Hydrazination of Pyridazines and Phthalazines [1,2]

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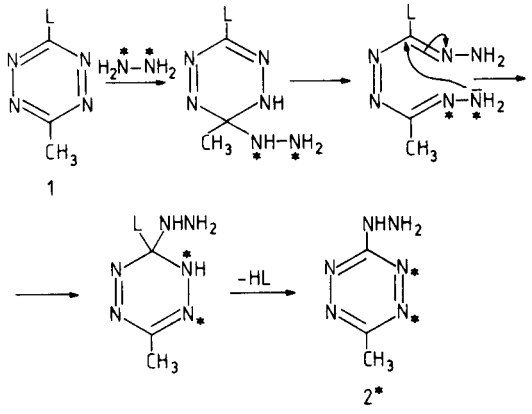
Received January 3, 1983

It is shown by ^{15}N-labelling techniques that hydrazination of pyridazines partly occurs according to a reaction pathway, involving addition of the nucleophile (hydrazine), ring opening and ring closure (S_N(ANRORC)-mechanism). It is also proved that phthalazines undergo hydrazination without ring opening (S_N(AE)-mechanism).

J. Heterocyclic Chem., **20**, 1259 (1983).

In a preceding paper [3] we reported the occurrence of S_N(ANRORC)^{ipso} mechanism [4] during hydrazination of 1,2,4,5-tetrazines. This mechanism has been elucidated by use of ^{15}N-labelling studies. The course of the reaction is exemplified in Scheme 1. 3-L-6-Methyl-1,2,4,5-tetrazine (**1**) undergoes first addition of ^{15}N-labelled hydrazine at C-6, whereafter ring opening and ring closure take place. It leads to the 3-hydrazino-6-methyl-1,2,4,5-tetrazine (**2***), in which the hydrazino group contains nitrogen atoms originally present in the tetrazine ring.



Only a minor part of the tetrazine molecules follow the S_N(ANRORC) pathway (**1**, L = Cl, 7%; **1**, L = Br, 19%; **1**, L = NH_2, 25%) [3]. The main part of **1** reacts according to the S_N(AE)^{ipso} pathway. In extending this work we became interested whether other (less reactive) diazines, containing the two nitrogen atoms in vicinal position, would also react with hydrazine according to the S_N(ANRORC) pathway. In this paper we deal with a ^{15}N-study of the hydrazination of some pyridazines and phthalazines.

Results and Discussion.

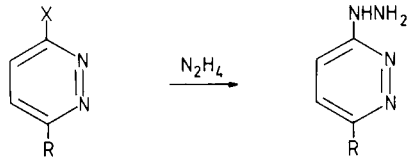
The compounds investigated were the 3-chloro- and 3-bromopyridazines (**3a-c**), the 1-chloro-, 1-bromo- and 1-iodophthalazines (**5a-d**) and 1-aminophthalazine (**5e**). The compounds were prepared according to known procedures; when the procedure of preparation was improved, it is described in the experimental section.

The hydrazination was carried out by reacting ^{15}N-double labelled pyridazines with unlabelled hydrazine and unlabelled pyridazines with ^{15}N-double labelled hydrazine in order to check if both methods give the same results. In the phthalazine series, labelled phthalazines **5a***-**5e*** were reacted with unlabelled hydrazine. In order to establish whether the nitrogen-15 is present in the exocyclic hydrazino group or in the diazine ring, the hydrazino group was reduced to an amino group by Raney nickel and hydrogen [5].

In Scheme 3 the expected position of the nitrogen-15 label is visualized, when a ring-labelled pyridazine **3*** [6] follows the S_N(ANRORC) pathway or the S_N(AE) pathway. When the hydrazination follows exclusively, the S_N(ANRORC) pathway the ^{15}N-label is only present in the exocyclic hydrazino group of **4** (*i.e.* **4B***) and after reduction, in the amino group of **7** (*i.e.* **7B***). Mass spectrometry of the amino compound **7*** will show that the excess of nitrogen-15 (as calculated from the M + 1 peak) is the same as originally present in the M + 2 peak of double labelled pyridazine **3***. If **3*** reacts exclusively according to the S_N(AE) pathway, the label remains in the ring and the M + 2 peak of **7** will contain the *same* excess of nitrogen-15 as present in the M + 2 peak of **3***. When both mechanisms operate the percentage S_N(ANRORC) mechanism is calculated from % S_N(ANRORC) = (M + 1)/[(M + 1) + (M + 2)] × 100%, in which M + 1 and M + 2 represent the excess of nitrogen-15, calculated from the intensity of the M + 1 and M + 2 peaks. When the hydrazination is carried out with ^{15}N-labelled hydrazine and unlabelled pyridazine the percentage S_N(ANRORC) mechanism is calculated from % S_N(ANRORC) = (M + 2)/[(M + 1) + (M + 2)] × 100%.

