# Furoxan rearrangement of some pyridofuroxan derivatives studied by $^{1}$H, $^{13}$C, $^{14}$N, $^{15}$N and $^{17}$O NMR spectroscopy

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ABSTRACT: Pyridofuroxan ([1,2,5]oxodiazolo[3,4-*b*]pyridine 1-oxide) undergoes isomerization between the *N1*-oxide and *N3*-oxide forms which can be observed by the $^{1}$H, $^{13}$C and $^{15}$N NMR spectroscopy but not by $^{14}$N and $^{17}$O NMR at ambient and low temperatures. The rearrangement becomes slower at low temperatures and at 233 K $^{1}$H NMR signals for the two structures become observable. $^{1}$H, $^{13}$C and $^{15}$N chemical shifts and $^{1}$H–$^{1}$H, $^{13}$C–$^{1}$H and $^{13}$C–$^{13}$C coupling constants are used to characterize both forms in the equilibrium mixture. From the $^{1}$H NMR integrals at 233 K equilibrium constants are calculated. Protonation studies using trifluoroacetic acid as a solvent showed the favoured site of protonation to be the pyridine N4 nitrogen atom. DFT shielding calculations are reported for the $^{13}$C, $^{15}$N and $^{17}$O nuclei which support the assignments given. From the point of view of structural changes, $^{1}J_{CC}$ data for 8-nitrotetrazolo[1,5-*a*]pyridine and *o*-nitroaminopyridine as precursors of the pyridofuroxans are given for comparison purposes. X-ray diffraction data on 5-methoxypyridofuroxan support the structural results obtained from the NMR investigations. Copyright © 2000 John Wiley & Sons, Ltd.

KEYWORDS: furoxan rearrangement; $^{1}$H, $^{13}$C, $^{14}$N, $^{15}$N and $^{17}$O NMR; protonation; DFT calculations

## INTRODUCTION

In order to obtain a more detailed characterization of pyridofuroxan ([1,2,5]oxodiazolo[3,4-*b*]pyridine 1-oxide) and some of its derivatives by NMR studies, we have become interested in the elucidation of isomerization of these compounds.[1,2] The rearrangement involves oxygen migration between the N1 and N3 atoms and valence isomerization which occurs most probably via *o*-dinitrosopyridine as the intermediate step (Fig. 1). Such a mechanism has been proposed by Dunkin *et al.*[3] and Murata and Tomioka[4] for an analogous rearrangement of benzofuroxan. However, no systematic studies devoted to substituent effects on the pyridofuroxan equilibrium have been performed so far and the number of NMR data published for this group of compounds is limited. The $^{1}$H NMR characteristics has been published by Boulton *et al.*[5] for pyridofuroxan itself and for its four methyl derivatives. $^{1}$H and $^{13}$C spectra have been measured for six variously substituted pyridofuroxans by Lowe-Ma *et al.*[6] However, no $^{15}$N NMR spectra have been published so far, which is not surprising, since neither the

measurement nor the unequivocal assignment of the signals present in these spectra is an easy task.

## EXPERIMENTAL

**Syntheses.** Pyridofuroxan and its derivatives were obtained as the result of oxidation of the corresponding *o*-nitroaminopyridines (compounds **1–4**, **6** and **8**) or in the thermolysis of corresponding nitrotetrazolo[1,5-*a*]pyridines (compounds **1** and **5**) (Fig. 2).[2] Compounds **5**, **9** and **10** were prepared according to procedure described previously (Fig. 2).[6] Selectively labelled (in positions 3 and 4) compound **1** was prepared by the thermolysis reaction of selectively labelled compound **11** (see Fig. 4). Data for unknown substituted pyridofuroxans are as follows.

*6-Chloropyridofuroxan* (**6**). MS: *m/z* 173, 171, 157, 155, 143, 141, 129, 127, 113, 111, 88, 86, 76. Analysis: calculated for $C_5H_2N_3O_2Cl$, H 1.17, C 34.99, N 24.90; found, H 1.08, C 34.80, N 24.78%. IR (KBr): 1618, 1572, 1518, 1503, 1492, 1418, 1338, 1238, 1169, 1050, 1030, 928, 873, 755, 698, 586 cm$^{-1}$.

*5-Methoxypyridofuroxan* (**7**). 2-Chloro-3-nitro-6-methoxypyridine (1.0 g) and sodium azide (0.38 g) were dissolved in 10% aqueous ethanol (50 ml) at ambient

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**Figure 1.** Valence tautomerism scheme for condensed furoxans



1)  R = H
2)  R = 5-CH$_3$
3)  R = 6-CH$_3$
4)  R = 7-CH$_3$
5)  R = 6-NO$_2$
6)  R = 6-Cl
7)  R = 5-OCH$_3$
8)  R = 7-Cl
9)  R = 5-NP(Ph)$_3$
10) R = 5-N$_3$

**Figure 2.** Numbering schemes and structures of the compounds studied. In the case of compounds **12** and **13** the numbering do not correspond to the IUPAC system

temperature, and 10% hydrochloric acid (5 ml) was added. The solution was then heated under reflux for 48 h. Evaporation to dryness, addition of water (20 ml) and filtration gave a yellow solid residue. Recristallization from ethanol–chloroform (50:50) gave **7** as pale yellow needles (0.62 g), 70%. MS: *m/z* 167, 151, 137, 121, 96, 94, 80, 64. M.p.: 139–140 °C. Analysis: calculated for C$_6$H$_5$N$_3$O$_3$, H 2.99, C 43.11, N 25.15; found, H 2.98, C 43.14, N 24.96%. IR (KBr): 1617, 1599, 1536, 1516, 1491, 1466, 1408, 1338, 1278, 1231, 1188, 1119, 1029, 992, 958, 832, 806, 759, 723, 690, 673, 567 cm$^{-1}$.

