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# Identification of 2-chloropyrazine oxidation products and several derivatives by multinuclear magnetic resonance

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**$^{1}$H, $^{13}$C, $^{14}$N and $^{15}$N NMR chemical shifts were used to prove the structures of the products of 2-chloropyrazine oxidation. It was shown that oxidation by hydrogen peroxide in acetic acid or *m*-chloroperbenzoic acid leads to the *N*4-oxide, whereas potassium persulfate in sulfuric acid gives the *N*1-oxide as the main product. Additionally, the results of NMR measurements of products from the nucleophilic substitution of the chlorine atom by azide anion, yielding the respective azides, and ethylation reactions of both 2-chloropyrazine *N*-oxides leading to the *N*-ethyl salts confirm the structures of both isomeric *N*-oxides. Protonation studies of the compounds obtained are also reported. The favoured protonation site is found to be the N atom that is not hindered by any substituents, and in some cases probably the oxygen atom of the *N*-oxide function. Copyright © 2003 John Wiley & Sons, Ltd.**

**KEYWORDS:** NMR; $^{1}$H NMR; $^{13}$C NMR; $^{14}$N NMR; $^{15}$N NMR; pyrazine; oxidation; ethylation; protonation

## INTRODUCTION

During the synthesis of pyrazine derivatives, which are used for the preparation of differently substituted azidopyrazines, it was observed that 2-chloropyrazine *N*-oxide obtained under various reaction conditions has different $^{1}$H NMR characteristics. This observation is not surprising since 2-chloropyrazine (**1**) contains two nitrogen atoms and both may be oxygenated. An application of different oxidation mixtures produces two different isomers: the *N*1- and the *N*4-oxide, which are known in the literature.[1,2] According to Mixan and Pews, the treatment of **1** with potassium persulfate in concentrated sulfuric acid at room temperature gives the *N*1-oxide,[1] whereas others suggested that oxidation of **1** with hydrogen peroxide in glacial acetic acid at 70 °C results in the isomeric *N*4-oxide[1,2] (Scheme 1). [The numbering of atoms in all compounds studied throughout this paper is according to 2-chloropyrazine (**1**).].

Klein *et al*.[2] characterized the product obtained only by elemental analysis and melting-point but based on these data alone the structure could not be determined unambiguously. A few years later, Mixan and Pews[1] proposed a mechanism for both reactions but they did not give any further analytical data confirming the structure of both *N*-oxides, except for the $^{1}$H NMR chemical shifts. Uchimaru *et al*. presented the electron ionization mass spectra of both 2-chloropyrazine *N*-oxides, but nothing was said about their fragmentation.[3] A few years later, Stanovnik *et al*.[4] and Jovanovic[5,6], using both 2-chloropyrazine *N*-oxides, prepared both isomeric azides and described them by means of $^{1}$H NMR data. Jovanovic also presented $^{15}$N NMR chemical shifts of differently substituted pyrazines and their *N*-oxides, but the results for both 2-chloropyrazine *N*-oxides were surprisingly identical.[7]

Taking into account the above results, there are still doubts about the structures of both 2-chloropyrazine *N*-oxides produced under different oxidation conditions. To clarify these uncertainties, all the reactions were carried out again and a detailed analysis of the multinuclear magnetic resonance spectra was performed. The structure of both possible *N*-oxide isomers was additionally confirmed by analysis of the NMR spectra of the *N*-ethyl salts, the products of ethylation of both isomeric *N*-oxides, and the azide derivatives of pyrazine *N*-oxides resulting from nucleophilic substitution of the chlorine atom by azide ion in both *N*-oxides. The results of the protonation of the compounds studied in trifluoroacetic acid (TFA) are also presented.

## RESULTS AND DISCUSSION

### Oxidation of 2-chloropyrazine (1)

Three methods of oxidation of 2-chloropyrazine (**1**) were used: potassium persulfate in concentrated sulfuric acid (A), hydrogen peroxide in glacial acetic acid (B) and *m*-chloroperbenzoic acid in methylene chloride (C) (Scheme 1). Although in all three cases white crystalline solids were obtained, the comparison of the $^{1}$H and $^{13}$C NMR spectra of all reaction products (Table 1) clearly proves that reactions B and C yield the same compound (probably **3**), whereas reaction A produces another isomer (probably **2**).