Quite similarly the hydrazination of the double labelled phthalazines **5*** with unlabelled hydrazine was studied. The presence of nitrogen-15 in the hydrazino group of **6*** was established by measuring the excess of nitrogen-15 as M + 1 in the amino compound **8***, obtained by reduction of the hydrazino group in **6*** by Raney nickel and hydrogen.

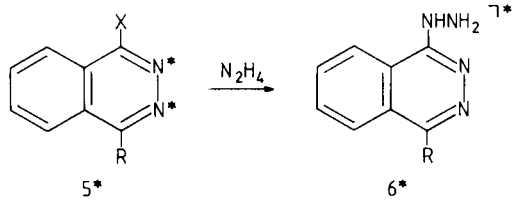
The results of the ^{15}N-studies on the hydrazination are summarized in Tables I and II.



3 4

a) X= Br, R= H
b) X= Br, R= CH_3
c) X= Cl, R= CH_3

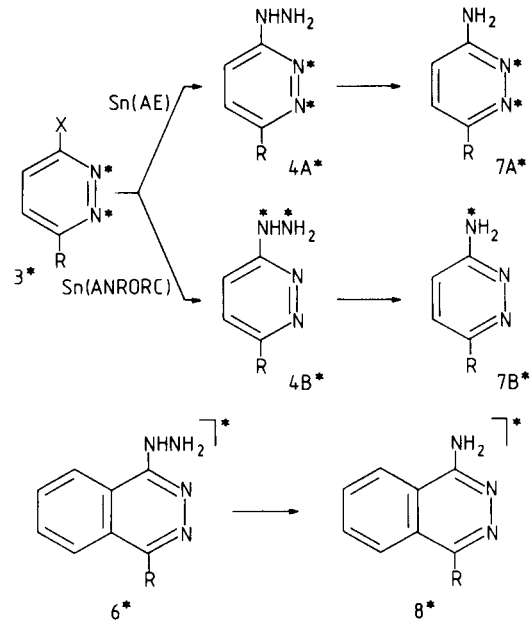
a) R= H
b) R= CH_3



5* 6*

a) X= Cl, R= H
b) X= Cl, R= CH_3
c) X= Br, R= H
d) X= I , R= H
e) X= NH_2, R= H

a) R= H
b) R= CH_3



3* 4A* 7A* 4B* 7B* 6* 8*

From these results it becomes evident that hydrazination of the pyridazines **3a-3c** occurs for only $\leq 30\%$ by the S_N(ANRORC) process. This result has also been found with the 1,2,4,5-tetrazines (**1**), but is in contrast to the amination of the halogenopyrimidines [7], halogenopteridines [8a] and halogeno-1,2,4-triazines [8b] with the strong nucleophilic amide ion, in which the S_N(ANRORC) pathway is the major route. The 3-bromo compound **3b** reacts faster than the 3-chloro compound **3c** (27% for **3b**, 17% for **3c**). The same tendency is found in the 3-L-6-methyl-1,2,4,5-tetrazines **1** (19% for **1**, L = Br, 7% for **1**, L = Cl) [3]. Comparison of the percentage S_N(ANRORC) for the 3-bromo compounds **3a** and **3b** show that the presence of a methyl group at position 6 does not influence this percentage considerably. The S_N(ANRORC) is initiated by addition of the hydrazine at C-6.

It is very likely that the remaining part of the compounds **3a-3c** will react according to the S_N(AE) pathway. The results, summarized in Table II, make it clear that the phthalazines **5*** do not react into the corresponding 1-hydrazino compounds **6*** with ring opening. The M + 2 excess of **6*** was due to a label *in* the ring, as the amino compounds **8*** contain the *same* excess of M + 2. They all react according to the S_N(AE) pathway. Whether the complete absence of a ring opening reaction during the hydrazination is due to the non-occurrence of an addition at C-4 (the initial step in the S_N(ANRORC) mechanism) or to the non-occurrence of ring opening, if the adduct at C-4 has been formed, is unclear [9].

