exhibit suppressive antimalarial activity. Several methods for the preparation of these compounds have been described[1-3] but they all show severe limitations.
Very recently an attractive synthesis of these compounds has been published by Werbel et al.[4] involving: i) the thiobenzoylation of hydrazinecarbohydrazonothioic acid methyl ester with (substituted phenyl)thioxomethyl thio acetic acid into a 1,2-dihydro-3-aryl-6-(methylthio)-1,2,4,5-tetrazine, ii) oxidation of this compound with bromine in acetic acid into 3-aryl-6-(methylthio)-1,2,4,5-tetrazine and iii) treatment with amines (Scheme 2.1).



Scheme 2.1

In most syntheses of the 6-(substituted)amino-3-aryl-1,2,4,5-tetrazines described in the literature so far, the (substituted)amino group is introduced by replacement of X in the 6-X-3-aryl-1,2,4,5-tetrazines.

2.2 RESULTS AND DISCUSSION

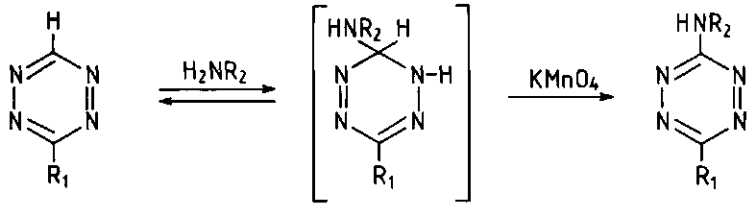
In this paper we report a new approach to the synthesis of 6-(substituted)amino-3-aryl-1,2,4,5-tetrazines, which differs from the other methods of preparation in this respect that the (substituted)amino group is introduced in a 3-aryl-1,2,4,5-tetrazine being *unsubstituted* at position 6. This method is not limited to aryl-tetrazines, but can also be applied for the preparation of 6-(substituted)amino-1,2,4,5-tetrazines, containing an *alkyl* group on position 3. The procedure is quite simple and is exemplified with the preparation of 6-amino-3-phenyl-1,2,4,5-tetrazine (1).

The red 3-phenyl-1,2,4,5-tetrazine (1 equivalent) is dissolved in liquid ammonia. The solution becomes yellow. After addition of 1 equivalent of potassium permanganate to the liquid ammonia solution and working-up 6-amino-3-phenyl-1,2,4,5-tetrazine (1) can be isolated in 74% yield. Use of ferric chloride or dichlorodicyanoquinone instead of potassium permanganate also gave 6-amino-3-phenyl-1,2,4,5-tetrazine but the yields were much lower. With air and oxygen only starting material could be retrieved.

We propose that by dissolving of 3-phenyl-1,2,4,5-tetrazine in liquid ammonia the yellow coloured 6-amino-3-phenyl-1,6-dihydro-1,2,4,5-tetrazine is formed (Scheme 2.2). Dihydro-1,2,4,5-tetrazines are known to be easily oxidized.[5] Potassium permanganate added to the liquid ammonia solution[6] is apparently sufficiently active to perform the oxidation at the low temperature. Attempts to isolate the 1,6-dihydrotetrazine derivative met with little success, only the starting material could be recovered.

Primary aliphatic amines were found to be as active as liquid ammonia. When 3-phenyl-1,2,4,5-tetrazine was dissolved in an excess of primary amine at 238 to 243 K and subsequently potassium permanganate was added the corresponding 6-alkylamino-3-phenyl-1,2,4,5-tetrazine could be isolated. The yields vary depending on the size of the alkyl group (Table 2.1). The reactions with the primary amines have to be carried out at low temperature, because otherwise decomposition occurs. Attempts to introduce an arylamino group by performing the reaction with aromatic amines were not succesful.

The generality of this reaction can be shown by the 6-(alkyl)amino-1,2,4,5-tetrazines (1-14) obtained by this amination-oxidation procedure. They are summarized in table 2.1, together with the yields, their microanalytical data, melting points and ^{1}H-NMR spectra. The mass spectral data are collected in table 2.2.



Scheme 2.2

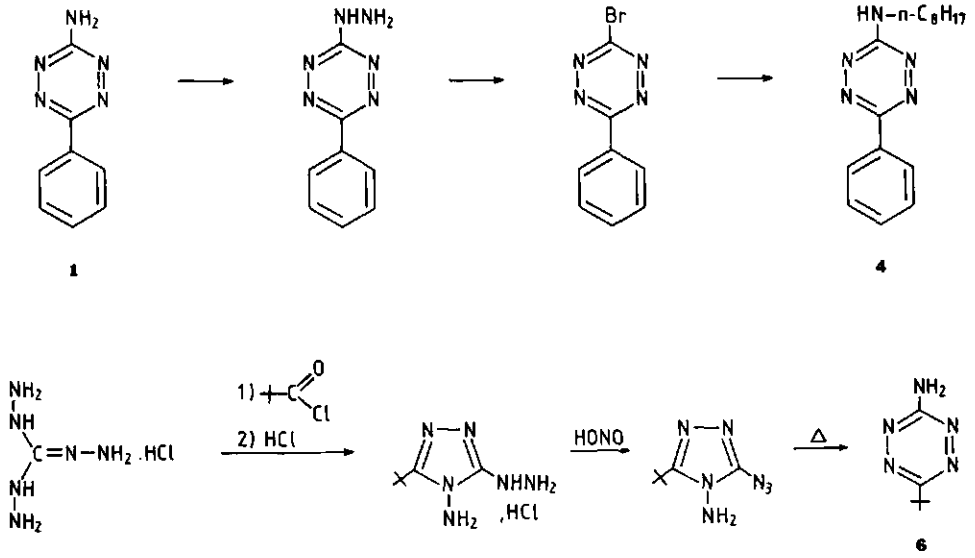
$R_1 = CH_3$, $t\text{-}C_4H_9$, C_6H_5, $p\text{-}Br\text{-}C_6H_4$
$R_2 = H$, C_2H_5, $i\text{-}C_3H_7$, $n\text{-}C_4H_9$, $n\text{-}C_8H_{17}$

Most of the compounds prepared by this method were not described in the literature before. The already known compounds 1 and 10 were prepared according to published routes[2] and their physical data compared with those of the compounds obtained in this study. They proved to be identical. Two compounds, *i.e.* 6-n-octylamino-3-phenyl-1,2,4,5-tetrazine (4) and 6-amino-3-t-butyl-1,2,4,5-tetrazine (6) were prepared independently according to a different route (Scheme 2.3).
Synthesis of compound 4 involves hydrazinolysis of 6-amino-3-phenyl-1,2,4,5-tetrazine (1) into 6-hydrazino-3-phenyl-1,2,4,5-tetrazine, conversion of this 6-hydrazino compound with bromine in acetic acid[7] into 6-bromo-3-phenyl-1,2,4,5-tetrazine and amino-debromination with 2 equivalents of n-octylamine at room temperature. Compound 6 was prepared from pivaloylchloride and triaminoguanidine according to the route given in scheme 2.3.[8] Both compounds proved to be identical with those, obtained by the amination-oxidation method.
Most mass spectra of 1,2,4,5-tetrazines published thusfar comprise 3,6-symmetrical

Footnotes Table 2.1:

a) 226°C.[1,2] b) 171°C.[2] c) 247°C.[4]
d) Exact mass measurement gave for $C_{10}H_{19}N_5$ (M^+) 209.1647 (theoretical 209.1640).
e) Exact mass measurements gave for $C_{14}H_{27}N_5$ (M^+) 265.2275 (theoretical 265.2266).
f) Compounds 1, 6, 10 and 14 are measured in aceton-d_6, all other compounds in $CDCl_3$.
g) $\beta\text{-}CH_2$ is the total multiplet due to the $\beta\text{-}CH_2$ and $\gamma\text{-}CH_2$ group in n-C_4H_9 and β, γ, δ, etc. CH_2 groups in n-C_8H_{17}.
h) $J_{NH\text{-}CH_2} = 5.8$ Hz.

No	R_1	HNR_2	m.p. °C	yield %	Analyses % Calcd./Found C	H	^{1}H-NMR δ (f) 3-position	HN	α-CH_2	β-CH_2(g)	ω-CH_3
1	C_6H_5	NH_2	213.5-214.5(a)	74	55.48 55.60	4.07 4.12	meta and para 7.46-7.60 ortho 8.26-8.48	7.45			
2	C_6H_5	HNC_2H_5	143-146	59	59.68 59.46	5.51 5.62		6.18	3.69(h)		1.38
3	C_6H_5	$HNn\text{-}C_4H_9$	126-127	44	62.86 63.08	6.59 6.53		6.23	3.67	1.56	1.00
4	C_6H_5	$HNn\text{-}C_8H_{17}$	105-108	38	67.33 67.05	8.12 7.95		5.83	3.67	1.30	0.86
5	C_6H_5	$HNi\text{-}C_3H_7$	152-154	18	61.37 61.35	6.09 5.99		5.77	4.38		1.38
6	$t\text{-}C_4H_9$	NH_2	114-117	72	47.04 46.78	7.24 7.35	1.44	6.95			
7	$t\text{-}C_4H_9$	HNC_2H_5	48-50	81	53.01 53.11	8.34 8.54	1.47	6.35	3.60(h)		1.31
8	$t\text{-}C_4H_9$	$HNn\text{-}C_4H_9$	oil	47	57.38 57.64	9.15 9.26(d)	1.50	6.27	3.58	1.50	1.10
9	$t\text{-}C_4H_9$	$HNn\text{-}C_8H_{17}$	oil	58	63.35 63.19	10.25 10.40(e)	1.48	6.33	3.57	1.29	0.87
10	CH_3	NH_2	170-171(b)	80	32.43 32.53	4.54 4.62	2.74	7.00			
11	CH_3	HNC_2H_5	91-92	76	43.15 43.38	6.52 6.69	2.83	6.14	3.63(h)		1.33
12	CH_3	$HNn\text{-}C_4H_9$	50-51	35	50.28 50.27	7.48 7.85	2.80	6.00	3.56	1.57	0.98
13	CH_3	$HNn\text{-}C_8H_{17}$	64-65.5	35	59.16 59.39	9.48 9.49	2.80	5.65	3.56	1.30	0.90
14	p-Br-C_6H_4	NH_2	241.5-242.5(c)	81	38.11 38.30	2.40 2.41	m. 7.77 o. 8.31	7.48			



Scheme 2.3

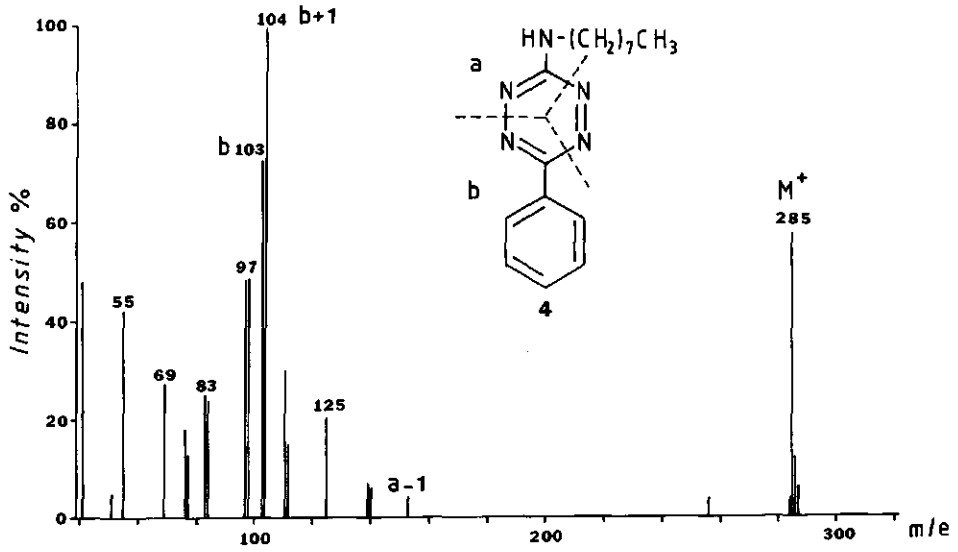


Figure 2.1 Mass spectrum of 6-n-octylamino-3-phenyl-1,2,4,5-tetrazine (4)

Table 2.2 Mass spectrometry (a) of compounds 1-14 of table 2.1

R_1 \ HNR_2		NH_2	HNC_2H_5	$HN\underline{n}\text{-}C_4H_9$	$HN\underline{n}\text{-}C_8H_{17}$
C_6H_5	M^+	173 11	201 21	229 75	285 58
	a	42 11	70 32	98 24	153(d) 4
	b	103 100	103 100	103 100	103 73
	inl.cond. (b)	probe 150°C	h.b. 150°C	probe 90°C	probe 90°C
$\underline{t}\text{-}C_4H_9$	M^+	153 10	181 12	209 10	265 12
	a	42 31	70 75	98 11	153(d) 6
	b-1 (c)	84 33	84 47	84 53	84 58
	$\underline{t}\text{-}C_4H_9$	57 100	57 100	57 100	57 79
	inl.cond.	probe 50°C	h.b. 130°C	h.b. 150°C	h.b. 170°C
CH_3	M^+	111 13	139 27	167 15	223 28
	a	42 97	70 41	98 3	153(d) 3
	b	41 100	41 27	41 55	41 100
	inl.cond.	h.b. 180°C	h.b. 140°C	probe 30°C	h.b. 180°C
p-Br-C_6H_4	M^+	253/251 15/16	$HN\underline{i}\text{-}C_3H_7$ / C_6H_5		
	a	42 8			
	b	183/181 96/100		M^+	215 23
				a	84 25
	b-Br	102 97		b	103 100
	inl.cond.	h.b. 185°C		inl.cond.	h.b. 160°C

(a) Only the most characteristic peaks are given.
All mass spectra were measured at 70 eV.
For each compound the first figure is the m/e value, the second figure is the intensity of the peak in percentage of the base peak.

(b) Inlet conditions: inlet system: - all glas heated inlet system (hot box = h.b.),
- direct inlet (probe).
inlet temperature.

(c) Fragment b is very small (< 1% for compound 6).

(d) (a-1), with the n-octylamino group no fragment a is observed.

disubstituted 1,2,4,5-tetrazines.[9,10] Like symmetrical disubstituted 1,2,4,5-tetrazines the unsymmetrical disubstituted compounds 1-14 show a very simple splitting pattern. Besides the molecular ion M^+ in nearly all our compounds the ion $(M-28)^+$ is observed, due to loss of N_2. The residual species show cleavage between the N-N bond resulting in two different fragments a and b (and a+1, a-1; b+1, b-1). Then the characteristic splitting pattern for the ions a and b is observed. As an example the mass spectrum of 6-n-octylamino-3-phenyl-1,2,4,5-tetrazine (4) is given (figure 2.1).

2.3 EXPERIMENTAL SECTION

Melting points are uncorrected. Mass spectra were determined on an AEI MS 902 mass spectrometer. ^{1}H-NMR spectra were recorded on a Varian EM 390 spectrometer or on a Hitachi-Perkin Elmer R-24B spectrometer. TMS was used as internal standard (δ 0 ppm). Column chromatography was carried out over Merck Silica gel 60 (70-230 mesh ASTM).

Preparation of starting materials

3-Phenyl-1,2,4,5-tetrazine. This compound was prepared according to the synthesis described by Lang, Johnson and Cohen.[11] We modified the oxidation step by using air or oxygen instead of bromine in acetic acid.

3-t-Butyl-1,2,4,5-tetrazine. This compound was prepared analogous to the synthesis of Lang et al.[11] Accordingly 16 g of pivalimido ethyl ether hydrochloride,[12] 31 g of formamidine acetate[13] and 50 mL of absolute ethanol were cooled at -10°C, 70 mL of hydrazine hydrate were added, keeping the temperature below 5°C. The mixture was stirred during 3 h at 25°C and then poured into 500 mL of water. The water layer was continuously extracted with boiling dichloromethane for 4 days; during this period air was bubbled through the boiling dichloromethane in order to oxidize the dihydrotetrazine.
After column chromatography on silica gel using as eluent pentane-dichloromethane, successively 0.40 g of 3,6-di-t-butyl-1,2,4,5-tetrazine (4%) was obtained, m.p. 95-97°C (lit.[10] 95-99°C); ^{1}H-NMR (CCl_4): δ 1.57 (s, t-C_4H_9) (lit.[10] δ 1.57) and 0.63 g. of 3-t-butyl-1,2,4,5-tetrazine, a red volatile oil, (4,5%); ^{1}H-NMR (CD_3OD): δ 1.58 (9H, s, t-C_4H_9), 10.45 (1H, s, H_6); MS: M^+, m/e = 138. Exact mass measurements gave for $C_6H_{10}N_4$ (M^+) 138.0907 (theoretical 138.0905).
Anal. Calcd. for $C_6H_{10}N_4$: C, 52.15; H, 7.30. Found: C, 52.51; H, 7.59.

3-Methyl-1,2,4,5-tetrazine. This compound was prepared from 6-amino-3-methyl-1,2,4,5-tetrazine as described previously.[14] The preparation of this compound, analogous to the synthesis of Lang et al.,[11] was not succesful; the yield was poor and it was difficult to separate 3-methyl-1,2,4,5-tetrazine from 3,6-dimethyl-1,2,4,5-tetrazine.

3-(p-Bromo)phenyl-1,2,4,5-tetrazine was also prepared analogous to the synthesis of Lang et al.,[11] overall yield 46%, m.p. 182-184°C; ^{1}H-NMR ($CDCl_3$): δ 7.75 (2H, d, meta H), 8.50 (2H, d, ortho H), 10.25 (1H, s, H_6); M^+, m/e = 238/236. Anal. Calcd. for $C_8H_5BrN_4$: C, 40.53; H, 2.13. Found: C, 40.61; H, 2.17.

Amination-oxidation procedure

As an example the procedure is given for 3-phenyl-1,2,4,5-tetrazine; the other 1,2,4,5-tetrazines were treated in a similar way.

A. With liquid ammonia

3-Phenyl-1,2,4,5-tetrazine (100 mg = 0.63 mmoles) was dissolved in 10 ml of liquid ammonia; immediately the yellow colour is observed. After 5 min 67 mg (0.42 mmole = 1 redox equivalent) of potassium permanganate were added at once. After 10 min, 25 ml of ethyl acetate was added slowly. The ammonia is evaporated off, the solution is filtered through silica gel. The ethyl acetate is evaporated off in vacuo and the solid residue is crystallized from ether/pentane.

B. With alkylamines

The procedure is the same as described under A) using about 3 ml of liquid alkylamine at low temperature (-35°C to -40°C). However, when using n-octylamine, due to the high melting point (0°C) of n-octylamine, a 1:1 mixture of n-octylamine and ethanol was used.

All compounds 1-14 were crystallized from ether/pentane.

6-n-Octylamino-3-phenyl-1,2,4,5-tetrazine (4)

A solution of 173 mg (1 mmole) of 1 in 4 ml of ethanol was refluxed with 0.10 ml (2 mmoles) of hydrazine hydrate during 1 h. After cooling to room temperature 6-hydrazino-3-phenyl-1,2,4,5-tetrazine separated out as crystals; they were filtered off and washed with 1 ml of ethanol, yield 139 mg (74%), m.p. 169-171°C (lit.[15] 178°C decomp); MS: M^+, m/e = 188. It was further characterized as its benzaldehyde

hydrazone; m.p. 213-214.5°C (lit.[15] 211-212°C); M^+, m/e = 276.
Anal. Calcd. for $C_{15}H_{12}N_6$: C, 65.20; H, 4.38. Found: C, 65.07; H, 4.25.

The 6-hydrazino compound was dissolved in 5 ml of acetic acid and oxidized with bromine according to the procedure published.[7] We obtained 149 mg of 6-bromo-3-phenyl-1,2,4,5-tetrazine (85%), m.p. 126-129°C (lit.[1,7] 131°C); MS: M^+, m/e = 238/236. To 149 mg (0.36 mmole) of the 6-bromo compound dissolved in 4 ml of tetrahydrofuran 0.22 ml (1.3 mmoles) of n-octylamine was added. The mixture was stirred at room temperature during 30 min, the solvent was evaporated off and the material was filtered through silica gel. Recrystallization from pentane gave 131 mg of 4, yield 73%, m.p. 105.5-107°C. IR, ^{1}H-NMR and mass spectrum are the same as for compound 4 obtained by the amination-oxidation procedure. Mixed melting point determination gave no depression.

6-Amino-3-t-butyl-1,2,4,5-tetrazine (6)

This compound was prepared from pivaloylchloride and triaminoguanidine hydrochloride analogous to the preparation of 6-amino-3-phenyl-1,2,4,5-tetrazine as described by Takimoto and Denault.[2,8] Yield 1% (!) m.p. 114-119°C. ^{1}H-NMR and mass spectrum are identical with those of compound 6 obtained by the amination-oxidation procedure.

Acknowledgement

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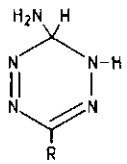
3 1,6-DIHYDRO-1,2,4,5-TETRAZINE, A NEUTRAL HOMOAROMATIC SYSTEM

3.1 INTRODUCTION

In a preceding paper[1] we described the formation of 6-amino-3-aryl(alkyl)-1,2,4,5-tetrazines by reaction of the appropriate 3-aryl(alkyl)-1,2,4,5-tetrazines with liquid ammonia and subsequent oxidation with potassium permanganate. As first step in this reaction sequence the formation of a σ-adduct between ammonia and the 1,2,4,5-tetrazine, i.e. 6-amino-3-aryl(alkyl)-1,6-dihydro-1,2,4,5-tetrazine (1) was proposed. In order to obtain some evidence for the intermediary existence of these σ-adducts, the ^{1}H NMR spectrum of 3-phenyl-1,2,4,5-tetrazine in liquid ammonia was measured. We observed that the ring hydrogen appeared at 1.51 ppm. This means an upfield shift of 8.84 ppm when we compare this chemical shift value with the one, found for the 6-hydrogen of 3-phenyl-1,2,4,5-tetrazine measured in deuteromethanol (10.35 ppm). This upfield shift clearly points to the formation of 1 (R=Ph) in liquid ammonia. However, it is very interesting that this chemical shift is observed at an unusually high field (1.51 ppm). The chemical shifts observed for adducts between pyrimidines,[3] 1,2,4-triazines,[4] pteridines[5] and amide ion or ammonia are between 4-5.5 ppm. This seems to indicate that the change of hybridization of C_6 ($sp^2 \rightarrow sp^3$) which occurs on adduct formation is not the only factor responsible for this considerable upfield shift of 8.84 ppm.



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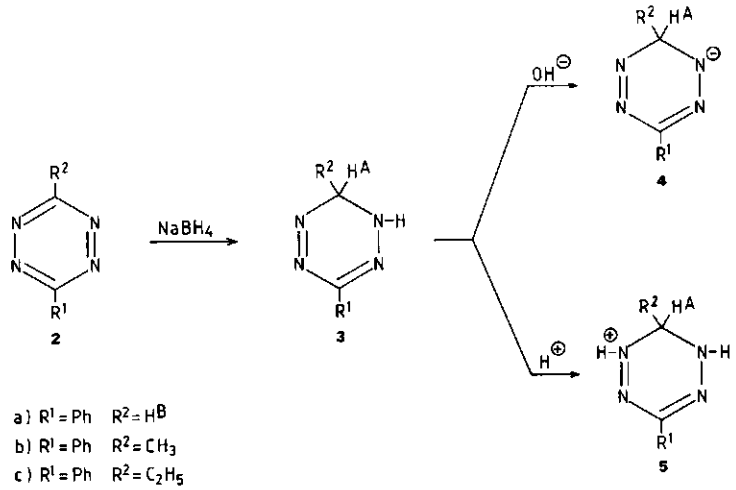
In order to obtain more insight into the structural features of adduct 1 (R=Ph), which could possibly explain this unexpected high upfield shift, we synthesized some 3-aryl(alkyl)-1,6-dihydro-1,2,4,5-tetrazines (3a-d) and studied the ^{1}H NMR spectra of these compounds, their conjugate bases 4 and conjugate acids 5 at various temperatures.

3.2 RESULTS AND DISCUSSION

The compounds 3a-d could be obtained in good yield by treatment of 1,2,4,5-tetra-

zines 2a-d with sodium borohydride.

The 1,6-dihydro structure was proven by the presence of N-H stretching vibrations at 3400 cm^{-1} and 3200 cm^{-1} in the IR spectra and by the ^1H NMR spectra (Tables 3.1 + 3.5).



Scheme 3.1

We observed that, whereas the ^1H NMR spectrum of 3a measured at 306 K gave only one signal (4.13 ppm) for both hydrogens at position 6, at low temperature (199 K) these hydrogens gave rise to two doublets, one at 2.13 ppm and the other at 6.13 ppm (Table 3.2). This phenomenon cannot be ascribed to the influence of the phenyl group at position 3, since 3-methyl-1,6-dihydro-1,2,4,5-tetrazine (3d) gave analogous results: at 306 K both hydrogens at position 6 have the same chemical shift (3.94 ppm), while at about 199 K both hydrogens appear as doublets with different chemical shift (see Table 3.2). Dissimilarity of both hydrogens at position 6 is also found in the conjugate base of 3a, i.e. 4a, obtained on treatment of 3a with sodium hydroxide.[6] The ^1H NMR spectrum of 4a shows already at 306K two absorptions, at 1.37 ppm and 6.18 ppm (Table 3.1); at lower temperature sharp doublets appear. When 3a is protonated (see experimental section) the 3-phenyl-1,6-dihydro-1,2,4,5-tetrazinium ion (5a) also shows dissimilarity of the hydrogens at position 6: at 306 K the ^1H NMR spectrum shows only a singlet at 4.55 ppm, whereas two doublets at 2.87 ppm and 6.23 ppm occur at about 200 K.