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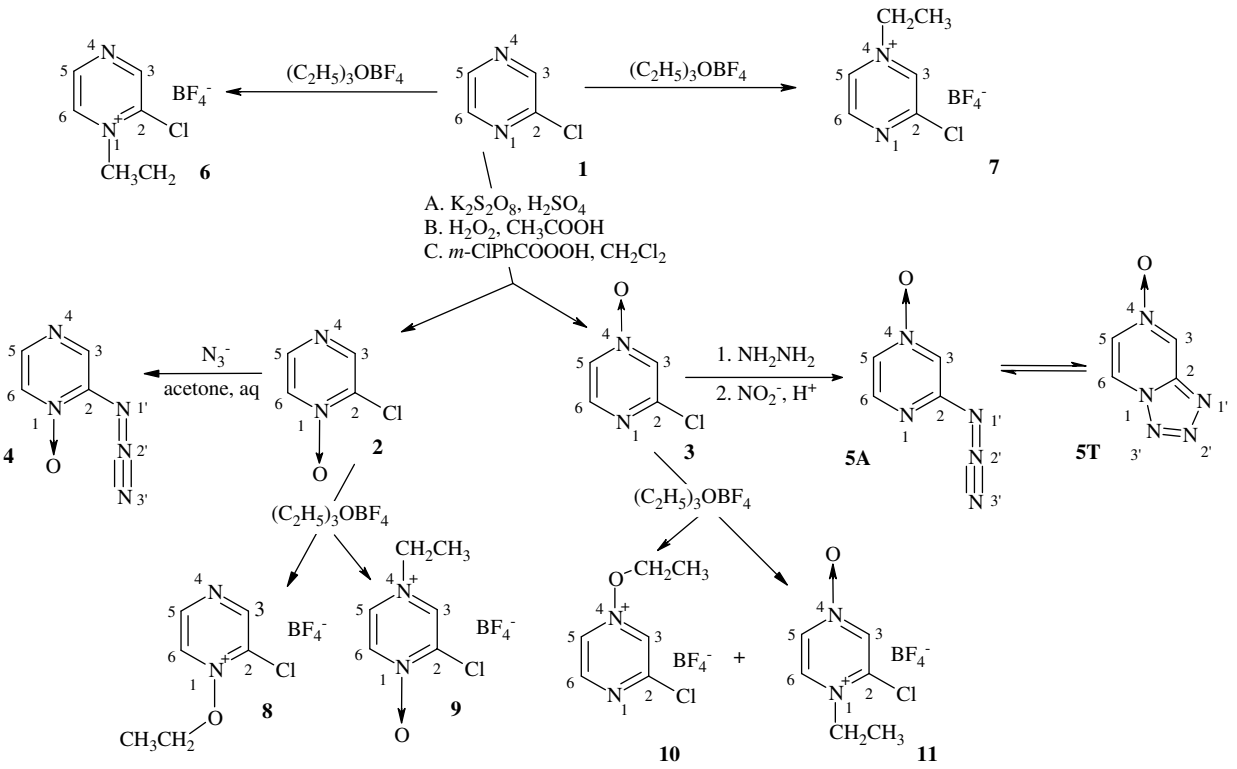

**Scheme 1.** Scheme of different reactions of 2-chloropyrazine **1** and its *N*-oxides **2** and **3**. Throughout this paper atoms of all compounds are numbered in accordance to **1**.

**Table 1.** $^{1}$H, $^{13}$C, $^{14}$N and $^{15}$N NMR data (in acetone, 303 K) for **1** and the products of reactions A, B and C (**2** and **3**)

| | **1**[b] | Product of reaction A: **2** | Product of reactions B and C: **3** |
|---|---|---|---|
| H3 | 8.69 | 8.75 | 8.39 |
| H5 | 8.60 | 8.45 | 8.21 |
| H6 | 8.47 | 8.39 | 8.35 |
| *J*(H3,H5) | 0.45 | —[d] | 1.50 |
| *J*(H5,H6) | 2.52 | 4.05 | 4.20 |
| *J*(H3,H6) | 1.45 | 0.60 | 0.70 |
| C2 | 149.8 | 139.7 | 151.9 |
| C3 | 145.4 | 148.5 | 134.3 |
| C5 | 143.6 | 146.3 | 134.6 |
| C6 | 144.8 | 135.9 | 147.3 |
| *J*(C3,H3) | 193.0 | 193.5 | 199.2 |
| *J*(C5,H5) | 186.3 | 188.8 | 195.4 |
| *J*(C6,H6) | 187.0 | 194.4 | 191.5 |
| *J*(C2,C3)[a] | 64.0 | 67.7 | 74.4 |
| *J*(C5,C6)[a] | 53.4 | 59.1 | 59.8 |
| N1 | −55.5 | −74.6[e] | −85.1[c] |
| | [220][c] | | [370][c] |
| N4 | −35.7 | −72.8[e] | −65.8 |
| | [230][c] | | [30][c] |

[a] $^{1}J(^{13}C,^{13}C)$ coupling constants measured in DMSO.

