Reactions of pyridazines and pyridazine 1-oxides
with nitrogen-containing nucleophiles

Dit proefschrift met stellingen van Dimby Eelco Klinge, doctorandus in de chemie, geboren te Groot-Ammers op 4 juli 1942, is goedgekeurd door de promotor, dr.H.C.van der Plas, hoogleraar in de organische chemie.

De rector magnificus van de Landbouwhogeschool,
J.P.H.van der Want

Wageningen, 29 maart 1976

D.E.Klinge

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Proefschrift
ter verkrijging van de graad van
doctor in de landbouwwetenschappen,
op gezag van de rector magnificus,
dr.ir.J.P.H.van der Want, hoogleraar in de virologie,
in het openbaar te verdedigen
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# Stellingen

1. De door Turner en Cheeseman gegeven grafiek waarin de $^{13}C$-substituent effecten van 2-gesubstitueerde pyrazinen zijn uitgezet tegen die van mono-gesubstitueerde benzenen, correleert niet met de door hen gemeten waarden.

   C.J.Turner en G.W.H.Cheeseman,
   Org.Magn.Reson. 6, 663 (1974).

2. Het is onvoldoende bewezen dat nematicide werking kan worden toegekend aan de uit de Helenium hybride "Moerheim Beauty" geïsoleerde verbinding 2,3-dihydro--2-hydroxy-3-methyleen-6-methylbenzofuraan.

   F.J.Gommers, Proefschrift, Groningen 1973.

3. De amino-dehalogenering van 2-chloor-3,6-difenylpyrazine kan volgens een ander mechanisme verlopen dan voorgesteld wordt door Lont et al.

   P.J.Lont, H.C.van der Plas en A.van Veldhuizen,
   Recl.Trav.Chim. Pays-Bas 92, 708 (1973).

4. Op grond van de vermelde $^{1}H$-NMR gegevens is niet te bewijzen dat 6-aryl-4,5-dibenzyl-3-oxo-2,3,4,5-tetrahydropyridazinen gevormd worden in de reactie van 6-aryl-2,3-dihydro-3-oxopyridazinen met benzylmagnesiumchloride.

   F.G.Baddar, N.Latif en A.A.Nada,
   J.Indian Chem. Soc. 1974, 618.

5. De conclusies die door Levine en Biehl zijn getrokken uit hun experimenten ter bestudering van het effect van de alkalianionen in de reactie van o-chloortolueen met alkaliamiden, zijn onvoldoende gefundeerd.

   R.Levine en E.R.Biehl,
   J.Org.Chem. 40, 1835 (1975).

6. Bij de verklaring van het verschil in reductiesnelheid van 2-jood-nitrobenzeen en 2-joodpyridine door 2-methylpiperidine, wordt ten onrechte het verschil in snelheid van de amino-dejodering buiten beschouwing gelaten.

   E.Farina, L.Nucci, G.Biggi, F.Del Cima en F.Pietra,
   Tetrahedron Lett. 1974, 3305.

7. Het mechanisme van de autoxidatie van 5-methyl-6,7-difenyl-5,6,7,8-tetrahydropterine voorgesteld door Jongejan et al., is ongeschikt als model voor de biologische werking van de co-factor 5-methyl-tetrahydro-foliumzuur.

   J.A.Jongejan, H.I.X.Mager en W.Berends,
   Tetrahedron 31, 533 (1975).

8. De groeiende relatie van het hoger beroepsonderwijs tot het wetenschappelijk onderwijs moet niet als argument gebruikt worden om "lichamelijke oefening" als verplicht algemeen vak voor het hoger beroepsonderwijs af te schaffen, maar om "lichamelijke oefening" als verplicht algemeen vak voor het wetenschappelijk onderwijs in te voeren.

   Wetsontwerp tot wijziging van artikel 16, derde lid
   Wet op het voortgezet onderwijs (Stb. 1967, 387).

D.E. Klinge
Reactions of pyridazines and pyridazine 1-oxides with nitrogen-containing nucleophiles

Ter nagedachtenis aan mijn vader

Aan mijn moeder

Ireen

Michiel en Daan

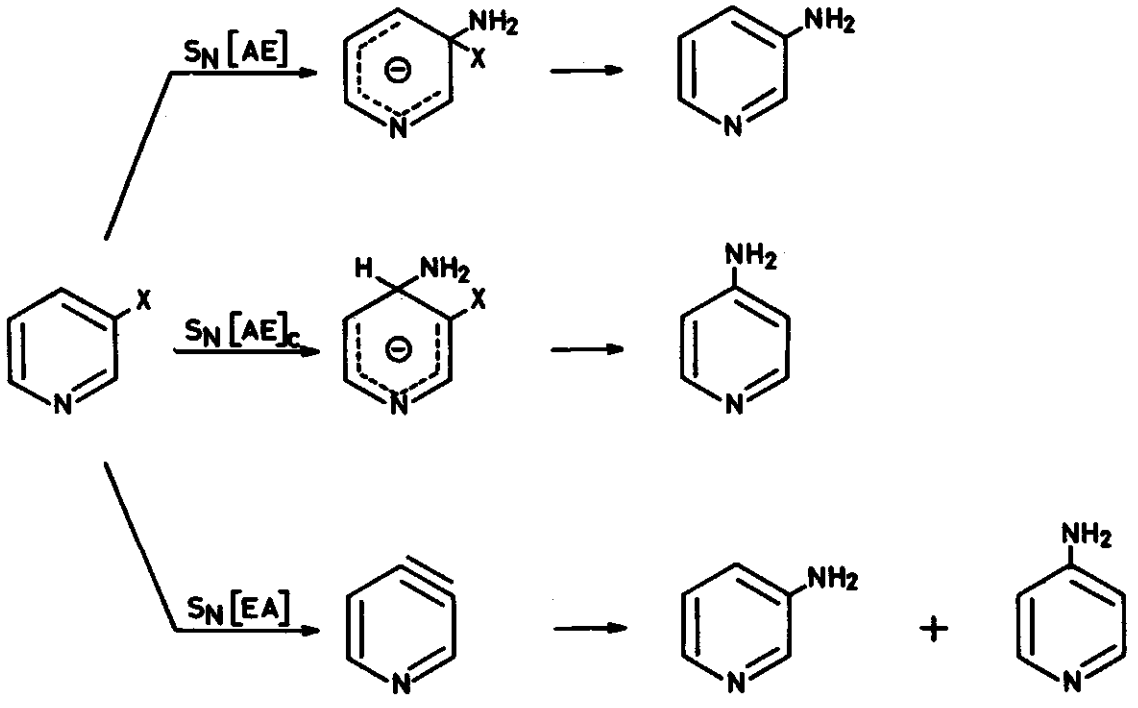
# Contents

# Introduction

There is a prevailing interest[1] in the Laboratory of Organic Chemistry, Agricultural University Wageningen, in the study of the behaviour of halogenoazaaromatics in reactions with nucleophiles (potassium amide[2-14], ammonia[15-18], lithium piperidide[19-22], potassium t-butanolate[23]). In the monocyclic systems especially the reactions of derivatives of pyridine[2-5], pyrimidine[6-9] and pyrazine[10] with potassium amide in liquid ammonia were studied extensively.

From these studies the mechanistic picture is emerging that in general halogenopyridines are more inclined to substitution reactions *without* ring opening than halogenopyrimidines and halogenopyrazines, which preferentially undergo substitutions involving an open-chain compound as intermediate.

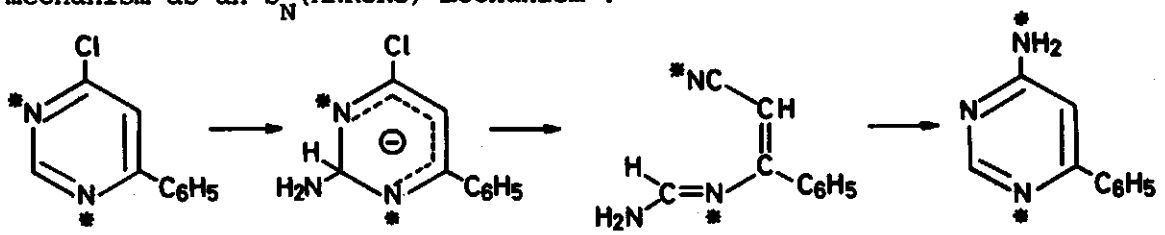
In principle the nucleophilic substitution reactions which are found to occur when halogenopyridines are treated with potassium amide in liquid ammonia and which do not involve an open-chain intermediate can be divided into three main categories (see Scheme 1): a. $S_N[AE]$ (the formation of a σ-intermediate by Addition of the amide ion on the ring carbon atom bearing the halogen atom, followed by Elimination of the halogen ion); b. $S_N[AE]$ - cinesubstitution (the attack of the amide ion takes place on a ring carbon atom to which the halogen atom is not attached, followed by protonation and the loss of hydrogen halide) and c. $S_N[EA]$ (a base-catalysed Elimination of hydrogen halide forming the intermediary didehydropyridine followed by Addition of ammonia). From the last-mentioned reaction a mixture of 3- and 4-aminopyridine results.




SCHEME 1

There is an interesting difference in the chemical behaviour of the halogenopyridines and the halogeno derivatives of the diazines, pyrimidine and pyrazine. As already indicated, the latter preferentially show substitution with ring opening on reaction with potassium amide in liquid ammonia. This is due to the fact that in general diazines easily form σ-adducts[24] with the amide ion at a ring carbon atom which is not substituted by a halogen atom (see for example structure (2) in Scheme 2). $^{1}$H-NMR[8d,9ab,10g,17,18a] and $^{13}$C-NMR[9c] spectroscopy present good evidence for the formation of these adducts. It is of interest to note that the open-chain intermediate which is formed after ring opening can undergo a ring closure leading to the *same* ring system as in the starting substance[1e,7,8,17].

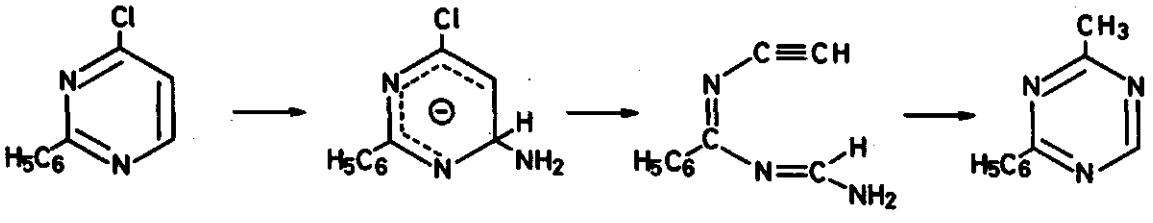
Experimental evidence for these so-called degenerate ring transformations was obtained by an extensive study of the $^{15}$N-scrambling in the reaction products obtained when [$^{15}$N] -halogenopyrimidines[7bcde,8,16b,17,22] and [$^{15}$N] -halogenopyrazines[10cde] are treated with potassium amide in liquid ammonia. See for example the conversion of 4-chloro-6-phenylpyrimidine (1) into 4-amino-6-phenylpyrimidine (4)(Scheme 2) involving an Addition of the Nucleophile (at C(2)), Ring Opening (into (3)) and Ring Closure. One refers to this substitution mechanism as an $S_N$(ANRORC)-mechanism[7].




1 2 3 4

*SCHEME 2*

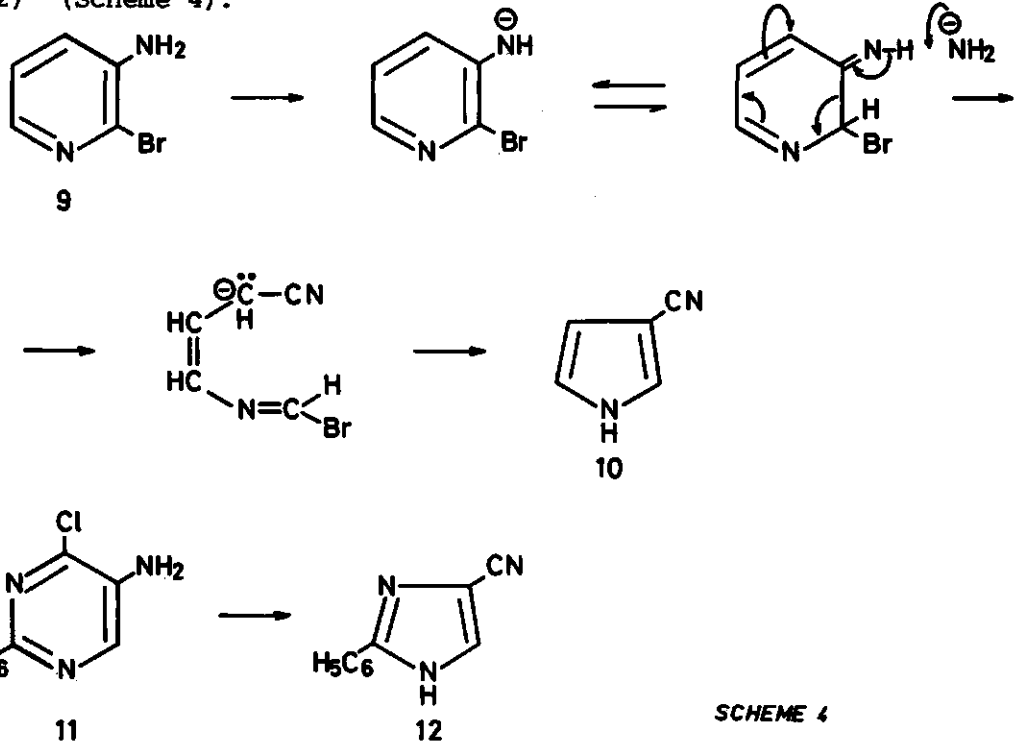
A very important feature of these reactions is that after addition and ring opening by fission of a carbon-carbon bond, an open-chain intermediate is formed which, if appropriate substituents are present, can undergo a ring closure leading to a *different* ring system than that of the starting substance[1e,10,16b,17,18b]. For example 4-chloro-2-phenylpyrimidine (5) reacts with an amide ion to give, via the σ-adduct (6), the open-chain intermediate (7). Ring closure through an internal nucleophilic attack of the amidine-nitrogen on the unsubstituted carbon atom of the triple bond results in the s-triazine derivative (8)(Scheme 3)[25-28].




5 6 7 8

*SCHEME 3*

Carbon-carbon bond fission in the azaheteroarene has also been observed when, besides a halogen atom, the heterocycle contains a substituent which can easily be deprotonated by the amide ion, for example an amino- or hydroxyl group. In that case the heterocyclic ring becomes negatively charged through mesomerism and therefore makes the ring less susceptible to nucleophilic addition. Interesting examples of reactions in which this carbon-carbon bond fission occurs are the ring contraction of 3-amino-2-bromopyridine (9) into 3-cyanopyrrole (10)[29] and of 5-amino-4-chloro-2-phenylpyrimidine (11) into 4(5)-cyano-2-phenylimidazole (12)[30] (Scheme 4).



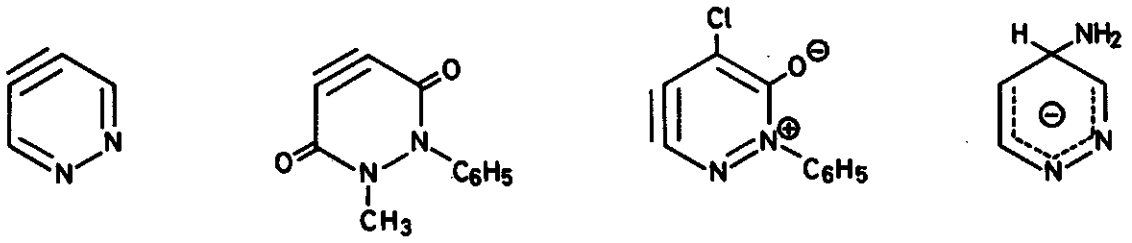

*SCHEME 4*

The experiences obtained in the pyrimidine and pyrazine field induced us to study the chemical behaviour of the third representative of the diazines i.e. the pyridazine[31]. Our interest was especially concentrated on the problem whether halogenopyridazine derivatives in reactions with potassium amide in liquid ammonia are more inclined to substitution reactions by $S_N[AE]$ or $S_N[EA]$ processes or to addition reactions being followed by ring opening. Calculations using the Extended Hückel Theory indicate[32] that 4,5-didehydropyridazine (13) is a far more stable intermediate than the well-established 3,4-didehydropyridine, so that it seemed very challenging to establish the occurrence of this didehydropyridazine.

There are several reactions reported in the literature in which didehydropyridazines are advanced but where their existence is not really proven. Kauffmann et al.[33] proposed the "4,5-didehydropyridazine (14)" as intermediate in the reaction of 1-methyl-2-phenyl-4-X (X=Cl, Br)- and -5-X (X=Br)-pyridazine-3,6-dione with piperidine. An isomeric mixture of 4- and 5-piperidinopyridazines was obtained, but since their ratio is not independent of the nature of the

halogen atom, a possible simultaneous occurrence of an $S_N[AE]$-substitution and an $S_N[AE]$-cinesubstitution can certainly not be excluded.

Maki et al.[34] suggested the bipolar"3,4-didehydropyridazine (15)"as one of the intermediates in the base-catalysed ring contraction reaction of 4,5-dichloro-2-phenyl-3(2H)-pyridazinone into 3-hydroxy-1-phenylpyrazole-5-carboxylic acid. In this case also the evidence for the intermediary existence of (15) is very poor and its occurrence seems highly speculative, since it is well-established [32] that the interaction of the nitrogen lone pair with the electrons in the carbon orbitals of the adjacent aryne bond leads to strong destabilisation.




13 14 15 16

*FIGURE 1*

In order to obtain more conclusive evidence for a 4,5-didehydropyridazine as an intermediate, the reaction of 3,6-disubstituted 4-halogenopyridazines with potassium amide in liquid ammonia was investigated in detail. The results are published in papers I[35] and II[36].

Extension of this work led us to a study on addition reactions of halogenopyridazines. It was already proven by $^1$H-NMR spectroscopy that the parent compound pyridazine gives an anionic σ-adduct with the *strongly* nucleophilic amide ion[37]; this addition takes place at C(4) i.e. (16). It seemed therefore of interest to study the structural requirements for adduct formation of pyridazine derivatives with the *weak* nucleophile ammonia. For that purpose a number of pyridazine derivatives were synthesized and their $^1$H- and $^{13}$C-NMR spectra were measured in liquid ammonia and methanolic ammonia. The results of these spectroscopic measurements are given in papers III[38] and IV[39].

Finally the possibility was studied of ring contraction reactions[40] of amino-halogeno-substituted pyridazines based on what is already known of the ring contractions of 3-amino-2-bromopyridine[29] and 5-amino-4-chloro-2-phenylpyrimidine[30]. The results of our investigation on ring contractions of 4-amino-3-bromo(chloro)- and 4-amino-3,6-dibromo(chloro)pyridazines are reported in paper V[41].

REFERENCES


1. See for a survey:
   a) H.J.den Hertog and H.C.van der Plas "Advances in Heterocyclic Chemistry", Ed. A.R.Katritzky, Vol.4, Academic Press, New York (1965).
   b) H.J.den Hertog and H.C.van der Plas "Chemistry of Acetylenes", Ed. H.G. Viehe, Marcel Dekker, New York (1969).
   c) A.J.Boulton, G.B.Barlin "Aromatic and Heteroaromatic Chemistry", Vol. I (1973), II (1974), III (1975), The Chemical Society, London.
   d) Th.Kauffmann, Angew.Chem.Int.Ed. 10, 20 (1971).
   e) H.C.van der Plas "Ring Transformations of Heterocycles", Vol.I and II, Academic Press, New York (1973).
   f) H.C.van der Plas "Lectures in Heterocyclic Chemistry", Ed. R.N.Castle and F.Elslager, Vol. II (1974).
   g) H.C.van der Plas and J.W.Streef "Aromatic and Heteroaromatic Chemistry", Vol.IV (1976), The Chemical Society, London.
2. L.van der Does and H.J.den Hertog, Recl.Trav.Chim.Pays-Bas 91, 1403 (1972).
3. H.J.den Hertog et al., Recl.Trav.Chim.Pays-Bas 93, 195 (1974).
4. R.Peereboom and H.J.den Hertog, Recl.Trav.Chim.Pays-Bas 93, 281 (1974).
5. P.Vrijhof, Thesis, Wageningen 1974.
6. H.W.van Meeteren and H.C.van der Plas, Recl.Trav.Chim.Pays-Bas 90, 105 (1971).
7. a) J.de Valk and H.C.van der Plas, Recl.Trav.Chim.Pays-Bas 90, 1239 (1971); b) 91, 1414 (1972); c) 92, 145 (1973); d) J.de Valk, H.C.van der Plas and J.W.A.de Bode, ibid. 92, 442 (1973); e) J.de Valk and H.C.van der Plas, ibid. 92, 471 (1973).
8. a) A.P.Kroon and H.C.van der Plas, Recl.Trav.Chim.Pays-Bas 92, 1020 (1973); b) 93, 111 (1974); c) 93, 227 (1974); d) A.P.Kroon, H.C.van der Plas and G.van Garderen, ibid. 93, 325 (1974).
9. a) J.P.Geerts, H.C.van der Plas and A.van Veldhuizen, Recl.Trav.Chim. Pays-Bas 92, 1232 (1973); b) J.P.Geerts, C.A.H.Rasmussen, H.C.van der Plas and A.van Veldhuizen, ibid. 93, 231 (1974); c) J.P.Geerts, H.C.van der Plas and A.van Veldhuizen, Org.Magn.Reson. 7, 86 (1975).
10. a) P.J.Lont, H.C.van der Plas and A.Koudijs, Recl.Trav.Chim.Pays-Bas 90, 207 (1971); b) P.J.Lont and H.C.van der Plas, ibid. 91, 850 (1972); c) P.J.Lont, H.C.van der Plas and A.J.Verbeek, ibid. 91, 949 (1972); d) P.J.Lont, H.C. van der Plas and E.Bosma, ibid. 91, 1352 (1972); e) P.J.Lont and H.C.van der Plas, ibid. 92, 311 (1973); f) 92, 449 (1973); g) P.J.Lont, H.C.van der Plas and A.van Veldhuizen, ibid. 92, 708 (1973).
11. a) H.J.den Hertog and D.J.Buurman, Recl.Trav.Chim.Pays-Bas 91, 841 (1972); b) 92, 304 (1973).