Table 3.1 Chemical shifts of the ring protons of compound 3a-d, 4a-c and 5a at 306 K in CD_3OD/D_2O 4:1

compound	H^A	H^B
3a	4.13 (s)	4.13 (s)
3b	2.22[a]	-
3c	2.26[b]	-
3d	3.94 (s)	3.94 (s)
4a	1.37 (d)	6.18 (d)
4b	1.18 (q)	-
4c	1.02 (t)	-
5a	4.55 (s)	4.55 (s)

a) AB_3 system for H^A and CH_3

b) Selective decoupling of CH_3 gives an A_2B spectrum for H^A and CH_2-

All these data strongly indicate that in the compound described above we deal with a species, having a homoaromatic[7] system. The 1,6-dihydro-1,2,4,5-tetrazine ring can be considered as a monohomotetrazole, in which the tetrazole part of the molecule has a rather regular five-memebered ring, allowing orbital overlap to form an aromatic 6π system (Hückel rule). Consequently the methylene group has to point out of the plane of the ring, orienting one of the hydrogens H^A above the plane of the aromatic tetrazole ring and placing the other hydrogen H^B in an exo-position.

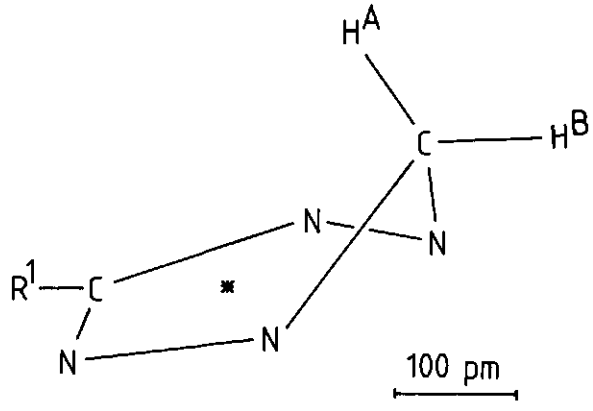


Figure 3.1 Perspective drawing of 1,6-dihydro-1,2,4,5-tetrazine

The chemical shift difference between H^A and H^B in the neutral species 3a and 3d (3.80-4.00 ppm) is in good agreement with the expected shift difference of about 3-4 ppm, which is calculated by approximation from the ring current effects in benzene.[8] From this result we concluded that there exists an induced ring current in 3a and 3d, which provides the explanation for the shift difference between H^A and H^B. From the results given in Table 3.2 it can be concluded that H^B is hardly affected by the charge in the ring; H^A however, strongly experiences the influence of this charge through space, a negative charge causing an upfield shift (4a), a positive charge causing a downfield shift (5a). This result is in accordance with the proposed conformation.
For comparison the ^1H NMR data for H^A and H^B of the homotropylium cation (6)[9,10] are included in Table 3.2.

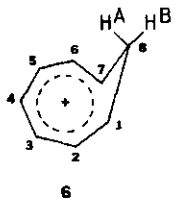


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Table 3.2 Chemical shifts of protons H^A and H^B below the exchange temperature in 1,6-dihydro-1,2,4,5-tetrazines (in which $R_2=H^B$) and in homotropylium cation (6)

compound	T_{coal}(K)	H^A	H^B	$\Delta\delta$	J_{AB}(Hz)
3a	243	2.13 (d)	6.13 (d)	4.00	7.5
3d	233	2.04 (d)	5.84 (d)	3.80	7.5
4a	318	1.37 (d)	6.18 (d)	4.81	6.6
5a	238	2.87 (d)	6.23 (d)	3.36	-[a]
6		-0.73 (d)	5.13 (d)	5.86	7.2

a) In this spectrum the signal remained broadened

The coupling constant $J_{A,B}$ of the homotropylium cation is of the same magnitude (7.2 Hz) as $J_{A,B}$ of the 1,6-dihydro-1,2,4,5-tetrazine system, thus indicating that the angle of N_1-C_6-N_5 is similar to that of C_1-C_8-C_7.
Figure 3.2 shows some ^1H NMR spectra of 3a at different temperatures. An increase in temperature (324 K) sharpens the singlet, a decrease (278 K) causes a broadening and at very low temperature (199 K) two doublets appear.

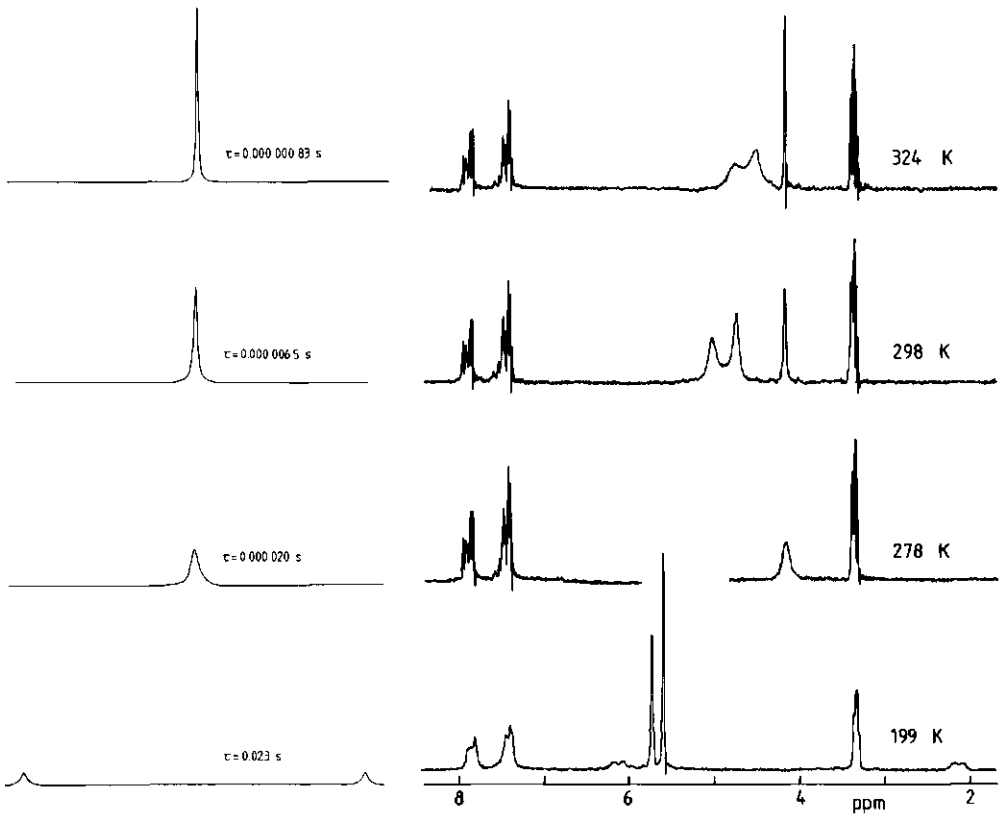
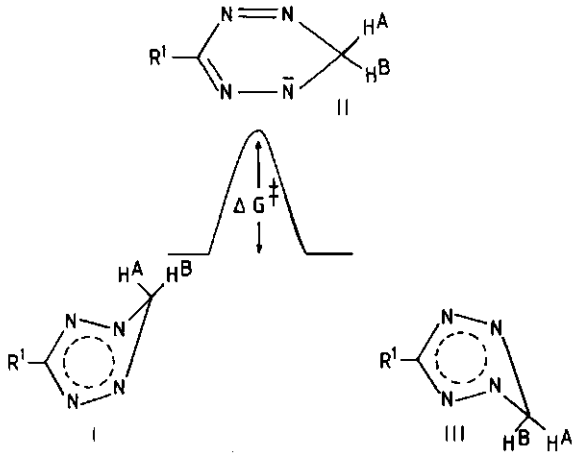


Figure 3.2 Measured (right) and calculated (left) line shape of H^A and H^B in 3-phenyl-1,6-dihydro-1,2,4,5-tetrazine (3a) in CD_3OD/D_2O (4:1) as a function of the temperature

At low temperature, the system is frozen to one conformation, at higher temperatures there is a rapid exchange (ring inversion) between the two possible forms I and III, Scheme 3.2. This inversion is visualized to proceed through a planar form II in which a considerable loss of delocalization energy appears.
The calculated spectra in figure 3.2 were obtained with a programmable pocket calculator; from the lifetime τ the kinetic parameters were calculated[11] by means of the Eyring equation: $\log (k/T) = 10.32 - (\Delta H^{\ddagger}/4.57\ T) + (\Delta S^{\ddagger}/4.57)$. The plot of $\log (k/T)$ against $(1/T)$ was calculated with the least square method (Table 3.3).



Scheme 3.2

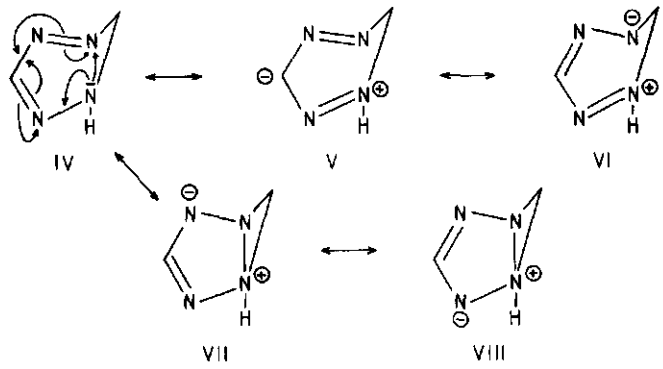
Table 3.3 Kinetic parameters of some 1,6-dihydro-1,2,4,5-tetrazines obtained by dynamic NMR measurements

compound	T_{coal}[a] (K)	n[b]	r	$\Delta H^{\ddagger}$ (kJ/mol)	$\Delta S^{\ddagger}$ (J/mol K)	$\Delta G^{\ddagger}$ (kJ/mol)
3a	243	8	-0.997	25.1 ± 0.8	-110 ± 3	51.9 ± 1.5
3d	233	9	-0.990	20.4 ± 1.1	-125 ± 4	49.5 ± 1.9
4a	318	6	-0.992	37.1 ± 2.4	- 98 ± 9	68.1 ± 3.8
5a	238	9	-0.997	21.7 ± 0.7	-123 ± 3	51.1 ± 1.6

a) The accuracy of the determination of the coalescence temperature was about 10 K

b) n is the number of temperatures used for the calculation

The entropy of activation is strongly negative and not very different for all four compounds; in the transition state the system is more localized and needs more solvation, thus decreasing the degrees of freedom. Since $T\Delta S^{\ddagger}$ is almost constant for these four compounds (Table 3.3), $\Delta H^{\ddagger}$ is linearly related to $\Delta G^{\ddagger}$; so it is reasonable to consider scheme 3.2 to explain the differences in enthalpy of activation. These can be visualized by considering the possible resonance structures, Scheme 3.3.



Scheme 3.3

Besides the classical resonance structures IV, V and VI the non-classical resonance structures VII and VIII are possible. In the neutral compound 3a the contribution of all these resonance structures is of less importance than for the anion 4a, due to a separation of charge in 3a versus delocalization of negative charge in 4a. Therefore ring inversion of 3a requires less energy than the corresponding process of 4a. In the protonated form 5a there is even more separation of charge, resulting in a smaller $\Delta H^{\ddagger}$.

One of the possible resonance structures, V, has a negative charge on carbon. In 3a (R^1=Ph) this negative charge can easily be accommodated. In 3d (R^1=CH_3) this accommodation is impossible, resulting in a lower resonance stabilization in the forms I and III of 3d, relative to 3a. Consequently the ring inversion of 3a requires more energy due to more initial state stabilization.

The delocalization energy of the 1,6-dihydro-1,2,4,5-tetrazines is between 50 and 70 kJ/mol. For comparison: the homotropylium cation has a delocalization energy of 93 kJ/mol and is thus more stabilized than the 1,6-dihydro-1,2,4,5-tetrazines.

In compounds 3b and 3c as well as in 4b and 4c with a methyl or ethyl group next to the hydrogen at position 6, the δ value of H^A is found at high field (2.22, 2.26, 1.18 and 1.02 ppm respectively).

This result leads to the conclusion that in these compounds the hydrogen is oriented above the plane of the ring and that the large group is in the *exo* position. In the other form there will be an interaction between the Van der Waals radii of the nitrogens and the hydrogens of the methyl group. A large substituent at the homotropylium cation is in the exo position too.[12] An increase in temperature in order to bring about a ring inversion was not successful since these species decompose on heating. This indicates that the other conformation cannot be obtained.

To gain more certainty about the proposed structure (figure 3.1), we have planned to obtain an X-ray analysis[7] of compound 3b or 3c.
With these results in mind the explanation of the high field chemical shift of the H_6 on adduct formation between 3-phenyl-1,2,4,5-tetrazine and liquid ammonia -as discussed in the beginning of this paper- is evident. The molecule is in the homotetrazole conformation; the amino group being large, is in the *exo* position and the hydrogen is oriented above the plane of the ring, and thus appears at high field in the ^1H NMR spectrum.
To our knowledge the occurrence of homoaromaticity in 1,6-dihydro-1,2,4,5-tetrazines has never been found and is in general unknown for aza-aromatic systems.[13,14] All adducts of amide to aza-aromatics known so far[13] have no homoaromatic properties. The chemical shift of 4-5.5 ppm observed in these systems excludes an orientation of the hydrogen attached to the sp^3 carbon atom above the plane of an aromatic ring, since this should result in a shift at much higher field.

3.3 EXPERIMENTAL SECTION

Melting points are uncorrected. Mass spectra were determined on an AEI MS 902 mass spectrometer. ^1H NMR spectra were recorded on a Varian EM 390 spectrometer equipped with a Varian EM 3940 variable temperature controller or on a Varian XL-100-15 spectrometer. TMS was used as internal standard (δ 0 ppm). In liquid ammonia the solvent peak was used as standard. The spectra were converted to the TMS scale by addition of 0.95 ppm. The pocket calculator was a Texas Instruments Ti-59 programmable calculator. Column chromatography was carried out over Merck Silica gel 60 (70-230 mesh).

Preparation of Starting Materials

3-phenyl-1,2,4,5-tetrazine (2a) and 3-methyl-1,2,4,5-tetrazine (2d). These compounds were prepared as described before.[15,16]

6-Methyl-3-phenyl-1,2,4,5-tetrazine (2b). This compound was prepared analogous to the procedure of Lang et al.[15] Accordingly 21.1 g of acetamidine hydrochloride,[17] 13.4 g of benzimido ethyl ether hydrochloride[17] and 50 mL of absolute ethanol were cooled at -10°C. Then 51 mL of hydrazine hydrate were added, keeping the temperature below 5°C. The mixture was stirred during 3h at 25°C and then poured into 370 mL of water. The crystals were filtered off and the water layer was continuously extracted with boiling chloroform for 2 days. The crystals were dissolved in the chloroform and oxygen was bubbled through this solution during 3 days. After

column chromatography on silica gel using as eluent petroleum ether 60-80°/dichloromethane 1.38 g of 2b (11%) was obtained, m.p. 74.5-76°C (Lit.[18] 75°C); MS : M^+, m/e= 172; ^{1}H NMR ($CDCl_3$) δ 3.01 (3H,s,CH_3), 7.38-7.54 (3H,m,m/p Ph), 8.36-8.55 (2H,m,oPh). Anal.Calcd. for $C_9H_8N_4$: C, 62.78; H, 4.68. Found: C, 62.60; H, 4.87.

6-Ethyl-3-phenyl-1,2,4,5-tetrazine (2c). This compound was prepared according to the same procedure as described for 2b; from 24.2 g of propionamidine hydrochloride 1.74 g of a dark purple oil of 2c (13%) was obtained. MS:M^+, m/e= 186. Exact mass measurements gave for $C_{10}H_{10}N_4(M^+)$: 186.0905 (theoretical 186.0905); ^{1}H NMR ($CDCl_3$): δ 1.54 (3H,t,CH_3), 3.36 (2H,q,CH_2), 7.39-7.63 (3H,m,m/p Ph), 8.40-8.60 (2H,m,oPh). Anal.Calcd. for $C_{10}H_{10}N_4$: C, 64.50; H, 5.41. Found: C, 64.29; H, 5.48.

Reductions with sodium borohydride, general procedure

To a solution of 2 mmol of 1,2,4,5-tetrazine (2a-2d) in 8 mL of ethanol and 4 mL of chloroform, a solution of 76 mg of $NaBH_4$ in 3 mL of ethanol and 1 mL of water was added dropwise. The colour changed from red to yellow. After stirring for 15 min some solid $NaBH_4$ was added in order to complete the reaction. Then water and 1 g of NH_4Cl were added. After extraction of the water layer with chloroform, drying of the extract over $MgSO_4$ and evaporation of the chloroform, 1,6-dihydro-1,2,4,5-tetrazine was obtained and purified by recrystallization from ether-pentane or by preparative thinlayer chromatography over silica gel PF_{254}, 2 mm, eluting with 5% ether in dichloromethane. The yields and physical data are summarized in table 3.4. For ^{1}H NMR spectroscopic data see tables 3.1 and 3.5. The compounds were stored at -20°C.

Table 3.4 Physical data of compounds 3a-3d obtained by sodium borohydride reduction

compound	yield (%)	m.p.(°C)	IR ($CHCl_3$)	Analyses %			
				Calcd.	C,H	Found	C,H
3a	80	83-85	3390,3210 NH	59.98	5.04	60.18	5.17
3b	68	106.5-108	3395,3200 NH	62.05	5.79	61.81	5.78
3c	55	95-96.5	3395,3210 NH	63.81	6.43	63.52	6.56
3d[a]	29	oil	3405,3220 NH	36.72	6.16	38.55	6.76

Notes Table 3.4:

a) This compound was found to be instable. It was impossible to obtain reproducible micro-analytical data because during weighing the compound evolved gas due to decomposition.
3d was further identified by comparing its UV spectroscopic data:
pH7.5 λ_{max}^{water} 421 (log ε 2.70), 306 (3.43); pH 12.9 λ_{max}^{water} 339 (3.34),
with those of 3,6-dimethyl-1,6-dihydro-1,2,4,5-tetrazine[6]:
pH7.5 λ_{max}^{water} 418 (log ε 2.66), 305 (3.43); pH 12.9 λ_{max}^{water} 347 (3.33).

Table 3.5 ^{1}H NMR data of compounds 3a-d, 4a-c and 5a at 306 K in CD_3OD/D_2O 4:1[a]

compound	6 CH_3	6 CH_2	CH_3	o Ph	m/p Ph	3 CH_3	NH[b]
3a				7.79-7.93(m)	7.34-7.48(m)		6.7(br.s)
3b	2.00(m)			" "	" "		5.3(br.s)
3c		2.51(m)	1.35(t)	" "	" "		6.2(br.s)
3d						2.48(s)	6.0(br.s)
4a				7.74-7.88(m)	7.16-7.42(m)		
4b	1.99(d)			" "	" "		
4c		2.45[c]	1.33(t)	" "	" "		
5a				7.81-7.95(m)	7.43-7.55(m)		

a) The chemical shifts of the protons on position 6 are in Table 3.1
b) In $CDCl_3$; the other protons are in similar positions as in CD_3OD/D_2O
c) quintet

Protonation of 1,6-dihydro-1,2,4,5-tetrazines 3a and 3b

Like tetrazoles[19], 1,6-dihydro-1,2,4,5-tetrazines are easily protonated as can be seen in figure 3.3.
In figure 3.3 the chemical shift of H^A of 3b is plotted against the mol of sulfuric acid added per mol 3b (open circles). For comparison (closed circles) the deprotonation of 3b to 4b is also given. After addition of 1 mol of sodium hydroxide per mol 3b the deprotonation is complete and the chemical shift remains

constant. The protonation of 3b to 5b gives about the same lineair *increase* in chemical shift as the *decrease* in deprotonation. After addition of 5 mol of sulfuric acid the linearity stops and the curve is slowly reaching a maximum. From analogy with the deprotonation we concluded that after addition of 5 mol of sulfuric acid a mono-protonated dihydrotetrazine is obtained, 5b. So the pK_a of 5b is about 0.4.[19] In the same way 3-phenyl-1,6-dihydro-1,2,4,5-dihydrotetrazine (3a) was protonated to 5a.

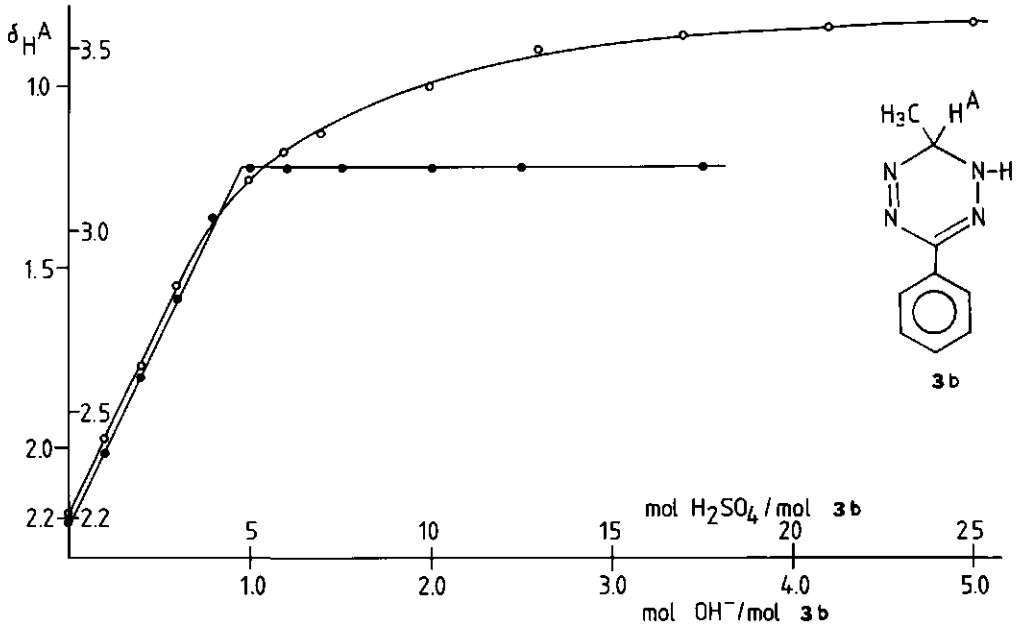


Figure 3.3 Chemical shifts of H^A of 6-methyl-3-phenyl-1,6-dihydro-1,2,4,5-tetrazine (3b) upon deprotonation (closed circles) and protonation (open circles) in CD_3OD/D_2O (4:1)

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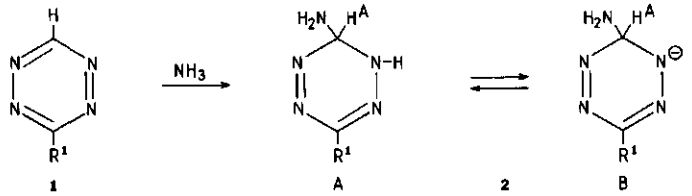
4 ^{13}C NMR INVESTIGATIONS OF THE ANIONIC HOMOAROMATIC σ-ADDUCTS FORMED BETWEEN LIQUID AMMONIA AND 1,2,4,5-TETRAZINES

4.1 INTRODUCTION

In a preceding paper[1] we proposed that 6-amino-3-phenyl-1,6-dihydro-1,2,4,5-tetrazine (2a) formed on addition of ammonia to 3-phenyl-1,2,4,5-tetrazine (1a) is a homoaromatic species (Scheme 4.1). σ-Adduct 2a is in the homotetrazole conformation, containing 6π electrons in the tetrazole ring and holding the hydrogen at the sp^3 carbon atom above the ring and the amino group in the exo position. It was found[1] that the delocalization stabilization in the parent compound 3-phenyl-1,6-dihydro-1,2,4,5-tetrazine (3a) was considerably smaller than in the conjugate base 4a (Scheme 4.2) (3a: 52 kJ/mol; 4a: 68 kJ/mol). Since these data indicate that deprotonation leads to a gain of resonance energy, it induced us to investigate whether in liquid ammonia the σ-adducts 2 are present as neutral species 2A or as anionic species 2B.[3]



a. R^1 = Ph
b. R^1 = CH_3
c. R^1 = t-C_4H_9

Scheme 4.1

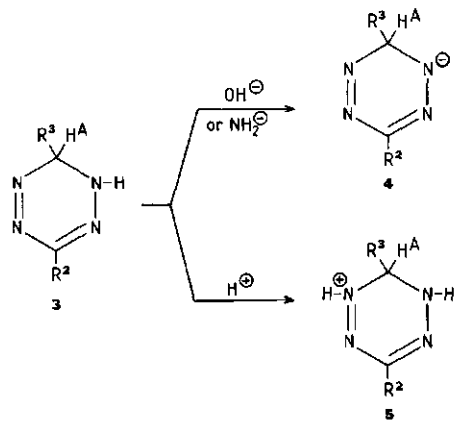
4.2 RESULTS AND DISCUSSION

A. ^1H and ^{13}C Chemical Shifts

In the ^1H NMR spectrum of the homoaromatic σ-adduct 2a H_6 has been found at 1.51 ppm; compared with the chemical shift of H_6 in 1a (10.35 ppm see Table 4.1) it indicates that on adduct formation this hydrogen undergoes an "anomalous" large upfield shift of 8.84 ppm.

In an extension of these studies we observed that on dissolving 3-methyl-1,2,4,5-tetrazine (1b) or 3-t-butyl-1,2,4,5-tetrazine (1c) in liquid ammonia, H_6 also undergoes an upfield shift of the same magnitude ($\Delta\delta$ = 8.55 ppm for 1b and $\Delta\delta$ = 9.15 ppm for 1c) (Table 4.1). These results suggest that also 2b and 2c are present in the homoaromatic conformation.