[b] $^{3}J$(C3,C6) = 14.3, $^{3}J$(C2,C5) = 18.9, $^{2}J$(C3,C5) = 7.0, $^{2}J$(C2,C6) = 6.0 Hz.

[c] Half-widths of the $^{14}$N NMR signals.

[d] Not determined owing to broadening of the signal caused by the influence of oxygen.

[e] Signals overlap in the $^{14}$N NMR spectrum.

Additionally, in the $^{1}$H NMR spectrum of the product of reaction A, small quantities of the product of reaction B = C (*ca* 7%) are also present. To explain which isomeric *N*-oxide was produced under the respective oxidation conditions, detailed analysis of the multinuclear magnetic resonance chemical shifts and coupling constants, presented in Table 1, was performed.

The assignment of $^{1}$H, $^{13}$C and nitrogen NMR chemical shifts for both *N*-oxides obtained in reactions A, B and C was made using results of 2D $^{1}$H–$^{13}$C *g*-HSQC, $^{1}$H–$^{13}$C and $^{1}$H–$^{15}$N *g*-HMBC experiments (for NMR nomenclature, see Experimental.), and also comparison of the multinuclear magnetic resonance data for *N*-oxides obtained with 2-chloropyrazine (**1**).

It is known that after oxidation of different substituted pyridines, nitrogen nuclei are shielded by *ca* 30 ppm, whereas shieldings of carbon nuclei directly bonded to pyridine nitrogen increase by *ca* 10 ppm in comparison with the parent compounds.[8] Although assignment of the $^{1}$H and $^{13}$C NMR chemical shifts of the products of reactions A, B and C was straightforward using results of the $^{1}$H–$^{13}$C *g*-HSQC/*g*-HMBC experiments and the above-mentioned information, the assignment of nitrogen signals was not an easy task. To assign the nitrogen signals unambiguously, the $^{14}$N NMR signal half-width was used. It is known that the half-width of $^{14}$N NMR signals of the *N*-oxide function is *ca* 10 times smaller than that of 'non-oxygenated' atoms.[9,10] In the case of the product of reaction A, both $^{14}$N signals overlap and it is difficult to determine their half-width accurately, but visually the signal at −74.6 ppm is sharper than that at −72.8 ppm. This means that the signal at

−74.6 ppm belongs to nitrogen possessing an oxygen atom, whereas that at −72.8 ppm corresponds to the free nitrogen atom. For the product of reactions B and C, the previously mentioned procedure can be easily repeated. The nitrogen signal of product B = C at −65.8 ppm (half-width *ca* 30 Hz) corresponds to oxygenated nitrogen, whereas the signal at −85.1 ppm (half-width *ca* 370 Hz) originates from the 'non-oxygenated' nitrogen atom. The half-widths of $^{14}$N NMR signals and results of $^{1}$H–$^{15}$N *g*-HMBC experiments for both *N*-oxides only support the assignment of the nitrogen shifts, but do not allow a differentiation between both *N*-oxide structures obtained.

To determine the structure of both oxidation products of **1**, a detailed analysis of the $^{13}$C NMR data was carried out. Comparison of $^{13}$C NMR chemical shifts of **1** and the products of reactions A and B = C leads to the following conclusion. Nuclei of the quaternary C-2 and tertiary C-6 atoms of the product of reaction A and both tertiary C-3 and C-5 carbons of the product of reactions B = C are more shielded by *ca* 10 ppm than the same nuclei in **1**.

Based on this information and the conclusions from nitrogen NMR, it can be assumed that the product of reaction A has the structure of the 2-chloropyrazine *N*1-oxide **2**, whereas the two other products (from reactions B and C) have the same structure of the 2-chloropyrazine *N*4-oxide **3**.

In the assignment of the $^{1}$H, $^{13}$C and nitrogen NMR chemical shifts with the use of $^{1}$H–$^{13}$C *g*-HSQC, $^{1}$H–$^{13}$C, $^{1}$H–$^{15}$N g-HMBC and additionally INADEQUATE experiments for both *N*-oxides **2** and **3**, it was observed that the values of $^{4}J$(H,H) are larger than $^{5}J$(H,H) and behave in the opposite way to those for **1** and other substituted pyrazines.[11] Additionally, production of the 2-chloropyrazine *N*-oxides is associated with changes of other $^{13}$C NMR parameters. The introduction of an oxygen on to the nitrogen atom causes an increase in the $^{1}J$($^{13}$C,$^{13}$C) and the $^{1}J$($^{1}$H,$^{13}$C) couplings of *ca* 4–10 and *ca* 3–8 Hz, respectively (Table 1).

