A. D. Counotte-Potman and H. C. van der Plas

Laboratory of Organic Chemistry, Agricultural University, Wageningen, The Netherlands

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Evidence is presented that the hydrazinolysis of 3-amino- (**5**) and 3-bromo-6-methyl-1,2,4,5-tetrazine (**7**) into the 3-hydrazino-6-methyl-1,2,4,5-tetrazine (**6***) with ^{15}N-labelled hydrazine leads to incorporation of ^{15}N in the 1,2,4,5-tetrazine ring. Thus in the hydrazino-deamination and hydrazino-debromination a SN(ANRORC) mechanism is operative. Based on quantitative mass spectrometry it was found that 20-25% of both **5** and **7** reacts according to this SN(ANRORC) mechanism. The mechanism of these degenerate ring transformations is discussed.

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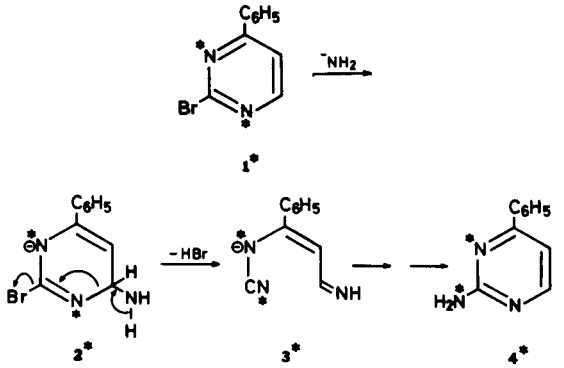
In our laboratory there is a continuing interest in the mechanism of reactions between nucleophiles and nitrogen-containing aromatics (1). The nucleophiles used in these studies are the amide ion (2), lithium piperidide (3), carbanions (4), phenyllithium (5), ammonia (6), hydrazine (7), hydroxylamine (8) and amidines (9). On studying the amino-dehalogenation in ^{15}N-labelled halogenopyrimidines we have discovered that, when potassium amide in liquid ammonia is used as aminating agent, as a general reaction pattern one of the ring nitrogens becomes exocyclic in the amino group and the nitrogen of the amide ion is built into the ring. An example of this degenerate ring transformation (10) is the formation of 2-amino-4-phenylpyrimidine (**4***) from 2-bromo-4-phenylpyrimidine (**1***) (11) (Scheme I). The reaction can be described to occur by attack of the amide ion on C_6, yielding the anionic 1:1 σ-adduct **2***. This adduct undergoes a base-catalysed ring opening into the *N*-cyano derivative **3***, which cyclizes into **4***. This mechanism is called the SN(ANRORC) mechanism (12). This mechanism is also found to occur – although to a lesser extent – with the weak nucleophile ammonia (13). All SN(ANRORC) reactions which occur with potassium amide and/or ammonia have in common that a one-atom piece of the original ring is replaced by the nitrogen atom of the nucleophile. Very recently examples of degenerate ring transformations became known in which a replacement of a two- and even a three-atom segment of the ring by two or three atoms of the nucleophile takes place. Thus it has been proven that in the reaction of 1-methylpyrimidinium iodide with benzamidine (9) in the formed 2-phenylpyrimidine the N_1-C_2-N_3 fragment of the ring originates from the amidine. With these results in mind we became interested whether hydrazine would be able to perform nucleophilic substitutions according to the SN(ANRORC) mechanism. For this reason a study was started on the reaction of substituted 1,2,4,5-tetrazines with hydrazine hoping to obtain evidence that during the hydrazinolysis two vincinal nitrogens of the *ring* of the substrate could be replaced by two nitrogens of hydrazine.