EXPERIMENTAL

Melting points are uncorrected. Mass spectra were determined on an AEI 902 mass spectrometer. The ^{1}H-nmr spectra were recorded on an

Table I

Labelling Studies of Pyridazines
^{15}N excess [a] in compounds **7***, % S_N(ANRORC)

Starting Compound	Reagent	7* (M + 1) (%)	7* (M + 2) (%)	S_N(ANRORC) (%)	S_N(ANRORC) Average (%)
3a	$*NH_2$-$*NH_2$	4.9	2.2	31	30
3a	$*NH_2$-$*NH_2$	5.3	2.2	29	
3b	$*NH_2$-$*NH_2$	5.6	2.6	32	27
3b*	NH_2-NH_2	1.4	5.1	22	
3c	$*NH_2$-$*NH_2$	7.6	1.5	17	17
3c*	NH_2-NH_2	0.9	4.9	16	

[a] Accuracy ±0.5%.

Table II

Labelling Studies of Phthalazines
^{15}N excess [a] in compounds **6*** [b] and **8***, % S_N(ANRORC)

Substrate	6* M + 2	6* M + 1	8* M + 2	8* M + 1	% S_N(ANRORC)
5a*	5.0	0.3	5.1	0.4	0
5c*	5.0	0.3	5.0	0.4	0
5d*	5.0	0.3	5.0	0.5	0
5e*	4.8	0.4	4.7	0.4	0
5b*	5.0	0.3	5.3	0.4	0

[a] Accuracy ±0.2%. [b] The phthalazin-3-ones, the starting substances for the preparation of **5*** have double ^{15}N-labelling for 5% (M + 2) and mono ^{15}N-labelling for 0.3% (M + 1).

Hitachi-Perkin Elmer R-24B spectrometer. Tetramethylsilane was used as internal standard (δ 0 ppm). Column chromatography was performed on Merck silica gel 60 (70-230 mesh ASTM). ^{15}N-Hydrazine-hydrate from Prochem was used. It contained 95 atom % of $^{15}N_2$ and was a 24.6% solution of ^{15}N-hydrazine-hydrate in water. This was mixed with unlabelled hydrazine-hydrate (100%, from Merck). To prepare the starting compounds with the ^{15}N label in the heteroaromatic ring ^{15}N-hydrazine sulfate from VEB Berlin-Chemie (Berlin Adlershof) was used, it contained 10.2% $^{15}N_2$ and 0.6% ^{15}N.

Preparation of Starting materials and Reference Compounds.

3-Bromopyridazine (**3a**) [10], 3-bromo-6-methylpyridazine (**3b**) [10], 3-chloro-6-methylpyridazine (**3c**) [11], 3-amino-6-methylpyridazine (**7**), R = CH_3) [5], 1-chloro[2,3-di-^{15}N]phthalazine (**5a***) [12], 1-chloro-4-methyl-[2,3-di-^{15}N]phthalazine (**5b***) [13] and 1-iodo[2,3-di-^{15}N]phthalazine (**5d***) [14] were prepared according to published procedures.

1-Bromo[2,3-di-^{15}N]phthalazine-1(2*H*)-one (**5c***).

[2,3-Di-^{15}N]phthalazin-1(2*H*)-one (0.5 g) [15] was reacted with 5 g of phosphorus oxybromide at 130° during 30 minutes. To the mixture 55 g of crushed ice was added and then 55 ml of 2*N* aqueous sodium hydroxide solution. The product was filtered off, yield 58%, mp 176-178° (lit [16] 175°).

3-Bromo-6-methyl[1,2-^{15}N]pyridazine (**3b***).

This compound was prepared from 6-methyl[1,2-^{15}N]pyridazin-3(2*H*)-one [10], obtained by reacting 1 g of ethyl 4-oxopentanoate with a solution of 0.93 g of ^{15}N-labelled hydrazine sulfate and 3 g of sodium acetate in 10 ml of water. The solution was boiled for 2.5 hours. All the further steps are carried out by the procedure as given in [10] and [11].

1-Aminophthalazine (**5e**).