In order to determine the structures of both *N*-oxides unambiguously, the detailed analysis of the multinuclear data for products of nucleophilic substitution of the chlorine atom and the ethylation reaction of both *N*-oxides were used.

## Azide derivatives of the 2-chloropyrazine *N*-oxides 2 and 3

The 2-chloropyrazine *N*-oxides **2** and **3**, similarly to 2-halopyridines and halopyrazines, react with nucleophiles, yielding the corresponding substituted pyrazine *N*-oxides. For instance, both *N*-oxides **2** and **3** react with hydrazine hydrate yielding the hydrazines, and with sodium azide producing the respective azides (Scheme 1). Treatment of hydrazines with sodium nitrite in acidic solutions leads to azide derivatives, which may exhibit azide–tetrazole tautomerism.[12–16] Analysis of both *N*-oxide structures studied (**2** and **3**) suggests that after the above-mentioned reactions such equilibrium could exist only in the case of the derivative of 2-chloropyrazine *N*4-oxide (**3**). In the case of the azide derivative of **2** (2-chloropyrazine *N*1-oxide) such tautomerism is not possible, because the nitrogen atom is blocked by oxygen (Scheme 1).

The products of oxidation of **1**, after treatment with hydrazine followed by reaction with sodium nitrite (product of reactions B and C) or sodium azide (product of reaction A), yield white crystalline solids, which first were measured in acetone solution by $^{1}$H NMR spectroscopy. In the $^{1}$H NMR spectrum of **4** obtained from the product of reaction A only one set of signals (three signals) was observed, confirming the absence of the azide–tetrazole equilibrium in this case. In the case of **5** obtained from the product of reactions B and C, the existence of the azide–tetrazole equilibrium is obvious, as the $^{1}$H NMR spectrum contains two sets of signals (six signals). The existence of both tautomeric forms (azide **A** and tetrazole **T**) is confirmed unambiguously by analysis of the $^{13}$C, $^{14}$N and $^{15}$N NMR spectra. Especially the positions of the $^{15}$N NMR signals are of great significance (Table 2). The presence of signals at −276.1 and +24.9 ppm clearly proves the existence of both forms in acetone solution.[15,16] The same compound dissolved in chloroform produces similar multinuclear spectra, but the integration of $^{1}$H, $^{13}$C and $^{15}$N signals is different to that obtained in acetone solution. A comparison of the $^{1}$H NMR integrals of **5** taken in acetone-$d_6$ and $CDCl_3$ indicates that in the less polar chloroform the content of the azide form is higher than in acetone solution. This phenomenon relating to solvent polarity is well known.[13–16]

From the point of view of NMR parameter changes, substitution of the chlorine atom by the azide anion causes a shielding increase of the respective nuclei. In the case of **4** and the azide form of **5**, nuclei C-3 and N-1 are more shielded than the parent chloropyrazine *N*-oxides **2** and **3** by *ca* 8 and 10–20 ppm, respectively. A closure of the azide

**Table 2.** $^{1}$H, $^{13}$C, $^{14}$N and $^{15}$N NMR data (in acetone, 303 K) for the azide derivatives of the pyrazine *N*-oxides **4** and **5**

| | **4** | **5A** | **5T** |
|---|---|---|---|
| H3 | 8.25 | 7.88 | 9.13 |
| H5 | 8.28 | 8.30 | 9.23 |
| H6 | 8.22 | 8.00 | 8.06 |
| *J*(H3,H5) | —[a] | 1.50 | 1.80 |
| *J*(H5,H6) | 4.10 | 4.20 | 5.90 |
| *J*(H3,H6) | 0.75 | 0.70 | 0.85 |
| C2 | 141.5 | 156.2 | 148.6 |
| C3 | 140.2 | 125.9 | 126.1 |
| C5 | 143.3 | 132.1 | 132.0 |
| C6 | 134.1 | 146.5 | 122.9 |
| N1 | −84.5 | −108.5 | −141.8 |
| | [50][b] | [220][b] | [110][b] |
| N4 | −69.8 | −62.7 | −76.4 |
| | [—][c] | [60][b] | [30][b] |
| N1′ | −295.3 | −276.1 | −67.7 |
| | [550][b] | [380][b] | [—][c] |
| N2′ | −146.0 | −142.6 | +24.9 |
| | [15][b] | [10][b] | [380][b] |
| N3′ | −134.3 | −138.8 | −30.1 |
| | [80][b] | [—][c] | [370][b] |

[a] Not determined owing to broadening of the signal caused by the influence of oxygen.