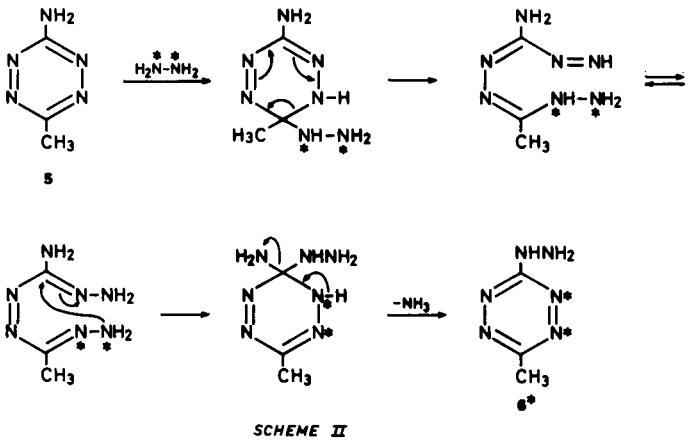


SCHEME I

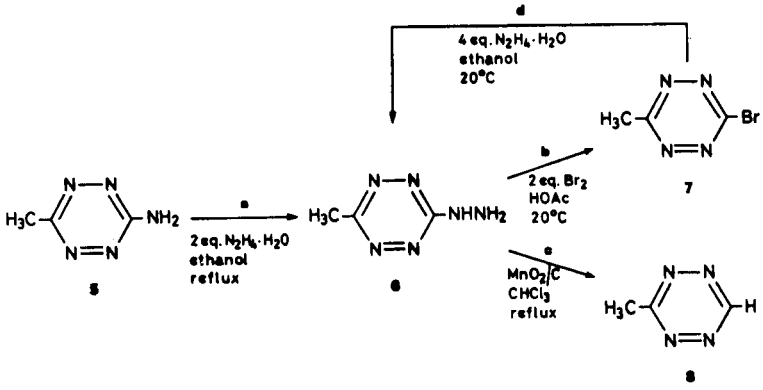
In this preliminary communication we would like to present the first results obtained in our study of the reactions of 3-amino-6-methyl-1,2,4,5-tetrazine (**5**) and 3-bromo-6-methyl-1,2,4,5-tetrazine (**7**) with hydrazine.

Hydrazinolysis of 3-Amino-6-methyl-1,2,4,5-tetrazine (**5**).

3-Amino-6-methyl-1,2,4,5-tetrazine (**5**) was prepared as described in the literature (14). Refluxing an ethanolic solution of **5** containing two equivalents of hydrazine hydrate gave in about 50% yield 3-hydrazino-6-methyl-1,2,4,5-tetrazine (**6**), characterized as its benzaldehyde hydrazone (15), besides a small amount of unreacted **5** (reaction **a**, Scheme III). In order to investigate if in this hydrazinodeamination a ring-opening is involved [SN(ANRORC) mechanism], we studied this reaction with ^{15}N labelled hydrazine.



SCHEME II



SCHEME III

It is evident from Scheme II (16) that in case the S_N(ANRORC) mechanism is operative the tetrazine ring in the final product **6*** will contain ^{15}N. To measure the amount of ^{15}N in the tetrazine ring we had to remove the hydrazino group in **6***. Because 3-hydrazino-6-methyl-1,2,4,5-tetrazine (**6**) is unstable and thus difficult to purify we used the crude reaction mixture containing unreacted **5** and the labelled product **6*** and converted **6*** into 3-bromo-6-methyl-1,2,4,5-tetrazine (**7***) by treatment with bromine in glacial acetic acid (17) (reaction **b**, Scheme III). 3-Amino-6-methyl-1,2,4,5-tetrazine (**5**) did not react with bromine under these conditions as was checked in a control experiment.

To be absolutely sure that in this oxidative bromination *no* ring-opening was involved we also applied a second method *i.e.* the oxidative removal of the hydrazino group on **6*** by manganese dioxide on carbon (18), yielding 3-methyl-1,2,4,5-tetrazine (**8***) (reaction **c**, Scheme III). Also this second method leaves **5** unchanged under the reaction conditions applied.