12. a) G.M.Sanders, M.van Dijk and H.J.den Hertog, Recl.Trav.Chim.Pays-Bas 93, 198 (1974); b) 93, 273 (1974); c) 93, 298 (1974); d) G.M.Sanders, M.van Dijk and H.J.den Hertog, Tetrahedron Lett. 1972, 4717.
13. A.Rykowski and H.C.van der Plas, Recl.Trav.Chim.Pays-Bas 94, 204 (1975).
14. a) J.Pomorski and H.J.den Hertog, Rocz.Ch. 47, 549 (1973); b) 47, 2123 (1973).
15. H.C.van der Plas et al., Recl.Trav.Chim.Pays-Bas 90, 1246 (1971).
16. a) R.Peereboom, H.C.van der Plas and A.Koudijs, Recl.Trav.Chim.Pays-Bas 93, 58 (1974); b) R.Peereboom and H.C.van der Plas, ibid. 93, 277 (1974); c) 93, 284 (1974).
17. E.A.Oostveen,H.C.van der Plas and H.Jongejan, Recl.Trav.Chim.Pays-Bas 93, 114 (1974).
18. a) A.Nagel, H.C.van der Plas and A.van Veldhuizen, Recl.Trav.Chim.Pays-Bas 94, 45 (1975); b) A.Nagel and H.C.van der Plas, Chem.Pharm.Bull. of Japan 23, 2678 (1975).
19. H.C.van der Plas and A.Koudijs, Recl.Trav.Chim.Pays-Bas 89, 129 (1970).
20. a) H.N.M.van der Lans and H.J.den Hertog, Recl.Trav.Chim.Pays-Bas 87, 549 (1968); b) H.N.M.van der Lans, H.J.den Hertog and A.van Veldhuizen, Tetrahedron Lett. 1971, 1875; c) H.N.M.van der Lans and H.J.den Hertog, ibid. 1973, 1887; d) H.N.M.van der Lans, Thesis, Wageningen 1973.
21. D.A.de Bie, H.C.van der Plas and G.Geurtsen, Recl.Trav.Chim.Pays-Bas 90, 594 (1971).
22. J.de Valk, H.C.van der Plas, F.Jansen and A.Koudijs, Recl.Trav.Chim. Pays-Bas 92, 460 (1973).
23. a) W.J.van Zoest and H.J.den Hertog, Recl.Trav.Chim.Pays-Bas 93, 166 (1974); b) W.J.van Zoest, Thesis, Wageningen 1975.
24. M.J.Strauss, Chem.Rev. 70, 662 (1970).
25. H.C.van der Plas et al., Recl.Trav.Chim.Pays-Bas 85, 1101 (1966).
26. H.W.van Meeteren and H.C.van der Plas, Recl.Trav.Chim.Pays-Bas 86, 15 (1967).
27. H.C.van der Plas and B.Zuurdeeg, Recl.Trav.Chim.Pays-Bas 88, 426 (1969).
28. H.C.van der Plas et al., Recl.Trav.Chim.Pays-Bas 88, 1156 (1969).
29. H.J.den Hertog et al.,Tetrahedron Lett. 1966, 4325.
30. H.W.van Meeteren and H.C.van der Plas, Tetrahedron Lett. 1966, 4517.
31. See for a survey on pyridazine chemistry: a) M.Tisler and B.Stanovnik, "Advances in Heterocyclic Chemistry", Ed. A.R.Katritzky, A.J.Boulton, Vol.9, Academic Press, New York and London (1968);
b) Th.L.Jacobs "Heterocyclic Compounds", Ed. R.C.Elderfield, Vol.6, Wiley-Interscience, New York (1957);
c) R.N.Castle "Pyridazines", The Chemistry of Heterocyclic Compounds, Vol. 28, Wiley-Interscience, New York (1973).

32. W.Adam, A.Grimison and R.Hoffmann, J.Amer.Chem.Soc. 91, 2590 (1969).
33. a) Th.Kauffmann and A.Risberg, Tetrahedron Lett. 1963, 1459 ;
b) Th.Kauffmann et al., ibid. 1964, 3563.
34. a) Y.Maki and M.Takaya, Chem.Pharm.Bull. of Japan 20, 747 (1972);
b) Y.Maki and G.P.Beardsley, Tetrahedron Lett. 1971, 1507.
35. D.E.Klinge, H.C.van der Plas and A.Koudijs, Recl.Trav.Chim.Pays-Bas 93, 201, (1974).
36. D.E.Klinge and H.C.van der Plas, Recl.Trav.Chim.Pays-Bas 95, 34 (1976).
37. J.A.Zoltewicz, L.S.Helmick, J.Amer.Chem.Soc. 94, 682 (1972).
38. D.E.Klinge and H.C.van der Plas, Recl.Trav.Chim.Pays-Bas 94, 233 (1975).
39. D.E.Klinge, H.C.van der Plas and A.van Veldhuizen, Recl.Trav.Chim.Pays-Bas 95, 21 (1976).
40. H.Igeta and T.Tsuchiya, J.Synth.Org.Chem.Japan 31, 867 (1973).
41. D.E.Klinge, H.C.van der Plas, G.Geurtsen and A.Koudijs, Recl.Trav.Chim. Pays-Bas 93, 236 (1974).

# Didehydrohetarenes (XXXIII)[1] Evidence for a 4,5-didehydropyridazine in the amination of 4-halogenopyridazines with potassium amide in liquid ammonia

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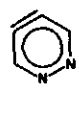
*(Received November 25th, 1973)*

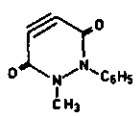
**Abstract.** 4-X-3-(methoxymethyl)-6-methylpyridazine (X = Cl, Br, I) on treatment with potassium amide in liquid ammonia at −33°C gives a mixture of 4- and 5-amino-3-(methoxymethyl)-6-methylpyridazine (ratio 1 : 5), which ratio is *independent* of the nature of the halogen atom. A 4,5-didehydropyridazine is proposed as intermediate.

## 1. Introduction

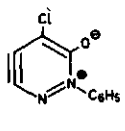
There is conclusive evidence for the occurrence of 3,4-didehydropyridine (3,4-pyridyne) and its derivatives in strong basic media[2] but not for its aza analogue the 4,5-didehydropyridazine (**1**) (4,5-pyridazyne). The few didehydropyridazine derivatives advanced are the following:
1-Methyl-2-phenyl-4,5-didehydropyridazine-3,6-dione (**2**) is postulated as intermediate in the reaction of 1-methyl-2-phenyl-4-X(X=Cl, Br)- and 5-X(X=Br)-pyridazine-3,6-dione with piperidine in order to explain the formation of an isomeric mixture of 4- and 5-piperidinopyridazines[3]; the didehydro compound **3** is suggested as intermediate in the base-catalysed ring contraction of 4,5-dichloro-2-phenyl-3(2*H*)-pyridazinone into 3-hydroxy-1-phenylpyrazole-5-carboxylic acid[4].
Recent calculations, using the extended Hückel theory, indicate[5] that 4,5-didehydropyridazine (**1**) is far more stable than 3,4-didehydropyridine. It is also more stable than the isomeric 3,4-didehydropyridazine, since the last-mentioned compound is strongly destabilized due to interaction of the nitrogen lone pair with the electrons in the carbon orbitals of the adjacent aryne bond.
Since the symmetry in the 4,5-isomer **1** does not allow the observation of orientation effects, we synthesized an unsymmetrically substituted 4-halogenopyridazine *i.e.* 3-(methoxymethyl)-6-methyl-4-X-pyridazine (X=Cl, Br, I) and studied its behaviour with potassium amide in liquid ammonia.



**1**



**2**

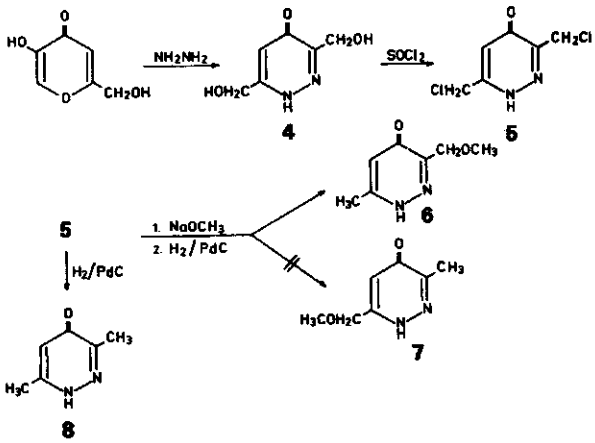


**3**

Excluding extremely different orientation effects of the methyl and the methoxymethyl groups generally, a mixture of two amino compounds should be formed if a 4,5-didehydropyridazine derivative is an intermediate. The ratio in which both amino compounds are present in the reaction mixture must then be independent of the nature of the 4-halogen atom.

## II. Synthesis of the 4-halogeno-3-(methoxymethyl)-6-methylpyridazines

3,6-Bis(hydroxymethyl)-4-oxo-1,4-dihydropyridazine (**4**) – easily prepared from kojic acid and hydrazine[6,7] – was converted with thionyl chloride into the corresponding 3,6-bis(chloromethyl)-4-oxo-1,4-dihydropyridazine **5**.
After treatment of **5** with 1 equiv. of sodium methoxide and a subsequent reduction of the resultant product with hydrogen, using palladium-on-charcoal as a catalyst, 3-(methoxymethyl)-6-methyl-4-oxo-1,4-dihydropyridazine (**6**; scheme 1) was obtained.



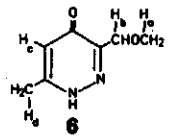
*Scheme 1*

In order to establish that in these series of reactions **6** was formed instead of its isomer **7**, we made use of the observation that in 3,6-dimethyl-4-oxo-1,4-dihydropyridazine (**8**) the PMR signal of the methyl group on position 6 (δ = 2.43 ppm) has a doublet structure ($J$ = 0.6 cps), the H(5)-signal (δ = 6.46 ppm) a quartet structure ($J$ = 0.6 cps), while the methyl group in position 3 (δ = 2.28 ppm) is unsplit.
It is evident that in the 4-oxo-1,4-dihydropyridazine **8** there is coupling between the methyl group on position 6 and the hydrogen on position 5, probably due to the considerable double bond character of the C(5)–C(6) bond. We observed

[1] *Georgine M. Sanders, M. van Dijk* and *H. J. den Hertog*, Recl. Trav. Chim. (Pays-Bas) **93**, 198 (1974).
[2] *H. J. den Hertog* and *H. C. van der Plas*, Dehydrohetarenes, chapter 17 in "Chemistry of Acetylenes", Editor H. G. Viehe. (Marcel Dekker, New York); *Th. Kauffmann* and *R. Wirthwein*, Angew. Chem. internat. Edit. **10**, 20 (1971).
[3] *Th. Kauffmann* and *A. Risberg*, Tetrahedron Lett. **1963**, 1459; *Th. Kauffmann, A. Risberg, J. Schulz* and *R. Weber, ibid.* **1964**, 3563.
[4] *Y. Maki* and *M. Takaya*, Chem. Pharm. Bull. of Japan **20**, 747 (1972); *Y. Maki, G. P. Beardsley*, Tetrahedron Lett. **1971**, 1507.
[5] *W. Adam, A. Grimison* and *R. Hoffmann*, J. Amer. Chem. Soc. **91**, 2590 (1969).
[6] *A. F. Thomas* and *A. Marxer*, Helv. Chim. Acta **41**, 1898 (1958).
[7] *I. Ichimoto, K. Fujii* and *C. Tatsumi*, Agr. Biol. Chem. **31**, 979 (1967).

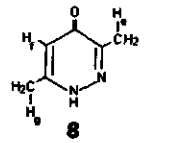
that also in the product obtained on treatment of **5** with sodium methoxide and subsequent reduction, the methyl group at $\delta = 2.48$ ppm has a doublet structure ($J = 0.5$ cps) and the H(5)-signal ($\delta = 6.60$ ppm) has the multiplicity of a quartet ($J \approx 0.5$ cps). Moreover the methylene group ($\delta = 4.60$ ppm) has a singlet structure.

*Table I PMR-data of the 1,4-dihydro-4-oxopyridazines* **6** *and* **8**.



**6**

a = 3.52 (s) ppm
b = 4.60 (s)
c = 6.60 (q) $J_{cd} = 0.5$ cps
d = 2.48 (d)



**8**

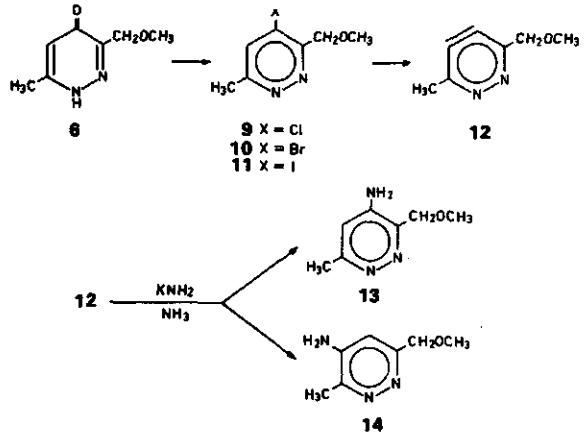
e = 2.28 (s) ppm
f = 6.46 (q) $J_{fg} = 0.6$ cps
g = 2.43 (d)

(PMR spectra in $D_2O$, $(CH_3)_3Si(CH_2)_3SO_3^-Na^+$ as internal standard)

From these observations it is evident that the methyl group at $\delta = 2.48$ ppm is situated in position 6 and the methylene group ($\delta = 4.60$ ppm) in position 3 clearly establishing that it is compound **6** and not **7** which is obtained from **5**.

The 3-(methoxymethyl)-6-methyl-4-X-pyridazines **9** (X=Cl), **10** (X=Br), and **11** (X=I) were prepared by standard procedures and are described in the experimental section.

The PMR spectra are in complete accordance with these structures (see Table III). It is worth mentioning that in the mass spectrum all three of the compounds show a low intensity M-peak, but a strong fragmentation (M-30)-peak ($M-CH_2O$). Similar observations have already been made previously[8].




*Scheme 2*

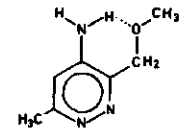
## III. Amination of the 4-halogeno-3-(methoxymethyl)-6-methylpyridazines

The amination of compounds **9**, **10** and **11** was carried out as described previously. After working-up and GLC analyses of the three reaction mixtures it was found that both the 4- and 5-amino products **13** and **14** are present. The ratios of the amino compounds **13** and **14** found in all three of the reaction mixtures are given in Table II. This ratio is independent of the nature of the halogen atom.

*Table II*

| Halogeno pyridazine | After amination: % compound **13** | % compound **14** |
|---|---|---|
| **9** | 16.7 ± 1.6 | 83.3 ± 1.6 |
| **10** | 17.1 ± 1.7 | 82.9 ± 1.7 |
| **11** | 16.9 ± 1.6 | 83.1 ± 1.6 |

The identity of **13** was proved by comparison with an authentic specimen, prepared from **9** by a reaction with ammonia. The isomeric compound **14** was identified by PMR, IR and mass spectrometry. It was observed that compound **13** is much more volatile on the GLC column (filling 20% OV-17 on anakrom ABS 70/80 mesh; separation factor $\alpha_{13/14} = 2.3$) very probably due to the occurrence of an intramolecular hydrogen bridge between the hydrogen of the amino group and the electronegative oxygen of the ether linkage.



**13**

The independency of the composition of the reaction products **13** and **14** on the nature of the halogeno substituent conclusively indicates that the amination of the 4-halogenopyridazines **9**, **10** and **11** proceeds *via* the 4,5-didehydropyridazine **12** as intermediate. No indication for the occurrence an $S_N$ (AE-mechanism) is found.

Considering the directing effect of both methyl and methoxymethyl groups on the addition of the nucleophile to the electrophilic "triple bond", we are faced with the problem whether these groups are ionized in this strongly basic medium, or not; ample evidence[9] is available in the literature on the deprotonation of methyl groups, amino and hydroxy groups, bound to pyridines in solution of potassium amide in liquid ammonia.

We observed that the PMR spectrum of a solution of 3-(methoxymethyl)-6-methylpyridazine (**15**) in liquid ammonia surprisingly does *not* change on addition of potassium amide, indicating that no ionisation takes place. Since the methoxymethylene group is more electron-attracting than the methyl group, we can expect that addition on position 5 is more favourable than addition on position 4[10]. The probability that the methoxymethylene group also exerts a steric effect on the addition at position 4, cannot be excluded.

## Experimental part

Melting points are uncorrected.

The PMR spectra were recorded on a Jeol JNM C-60 H spectrometer. Tetramethylsilane (TMS, $\delta = 0$) was used as an internal standard when the spectrum was measured in acetone-d6 or $CDCl_3$; when the spectrum was taken in $D_2O$, sodium 3-(trimethylsilyl)-propanesulfonate ($\delta = 0$) was the internal standard.

The IR spectra were recorded with a Hitachi, model EPI-G3, and the mass spectra with an AEI MS 902 instrument.

Gas-liquid chromatographic analyses were carried out with a Becker Unigraph with flame ionisation detection, using an 1 m R.S. column containing 20% OV-17 on anakrom ABS 70/80 mesh (temperature 170°C, velocity nitrogen 50 ml/50 sec).

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[8] *Q. N. Porter* and *J. Baldos*, "Mass spectrometry of heterocyclic compounds" Wiley Interscience, New York 1971, p. 299.

[9] *J. A. Zoltewicz* and *L. S. Helmick*, J. Org. Chem. **38**, 658 (1973).

[10] *R. W. Hoffmann*, "Dehydrobenzene and cycloalkynes", Academic Press New York 1967.