[b] The half-widths of the $^{14}$N NMR signals.

[c] Not determined because of $^{14}$N signal overlap.

group to the tetrazole ring (in the case of azide **5**) causes a shielding increase of N-1 and N-4 nuclei by *ca* 30 and 15 ppm, respectively. Additionally, the closure of the azide group to the tetrazole moiety is associated with an increased shielding (by *ca* 23 ppm) of the C-6 nucleus.

The above analysis of the multinuclear data for the product of nucleophilic substitution of the chlorine atom in both isomeric *N*-oxides completely confirms the path of oxidation reactions A, B and C for **1**, i.e. potassium persulfate in sulfuric acid at room temperature yields the *N*1-oxide **2** whereas hydrogen peroxide and *m*-chloroperbenzoic acid give the *N*4-oxide **3**.

## Ethylation of the 2-chloropyrazine *N*-oxides 2 and 3

Additional evidence for the 2-chloropyrazine *N*-oxide structures **2** and **3** is obtained from the analysis of the multinuclear spectra of ethylation products of the 2-chloropyrazine *N*-oxides with triethyloxonium tetrafluoroborate (Scheme 1).

Ethylation of **1** leads theoretically to two different products, the *N*1-ethyl (**6**) and *N*4-ethyl (**7**) salts. A detailed analysis of the $^{1}H$, $^{13}C$ and $^{15}N$ NMR chemical shifts of the product (Table 3) indicates that only one compound is obtained. The strong shielding increase of the N-4 nucleus in this compound by *ca* 100 ppm and the decrease in shielding of the N-1 nucleus by *ca* 20 ppm, compared with the $^{15}N$ NMR results for **1** (Table 1), prove the existence of the *N*4-ethyl 2-chloropyrazinium salt **7**. The ethylation causes also a decrease in the shielding of all protons by *ca* 0.6–0.8 ppm, a shielding increase for carbon nuclei (C-3 and C-5) directly bonded to ethylated nitrogen by *ca* 6 ppm and simultaneously a shielding decrease for two other carbon nuclei by the same value.

**Table 3.** $^{1}H$, $^{13}C$ and $^{15}N$ NMR data (in acetone 303 K) for the *N*-ethyl salts **7** and **9**–**11**

| | **7** | **9** | **10** | **11** |
|---|---|---|---|---|
| H3 | 9.46 | 9.55 | 9.86 | 9.20 |
| H5 | 9.22 | 9.05 | 9.53 | 8.81 |
| H6 | 9.36 | 9.03 | 9.47 | 9.10 |
| C*H*$_2$ | 4.94 | 4.76 | 5.05 | 4.83 |
| C*H*$_3$ | 1.80 | 1.73 | 1.57 | 1.67 |
| *J*(H3,H5) | —[a] | 2.0 | 0.8 | 2.2 |
| *J*(H5,H6) | 3.2 | 5.5 | 3.9 | 5.6 |
| *J*(H3,H6) | —[a] | —[a] | 1.6 | —[a] |
| C2 | 154.0 | 143.5 | 154.8 | 147.2 |
| C3 | 139.4 | 142.3 | 135.5 | 140.4 |
| C5 | 136.9 | 140.0 | 133.2 | 139.2 |
| C6 | 151.2 | 140.1 | 152.2 | 142.5 |
| *C*H$_2$ | 59.8 | 58.0 | 81.6 | 55.8 |
| *C*H$_3$ | 15.9 | 15.7 | 13.2 | 14.4 |
| N1 | −35.2 | −63.5 | −37.3 | −181.1 |
| | [720][b] | [70][b] | [800][b] | [120][b] |
| N4 | −141.7 | −179.0 | −110.3 | −53.9 |
| | [50][b] | [45][b] | [310][b] | [90][b] |

[a] Not determined owing to broadening of the signal caused by the oxygen or introduction of the ethyl group.
[b] The half-widths of the $^{14}N$ NMR signals.

Similar analysis of the results of ethylation of both 2-chloropyrazine *N*-oxides **2** and **3** suggests creation of four isomers, **8**–**11** (Scheme 1), but the NMR data indicate existence of only three *N*-ethyl salts for both *N*-oxides. After ethylation of **2** only one set of signals is observed in the $^{1}H$, $^{13}C$ and $^{15}N$ NMR spectra. The increase of the C-3 and C-5 shieldings by *ca* 6 ppm and the strong $^{15}N$ shielding increase of the N-4 nucleus by *ca* 100 ppm indicate the existence of *N*4-ethyl-2-chloropyrazinium tetrafluoroborate *N*1-oxide (**9**). No traces of the second isomeric *N*-ethyl salt **8** are observed in multinuclear spectra of the ethylation product because the bulky chlorine atom probably hinders access of the ethyl group to the oxygen atom.