Further evidence for the formation of σ-adduct 2a-c was provided by comparison of the ^{13}C chemical shifts of C_6 in compounds 1a-c, when dissolved in deuteromethanol and in liquid ammonia. In liquid ammonia C_6 is found to resonate about 65-85 ppm at higher field than in methanol; this is due to adduct formation, changing the hybridization of C_6 ($sp^2 \rightarrow sp^3$). For comparison the ^{13}C chemical shifts of C_3 and C_6 in the model compounds 3-phenyl-1,6-dihydro-1,2,4,5-tetrazine (3a) and 3,6-dimethyl-1,6-dihydro-1,2,4,5-tetrazine (3d)[4] together with those of their conjugate bases 4a and 4d (Scheme 4.2) are included in Table 4.1. These chemical shifts agree reasonably well with those of C_3 and C_6 in the σ-adducts 2a-c; also the coupling constants J_{C_6H} are of the same magnitude (see Table 4.1). Variations in the coupling constants will be discussed in section B.



a. R^2 = Ph, R^3 = H^B
b. R^2 = Ph, R^3 = CH_3
c. R^2 = Ph, R^3 = C_2H_5
d. R^2 = CH_3, R^3 = CH_3

Scheme 4.2

Table 4.1 The ^{1}H and ^{13}C chemical shifts and the coupling constants J_{C_6H}(Hz) of 3-phenyl- (1a), 3-methyl- (1b) and 3-t-butyl-1,2,4,5-tetrazine (1c) in deuteromethanol and of the σ-adducts 2a, 2b, 2c in liquid ammonia. The chemical shifts and J_{C_6H} of the model compounds 3a and 4a and 3d and 4d

Compound	Solvent	H_6	C_6	J_{C_6H}	C_3	others
1a	CD_3OD	10.35	159.5	215	168.0	
2a	NH_3	1.51	94.4	156	155.5	
		Δδ=8.84	Δδ=65.1			
1b	CD_3OD	10.26	159.3	213	171.8	$\underline{CH}_3$ 3.03 $\underline{C}H_3$ 21.7
2b	NH_3	1.71	72.8	156	156.5	$\underline{CH}_3$ 2.20 $\underline{C}H_3$ 14.3
		Δδ=8.55	Δδ=86.5			
1c	CD_3OD	10.45	158.9	213	179.5	$\underline{CH}_3$ 1.58 $\underline{C}H_3$ 29.4[d]
2c	NH_3	1.3[c]	85.4	156	155.0	$\underline{CH}_3$[c] $\underline{C}H_3$ 26.4[d]
		Δδ= ∿ 9	Δδ=73.5			
3a	CD_3OD/D_2O	4.13[e]	66.3	159	155.2	
4a	CD_3OD/D_2O[a]	f	78.0	153	156.3	
3d	CD_3OD	1.83	71.9	156	153.1	$3\underline{CH}_3$ 2.38 $3\underline{C}H_3$ 17.4
						$6\underline{CH}_3$ 1.83 $6\underline{C}H_3$ 14.2
4d	NH_3[b]	-	83.5	144	151.2	$3\underline{CH}_3$ 18.4 $6\underline{C}H_3$ 17.7
	CD_3OD/D_2O[a]	0.87				$3\underline{CH}_3$ 2.40 $6\underline{CH}_3$ 1.87

a 1.5 eq. sodium hydroxide

b 2 eq. potassium amide

c the signals are almost under the signal of NH_3; the value cannot be given in two decimales

d the quaternary C could not be distinguished because of aliphatic impurities

e below the exchange temperature H^A 2.13 H^B 6.13 ppm (see reference 1)

f H^A 1.37 H^B 6.18 ppm (see reference 1)

In order to determine whether in liquid ammonia the σ-adducts 2 are present as neutral (2A) or anionic species (2B) two approaches were taken. In a previous paper[1] we have described the preparation and ^{1}H NMR spectra of the *conjugate* bases of the 1,6-dihydro-1,2,4,5-tetrazines, i.e. 4a-c. The chemical shifts of H_6 (δH^A) in these anions are linearly correlated ($r = 0.96$, $t\alpha = 3.49$[5]) with the σ_I values[6] of the geminal group (H, CH_3, C_2H_5). Substitution of the σ_I value of 0.022 for the amino group gives a δH^A of 1.56 ppm for the σ-adduct 2a, being nearly

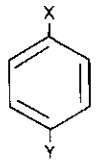
equal to the experimentally observed value of 1.51 ppm (Table 4.2). These data lead to the *tentative* conclusion that σ-adduct 2a is present in liquid ammonia as anionic species 2B.

Table 4.2 The chemical shift of H^A (δH^A) in 2a, 4a, 4b and 4c and the σ_I values of H, CH_3, C_2H_5, NH_2

Compound	σ_I	δH^A
4a	0.000	1.37
4b	-0.031	1.18
4c	-0.039	1.02
2a	0.022	1.51[a]

a calculated by least square analysis of 4a, 4b and 4c: 1.56 ($r=0.96$, $t_\alpha=3.49$)

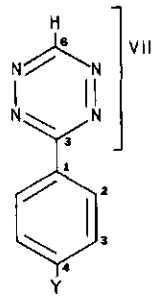
The second more reliable method was based on a report[7,8] that in 1-X,4-Y-benzenes (6) there exists a linear dependence between the values of the substituent chemical shift of C_4 (SCS-4) and the electron demand of the substituent X at C_1. The SCS-4 values are defined as $\left[\delta C_4(Y\neq H) - \delta C_4(Y=H)\right]$ ppm[7]. The substituents X which have been investigated were either neutral of cationic groups. A quantitative measure of the electron donating or withdrawing properties of the group X was determined from the ^{13}C chemical shift values of C_4 (δC_4) of the 1-X,4-Y-benzenes (6), in which Y=H; δC_4 is linearly related with the σ_p^+ values.[9]
We tried to establish whether this relationship could also be applied for Y=Br, OCH_3,CH_3 and X is the 1,2,4,5-tetrazinyl group *(VII)*, the 6-amino-1,2,4,5-tetrazinyl group *(VIII)*, the 1,6-dihydro-1,2,4,5-tetrazinyl group *(IX)* and the anionic 1,6-dihydro-1,2,4,5-tetrazinyl group *(X)*, see Scheme 4.3.



X = (substituted)-1,2,4,5-tetrazinyl groups VII - XI

Y = H, Br, OCH_3, CH_3.

6



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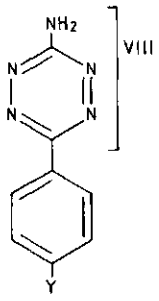

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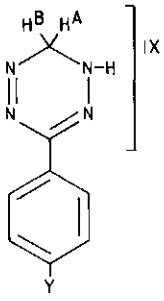

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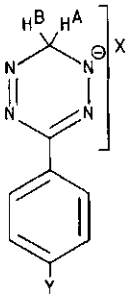

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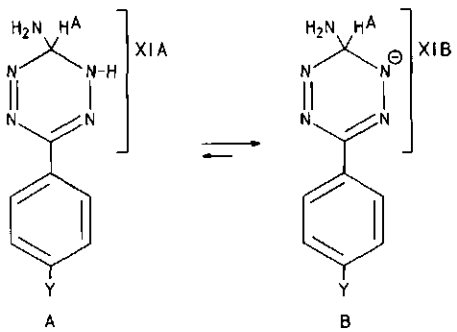


A 11 B

Scheme 4.3

Therefore we prepared the 3-(*p*-Y-phenyl)-1,2,4,5-tetrazines (7) from which by reaction with liquid ammonia and subsequent oxidation with potassium permanganate[10] the corresponding 6-amino compounds 8 were prepared. Sodium borohydride reduction of 7 gave the 3-(*p*-Y-phenyl)-1,6-dihydro-1,2,4,5-tetrazines (9), which by treatment with potassium hydroxide gave the corresponding anions 10.
In table 4.3 δC_4 and the SCS-4 values of these compounds are collected. From these data we concluded that the (substituted)-1,2,4,5-tetrazinyl groups can be arranged according to decreasing electron withdrawing properties *X < IX < VIII < VII*.
In figure 4.1 the SCS-4 values are plotted against δC_4(Y=H). This plot shows

indeed a linear relationship for the (substituted)-1,2,4,5-tetrazinyl groups (*VII-X*), indicating that the continuity of the C_4 shift variations is an extended range, also for substituents being in the anionic form.

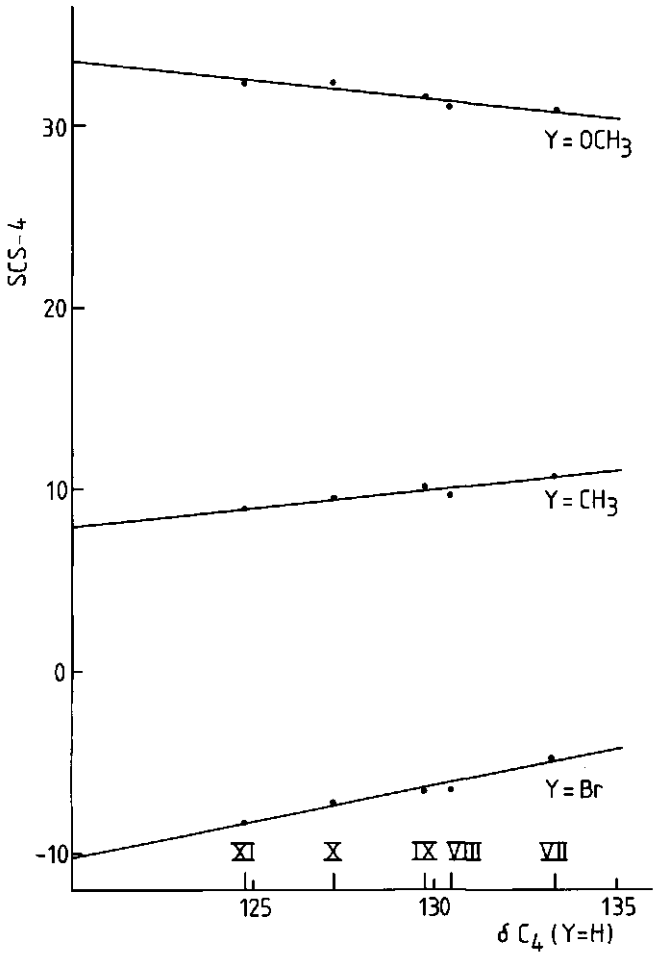


Figure 4.1 Plot of SCS-4 against δC_4(Y=H) of 1-X,4-Y-benzenes (6) (Y=OCH_3,CH_3,Br)

Table 4.3 ^{13}C chemical shifts[a] for C_4 (δC_4) and substituent chemical shifts[b,c] (SCS-4) of 1-X,4-Y-benzenes (6)

subst. X[d]	Substituent Y							Solvent
	Br		OCH_3		CH_3		H	
	δC_4	SCS-4	δC_4	SCS-4	δC_4	SCS-4	δC_4	
VII	128.63	-4.61	164.01	+30.77	143.96	+10.72	133.24	$CDCl_3$
VIII	123.98	-6.44	161.28	+30.86	140.15	+ 9.73	130.42	DMSO-d_6
IX	123.27	-6.45	161.22	+31.50	139.88	+10.16	129.72	CD_3OD/D_2O
X	120.04	-7.13	159.44	+32.27	136.71	+ 9.54	127.17	CD_3OD/D_2O[e]
XI	116.53	-8.22	157.00	+32.25	133.58	+ 8.83	124.75	NH_3

a the complete spectra are in table 4.7

b SCS-4= $\left[\delta C_4(Y\neq H)-\delta C_4(Y=H)\right]$ ppm

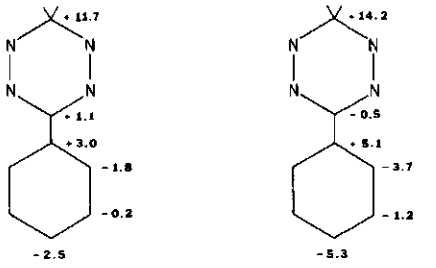
c positive values correspond to downfield shift

d for an explanation of symbols *VII*-*XI*, see Scheme 4.3

e 1.5 eq. sodium hydroxide

The SCS-4 values of the 6-amino-1,6-dihydro-1,2,4,5-tetrazinyl group *XI* of the σ-adduct 11 and its δC_4(Y=H) nicely fit in these plots. From this plot it is evident that group *XI* resembles mostly the anionic 1,6-dihydro-1,2,4,5-tetrazinyl group *(X)*, strongly suggesting that in σ-adduct 11 the heterocyclic substituent is present in the anionic form *XI*B. Since the σ_I values of the hydrogen and the amino group are only slightly different (see Table 4.2) we had expected to find that the electron demand of group *XI*B in the *anionic* σ-adduct will be about equal to that of the anionic 1,6-dihydro group *X*. However, from our measurements group *XI*B seems to be a stronger electron donor than group *X*. To prove that this difference is due to a solvent effect, the ^{13}C chemical shift data of 3-phenyl-1,6-dihydro-1,2,4,5-tetrazine (9,Y=H) when dissolved in liquid ammonia (tetrazine ring: C_6 80.5; C_3 154.7; benzene ring: C_1 139.3; C_2 121.7; C_3 128.5; C_4 124.4 ppm), were compared with those of 9 (Y=H) and 10 (Y=H) in CD_3OD/D_2O (see Table 4.7, experimental section). The chemical shift differences between 10 (Y=H) and 9 (Y=H) and between $\left[9\ (Y=H)\ \text{in}\ NH_3\right]$ and 9 (Y=H) are in scheme 4.4. From these data it is evident that $\left[9\ (Y=H)\ \text{in}\ NH_3\right]$ is deprotonated and present as anionic species 10 (Y=H) with more negative charge localized on the *ortho* and *para* positions; this

results in a larger upfield shift in liquid ammonia than for 10 (Y=H) measured in CD_3OD/D_2O.



10(Y=H) - 9(Y=H) [9(Y=H) in NH_3] - 9(Y=H)

Scheme 4.4

Comparison of δC_4 of 10 (Y=H) in liquid ammonia (124.4 ppm) with δC_4 of the σ-adduct 11 (Y=H) (124.8 ppm) shows that the effect of the 6-amino-1,6-dihydro-1,2,4,5-tetrazinyl group *XI* is very much like that of the anionic group *X*. All these results lead to definitive conclusion that in the σ-adducts 11 the 1,2,4,5-tetrazinyl group is present in the anionic form (*XI*B).

A least square analysis of the SCS-4 as a function of δC_4 is given in table 4.4 and compared with the literature values.[7,8] For all three substituents Y, i.e. Br, OCH_3 and CH_3 we obtained a straight line with a good degree of probability (tα) and a reasonable correlation coefficient. For Y=OCH_3 the slope and the intercept are in reasonable agreement with the data obtained by both Hügel et al.[7] and Membrey et al.[8], for Y=CH_3 there is a reasonable agreement with Hügel, for Y=Br we obtained a steeper slope.

B. Coupling constants J_{C_6H}

3-Phenyl-1,6-dihydro-1,2,4,5-tetrazine (3a=[9 (Y=H)]), its conjugate base 4a=[10 (Y=H)] and conjugate acid 5a exist in two homotetrazole conformations, one with the CH_2 group pointing upwards and the other with the CH_2 group downwards. In these systems is a rapid inversion between these two forms, which is frozen on lowering the temperature.[1] This phenomenon is not changed by the presence of a substituent Y at position 4 of the aryl ring.[13]

The ^{13}C NMR measurements of the compounds (9 (Y=H,OCH_3), 10 (Y=H,Br,OCH_3,CH_3), and 5a), were carried out at 273K. At this temperature only the conjugate bases 10

Table 4.4 Least square analysis of $\delta(C_4)$ as a function of SCS-4 comparison with literature values[7,8]

		this work	Hügel et al[7]	Membrey et al[a,8]
Y=Br	r	0.977[b]	0.984	0.975
	slope	0.40±0.05	0.28±0.01	0.24
	intercept	-58±10	-42.2±1.7	-36.7
	n	5	24	25
$Y=OCH_3$	r	0.919[c]	0.896	0.825
	slope	-0.21±0.05	-0.18±0.02	-0.13
	intercept	58±4	55.2±1.6	48.4
	n	5	24	52
$Y=CH_3$	r	0.948[d]	0.947	0.975
	slope	0.21±0.04	0.30±0.02	0.35
	intercept	-17±6	-25±4	-35.1
	n	5	25	56

[a] The values of the intercept were converted to the same scale by substituting 128.6 (value of benzene) for S_p^H, X in fig. 2 of Membrey et al.
because of the lack of data no standard deviations could be calculated

[b] t_α=7.88

[c] t_α=4.04

[d] t_α=5.19

exist in one form[1] and two different coupling constants were observed for C_6 of 10. By selective decoupling in 10 (Y=Br) it was established that the smaller one (147 Hz) originates from coupling with H^A (i.e. the hydrogen above the plane of the ring) and the larger one (159 Hz) with H^B (i.e. the hydrogen in the exo position) (see Table 4.5). In 1,6-dihydro-3-phenyl-1,2,4,5-tetrazine (3a), measured at 223 K (this is below the exchange temperature), two identical coupling constants were observed ($J_{CH}{}^A = J_{CH}{}^B$ = 159 Hz). The difference of $J_{CH}{}^A$ between the neutral and anionic species is 12 Hz and is equal to the one observed between 3,6-dimethyl-1,6-dihydro-1,2,4,5-tetrazine (3d) and its conjugate base 4d. Nearly the same difference but in the *opposite* direction is found between $J_{CH}{}^A$ in 3d and in its conjugate acid 5d (156 and 169 Hz). 3-phenyl-1,6-dihydro-1,2,4,5-tetrazinium ion (5a) has an average coupling constant of 165 Hz; however, below the exchange

temperature it was not soluble enough to measure the coupling constants separately. Since the positive charge in 5d caused the coupling constant $J_{CH}{}^{A}$ to be larger and since $J_{CH}{}^{B}$ is constant in 3a and 4a, this average coupling constant of 165 Hz makes it plausible that $J_{CH}{}^{A}$ in 5a is about 170 Hz.

Table 4.5 Coupling constants (Hz) $J_{CH}{}^{A}$ and $J_{CH}{}^{B}$ in the various homoaromatic compounds[a]

Compound	$J_{CH}{}^{A}$	$J_{CH}{}^{B}$	J_{C_6H} av[b]	Temperature (K)
2a=[11 (Y=H)]	156			223
2b	156			223
2c	156			223
11 ($Y=OCH_3$)	156			223
3d	156			308
4d	144			223
5d	169			273
3a=[9 (Y=H)]	159[c]	159[c]	159	273
9 ($Y=OCH_3$)			159	273
4a=[10 (Y=H)]	147	160	153	273
10 (Y=Br)	147[d]	159	153	273
10 ($Y=OCH_3$)			153	273
10 ($Y=CH_3$)	148	157	153	273
5a	170[e]		165	308

[a] H^{A} is above the plane of the ring, H^{B} is in the exo position

[b] calculated from: J_{C_6H} average= $\frac{J_{CH}{}^{A} + J_{CH}{}^{B}}{2}$

[c] measured below the exchange temperature (223K) irradiation of H^{A} or H^{B} leaves a doublet

[d] irradiation of H^{A} leaves a doublet with the largest coupling constant, irradiation of H^{B} leaves a doublet with the smallest coupling constant

[e] This compound did dissolve very poorly below the exchange temperature, so the coupling constants could not be determined separately

That $J_{CH}{}^{A}$ depends on the charge of the tetrazole ring, whereas $J_{CH}{}^{B}$ remains constant can be explained as follows[14]: in case of the anionic species, H^{A} is attracted by the negative charge, the electrons of the C-H^{A} bond are released to

carbon leading to a decrease of the percentage of s-character of the bond and a decrease of the $J_{CH}{}^{A}$. Reversely $J_{CH}{}^{A}$ is increased in case the homoaromatic species is positively charged. The influence-through-space of the charge in the tetrazole ring on H^{A} whereas H^{B} is hardly influenced, has also been observed with the ^{1}H NMR chemical shift data.[1]

Comparison of $J_{CH}{}^{A}$ of the σ-adducts 2a-c with those of 4a and 4d shows that there is a linear relationship[15] with the σ_I values of the substituents (NH_3, H, CH_3) geminal to H^{A} (r=0.93, tα=2.52), but that there is no linear dependence with the neutral compounds 3a and 3d. This is another additional proof of the anionic character of the σ-adducts and implies that also 2b and 2c, when dissolved in liquid ammonia, are present in the anionic form 2B.

CONCLUSION

From all spectroscopic data available we conclude that the σ-adducts of ammonia to (substituted)-1,2,4,5-tetrazines are anionic species. The driving force for the deprotonation is probably the greater resonance stabilization of the homoaromatic anion with respect to the homoaromatic neutral compound.[1]

4.3 EXPERIMENTAL SECTION

Melting points are uncorrected. Mass spectra were determined on an AEI MS 902 mass spectrometer. ^{1}H NMR spectra were recorded on a Varian EM 390 spectrometer or on a Varian XL-100-15 spectrometer. TMS was used as internal standard (δ 0 ppm). In liquid ammonia the solvent peak was used as standard. The spectra were converted to the TMS scale by addition of 0.95 ppm. ^{13}C NMR spectra were recorded on a Varian XL-100-15 spectrometer. TMS was used as internal standard (δ 0 ppm). In liquid ammonia trimethylamine (δ 47.5 ppm) was used as internal standard. The solutions were about 0.4 molair. Typical spectral parameters for ^{13}C NMR were as follows: spectral width 5120 Hz (1.25 Hz/point), acquisition time 0.8s, pulse delay 0-1.2s, pulse width 10-20 μs. UV spectra were measured on a Perkin Elmer 550 spectrophotometer. Column chromatography was carried out over Merck Silica gel 60 (70-230 mesh).

Table 4.6 ^{1}H-NMR chemical shift data of 3-(p-Y-phenyl)-1,2,4,5-tetrazines 7-11 (Y=Br,OCH_3,CH_3)[a]
Influence of the (substituted)-1,2,4,5-tetrazinyl groups *VII-XI* on the ortho and meta ^{1}H-chemical shifts of benzene[b]

Compound	H^A	H^B	OCH_3/CH_3	H_2	H_3	X	$\Delta\delta^c$ ortho	$\Delta\delta^c$ meta
7 (Y=Br)	10.25			8.50	7.75			
7 (Y=OCH_3)	10.11		3.93	8.55	7.07	*VII*	-1.34	-0.26
7 (Y=CH_3)	10.16		2.47	8.49	7.38			
8 (Y=Br)	-			8.18	7.75			
8 (Y=OCH_3)	-		3.87	8.21	7.11	*VIII*	-1.04	-0.26
8 (Y=CH_3)	-		2.40	8.16	7.36			
9 (Y=Br)	4.15			7.77	7.57			
9 (Y=OCH_3)	4.08		3.85	7.82	7.02	*IX*	-0.61	-0.13
9 (Y=CH_3)	4.11		2.37	7.75	7.24			
10 (Y=Br)	1.37	6.19		7.67	7.47			
10 (Y=OCH_3)	1.34	6.13	3.85	7.69	6.95	*X*	-0.48	-0.05
10 (Y=CH_3)	d		2.35	7.64	7.15			
11 (Y=Br)	1.59			7.71	7.47			
11 (Y=OCH_3)	1.50		3.68	7.63	6.83	*XI*	-0.47	+0.01
11 (Y=CH_3)	1.55		2.28	7.65	7.10			

[a] solvents as in table 4.7

[b] benzene δ 7.27 ppm; the effects of Br, OCH_3 and CH_3 were taken from Jackman and Sternhell[12] negative sign denotes downfield shift; no correction was made for the change in solvent

[c] the accuracy is $\pm$ 0.05 ppm

[d] for this compound 307 K is apparently the coalescence temperature, no signals were observed

Preparation of starting materials

3-Phenyl-1,2,4,5-tetrazine (1a),[17] *3-methyl-1,2,4,5-tetrazine (1b),*[18] *3-t-butyl-1,2,4,5-tetrazine (1c),*[10] *3-(p-bromophenyl)-1,2,4,5-tetrazine (7, Y=Br),*[10] *3-(p-methoxyphenyl)-1,2,4,5-tetrazine (7, Y=OCH_3),*[17] *6-R^3-3-phenyl-1,6-dihydro-1,2,4,5-tetrazine (3a, R^3=H)*[1] *(3b, R^3=CH_3)*[1] *(3c, R^3=C_2H_5)*[1] *and 3,6-dimethyl-1,6-dihydro-1,2,4,5-tetrazine (3d)*[4] were prepared according to known synthetic procedures.