**1. Preparation of the starting materials**

a. *3,6-Bis(hydroxymethyl)-4-oxo-1,4-dihydropyridazine* (**4**) *and 3,6-dimethyl-4-oxo-1,4-dihydropyridazine* (**8**)

These compounds were prepared by the procedures described in the literature[6].

b. *3,6-Bis(chloromethyl)-4-oxo-1,4-dihydropyridazine* (**5**)

After treating 7.0 g (45 mmoles) of **4** with 50 ml of 6*N* HCl and evaporating off the excess of the aqueous hydrochloric acid, a residue was obtained, which was reacted with 20 ml of freshly distilled thionyl chloride at 0°C during 1–2 h. When the excess of thionyl chloride had been removed by shaking with petroleum ether (b.r. 60–80°C), the residue was mixed with sodium bicarbonate. This mixture was extracted with boiling ethyl acetate. This extraction was repeated several times, each time using fresh ethyl acetate. The combined extracts were dried over $MgSO_4$, after which the solvent was evaporated. A yellow coloured solid with a characteristic odour remained. Yield 3,8 g (45%); m.p. 206°C (lit.[6]: m.p. 206°C).

c. *3-(Methoxymethyl)-6-methyl-4-oxo-1,4-dihydropyridazine* (**6**)

1.9 g (10 mmoles) of **5** were reacted with 1 equiv. of sodium methoxide in absolute methanol during 24 h at 20°C. The solvent was then removed and the residue dissolved in 45 ml of acetic acid and 45 ml of ethanol. This solution was mixed with 3 g of sodium acetate and then reduced with hydrogen using 250 mg of palladium-on-charcoal catalyst. When hydrogen was no longer taken up the catalyst was filtered off, the solvent removed and the residue extracted with ethyl acetate. The combined extracts were dried over $MgSO_4$ and after evaporating the solvent, 1.4 g (90%) of a colourless solid remained, m.p. 179–180°C (subl.); ν C=O: 1623 $cm^{-1}$ (in $CHCl_3$). Analysis: $C_7H_{10}N_2O_2$ (154.17); Calc. C 54.53, H 6.54; found C 54.7, H 6.6.

d. *4-Chloro-3-(methoxymethyl)-6-methylpyridazine* (**9**)

1.0 g (6.5 mmoles) of **6** was refluxed with 15 ml of phosphorus oxychloride for 45 min. The excess of phosphorus oxychloride was removed *in vacuo* and the residue, after having been cooled, was poured on to ice. Thereupon the solution was made alkaline with ammonia and extracted with chloroform. The chloroform extracts were dried over $MgSO_4$, after which the solvent was distilled off. A residue was obtained, which after recrystallisation from petroleum ether (b.r. 40–60°C) gave 0.83 g (73%) of colourless crystals; m.p. 47–48°C. See Table III for its PMR data. Analysis: $C_7H_9ClN_2O$ (172.62); calc. C 48.70, H 5.26; found C 48.2, H 5.2.
The chloro compound **9**, like the bromo compound **10** and the iodo compound **11**, was found to be unstable on standing in the dry state; it was stored in a solution of petroleum ether (b.r. 40–60°C).

e. *4-Bromo-3-(methoxymethyl)-6-methylpyridazine* (**10**)

1.0 g (6.5 mmoles) of **6** and 4.0 g of phosphorus oxybromide were heated together at 30–40°C for 1 h, while this mixture was intensively shaken. After having been cooled, the reaction mixture was added in small portions at a time to ice-water, after which the solution was made alkaline with ammonia and worked up as already described in section 1.d. Yield 0.27 g (20%); m.p. 58–60°C; see Table III for its PMR data. Analysis: $C_7H_9BrN_2O$ (217.07); calc. C 38.73, H 4.18; found C 39.1, H 3.9. For the stability of the bromo compound see the remark in section 1.d.

f. *4-Iodo-3-(methoxymethyl)-6-methylpyridazine* (**11**)

This compound was prepared from the chloro compound **9** by a reaction with sodium iodide in ethyl methyl ketone in acid medium by the same procedure as given for the conversion of 2-chloroquinoxaline into 2-iodoquinoxaline[11]. Yield 20%; m.p. 62–63°C (after recrystallisation from petroleum ether (b.r. 40–60°C). For its PMR data see Table III. Analysis: $C_7H_9IN_2O$ (264.08); calc. C 31.84, H 3.44; found C 32.0, H 3.6. For the stability of the iodo compound see the remark in section 1.d.

*Table III Chemical shifts of the protons (expressed in δ) of the 4- and 5-substituted 3-(methoxymethyl)-6-methylpyridazines.*

| Compound | $OCH_3$ | $CH_2$ | *H* arom | $CH_3$ | solvent |
|---|---|---|---|---|---|
| **9** | 3.50 ppm | 4.87 ppm | 7.45 ppm | 2.75 ppm | $CDCl_3$ |
| **10** | 3.50 | 4.90 | 7.67 | 2.73 | $CDCl_3$ |
| **11** | 3.51 | 4.85 | 7.95 | 2.70 | $CDCl_3$ |
| **13** | 3.38 | 4.78 | 6.76 | 2.46 | acetone-d6 |
| **14** | 3.40 | 4.55 | 6.87 | 2.53 | acetone-d6 |

**2. General procedure for the reactions of the halogenopyridazines 9, 10 and 11 with potassium amide in liquid ammonia**

Three mmoles of the halogeno compound were treated during ½ h with a solution of a fourfold molar amount of potassium amide in 50 ml liquid ammonia at −33°C ($[KNH_2] = 0.24$). The reaction was terminated by addition of ammonium chloride, after which the ammonia was evaporated. After extraction with chloroform and evaporation of the solvent, a crude residue was obtained, which on GLC showed only peaks of the two amino compounds **13** and **14**; also in the PMR spectrum of this crude residue, signals were observed which could only be ascribed to the two amino isomers. Since no organic material remained in the residue from the evaporation of ammonia, these results indicate a complete and exclusive formation of the two amino products; no byproducts were observed. The ratio of the two amino isomers was determined by comparing the peak area of the methylene group at δ 4.78 ppm in **13** and at δ 4.55 ppm in **14**.
The amino compounds **13** and **14** were separated by preparative GLC. We observed in the mass spectrum of both amino isomers a strong fragmentation (*M*-30)-peak just as in the mass spectra of compounds **9**, **10** and **11** described in section III.

*4-Amino-3-(methoxymethyl)-6-methylpyridazine* (**13**) has a m.p. of 133–135°C. It was found to be identical in all respects (m.p., mixed m.p., IR, PMR and mass spectra) with an authentic specimen (see section 3). For its PMR data see Table III. Analysis: $C_7H_{11}N_3O$ (153.18) calc. C 54.88, H 7.24; found C 54.6, H 7.2. $NH_2$ stretching vibrations 3490 $cm^{-1}$ and 3380 $cm^{-1}$; $NH_2$ deformation frequency at 1618 $cm^{-1}$ (in $CHCl_3$).

*5-Amino-3-(methoxymethyl)-6-methylpyridazine* (**14**) has a m.p. of 85–87°C. For its PMR data see Table III. Analysis: $C_7H_{11}N_3O$ (153.18) calc. C 54.88, H 7.24; found C 54.5 H 7.3. $NH_2$ stretching vibrations 3492 $cm^{-1}$ and 3400 $cm^{-1}$; $NH_2$ deformation frequency at 1622 $cm^{-1}$ (in $CHCl_3$).

**3. 4-Amino-3-(methoxymethyl)-6-methylpyridazine** (**13**)

100 mg (0.6 mmoles) of **9** and 10 ml of ethanolic ammonia, saturated at 0°C, were heated in a sealed tube at 130°C for 20 h. The reaction mixture was evaporated to dryness and the residue was extracted with chloroform. By preparative GLC 61 mg of **13** (=67%) were isolated; m.p. 133–135°C.
It was in all respects (m.p., mixed melting point, GLC data, IR, PMR and mass spectrum) identical with one of the amino compounds obtained by amination of the halogenopyridazine **9**, **10** or **11**.

**4. 3-(Methoxymethyl)-6-methylpyridazine** (**15**)

840 mg (4.8 mmoles) of **9**, 2.0 g of sodium acetate in 30 ml of ethanol and 30 ml of acetic acid were reduced by hydrogen using a 0.5 g palladium-on-charcoal catalyst. When the take up of hydrogen ceased the catalyst was filtered off and the solution was evaporated to dryness. Compound **15** was isolated by column chromatography through silicagel using chloroform as eluent. 346 mg of an oil were obtained. PMR data: $\delta OCH_3 = 3.47$, $\delta CH_2 = 4.73$, $\delta CH_3 = 2,72$, $\delta H(4) = 7.50$ (d), $\delta H(5) = 7.73$ (d), $J_{4,5} = 8.25$ cps.

**Acknowledgement**

We are indebted to Drs. *C. A. Landheer* for mass spectroscopic data, to Mr. *W. P. Combé* for carrying out the microanalyses, to Mr. *A. van Veldhuizen* for measuring PMR and IR spectra and to Mr. *W. Ch. Melger* for advice on the GLC analyses.

[11] *P. J. Lont* and *H. C. van der Plas*, Recl. Trav. Chim. (Pays-Bas) **91**, 850 (1972).

# Didehydrohetarenes (XXXVII)[1]. On the existence of 4,5-didehydropyridazine[2]

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*(Received October 13th, 1975)*

**Abstract.** Reaction of 4-chloro-3,6-diphenylpyridazine with potassium amide in liquid ammonia gives 4-amino-3,6-diphenylpyridazine and imino-4,4'-bis(3,6-diphenylpyridazine). Starting with 4-chloro-3,6-diphenylpyridazine-[5-$^{13}$C], it was proved by quantitative $^{13}$C-NMR measurements that both products are formed via the intermediacy of 4,5-didehydro-3,6-diphenylpyridazine.

## 1. Introduction and amination reaction

A reliable test for the formation of 1,2-didehydrobenzene [benzyne (**1**)], its two diaza analogues 2,3-didehydropyrazine (**2**) and 4,5-didehydropyridazine (**3**, R = H) and its tetraaza analogue 5,6-didehydro-1,2,3,4-tetrazine (**4**) as possible transient intermediates in the reactions of halogenobenzenes or the corresponding halogenoazaaromatics, respectively, with potassium amide in liquid ammonia, involves the introduction of a labelled atom at one ring atom position in the starting halogeno compound. In 1953 a definite proof was obtained by this approach for the formation of benzyne in the reaction of 1-halogenobenzene-[1-$^{14}$C] with potassium amide in liquid ammonia yielding an almost 1 : 1 mixture of 1- and 2-aminobenzene-[1-$^{14}$C][3]. Using the same approach we established some years ago that the amination of 2-chloroquinoxaline-[2-$^{14}$C] with potassium amide in liquid ammonia yields only 2-aminoquinoxaline-[2-$^{14}$C], unequivocally proving that in this amination the symmetrical 2,3-didehydroquinoxaline (**5**) could not be involved as intermediate[4].

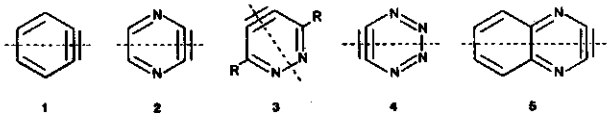
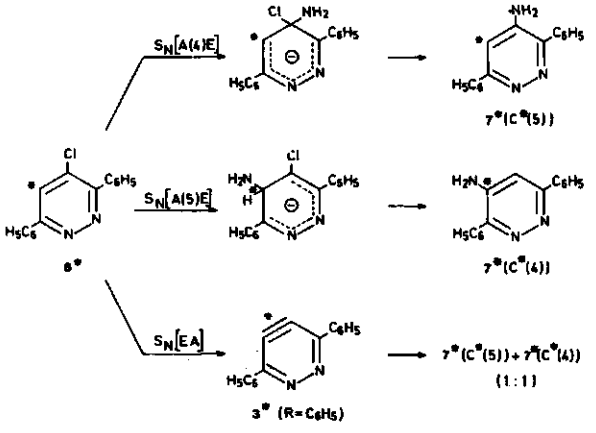


*Fig. 1*

Recently, we obtained some evidence for the intermediacy of 3-(methoxymethyl)-6-methyl-4,5-didehydropyridazine in the reaction of 4-X-3-(methoxymethyl)-6-methylpyridazine (X = Cl, Br, I) with potassium amide in liquid ammonia[5]. This conclusion was based on the fact that the ratio of the two isomeric 4- and 5-amino-3-(methoxymethyl)-6-methylpyridazines (1 : 5) was found to be independent of the nature of the halogen atom. The great difference in the ratio of both amino isomers was supposed to be determined by the difference in orientation effects of both substituents combined with a hydrogen bonding phenomena between the incoming amino group and the methoxymethylene group. In order to cancel out the different orientation effects due to different substituents located at the 3- and 6-position of a 4,5-didehydropyridazine derivative, we have studied the reaction of 4-chloro-3,6-diphenylpyridazine (**6**) with potassium amide in liquid ammonia.

This reaction led to the formation of two products which were identified by their spectroanalytical data as 4-amino-3,6-diphenylpyridazine (**7**) and imino-4,4'-bis(diphenylpyridazine) (**15**) (*vide* Experimental).

It is evident from what has been pointed out above that the occurrence of 3,6-diphenyl-4,5-didehydropyridazine (**3**, R = $C_6H_5$) as a possible intermediate in this reaction can be detected when we use the halide 4-chloro-3,6-diphenylpyridazine-[5-$^{13}$C] (**6***)[6] and study by quantitative $^{13}$C-NMR spectroscopy the distribution of the $^{13}$C-label over the carbon atoms C(4) and C(5) in the formed 4-amino-3,6-diphenylpyridazine (**7***). From the three different routes given in Scheme 1 for nucleophilic displacements it is evident that a quantitative determination of the distribution of the $^{13}$C-label over the positions 4 and 5 of the pyridazine ring provides us with an excellent method for establishing the actual pathway for this amination reaction since the normal $S_N$[A(4)E] substitution gives **7***[C*(5)], the $S_N$[A(5)E] cine-substitution process gives **7***[C*(4)] while the hetaryne $S_N$(EA) reaction distributes the label equally over the two positions 4 and 5 giving a 1 : 1 mixture of **7***[C*(5)] and **7***[C*(4)].



*Scheme 1*

## 2. Synthesis of 4-chloro-3,6-diphenylpyridazine-[5-$^{13}$C] (6*)

The reaction which was found to be useful for the synthesis of **6*** was the well-known Diels Alder reaction[7,8] of 1,1-diethoxyethene with 3,6-diphenyltetrazine. It leads to an

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[1] Part XXXVII in the series on Didehydrohetarenes from this laboratory. Previous paper in this series: *Georgine M. Sanders, M. van Dijk* and *H. J. den Hertog*, Recl. Trav. Chim. (Pays-Bas) **95**, 31 (1976).

[2] Part V on Pyridazines from this laboratory. See for part IV *D. E. Klinge, H. C. van der Plas* and *A. van Veldhuizen*, Recl. Trav. Chim. (Pays-Bas) **95**, 21 (1976).

[3] *J. D. Roberts, H. E. Simmons, L. A. Carlsmith* and *C. W. Vaughan*, J. Amer. Chem. Soc. **75**, 3290 (1953).

[4] *P. J. Lont, H. C. van der Plas* and *A. J. Verbeek*, Recl. Trav. Chim. (Pays-Bas) **91**, 949 (1972).

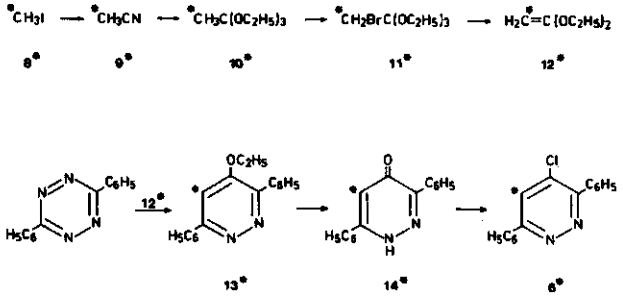
[5] *D. E. Klinge, H. C. van der Plas* and *A. Koudijs*, Recl. Trav. Chim. (Pays-Bas) **93**, 201 (1974).

[6] In this paper all the labelled compounds are indicated by an asterisk, the corresponding unlabelled compounds are given without an asterisk.

[7] *J. Sauer, A. Mielert, D. Lang* and *D. Peter*, Ber. **98**, 1435 (1965).

[8] *J. Sauer* and *G. Heinrichs*, Tetrahedron Lett. **1966**, 4979.

adduct which easily loses nitrogen and subsequently ethanol yielding 4-ethoxy-3,6-diphenylpyridazine. The synthesis of 1,1-diethoxyethene-[2-$^{13}$C] (**12***) required for the preparation of **6*** was performed as follows: acetonitrile-[2-$^{13}$C] (**9***) which was prepared from methyl-[$^{13}$C] iodide (**8***) by refluxing with a mixture of potassium cyanide and glycerol, was converted into triethyl orthoacetate-[2-$^{13}$C] (**10***) by an acid-catalysed reaction with ethanol. From this compound the triethyl 2-bromoorthoacetate-[2-$^{13}$C] (**11***) was obtained by a reaction with bromine at low temperature. The conversion into **12*** was performed by refluxing **11*** with powdered sodium in benzene. Reaction of **12*** with 3,6-diphenyltetrazine in benzene gave 3,6-diphenyl-4-ethoxypyridazine-[5-$^{13}$C] (**13***). This was converted by treatment with hydrochloric acid into the 4-oxo compound **14***. Transformation of **14*** into 4-chloro-3,6-diphenylpyridazine-[5-$^{13}$C] (**6***) was achieved by refluxing with phosphoryl chloride (Scheme 2).

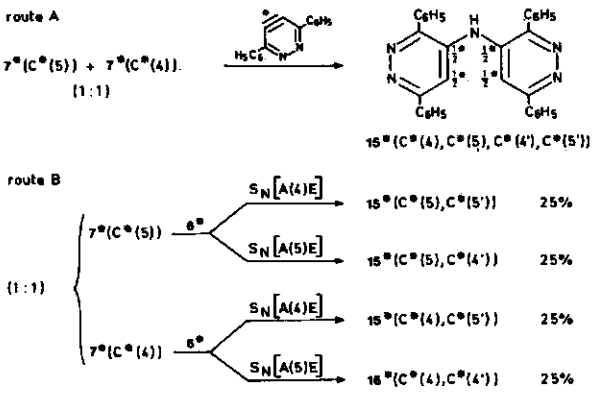


*Scheme 2*

### 3. Calculation of $^{13}$C-distribution using quantitative $^{13}$C-NMR spectroscopy[9]. Discussion of reaction mechanism

The quantitative $^{13}$C-NMR measurements in **6*** were carried out by comparison of the peak area of C(5) of the unlabelled chloro compound **6** with that of the $^{13}$C-enriched chloro compound **6***. Both spectra were taken with exactly the same concentrations and with the same parameters of the NMR records. Since, under these conditions, the total peak area of the carbon atoms of the two phenyl groups in the record of the unlabelled and the labelled chloro compound are the same, from the quotient of the peak areas of C(5) in **6** and C*(5) in **6*** a reasonable value for the $^{13}$C-enrichment could be calculated: chloro compound **6***: quotient C*(5)/C(5) = 4.6; this means that 4.6 × 1.1% (being the natural abundance of $^{13}$C in C(5) of the unlabelled compound) = 5.1% $^{13}$C is present in the C*(5) of the labelled compound. The enrichment in that position is thus 5.1–1.1 = 4.0%[10]. By the same method the label distribution and the total percentage of $^{13}$C-enrichment in the amino product **7*** was calculated: amino product **7***: quotient C*(4)/C(4) = 2.7; enrichment is (2.7 × 1.1%) − 1.1% = 1.9%; quotient C*(5)/C(5) = 2.7; enrichment (2.7 × 1.1%) − 1.1% = 1.9%. Total enrichment 3.8%[10].

These experimental results showed that after amination of **6*** the label distribution in **7*** over C(4) and C(5) is 1 : 1. From this result the conclusion is drawn that in this amination the amino compound is formed by a $S_N$(EA) process. The simultaneous occurrence of two mechanisms *i.e.* $S_N$[A(4)E] and $S_N$[A(5)E] both of which should compete for exactly 50% cannot definitively be excluded, but seems very unlikely. Measurement of the label distribution in the coupling product imino-4,4'-bis(3,6-diphenylpyridazine) (**15***) gave the following result: in the coupling product **15*** the quotient C*(4)C*(4')/C(4)C(4') is 2.8; enrichment (2.8 × 2.2%) − 2.2% = 4.0%; quotient C*(5)C*(5')/C(5)C(5') = 2.8; enrichment (2.8 × 2.2%) − 2.2% = 4.0%[10]. Total enrichment in this dimer is thus 8.0%. This means that each pyridazine nucleus contains 4.0% of $^{13}$C-enrichment. The $^{13}$C-label is thus equally distributed over the positions 4,4' and 5,5'. The several mechanisms which lead to this equal distribution are summarized in Scheme 3. Three possibilities for the operation of the reaction may be considered, (a) route A, (b) route B or (c) a simultaneous operation of a combination of routes A and B. The result of the $^{13}$C-distribution in compound **15*** is considered to be a good indication for *the intermediacy of a 4,5-didehydropyridazine* (**3***, R = $C_6H_5$), since it seems less probable that the reactions given in route B are also competing at exactly the same rate.



*Scheme 3*

Calculations using the extended Hückel theory predict[11] that the 4,5-didehydropyridazine should be far more stable than the widely accepted and well established 3,4-didehydropyridine. It is remarkable that after the discovery of the 3,4-didehydropyridine[12] it took nearly fifteen years before the existence of 4,5-didehydropyridazine could be proven clearly.