This compound was prepared from 1-hydrazinophthalazine (for the preparation see below) and Raney nickel and hydrogen, analogously to the procedure given for the preparation of 3-amino-6-methylpyridazine from 3-hydrazino-6-methylpyridazine [5]. The reaction was carried out in a Parr apparatus and the reduction time was 1 night. The amino compound was isolated by column chromatography on silica gel with chloroform/5% methanol as eluent; yield 50%, mp 210-212° (lit [12] 212-213°).

3-Aminopyridazine (**7**, R = H).

This compound was obtained by Raney nickel/hydrogen reduction of hydrazino compound **4a** (see reference [5]), reaction time, 2.5 hours. Isolation by column chromatography on silica gel with chloroform/5% methanol as eluent, mp 174-176° (lit [10] 172°).

Hydrazinolysis Reactions:

a) Halogenopyridazines.

Halogenopyridazines **3** or **3*** (1 mmole) was dissolved in 0.5 ml of butanol and 2 mmoles of hydrazine-hydrate were added. The mixture was refluxed during 4 hours and evaporated to dryness. Based on nmr, 80% of the chloro compound was converted to the hydrazino compound; the bromo compounds were converted for 100%. The hydrazino compounds **4** were compared with samples prepared according to literature procedures [5,17].

b) Halogenophthalazines.

Halogenophthalazine **5*** (1 mmole) in 0.6 ml of ethanol and 10 mmoles of hydrazine-hydrate were refluxed during 2 hours. After cooling the hydrazino compound was filtered off [18].

c) Aminophthalazine.

A solution of 1 mmole of **5e*** in 0.6 ml of ethanol and 10 mmoles of hydrazine-hydrate were refluxed during 20 hours. After cooling the hydrazino compound was filtered off [19].

Acknowledgement.

We thank Mr. R. van der Molen and Mr. H. Jongejan for carrying out some experiments and Drs. C. A. Landheer for the mass spectrometric data.

REFERENCES AND NOTES

[1] Part 31 on the S_N(ANRORC) mechanism. For part 30 see Henk C. van der Plas, Valery N. Charushin and Beb van Veldhuizen, *J. Org. Chem.*, **40**, 1354 (1983).

[2] Part 9 on pyridazines from this laboratory. For part 8 see H. Hara and H. C. van der Plas, *J. Heterocyclic Chem.*, **19**, 1205 (1982).

[3] A. Counotte-Potman, H. C. van der Plas, A. van Veldhuizen and C. A. Landheer, *J. Org. Chem.*, **46**, 5102 (1981).

[4] H. C. van der Plas, *Acc. Chem. Res.*, **11**, 462 (1978); H. C. van der Plas, "Lectures in Heterocyclic Chemistry", Vol VI, S1-S23, R. N. Castle and T. Kappe, eds, HeteroCorporation, Tampa, FL, 1982.

[5] C. A. Barlin and C. Y. Yap, *Aust. J. Chem.*, **30**, 2319 (1977).

[6] An asterix indicates that the compound is (possibly) labelled with nitrogen-15.

[7] A. P. Kroon, H. C. van der Plas and G. van Garderen, *Rec. Trav. Chim.*, **93**, 325 (1974).

[8a] J. Nagel and H. C. van der Plas, *Tetrahedron Letters*, 2021 (1978); [b] A. Rykowski and H. C. van der Plas, *Rec. Trav. Chim.*, **92**, 449 (1973).

[9] A similar pattern has been observed in the amination of 2-chloro-3,6-diphenylpyrazine into 2-amino-3,6-diphenylpyrazine by treatment with potassium amide in liquid ammonia. It has been proved that in this reaction addition of the amide ion initially occurs at C-5; this adduct does not undergo ring opening. The product is formed by addition of the amide ion at C-2, followed by rapid chloride ion expulsion. The addition at C-5 seems kinetically controlled. P. J. Lont, H. C. van der Plas and A. van Veldhuizen, *ibid.*, **92**, 708 (1973).

[10] G. Grundman, *Chem. Ber.*, **81**, 1 (1948).

[11] W. G. Overend and L. F. Wiggins, *J. Chem. Soc.*, 239 (1947).

[12] C. M. Atkinson, C. W. Brown and J. C. E. Simpson Sr., *ibid.*, 1081 (1956).

[13] E. M. F. Stephenson, *ibid.*, 1913 (1963).

[14] N. Hirsch and D. G. Orphanos, *Can. J. Chem.*, **44**, 1551 (1966).