Table 4.7 ^{13}C NMR data[a] of compounds 7[b], 8[c], 9[d], 10[e], 11[f] and 5a[g]

	tetrazine ring		benzene ring				
Compound	C_6	C_3	C_1	C_2	C_3	C_4	others
7 (Y=H)	158.1	166.7	131.8	128.5	129.5	133.2	
7 (Y=Br)	158.1	166.2	130.8	129.8	132.9	128.6	
7 (Y=OCH_3)	157.5	166.1	124.2	130.3	115.0	164.0	55.5 OCH_3
7 (Y=CH_3)	157.9	166.3	129.2	128.4	130.2	144.0	21.7 CH_3
8 (Y=H)	159.4	163.1	133.2	125.7	129.1	130.4	
8 (Y=Br)	158.7	162.9	132.4	127.6	132.1	124.0	
8 (Y=OCH_3)	159.3	162.9	125.6	127.3	114.6	161.3	55.3 OCH_3
8 (Y=CH_3)	159.4	163.0	130.5	125.6	129.7	140.2	21.0 CH_3
9 (Y=H)[h]	66.3	155.2	134.2	125.4	129.7	129.7	
9 (Y=Br)	66.6	154.4	133.9	127.1	132.8	123.3	
9 (Y=OCH_3)	66.5	155.2	127.0	127.0	115.1	161.2	55.9 OCH_3
9 (Y=CH_3)	66.4	155.4	131.7	125.5	130.4	139.9	21.4 CH_3
10 (Y=H)[i]	78.0	156.3	137.2	123.6	129.5	127.2	
10 (Y=Br)	78.2	155.4	136.6	125.1	132.3	120.0	
10 (Y=OCH_3)	78.1	156.2	130.7	125.1	114.8	159.4	55.9 OCH_3
10 (Y=CH_3)	78.0	156.4	134.6	123.7	130.0	136.7	21.2 CH_3
11 (Y=H)[j]	94.4	155.5	138.7	122.1	128.6	124.8	
11 (Y=Br)	94.9	154.7	138.3	123.7	131.2	116.5	
11 (Y=OCH_3)	94.2	155.2	131.7	123.3	113.6	157.0	55.3 OCH_3
11 (Y=CH_3)	94.6	155.5	136.2	122.2	129.0	133.6	20.8 CH_3
5a	62.4	156.0	130.5	126.1	129.9	131.2	

[a] For each series of compounds in at least one compound the shifts were assigned by selective decoupling. The other chemical shifts could be assigned by the coupling patterns and the empirical parameters for the chemical shifts in substituted benzenes.[16]

[b] in $CDCl_3$

[c] in DMSO-d6

[d] in CD_3OD/D_2O 4:1

[e] in CD_3OD/D_2O 4:1 with 1.5 eq sodium hydroxide

[f] in NH_3

[g] in CD_3OD/D_2O 4:1, 0.61M sulphuric acid

[h] [9 (Y=H)]=3a

[i] [10 (Y=H)]=4a

[j] [11 (Y=H)]=2a

3-(p-Methylphenyl)-1,2,4,5-tetrazine (7, Y=CH_3). This compound was prepared analogously to the procedure of Lang et al.[17] After column chromatography on silica gel using as eluent petroleum ether (60-80°)/dichloromethane, 7 (Y=CH_3) was obtained in a yield of 8%; mp 86-88°C (lit.[19] 84.5°C); MS:M^+, m/e = 172. Anal.Calcd. for $C_9H_8N_4$: C, 62.78; H, 4.68. Found: C, 62.97; H, 4.82. In addition 5% of 3,6-di-(p-methylphenyl)-1,2,4,5-tetrazine was obtained m.p. 248.5-249°C (lit.[20] 235°C); MS:M^+, m/e = 262. Anal.Calcd. for $C_{16}N_{14}N_4$: C, 73.26; H, 5.38. Found: C, 73.41; H, 5.52.

6-Amino-3-(p-Y-phenyl)1,2,4,5-tetrazine (8, Y=H,Br,OCH_3,CH_3). Compound 8 (Y=H,Br) was prepared as described before[10] and compound 8 (Y=OCH_3, CH_3) was prepared according to the procedure described before[10] by dissolving 7 (Y=OCH_3, CH_3) in liquid ammonia and subsequent oxidation with potassium permanganate.
8 (Y=OCH_3): yield 86%; mp 262-264°C (lit.[21] 257-259°C) ; MS:M^+, m/e=203. Anal. Calcd. for $C_9H_9N_5O$: C, 53.19; H, 4.40. Found: C, 53.19; H, 4.42.
8 (Y=CH_3): yield 82% mp 242-243°C (lit.[21] 233-234°C); MS:M^+, m/e=187. Anal. Calcd. for $C_9H_9N_5$: C, 57.74; H, 4.85. Found: C, 57.53; H, 4.89.

3-(p-Y-Phenyl)-1,6-dihydro-1,2,4,5-tetrazines (9, Y=Br,OCH_3,CH_3). The compounds were prepared by sodium borohydride reduction of 7.[1] They were purified by recrystallization from benzene or by preparative thin-layer chromatography over silica gel PF_{254}, 2mm, eluting with dichloromethane with 5 % ether.
As mentioned before,[22] these compounds decompose during mass spectrometric measurements and do not show a M^+ peak.
9 (Y=Br): yield 42%; mp 115-117°C, IR (chloroform) 3410, 3220 NH-stretch. Anal. Calcd. for $C_8H_7BrN_4$: C, 40.19; H, 2.95. Found: C, 40.66; H, 3.12.
9 (Y=OCH_3): yield 35%; mp 99-101°C, IR (chloroform) 3400, 3210 NH-stretch. Anal. Calcd. for $C_9H_{10}N_4O$: C, 56.83; H, 5.30. Found: C, 57.02; H, 5.40.
9 (Y=CH_3): yield 44%; from thin-layer chromatography of the mother liquor an additional 22% was obtained. Melting range 100-104°C, IR (chloroform) 3400, 3220 NH-stretch. Anal. Calcd. for $C_9H_{10}N_4$; C, 62.05; H, 5.79. Found: C, 62.23; H, 5.83.

Determination of the pK_a of 6-R^3-3-phenyl-1,6-dihydro-1,2,4,5-tetrazines (3a, R^3=H) (3b, R^3=CH_3) (3c, R^3=C_2H_5). Calculation of the pK_a of 2a.

The pK_a was determined by UV spectroscopy.[23] Each compound was measured in seven buffer solutions of different pH[24] and in a buffer solution of pH 7.5 (neutral species) and pH 12.9 (conjugate base). A stock solution in 10 mL of ethanol was

prepared from which 1 mL was added to the buffer solutions. The pK_a values are: 3a, 10.01±0.03; 3b, 9.77±0.09; 3c, 9.92±0.08. UV spectroscopic data: pH 7.5 λ_{max} 3a: 432 (log ε 2.93), 275 (4.05); 3b: 431 (2.86), 275 (4.06); 3c: 433 (2.91), 277 (4.08).
pH 12.9 λ_{max} 4a: 389 (log ε 3.28), 303 (4.15); 4b: 385 (3.30), 303 (4.17); 4c: 390 (3.26), 304 (4.17).
The pK_a value of 2a was approximated by averaging the pK_a values of 3a, 3b and 3c, which results in 9.90±0.12.[25]

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4.4 REFERENCES AND NOTES

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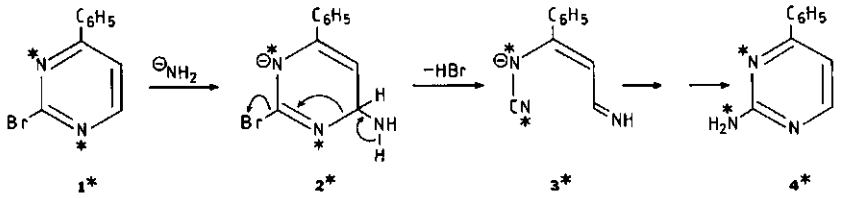
5 DEGENERATE RING TRANSFORMATIONS IN REACTIONS OF 1,2,4,5-TETRAZINES WITH HYDRAZINE

5.1 INTRODUCTION

In our laboratory there is a continuing interest in the mechanism of reactions between nucleophiles and nitrogen-containing aromatics[1]. The nucleophiles used in these studies are the amide ion[2], lithium piperidide[3], carbanions[4], phenyllithium[5], ammonia[6], hydrazine[7], hydroxylamine[8] and amidines[9]. On studying the amino-dehalogenation in ^{15}N-labelled halogenopyrimidines we have discovered that, when potassium amide in liquid ammonia is used as aminating agent, as a general reaction pattern one of the ring nitrogens becomes exocyclic in the amino group and the nitrogen of the amide ion is built into the ring. An example of this degenerate ring transformation[10] is the formation of 2-amino-4-phenylpyrimidine (4^*) from 2-bromo-4-phenylpyrimidine (1^*)[11] (Scheme 5.1).



Scheme 5.1

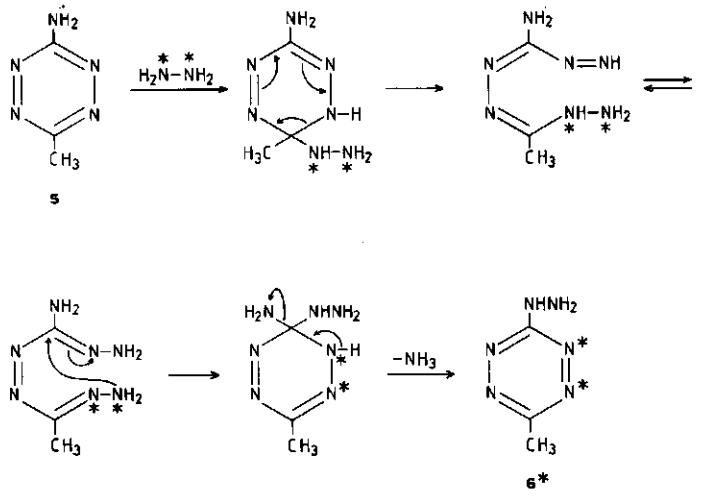
The reaction can be described to occur by attack of the amide ion on C_6, yielding the anionic 1:1 σ-adduct 2^*. This adduct undergoes a base-catalysed ring opening into the *N*-cyano derivative 3^*, which cyclizes into 4^*. This mechanism is called the S_N(ANRORC) mechanism[12]. This mechanism is also found to occur - although to a lesser extent - with the weak nucleophile ammonia[13]. All S_N(ANRORC) reactions which occur with potassium amide and/or ammonia have in common that a one-atom piece of the original ring is replaced by the nitrogen atom of the nucleophile. Very recently examples of degenerate ring transforma-

tions became known in which a replacement of a two- and even a three-atom segment of the ring by two or three atoms of the nucleophile takes place. Thus it has been proven that in the reaction of 1-methylpyrimidinium iodide with benzamidine[9] in the formed 2-phenylpyrimidine the N_1- C_2- N_3 fragment of the ring originates from the amidine. With these results in mind we became interested whether hydrazine would be able to perform nucleophilic substitutions according to the S_N(ANRORC) mechanism. For this reason a study was started on the reaction of substituted 1,2,4,5-tetrazines with hydrazine hoping to obtain evidence that during the hydrazinolysis two vincinal nitrogens of the *ring* of the substrate could be replaced by two nitrogens of hydrazine.
In this preliminary communication we would like to present the first results obtained in our study of the reactions of 3-amino-6-methyl-1,2,4,5-tetrazine (5) and 3-bromo-6-methyl-1,2,4,5-tetrazine (7) with hydrazine.

5.2 RESULTS AND DISCUSSION

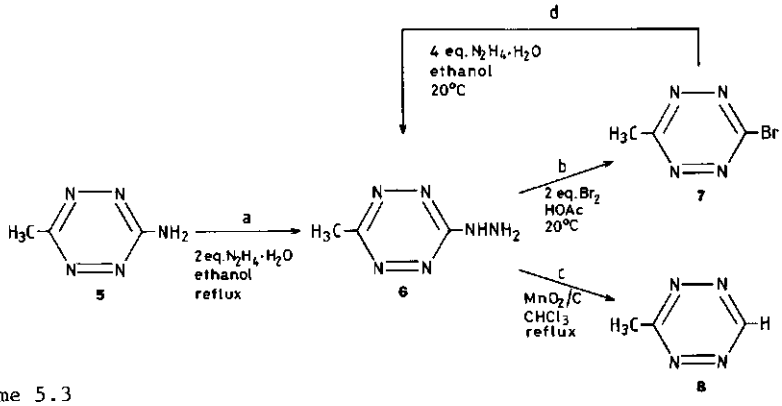
Hydrazinolysis of 3-amino-6-methyl-1,2,4,5-tetrazine (5)

3-Amino-6-methyl-1,2,4,5-tetrazine (5) was prepared as described in the literature[14]. Refluxing an ethanolic solution of 5 containing two equivalents of hydrazine hydrate gave in about 50% yield 3-hydrazino-6-methyl-1,2,4,5-tetrazine (6), characterized as its benzaldehyde hydrazone[15], besides a small amount of unreacted 5 (reaction a, Scheme 5.3). In order to investigate if in



Scheme 5.2

this hydrazinodeamination a ring-opening is involved [S_N(ANRORC) mechanism], we studied this reaction with ^{15}N-labelled hydrazine.



Scheme 5.3

It is evident from Scheme 5.2[16] that in case the S_N(ANRORC) mechanism is operative the tetrazine ring in the final product 6^* will contain ^{15}N. To measure the amount of ^{15}N in the tetrazine ring we had to remove the hydrazino group in 6^*. Because 3-hydrazino-6-methyl-1,2,4,5-tetrazine (6) is unstable and thus difficult to purify we used the crude reaction mixture containing unreacted 5 and the labelled product 6^* and converted 6^* into 3-bromo-6-methyl-1,2,4,5-tetrazine (7^*) by treatment with bromine in glacial acetic acid[17] (reaction b, Scheme 5.3). 3-Amino-6-methyl-1,2,4,5-tetrazine (5) did not react with bromine under these conditions as was checked in a control experiment. To be absolutely sure that in this oxidative bromination *no* ring-opening was involved we also applied a second method *i.e.* the oxidative removal of the hydrazino group on 6^* by manganese dioxide on carbon[18], yielding 3-methyl-1,2,4,5-tetrazine (8^*)(reaction c, Scheme 5.3). Also this second method leaves 5 unchanged under the reaction conditions applied.
The percentage of ^{15}N in 6^*, 7^* and 8^* was determined by quantitative mass spectrometry comparing the M+2 peak of the double ^{15}N-labelled compounds 6^*, 7^* and 8^* with that of the unlabelled reference compounds 6, 7 and 8[19]. The percentage of compound 5 which reacts according to the S_N(ANRORC) mechanism was calculated by dividing the percentage of ^{15}N in 7^* and 8^* by that of 6^*. The results of these measurements are summarized in Table I (see reaction sequence 1 and 2).

From these data it is evident that the hydrazinolysis of the aminotetrazine 5 into 6^* occurs for about 25% according to an S_N(ANRORC) process. The remaining 75% must react by the AE (Addition-Elimination) mechanism. The fact that by both degradation methods (6^* into 7^* as well as 6^* into 8^*) nearly the same ANRORC-percentage is found, ensures us that in the oxidative bromination no ring-opening is involved.

Hydrazinolysis of 3-bromo-6-methyl-1,2,4,5-tetrazine (7)

3-Bromo-6-methyl-1,2,4,5-tetrazine (7) was prepared by the reaction pathway a,b of Scheme 5.3 . Hydrazinolysis of 7 with ^{15}N-labelled hydrazine gave the 3-hydrazino compound 6^* (reaction d, Scheme 5.3). The 3-bromo compound 7 reacts faster than the 3-amino compound 5, since 7 was found to be completely converted into 6^*. After removal of the hydrazino group in 6^* by oxidative bromination (Scheme 5.3) and measuring the ^{15}N content in 6^* and 7^* by mass spectrometry[19] we found that the hydrazinolysis of 7 occurs for 20.5 $\pm$ 2.4% according to the S_N(ANRORC) mechanism (reaction sequence 3, Table I). In a duplicate reaction labelled 3-bromo-6-methyl-1,2,4,5-tetrazine (7^*) - obtained in the reaction sequence 1 (Table I) and containing 1.77 $\pm$ 0.09% ^{15}N - was used as starting substance. Reaction with *unlabelled* hydrazine gave results which are shown in reaction sequence 4 (Table I). In this reaction[20] we found that 18 $\pm$ 8% of 7^* reacted according to the S_N(ANRORC) mechanism. Although this last measurement is inaccurate due to the low percentage of ^{15}N in the ring of the starting bromide 7^* we can conclude that the hydrazinolysis of 3-bromo-6-methyl-1,2,4,5-tetrazine (7) occurs for about 20% by the S_N(ANRORC) mechanism. With these few examples we have shown that in the hydrazinolysis of some 1,2,4,5-tetrazines ring-opening reactions occur.

Table I. ^{15}N excess in compounds 6^*, 7^* and 8^*

Reaction sequence	Starting material	% ^{15}N in compounds 6^*, 7^* and 8^*				% Reacting by S_N(ANRORC)
1	5	6^*	7.12 $\pm$ 0.31	7^*	1.77 $\pm$ 0.09	24.9 $\pm$ 1.6
2	5	6^*	6.60 $\pm$ 0.42	8^*	1.70 $\pm$ 0.11	25.8 $\pm$ 2.3
3	7	6^*	5.76 $\pm$ 0.54	7^*	1.18 $\pm$ 0.09	20.5 $\pm$ 2.4
4	7^*	6^*	1.79 $\pm$ 0.03	7^*	1.63 $\pm$ 0.06	18 $\pm$ 8

Table II. Mass spectrometry at high resolvent power

Compound	Formula	Experimental	Theoretical
5 (2H)(a)	$C_3H_7N_5$	113.0697	113.0701
($2^{15}N$)(b)	$C_3H_5{}^{15}N_2N_3$	-----	113.0486
6 (2H)	$C_3H_8N_6$	128.0804	128.0810
($2^{15}N$)	$C_3H_6{}^{15}N_2N_4$	128.0592	128.0594
7 (2H)	$C_3H_5BrN_4$	177.9661	177.9678
($2^{15}N$)	$C_3H_3Br{}^{15}N_2N_2$	177.9459	177.9462
8 (2H)	$C_3H_6N_4$	98.0583	98.0592
($2^{15}N$)	$C_3H_4{}^{15}N_2N_2$	98.0369	98.0370

(a) (2H) refers to the dihydro compound
(b) ($2^{15}N$) refers to the double ^{15}N-labelled product

5.3 EXPERIMENTAL SECTION

Melting points are uncorrected. ^{15}N contents were determined on an AEI MS 902 mass spectrometer. Pmr spectra were recorded on a JEOL C-60 spectrometer or on a Hitachi-Perkin Elmer R-24B spectrometer. TMS was used as internal standard. Column chromatography was carried out over Merck Silica gel 60 (70-230 mesh ASTM).

Double ^{15}N-labelled hydrazine hydrate

Since double ^{15}N-labelled hydrazine hydrate was not commercially available it was prepared from ^{15}N-labelled hydrazine sulphate (from VEB Berlin-Chemie, Berlin Adlershof).

^{15}N-labelled hydrazine sulphate (1.3012 g., 10 mmoles) were dissolved in 10 ml of distilled water at 80°. During 1.5 hours, 2.9970 g. of barium hydroxide octahydrate (9.5 mmoles) were added portionwise; then the mixture was refluxed for 1.5 hours. The precipitated barium sulphate was filtered off. Water was removed by azeotropic distillation with 146 ml. of benzene and 59 ml. of ethanol, the excess of benzene was also removed (azeotrope benzene-ethanol). The solution of ^{15}N-labelled hydrazine hydrate in ethanol was stored at -20°. By a redox-titration with potassium iodate[21] the ethanolic solution was found to contain 9.4 mmoles of hydrazine hydrate (yield 99%).

The reactions with ^{15}N-labelled materials were carried out as described below

for the reactions with unlabelled compounds.

Hydrazinolysis of 3-amino-6-methyl-1,2,4,5-tetrazine (5)(Reaction a, Scheme 5.3)

A solution of 111 mg. (1 mmole) of 5 in 4 ml. of ethanol was refluxed with 100 µl. of hydrazine hydrate (2 mmoles)[15] during 1.5 hours. After evaporation of the solvent the residue was extracted with hot benzene (3x). The benzene layer was dried over magnesium sulphate and evaporated. 3-Hydrazino-6-methyl-1,2,4,5-tetrazine (6) was characterized by mass spectrometry; M^+, m/e = 126 and as benzaldehyde hydrazone; M^+, m/e = 214 ; m.p. 190.5-191°(lit.[15] 196-198°); pmr (DMSO-d_6): δ 2.78 (s,3H,CH_3), 7.30-7.86 (m,5H,phenyl), 8.45 (s,1H,C-H), 12.40 (s,1H,N-H).

3-bromo-6-methyl-1,2,4,5-tetrazine (7)(Reaction sequence a,b,Scheme 5.3)

A solution of 111 mg.(1 mmole) of 5 in 4 ml. of ethanol was refluxed with 100 µl. of hydrazine hydrate (2 mmoles)[15] during 1.5 hours. After evaporation of the solvent the residue was extracted with hot benzene (3x). The benzene layer was dried over magnesium sulphate and evaporated. This crude residue (containing unreacted 5 and 6) was dissolved in 2.6 ml. of glacial acetic acid and 68 µl. of bromine were added. This solution was stirred at room temperature during 1 hour; 5.2 g. of crushed ice, about 30 ml. of ether and sodium carbonate - until the solution became basic - were added. The water layer was extracted with ether; the ethereal extracts were washed with some ml. of a 5% sodium bicarbonate solution and then with a few ml. of a saturated sodium chloride solution. After drying over magnesium sulphate and evaporating off the ether, the bromo compound 7 was separated from 5 by column chromatography on silica gel elution with benzene. After recrystallization from petroleum ether (40-60°) we obtained 63 mg. of 3-bromo-6-methyl-1,2,4,5-tetrazine (7), yield 36%, m.p. 86-88°; pmr (perdeuteriomethanol): δ 3.00 (s,CH_3); M^+, m/e = 176/174. Anal. Calcd. for $C_3H_3BrN_4$: C, 20.59; H, 1.73. Found: C, 20.74; H, 1.67.

3-methyl-1,2,4,5-tetrazine(8)(Sequence a,c. Scheme 5.3)

This compound was prepared from 5 by hydrazinolysis and subsequent oxidation. The hydrazinolysis of 5 occurs in the same way as described above. After evaporation of the benzene-layer obtained by extraction of the reaction mixture (2 mmoles of 5 with hydrazine hydrate), the residue was dissolved in 10 ml of chloroform and 525 mg. bf manganese dioxide on carbon[18] were added. After re-

fluxing this mixture during 1 hour the manganese dioxide on carbon was filtered off and the product was adsorbed on silica gel. 3-Methyl-1,2,4,5-tetrazine (8) was obtained by column chromatography on silica gel using ether-petroleumether (40-60°) as eluent. After careful removal of most of the solvent we obtained a red, highly volatile oil, still containing some eluent. Pmr (deuteriochloroform): δ 3.10 (s,3H,CH_3), 10.27 (s,1H,H); M^+, m/e = 96. Exact mass measurements gave for $C_3H_4N_4$ (M^+) 96,043608 (theoretical 96.043594). Attempts to characterize 8 by a picrate, a chloroaurate or a quaternary salt failed.
Anal.Calcd. for $C_3H_4N_4$: C, 37.49; H, 4.20. Found: C, 36.98; H, 3.96.

Acknowledgement

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5.4 REFERENCES AND NOTES

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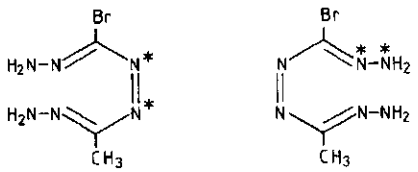
19. We met in the determination of the ^{15}N-content by measuring the increase of M+2 peak the difficulty that the mass spectra of all 1,2,4,5-tetrazines used as reference compounds in this study, *i.e.* 5, 6, 7 and 8 contain a few percent of a M+2 peak (2-5%). This M+2 peak is due to the presence of an impurity - which by mass spectrometry must be assigned to a dihydro compound - which unfortunately could not be removed by any means. The coincidence of the M+2 peak of the dihydro compound with that of the double ^{15}N-labelled product made it necessary to measure the mass spectrum at high resolvent power. The two M+2 peaks are then split, as indicated in Table II. The percentage of ^{15}N can then be calculated by dividing the peak height of the M+2 peak of the double ^{15}N-labelled compound in the high resolution spectrum by the peak height of the M-peak.

20. The percentage of starting 1,2-^{15}N-bromotetrazine 7^* reacting by the S_N(ANRORC) mechanism can be calculated by the formula $\left[2(6^* - 7^*)/6^*\right] \times 100\%$ in which 7^* refers to the end-product of this reaction sequence. The factor 2 in this formula arises from the fact that if the 1,2-^{15}N-bromotetrazine 7^* reacts completely by the S_N(ANRORC) mechanism only 50% of the label in the ring can be lost, because in the adduct the ring can be opened in two ways leading to a or b (see Scheme 5.4).



Scheme 5.4

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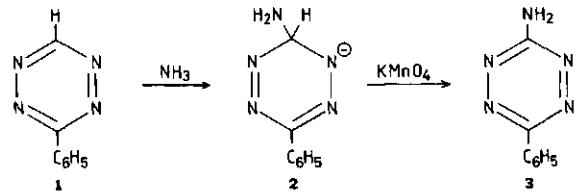
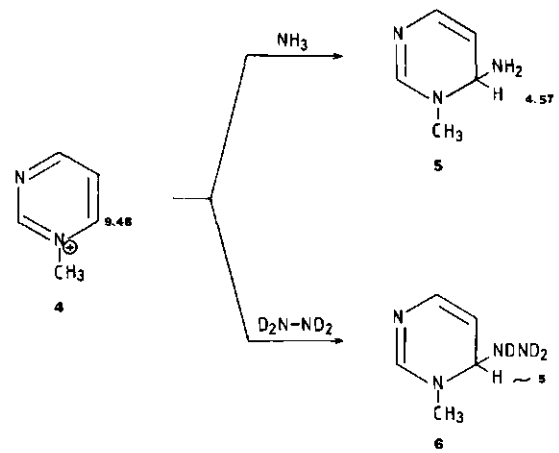
6 THE OCCURRENCE OF THE S_N(ANRORC) MECHANISM IN THE HYDRAZINATION OF 1,2,4,5-TETRAZINES

6.1 INTRODUCTION

In a preceding paper[1] we obtained firm evidence that the anion 6-amino-1,6-dihydro-3-phenyl-1,2,4,5-tetrazine (2), formed upon addition of ammonia to 3-phenyl-1,2,4,5-tetrazine (1) is homoaromatic. This σ-adduct is in the homotetrazole conformation, containing 6π electrons in the tetrazole ring, holding the amino group in the exo position and the hydrogen at the sp^3 carbon atom above the ring. This hydrogen is located in the shielding regio, resulting in a chemical shift at high field (δ=1.51 ppm).