## Experimental part

The carbon spectra were obtained with a Varian CFT-20. The spectrometer was equipped with a 16K computer. The spectral width was 4000 Hz, pulse width 12 μs, pulse delay 0.6 s, acquisition time 1.023 s. Number of transients: for the chloro compound **6*** and the coupling product **15*** 2500, for the amino compound **7*** 25000. The concentrations of the solutions for $^{13}$C-NMR records were for the chloro compound: 0.53 M ($CDCl_3$); amino compound 0.10 M (DMSO-$d_6$); coupling product: 0.07 M ($CDCl_3$).

### 1. Synthesis of 4-chloro-3,6-diphenylpyridazine-[5-$^{13}$C] (6*)

#### a. *Acetonitrile-[2-$^{13}$C]* (9*)

40.0 g (280 mmoles) of methyl-[$^{13}$C] iodide (**8***) (about[13] 3.8 atom % $^{13}$C) were mixed with 25 ml of dry glycerol and 18.2 g (330 mmoles) of potassium cyanide were added. During the stirring of this heterogeneous system at 25° an exothermic reaction occurs. After 4 h,

[9] We gratefully acknowledge the help of Dr. *M. J. A. de Bie*, Drs. *N. J. Koole* and Ir. *T. Spoormaker* (NMR section of the laboratory of Organic Chemistry of the University, Croesestraat 79, Utrecht) for the quantitative $^{13}$C-NMR measurements.

[10] An approximation of the deviation in the calculated values based on the error in the calculation of the peak area as being the most important source of errors is about 10%.

[11] *W. Adam, A. Grimison* and *R. Hoffmann*, J. Amer. Chem. Soc. **91**, 2590 (1969).

[12] *M. J. Pieterse*, Thesis, Amsterdam 1962; *M. J. Pieterse* and *H. J. den Hertog*, Recl. Trav. Chim. (Pays-Bas) **80**, 1376 (1961).

[13] 5.0 g of methyl-[$^{13}$C] iodide, about 61 atom % $^{13}$C was diluted with unlabelled methyl iodide to 80.0 g (560 mmoles, about 3.8 atom % $^{13}$C).

9* was slowly distilled from the reaction mixture using an oil bath which was heated to a final temperature of 180°. Yield 10.3 g of 9* (90%).

b. *Triethyl orthoacetate-[2-$^{13}C$]* (10*)

The procedure was followed as given in the literature[14] for the one-step acid-catalysed conversion of nitriles into ortho esters. It seemed necessary for continuation of the reaction to allow the reaction temperature to rise to 40° during the passing through of dry hydrogen chloride. Starting with 10.3 g (252 mmoles) of acetonitrile-[2-$^{13}C$] (9*), 11.6 g of 10* (28%) was obtained. B.p. 144–145°. (Lit.[14] 59–78%, b.p. 70–80°/60 mm).
$^{13}C$-NMR data[15]: C(1) 114.3 ppm, C(2) 20.7 ppm, $OCH_2CH_3$ 57.5 ppm, $OCH_2CH_3$ 15.6 ppm.

c. *Triethyl 2-bromoorthoacetate-[2-$^{13}C$]* (11*)

11.5 g (72 mmoles) of bromine were added in 2 h, with stirring, to 11.6 g (72 mmoles) of triethyl orthoacetate-[2-$^{13}C$] (10*). The reaction temperature was kept between 0–5°. After addition of 10 ml of dry ether, the reaction mixture was vigorously stirred at room temperature for about 15 min. The working-up procedure was carried out as described in the literature[17]. Yield 8.7 g of 11* (50%). B.p. 88–92°/20 mm (Lit.[17] 72%, b.p. 77–79°/9 mm).

d. *1,1-Diethoxyethene-[2-$^{13}C$]* (12*)

The dehydrobromination of 11* was performed as described in the literature[18] and carried out in a nitrogen atmosphere. The powdered sodium was prepared in refluxing toluene, but for the reaction benzene was used. After termination of the reaction, 12* was not isolated but, after filtration of the coloured material, the remaining clear reaction mixture was immediately used for the coupling reaction with 3,6-diphenyltetrazine.

e. *3,6-Diphenyl-4-ethoxypyridazine-[5-$^{13}C$]* (13*)

The Diels-Alder reaction was carried out in a nitrogen atmosphere using benzene as a solvent[7,8] (see section d). Since the quantity of 1,1-diethoxyethene-[2-$^{13}C$] was not determined (see section d), small portions of 3,6-diphenyltetrazine were added to the refluxing reaction mixture till the characteristic violet colour of the tetrazine compound failed to disappear. The reaction rate is slow, so it took two days before the ketene acetal (12*) was completely consumed. The solvent was then evaporated *in vacuo* and the excess of the tetrazine compound was removed by several washings of the residue with petroleum ether (b.r. 40–60°). By this procedure the residue changed in colour from violet to pale-yellow. Yield 3.0 g of 13* (30% from 11*). M.p. 102–104° (Lit.[7] m.p. 100–104°).

f. *3,6-Diphenylpyridazin-4-one-[5-$^{13}C$]* (14*)

3.0 g (10.9 mmoles) of 13* were distributed over six Carius tubes. To each one 10 ml of concentrated hydrochloric acid were added, then the tubes were sealed and heated at 150° for 6 h. After the reaction, the acidic solution was evaporated to dryness, water was added and the solution was neutralized with sodium bicarbonate. The precipitate formed was isolated, yielding 2.5 g of 14* (92%). M.p. > 300° (Lit.[19] m.p. 330°). Analysis of the unlabelled compound $C_{16}H_{12}N_2O$ (248.27); calc. C 77.40, H 4.87; found C 77.3, H 5.1.

g. *4-Chloro-3,6-diphenylpyridazine-[5-$^{13}C$]* (6*)

2.5 g (9.4 mmoles) of 14* were refluxed with 20 ml of freshly distilled phosphoryl chloride for 2 h. The excess of phosphoryl chloride was removed *in vacuo* and the residue, after having been cooled, was poured on to ice. The solution was then made neutral with ammonia keeping the temperature below 20°. The precipitate of 6* was filtered off and recrystallized from ethanol. Yield 2.3 g of 6* (85%). M.p. 135–136° (Lit.[19] m.p. 138°). Analysis of the unlabelled compound $C_{16}H_{11}ClN_2$ (266.72): calc. C 72.05, H 4.16; found C 71.9, H 4.3. $^{13}C$-NMR data[20]: C(3) 158.4 ppm, C(4) 134.9 ppm, C(5) 124.8 ppm, C(6) 158.0 ppm.

**2. Amination of 4-chloro-3,6-diphenylpyridazine-[5-$^{13}C$] (6*)**

1.0 g (3.8 mmoles) of 4-chloro-3,6-diphenylpyridazine-[5-$^{13}C$) (6*) was added to a solution of a fifteenfold molar amount of potassium amide in 250 ml of liquid ammonia at −33° ([$KNH_2$] = 0.23) in small portions during 6 h. The reaction mixture was then stirred for another hour after which the reaction was terminated by addition of ammonium chloride. The ammonia was evaporated and the residue was extracted with ten portions of 75 ml of boiling benzene each. After cooling, all the precipitates were collected and recrystallized from ethyl acetate. Yield 190 mg of 4-amino-3,6-diphenylpyridazine-[4,5-$^{13}C$] (7*) (21%). M.p. 290–295°.
$^1H$-NMR data: phenyl groups 7.35–8.10 ppm, H(5) 7.24 ppm; $^{13}C$-NMR data[20]: C(3) 151.2 ppm, C(4) 146.9 ppm, C(5) 108.6 ppm, C(6) 159.5 ppm; N–H stretching vibration at 3475 $cm^{-1}$ and 3285 $cm^{-1}$; parent peak in the mass spectrum 247; analysis $C_{16}H_{13}N_3$ (247.29): calc. C 77.71, H 5.30; found C 77.3, H 5.3. The compound was in all respects identical (IR, NMR spectra and melting point) with the compound obtained in section 3.
From the filtrates of the ten benzene portions a second product was isolated by evaporation of the benzene, which afforded 200 mg of imino-4,4'-bis(3,6-diphenylpyridazine) (15*) (10%). M.p. 258–260°. $^1H$-NMR data: phenyl groups 7.34–7.64 ppm (6H), 8.02–8.16 ppm (4H), H(5) 7.86 ppm; $^{13}C$-NMR data[20]: C(3) 152.2 ppm, C(4) 137.8 ppm, C(5) 108.8 ppm, C(6) 158.3 ppm; –NH– stretching vibration at 3410 $cm^{-1}$; $M^+$ = 477; analysis $C_{32}H_{23}N_5$ (477.54): calc. C 80.48, H 4.85; found C 80.6, H 5.0.

**3. 4-Amino-3,6-diphenylpyridazine (7)**

0.5 g (1.9 mmoles) of 4-chloro-3,6-diphenylpyridazine (6) was mixed with a little phenol and anhydrous cupric sulfate and refluxed for 4 h while ammonia was led into this mixture. The solution was acidified to pH ~3 with dilute hydrochloric acid. The phenol was removed by steam distillation and the residue was extracted with dilute aqueous hydrochloric acid. The combined acidic aqueous layers were made alkaline with ammonia, the precipitate was filtered off and recrystallized from ethanol: 0.28 g of 7 (60%) was obtained. M.p. 292–295°.

**Acknowledgement**

We are indebted to Drs. *C. A. Landheer* for mass spectrometric data, to Mr. *A. van Veldhuizen* for measuring $^1H$-NMR, $^{13}C$-NMR and IR spectra and to Mr. *W. P. Combé* for carrying out the microanalyses.

**Note added in proof**

Since our paper was accepted, a publication has appeared[21] describing the generation of 3,6-diphenyl-4,5-didehydropyridazine by oxidation of 1-amino-4,7-diphenyltriazolo-[4,5-*d*]pyridazine with lead tetra-acetate at room temperature. The intermediacy of this aryne was proven by interception with tetracyclone, yielding 1,4,5,6,7,8-hexaphenylphthalazine, or with furan giving 5,8-epoxy-5,8-dihydro-1,4-diphenylphthalazine

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[14] *R. H. DeWolfe*, Synthesis **1974**, 153.
[15] Interpretation of the $^{13}C$-NMR spectrum is based on the results of $^{13}C$-measurements mentioned in the literature[16] and on a comparison of the $^{13}C$-spectra of the unlabelled and the labelled compound.
[16] *P. C. Lauterbur*, Ann. N.Y. Acad. Sci. **70**, 841 (1958).
[17] *F. Beyerstedt* and *S. M. McElvain*, J. Amer. Chem. Soc. **59**, 1273 (1937).
[18] *Ph. M. Walters* and *S. M. McElvain*, J. Amer. Chem. Soc. **62**, 1482 (1940).
[19] *T. Aiello*, *V. Spiro* and *G. C. Vaccaro*, Gazz. chim. ital. **89**, 2232 (1959).
[20] Interpretation of the $^{13}C$-NMR spectrum is based on the results of $^{13}C$-measurements in literature[2] and on comparison of the $^{13}C$-spectra of the unlabelled and the labelled compound.
[21] *Th. L. Gilchrist*, *G. E. Gymer* and *Ch. W. Rees*, J. Chem. Soc. Perkin I, **1975**, 1747.

# NMR studies on σ-adducts of heterocyclic systems with nucleophiles (Part VII)[1]. $^1$H-NMR investigations on σ-adduct formation of pyridazine, of pyridazine 1-oxide and some of its derivatives with ammonia. A new substitution mechanism[2]

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*(Received June 16th, 1975)*

**Abstract.** In the reaction of 6-chloro-3-methoxy-4-nitropyridazine 1-oxide with methanolic ammonia and with liquid ammonia, amino-demethoxylation occurs. By using $^1$H-NMR spectroscopy we observed that with ammonia a σ-adduct at C(5) is formed. The unusual substitution reaction at C(3) is proposed to take place *in* this σ-adduct. This new substitution mechanism is discussed.

## Introduction

Recent $^1$H- and $^{13}$C-NMR studies have shown that diazines and several substituted diazines when dissolved in liquid ammonia containing potassium amide, form anionic σ-adducts. In this laboratory it was recently established that the σ-adducts **1–4** are formed with 2-chloro-3,6-diphenylpyrazine[3], 4-R-5-bromopyrimidines[4], 2-X-4-phenylpyrimidines[5] and 4-chloro-2-R-pyrimidines[6], respectively. Also in liquid ammonia, being free from amide ions, σ-adduct formation is observed: pteridine[7] gives the adduct **5** or **6** (depending on the temperature) and with *N*-methylpyrimidinium salts[8] the adduct **7** is formed.

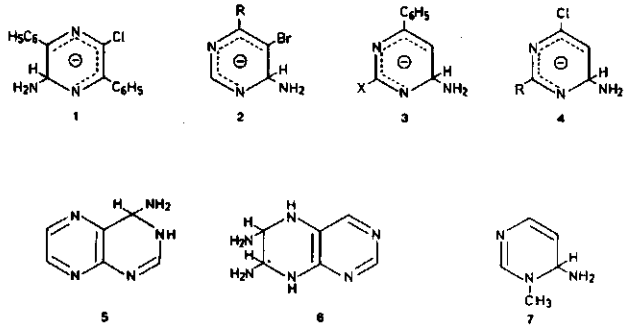

*Fig. 1*

Our recent work on the formation of didehydro intermediates[9] and ring transformations[2] in reactions of halogenopyridazines with potassium amide in liquid ammonia induced us to study the reaction of pyridazine derivatives, containing different leaving groups at different positions of the ring. In this paper we report on the reaction of 6-chloro-3-methoxy-4-nitropyridazine 1-oxide (**8**) with methanolic ammonia and with liquid ammonia.

## Reaction of 6-chloro-3-methoxy-4-nitropyridazine 1-oxide (8) with methanolic ammonia

On reacting 6-chloro-3-methoxy-4-nitropyridazine 1-oxide (**8**) with methanolic ammonia at 0°C for 1 h, amino-demethoxylation takes place leading to the corresponding 3-amino compound (**9**) in good yield. The structure assignment of **9** was based on: *(i).* the $^1$H-NMR spectrum ($CDCl_3$) showing a singlet at δ = 8.50 (1H); *(ii).* the IR spectrum (KBr) featuring at 3430 cm$^{-1}$ and at 3265 cm$^{-1}$ the NH-stretching vibration absorptions and at 1308 cm$^{-1}$ the stretching vibration of the $N^+-O^-$ group; *(iii).* the mass spectrum showing the molecular peaks at *m/e* = 190–192, fragmentation peaks at *m/e* = 174–176 (*M*-16, loss of the oxygen of the $N^+-O^-$ function) and *(iv).* the elemental analyses. Chemical evidence was obtained by reduction of **9** with hydrogen – using a mixture of Raney nickel and palladium on charcoal as a catalyst – to 3,4-diaminopyridazine, its hydrochloride being identical with an authentic specimen[10], with respect to its melting point, IR spectrum and $^1$H-NMR spectrum ($D_2O$) δ = 6.91 (d) and δ = 8.30 (d) (*J* = 6.0 Hz). Until now amino-demethoxylation in compound **8** has not been observed[11]; usually reaction of **8** with nucleophiles such as the methoxy, mercapto or azido anion – also in methanol as solvent – leads to substitution at C(4) and only in one case, with benzylamine, has substitution of the chlorine atom at C(6) been reported[12]. This interesting reactivity at C(3) in **8** induced us to study the conversion of **8** into **9** in more detail. We observed that in the $^1$H-NMR spectrum of a solution of **8** in methanolic ammonia the proton at C(5) is considerably shifted upfield (about 3.5 ppm) as compared with the chemical shift of H(5) in **8** in the solvent $CDCl_3$[13] (see Table I). Based on this observation and on those obtained in earlier studies[3–6] in our laboratory, we have to conclude that in methanolic ammonia a σ-adduct is formed; structure **10** was assigned to this adduct. As an

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[1] See part VI in these series: *J. P. Geerts, H. C. van der Plas* and *A. van Veldhuizen*, Org. Magn. Reson. **7**, 86 (1975).

[2] Part III on pyridazines from this laboratory. See for part II: *D. E. Klinge, H. C. van der Plas, G. Geurtsen* and *A. Koudijs*, Recl. Trav. Chim. Pays-Bas **93**, 236 (1974).

[3] *P. J. Lont, H. C. van der Plas* and *A. van Veldhuizen*, Recl. Trav. Chim. Pays-Bas **92**, 708 (1973).

[4] *J. P. Geerts, C. A. H. Rasmussen, H. C. van der Plas* and *A. van Veldhuizen*, Recl. Trav. Chim. Pays-Bas **93**, 231 (1974).

[5] *A. P. Kroon, H. C. van der Plas* and *G. van Garderen*, Recl. Trav. Chim. Pays-Bas **93**, 325 (1974).

[6] *J. P. Geerts, H. C. van der Plas* and *A. van Veldhuizen*, Recl. Trav. Chim. Pays-Bas **92**, 1232 (1973).

[7] *A. Nagel, H. C. van der Plas* and *A. van Veldhuizen*, Recl. Trav. Chim. Pays-Bas **94**, 45 (1975).

[8] *E. A. Oostveen, H. C. van der Plas* and *H. Jongejan*, Recl. Trav. Chim. Pays-Bas **93**, 114 (1974).

[9] Part I on pyridazines: *D. E. Klinge, H. C. van der Plas* and *A. Koudijs*, Recl. Trav. Chim. Pays-Bas **93**, 201 (1974).

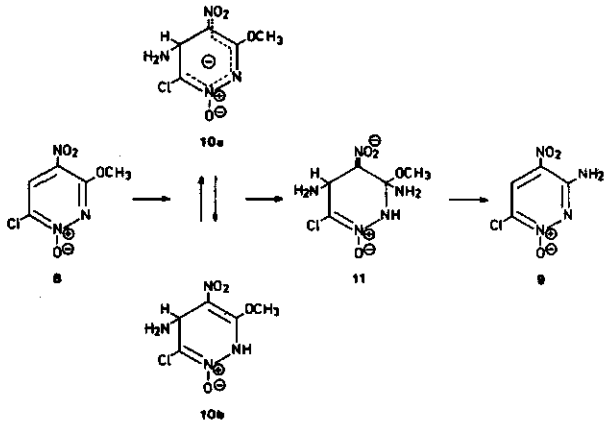
[10] *W. D. Guither, D. G. Clark* and *R. N. Castle*, J. Heterocycl. Chem. **2**, 67 (1965).

[11] The replacement of an alkoxy group at C(3) in pyridazine 1-oxides has also been found to take place in reactions of 3-alkoxy-4-nitro- (and 4,6-dinitro)pyridazine 1-oxides with amines. See: *M. Yanai, T. Kinoshita, S. Takeda* and *H. Sadaki*, Chem. Pharm. Bull. **20**, 166 (1972).

[12] *T. Novinson, R. K. Robins* and *D. E. O'Brien*, J. Heterocycl. Chem. **10**, 835 (1973).

[13] It is known[3,6], that the influence on the chemical shifts of protons of aza-aromatics, on changing the solvent from $CDCl_3$ to liquid ammonia, is very small.

interesting contrast we observed, using $^1$H-NMR spectroscopy, that in a solution of **8** in methanol, containing sodium azide, an adduct of type **10** (replacement of $NH_2$ by $N_3$) is not formed. Based on this remarkable difference we propose that *amino-demethoxylation takes place in the primarily formed covalent adduct* $\mathbf{10^a} \rightleftharpoons \mathbf{10^b}$[14], but that the azido-denitration takes place in **8** itself *via* the usual Meisenheimer adduct at C(4). In $\mathbf{10^a} \rightleftharpoons \mathbf{10^b}$ the nitrovinylether moiety can easily undergo addition by the ammonia yielding the intermediate **11** which finally gives **9**.



*Scheme 1*

It might be of importance to point out that the explanation given for the replacement reaction in **8** – *i.e.* the amino-demethoxylation occurs in the adduct **10** – is different from the proposal given previously for the mechanism of the slowly occurring amination of 2-chloro-3,6-diphenylpyrazine into 2-amino-3,6-diphenylpyrazine[3] with potassium amide in liquid ammonia at −33°C. Although also in this reaction there is excellent evidence for the formation of a rather stable σ-adduct – *i.e.* **1** – it was suggested in that study that the replacement of the chlorine atom by the amino group does not occur in **1**, but in 2-chloro-3,6-diphenylpyrazine itself being present in low concentration due to the equilibrium with **1** lying far over to the left. However, the result mentioned in this paper makes this explanation doubtful, since it cannot be excluded that an amino-dehalogenation takes place leading to 2-amino-3,6-diphenylpyrazine also in adduct **1** (or its protonated form). It is clear that more work is necessary to settle this interesting problem.

A suggestion why adduct formation at C(5) in **8** by ammonia is preferred to adduct formation at C(4) in **8** by the azide anion might be the stabilisation of adduct **10** due to hydrogen bridge formation[15] between the incoming amino group and the nitro group.