In the second case, where **3** (product of reactions B and C) was ethylated, two sets of signals were present in the multinuclear spectra of the ethylation product. Based on the $^{1}H$ NMR integrals, the percentages of both salts were determined. The comparison of the differences in the multinuclear NMR data presented in Table 3 for the less abundant form (25%) with those of **3** and their comparison with differences in multinuclear data between **1** and **7**, presented above, indicate the existence of the *N*1-ethyl salt **11**.

The analysis of multinuclear NMR data of the second, more abundant salt (75%) leads to the conclusion that 2-chloropyrazine *N*4-oxide (**3**) is also ethylated at the oxygen atom. Direct proof of this statement is obtained from strong changes in the shieldings of several nuclei that are not comparable to the remaining *N*-ethyl salts **7**, **9** and **11**. The decrease in the shieldings of N-1 by *ca* 50 ppm, of the $CH_2$ carbon by *ca* 25 ppm and a modest shielding increase for the N-4 nucleus by *ca* 45 ppm, when compared with those of **3**, strongly indicate the presence of the second isomer, *N*4-ethoxy-2-chloropyrazinium tetrafluoroborate (**10**).

## Protonation of 2-chloropyrazine (1), its *N*-oxides 2 and 3 and the azide derivatives of the pyrazine *N*-oxides 4 and 5

Compounds **1**–**5** were dissolved in TFA in order to determine their protonation sites. Each of them contains at least two nitrogen atoms and thus may be protonated at two different positions. Compounds **2**–**5** additionally possess an oxygen atom, which may also be protonated. To determine the site of protonation, multinuclear spectra were registered and the results are given in Table 4.

The NMR data, especially the $^{15}N$ NMR chemical shifts, indicate that **1** and **2** undergo protonation at N-4. This is demonstrated by the strong shielding increase of the N-4 nucleus by *ca* 80–90 ppm compared with its position in aprotic solution, whereas the N-1 nucleus experiences only a small opposite effect (*ca* 7–10 ppm).

In the case of protonation of **3** (*N*4-oxide), both nuclei are only slightly shielded compared with their positions in acetone (by *ca* 1 and 15 ppm for N-1 and N-4, respectively). These small effects suggest protonation at the oxygen rather than at nitrogen, although in the case of the derivatives of the pyridine *N*-oxides, the nitrogen nucleus is shifted by *ca* 40 ppm after protonation.[8]

Compound **5** in TFA solution exists in azide–tetrazole equilibrium. Based on $^{1}H$ NMR integrals, the content of

**Table 4.** $^{1}H$, $^{13}C$ and $^{15}N$ NMR chemical shifts (in TFA, 303 K) for the protonated compounds **1**–**5**

| | **1** | **2** | **3** | **4** | **5A** | **5T** |
|---|---|---|---|---|---|---|
| H3 | 8.65 | 8.97 | 8.52 | 8.42 | 8.10 | 9.59 |
| H5 | 8.57 | 8.70 | 8.44 | 8.41 | 8.20 | 8.30 |
| H6 | 8.78 | 8.72 | 8.60 | 8.61 | 8.57 | 9.08 |
| C2 | 151.9 | 144.3 | 152.0 | 146.9 | 157.1 | 145.2 |
| C3 | 138.6 | 140.9 | 134.3 | 131.0 | 124.7 | 129.7 |
| C5 | 135.8 | 138.0 | 133.3 | 132.4 | 128.3 | 129.6 |
| C6 | 146.9 | 138.1 | 146.2 | 137.6 | 146.5 | 122.7 |
| N1 | −48.6 | −67.3 | −86.1 | −75.9 | −94.5 | −138.6 |
| N2 | −116.9 | −166.0 | −81.0 | −179.6 | −93.5 | −94.8 |
| N1′ | — | — | — | −287.8 | −272.8 | —[b] |
| N2′ | — | — | — | −149.2 | −149.1 | +14.4 |
| N3′ | — | — | — | —[a] | −136.3 | −29.2 |

[a] Not observed in the $^{14}N$ NMR spectrum and the $^{1}H$–$^{15}N$ *g*-HMBC experiment.