Scheme 6.1



Scheme 6.2

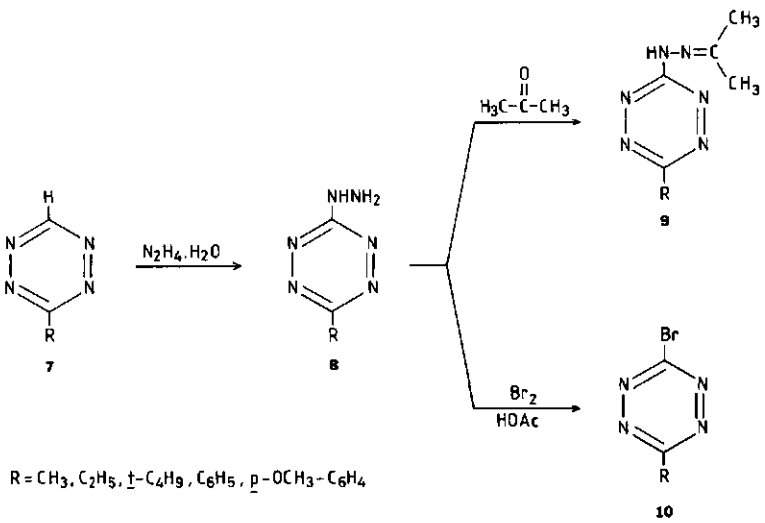
In the literature it is described[4] that addition of ammonia to the C_6-N_1 bond in 1-methylpyrimidinium iodide (4) is accompanied by an upfield shift of H_6 ($\Delta\delta$=4.91 ppm).[4] In hydrazine-hydrate about the same upfield shift ($\Delta\delta$=4.5-5 ppm)[5] was observed, from which it was concluded that in hydrazine an analogous σ-adduct, i.e. 6-hydrazino-1-methyl-1,6-dihydropyrimidine (6) was formed.
From the σ-adduct 2, 6-amino-3-phenyl-1,2,4,5-tetrazine (3) was obtained upon oxidation with potassium permanganate[6]; the reaction of 1 → 3 can be considered as a Chichibabin amination.[7] It has been published that the Chichibabin amination of 4-phenylpyrimidine[8] and phenyl-1,3,5-triazine[9] occurs according to the S_N(ANRORC) mechanism,[10] describing a reaction sequence involving Addition of the Nucleophile to the heterocycle, Ring Opening and Ring Closure.
In an extension of our studies on the amination of 1,2,4,5-tetrazines by liquid ammonia, we became interested whether 1,2,4,5-tetrazines are also appropriate systems for Chichibabin hydrazination by hydrazine-hydrate. The use of sodium hydrazide in the Chichibabin hydrazination of some azaaromatic systems has been reported.[11] We were particularly interested whether the hydrazination -if it occurs- is accompanied by the intermediate formation of a 1:1 σ-adduct having homoaromatic (and anionic) properties and whether the hydrazination would occur according to the S_N(ANRORC) process.
In a previous paper[12] we already presented some evidence that in the hydrazinolysis of 6-amino- and 6-bromo-3-methyl-1,2,4,5-tetrazine an S_N(ANRORC) mechanism is operative. In this paper we wish to present an extension of these hydrazino-deamination and hydrazino-dehalogenation reactions and especially the results of our study with ^{15}N-labelled hydrazine and the NMR spectroscopy of the intermediates in the hydrazination involved.

6.2 RESULTS AND DISCUSSION

A. Chichibabin hydrazination of 1,2,4,5-tetrazines

On treatment of 1 equivalent of the 1,2,4,5-tetrazines 7 with 3 equivalents of hydrazine-hydrate in ethanol at 298 K the corresponding hydrazino compound 8 is formed (yields between 9-15%) together with a number of unidentified coloured (not red) and colourless products; 10-15% of starting material 7 is retrieved (Table 6.6). To make separation of the hydrazino compounds 8 from the rest of the complex reaction mixture possible, they were converted into the more stable acetone-hydrazones 9.
To investigate whether in the formation of 8 the S_N(ANRORC) mechanism is operative the hydrazinations were carried out with ^{15}N double labelled hydrazine. If an

S_N(ANRORC) process occurs, it may lead to the incorporation of ^{15}N into the 1,2,4,5-tetrazine ring; if not, the label will only be present in the exocyclic nitrogens of the hydrazino group. To establish which percentage of the ^{15}N-label is present in the tetrazine ring or in the hydrazino group of the hydrazino compounds 8^*,[13] the excess of ^{15}N-label in the acetone-hydrazones 9^* and in the corresponding bromo compounds 10^* -obtained by oxidation of 8^* with bromine in acetic acid-[14] was measured. The mass spectrometric measurements were carried out at high resolving power,[15] the results are given in table 6.1. No label was found in the recovered starting material 7.



Scheme 6.3

From the data in table 6.1 it is evident that during the formation of the hydrazino compounds 8^* (R=CH_3,C_2H_5) at least part of the ^{15}N-label of hydrazine is incorporated into the 1,2,4,5-tetrazine ring.

In order to obtain additional evidence for the reaction mechanism we tried to establish by ^1H and ^{13}C NMR spectroscopy which intermediary species are present during the reaction.

Comparison of the proton chemical shifts of 1,2,4,5-tetrazines 7 dissolved in deuteromethanol with those observed upon dissolving 7 in a 1:1 mixture of hydrazine-hydrate and deuteromethanol at 233 K (table 6.2) shows that H_6 undergoes a large upfield shift ($\Delta\delta$ between 8.25 and 8.92 ppm). This considerable upfield

Table 6.1 ^{15}N excess in acetone-hydrazones 9* and in the 6-bromo compounds 10*

R	% ^{15}N 9*	% ^{15}N 10*	ANRORC %	ANRORC average
CH_3	6.5	1.70	26.2	24.6
	24.6	5.7	23.0	
C_2H_5	5.7	1.60	28.0	28.5
	6.3	1.82	28.9	
$\underline{t}$-C_4H_9	8.0	0	0	0
	20.7	0	0	
C_6H_5	10.6	0.44	4.2	3.5
	9.3	0.27	2.9	
S.D. average	0.4	0.15	2.6	2.6

shift, being of the same magnitude as observed in liquid ammonia ($\Delta\delta \approx 8.7$ ppm),[1] can only be explained if we assume the formation of the σ-adducts 11, present in the homoaromatic conformation (scheme 6.4). No ^{1}H NMR signals of the starting material 7 could be detected.

The formation of σ-adducts 11 was further proven by comparison of the ^{13}C chemical shifts of C_6 in 7 dissolved in deuteromethanol and in a 1:1 mixture of hydrazine-hydrate and deuteromethanol. The upfield shift of $\Delta\delta$=59-62 ppm observed for C_6 in the last mentioned solvent system confirms the formation of 11; this upfield shift confirms the change in hybridization of C_6 ($sp^2 \rightarrow sp^3$). Also the decrease of the coupling constant J_{C_6H}, from 213-215 Hz in 7 to 159-160 Hz in 11 is in agreement with the adduct formation; the value of 159 Hz is of the same magnitude as in the ammonia adduct 2 (156 Hz).[1]

The question whether the σ-adducts 11 are present as neutral species 11A or as anionic species 11B was answered by applying the method discussed in a previous paper.[1]

For 3-(p-Y-phenyl)-1,2,4,5-tetrazine derivatives (Y=Br,OCH_3,CH_3) there exists a linear relationship between the ^{13}C substituent chemical shift at C_4 of the aryl ring (SCS-4)[17] and δC_4(Y=H), which is a measure of the electron demand of the (substituted)-1,2,4,5-tetrazinyl groups.[1] Therefore we determined the δC_4 values of the σ-adducts 11 (R=C_6H_5, p-OCH_3-C_6H_4).

Table 6.2 ^{1}H and ^{13}C chemical shifts and the coupling constants J_{C_6H}(Hz) of 7 and 16 in deuteromethanol and in a mixture of hydrazine-hydrate and deuteromethanol at various temperatures

R	solvent	temp. (K)	H_6	C_6	J_{C_6H}	C_3	others
7 CH_3	CD_3OD	308	10.26	159.3	213	171.8	$\underline{C}H_3$ 3.03 $\underline{C}H_3$ 21.7
11	a	233	1.71	98.9	159	153.6	$\underline{C}H_3$ 2.42 $\underline{C}H_3$ 18.2
			$\Delta\delta$=8.55	$\Delta\delta$=60.4			
13	a	253	6.92	143	200	152	$\underline{C}H_3$ 1.88 $\underline{C}H_3$ 16.9
7 C_2H_5	CD_3OD	308	10.32	159.5	213	175.1	$\underline{C}H_2$ 3.26 $\underline{C}H_3$ 1.44
							$\underline{C}H_2$ 29.7 $\underline{C}H_3$ 12.3
11	a	233	1.65	97.5	159	158.4	$\underline{C}H_2$ 2.76 $\underline{C}H_3$[b] 1.19
			$\Delta\delta$=8.67	$\Delta\delta$=62.0			$\underline{C}H_2$ 24.8 $\underline{C}H_3$[c]
13	a	253	6.98	141.7	200	153.8	$\underline{C}H_2$ 2.22 $\underline{C}H_3$[b]
							$\underline{C}H_2$ 23.7 $\underline{C}H_3$
7 $\underline{t}$-C_4H_9	CD_3OD	308	10.45	158.9	213	179.5	$\underline{C}H_3$ 1.58 $\underline{C}H_3$[d] 29.4
11	a	233	1.53	97.3	160	160.1	$\underline{C}H_3$ 1.31 $\underline{C}H_3$[d] 27.1
			$\Delta\delta$=8.92	$\Delta\delta$=61.6			
13	a	273	6.95	141.6	200	163.6	$\underline{C}H_3$ 1.20 $\underline{C}H_3$[d] 27.3
7 C_6H_5	CD_3OD	308	10.35	159.5	215	168.0	Ph: C_1 133.6 C_2 129.3
							C_3 130.6 C_4 134.1
11	$N_2H_4.H_2O$	253	2.10	100.1	159	156.5	C_1 136.8 C_2 122.7
			$\Delta\delta$=8.25	$\Delta\delta$=59.4			C_3 129.5 C_4 126.6
13	$N_2H_4.H_2O$	308	7.15	142.5	201	150	C_1 e C_2 127.0
							C_3 129.6 C_4 131.4
13	f	308	6.84	142.2	201	150.4	C_1 e C_2 127.5
							C_3 129.7 C_4 131.6
11	a	233	2.05	99.7	-	156.8	C_1 137.2 C_2 123.3
			$\Delta\delta$=8.30	$\Delta\delta$=59.8			C_3 129.7 C_4 127.1
7 $\underline{p}$-OCH_3-C_6H_4	$CDCl_3$	308	10.11	157.5	213	166.1	C_1 124.2 C_2 130.3
							C_3 115.0 C_4 164.0
	a	233	-	99.7	-	156.6	C_1 130.1 C_2 124.7
				$\Delta\delta$=57.8			C_3 114.8 C_4 159.0
16	CD_3OD	308	-	-	-	166.3[g]	$\underline{C}H_3$ 2.98 $\underline{C}H_3$ 20.5[g]
17	a	233	-	-	-	-	$\underline{C}H_3$ 3.02 (broad)
	a	273[h]				150.6[i]	$\underline{C}H_3$ 1.87 $\underline{C}H_3$ 16.1

Notes Table 6.2:

a $N_2H_4.H_2O/CD_3OD$ (1:1)

b CH_3 was not determined, 15.0 ppm was set at 0 ppm

c due to contamination with ether it is difficult to assign the CH_3 shift with certainty

d the quaterny C could not be observed because of aliphatic impurities

e C_1 could not be observed

f 2 equivalents $N_2H_4.H_2O$ in CD_3OD

g in $CDCl_3$, see reference 23

h at intermediate temperatures 3.02 disappears, while 1.87 is formed

i also starting material present; minor peaks: 166.9; 20.8 ppm

The SCS-4 value and the δC_4(Y=H) value for the 6-hydrazino-1,6-dihydro-1,2,4,5-tetrazinyl group nicely fit in this plot (r=0.923, t_α=4.16) (table 6.3). From this plot it is evident that the electron demand of the 6-hydrazino-1,6-dihydro-1,2,4,5-tetrazinyl group resembles mostly that of the 1,6-dihydro-1,2,4,5-tetrazinyl anion. As the σ_I values of the hydrazino group[18] and hydrogen are not very different, we concluded that the σ-adducts 11 are present as *anionic* homoaromatic species in hydrazine-hydrate/methanol.

Table 6.3 δC_4 and SCS_4[a,b] for 3-(p-Y-phenyl)-1,2,4,5-tetrazine derivatives (Y=H,OCH_3)[c]

substituted 1,2,4,5-tetrazinyl group	Y=OCH_3		Y=H	solvent
	δC_4	SCS-4	δC_4	
tetrazinyl-	164.01	30.77	133.24	$CDCl_3$
6-aminotetrazinyl-	161.28	30.86	130.42	DMSO-d_6
1,6-dihydrotetrazinyl-	161.22	31.50	129.72	CD_3OD/D_2O
1,6-dihydrotetrazinyl-anion	159.44	32.27	127.17	CD_3OD/D_2O[d]
6-hydrazino-1,6-dihydrotetrazinyl-anion	159.03	31.98	127.05	$N_2H_4.H_2O/CD_3OD$ (1:1)

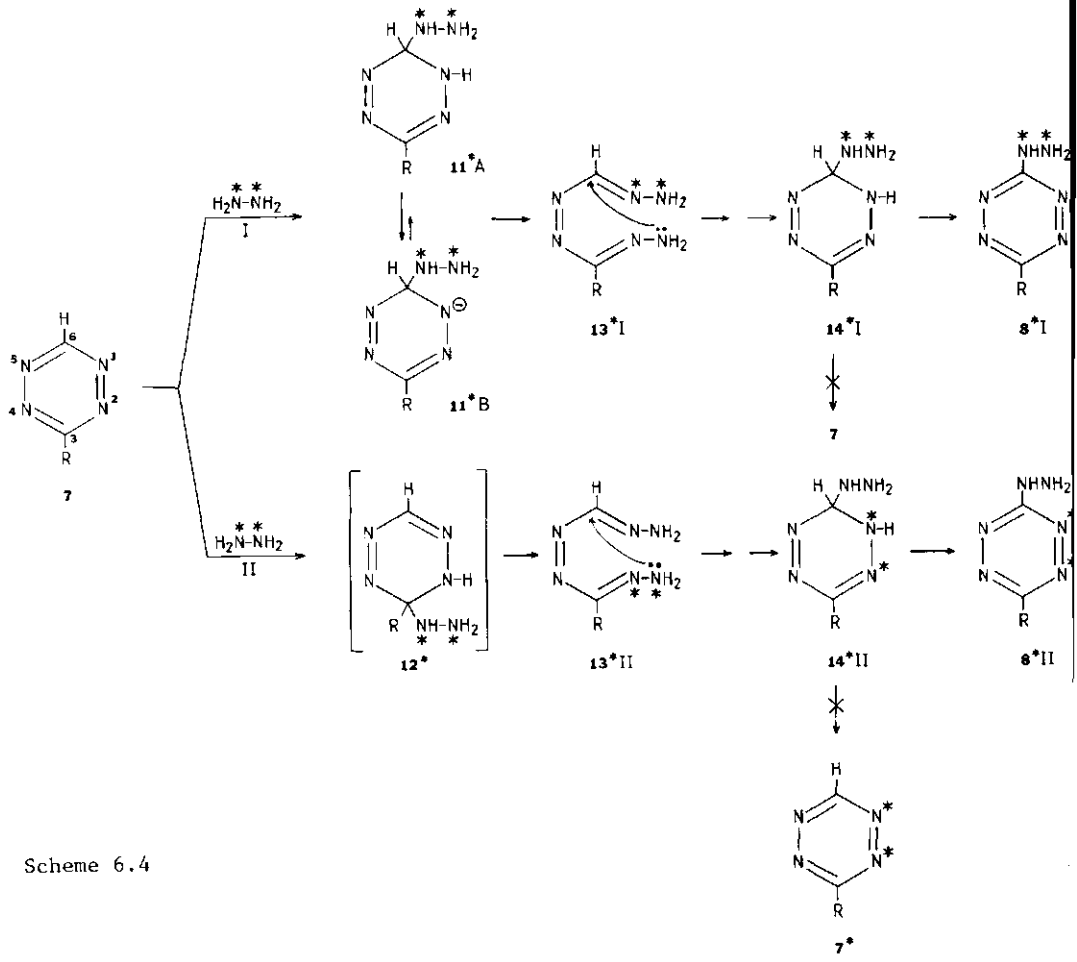
a SCS-4 = $\left[\delta C_4(Y\neq H)-\delta C_4(Y=H)\right]$ ppm, positive value corresponds to downfield shift

b r=0.923; slope 0.24±0.06; intercept 62±7; t_α=4.16

c values are from reference 1

d 1.5 equivalent NaOH

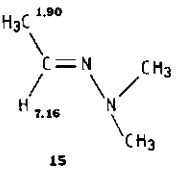
On warming the solutions of 11 in hydrazine-hydrate/methanol (from 233 K to 253 K ($R=CH_3$, C_2H_5) or to 273 K ($R=\underline{t}\text{-}C_4H_9$) or to 308 K ($R=C_6H_5$)), both the ^1H and ^{13}C NMR adduct signals slowly disappear and new signals with completely different chemical shifts come up. They could be attributed to open-chain intermediates 13.



Scheme 6.4

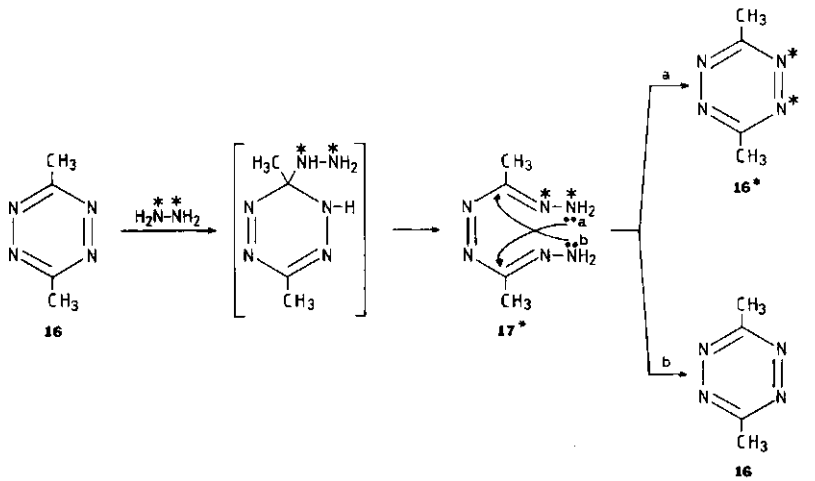
Evidence for the formation of 13 is based on two facts a) in all these open-chain intermediates 13, with different groups R, both H_6 and C_6 are found in a narrow chemical shift range (H_6 between 6.92-7.15 ppm; C_6 between 141-143 ppm) and b) the chemical shifts of H_6 are of the same magnitude as found for the H-C=N-group in N,N-dimethylacetaldehyde-hydrazone (15).[19] The ^1H chemical shift of the methyl group in 13 ($R=CH_3$) at 1.88 ppm is also in surprising good agreement with that

found for the C-methyl group in 15 (1.90 ppm).



15

Moreover, when 3,6-dimethyl-1,2,4,5-tetrazine (16) was dissolved in a 1:1 mixture of hydrazine-hydrate and deutero-methanol at 273 K and the ^{1}H and ^{13}C NMR spectra of these solutions were measured, chemical shifts were found, which could only be attributed to the di-hydrazone 17. Species 17 showed only *one* methyl group indicating that in 17 both methyl groups are identical. The ^{1}H chemical shift for the hydrogens of the methyl group ($\underline{CH}_3$=1.87 ppm) is about the same as found for 13 (R=CH_3, 1.88 ppm). Also nearly identical ^{13}C chemical shifts were observed for C_3 =150.6 ppm and $\underline{CH}_3$=16.1 ppm compared with those in 13 (R=CH_3) (table 6.2). If 16 is treated with ^{15}N double labelled hydrazine (7% ^{15}N), part of the label is found in the 1,2,4,5-tetrazine ring of the recovered 16 (0.6% ^{15}N). This can be explained by ring closure of the symmetrical open-chain intermediate 17^{*} (scheme 6.5).



Scheme 6.5

No NMR evidence has been obtained for the intermediacy of 12^{*}. Its occurrence is necessary however to explain the formation of 8^{*}II from 7 (R=CH_3, R=C_2H_5) having both labelled nitrogens in the 1,2,4,5-tetrazine ring.

All NMR data and the results of ^{15}N-labelling are in agreement with the mechanism proposed in scheme 6.4. Attack at C_6 (route I) is yielding the initial homoaroma-

tic σ-adduct anion $11^{*}B$, which on opening of the 1,2,4,5-tetrazine ring yields $13^{*}I$. Attack at C_3, in route II, gives an unstable adduct 12^{*}, which is not observed by NMR. Ring opening yields open-chain intermediate $13^{*}II$, being identical with $13^{*}I$, except that the ^{15}N-label is present in a different position. The ring closure takes place by attack on C_6, leading to the most stable adduct 14^{*}, which is oxidized by hydrazine[20] present in the reaction mixture.

That ring closure occurs by attack of the hydrazino nitrogen on C_6 and not on C_3, to which R is attached, is probably due to the homoaromatic stabilization of intermediate 14. Homoaromaticity is less likely, when two large groups (R and hydrazino as in 12^{*}) are present at the methylene bridge.[21] This mechanism is in agreement with the fact that 7 (R=C_6H_5, t-C_4H_9) does not, or only to a very small extent, react with formation of ring labelled $8^{*}II$ (R=C_6H_5, t-C_4H_9). Both groups are blocking groups and probably retard or prevent addition at C_3, to which these substituents are attached.

The fact that in all reactions the recovered starting material 7 is unlabelled indicates that $14^{*}I$ or $14^{*}II$ do not decompose into 7 or 7^{*}. The recovered starting material 7 is probably *unreacted* starting material.

From all the data presented we concluded that *both* routes (I and II) of scheme 6.4, leading to the ring-labelled hydrazino compound ($8^{*}II$), as well as to the ring-unlabelled hydrazino compound ($8^{*}I$) occur with an *opening* of the 1,2,4,5-tetrazine ring. Both substitutions can be considered as an S_N(ANRORC) mechanism. The only difference between the two routes is the place of initial attack (C_3 or C_6). If a blocking group is present on C_3, attack only takes place at C_6 and no label is found to be built into the ring.

To our knowledge this is the first example of a reaction in which both the ring-labelled and the exocyclic-labelled compound follow the S_N(ANRORC) pathway. Thus in these reactions no evidence for an S_N(AE) mechanism has been obtained.

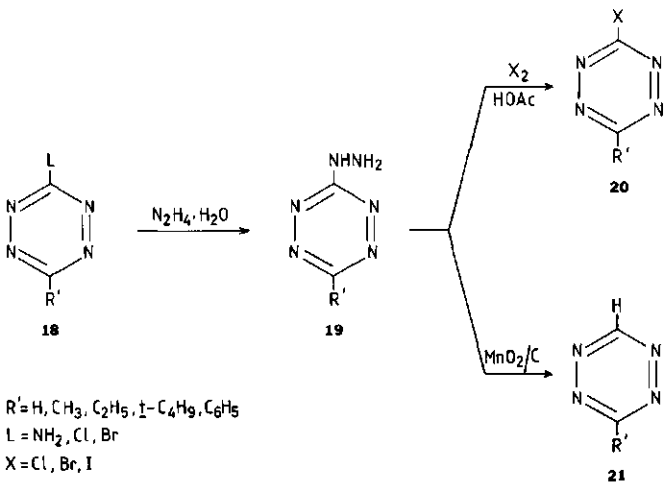
B. Hydrazino-deamination and hydrazino-dehalogenation of 1,2,4,5-tetrazines

On refluxing 18 (L=NH_2) in ethanol containing 2 equivalents of hydrazine-hydrate 6-hydrazino-3R'-1,2,4,5-tetrazines (19) are obtained in yields between 40 and 70% (depending on substituent R'), together with recovered starting material 18. The yields and reaction conditions are mentioned in table 6.6.

When the leaving group L is Br or Cl, compounds 18 (L=Br,Cl) react in ethanol containing 3 equivalents of hydrazine-hydrate much faster; already at 293 K they are quantitatively converted into 19 (table 6.6).