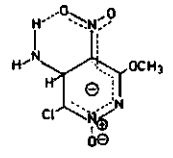
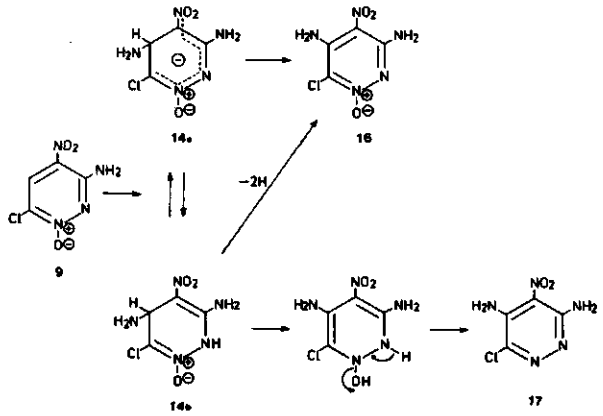


*Fig. 2*

The possibility that difference in nucleophilicity between ammonia and the azide anion might determine the position of adduct formation, seems not very likely, since a competitive study[16] of nucleophilic reactivity constants in the solvent methanol, indicates that ammonia is only a little weaker nucleophile than the azide anion.

**Reaction of 6-chloro-3-methoxy-4-nitropyridazine 1-oxide (8) and of 3-amino-6-chloro-4-nitropyridazine 1-oxide (9) with liquid ammonia**

When 6-chloro-3-methoxy-4-nitropyridazine 1-oxide (**8**) was dissolved in liquid ammonia at −33°C, it was also converted into the 3-amino compound (**9**). The reaction does not stop at this stage, but continues with the formation of two new compounds to which we assigned the structure of 6-chloro-3,5-diamino-4-nitropyridazine 1-oxide (**16**) (15%) and of the deoxygenated compound **17** as a minor product (Scheme 2).



*Scheme 2*

The structure assignment of **16** was based on: *(i).* the $^1$H-NMR spectrum (DMSO-$d_6$) showing no absorption in the aromatic region, but only a broad absorption of amino groups; *(ii).* the IR spectrum (KBr) with characteristic NH-stretching vibrations at 3455 $cm^{-1}$, 3435 $cm^{-1}$, 3340 $cm^{-1}$ and 3285 $cm^{-1}$, and with the stretching vibration of the $N^+-O^-$ group at 1290 $cm^{-1}$; *(iii).* the mass spectrum, showing parent peaks at $m/e$ = 205–207 and fragmentation peaks at 189–191 ($M$-16, loss of the oxygen from the $N^+-O^-$ function); and *(iv).* the exact mass determination ($C_4H_4{}^{35}Cl\,N_5O_3$) calc. 205.0003, found 205.0002. The structure assignment of **17** was based on: *(i).* the $^1$H-NMR spectrum (DMSO-$d_6$), no aromatic protons but only a broad absorption of amino groups; *(ii).* the IR spectrum (KBr) which did not show the characteristic stretching vibration of the $N^+-O^-$ group at about 1300 $cm^{-1}$; *(iii).* the mass spectrum which gave parent peaks at $m/e$ 189–191 but no fragmentation peaks at $M$-16; and *(iv).* the exact mass determination ($C_4H_4{}^{35}Cl\,N_5O_2$) calc. 189.0033, found 189.0054. Reduction of the reaction mixture obtained on amination of **9**, with hydrogen, using the "mixed" catalyst (see above), yielded 3,4,5-triaminopyridazine. The structure assignment was based on the $^1$H-NMR spectrum of its hydrochloride [δ = 8.00 (DMSO-$d_6$)] and by comparison with the recorded IR spectrum and the melting point of the hydrochloride of an authentic specimen[10].

It was proved that 3-amino-6-chloro-4-nitropyridazine 1-oxide (**9**) is a precursor of compounds **16** and **17**, since on reaction of **9** with liquid ammonia at −33°C **16** and **17** are indeed formed.

Observing the $^1$H-NMR spectrum of **8** in liquid ammonia at −55°C, the same adduct **10** – the proton at C(5) is shifted upfield about 3.7 ppm – is found to be present as in methanolic ammonia. The conclusion seems justified therefore that the formation of **9** by liquid ammonia will take place by the same route as mentioned for the methanolic ammonia process. Furthermore, it was observed that **9** dissolved in methanolic ammonia at 0°C as well as in liquid ammonia at −33°C also gives a σ-adduct. Upfield shifts of the hydrogen atom at C(5) of 3.6 ppm, and 3.9 ppm, respectively, were found – indicating the presence of $\mathbf{14^a}$ or its protonated form $\mathbf{14^b}$ (Table I). It

[14] It is of interest to notice, that the extreme ease with which the chlorine atom at C(6) in 6-chloropteridine is replaced in acidic medium is suggested to occur *in* the C(7)–C(8) covalent hydrate. See: *A. Albert, T. J. Batterham* and *J. J. McCormack*, J. Chem. Soc. (B) **1966**, 1105.

[15] *M. J. Strauss*, Chem. Rev. **70**, 662 (1970).

[16] Aliphatic Nucleophilic Substitution, *S. R. Hartshorn*, Cambridge at the University Press 1973.

*Table I Chemical shifts of the ring protons (expressed in δ) of pyridazine and of pyridazine 1-oxide and some of its derivatives.*

| | a = $CDCl_3$; b = DMSO-$d_6$ | | | | liquid $NH_3$ | | | | $NH_3+CD_3OD$ |
|---|---|---|---|---|---|---|---|---|---|
| | H(3), | H(4), | H(5), | H(6) | H(3), | H(4), | H(5), | H(6) | H(5) |
| pyridazine (14)[a,c] | 9.40 | 8.00 | 8.00 | 9.40 | 9.34 | 7.84 | 7.84 | 9.34 | |
| pyridazine 1-oxide (15)[a,d] | 8.50 | 7.17 | 7.75 | 8.25 | 8.67 | 7.40 | 8.05 | 8.50 | |
| 4-nitropyridazine 1-oxide (13)[b,e] | 9.50 | | AB-centre at 8.60 | | 8.03 | | 4.55 | 6.65 | |
| 3-methoxypyridazine 1-oxide (18)[a,f] | | 6.79 | 7.77 | 8.09 | | 7.08 | 8.01 | 8.30 | |
| 6-chloro-3-methoxypyridazine 1-oxide (19)[a,g] | | 6.72 | 7.70 | | | 7.17 | 8.38 | | |
| 6-chloro-3-methoxy-4-nitropyridazine 1-oxide (8)[a] | | | 8.53 | | | | 4.82 | | 5.06 |
| 3-amino-6-chloro-4-nitropyridazine 1-oxide (9)[b] | | | 8.60 | | | | 4.68 | | 5.00 |
| 6-chloro-3-hydroxy-4-nitropyridazine 1-oxide (12)[b] | | | 8.85 | | | | 8.55 | | |

[a] Solvent $CDCl_3$; [b] solvent DMSO-$d_6$; [c] the spectrum consists of two symmetrical triplets of an $A_2X_2$ type[27,28] in both solvents[29]; [d] all the coupling constants measured in liquid ammonia are in good agreement with those given in literature[29] using $CDCl_3$ as solvent; [e] $^1$H-NMR data of **13** measured in $CDCl_3$ are given in literature[29], in liquid ammonia: $J_{3,5} = \sim 1.0$ Hz; $J_{5,6} = 5.3$ Hz; [f] coupling constants measured in $CDCl_3$ as solvent are given in literature[29], in liquid ammonia: $J_{4,5} = 9.0$ Hz; $J_{5,6} = 6.0$ Hz; [g] $J_{4,5} = 8.8$ Hz ($CDCl_3$)[29]; $J_{4,5} = 8.8$ Hz ($NH_3$).

may be concluded therefore that the conversion of **9** into **16** and **17** also starts with the formation of an adduct. By loss of a hydride ion or by an oxidation process aromatisation can take place leading to **16**; by loss of water – as indicated in Scheme 2 – the deoxygenated compound **17** can be formed.

## Structural requirements for adduct formation of pyridazine derivatives with liquid ammonia

As already pointed out, adduct formation of **9** with ammonia has not been established previously and this induced us to investigate which structural requirements have to be fulfilled in order to observe adducts of pyridazines with ammonia.

It was already established that the addition of nucleophiles to azahetarenes occurs more easily with an increasing number of ring nitrogen atoms or by introduction of nitro groups[17–19]. It was proved by $^1$H-NMR spectroscopy that the parent compound pyridazine gives a σ-adduct with potassium amide in liquid ammonia at C(4)[20]. We found, however, that with the much weaker nucleophile ammonia, pyridazine, pyridazine 1-oxide, 3-methoxypyridazine 1-oxide[21] and 6-chloro-3-methoxypyridazine 1-oxide do not give a σ-adduct, but that the presence of a nitro group at C(4) in pyridazine 1-oxide – *i.e.* **13** – supports the formation of an adduct (see Table I).

Furthermore, it was found that the presence of substituents in the pyridazine compound which contain a proton abstractable by ammonia prevents addition. Apparently, in the negatively charged ion nucleophilic addition is strongly inhibited. To illustrate this with an example: while there is clear $^1$H-NMR evidence for adduct formation of 3-methoxy- and of 3-amino-6-chloro-4-nitropyridazine 1-oxide, 6-chloro-3-hydroxy-4-nitropyridazine 1-oxide (**12**) undergoes deprotonation and no adduct is formed (Table I). A study of the $^{13}$C-NMR spectra of the adducts **10**, **14**, of the adduct of 4-nitropyridazine 1-oxide and of the anion of **12** formed with liquid ammonia was undertaken. The provisional results obtained so far support the proposals made in this publication; they will be published elsewhere.

## Experimental part

Melting points are uncorrected. The $^1$H-NMR spectra were recorded on a Jeol JNM C-60 H spectrometer. The spectra were taken in $CDCl_3$, DMSO-$d_6$ or methanolic ammonia using TMS (δ = 0) as internal standard; in liquid ammonia $(CH_3)_3N$ (δ = 2.13) was used as internal standard. The techniques for preparing and measuring the solutions in liquid ammonia has been described earlier[4]. The mass spectra were recorded with an AEI MS 902 instrument.

a. *The following compounds were prepared by procedures given in the literature*

Pyridazine 1-oxide (**15**)[22]; 4-nitropyridazine 1-oxide (**13**)[22]; 3-methoxypyridazine 1-oxide (**18**)[23]; 6-chloro-3-methoxy-4-nitropyridazine 1-oxide (**8**)[24] and 6-chloro-3-hydroxy-4-nitropyridazine 1-oxide (**12**)[24].

b. *6-Chloro-3-methoxypyridazine 1-oxide* (**19**)

This compound being the starting substance for the preparation of **8**, was obtained from 6-chloro-3-methoxypyridazine using permaleic acid in $CHCl_3$ according to the procedure described for the preparation of 4-chloro-6-methylpyrimidine 1-oxide[25]. Yield 93‰ m.p. 160–161°C (Lit.[26]: yield 32‰ m.p. 159–161°C).

c. *3-Amino-6-chloro-4-nitropyridazine 1-oxide* (**9**)

820 mg (4.0 mmoles) of 6-chloro-3-methoxy-4-nitropyridazine 1-oxide (**8**) were dissolved in 20 ml of absolute methanol. This solution was saturated at 0°C with liquid ammonia. After 1 h at 0°C, the solvent was removed and the residue was purified by column chromatography through silica gel using chloroform as eluent. Yield 0.46 g of **9** (60%); m.p. 221–222°C (ethanol). Analysis: $C_4H_3ClN_4O_3$ (190.55) calcd. C 25.21, H 1.59; found C 25.4, H 1.8.

d. *Reduction of 3-amino-6-chloro-4-nitropyridazine 1-oxide* (**9**) *to 3,4-diaminopyridazine*

190 mg (1.0 mmole) of **9** were dissolved in 20 ml of methanol. After adding the catalyst (1.0 g of Raney nickel mixed with 0.2 g of palladium-on-charcoal) the reaction mixture was shaken in an atmosphere of hydrogen during 15 h. After removing the catalyst by filtration, the solvent was evaporated to dryness. The residue was dissolved in absolute ethanol and dry hydrogen chloride gas was led through the solution. The solution was then cooled and a sufficient amount of dry ether was added to precipitate the 3,4-diaminopyridazine hydrochloride. Yield 75 mg (51%). M.p. 198–200°C (Lit.[10] 200–201°C).


[17] *G. Illuminati*, Adv. Heterocycl. Chem., Vol. 3, p. 285 (1964).
[18] *C. A. Fyfe*, Tetrahedron Lett. **1968**, 659.
[19] *P. Bemporad, G. Illuminati* and *F. Stegel*, J. Amer. Chem. Soc. **91**, 6742 (1969).
[20] *J. A. Zoltewicz, L. S. Helmick*, J. Amer. Chem. Soc. **94**, 682 (1972).
[21] *T. Itai* and *S. Kamiya*, Chem. Pharm. Bull. **11**, 348 (1963).
[22] *T. Itai* and *S. Natsume*, Chem. Pharm. Bull. **11**, 83 (1963).
[23] *H. Igeta*, Chem. Pharm. Bull. **7**, 938 (1959).
[24] *T. Itai* and *S. Sako*, Chem. Pharm. Bull. **10**, 933 (1962).
[25] *R. Peereboom, H. C. van der Plas* and *A. Koudijs*, Recl. Trav. Chim. Pays-Bas **93**, 58 (1974).
[26] *T. Itai* and *S. Sako*, Chem. Pharm. Bull. **10**, 989 (1962).
[27] *K. Tori* and *M. Ogata*, Chem. Pharm. Bull. **12**, 272 (1964).
[28] Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, *L. M. Jackmann* and *S. Sternhell*, Pergamon Press 2nd Edition 1969, p. 134.
[29] *K. Tori, M. Ogata* and *H. Kano*, Chem. Pharm. Bull. **11**, 235 (1963).

e. *3,5-Diamino-6-chloro-4-nitropyridazine 1-oxide* (16)

200 mg (1.1 mmoles) of 3-amino-6-chloro-4-nitropyridazine 1-oxide (9) were dissolved in 50 ml of liquid ammonia at −33°C. After 10 h the ammonia was evaporated and the residue was examined by DLC (chloroform/ethyl acetate 1/1). The complicated mixture was boiled in methyl ethyl ketone and this extract was, after filtration, used for preparative DLC (tetra/ethyl acetate 2/1). Using the normal working-up procedure, 37 mg (15%) of 16 were obtained, m.p. 285–287°C. Also a small amount of 17 was isolated, m.p. 278–280°C. Reduction of the total reaction mixture, obtained in another amination experiment with 200 mg of 9, according to the procedure as given in section d, yielding, after work-up (see section d), 40 mg of 3,4,5-triaminopyridazine hydrochloride (m.p. 210–212°C; lit.[10] 212–214°C).

**Acknowledgement**

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# NMR studies on σ-adducts of heterocyclic systems with nucleophiles (Part VIII)[1] $^{13}$C-NMR data of pyridazines and some of their covalent amination products[2]

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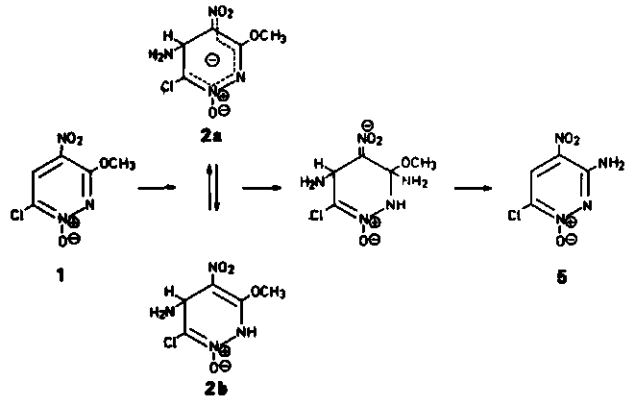
**Abstract.** $^{13}$C-NMR data of several 3-mono- and 3,6-di-substituted pyridazines, 3-, 4- and 6-mono- and 3,6-di-substituted pyridazine 1-oxides and 4-nitro-3,6-disubstituted pyridazine 1-oxides are reported. $^{13}$C substituent effects of some substituents in the 3-, 4- and 6-position of the pyridazine ring and that of the *N*-oxide function are calculated. The $^{13}$C-NMR spectra of the σ-adducts of 4-nitro-3,6-disubstituted pyridazine 1-oxides with liquid ammonia are described.

## Introduction

In our study on nucleophilic displacement reactions in pyridazines, we postulated that the amino-demethoxylation in 6-chloro-3-methoxy-4-nitropyridazine 1-oxide (1) – this reaction occurs with liquid ammonia as well as with methanolic ammonia – takes place in the initially formed σ-adduct **2**[2]. Since to the best of our knowledge no example of a nucleophilic substitution in heteroaromatics has been presented in which covalent amination precedes displacement it seemed of interest to obtain a more profound understanding of this unusual behaviour. For that purpose we started a $^{13}$C-NMR study of **1** and its adduct **2**. The study on the carbon-shielding effects in azine aromatics has been concentrated mainly on pyridine derivatives[3,4], pyrimidine derivatives[5] and mono-substituted pyrazines[6] whereas $^{13}$C-NMR spectroscopy of pyridazines and their σ-adducts has never been carried out. Hence it seemed useful to extend our study to other pyridazine derivatives. In this paper $^{13}$C-NMR data on several 3-mono- and 3,6-di-substituted pyridazines, 3-, 4- and 6-mono- and 3,6-di-substituted pyridazine 1-oxides, and 4-nitro-3,6-disubstituted pyridazine 1-oxides are reported.




*Scheme 1*

From these data the $^{13}$C substituent effects of several substitutents in the 3-, 4- and 6-position of the pyridazine ring and that of the *N*-oxide function have been calculated.

## Result and discussion

### 1. $^{13}C$ shielding and deshielding effects in 3-mono- and 3,6-di-substituted pyridazines

The $^{13}$C-NMR data of several 3-mono- and 3,6-di-substituted pyridazine derivatives are given in Table I. Most of the spectra are taken in $CDCl_3$, some in DMSO-$d_6$ depending on the solubility of the compounds. The difference of the $^{13}$C chemical shift in these solvents is generally found to be small (max. 1.0 ppm) as appears, for example, from the spectra of 4-nitropyridazine 1-oxide and of 3-methoxypyridazine 1-oxide taken in both solvents (see Table III). Spectral assignment of the $^{13}$C resonances in the pyridazine derivatives, such as in the 3-substituted pyridazines (**3**) was performed by measuring the proton-decoupled, proton-coupled and selectively proton-decoupled $^{13}$C spectrum.

*Table I Carbon-13 shifts (ppm) and coupling constants $^1J(CH)$ (Hz) of pyridazine and some of its derivatives.*

| substituent | C(3) | $^1J(CH)^c$ | C(4) | $^1J(CH)^c$ | C(5) | $^1J(CH)^c$ | C(6) | $^1J(CH)^c$ |
|---|---|---|---|---|---|---|---|---|
| none[a] | 151.9 | 180 | 126.6 | 168 | 126.6 | 168 | 151.9 | 180 |
| 3-Cl[a] | 157.4 | | 128.9[d] | 173 | 128.6[d] | 178 | 150.7 | 185 |
| 3-$OCH_3$[a] | 165.5 | | 117.3 | 170 | 129.1 | 170 | 147.5 | 183 |
| 3-$C_6H_5$[a] | 159.4 | | 123.9 | 168 | 126.9 | 167 | 150.1 | 189 |
| 3,6-di-Cl[a] | 156.3 | | 130.9 | 180 | 130.9 | 180 | 156.3 | |
| 3,6-di-$OCH_3$[a] | 162.4 | | 121.4 | 165 | 121.4 | 165 | 162.4 | |
| 6-Cl-3-$OCH_3$[a] | 164.7 | | 120.4 | 170 | 131.0 | 175 | 151.3 | |
| 6-$NH_2$-3-Cl[b] | 145.3 | | 129.1 | 175 | 117.8 | 170 | 160.5 | |

[a] $CDCl_3$; [b] DMSO-$d_6$; [c] $^1J(CH)$ means one-bond carbon to hydrogen coupling constant.
[d] Or in opposition.