[b] Not observed in the $^{15}N$ NMR invgate and the $^{14}N$ NMR spectra, or in the $^{1}H$–$^{15}N$ *g*- HMBC experiment.

both forms determined as 21% azide and 79% tetrazole form. This observation is in agreement with the known tendency of the tetrazole ring to open in acidic conditions. However, small changes of the $^{15}N$ NMR chemical shifts of the N-1 and N-4 nuclei in both tautomeric forms provide the proof that proton–nitrogen interaction is very weak. This statement is also supported by small changes of the $^{13}C$ NMR chemical shifts for **5** after protonation. For **1** and **2**, where the proton–nitrogen interaction is very strong, the increase in $^{13}C$ shieldings (of carbon nuclei in direct neighborhood of 'protonated' nitrogen N-4) is very significant (*ca* 8 ppm). In the case of **3** and its azide derivative **5** in both tautomeric forms **A** and **T**, this increase is small (*ca* 3 ppm). Based on these observations, it can be stated that **3** and both tautomeric forms of **5** are protonated at the oxygen atom of the N—O function rather than not protonated at all.

In contrast to weak protonation of both tautomeric forms of the 2-azidopyrazine *N*4-oxide **5**, the 2-azidopyrazine *N*1-oxide **4** is fully *N*-protonated. Direct evidence of protonation is provided by the strong $^{15}N$ shielding increase of the N-4 nucleus by *ca* 100 ppm. Protonation is also supported by a strong $^{13}C$ shielding increase of the C-3 and C-5 nuclei by *ca* 8 ppm.

## Conclusions

The analysis of NMR data presented above provides sufficient evidence to conclude that oxidation of the 2-chloropyrazine with potassium persulfate (reaction A) leads to the 2-chloropyrazine *N*1-oxide **2**, whereas the two remaining reactions (with hydrogen peroxide and *m*-chloroperbenzoic acid) lead to the *N*4-oxide isomer **3**.

Compared with the substrate, the *N*-oxides can be characterized by the shielding increase of the nitrogen nuclei (by *ca* 30 ppm), the shielding increase of the carbon nuclei of the atom located next to the oxygenated nitrogen atom (by *ca* 10 ppm) and the decrease in the value of the $^{14}N$ NMR signal half-width for the oxygenated nitrogen nucleus (4–10-fold). Moreover, the presence of the bulky atoms such as chlorine at position 2 of pyrazine is responsible for differentiation of the nitrogen shielding effects after oxidation (*ca* 20 and 40 ppm for both nitrogens of **2**, whereas for **3** these changes are similar and *ca* 30 ppm).

Large and regular changes of the NMR parameters, especially $^{13}C$ and $^{15}N$ NMR chemical shifts, resulting from the structural modifications caused by alkylation and the nucleophilic substitution of the chlorine atom allow the determination of the structural of the derivatives obtained. They also, indirectly, confirm the structural differentiation among the *N*-oxides, depending on the conditions of the oxidation of the differently substituted pyrazines.

## EXPERIMENTAL

### Compounds

The compounds studied were prepared according to known methods presented in Scheme 1.

2-Chloropyrazine *N*1-oxide (**2**) was obtained according to the literature[1] and purified by liquid chromatography [$C_6H_{14}$–$CHCl_3$ (70 : 30)]. EI-MS (at 33 °C): *m*/*z* 132 (33.6%), 130 (100%), 116 (3.7%), 114 (11.1%), 79 (15.8%), 77 (6.5%), 75 (15.4%), 68 (12.7%), 60 (15.7%), 52 (15.3%). IR ($CHCl_3$): 3113 (m), 1581 (m), 1498 (w), 1450 (s), 1399 (s), 1318 (s), 1282 (w), 1179 (m), 1153 (w), 1121 (m), 1043 (m), 912 (w), 875 (m), 868 (m), 577 (w), 565 (m), 545 $cm^{-1}$ (m). Analysis: calculated for $C_4H_3N_2OCl$, H 2.30, C 36.78, N 21.46; found, H 2.15, C 36.45, N 21.22%. The $^{1}H$, $^{13}C$, $^{14}N$ and $^{15}N$ NMR data in acetone-$d_6$ and TFA solutions are collected in Tables 1 and 4, respectively.

2-Chloropyrazine *N*4-oxide (**3**) was obtained according to the literature.[2] EI-MS (at 33 °C): *m*/*z* 132 (34.1%), 130 (100%), 116 (5.3%), 114 (15.7%), 79 (20.8%), 77 (12.6%), 75 (30.0%), 68 (6.7%), 60 (12.3%), 52 (24.3%). IR ($CHCl_3$): 3123 (m), 1582 (s), 1543 (w), 1496 (m), 1463 (m), 1436 (s), 1410 (s), 1330 (s), 1317 (m), 1236 (m), 1173 (w), 1115 (s), 1092 (s), 1001 (s), 939 (s), 844 (m), 823 (w), 615 (w), 543 $cm^{-1}$ (w). Analysis: calculated for $C_4H_3N_2OCl$, H 2.30, C 36.78, N 21.46; found, H 2.21, C 36.56%, N 21.34%. The $^{1}H$, $^{13}C$, $^{14}N$ and $^{15}N$ NMR data in acetone-$d_6$ and TFA solutions are collected in Tables 1 and 4, respectively.