In order to investigate whether also in the formation of these hydrazino compounds 19 the S_N(ANRORC) mechanism is operative, the reactions were carried out with ^{15}N

double labelled hydrazine. After extraction with benzene, the crude reaction product was not further purified and directly measured in the mass spectrometer. To establish which percentage of ^{15}N was present in the 1,2,4,5-tetrazine ring or on the exocyclic nitrogens of the labelled hydrazino compounds 19*, these compounds were converted to the corresponding 6-halogeno-3R'-1,2,4,5-tetrazines (20*, X=Cl,Br,I) by oxidation with halogen[14] in acetic acid; or -in some cases- to the corresponding 3R'-1,2,4,5-tetrazines (21*) by oxidation with manganese dioxide on carbon.[22]



Scheme 6.6

The excess of ^{15}N in compounds 19*, 20* and 21* as found by mass spectrometric measurement at high resolving power[15] is given in table 6.4. No label was found in the recovered 6-amino-3R'-1,2,4,5-tetrazines (18, L=NH_2).
From these data it is evident that part of the hydrazino compounds 19* is formed from 18 by the S_N(ANRORC) mechanism in a decreasing order: L=NH_2>L=Br>L=Cl.
In order to gain more insight in the reaction course of the hydrazinolysis we investigated by ^1H and ^{13}C NMR spectroscopy which intermediary species are present.
The reactions of 18 (L=Br,Cl) could not be followed by NMR spectroscopy, since these compounds react very fast with hydrazine.
On dissolving 6-amino-1,2,4,5-tetrazine (18, R'=H; L=NH_2) in hydrazine-hydrate/deuteromethanol (1:3) at 273 K, the formation of the σ-adduct 22 (R'=H) was not observed (see table 6.5). The ^1H NMR signal δ=6.98 ppm was attributed to the open-

Table 6.4 ^{15}N excess in compounds 19*, 20* and 21*

Starting mat. 18		% ^{15}N	% ^{15}N		ANRORC	ANRORC
R'	L	19*	20*/21*		%	average
H	NH_2 [a]	6.4	1.27	X=I	20.0	21.6
		6.1	1.42	X=I	23.2	
CH_3	NH_2 [a]	7.1	1.77	X=Br	24.9	25.3
		6.6	1.70	21*	25.8	
C_2H_5	NH_2 [a]	6.1	0.99	X=Br	16.3	17.9
		6.3	1.22	X=Br	19.5	
$\underline{t}$-C_4H_9	NH_2 [a]	6.4	0	X=Br	0	0
		6.4	0	X=Br	0	
C_6H_5	NH_2 [a]	5.0	0	21*	0	0
		5.5	0	21*	0	
CH_3	Cl	5.3	0.22	X=Br	4.1	6.5
		19.4	1.71	X=Br	8.8	
CH_3	Br	5.8	1.18	X=Br	20.5	19.3
					18 [b]	
C_2H_5	Br	5.2	0.19	X=Br	3.6	2.3
		5.2	0.05	X=Br	1.0	
S.D. average		0.4	0.15		2.6	2.6

a no label was found in recovered starting material

b see reference 12

chain intermediate 23 (R'=H). This conclusion was based on comparison with the chemical shift of H_6 in 13 (6.92-7.15 ppm), table 6.2. About the same shift for 23 is also found in a mixture containing 1 equivalent of 18 (R'=H; L=NH_2) and 2 equivalents of hydrazine-hydrate in deuteromethanol. The values of the ^{13}C chemical shifts of C_3 of 23 (δ=144.9 ppm) and J_{C_3H} of 23 (199 Hz) (table 6.5) also correspond nicely with those of C_6 (δ=141-143 ppm) and J_{C_6H} (200 Hz) of the open-chain compounds 13, see table 6.2.

Table 6.5 ^{1}H and ^{13}C spectroscopic data of 6-amino-3R'-1,2,4,5-tetrazines (18 R'=H,CH_3,C_2H_5;L=NH_2) in deuteromethanol and in a mixture of hydrazine-hydrate and deuteromethanol

R'	solvent	temp.(K)	H_3	C_3	J_{C_3H}	C_6	others
18 H	CD_3OD	308	9.70	154.2	213	166.7	
23	a	b	6.91	144.9	199	154.3	
	c	233	9.70				
	c	273	6.98[d]				
18 CH_3	CD_3OD	308		162.7		165.0	$\underline{C}H_3$ 2.73 $\underline{C}H_3$ 19.9
23	a	e		153.3[f]		155.0[f]	$\underline{C}H_3$ 1.85 $\underline{C}H_3$ 15.9
	a	g					$\underline{C}H_3$ 1.85; 2.32; 2.68
18 C_2H_5	CD_3OD	308		166.4		165.0	$\underline{C}H_2$ 3.12 $\underline{C}H_3$ 1.45 $\underline{C}H_2$ 28.1 $\underline{C}H_3$ 12.9
23	a	h		157.7		155.2	$\underline{C}H_2$ 2.22 $\underline{C}H_3$ 1.18 $\underline{C}H_2$ 24.4 $\underline{C}H_3$ 11.3
	a	g					$\underline{C}H_2$ 2.22, 2.77, 3.14 $\underline{C}H_3$ 1.18, 1.33, 1.40

a 2 equivalents $N_2H_4.H_2O$ in CD_3OD

b 45 min. at 208 K, measured at 263 K

c $N_2H_4.H_2O/CD_3OD$ (1:3)

d at intermediate temperatures 9.70 is broadened and disappears, while 6.98 is formed

e 3h at 323K, measured at 303 K

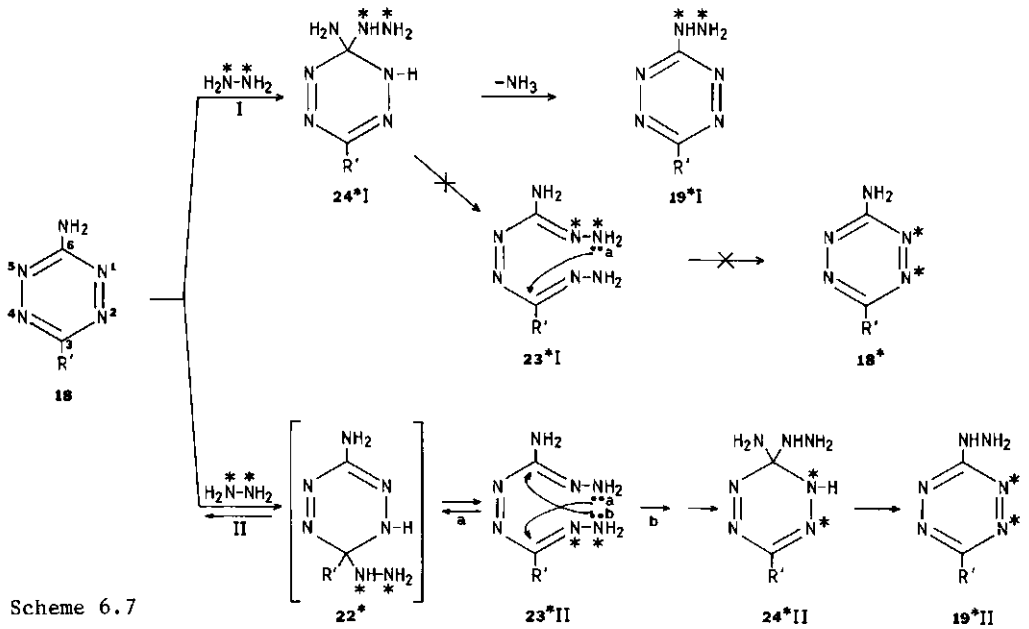
f signals may be interchanged

g measured at 323K during 8h

h 3h at 323K, measured at 258K

The ^{1}H NMR spectra of 6-amino-3-methyl-1,2,4,5-tetrazine (18 R'=CH_3; L=NH_2) with 2 equivalents of hydrazine-hydrate measured at 323 K during 8 hours were analyzed carefully. Four different stages could be discerned, showing the appearance and disappearance of signals. The chemical shifts observed for the methyl group in these four stages indicated by i, ii, iii, iv are: i) 2.73 and 1.85; ii) 2.73, 1.85 and 2.32; iii) 1.85 and 2.32; iv) 2.32 and 2.68 ppm. The peaks at 2.73 and

2.68 ppm were assigned to starting material 18 (R'=CH_3; L=NH_2) and hydrazino product 19 (R'=CH_3) respectively. The peak at 1.85 ppm is attributed to R'=CH_3 in open-chain intermediate 23, because it is in agreement with 1.88 ppm, found for the open-chain intermediate 13 (R=CH_3), table 6.2. The resonance signal at 2.32 ppm can probably be attributed to compound 24-I,II (R'=CH_3). Compound 24-II is obtained by ring closure of 23-II according to route b and 24-I by attack of hydrazine on C_6 of 18 (R'=CH_3; L=NH_2) (route I, scheme 6.7). This shift is resembling the one at 2.42 ppm found for the CH_3 group of σ-adduct 11 (R=CH_3). From stage i) the corresponding ^{13}C NMR spectra were measured; the ^{13}C chemical shifts of 23 are resembling those of the open-chain intermediates 13 in table 6.2. The same results were obtained on measuring the ^{1}H and ^{13}C NMR spectra of 6-amino 3-ethyl-1,2,4,5-tetrazine (18, R'=C_2H_5; L=NH_2), see table 6.5. All the NMR data and results of ^{15}N-labelling support the mechanism proposed in scheme 6.7.



Scheme 6.7

In contrast to the reaction course presented for the Chichibabin amination of 7 (scheme 6.4), we have to conclude that in the hydrazino-deamination a somewhat different reaction sequence takes place (scheme 6.7). The ring-labelled hydrazino compound 19*II is obtained by an S_N(ANRORC) mechanism (route II) and the hydra-

zino compound with ^{15}N-label in the side-chain, i.e. 19*I, is formed by the $S_N(AE)$ mechanism (route I). Compound 19*II is formed *via* the open-chain intermediate 23*II. The possible occurrence of 23*I as intermediate can be excluded, since then ring labelled 18* would have been formed; this is however not the case.
That no $S_N(ANRORC)$ mechanism is involved in the formation of the hydrazino compounds 19 (R'=C_6H_5, t-C_4H_9) from 18 (R'=C_6H_5, t-C_4H_9) is in agreement with the proposed mechanism since addition to position 3, leading to 22*, is prevented due to the blocking effects of these groups.

6.3 EXPERIMENTAL SECTION

Melting points are uncorrected. Mass spectra were determined on an AEI MS 902 mass spectrometer. Exact mass measurements and intensity ratio measurements of the M and (M+2) peaks were carried out at a resolving power of 10000. ^1H NMR spectra were recorded on a JEOL NM C-60H, a Varian EM 390 or on a Varian XL-100-15 spectrometer. TMS was used as internal standard (δ=0 ppm). ^{13}C NMR spectra were recorded on a Varian XL-100-15 spectrometer. TMS was used as internal standard. Typical spectral parameters for ^{13}C NMR were as follows: spectral width 5120 Hz (1.25 Hz/point), acquisition time 0.8 s, pulse delay 0-1.2 s, pulse width 10-20 μs. UV spectra were measured on a Perkin Elmer 550 spectrophotometer. Column chromatography was carried out over Merck Silica gel 60 (70-230 mesh).

Preparation of starting materials

3-R-1,2,4,5-tetrazines (7, R=CH_3,[12] *t-C_4H_9,*[6] *C_6H_5,*[24] *p-OCH_3-C_6H_4*[24]*) and 6-amino-1,2,4,5-tetrazines (18, R'=H,*[25] *CH_3,*[25] *C_2H_5,*[25] *C_6H_5;*[6] *L=NH_2)* were prepared according to known synthetic procedures. Compounds 18 (R'=H, C_2H_5; L=NH_2) were only mentioned in reference 25, but no physical data were given.

3-Ethyl-1,2,4,5-tetrazine (7, R=C_2H_5) was prepared by hydrazinolysis of 6-amino-3-ethyl-1,2,4,5-tetrazine (18, R'=C_2H_5; L=NH_2) and subsequent oxidation of the hydrazino compound with manganese dioxide on carbon,[22] analogously as described before.[12] This oxidation reaction is almost quantitative.

6-Bromo-1,2,4,5-tetrazines (10, R=C_2H_5, t-C_4H_9) were prepared by hydrazinolysis of 6-amino-1,2,4,5-tetrazines (18, R'=C_2H_5, t-C_4H_9; L=NH_2) and subsequent oxidation of the hydrazino compounds with two equivalents of bromine in acetic acid according to the procedure described before for 6-bromo-3-methyl(phenyl)-1,2,4,5-

tetrazine (10, R=CH_3,[12] C_6H_5[6]). These reactions give almost quantitative yields.

6-Halogeno-1,2,4,5-tetrazines (20, X=Cl, Br, I; R'=H, CH_3, C_2H_5, t-C_4H_9, C_6H_5) were prepared from the corresponding 6-amino compounds 18 (R'=H, CH_3, C_2H_5, t-C_4H_9, C_6H_5; L=NH_2) analogously to the preparation of the 6-bromo compounds 10. With the other halogens the oxidation reaction is also almost quantitative.

The hydrazinolysis reactions

These were carried out under conditions and with results as given in table 6.6. The hydrazino compounds 8 and 19 were identified as their benzaldehyde-hydrazones[6,12] or as their acetone-hydrazones 9.

Acetone-hydrazones 9 (R=CH_3, C_2H_5, t-C_4H_9, C_6H_5) were prepared by reflux of 1 mmol of pure hydrazino compound 8 or of a mixture containing hydrazino compound 8 with 2 mL of acetone during 5 min. This reaction is quantitative.

Table 6.6 Reaction conditions and yields of the hydrazinolysis of 1,2,4,5-tetrazines 7 and 18[a]

starting material	$N_2H_4.H_2O$ equivalents	temp. (K)	time (min)	hydrazino compound[b,c] %	recovered[b] start.mat. %
7 R=CH_3	3	298	45 N_2	12	10
7 R=C_2H_5	3	298	45 N_2	15	14
7 R=t-C_4H_9	3	298	45 N_2	12	12
7 R=C_6H_5	3	298	45 N_2	9	15
18 R'=H L=NH_2	2	351	90	62	2
18 R'=CH_3 L=NH_2	2	351	90	47	35
18 R'=C_2H_5 L=NH_2	2	351	90	50	27
18 R'=t-C_4H_9 L=NH_2	2	351	90	34	33
18 R'=C_6H_5 L=NH_2	2	351	90	70	2
18 R'=CH_3 L=Cl	3	293	20	>90	0
18 R'=CH_3 L=Br	3	293	20	>90	0
18 R'=C_2H_5 L=Br	3	293	20	>90	0

a reactions were carried out on 1 mmol scale in 4 ml of ethanol

b yields were determined by UV measurement

c the hydrazino compounds were converted to the acetone-hydrazones

Table 6.7 Physical data of the new 1,2,4,5-tetrazines, prepared in this study

compound	mp	mass spectra m/e	^{1}H NMR spectra δ	Analyses % Calcd. C H	Found C H
7 R=C_2H_5	oil	M^+110	table II	43.63	44.41[a]
($C_4H_6N_4$)				5.49	5.71
8 R=C_2H_5		M^+140			
8[b] R=C_2H_5	161-162.5	M^+228	1.47(t,CH_3)3.15(q,CH_2)7.31-7.90(m,Ph) 8.33(s,CH) 12.33 (NH) DMSO-d_6	57.88	57.84
($C_{11}H_{12}N_6$)				5.30	5.19
8 R=$\underline{t}C_4H_9$		M^+168	1.41(S,CH_3)5.0 (NH) DMSO-d_6		
8 R=C_6H_5		M^+188	4.69(s,NH_2) 9.70(s,NH) 7.50-7.64(m,$\underline{m}/\underline{p}$Ph) 8.20-8.35(m, $\underline{o}$Ph) DMSO-d_6		
9 R=CH_3	112-115	M^+166	2.02(s,$(CH_3)_2$)2.74(s,CH_3) 10.71(NH) DMSO-d_6	43.36	43.65
($C_6H_{10}N_6$)				6.07	6.25
9 R=C_2H_5	106-109	M^+180	1.33(t,CH_3)2.00(s,$(CH_3)_2$) 3.07 (q,CH_2) 10.76NH DMSO-d_6	46.65	46.85
($C_7H_{12}N_6$)				6.71	6.86
9 R=$\underline{t}$-C_4H_9	72.5-77.5	M^+208	1.44(s,CH_3) 203(s,$(CH_3)_2$) 10.86 (NH) DMSO-d_6	51.90	51.60
($C_9H_{16}N_4$)				7.74	7.86
9 R=C_6H_5	180-182	M^+228	2.07(s,$(CH_3)_2$) 7.52-7.61 (m,m/pPh) 8.22-8.36(m,$\underline{o}$Ph) 11.06 (NH) DMSO-d_6	57.88	57.68
($C_{11}H_{12}N_6$)				5.30	5.31
10 R=C_2H_5	34.5-35.5	M^+190/188	1.46(t,CH_3) 3.25(q,CH_2) $CDCl_3$	25.41	25.62
($C_4H_5BrN_4$)				2.67	2.52
10 R=$\underline{t}$-C_4H_9	oil	M^+218/216	1.57(s,CH_3) $CDCl_3$	33.20	33.34
($C_6H_9BrN_4$)				4.18	4.02
18 R'=H, L=NH_2[c]	170-170.5	M^+97	7.20(NH) 9.66(s,H) CD_3COCD_3	24.74	24.99
				3.11	3.11
($C_2H_3N_5$)				N72.14	N72.04
18 R'=C_2H_5 L=NH_2[c]	126.5-127	M^+125	1.49(t,CH_3) 3.09(q,CH_2) 7.08 (NH) CD_3COCD_3	38.39	38.58
($C_4H_7N_5$)				5.64	5.33
18 R'=CH_3 L=Cl	83.5-84.5	M^+132/130	3.00(s,CH_3) CD_3OD	27.60	27.94
($C_3H_3ClN_4$)				2.32	2.27
19 R'=H		M^+112			
19[b] R'=H	187-187.5	M^+200	7.31-7.82(m,Ph) 8.30(s,CH) 9.92(s,H) 12.35 (NH) DMSO-d_6	53.99	54.11
($C_9H_8N_6$)				4.03	3.81
10 R'=H X=I	oil	M^+208	10.25(s,H) $CDCl_3$	11.55	d
(C_2HIN_4)				0.48	

Notes Table 6.7:

a exact mass measurements gave for $C_4H_6N_4(M^+)$ 110.0596 (theor. 110.0592)

b benzaldehyde-hydrazone

c compound is mentioned in reference 25, but no physical data are given

d exact mass measurements gave for $C_2HIN_4(M^+)$ 207.92478 (theor. 207.92478) this compound is unstable and can be stored for short time at -20°C

The melting points, the ^1H NMR data, the mass spectrometric measurements and the microanalyses of the new compounds are summarized in table 6.7.

Acknowledgement

We are indebted to Mr.H.Jongejan for carrying out the microanalyses and to Mr. W.P.Combé for his contribution to the mass spectrometric data.

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7 THE CRYSTAL STRUCTURE OF HOMOAROMATIC 6-ETHYL-3-PHENYL-1,6-DIHYDRO-1,2,4,5-TETRAZINE

7.1 INTRODUCTION

As described in this thesis 1,6-dihydro-1,2,4,5-tetrazines can be considered as homoaromatic[1,2] species. The aromatic sextet is formed by the two double bonds and the lone pair of N_1. In order to make the electron delocalization in the aromatic ring possible homoaromatic compounds are puckered and consequently the p_z orbitals of the atoms adjacent to the methylene bridge are canted. The overlap becomes restricted to single lobes at the side of the molecule opposite to the bridging atom. For this reason the conformation of the 1,6-dihydro-1,2,4,5-tetrazines can be imagined as containing an approximately planar tetrazole ring (figure 7.1) with a shortened N(1)- N(5) distance with respect to the corresponding distance in 1,2,4,5-tetrazine, so that the above mentioned overlap and delocalization is possible.

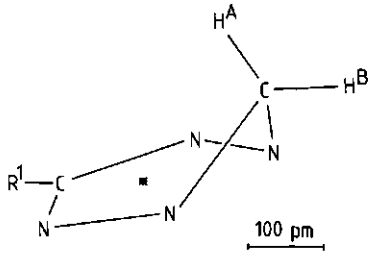
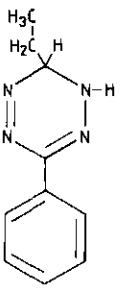


Figure 7.1 Perspective drawing of 1,6-dihydro-1,2,4,5-tetrazine

Since the title compound is easily obtained in crystalline form, it is possible to obtain *direct* information about the correctness of this assumption by a crystal structure determination. This work was carried out by Dr.C.H.Stam at the Laboratory of Crystallography of the University of Amsterdam.
6-Ethyl-3-phenyl-1,6-dihydro-1,2,4,5-tetrazine (1) was found to exist in one conformation in solution[3]. The hydrogen at the sp^3 carbon atom is above the tetrazole ring and the alkyl group is in the exo position. In contrast, in 3-phenyl-1,6-dihydro-1,2,4,5-tetrazine (2) there is an inversion between two

conformations, one with the methylene group pointing upwards and the other with the methylene downwards[3].

Scheme 7.1



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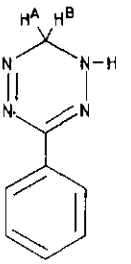

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7.2 RESULTS AND DISCUSSION

The measurements were carried out at 223 K (because the compound decomposes at room temperature). The crystals are orthorhombic with cell constants a = 8.3489 (8), b = 10.2516 (5) and c = 23.041 (2) Å. The space group is P_{bca} with 8 molecules per unit cell. 1454 independent reflections were collected, using graphite monochromated CuK_α radiation. The structure was solved by a straightforward application of the symbolic addition program set SIMPEL[4] and refined to a R value of 0.053.

The fractional coordinates are listed in table 7.1.

The conformation of the molecule is shown in figure 7.2

The nitrogen atoms N_1, N_2, N_4 and N_5 are coplanar within 0.005 Å. A projection onto this plane is presented in figure 7.3. The bond length and interbond angles are listed in table 7.2; the most important of these are indicated in figure 7.4.

From figures 7.2 and 7.3 it is clear that the molecule is *boat* shaped with both C_3 and C_6 upwards, and not as in figure 7.1. The sp^3 carbon atom is pointing upwards with a dihydral angle of 49.3° between the N(1)- C(6)- N(5) and the N(1)- N(2)- N(4)- N(5) planes; C_3 is tilted 26.7° as indicated in figure 7.3. Figure 7.3 reveals also that C_3 is not purely sp^2 hybridized, but it is slightly umbrella shaped. The reason why C_3 is also upwards is not clear. It might be due to a Van der Waals repulsion between nitrogens N_2 and N_4 and H_8 and H_{12} of the phenyl group, although the crystal structure of 3,6-diphenyl-1,2,4,5-tetrazine is planar[5].

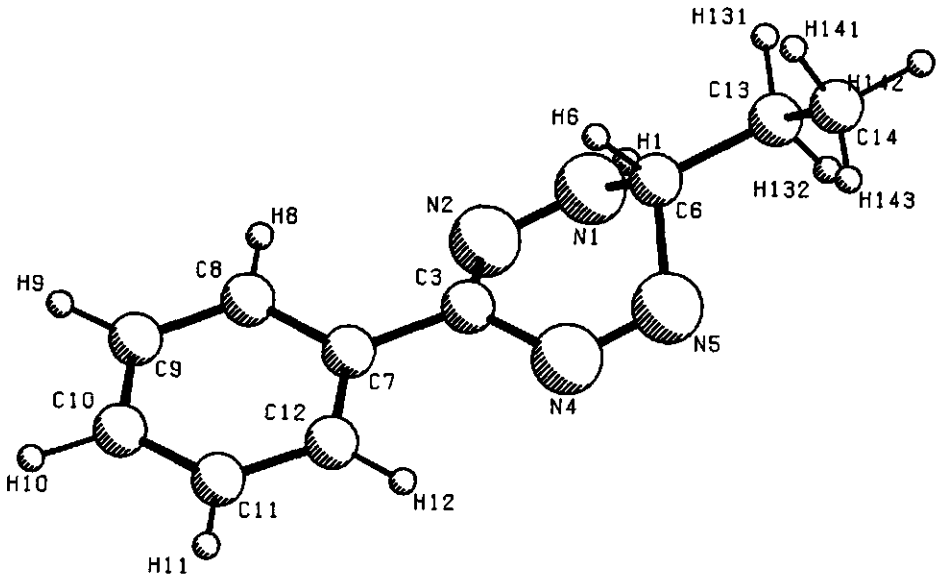


Figure 7.2 Three dimensional structure of 1

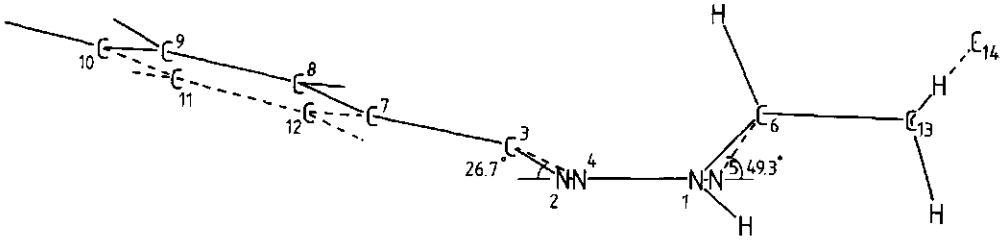


Figure 7.3 Projection onto the N(1)- N(2)- N(4)- N(5) plane

Table 7.1 Fractional coordinates in 6-ethyl-3-phenyl-1,6-dihydro-1,2,4,5-tetrazine (1)[a]

	X	Y	Z
N(1)	.3181(3)	.3972(2)	.5544(1)
N(2)	.3581(3)	.3482(2)	.6053(1)
C(3)	.4149(3)	.2269(3)	.6022(1)
N(4)	.3601(3)	.1478(3)	.5575(1)
N(5)	.3204(3)	.1982(2)	.5092(1)
C(6)	.3807(4)	.3347(3)	.5035(1)
C(7)	.4924(3)	.1679(3)	.6529(1)
C(8)	.5496(4)	.2464(3)	.6980(1)
C(9)	.6262(5)	.1920(3)	.7453(2)
C(10)	.6527(4)	.0565(3)	.7475(2)
C(11)	.6001(4)	- .0201(3)	.7028(2)
C(12)	.5202(3)	.0329(3)	.6559(1)
C(13)	.3289(3)	.3964(3)	.4471(1)
C(14)	.4064(5)	.3314(4)	.3954(1)
H(1)	.247 (5)	.468 (4)	.550 (1)
H(6)	.508 (4)	.332 (3)	.510 (1)
H(8)	.530 (5)	.341 (4)	.696 (2)
H(9)	.677 (5)	.240 (4)	.777 (1)
H(10)	.713 (5)	.018 (4)	.785 (2)
H(11)	.623 (5)	- .120 (4)	.704 (2)
H(12)	.475 (4)	- .023 (4)	.625 (1)
H(131)	.355 (4)	.496 (4)	.448 (1)
H(132)	.208 (6)	.389 (4)	.444 (2)
H(141)	.526 (7)	.347 (5)	.394 (2)
H(142)	.373 (5)	.374 (4)	.355 (2)
H(143)	.379 (6)	.246 (5)	.394 (2)

[a] The estimated standard deviations are in parentheses

As predicted from the ^{1}H NMR spectroscopic data[3], H_6 is indeed found above the tetrazole ring and the ethyl group is in the exo position.
The phenyl group is planar within 0.02 Å and the plane of the phenyl group is twisted with respect to the N(2)- C(3)- N(4) plane by 8°, C_{12} is rotated towards N_4, C_8 is rotated away from N_2. This can be seen from the Newman projection along the C(7)- C(3) bond (figure 7.5a).
Another important piece of information from this X-ray structural determination is the fact that N_1, which carries the hydrogen, is sp^2 hybridized. This can be concluded from the Newman projections along the N(1)- N(2) and the N(1)- C(6) bonds in figure 7.5 b,c.