The percentage of ^{15}N in **6***, **7*** and **8*** was determined by quantitative mass spectrometry comparing the M+2 peak of the double ^{15}N-labelled compounds **6***, **7*** and **8*** with that of the unlabelled reference compounds **6**, **7** and **8** (19). The percentage of compound **5** which reacts according to the S_N(ANRORC) mechanism was calculated by dividing the percentage of ^{15}N in **7*** or **8*** by that of **6***. The results of these measurements are summarized in Table I (see reaction sequence 1 and 2).

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

Hydrazinolysis of 3-Bromo-6-methyl-1,2,4,5-tetrazine (**7**).

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

Table I

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

EXPERIMENTAL

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

Double ^{15}N-labelled Hydrazine Hydrate.

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

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

The reactions with ^{15}N-labelled materials were carried out as described below for the reactions with unlabelled compounds.

Hydrazinolysis of 3-Amino-6-methyl-1,2,4,5-tetrazine (**5**) (Reaction **a**, Scheme III).

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

3-Bromo-6-methyl-1,2,4,5-tetrazine (**7**) (Reaction Sequence **a**, **b**, Scheme III).

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

Anal. Calcd. for $C_3H_3BrN_4$: C, 20.59; H, 1.73. Found: C, 20.74; H, 1.67.

3-Methyl-1,2,4,5-tetrazine (**8**) (Reaction Sequence **a**, **c**, Scheme III).

This compound was prepared from **5** by hydrazinolysis and subsequent oxidation. The hydrazinolysis of **5** occurs in the same way as described above. After evaporation of the benzene-layer obtained by extraction of the reaction mixture (2 mmoles of **5** with hydrazine hydrate), the residue was dissolved in 10 ml. of chloroform and 525 mg. of manganese dioxide on carbon (18) were added. After refluxing this mixture during 1 hour the manganese dioxide on carbon was filtered off and the product was adsorbed on silica gel. 3-Methyl-1,2,4,5-tetrazine (**8**) was obtained by column chromatography on silica gel using ether-petroleum-ether (40-60°) as eluent. After careful removal of most of the solvent we obtained a red, highly volatile oil, still containing some eluent. Pmr (deuteriochloroform): δ 3.10 (s, 3H, CH_3), 10.27 (s, 1H, H); M^+, m/e = 96. Exact mass measurements gave for $C_3H_4N_4$ (M^+) 96.043608 (theoretical 96.043594). Attempts to characterize **8** by a picrate, a chloroaurate or a quaternary salt failed.

Anal. Calcd. for $C_3H_4N_4$: C, 37.49; H, 4.20. Found: C, 36.98; H, 3.96.

Acknowledgement.

We are indebted to Drs. C. A. Landheer, Drs. G. J. Ensing and Mr. W. P. Combé for mass spectrometric data and to Mr. H. Jongejan for carrying out the microanalyses.

REFERENCES AND NOTES

(1) For Part XIX on the SN(ANRORC) mechanism from this laboratory, see C. A. H. Rasmussen and H. C. van der Plas, *Rec. Trav. Chim.*, 1978 in press.

Table II

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

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

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(15) I. Ya. Postovskii, A. P. Novikova and V. A. Ershov, *Zh. Org. Khim.*, **6**, 1104 (1970).

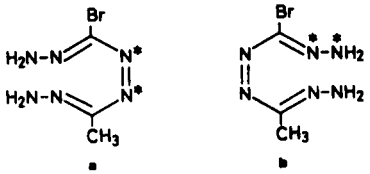
(16) The ^{15}N-labelled compounds are distinguished from the unlabelled ones by an asterix.

(17) V. A. Ershov and I. Ya. Postovskii, *Khim. Geterotsikl. Soedin.*, 7, 571 (1971).

(18) L. A. Carpino, *J. Org. Chem.*, **35**, 3971 (1970).

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

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



SCHEME IV

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