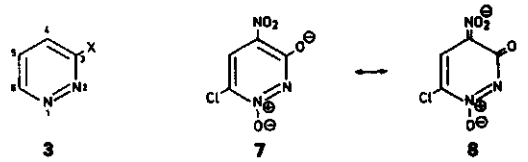



*Fig. 1*

*a.* In the proton-decoupled spectrum, C(3) is distinguishable from C(4), C(5) and C(6) by its small signal, based on the

[1] See for part VII in these series: *D. E. Klinge* and *H. C. van der Plas*, Recl. Trav. Chim. Pays-Bas **94**, 233 (1975).
[2] Part IV on pyridazines from this laboratory. See for part III, reference 1.
[3] *H. L. Retcofsky* and *R. A. Friedel*, J. Phys. Chem. **71**, 3592 (1967); **72**, 290, 2619 (1968).
[4] *H. L. Retcofsky* and *F. R. McDonald*, Tetrahedron Lett. **1968**, 2575.
[5] *J. P. Geerts, H. C. van der Plas* and *A. van Veldhuizen*, Org. Magn. Res. **7**, 86 (1975).
[6] *C. J. Turner* and *G. W. H. Cheeseman*, Org. Magn. Res. **6**, 663 (1974).

*Table II Carbon-13 substituent effects of substituted pyridazines in ppm.*

| | *Direct* effect | | | | *Ortho* effect | | | | *Meta* effect | | | | *Para* effect | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 3-X-pyridazine | benzene | 2-X-pyridine | 2-X-pyrazine | 3-X-pyridazine | benzene | 2-X-pyridine | 2-X-pyrazine | 3-X-pyridazine | benzene | 2-X-pyridine | 2-X-pyrazine | 3-X-pyridazine | benzene | 2-X-pyridine | 2-X-pyrazine |
| Substituent | | | | | | | | | | | | | | | | |
| $OCH_3$[a] | +13.6 | +31.4 | +14.2 | +15.6 | − 9.3 | −14.4 | −13.1 | − 3.4 | +2.5 | +1.0 | +1.8 | +0.8 | − 4.4 | −7.7 | − 7.6 | − 2.4 |
| Cl[a,c] | + 5.5 | + 6.2 | + 1.4 | + 4.7 | + 2.2 | + 0.4 | + 0.3 | + 0.3 | +2.1 | +1.3 | +3.0 | −0.7 | − 1.2 | −1.9 | − 0.8 | − 2.4 |
| $NH_2$[b] | + 9.8 | +18.0 | + 9.8 | +13.6 | −10.9 | −13.3 | −15.0 | −10.4 | +0.3 | +0.9 | +1.7 | −1.4 | −12.1 | −9.8 | −10.5 | −11.4 |
| $C_6H_5$[a,c] | + 7.5 | +13.1 | − | − | − 2.7 | − 1.1 | − | − | +0.3 | +0.4 | − | − | − 1.8 | −1.2 | − | − |

[a] $CDCl_3$: [b] DMSO-$d_6$; [c] *direct* effect in 4-X-pyrimidine[5]: Cl = +4.0, $C_6H_5$ = +6.9.

known phenomenon[7,8] that a carbon atom being substituted has a longer relaxation time in comparison with the one bearing a proton.

*b.* In the proton-coupled spectrum, C(3) showing no multiplicity can be easily assigned; C(6)[9] can be distinguished from C(4) and C(5) by the one-bond carbon to hydrogen coupling constant [$^1J$(CH)] since the $^1J$(CH) of a carbon adjacent to the ring nitrogen is known to be larger than the $^1J$(CH) of carbons in more remote positions from the ring nitrogen[7,8].

*c.* Selective proton decoupling experiments enabled us to assign the $^{13}$C resonances definitively. On irradiation of vH(4) the doublet assigned to C(4) collapses into a singlet; the same occurs with the doublets assigned to C(5) and C(6) on irradiation of vH(5) and vH(6), respectively.

From the $^{13}$C resonances of pyridazine and those of some monosubstituted pyridazines, we calculated the substituent effects of a chloro, methoxy and phenyl substituent at position C(3). From the difference in chemical shifts of the $^{13}$C resonances of 3-chloropyridazine and 3-amino-6-chloropyridazine we calculated the substituent effect of an amino group at C(3). The sign and the magnitude of the effects of different substituents on $^{13}$C resonances of C(3) (*direct* effect), C(4) (*ortho* effect), C(5) (*meta* effect) and C(6) (*para* effect) are summarised in Table II.

For comparison, the corresponding substituent effects in benzene[7,8], pyridines[3,4] and pyrazines[6] are included in Table II. An important conclusion which can be drawn by comparison of these results is that the magnitude of the *direct* shielding increment, specially that of the amino and methoxy groups, is much less in pyridazine than in benzene. Apparently, the ring nitrogens compete for the available electronic charge with the electron attracting substituent at C(3) leading to less electronic charge removal from C(3) than in the corresponding position in benzene. The *direct* substituent effects parallel the ones found in 2-substituted pyridines and might be considered as an indication that the additional ring nitrogen has little influence in controlling this *direct* effect on C(3). A similar conclusion has been reached for monosubstituted pyrazines[6]. The *para* substituent effect has the greatest value for the powerful electron-donating group – *i.e.* the amino group – indicating that this *para* effect is probably strongly related with the mesomeric effect of the substituent.

### 2. *The $^{13}$C shielding of the $N^+-O^-$ function in pyridazine 1-oxide derivatives*

The $^{13}$C-NMR data of pyridazine 1-oxide and some of its mono- and di-substituted derivatives are given in Table III.

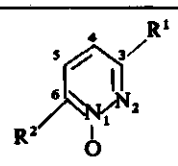
*Table III Carbon-13 shifts (ppm) and coupling constants $^1J(CH)^a$ (Hz) of pyridazine 1-oxide and some of its derivatives.*

| substituent | C(3) | $^1J$(CH) | C(4) | $^1J$(CH) | C(5) | $^1J$(CH) | C(6) | $^1J$(CH) |
|---|---|---|---|---|---|---|---|---|
| none[a] | 150.9 | 183 | 116.6 | 175 | 134.9 | 174 | 134.4 | 190 |
| 3-Cl[a] | 153.6 | | 117.8 | 180 | 135.7 | 176 | 132.9 | 200 |
| 6-Cl[a] | 148.8 | 188 | 116.5 | 180 | 135.0 | 178 | 138.6 | |
| 3-$OCH_3$[a] | 165.7 | | 107.2 | 176 | 135.9 | 170 | 127.7 | 193 |
| 3-$OCH_3$[b] | 165.4 | | 106.6 | 182 | 136.6 | 175 | 127.8 | 194 |
| 4-$NO_2$[a] | 146.0 | 196 | −[***] | | 128.5 | 186 | 134.5 | 200 |
| 4-$NO_2$[b] | 146.2 | 198 | 135.4 | | 129.5 | 184 | 135.0 | 204 |
| 6-Cl-3-$OCH_3$[a] | 164.2 | | 109.0 | 179 | 136.0 | 175 | 130.9 | |
| 6-$NH_2$-3-Cl[b] | 146.3 | | 120.1 | 178 | 118.5 | 172 | 137.0 | |

[a] $CDCl_3$; [b] DMSO-$d_6$; [c] $^1J$(CH) means one-bond carbon to hydrogen coupling constant.
[***] No signal due to low solubility.

By comparison of these data with those of the corresponding deoxygenated compounds, we calculated the influence of the $N^+-O^-$ function on the chemical shift of the ring-carbon atoms (Table IV). The data show that the carbon atoms *ortho* and *para* to the $N^+-O^-$ function *i.e.* C(6) and C(4), respectively, undergo a shielding effect, the *meta* carbon atom *i.e.* C(5) a deshielding effect, while the influence of the $N^+-O^-$ function especially at C(3) shows a relatively important variation depending on the substituent. The interesting observation was made that the set of substituent effects of the $N^+-O^-$ function obtained from the $^{13}$C-NMR data of 6-amino-3-chloropyridazine and 6-amino-3-chloropyridazine 1-oxide – on C(3) + 1.0, on C(4) – 9.0, on C(5) + 0.7 and on C(6) −23.5 – considerably deviates – especially on C(5) – from the average value of these effects calculated from Table IV: *i.e.* on C(3) −1.6, on C(4) −10.8, on C(5) +7.1, and on

*Table IV Carbon-13 substituent effect (ppm) of the N-oxide function by comparison of some pyridazines and their N(1)-oxides.*




| | C(3) | C(4) | C(5) | C(6) |
|---|---|---|---|---|
| $R^1=R^2=H$ | −1.0 | −10.0 | +8.3 | −17.5 |
| $R^1$=Cl, $R^2$=H | −3.8 | −11.0 | +7.0 | −17.8 |
| $R^1$=H, $R^2$=Cl | −1.9 | −12.2 | +6.2 | −18.8 |
| $R^1=OCH_3$, $R^2=H$ | +0.2 | −10.1 | +6.8 | −19.8 |

[7] *J. B. Stothers* in "Organic Chemistry" (*A. T. Blomquist* and *H. Wasserman* Ed.), Vol. 24, Carbon-13 NMR Spectroscopy, Academic Press, N.Y. (1972).
[8] *G. C. Levy* and *G. L. Nelson*, Carbon-13 Nuclear Magnetic Resonance for Organic Chemist. Wiley-Interscience N.Y. 1972.
[9] In case of 3-X-pyridazine 1-oxide the C(6) assignment could also be based on the fact that due to a magnetic anisotropic effect[10] the C(6) doublet in a total proton coupled $^{13}$C spectrum is always present as two broad signals. The C(4) and C(5) doublets are on the contrary sharp and always show a small $^2$J(CH).
[10] *M. J. Cook* and *A. R. Katritzky*, Adv. Heterocycl. Chem., Vol. 17 (1974).

*Table V. Carbon-13 shifts of 4-nitropyridazine 1-oxide derivatives in the solvents DMSO-$d_6$ and liquid ammonia, respectively.*

| substituent | $^{13}$C-NMR data in ppm (DMSO-$d_6$) | | | | $^{13}$C-NMR data in ppm (liquid $NH_3$) | | | |
|---|---|---|---|---|---|---|---|---|
| | C(3) | C(4) | C(5) | C(6) | C(3) | C(4) | C(5) | C(6) |
| none (4) | 146.2 | 135.6 | 129.8 | 135.0 | 147.7 | 115.8 | 45.0 | 121.4 |
| 6-Cl-3-$OCH_3$ (1) | 156.6 | 127.2 | 131.8 | 131.8 | 160.2 | 104.6 | 53.2 | 122.2 |
| 6-Cl-3-$NH_2$ (5) | 152.7 | 126.2 | 131.2 | 122.4 | 155.2 | 106.6 | 51.4 | 117.4 |
| 6-Cl-3-OH (6) | 157.7 | 127.2 | 132.4 | 129.0 | 161.0 | 120.6* | 131.2 | 129.2* |

* Or in opposition.

C(6) −18.5. Just as in the pyridazines we observed that in the pyridazine 1-oxide derivatives the difference in magnitude of $^1J$(CH) is dependent on the position of the ring-carbon atom. The $^1J$(CH) of carbons in α-position to the $N^+-O^-$ function is around 190–200 Hz, of carbons in β- and γ-position of the $N^+-O^-$ function 170–180 Hz and of carbons in δ-position of the $N^+-O^-$ function (thus α of the other ring nitrogen) 180–190 Hz (see Table III). These relatively large differences may have diagnostic value and may be very useful for spectral assignments.

The *ortho* substituent effect of a nitro group at C(4) is calculated from the $^{13}$C-NMR data of pyridazine 1-oxide and 4-nitropyridazine 1-oxide: on C(3)-4.9 and on C(5)-6.4. Its *meta* substituent effect is, in agreement with *meta* effects of other substituents, very small (+0.1).

### 3. *$^{13}$C-NMR spectra of 3,6-disubstituted 4-nitropyridazine 1-oxides and of their σ-adducts with liquid ammonia*

For the results of the measurements of $^{13}$C-resonances in several 3,6-disubstituted-4-nitropyridazine 1-oxide derivatives using DMSO-$d_6$ as solvent, see Table V. In order to be able to distinguish between several of the close-lying $^{13}$C absorptions, we applied the substituent-additivity relation rule[7,8]. When the calculated shielding increments (see Table II), exerted by the several substituents in different positions, are combined we observed that the differences between calculated shifts and measured shifts are on the average of 0–2 ppm. These differences are larger than those observed with pyrimidines[5], but they certainly are within the limit for the correct assignment of the $^{13}$C resonances. Moreover, in addition, the $^1J$(CH) confirms the assignment.

When the spectra of 4-nitropyridazine 1-oxide (4), 6-chloro-3-methoxy-4-nitropyridazine 1-oxide (1) and 3-amino-6-chloro-4-nitropyridazine 1-oxide (5) are measured in liquid ammonia at −55°, we observed that C(5) especially resonates at a much higher field than in the solvent DMSO-$d_6$. The upfield shift of C(5) amounts to about 78–85 ppm (see Table VI).

*Table VI Spectroscopic data of the compounds* 4, 1, 5 *and* 6.

| | Δδ C(5) in ppm when changing the solvent from DMSO-$d_6$ to liquid ammonia | $^1J$[C(5)H] in Hz measured in the solvent | |
|---|---|---|---|
| | | DMSO-$d_6$ | liquid $NH_3$ |
| 4 | −84.8 ppm; adduct formation | 184 Hz | 149 Hz |
| 1 | −78.6 " ; " " | 176 | 155 |
| 5 | −79.8 " ; " " | 178 | 148 |
| 6 | − 1.2 " ; anion formation | 181 | 175 |

This considerable upfield shift must be ascribed to rehybridisation of C(5) ($sp^2 \rightarrow sp^3$) due to the formation of a covalent σ-adduct at C(5) (see Scheme 1). This upfield shift value is in good agreement with the $^{13}$C shielding difference of about 90 ppm observed on adduct formation in pyrimidines. Also in accordance with this phenomenon of σ-adduct formation is the significant change of $^1J$(CH). Whereas in the compounds 1, 4, 5 a $^1J$[C(5)H] is observed of around 180 Hz, in the σ-adduct of these compounds the tetrahedral C(5) gives a $^1J$[C(5)H] of about 150 Hz (Table VI).

Parallel to the upfield shift of C(5) is that of the carbon atoms C(4) and C(6), neighbouring the $sp^3$ carbon atom; this upfield shift is much smaller (about 20 ppm for C(4), 5-14 ppm for C(6)). Whether this shielding effect has to be ascribed to the presence of a negative charge in the ring, to the hybridisation change of C(5) or to both influences, is unknown.

Dissolving 6-chloro-3-hydroxy-4-nitropyridazine 1-oxide (6) in liquid ammonia the interesting observation was made that C(5) undergoes an upfield shift of only 1.2 ppm, and that $^1J$[C(5)H] is not significantly changed. The explanation we advance is that compound 6 with ammonia does not form a σ-adduct but undergoes proton abstraction, leading to a negatively charged ion in which a nucleophilic addition is strongly hindered. The observed shift on C(4), when changing the solvent from DMSO-$d_6$ to liquid ammonia [Δδ C(4) = −6.6 ppm] is in good agreement with that proposal since in the anion a considerable part of the negative charge is present in the nitro group (see mesomeric structures 7 and 8).

## Experimental section

All carbon spectra were obtained with a Varian XL-100-15 spectrometer operating at 25.2 MHz. The spectrometer was equipped with a Varian Fourier Transform unit. The pulse separation was chosen as 2–5 s, for 4-nitropyridazine 1-oxide 20 s. The spectral width was 5000 Hz (1.25 Hz/point). In $CDCl_3$ solutions $^{13}$C-chemical shifts were measured from internal TMS, while in ammonia solutions $^{13}$C-chemical shifts were measured from internal $(CH_3)_3N$ and were converted to the TMS scale by adding 47.5 ppm. The $CDCl_3$ solvent was used as field-frequency lock; in case of liquid ammonia as solvent field-frequency lock was based on the $^{19}$F-NMR signal of a capillary of hexafluorbenzene positioned along the longitudinal axis of the 12 mm (o.d.) sample tubes employed. The probe temperature when measuring samples in liquid ammonia was −55°.

The substituent effects are given in ppm, relative to internal TMS standard; downfield shifts are indicated by a positive sign.

The techniques of preparation of the solutions in liquid ammonia has been described earlier[11].

All pyridazine compounds mentioned were prepared by procedures given in the literature[1,12].

[11] *A. Nagel, H. C. van der Plas* and *A. van Veldhuizen*, Recl. Trav. Chim. Pays-Bas **94**, 45 (1975).

[12] *R. N. Castle*, Pyridazines. The Chemistry of Heterocyclic Compounds Vol. 28, Wiley-Interscience N.Y. 1973.

# Ring transformations in reactions of heterocyclic halogeno compounds with nucleophiles (XXXVI)[1] Conversion of 4-amino-3-halogenopyridazines into pyrazoles and of 4-amino-3,6-dihalogenopyridazines into 1,2,4-triazoles[2]

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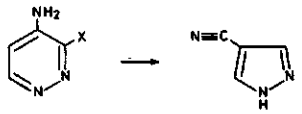
**Abstract.** On treatment of 4-amino-3-X-pyridazine (X=Cl, Br) with potassium amide in liquid ammonia 4-cyanopyrazole is formed. Under the same reaction conditions 4-amino-3,6-di-X-pyridazine (X=Cl, Br) undergoes a ring contraction into 3-(cyanomethyl)-1,2,4-triazole.
The mechanism of both ring contractions is discussed.

## I. Introduction

In this laboratory it has been found that aza- and diazaaromatics which contain a halogen substituent on a carbon atom in an α-position to the ring nitrogen, as well as an amino group in the β-position, undergo ring contraction on treatment with potassium amide in liquid ammonia[3]. Examples of these ring contractions are the conversions of 3-amino-2-bromopyridine into 3-cyanopyrrole[4], of 3-amino-2-bromoquinoline into 3-cyanoindole[5], and of 5-amino-4-chloro-2-phenylpyrimidine into 4(5)-cyano-2-phenylimidazole[6]. A characteristic feature of all these reactions is that the novel heterocyclic ring which is formed on ring contraction contains the same number of ring nitrogen atoms as the starting substance (pyridine → pyrrole, quinoline → indole, pyrimidine → imidazole). In our study on reactions of halogenopyridazines with potassium amide, we became interested to find out whether 4-aminohalogenopyridazines also would undergo ring contraction on treatment with potassium amide.

## II. Treatment of 4-amino-3-halogenopyridazines with potassium amide

Treatment of 4-amino-3-X-pyridazine (**1**, X=Cl) with a sixfold molar amount of potassium amide in liquid ammonia at −33°C, yields a compound A of which the IR spectrum features at 3250 $cm^{-1}$ a NH-stretching vibration absorption and at 2230 $cm^{-1}$ the stretching vibration of a CN group; the PMR spectrum of a solution of A (acetone-d6) shows a singlet at δ = 8.26 ppm (2H) and a broad absorption at δ = 6.86 ppm[7] (1H); in the mass spectrum the parent peak was observed at *m/e* = 93 and a fragmentation peak at *m/e* = 66 (loss of HCN). Based on these data, the structure of 4-cyanopyrazole (**3**) was assigned to compound A. This structure assignment was proved to be correct on comparison with an authentic specimen (Scheme 1).




**1** X=Cl
**2** X=Br

**3**

*Scheme 1*

The same ring contraction was also observed with 4-amino-3-X-pyridazine (**2**, X=Br); the yield of **3** was somewhat enhanced. Both reactions provide us with novel interesting examples of a potassium amide catalysed ring contraction and underline the general reaction pattern, which has been discussed above with other azines.
Although there are several base-catalysed ring contractions of *N*-substituted pyridazines known in literature[8] *e.g.:* the conversion of 3,5-dichloro (and 4,5-dichloro)-1-phenyl-6-(1*H*)-pyridazone into the 3-hydroxy-1-phenylpyrazole-5-

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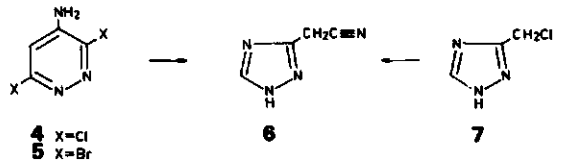
[1] Previous paper in these series: *H. J. den Hertog, H. Boer, J. W. Streef, F. C. A. Vekemans* and *W. J. v. Zoest*, Recl. Trav. Chim. (Pays-Bas) **93**, 195 (1974).
[2] Part II on pyridazines from this laboratory. See for part I: *D. E. Klinge, H. C. van der Plas* and *A. Koudijs*, Recl. Trav. Chim. (Pays-Bas) **93**, 201 (1974).
[3] For a review on ring transformations of azines see *H. C. van der Plas*, Lectures in Heterocyclic Chem., Vol. II, S-83 1974.
[4] *H. J. den Hertog, R. J. Martens, H. C. van der Plas* and *J. Bon*, Tetrahedron Lett. **1966**, 4325.
[5] *H. J. den Hertog* and *D. J. Buurman*, Tetrahedron Lett. **1967**, 3657.
[6] *H. W. van Meeteren* and *H. C. van der Plas*, Tetrahedron Lett. **1966**, 4517.
[7] We are indebted to Mrs. *P. Cohen-Fernandes* of the Gorlaeus Laboratory at Leiden for providing with the IR spectrum and the PMR spectrum of 4-cyanopyrazole.
[8] *H. C. van der Plas*, "Ring transformations of Heterocycles" Vol. 2. Academic Press (London and New York) 1973.

carboxylic acid[9] (a recent report suggests a pyridazyne as intermediate[10]), the ring transformation of 4,5-dibromo-1-phenyl-6(1*H*)-pyridazone into the 4-hydroxypyrazole derivative[11] and the conversion of 4-hydroxy-2-methyl-1-phenyltetrahydropyridazine-3,6-dione into the 5-pyrazolone-3-carboxylic acid[12], the ring contraction of pyridazines, in which no group is attached to the nitrogen, into pyrazoles is without precedent.