2-Azidopyrazine *N*1-oxide (**4**): the product obtained according to the literature[6] was contaminated with **2** (50 : 50), so it was characterized only by NMR spectroscopy. The $^{1}H$, $^{13}C$, $^{14}N$ and $^{15}N$ NMR data in acetone-$d_6$ and TFA solutions are collected in Tables 2 and 4, respectively.

2-Azidopyrazine *N*4-oxide (**5A**) was obtained according to the literature.[4,5] EI-MS (at 109 °C): *m*/*z* 137 (100%), 83 (2.4%), 82 (52.7%), 66 (10.8%), 65 (2.8%), 53 (33.7%), 52 (45.8%). IR ($CHCl_3$): 2400 (w), 2247 (w), 2205 (w), 2161 (w), 2141 (s), 2089 (w), 1650 (w), 1593 (s), 1505 (m), 1489 (w), 1451 (s), 1427 (m), 1343 (w), 1289 (m), 1239 (s), 1110 (m), 1005 (m), 967 (m), 930 (w), 842 (m), 643 (w), 627 $cm^{-1}$ (w). Analysis: calculated for $C_4H_3N_5O$, H 2.19, C 35.04, N 51.09; found, H 2.10, C 34.86, N 50.86%. The $^{1}H$, $^{13}C$, $^{14}N$ and $^{15}N$ NMR data in acetone-$d_6$ and TFA solutions are collected in Tables 2 and 4, respectively.

Preparation of the *N*-ethyl salts [**7**, **9**–**11**] was carried out according to the literature.[17,18] The $^{1}H$, $^{13}C$, $^{14}N$ and $^{15}N$ NMR data in acetone-$d_6$ are collected in Table 3.

### Spectra

The $^{1}H$, $^{13}C$, $^{14}N$ and $^{15}N$ NMR spectra were measured at 303 K on a Bruker DRX 500 spectrometer equipped with a TBI 500SB H-C/BB-D-05 Z-G probehead, operating at 500.133, 125.773, 36.141 and 50.690 MHz for $^{1}H$, $^{13}C$, $^{14}N$ and $^{15}N$ nuclei, respectively. Standard procedures were used to record the $^{1}H$, $^{13}C$, $^{14}N$ and $^{15}N$ NMR spectra employing, among others, power-gated and inverse-gated (invgate) decoupling sequences. The $^{1}J(^{13}C,^{13}C)$ spin couplings were obtained using the INADEQUATE sequence.

Two-dimensional $^{1}H$–$^{13}C$ *g*-HSQC (gradient-selected heteronuclear single quantum coherence; C,H correlation

via double INEPT transfer in the phase-sensitive mode) and $^{1}H-^{13}C$ as well as $^{1}H-^{15}N$ *g*-HMBC (gradient-selected heteronuclear multiple bond coherence; long-range correlation experiment) were performed using standard Bruker software and the following parameters: the spectral widths in $F_2$ and $F_1$ were *ca* 10 ppm for $^{1}H$, 80–160 ppm for $^{13}C$ and 100–400 ppm for $^{15}N$. The relaxation delay was usually *ca* 2.0 s, the refocusing delay in the *g*-HSQC experiment was *ca* 1.20 ms and delays for long-range evolutions were *ca* 80 and 80–320 ms for $^{1}H/^{13}C$ *g*-HMBC and $^{1}H/^{15}N$ *g*-HMBC experiments, respectively. The 2D spectra were acquired as 2048 × 512 or 1024 × 256 hypercomplex files, with 4–8 transients for each 512 or 256 time increments, using appropriate 90° and 180° pulse widths for the $^{1}H$, $^{13}C$ and $^{15}$ N channels.

For the $^{1}H$ and $^{13}C$ spectra in acetone-$d_6$, internal TMS was used as the chemical shift standard, whereas external nitromethane was applied as the standard for the $^{14}N$ and $^{15}N$ NMR measurements. In the case of the $^{1}H$ and $^{13}C$ spectra in TFA solutions, external DMSO-$d_6$ was used as the chemical shift standard. The concentrations of all solutions were between 0.05 and 0.2 mol dm$^{-3}$ and only in the case of INADEQUATE experiments were the concentrations *ca* 2 mol dm$^{-3}$.

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