Table 7.2 Bond distances (Å, 1 Å = 100 pm) and interbond angles[a] in 6-ethyl-3-phenyl-1,6-dihydro-1,2,4,5-tetrazine (1)[b]

N(1) - N(2)	1.319(4)	N(1) - N(2) - C(3)	113.4(3)
N(1) - H(1)	.94 (4)	N(2) - N(1) - H(1)	123 (2)
N(2) - C(3)	1.333(4)	C(6) - N(1) - H(1)	119 (2)
C(3) - N(4)	1.388(4)	N(2) - C(3) - N(4)	117.9(3)
N(4) - N(5)	1.271(4)	N(2) - C(3) - C(7)	120.0(3)
N(5) - C(6)	1.493(4)	C(6) - N(5) - N(4)	111.7(3)
C(6) - N(1)	1.435(4)	C(3) - N(4) - N(5)	119.9(3)
C(6) - H(6)	1.07 (4)	N(1) - C(6) - N(5)	102.9(3)
C(6) - C(13)	1.509(4)	N(2) - N(1) - C(6)	117.7(3)
C(3) - C(7)	1.466(4)	N(1) - C(6) - H(6)	105 (2)
C(7) - C(8)	1.398(4)	N(5) - C(6) - C(13)	111.9(3)
C(8) - C(9)	1.381(5)	N(5) - C(6) - H(6)	107 (2)
C(9) - C(10)	1.408(5)	C(13)- C(6) - H(6)	115 (2)
C(10)- C(11)	1.368(6)	N(1) - C(6) - C(13)	114.4(3)
C(11)- C(12)	1.381(5)	N(4) - C(3) - C(7)	119.7(3)
C(12)- C(7)	1.405(4)	C(3) - C(7) - C(8)	120.4(3)
C(8) - H(8)	.99 (4)	C(3) - C(7) - C(12)	121.2(3)
C(9) - H(9)	.98 (4)	C(8) - C(7) - C(12)	118.3(3)
C(10)- H(10)	1.08 (5)	C(7) - C(8) - C(9)	120.8(3)
C(11)- H(11)	1.04 (4)	C(8) - C(9) - C(10)	120.0(4)
C(12)- H(12)	.98 (3)	C(9) - C(10)- C(11)	119.3(4)
C(13)- H(14)	1.511(4)	C(10)- C(11)- C(12)	121.2(3)
C(13)- H(131)	1.04 (4)	C(7) - C(12)- C(11)	120.4(3)
C(13)- H(132)	1.01 (5)	C(6) - C(13)- C(14)	111.8(3)
C(14)- H(141)	1.01 (6)		
C(14)- H(142)	1.07 (5)		
C(14)- H(143)	.91 (6)		

[a] the average value of the C(n) - C(m) - H(m) bond angle is 120° in case C(m) is sp^2 and 109° in case C(m) is sp^3 hybridized

[b] the estimated standard deviations are in parentheses

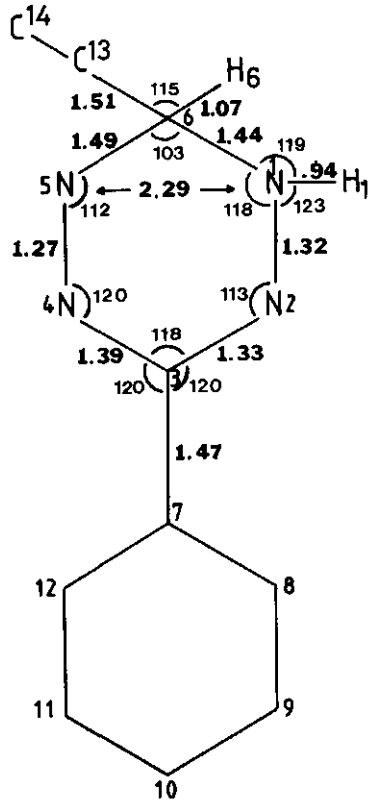


Figure 7.4 Bond distances (Å) and interbond angles of 1

The sp^2 hybridization of N_1 is essential to the proper orientation of the lone pair electrons, necessary for overlap and electron delocalization. Connection of the Newman projections along the N(1) - N(2) and the N(5) - N(4) bond results in figure 7.6. The p_z orbitals of the nitrogen atoms are perpendicular to the plane of the sp^2 hybridized orbitals as indicated in figure 7.6. From this figure it is clear that the p_z orbitals of N_1 and N_5 are pointing towards each other and that consequently the homoallylic participation [1,6] is probable.
We observed in the frozen conformation of 3-phenyl-1,6-dihydro-1,2,4,5-tetrazine (2) a ^1H chemical shift difference between H^A (the hydrogen above the tetrazole ring) and H^B (the hydrogen in the exo position) of $\Delta\delta$ = 4 ppm [3]. This shift difference was attributed to the presence of a ring current.

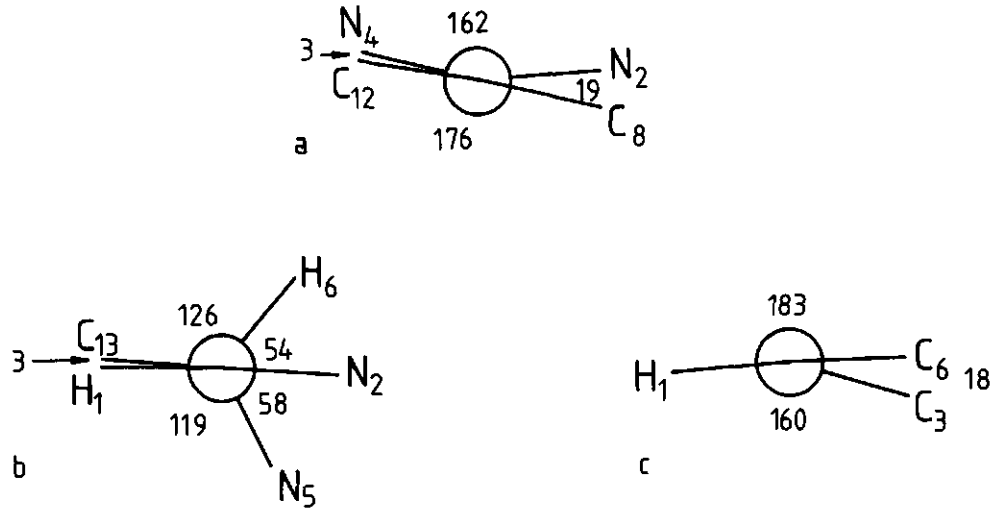


Figure 7.5 Newman projections
a. along the C(7)- C(3) bond
b. along the N(1)- C(6) bond
c. along the N(1)- N(2) bond

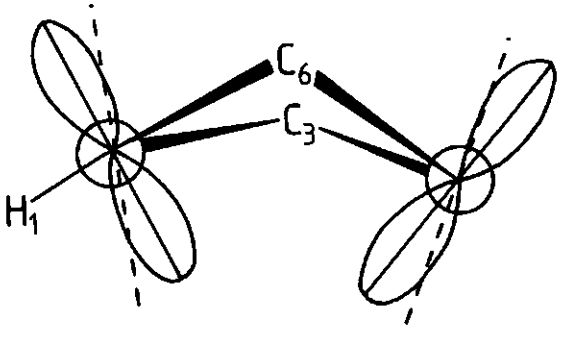


Figure 7.6 Newman projections along the N(1)-N(2) and the N(5)-N(4) bonds

If we assume that the conformation of 2 is the same as for 1 and that the conformation in solution is the same as in the crystal, we can approximate the difference between H^A and H^B by using the ring current effects in benzene[7]. A projection of these ring current effects on figure 7.3 indicates that H^A is in the shielding - and H^B in the deshielding regio; $\Delta\delta = \sim 6$ ppm. The observed value is lower, probably because the ring current in this puckered homoaromatic system is not as efficient as in benzene.

A review of the relation between bond lenghts and bond order for bonds between sp^2 hybridized carbon- and nitrogen atoms was found in the literature[8], see table 7.3. A localized single bond has a bond order of 1.0; a localized double bond of 2.0.

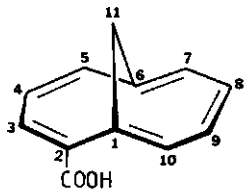
Table 7.3 Bond lengths (Å) and bond orders for bonds between C and N atoms in which both atoms are assumed to have sp^2 hybridization

Bond type	Bond order		
	1.0	1.5	2.0
C-C	1.48	1.39	1.34
C-N	1.45	1.34	1.27
N-N	1.41	1.31	1.23

The dimensions of 1,2,4,5-tetrazine are[9]: C-N 1.33 Å; N-N 1.32 Å; C-N-N 115° and N-C-N 127°.

Comparison with the bond angles and distances in 1 (figure 7.4) reveals that both the N(1) - N(2) (1.32 Å) and the N(4) - N(5) (1.27 Å) distance are larger than in the localized double bond (1.23 Å) and smaller than in the single bond (1.41 Å). Especially the N(1) - N(2) distance is of the same magnitude as in 1,2,4,5-tetrazine (1.32 Å). Also the N(2) - C(3) (1.33 Å) and the N(4) - C(3) (1.39 Å) bond lengths are between single and double. These intermediate bond lengths (between single and double) are in agreement with the delocalization of electrons over the aromatic tetrazole ring. There exists a relationship between the bond length and bond order for N-N and C-N bonds[8]. From these the approximate bond orders were estimated: N(1) - N(2): 1.45; N(2) - C(3): 1.55; C(3) - N(4): 1.23; N(4) - N(5): 1.78. It is striking that especially the N(1) - N(2) bond is so aromatic.

Only the N(1) - N(5) distance is rather long (2.29 A), this is not necessarily in conflict with the homoaromatic character, however, because in some homoaromatic systems a similar distance is observed by X-ray crystal analysis. For example in 1,6-methano [10] annulene-2-carboxylic acid (3) the 1,6 distance is 2.26 Å [10] and in 4 the 1,6-distance is 2.30 Å [11]; yet in these compounds a considerable 1,6 overlap was established[12]. It is regrettable, however, that there are not more crystal structural data available for comparison.



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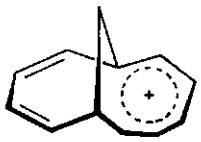

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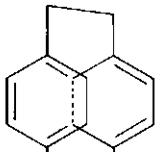
Scheme 7.2

As the tetrazine part of 1 is boat shaped, the tetrazole ring of the homotetrazole is not planar, but puckered. There are some examples of 'bent aromaticity' in the literature. A nice example is the [2,2] paracyclophane system (5)[13]. In this strained molecule the benzene rings are boat shaped. Although the gradients amount to 13°, yet the benzene rings preserve their normal aromatic properties.



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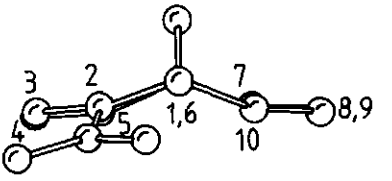
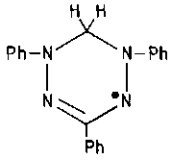
Other examples are the species 3 and 4 in which the ten and eleven carbon atoms of the annulene part of the molecule are not coplanar[10,11], but puckered as shown in figure 7.7.
From these examples it is clear that electron delocalization occurs also in a not perfectly planar system.
It is obvious then that the crystal structure of 1 is in good agreement with the homoaromatic description presented in this thesis.

A compound that is very similar to 1,6-dihydro-1,2,4,5-tetrazine is 2,4,6-triphenylverdazyl (6)[14].

Figure 7.7 Puckered structure of 3

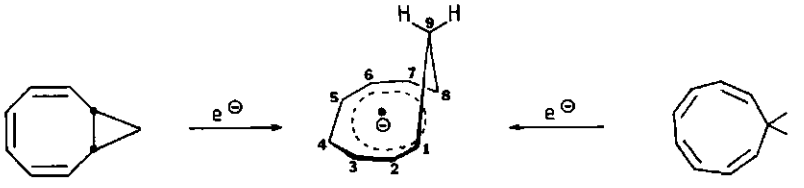




6

The structure of this crystalline radical has been elucidated by X-ray analysis[15]. The most important bond lengths and bond angles are indicated in figure 7.8. The dihedral angle between the planes N(2) - C(3) - N(4) and N(1) - N(2) - N(4) - N(5) is 42.9°, C_6 is tilted 9.5°. The phenyl group at C_6 is essentially coplanar with the plane through N_1, N_5 and C_6, but the other phenyl groups are twisted by 23° (at N_2) and 13° (at N_4).

So compound 6 is also in a boat conformation. The nitrogen atoms N_2 and N_4 are sp^2 hybridized. This is in agreement with the equal sharing of the unpaired electron among the *four* nitrogen atoms observed by ESR spectroscopy[16]. Compound 6 shows a ring inversion[17], like the 1,6-dihydro-1,2,4,5-tetrazines[3]; kinetic parameters were not determined however.



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Scheme 7.3

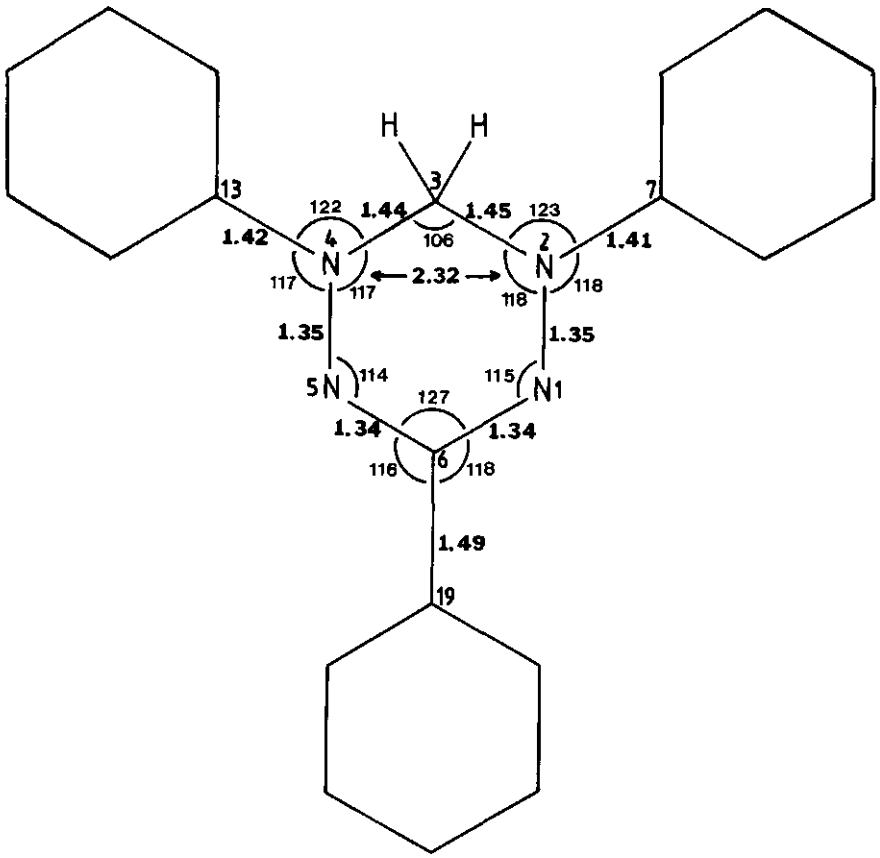

Figure 7.8
Bond distances (Å) and
interbond angles of 6

A comparison of the bond lengths and angles of 1 and 6 (figures 7.4 and 7.8) reveals that there is considerable similarity between these structures. The verdazyl 6 is a 7π electron system, whereas 1,6-dihydro-1,2,4,5-tetrazine 1 is a 6π electron homoaromatic system.
An example of a 9π electron system, the monohomocyclooctatetraene anion radical (7), having homoaromatic properties has been described[18].
The C_9 protons reveal very different a_H values in the ESR spectrum, indicating that C_9 is tilted out of the plane of the molecule. The tilting of the p_z orbitals results in 1,8-interaction, which necessitates the decription of this species as a homoconjugated cyclooctatetraene.

As a consequence one may wonder why the methylene group in the verdazyl 6 points out of the N(1) - N(2) - N(4) - N(5) plane and why also the rest of the crystal structure of 6 resembles that of the homoaromatic 1,6-dihydro-1,2,4,5-tetrazines described in this thesis. Either this conformity is accidental, or it may lead to the conclusion that homoaromatic properties must be ascribed to this 7π electron system. This could be investigated by measurement of the a_H values of the protons at C_3 at a temperature, where the ring inversion is frozen.

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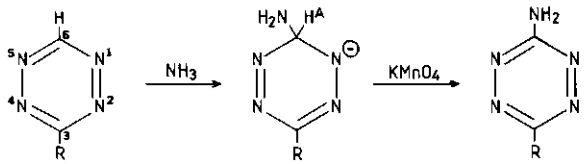
8 GENERAL DISCUSSION

The central theme in the study described in this thesis was the investigation into the occurrence of the S_N(ANRORC) mechanism during the reactions of hydrazine with the red coloured 1,2,4,5-tetrazines. As a part of this study we were interested whether a σ-adduct is formed as first step in this process.

8.1 HOMOAROMATICITY AND σ-ADDUCTS

Measurement of the ^{1}H chemical shifts of the yellow solutions of 3-aryl(alkyl)-1,2,4,5-tetrazines (1) in hydrazine-hydrate/methanol or in liquid ammonia at 230 K revealed an upfield shift of $\Delta\delta = \sim 8.5$ ppm in hydrazine[1] and $\Delta\delta = 8.7$ ppm in liquid ammonia[2] (chapters 4 and 6). This upfield shift is extraordinary large in comparison with the upfield shift ($\Delta\delta$) of 4-5 ppm usually observed on addition of liquid ammonia to heteroaromatics (see for example scheme 1.6). 3-Aryl(alkyl)-1,2,4,5-tetrazine (1) is (almost quantitatively) converted into the 6-amino compound 3 on dissolving it in liquid ammonia and addition of an oxidizing agent[3] to this solution (chapter 2). This indicates that 6-amino-3-aryl(alkyl)-1,6-dihydro-1,2,4,5-tetrazine (2), the same species as the expected σ-adduct, must exist as intermediate in liquid ammonia.



Scheme 8.1 1 2 3

A ^{1}H NMR study of the yellow coloured 1,6-dihydro-1,2,4,5-tetrazines as model compounds for these σ-adducts was undertaken (chapter 3). These compounds could easily be prepared by sodium borohydride reduction of the corresponding 1,2,4,5-tetrazines. At low temperature[4] we observed a great difference between the chemical shifts of H^A and H^B for 3-phenyl-1,6-dihydro-1,2,4,5-tetrazine (4a).

This difference can be explained if we assume that this species is present in the monohomotetrazole conformation. The tetrazole part of the molecule was supposed to be approximately planar, in analogy with the calculated structures of the isoelectronic homocyclopentadienyl anion[5] (see fig.8.1) and the homotropylium cation[6].

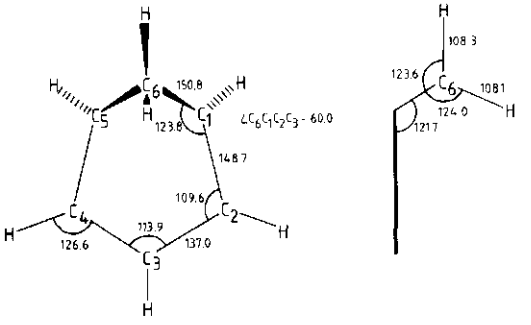
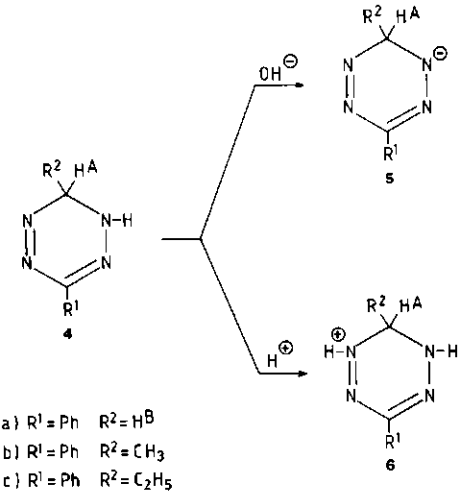


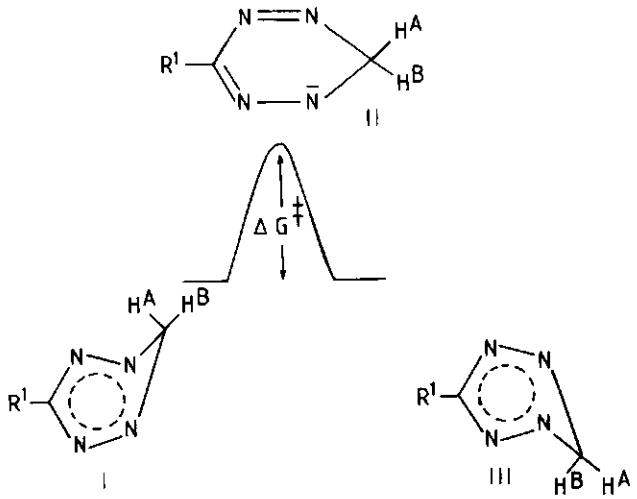
Figure 8.1 Calculated structure of homocyclopentadienyl anion

The aromatic sextet is formed by two double bonds and the lone pair of N_1. The methylene group points out of the plane of the tetrazole ring. The p_z orbitals of the atoms adjacent to the methylene bridge are canted by this puckering, making overlap and electron delocalization possible. Hydrogen H^A is above the ring current of the tetrazole ring, in the shielding regio and resonates at high field (δ = 2.13 ppm) and hydrogen H^B is in the expo position, in the deshielding regio (δ = 6.13 ppm)(see scheme 8.3). This homoaromatic species shows a ring inversion at normal NMR temperature (308 K). The kinetic parameters of 4a and 4d and the conjugate base 5a and conjugate acid 6a were determined by dynamic NMR measurements (chapter 3).
$\Delta G^{\ddagger}$ was visualized as the difference in free energy between the homotetrazole conformation I and a planar species II in which a considerable amount of resonance energy is lost; although the bridge-flipping process may contain more intermediates, as was found for the homotropylium cation (see scheme 1.10).



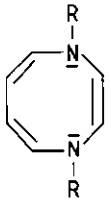
a) $R^1 = Ph$ $R^2 = H^B$
b) $R^1 = Ph$ $R^2 = CH_3$
c) $R^1 = Ph$ $R^2 = C_2H_5$
d) $R^1 = CH_3$ $R^2 = H^B$
e) $R^1 = CH_3$ $R^2 = CH_3$

Scheme 8.2

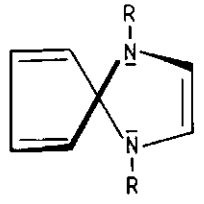


Scheme 8.3

It was obvious from these kinetic parameters that the resonance energy of the anionic homoaromatic species 5a (68 kJ/mol) is larger than that of the neutral - 4a (52 kJ/mol) and the cationic species 6a (51 kJ/mol). This can be ascribed to the fact that separation of charge (in 4a and 6a) is energetically less favourable than delocalization of negative charge (in 5a).
An interesting extension of this topic would be the investigation into the influence of substituents attached to N_1 on the homoaromaticity. The more so as the aromaticity of diaza [8] annulenes (7), in which the 10 π electron system is formed by three double bonds and two nitrogen lone pairs, depends on the substituents attached to the nitrogen atoms. Donor-substituted derivatives have a planar structure 7a with strong 10-electron delocalization, whilst acceptor-substituted derivatives prefer the twist-boat-chair conformation 7b, and are therefore not diatropic[7].



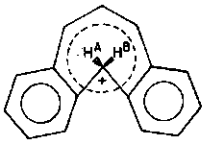
7a



7b

Scheme 8.4

Annellation on positions adjacent to the methylene bridge of homotropylium cation (8), causes a decrease of $\Delta\delta$, due to the rigidity of the benzene rings, which hinders the optimal tilting of the methylene bridge[8].



8

The ring inversion of the homotetrazole (scheme 8.3) is no longer possible if one of the hydrogens of the methylene group is replaced by an alkyl group. These compounds were found to exist in one sole conformation. As the hydrogen H^A resonates at high field (4b : δH^A = 2.22 ppm; 4c : δH^A = 2.26 ppm; 4e : δH^A = 1.94 ppm) we concluded that it is oriented above the tetrazole ring and the alkyl group is in the *exo* position (chapter 3).

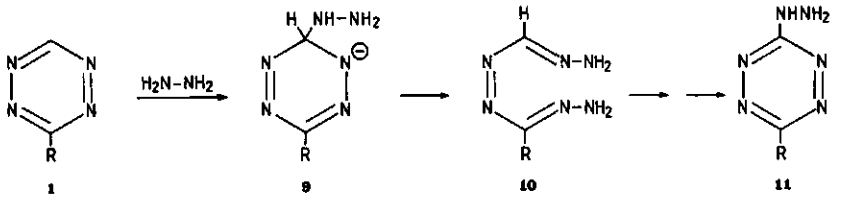
A large substituent at the homotropylium cation is in the *exo* position too[9,10]. The amino- and hydrazino group of the σ-adducts of 1,2,4,5-tetrazines, are also large substituents; so they will be found in the *exo* position. Consequently hydrogen H^A is above the tetrazole ring, in the shielding regio. This explains the "anomalous" large upfield shift (Δδ between 8-9 ppm), observed for H^A. Another interesting aspect, that became obvious from our NMR study, is that the charge of the tetrazole ring exerts an influence through space on H^A, above the tetrazole ring and that H^B, in the *exo* position, is hardly affected. H^A was shifted upfield by a negative charge and downfield by a positive charge (chapter 3). The ^{13}C - ^1H coupling constant J_{CH^A} was smaller when the ring was negatively charged and larger when the ring carried a positive charge (chapter 4).