### III. Treatment of 4-amino-3,6-dihalogenopyridazines with potassium amide

When reacting 4-amino-3,6-dichloropyridazine (**4**) or 4-amino-3,6-dibromopyridazine (**5**) with potassium amide in liquid ammonia, from both reaction mixtures a compound could be isolated to which we assigned the structure of 3-(cyanomethyl)-1,2,4-triazole (**6**). The structure evidence for **6** is based on: *a* its IR spectrum which showed absorptions at 3250 $cm^{-1}$ (NH) and at 2265 $cm^{-1}$ (CN); *b* its PMR spectrum (acetone-d6) which revealed a singlet at $\delta = 8.4$ ppm (1H), a singlet at $\delta = 4.0$ ppm (2H) and an unsharp NH-absorption at $\delta = 11.5$ ppm; *c* its mass spectrum which showed a parent peak at $m/e = 108$ and a fragmentation peak at $m/e = 81$ (loss of HCN); *d* mixed melting point determination with an authentic specimen – prepared from 3-(chloromethyl)-1,2,4-triazole (**7**) with potassium cyanide – showing no depression (Scheme 2).

The conversion of a pyridazine ring into a triazole is unprecedented and is very unusual since it is in fact the *first* example of a potassium amide catalysed ring contraction in which the number of ring nitrogen atoms in the product formed is increased in comparison with that of the starting material.

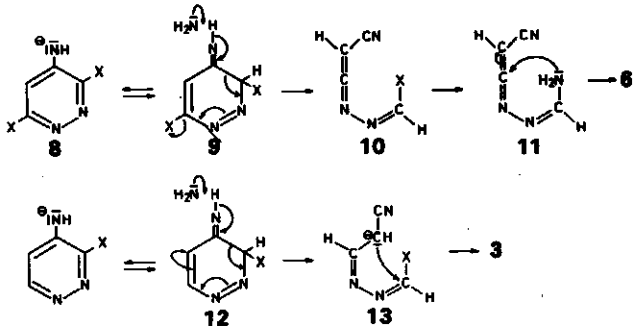



*Scheme 2*

### IV. Discussion

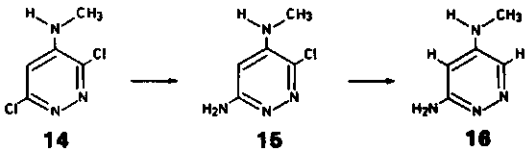
Considering the mechanism of the ring contraction reactions the interesting question arises why in case of **1** and **2** a pyrazole ring, in case of **4** and **5** a 1,2,4-triazole ring, is produced.

Following previous suggestions we assume that in the ring contraction of the pyridazine ring into the 1,2,4-triazole ring the first step is the base-catalysed deprotonation of the amino group into the anion **8**, being possibly in equilibrium with its C-conjugated acid **9**. A further deprotonation of the imino group with subsequent fission of the C(3)–C(4) bond and loss of a halogen anion yields the (cyanoketenimino)-imidoyl halogenide **10**. This highly reactive imidoyl halogenide is converted into the amidrazone **11** which can easily cyclise into **6** by addition of the amino group across the azomethine bond in the ketenimino group. This mechanism can explain why the 4-amino-3-halogeno compounds **1** and **2** do not give a 1,2,4-triazole, but a pyrazole. The ring cleavage of **12** *cannot* lead to an intermediate with a ketenimine structure but gives the carbanion **13**. The ring cyclisation occurs now by a nucleophilic attack of this carbanion moiety to the imidoyl halogenide function leading to a pyrazole; it must be concluded that the ring cyclisation occurs at a faster rate than replacement of the halogen atom by an amino group (Scheme 3).




*Scheme 3*

These ring contractions can only occur when the pyridazine ring is substituted at position 4 with a group containing *two* hydrogens easily split off in this strong basic medium (*e.g.* an $NH_2$ group). This has been proved by studying the reaction of 3,6-dichloro-4-(methylamino)pyridazine (**14**) with potassium amide. No ring contraction reaction was observed even when an extremely high potassium amide concentration was used. Only 6-amino-3-chloro-4-(methylamino)-pyridazine (**15**) was formed.

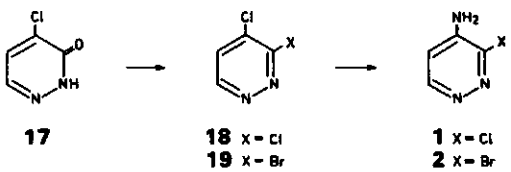



*Scheme 4*

That **15** and not the isomeric 3-amino-6-chloro-4-(methylamino)pyridazine was obtained was proved by dehalogenation with hydrogen and palladium-on-charcoal yielding compound **16**. Structure **16** was identified by PMR-spectroscopy, showing two doublets at $\delta = 7.97$ ppm (H(3)) and at $\delta = 5.85$ ppm (H(5)), both with coupling constant of 2.6 cps, clearly a *meta*-coupling[13] (Scheme 4).

### V. Syntheses of the starting substances 1, 2, 4 and 5

The amino compounds **1** and **2** were prepared as given in Scheme 5. **18** as well as **19**, obtained on treatment of the 4-chloro-3-pyridazone (**17**) with phosphorus pentachloride or phosphorus pentabromide, respectively, are rather unstable compounds; they were not isolated but immediately converted into **1** or **2**, respectively, by heating with ethanolic ammonia.




*Scheme 5*

[9] *T. Takahashi, N. Furukawa* and *Y. Maki*, Yakugaku Zasshi **86**, 867 (1966).
[10] *Y. Maki* and *G. P. Beardsley*, Tetrahedron **1971**, 1507.
[11] *F. Kuhelj, B. Stanovnik* and *M. Tisler*, Croat. Chem. Acta, **38**, 299 (1966).
[12] *J. Druey, K. Meier* and *A. Staehelin*, Pharm. Acta Helv. **38**, 498 (1963); *K. Dury*, Angew. Chem. **77**, 282 (1965).
[13] *K. Tori* and *M. Ogata*, Chem. Pharm. Bull. **12**, 272 (1964).

It was found that the 4-amino-3-bromopyridazine (**2**) is not quite pure, but contains according to the mass spectrum about 10% of an amino-chloropyridazine, probably 3-amino-4-chloropyridazine. This was proved by reduction of the reaction mixture by hydrogen and palladium-on-charcoal: besides 4-aminopyridazine, about 10% of 3-aminopyridazine was shown to be present in the reaction mixture by PMR spectroscopy. Attempts to synthesize compound **2** by bromination of 4-aminopyridazine with HBr and $H_2O_2$, using the same procedure[14] as given in the literature for the chlorination of 3-aminopyridine to 3-amino-2-chloropyridine, failed. A compound was formed which according to its PMR, IR and mass spectrum was 4-amino-5-bromopyridazine (**22**).

In the PMR spectrum of **22** we did *not* observe a coupling constant between H(3) and H(6). In the literature divergent values for $J_{3,6}$ are reported (1.38 cps[15] and 3.5 cps[13,16]). In order to evaluate the influence of an 4-amino group on the magnitude of the $J_{3,6}$ we prepared the reference compound 4-amino-5-chloropyridazine in the same way as described in the literature[17]. A compound[18] was obtained, m.p. 120°C (lit.[17] 73°C), m.p. picrate 212°C (lit.[17] 212°C), the PMR spectrum of which also showed no coupling between H(3) and H(6).

Compound **5** was obtained by heating 3,4,6-tribromopyridazine (**20**) or 3,6-dibromo-4-chloropyridazine (**21**) with ethanolic ammonia at about 100°C; the same procedure was used for the preparation of **4** from 3,4,6-trichloropyridazine[19].

## Experimental part

Melting points are uncorrected. The PMR spectra were recorded on a Jeol JNM C-60 H spectrometer. The spectra were taken in acetone-d6 or $CDCl_3$ using tetramethylsilane (TMS, $\delta = 0$) as an internal standard; when the spectrum is taken in $D_2O$, sodium 3-(trimethylsilyl)propane-1-sulfonate ($\delta = 0$) was the internal standard (see for PMR data section 5). The IR spectra were recorded with a Hitachi model EPI-G3, and the massspectra with an AEI MS 902 instrument.

### 1. Preparation of the starting and reference compounds

*a)* The following compounds were prepared by the procedures given in the literature:

4-amino-3,6-dichloropyridazine (**4**)[20], and 3,6-dichloro-4-(methylamino)pyridazine (**14**)[21].

b) *4-Amino-3-chloropyridazine* (**1**)

1.0 g (6.7 mmoles) of 3,4-dichloropyridazine (**18**)[22] was dissolved in 12 ml of absolute ethanol. This solution was saturated at 0°C with ammonia and then heated in a sealed tube for 6 h at 125°C. The solvent was removed and the residue was extracted with boiling ethyl acetate. After evaporation of the solvent the residue was purified by column chromatography through silica gel using a mixture of ethyl acetate and methanol (10 : 1) as eluent, yielding 450 mg of **1** (52%), m.p. 140–142°C (lit.[23] 141–142.5°C). Analysis: $C_4H_4ClN_3$ (129.55) calc. C 37.08, H 3.11; found C 36.5, H 3.1.

c) *4-Amino-3-bromopyridazine* (**2**)

1.0 g (7.7 mmoles) of 4-chloro-3-pyridazone (**17**)[22] and 1.66 g (3.8 mmoles) of phosphorus pentabromide were intensively mixed at 100°C during 3 h. After cooling, the reaction mixture was added in small portions at a time to crushed ice. This solution was made alkaline with 2*N*-ammonia while the temperature was kept below 5°C. The alkaline aqueous solution was extracted with chloroform. After drying over anhydrous magnesium sulfate, the chloroform was removed and 1.1 g of crude **19** remained.

This compound was very unstable and was used immediately for its conversion to 4-amino-3-bromopyridazine (**2**). The reaction and the purification was carried out according to the same procedure as given in section 1b. The yield of product obtained was 280 mg. However the compound was not pure (m.p. 114–118°C), about 10% of 3-amino-4-chloropyridazine was present (see section V). The reaction with potassium amide was studied with this somewhat impure product.

d) *3,6-Dibromo-4-chloropyridazine* (**21**)

20.0 g (136 mmoles) of 4-chloro-3,6-pyridazinedione[19] and 40.0 g (93 mmoles) of phosphorus pentabromide were well mixed and heated on the steam bath for 8 h. The reaction mixture was cooled to −10°C and added in small portions at a time to a mixture of ammonia (2*N*) and ice. The pH was kept at about 8 and the temperature was not allowed to rise above 0°C. The crude product was filtered off and washed successively with 25 ml of 1*N*-sodium hydroxide solution at 0°C, and with cold water. The precipitate was intensively dried *in vacuo* over phosphorus pentoxide, followed by extraction in a Soxhlet apparatus for 2 days with petroleum ether (b.r. 60–80°C). The solvent was removed and the residue was distilled at 140°C/3 mm. Yield of **21**, 27.7 g (74%), m.p. 62.5–64°C. Analysis: $C_4HBr_2ClN_2$ (272.35) calc. C 17.64, H 0.37, N 10.29; found C 17.9, H 0.8, N 10.3.

e) *3,4,6-Tribromopyridazine* (**20**)

15.0 g (102 mmoles) of 4-chloro-3,6-pyridazinedione[19] were heated during 3 h at 140°C with 65.0 g (226 mmoles) of phosphoryl bromide. After cooling to 0°C, the reaction mixture was carefully poured out on to ice and made alkaline with an 28% aqueous solution of ammonia. The precipitate was collected, washed with water and distilled with steam. The crystals were filtered off and dried over anhydrous magnesium sulfate. Yield 18.0 g of **20** (56%), m.p. 95–96°C. Analysis: $C_4HBr_3N_2$ (316.81) calc. C 15.16, H 0.32, N 8.84; found C 15.5, H 0.6, N 8.8.

f) *4-Amino-3,6-dibromopyridazine* (**5**)

1) 1.0 g (3.1 mmoles) of 3,4,6-tribromopyridazine (**20**) and 15 ml of ethanolic ammonia, saturated at 0°C, were heated in a sealed tube at 100°C for 2 h. The contents of the tube were evaporated to dryness *in vacuo*. The residue was recrystallized from aqueous ethanol. Yield 0.5 g of **5** (64%), m.p. 225–226°C. Analysis: $C_4H_3Br_2N_3$ (252.92) calc. C 18.99, H 1.20, N 16.62; found C 19.3, H 1.1, N 16.4.

2) 1.0 g (3.7 mmoles) of 3,6-dibromo-4-chloropyridazine (**21**) was submitted to the same procedure as described in section 1f-1; the reaction time was 5 h instead of 2 h. After recrystallization from aqueous ethanol the yield of **5** was 0.55 g (60%), m.p. 225–226°C.

g) *3-(Cyanomethyl)-1,2,4-triazole* (**6**)

3.0 g (25.5 mmoles) of 3-(chloromethyl)-1,2,4-triazole (**7**)[24] were dissolved in 20 ml of 96% ethanol and added dropwise to a solution of 2.5 g (39 mmoles) of potassium cyanide in 30 ml of water. This solution was refluxed for 2 h. After dilution with 50 ml of water, the solution obtained was neutralized with concentrated sulfuric acid and continuously extracted with ether during 4 days. The ethereal solution was dried over anhydrous magnesium sulfate. After evaporation of the solvent 1.18 g (40%) of **6** remained, m.p. 137–139°C (from toluene). Analysis: $C_4H_4N_4$ (108.10) calc. C 44.44, H 3.73; found C 44.2, H 3.5.

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[14] *O. von Schickh, A. Binz* und *A. Schulz*, Ber. **69**, 2593 (1936).
[15] *V. M. S. Gil* and *A. J. L. Pinto*, Mol. Phys. **16**, 623 (1969); Physical Methods in heterocyclic chemistry *A. R. Katritzky*, Vol. IV, Academic Press (New York and London) 1971.
[16] Applications of nuclear magnetic resonance spectroscopy in organic chemistry. *L. M. Jackmann* and *S. Sternhell*, Pergamon Press 2nd Edition 1969.
[17] *T. Kuraishi* and *R. N. Castle*, J. of Heterocyclic Chem. **1**, 42 (1964).
[18] Analysis: $C_4H_4ClN_3$ (129.55) calc. C 37.08, H 3.11; found C 37.2, H 3.2.
[19] *R. H. Mizzoni* and *P. E. Spoerri*, J. Amer. Chem. Soc. **76**, 2201 (1954).
[20] *T. Kuraishi*, Chem. Pharm. Bull. **4**, 137 (1956).
[21] *R. Schönbeck* und *E. Kloimstein*, Monatsh. Chem. **99**, 15 (1968).
[22] *M. Yanai* and *T. Kinoshita*, Yakugaku Zasshi **85**, 344 (1965).
[23] *M. Yanai* and *T. Kinoshita*, Yakugaku Zasshi **82**, 857 (1962).
[24] *R. G. Jones* and *C. Ainsworth*, J. Amer. Chem. Soc. **77**, 1538 (1955).

**2. Reactions of the halogenopyridazines 1, 2, 4, 5 and 14 with potassium amide in liquid ammonia**

a) *4-Amino-3-chloropyridazine* (1)

130 mg (1 mmole) of **1** were treated during 11 h with a solution of potassium amide in 50 ml of liquid ammonia ($[KNH_2] = 0.12$) at −33°C. The reaction was terminated by addition of ammonium chloride and the ammonia was evaporated. The residue was extracted with ethyl acetate, dried over anhydrous magnesium sulfate and the solvent was removed. Yield: 47 mg of 4-cyanopyrazole (**3**) (50%). After sublimation m.p. 89–90°C (lit. [25] 91–92°C).

b) *4-Amino-3-bromopyridazine* (2)

174 mg (1 mmole) of **2** were treated with potassium amide as described in section 2a, except that the reaction time was 6 h instead of 11 h. Yield: 62 mg of 4-cyanopyrazole (**3**) (67%). After sublimation, m.p. 89–90°C (lit. [25] 91–92°C).

c) *4-Amino-3,6-dichloropyridazine* (4)

164 mg (1 mmole) of **4** were treated during 18 h at −33°C with a solution of potassium amide in 75 ml of liquid ammonia ($[KNH_2] = 0.16$) at −33°C. After working up as usual the residue was extracted five times with 100 ml of boiling ether. The ether was distilled off *in vacuo*. Yield 26 mg of 3-(cyanomethyl)-1,2,4-triazole (**6**) (24%), m.p. 137–139°C (from toluene). This melting point was not depressed when mixed with an authentic specimen of **6** (section 1g). Also the IR and PMR spectra were identical with those of compound **6**.
Analysis: $C_4H_4N_4$ (108.10); calc. C 44.44, H 3.73; found: C 44.7, H 3.5.

d) *4-Amino-3,6-dibromopyridazine* (5)

253 mg (1 mmole) of **5** were treated with potassium amide as described in section 2c, except that the potassium amide concentration was 0.12 instead of 0.16, and that the reaction time was only 5 h. Yield 63 mg of 3-(cyanomethyl)-1,2,4-triazole (**6**) (60%), m.p. 137–139°C (from toluene).

e) *3,6-Dichloro-4-(methylamino)pyridazine* (14)

178 mg (1 mmole) of **14** were treated during 28 h at −33°C with a solution of potassium amide in 20 ml of liquid ammonia. ($[KNH_2] = 0.65$) at −33°C. After termination of the reaction and evaporation of the ammonia, the residue was extracted extensively with 50 ml of dry ether in a Soxhlet apparatus. The ether was removed *in vacuo*. Yield 100 mg of 6-amino-3-chloro-4-(methylamino)pyridazine (**15**) (63%), m.p. 190–191°C (from benzene). Analysis: $C_5H_7ClN_4$ (158.60); calc. C 37.86, H 4.45; found C 37.7, H 4.5. PMR data: δH(5) = 5.97 ppm (s), $\delta N-CH_3$ = 2.85 ppm (d, $J$ = 5 cps), $\delta NH_2$ and δNH = 5.5 ppm (broad).

[25] *S. Trofimenko*, J. Org. Chem. **28**, 2755 (1963).

3. *3-Amino-5-(methylamino)pyridazine* (16)

To 117 mg (0.74 mmoles) of **15** in 4.5 ml of ethanol and 4.5 ml of acetic acid were added 300 mg of sodium acetate. This solution was reduced by hydrogen using 25 mg of palladium-on-charcoal as catalyst. To complete the reduction, after 1 h a second amount of 25 mg of catalyst was added. When the hydrogen-taken up ceased, the catalyst was filtered off and the solution was evaporated to dryness. Extraction of the residue afforded 57 mg of **16** (62%), m.p. 205–206°C. Analysis: $C_5H_8N_4$ (124.15) calc. C 48.37, H 6.50; found C 48.3, H 6.7.

4. *4-Amino-5-bromopyridazine* (22)

To a solution of 475 mg (5 mmoles) of 4-aminopyridazine[20] in 15 ml of 47–50% hydrobromic acid were added slowly 7 ml of 15% hydrogen peroxide at 80°C. After 1½ h at 80°C, the solution was made alkaline with sodium hydrogen sulfite, followed by dilute ammonia. This mixture was extracted with ethyl acetate. The solvent was removed, yielding 330 mg of **22** (38%), m.p. 134–136°C (from benzene); m.p. picrate 216–217°C. Analysis: $C_{10}H_7BrN_6O_7$ (403.12) calc. C 29.79, H 1.75; found C 30.5, H 2.1.