8.2 ANIONIC CHARACTER OF HOMOAROMATIC σ-ADDUCTS

In chapter 3 it was found that the delocalization energy of the parent compound 3-phenyl-1,6-dihydro-1,2,4,5-tetrazine (4a) is considerably smaller (52 kJ/mol) than that of the conjugate base 5a (68 kJ/mol). The pK_a value of 6-R^2-3-phenyl-1,6-dihydro-1,2,4,5-tetrazines (4a, 4b and 4c) is approximately 10 (chapter 4); so they possess fairly acidic properties. The fact that deprotonation leads to a gain in resonance energy induced us to investigate whether σ-adducts 2 are present as neutral or as anionic species in liquid ammonia. This problem was solved by an extension of a ^{13}C NMR procedure described in the literature (chapter 4). In 1-X-4-Y-benzenes the substituent chemical shift of C_4 (SCS-4 = $[\delta C_4(Y \neq H) - \delta C_4(Y=H)]$ ppm[11]) is linearly related with the electron demand of the substituent X at C_1. The substituents X which have been investigated were either neutral or cationic groups [11,12]. We established that this relation can be extended to anionic substituents X, in that for X the (substituted)-1,2,4,5-tetrazinyl groups and for Y the substituents Br, OCH_3 and CH_3 were taken. A linear dependence was found for the (SCS-4) values and the electron demand of the (substituted)-1,2,4,5-tetrazinyl groups. From this relationship the σ-adduct 2 was found to be an anionic species. This indicates that the gain of resonance energy is actually so large that the proton is released to ammonia.
A homoaromatic σ-adduct anion is even formed in hydrazine-hydrate/methanol, which is a weaker basic system than ammonia (chapter 6).

8.3 HYDRAZINOLYSIS AND S_N(ANRORC)

As mentioned above hydrazine forms a σ-adduct 9 with 3-alkyl(aryl)-1,2,4,5-tetrazines at low temperature (230 K).



Scheme 8.5

When the temperature of the mixture of 3-alkyl(aryl)-1,2,4,5-tetrazine and hydrazine-hydrate/methanol in the NMR tube is raised (to values between 273 and 295 K), NMR evidence was obtained for the opening of the dihydrotetrazine ring (chapter 6). An open-chain compound 10 is formed, which is probably stabilized by four intramolecular hydrogen bonds, as indicated in figure 8.2.

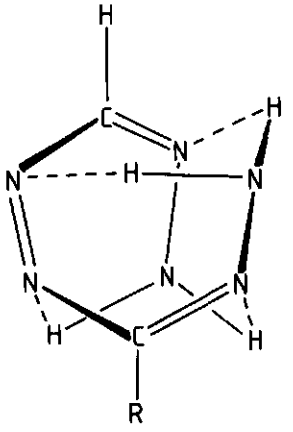


Figure 8.2 Intramolecular hydrogen bridges of 10

Subsequently, ring closure and oxidation to the 6-hydrazino product 11 takes place during the working up.
This reaction can be considered as an S_N(ANRORC) process. It is exceptional that the reaction in which ^{15}N-label is found in the exocyclic hydrazino group (upon attack at C_6) as well as the one that builds the ^{15}N-label into the 1,2,4,5-tetrazine ring (upon attack at C_3) proceed by a Ring Opening - Ring Closure process (see scheme 6.4). If the substituent on C_3 is a phenyl- or a t-butyl group this position is blocked and the reaction sequence starts with an attack at C_6. If the substituent at C_3 is a (m)ethyl group both C_3 and C_6 may be attacked. No evidence for an S_N(AE) mechanism has been obtained in these reactions.
The occurrence of the S_N(ANRORC) mechanism was also observed during hydrazinodeaminations and hydrazino-dehalogenations of 6-amino- and 6-halogeno-3-alkyl (aryl)-1,2,4,5-tetrazines[1,13]. The influence of the leaving group L, at position 6 (see scheme 6.6) on the fraction of hydrazino compounds formed by the S_N(ANRORC) mechanism was found, in decreasing order, to be : L = NH_2 > L = Br > L = Cl.
The influence of the substituent R', at position 3, is as follows: If R' is the phenyl- or t-butyl group attack at C_3 is blocked. In these cases the reaction takes place by the S_N(AE) mechanism. The influence of H, CH_3 and C_2H_5 is almost the same, when L = NH_2, approximately 20-25% of the hydrazino compounds is formed by the S_N(ANRORC) pathway. When L = Br steric hindrance due to the ethyl group is more pronounced compared to that of the methyl group (chapters 5 and 6).

8.4 CRYSTAL STRUCTURE AND HOMOAROMATICITY

The crystal structure of 6-ethyl-3-phenyl-1,6-dihydro-1,2,4,5-tetrazine (4c) was elucidated by X-ray structural analysis (chapter 7). This reveals that the compound is in a *boat* conformation. The sp^3 carbon atom (C_6) is pointing upwards with a dihedral angle of 49.3° between the N(1)- C(6)- N(5) and the N(1)- N(2)- N(4)- N(5) planes; C_3 is tilted 26.7° (see figure 8.3). The ethyl group at C_6 is in the *exo* position and H_6 is above the tetrazole ring; in agreement with the structure predicted by NMR spectroscopy (chapter 3). N_1 is sp^2hybridized. This sp^2 hybridization of N_1 is essential for proper orientation of the lone pair electrons, necessary for overlap and electron delocalization.
Both the N-N and C-N distances in the tetrazole ring were found to be intermediate between single and double bond length[14], in agreement with the delocalized character. Only the N(1)- N(5) distance was found to be rather long (2.29 Å). This is not necessarily in conflict with homoaromaticity however, because in some homo-

aromatic systems a similar distance was observed[15,16]. As the tetrazine part of 4c is boat-shaped, the tetrazole ring of the homotetrazole is not planar, but puckered.

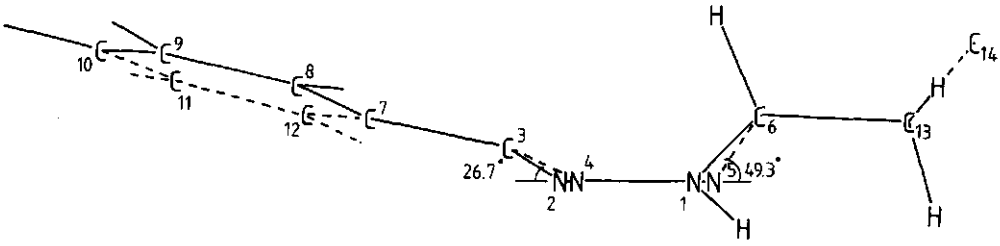
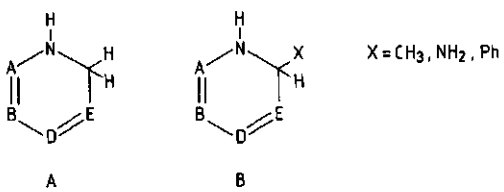


Figure 8.3 Projection onto the N(1)-N(2)-N(4)-N(5) plane

There are several examples in the literature however, from which it is clear that cyclic electron delocalization is also possible in a not perfectly planar system[15-17].
From this crystal structure we came to the conclusion that the observed conformation is in agreement with the ^{1}H NMR spectroscopic data, from which the presence of a ring current and consequently the homoaromatic model was proposed.

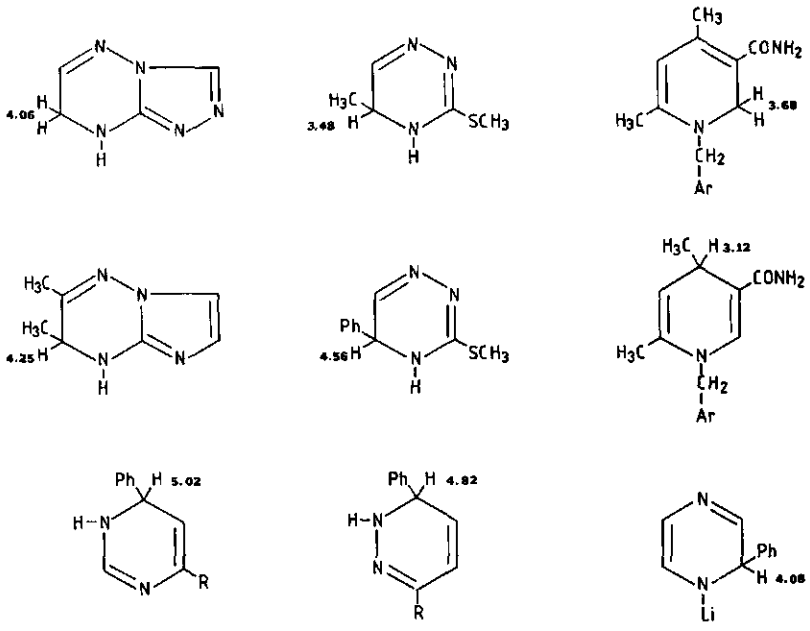
8.5 HOMOAROMATICITY AND OTHER DIHYDROHETEROAROMATIC COMPOUNDS

One may wonder whether homoaromaticity is found in general for dihydroheteroaromatic species of structure A.



Scheme 8.6

This question can be answered by comparing the ^1H chemical shifts of the hydrogens at the sp^3 carbon atom of A with that of B, in which one of the $-CH_2-$ hydrogen atoms is replaced by a large substituent X.
As we have seen from the literature[9,10] and from the results described in this thesis, the large substituent X in structure B will be found in the exo position of a possible homoaromatic conformation. The hydrogen at the sp^3 carbon atom will consequently be located above the ring current and will be found at high field. The shielding constant of the group X (CH_3: 0.47 ppm; NR_2: 1.57 ppm; Ph: 1.85 ppm)[18] must be taken into account. In a structure like A, there may be an equilibrium between two forms, like we found for 3-phenyl-1,6-dihydro-1,2,4,5-tetrazine (chapter 3), which may result in an average value of 3-5 ppm. A survey of several ^1H NMR data from the literature[19-22] is given in scheme 8.7. The ^1H NMR data of the σ-adducts formed between liquid ammonia or amide ion and several heteroaromatics (see scheme 1.6) may also be drawn into this comparison.

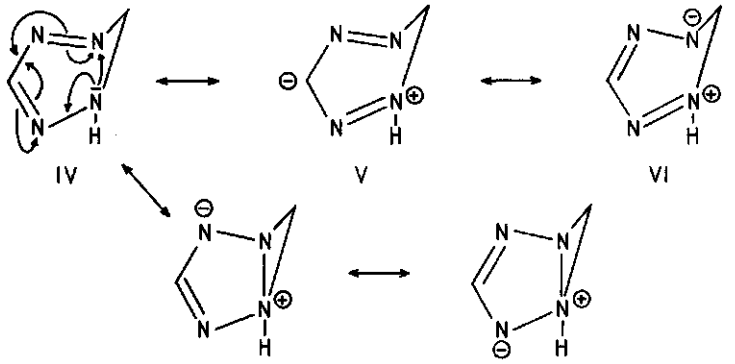


Scheme 8.7

None of the ^{1}H NMR values of structures B is found at extraordinary high field, and consequently there is no indication that other dihydroheteroaromatics display homoaromatic properties.

The calculations of Bodor and Pearlman[23] revealed that the stability of 1,4-dihydropyridine is due to a homoaromatic contribution. Some highly substituted 1,4-dihydropyridines were found to exist in a boat conformation[24,25]. Although these two facts indicate that there is a possible similarity between 1,4-dihydropyridines and 1,6-dihydro-1,2,4,5-tetrazines, a simple 1,4-dihydropyridine - N-benzyl-1,4-dihydronicotinamide[26] - is perfectly planar with localized double bonds and is not homoaromatic.

Finally, the question remains *why* homoaromaticity is observed with 1,6-dihydro-1,2,4,5-tetrazines and not with other dihydroheteroaromatic compounds. The following may be an explanation : It is obvious from the possible resonance structures of 1,6-dihydro-1,2,4,5-tetrazines, as shown in scheme 8.8, that the negative charge is located on the carbon atom once (V) and on one of the nitrogen atoms (VI, VII and VIII), which are more capable of accommodating the negative charge, three times.



Scheme 8.8

The resonance structures VI, VII and VIII will consequently be of more importance for the homoaromatic stabilization. In contrast, substitution of nitrogens by carbon atoms in the heteroaromatic ring results in a larger amount of resonance structures with negative charge on carbon and thereby in less stabilization. The gain in resonance energy, due to electron delocalization in a possible homoaromatic species, is then probably cancelled by the destabilization due to the

negative charge on carbon.
Secondly, the ring current in an aromatic species, containing hetero aroms, is not a perfect cycle as in aromatic species with equal atoms. The tetrazole ring of 1,6-dihydro-1,2,4,5-tetrazine contains four nitrogen atoms and one carbon atom, making a reasonable symmetry of the ring current possible. Replacement of some nitrogens by carbon atoms results in a decrease of symmetry and thereby probably in a decrease of the efficiency of the ring current.
Both effects possibly explain why 1,6-dihydro-1,2,4,5-tetrazines are and other dihydroheteroaromatic compounds are not (or hardly) homoaromatic.
In the future we hope to obtain more solid arguments by theoretical calculations on these systems.

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SUMMARY

This thesis describes some nucleophilic substitution reactions between the red 1,2,4,5-tetrazines and hydrazine-hydrate or ammonia. Special attention was paid to the occurrence of the S_N(ANRORC) mechanism in these substitution reactions. This mechanism comprises a sequence of reactions, involving the Addition of a Nucleophile to a heteroaromatic species, followed by a Ring-Opening and Ring Closure reaction to the substitution product.

σ-Adducts, namely 6-hydrazino- and 6-amino-3-aryl(alkyl)-1,6-dihydro-1,2,4,5-tetrazines, are formed upon addition of hydrazine or ammonia to 3-aryl(alkyl)-1,2,4,5-tetrazines. This is accompanied by a change in colour from red to yellow. These adducts can be observed by NMR spectroscopy. In heteroaromatics in liquid ammonia, an upfield shift ($\Delta\delta$) of 4-5 ppm is usually measured for the hydrogen atom, attached to the carbon atom to which addition takes place. An extraordinary large upfield shift is observed however upon addition to 1,2,4,5-tetrazines; $\Delta\delta = \sim 8.5$ ppm in hydrazine and $\Delta\delta = \sim 8.7$ ppm in liquid ammonia (at 230 K, chapters 4 and 6).

The fact that 3-aryl(alkyl)-1,2,4,5-tetrazines are converted into the 6-amino compounds by oxidation of the intermediate in liquid ammonia (chapter 2), indicates that an intermediary 1,6-dihydro-6-amino structure must exist.

^{1}H NMR measurements at various temperatures of 1,6-dihydro-1,2,4,5-tetrazines as model compounds for these σ-adducts gave an explanation for the large upfield shift ($\Delta\delta$). 1,6-Dihydro-1,2,4,5-tetrazines and their conjugate acids and bases were found to be homoaromatic and they are present in the monohomotetrazole conformation. The hydrogens at the sp^3 carbon atom have a different orientation towards the tetrazole ring. One (H^A) is oriented above the aromatic ring, in the shielding regio; H^B is in the exo position, in the deshielding regio; thus resulting in a large difference in chemical shift. The homoaromatic species show a ring inversion. The kinetic parameters ($\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$ and $\Delta G^{\ddagger}$) were determined by dynamic NMR measurements (chapter 3). Since a large substituent at C_6 of the homotetrazole (e.g. methyl or ethyl) is found exclusively in the exo position, the hydrogen of the above mentioned σ-adducts is oriented above the ring current of the tetrazole ring, resulting in a chemical shift at high field.

The charge of the tetrazole ring exerts an influence through space on H^A, H^B is hardly influenced. This became obvious from δH^A in ^1H NMR and J_{CH^A} in ^{13}C NMR (chapters 3 and 4).

The homoaromatic σ-adducts in liquid ammonia and even in hydrazine-hydrate/methanol are anionic species, as was primarily proven by a ^{13}C NMR study (chapters 4 and 6). The driving force for the deprotonation is probably the larger resonance stabilization of the homoaromatic anion with respect to the neutral homoaromatic species.

3-Alkyl(aryl)-1,2,4,5-tetrazines were found to undergo a Chichibabin hydrazination into 6-hydrazino-3-alkyl(aryl)-1,2,4,5-tetrazines on treatment with hydrazine-hydrate. The first step in this reaction sequence was the formation of a homoaromatic σ-adduct. Subsequently an open-chain intermediate was observed by NMR, on raising the temperature. Finally the hydrazino compound is formed by ring closure. This reaction sequence can be considered as an S_N(ANRORC) process. With ^{15}N-labelled hydrazine, only part of the label was found to be built in the 1,2,4,5-tetrazine ring of the 6-hydrazino compounds. This is the first example of a reaction in which both the hydrazino compound with the ^{15}N-label in the ring and with the ^{15}N-label in the exocyclic hydrazino group are formed according to the S_N(ANRORC) mechanism (chapter 6).

During the hydrazino-deamination and hydrazino-dehalogenation of 6-amino- and 6-halogeno-1,2,4,5-tetrazines only a part of the molecules was found to react according to the S_N(ANRORC) process. The other part followed the alternative S_N(AE), Addition-Elimination, pathway (chapters 5 and 6).

The crystal structure of 6-ethyl-3-phenyl-1,6-dihydro-1,2,4,5-tetrazine was elucidated by X-ray structural analysis very recently. This analysis revealed that the molecule is in a *boat*-conformation. C_6 points upwards with a dihedral angle of 49.3° and C_3 with an angle of 26.7°. N_1 was found to be sp^2 hybridized and the N(1)-N(2), N(2)-N(3), C(3)-N(4) and N(4)-N(5) bond distances were found to be between single- en double bond length, in agreement with the expected electron delocalization. Therefore we came to the conclusion that the crystal structure agrees with the homoaromatic character of the compound (chapter 7).

SAMENVATTING

In dit proefschrift worden enige nucleofiele substitutie-reacties beschreven van de rode 1,2,4,5-tetrazines met hydrazine-hydraat en ammoniak. Daarbij werd vooral aandacht geschonken aan de vraag of tijdens deze reacties het S_N(ANRORS) mechanisme optreedt. Dit mechanisme beschrijft een serie opeenvolgende reacties die bestaat uit de Additie van een Nucleofiel aan de heteroaromaat, gevolgd door Ring Opening en Ring Sluiting tot het substitutieprodukt.

Bij de additie van hydrazine of ammoniak aan 3-aryl(alkyl)-1,2,4,5-tetrazines, die gepaard gaat met een kleurverandering van rood naar geel, worden de σ-adducten 6-hydrazino- en 6-amino-3-aryl(alkyl)-1,6-dihydro-1,2,4,5-tetrazines gevormd. Deze kan men waarnemen met NMR spectroscopie. Bij de meeste heteroaromaten vindt men in vloeibare ammoniak voor het waterstofatoom, gebonden aan het koolstofatoom waaraan de additie plaats vindt, een verschuiving naar hoger veld ($\Delta\delta$) van 4-5 ppm. Bij de additie aan 1,2,4,5-tetrazines treedt echter een veel grotere verschuiving naar hoger veld op; $\Delta\delta = \sim 8.5$ ppm in hydrazine en $\Delta\delta = \sim 8.7$ ppm in vloeibare ammoniak (bij 230 K, hoofdstuk 4 en 6).

Uit het feit dat 3-aryl(alkyl)-1,2,4,5-tetrazines in vloeibare ammoniak door toevoegen van een oxydator omgezet kunnen worden in 6-aminoverbindingen (hoofdstuk 2), blijkt dat er een 1,6-dihydro-6-aminoverbinding als intermediair aanwezig moet zijn.

Door bij verschillende temperatuur de ^{1}H NMR spectra te meten van 1,6-dihydro-1,2,4,5-tetrazines als modelverbindingen voor de σ-adducten, konden we een verklaring vinden voor de grote $\Delta\delta$ waarde. 1,6-Dihydro-1,2,4,5-tetrazines en hun geconjugeerde base en - zuur blijken een nieuw soort homoaromaten te zijn. Ze komen voor in de monohomotetrazool conformatie. De waterstofatomen aan het sp^3 koolstofatoom zijn verschillend georiënteerd ten opzichte van de tetrazool ring. H^A ligt boven de aromaat, in het shieldinggebied en H^B neemt de exopositie, in het deshieldinggebied, in. Dit veroorzaakt een groot verschil in chemische verschuiving tussen H^A en H^B. De homoaromatische deeltjes vertonen een ringinversie. Met dynamische NMR metingen konden de kinetische parameters ($\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$ en $\Delta G^{\ddagger}$) bepaald worden (hoofdstuk 3).

Aangezien een grote substituent aan C_6 van de homotetrazool (bijvoorbeeld methyl of ethyl) de exopositie blijkt in te nemen, ligt bij de bovengenoemde

σ-adducten het waterstofatoom boven de kringstroom van de tetrazool ring en resoneert bij hoog veld.
Uit de δH^A waarden van ^1H NMR en de koppelingsconstanten $J_{CH}{}^A$ bij ^{13}C NMR blijkt dat H^A - door de ruimte - beinvloed wordt door de lading van de tetrazool ring. H^B ondervindt daar in de exopositie nauwelijks invloed van (hoofdstuk 3 en 4).
Zoals vooral uit een studie met ^{13}C NMR blijkt, zijn de homoaromatische σ-adducten in vloeibare ammoniak en zelfs in hydrazine-hydraat/methanol als anionen aanwezig (hoofdstuk 4 en 6). Zij worden waarschijnlijk gedeprotoneerd doordat de resonantie stabilisatie in een homoaromatisch anion groter is dan in een neutrale homoaromaat.
3-Alkyl(aryl)-1,2,4,5-tetrazines kunnen met hydrazine-hydraat omgezet worden in 6-hydrazino-3-alkyl(aryl)-1,2,4,5-tetrazines. Met NMR werd vastgesteld dat het eerste stadium van deze Chichibabin reactie de vorming van een homoaromatisch σ-adduct is, dat bij hogere temperatuur in een open-keten intermediair overgaat. Ringsluiting levert de hydrazinoverbinding. Deze opeenvolgende reacties kunnen beschouwd worden als een S_N(ANRORS) proces. Wanneer deze reacties met ^{15}N-gelabeld hydrazine worden uitgevoerd, blijkt het label slechts voor een deel te worden ingebouwd in de 1,2,4,5-tetrazine ring van de 6-hydrazino-verbindingen. Met dit resultaat hebben we het eerste voorbeeld gevonden van een reactie waarbij zowel de hydrazinoverbinding met het ^{15}N-label in de ring, als de verbinding met het ^{15}N-label in de exocyclische hydrazinogroep volgens het S_N(ANRORS) mechanisme wordt gevormd (hoofdstuk 6).
De hydrazino-deaminering en hydrazino-dehalogenering van 6-amino- en 6-halogeno-1,2,4,5-tetrazines verlopen slechts voor een deel volgens het S_N(ANRORS) mechanisme. Naast het S_N(ANRORS) proces treedt het concurrerende S_N(AE), Additie-Eliminatie, mechanisme op (hoofdstuk 5 en 6).
Zeer recent werd de kristalstructuur van 6-ethyl-3-fenyl-1,2,4,5-tetrazine opgehelderd. Er werd voor dit molecuul een bootvormige structuur gevonden, met zowel C_6 als C_3 omhoog. C_6 staat 49.3° omhoog, C_3 26.7°. N_1 blijkt sp^2-gehybridiseerd te zijn en de bandlengtes van de N(1) - N(2), N(2) - C(3), C(3) - N(4) en N(4) - N(5) bindingen liggen tussen die van enkele en dubbele bindingen in. Dit is in overeenstemming met de verwachte delokalisatie van elektronen. Daardoor konden we concluderen dat de kristalstructuur overeenstemt met het homoaromatisch karakter van de verbinding (hoofdstuk 7).

CURRICULUM VITAE

Op 7 mei 1953 ben ik geboren te Arnhem. Aan het plaatselijk Christelijk Lyceum heb ik vanaf 1964 de eerste drie jaar van de gymnasiumopleiding gevolgd; aan de Nijmeegse Scholengemeenschap werd deze in 1970 beëindigd met het behalen van het diploma gymnasium-β.
Aansluitend begon ik aan de Katholieke Universiteit in Nijmegen aan de Scheikundestudie. Het kandidaatsexamen, S_2, behaalde ik in juni 1973.
De bijvakken waren : Organische Chemie, onder leiding van Prof.Dr.R.J.F.Nivard (Synthese van Gliotoxine-analoga) en Farmacologie onder leiding van Prof.Dr. J.M.van Rossum. Als hoofdvak heb ik Biochemie gedaan verdeeld over Klinische Chemie onder leiding van Prof.Dr.A.P.Jansen en onderzoek aan messenger-RNA onder leiding van Prof.Dr.H.Bloemendal.
In 1974 behaalde ik de deskundigheid stralingshygiëne op C-niveau en in 1975 de onderwijsbevoegdheid. Het doctoraalexamen werd op 31 mei 1976 afgelegd.
Sinds maart 1976 ben ik werkzaam op de afdeling Organische Chemie van de Landbouwhogeschool in Wageningen. Daar geef ik practicumonderwijs aan studenten in verschillende studiefasen. Tevens begon ik, onder leiding van Prof.Dr. H.C.van der Plas aan het promotie-onderzoek, dat nu in 1981, leidt tot mijn promotie.