5. *Table Chemical shifts of the ring protons (expressed in δ) of some di- and tri-substituted pyridazines.*

| Pyridazine derivative | H(3) | H(4) | H(5) | H(6) | $J$ in cps |
|---|---|---|---|---|---|
| 4-Cl-3-one (17)[a] | | | 7.66 (d) | 7.84 (d) | $J_{5,6}$ = 4.5 |
| 3,4-di-Cl (18)[b] | | | 7.69 (d) | 9.09 (d) | $J_{5,6}$ = 5.1 |
| 4-$NH_2$-3-Cl (1)[a] | | | 6.97 (d) | 8.60 (d) | $J_{5,6}$ = 5.5 |
| 4-$NH_2$-3-Br (2)[a] | | | 7.00 (d) | 8.60 (d) | $J_{5,6}$ = 5.5 |
| 4-$NH_2$-5-Br (22)[a] | 8.79* | | | 8.84* | |
| 4-$NH_2$-5-Cl[a] | 8.65* | | | 8.73* | ** |
| 4-Cl-3,6-dione[c] | | | 7.09 | | |
| 4-Cl-3,6-di-Br (21)[b] | | | 7.84 | | |
| 3,4,6-tri-Br (20)[b] | | | 8.00 | | |
| 4-$NH_2$-3,6-di-Br (5)[a] | | | 7.09 | | |
| 3,4,6-tri-Cl[a] | | | 8.18 | | |
| 4-$NH_2$-3,6-di-Cl (4)[a] | | | 6.94 | | |
| 3,6-di-Cl-4-$NHCH_3$ (14)[a] | | | 6.81 | | |
| 3-Cl-4-$NHCH_3$-6-$NH_2$ (15)[a] | | | 5.97 | | |
| 3-$NH_2$-5-$NHCH_3$ (16)[a] | | 5.85 (d) | | 7.97 (d) | $J_{4,6}$ = 2.6 |

[a] Solvent acetone-d6.
[b] Solvent $CDCl_3$.
[c] Solvent $D_2O$.
* The assignment of the proton chemical shift was based on the reasonable assumption that the H(3)-atom, being adjacent to the amino group, appears at a higher field than the H(6)-atom.
** In the PMR spectrum of 4-$NH_2$-5-Cl-pyridazine recorded on a Varian XL-100 (acetone-d6), we observed a small coupling constant: $J_{3,6}$ = 0.65 cps.

**Acknowledgement**

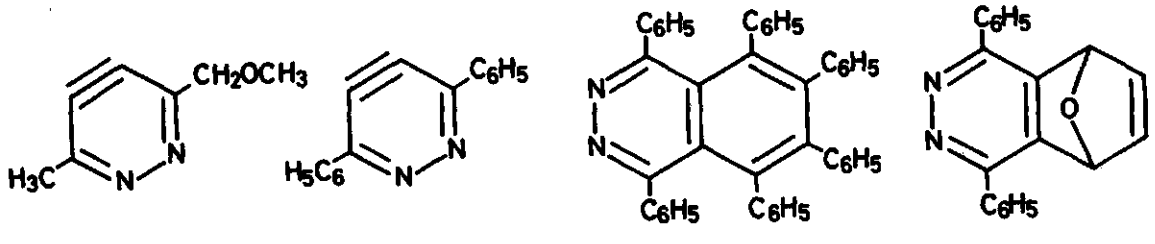
We are indebted to Drs. *C. A. Landheer* for mass spectroscopic data, to Mr. *W. P. Combé* for carrying out the microanalyses, to Mr. *A. van Veldhuizen* for measuring PMR and IR spectra and to Mr. *N. Rensen* for taking part in some of the experiments.

# Discussion

As already pointed out in the introduction, at the start of our work conclusive evidence for the intermediacy of a 4,5-didehydropyridazine has never been presented[1,2]. In this thesis experiments are described proving unequivocally the transient existence of a 4,5-didehydropyridazine. This evidence is based on the results of two investigations:

a. Amination of 4-X-3-(methoxymethyl)-6-methylpyridazine (X=Cl,Br,I) gives an isomeric mixture of 4- and 5-amino-3-(methoxymethyl)-6-methylpyridazine in a ratio of 1 : 5, which ratio is found to be *independent* of the nature of the halogen atom. This can only be explained if a 3-(methoxymethyl)-6-methyl-4,5-didehydropyridazine (1) occurs as intermediate. The favoured addition of the amide ion to C(5) in (1) is due to the stronger electron-attracting character[3] of the methoxymethyl group as compared to that of the methyl group (Paper I)[4].

b. Amination of 4-chloro-3,6-diphenylpyridazine-5-$^{13}$C gives two products i.e. 4-amino-3,6-diphenylpyridazine-(4,5)-$^{13}$C and imino-4,4'-bis(3,6-diphenyl-pyridazine)-(4,4')(5,5')-$^{13}$C. Using quantitative $^{13}$C-NMR spectroscopy, the distribution of the $^{13}$C-label over the positions 4 and 5 in the 4-amino compound and over the positions 4,4' and 5,5' in the coupled product was calculated. Since in both compounds an exact 1 : 1 distribution[5] over these positions was found the result was considered as sound evidence for the existence of a 4,5-didehydropyridazine i.e. 3,6-diphenyl-4,5-didehydropyridazine (2)(Paper II)[6].




1 2 3 4

*FIGURE 1*

When our work was completed, it was reported[7] that the thermal fragmentation reaction of 4,5,8-triphenylpyridazino [4,5-d] triazine also leads to the intermediary 3,6-diphenyl-4,5-didehydropyridazine (2). This was proven by interception of this intermediate with tetracyclone and with furan yielding respectively, after CO-evolution, 1,4,5,6,7,8-hexaphenylphthalazine (3) and 5,8-epoxy-5,8-dihydro-1,4-diphenylphthalazine (4).

From these results it is evident that the 4-chloropyridazines react towards potassium amide in liquid ammonia quite similar to the 3- and 4-chloropyridines.

This leads to the conclusion that in 4-chloropyridazines the dehydrohalogenation is thus strongly favoured above addition reactions, which are characteristic for the 4-chloropyrimidines and the 2-chloropyrazines. The high acidity of position 4(5) of the pyridazine ring[8] in comparison with that of the position 3(6) is in agreement with this conclusion.

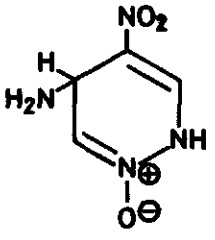
The study of the σ-adduct formation[9] between pyridazine derivatives and *weak* nucleophiles (liquid ammonia and methanolic ammonia) has indicated that the presence of a nitro group in the pyridazine ring is a necessary structural requirement.

Data on the position of adduct formation were furnished by using $^{1}$H-NMR (Paper III)[10] and $^{13}$C-NMR spectroscopy (Paper IV)[11]. From these data it is clear that the attack of ammonia takes place at C(5), see structure (5). This is in agreement with the position of adduct formation between the parent compound pyridazine and the strong nucleophile potassium amide[12]. The assignments are essentially based on the important upfield shift of the H(5) proton absorption ($\Delta\ \delta \approx 4$ ppm) and of the C(5) carbon absorption ($\Delta\ \delta \approx 80$ ppm). Both shifts are due to the change of hybridisation of C(5) ($sp^2 \rightarrow sp^3$) when the adduct is formed. Based on this spectroscopic method 4-nitropyridazine 1-oxide was observed to give an adduct, unlike pyridazine and pyridazine 1-oxide. Apparently the pyridazine ring needs the highly electron-attracting nitro group to make the ring susceptible for attack with weak nucleophiles[13-15]. Hydrogen bridge formation between the nitro group at C(4) and the incoming amino group is certainly one of the important factors which determines the position of attack of the nucleophile.

Furthermore it was proven that addition at C(5) also occurs when 6-chloro-3-methoxy-4-nitropyridazine 1-oxide is dissolved in liquid ammonia or in methanolic ammonia. A surprising fact is observed when these solutions were kept for 1 h at 0°. A nucleophilic displacement occurs in which not the nitro group is replaced, as is usually observed in reactions of this compound with other nucleophiles (methoxy, mercapto or azido ion), but the methoxy group, yielding the new compound 3-amino-6-chloro-4-nitropyridazine 1-oxide. From the spectroscopic data and the structure of the amination product it was suggested that this amino-demethoxylation must take place *in* the σ-adduct (6) via the diadduct (7). Examples of this type of nucleophilic substitution have never been observed before. This new mechanism certainly deserves great attention and needs to be investigated in more detail to determine its potentially broad scope and its general applicability in highly activated systems.

Application of $^{1}$H- and $^{13}$C-NMR spectroscopy furnishes the evidence of the presence of the σ-adduct (8) in a solution of 3-amino-6-chloro-4-nitropyridazine

1-oxide in both liquid ammonia and in methanolic ammonia. This adduct slowly converts into 6-chloro-3,5-diamino-4-nitropyridazine 1-oxide and into 6-chloro-3,5-diamino-4-nitropyridazine. It was observed by the same technique,however, that 6-chloro-3-hydroxy-4-nitropyridazine 1-oxide does not give a σ-adduct, but undergoes deprotonation of its hydroxyl group, yielding the anion (9) which provides the nucleus with an electron density strongly inhibiting the additions of nucleophiles (Papers III and IV)[10,11].

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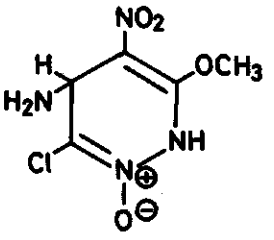


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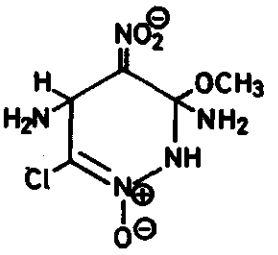


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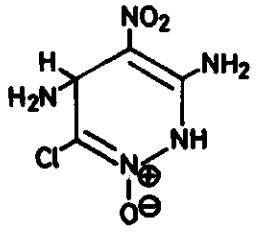


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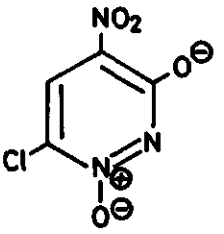


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*FIGURE 2*

Finally the occurrence of two new ring contractions[16] of pyridazines was observed in reactions with the amide ion.

a. Treatment of 4-amino-3-bromo(chloro)pyridazine by potassium amide yields 4-cyanopyrazole. The mechanism of this ring contraction is somewhat similar to the one already given in the introduction for the conversion of 3-amino-2-bromo-pyridine into 3-cyanopyrrole[17] and of 5-amino-4-chloro-2-phenylpyrimidine into 4(5)-cyano-2-phenylimidazole[18].

b. The conversion of 4-amino-3,6-dibromo(chloro)pyridazine into 3-(cyano-methyl)-1,2,4-triazole. This ring contraction is novel and unprecedented and has the interesting feature that in the ring contraction product the number of ring nitrogen atoms, in comparison with that of the starting substance, has increased. This is in contrast to all the previously reported examples of ring contractions, in which the number of ring nitrogen atoms in starting substance and ring contraction product is the same.

The mechanisms of both ring contractions have been discussed extensively in paper V[19]. It was proven that a substituent with *two* acid-labile hydrogen atoms ($NH_2$ group) is a necessary structural requirement for the occurrence of these ring contractions; no ring contraction was observed when a methylamino group is present instead of the amino group. In that case only with an extremely high

concentration of potassium amide, a substitution of the chloro atom at C(6) slowly occurred. This unusually low reactivity of the chloro atom at position 3(6) towards potassium amide is observed[20-22] in many 3-chloro-6-X-pyridazines (X=H, Cl, $OCH_3$, $C_6H_5$) and is quite surprising compared to the high reactivity of 2-chloropyridine, 4-chloropyrimidine and 2-chloropyrazine[23-25]. A reason for this deviating behaviour is not quite clear and certainly needs more study. A possible explanation may be that the lone-pair nitrogen $sp^2$-orbitals interact, leading to a decreased reactivity at position 3(6)[3,26]. Alternatively it cannot be excluded that ring deprotonation by potassium amide occurs, yielding an anion which makes a nucleophilic attack unfavourable. However, no proof of this possibility could be obtained by $^1$H-NMR or $^{13}$C-NMR measurements.

REFERENCES


1. a) Th.Kauffmann and A.Risberg, Tetrahedron Lett. 1963, 1459;
   b) Th.Kauffmann et al., ibid. 1964, 3563.
2. a) Y.Maki and M.Takaya, Chem.Pharm.Bull.of Japan 20, 747 (1972);
   b) Y.Maki, G.P.Beardsley, Tetrahedron Lett. 1971, 1507.
3. R.W.Hoffmann "Dehydrobenzene and cycloalkynes", Academic Press, New York (1967).
4. D.E.Klinge, H.C.van der Plas and A.Koudijs, Recl.Trav.Chim.Pays-Bas 93, 201 (1974).
5. J.D.Roberts, H.E.Simmons, L.A.Carlsmith and C.W.Vaughan, J.Amer.Chem.Soc. 75, 3290 (1953).
6. D.E.Klinge and H.C.van der Plas, Recl.Trav.Chim.Pays-Bas 95, 34 (1976).
7. Th.L.Gilchrist, G.E.Gymer and Ch.W.Rees, J.Chem.Soc.Perkin I 1975, 1747.
8. J.A.Zoltewicz, G.Grahe and C.L.Smith, J.Amer.Chem.Soc. 91, 5501 (1969).
9. M.J.Strauss, Chem.Rev. 70, 662 (1970).
10. D.E.Klinge and H.C.van der Plas, Recl.Trav.Chim.Pays-Bas 94, 233 (1975).
11. D.E.Klinge, H.C.van der Plas and A.van Veldhuizen, Recl.Trav.Chim.Pays-Bas 95, 21 (1976).
12. J.A.Zoltewicz, L.S.Helmick, J.Amer.Chem.Soc. 94, 682 (1972).
13. G.Illuminati "Advances in Heterocyclic Chemistry", Ed. A.R.Katritzky, Vol.3, Academic Press, New York (1964).
14. C.A.Fyfe, Tetrahedron Lett. 1968, 659.
15. P.Bemporad, G.Illuminati and F.Stegel, J.Amer.Chem.Soc. 91, 6742 (1969).
16. H.Igeta and T.Tsuchiya, J.Synth.Org.Chem.Japan 31, 867 (1973).
17. H.J.den Hertog et al., Tetrahedron Lett. 1966, 4325.
18. H.W.van Meeteren and H.C.van der Plas, Tetrahedron Lett. 1966, 4517.

19. D.E.Klinge, H.C.van der Plas, G.Geurtsen and A.Koudijs, Recl.Trav.Chim. Pays-Bas 93, 236 (1974).
20. D.E.Klinge, Unpublished results.
21. E.A.Steck, J.Org.Chem. 24, 1597 (1959).
22. W.E.Taft, J.Adams and W.V.Curran, J.Org.Chem. 26, 605 (1961).
23. H.C.van der Plas "Ring Transformations of Heterocycles", Vol.I and II, Academic Press, New York (1973).
24. H.C.van der Plas "Lectures in Heterocyclic Chemistry", Ed. R.N.Castle and E.F.Elslager, Vol.II (1974).
25. H.C.van der Plas and J.W.Streef "Aromatic and Heteroaromatic Chemistry", Vol.IV (1976), The Chemical Society, London.
26. S.F.Mason, Chem.Soc.Special Publ. No.12 (1958).

# Samenvatting

In dit proefschrift is een orienterend onderzoek beschreven naar het chemisch gedrag van halogeen-pyridazinen en halogeen-pyridazine-N-oxiden met kaliumamide in vloeibare ammoniak, met methanolische ammoniak en met vloeibare ammoniak. Dit onderzoek hangt nauw samen met uitvoerige studies over de reactiviteit van pyridinen, pyrimidinen en pyrazinen, die de afgelopen jaren in het laboratorium voor Organische Chemie te Wageningen zijn verricht.
De resultaten van het door ons uitgevoerde onderzoek zijn in een vijftal publikaties verwerkt en laten zich als volgt samenvatten:

Publikatie I: 4-X-3-(methoxymethyl)-6-methylpyridazine (X=Cl, Br, I) geeft na aminering een mengsel van 4- and 5-amino-3-(methoxymethyl)-6-methylpyridazine (verhouding 1 : 5); het is gebleken dat deze verhouding onafhankelijk is van de aard van het halogeen atoom. Daarom wordt als intermediair in deze reactie het 3-(methoxymethyl)-6-methyl-4,5-didehydropyridazine aangenomen.

Publikatie II: De reactie van 4-chloor-3,6-difenylpyridazine met kaliumamide in vloeibare ammoniak levert twee produkten op, namelijk 4-amino-3,6-difenylpyridazine en imino-4,4'-bis(3,6-difenylpyridazine). Uitgaande van 4-chloor-3,6-difenylpyridazine-$[5\text{-}^{13}C]$ werd, door middel van quantitatieve $^{13}C$-NMR spectrometrie, van beide aminoverbindingen aangetoond dat zij gevormd zijn via het symmetrisch intermediair 3,6-difenyl-4,5-didehydropyridazine.

De resultaten vermeld in I en II geven voor het eerst zeer gefundeerde aanwijzingen voor het bestaan van een intermediair 3,6-digesubstitueerd 4,5-didehydropyridazine in reacties van 3,6-digesubstitueerde 4-halogeenpyridazinen met kaliumamide in vloeibare ammoniak.

Publikatie III: In de reactie van 6-chloor-3-methoxy-4-nitropyridazine 1-oxide met methanolische ammoniak en met vloeibare ammoniak treedt amino-demethoxylering op. Met behulp van $^{1}H$-NMR metingen kon worden aangetoond dat deze substitutie op een zeer ongewone wijze verloopt, n.l. *in* het op C(5) gevormde Meisenheimer complex.

Publikatie IV: Van verschillende 3-mono- en 3,6-digesubstitueerde pyridazinen, 3-, 4- en 6-mono- en 3,6-digesubstitueerde pyridazine 1-oxiden en 4-nitro-3,6-digesubstitueerde pyridazine 1-oxiden zijn de $^{13}$C-absorpties bepaald. Hieruit werden de $^{13}$C-substituent effecten van substituenten in de 3-, 4- en 6-positie van de pyridazine ring en die van de N-oxide functie berekend. Door toepassing van deze substituent effecten konden de $^{13}$C-NMR spectra van de σ-adducten van 4-nitro-3,6-digesubstitueerde pyridazine 1-oxiden met vloeibare ammoniak worden geinterpreteerd.

Uit de resultaten van de $^{1}$H-NMR en $^{13}$C-NMR metingen vermeld in III en IV kon zeer duidelijk worden vastgesteld dat 3-methoxy-4-nitropyridazine 1-oxiden een nucleofiele substitutie op C(3) kunnen ondergaan volgens een mechanisme, dat tot nu toe niet eerder in de literatuur is beschreven.

Publikatie V: Bij de behandeling van 4-amino-3-X-pyridazine (X=Cl, Br) met kaliumamide in vloeibare ammoniak wordt 4-cyaanpyrazool gevormd. Onder dezelfde reactie omstandigheden ondergaat 4-amino-3,6-di-X-pyridazine (X=Cl, Br) een ringcontractie tot 3-(cyaanmethyl)-1,2,4-triazool.

De in V beschreven ringcontractie tot 4-cyaanpyrazool kan worden beschouwd als een nieuw voorbeeld van een reactie, die reeds in andere ringsystemen beschreven is. De in V beschreven ringcontractie tot 3-(cyaanmethyl)-1,2,4-triazool is echter het eerste voorbeeld van een door kaliumamide gekatalyseerde ringcontractie, waarbij het gevormde vijfringsysteem *meer* stikstofatomen bevat dan het oorspronkelijke zesringsysteem.

Bij het verschijnen van dit proefschrift gaat mijn dank uit naar mijn promotor Prof.Dr.H.C.van der Plas voor zijn stimulerende invloed en enthousiaste begeleiding;
naar mevrouw M.Snell en de heer A.Schuchhard voor het verzorgen van het manuscript;
en naar alle leden van de vakgroep Organische Chemie voor de prettige samenwerking.

# Curriculum vitae

Na het behalen van het diploma HBS-B te Utrecht in 1961, heb ik de militaire dienstplicht vervuld. In 1963 begon ik met de scheikunde studie aan de Rijksuniversiteit te Utrecht. Het kandidaatsexamen (letter g) werd afgelegd in april 1968; het doctoraalexamen, onder leiding van Prof.Dr.J.F.Arens (hoofdvak:organische chemie) en Prof.Dr.Ir.P.M.Heertjes (bijvak:chemische technologie, Technische Hogeschool Delft) in juni 1970.

Van september 1970 tot augustus 1975 ben ik als wetenschappelijk medewerker verbonden geweest aan het Laboratorium voor Organische Chemie van de Landbouwhogeschool te Wageningen, waar onder leiding van Prof.Dr.H.C.van der Plas het onderzoek voor dit proefschrift werd verricht.

Sinds augustus 1975 ben ik als docent schei- en natuurkunde verbonden aan de "Opleiding voor middelbaar en hoger laboratoriumpersoneel STOVA" te Wageningen.