*7-Chloropyridofuroxan (**8**).* MS: *m/z* 173, 171, 157, 155, 143, 141, 127, 125, 113, 111, 90, 88, 86, 76. Analysis: calculated for C$_5$H$_2$N$_3$O$_2$Cl, H 1.17, C 34.99, N 24.90; found, H 1.10, C 34.82, N 24.84%. IR (KBr): 1608, 1577, 1529, 1511, 1496, 1416, 1331, 1196, 1044, 1012, 949, 853, 615, 552 cm$^{-1}$.

**Spectra.** Bruker AM 500 and DRX 500 spectrometers operating at 500.13, 125.76, 36.45, 50.68 and 67.80 MHz for $^1$H, $^{13}$C, $^{14}$N, $^{15}$N and $^{17}$O, respectively were used for the measurement of all the spectra. The concentrations of

acetone solutions of compounds studied were between 0.5 and 1 mol dm$^{-3}$. The temperature at which the spectra were measured was 233 K with exception of compounds **7**, **9** and **10**, for which the temperature was 303 K.

Standard experimental conditions and standard Bruker programs for XHCORRD (optimized for $^1J_{CH} = 160$–170 Hz, INVGATE and INADEQUATE (optimized for 65 Hz) for $^1J_{CC}$ were used. Moreover, GHMBC $^1$H–$^{15}$N correlation experiments were used to confirm the proper assignment of the $^{15}$N signals. The $^1$H and $^{13}$C spectra data are given relative to the TMS signal at 0.0 ppm at 233 K. Nitromethane, whose signal is at 0.0 ppm, was used as an external standard for the $^{15}$N NMR spectra. No correction of the calibrations for the $^{15}$N NMR spectra at low temperatures was made. For $^{17}$O NMR measurements at 303 K external H$_2$O was used as the standard. IR spectra in KBr pellets were measured using a Perkin Elmer 2000 FT-IR spectrometer and mass spectra were measured using an ADM-604 instrument.

**Calculations.** DFT nuclear shielding calculations were made using the deMon[7] program with experimental and optimized molecular geometries.

**Table 1.** ^{1}H NMR chemical shifts (ppm) and [1]H–[1]H coupling constants (Hz) in acetone-$d_6$ ($T$ = 233 K) of the compounds studied

|  | 1 I | 1 II | 2 I | 2 II | 3 I | 3 II | 4 I | 4 II | 5 I |
|---|---|---|---|---|---|---|---|---|---|
| H5 | 8.99 | 8.80 | — | — | 8.82 | 8.62 | 8.70 | 8.59 | 9.59 |
| H6 | 7.53 | 7.69 | 7.40 | 7.56 | — | — | 7.23 | 7.43 | — |
| H7 | 8.16 | 8.39 | 7.98 | 8.22 | 7.80 | 8.03 | — | — | 8.89 |
| CH$_3$ | — | — | 2.69 | —[a] | 2.54 | 2.56 | 2.62 | 2.65 | — |
| H5–H6 | 3.80 | 3.75 | — | — | — | — | 4.03 | 3.96 | — |
| H6–H7 | 9.05 | 9.25 | 9.16 | 9.30 | — | — | — | — | — |
| H5–H7 | 1.60 | 1.35 | — | — | —[b] | —[b] | — | — | 2.38 |

|  | 5 II | 6 I | 6 II | 7 I[c] | 8 I | 8 II | 9 I[c] | 10 I T[c,d] | 10 I A[c,d] |
|---|---|---|---|---|---|---|---|---|---|
| H5 | 9.36 | 8.91 | 8.73 | — | 8.84 | 8.71 | — | — | — |
| H6 | — | — | — | 6.94 | 7.60 | 7.86 | 7.23 | 7.73 | 6.70 |
| H7 | 9.09 | 8.38 | 8.59 | 7.89 | — | — | 7.00 | 7.63 | 7.71 |
| CH$_3$ | — | — | — | 4.08 | — | — | — | — | — |
| H5–H6 | — | — | — | — | 4.34 | 4.29 | — | — | — |
| H6–H7 | — | — | — | 9.39 | — | — | 9.35 | 9.80 | 9.30 |
| H5–H7 | 2.05 | 2.28 | 2.06 | — | — | — | — | — | — |

[a] Overlapped with signal of methyl group of **2 I**.
[b] Not determined because of coupling constants with methyl group,
[c] Measured at 303 K.
[d] **T** = tetrazole form and **A** = azide form of **10 I**.

**X-ray structure of 5-methoxypyridofuroxan (7).** The crystal system of 5-methoxypyridofuroxan (**7**) was orthorhombic and the space group was $Pna2_1$, $Z = 2$; unit cell parameters $a = 7.4470(1)$, $b = 14.935(3)$ and $c = 6.3630(1)$ Å, $V = 107.7$ 2 Å$^3$, $\mu$(Cu **K**$\alpha$) = 1.54178 Å, $D_c = 1.569$ mg m$^{-3}$. Data were collected at 293 K on an Enraf-Nonius MACH3 diffractometer using the $\omega-2\theta$ scan technique for the $\theta$ range 5.93–73.24°. Among 555 measured reflections, 555 were independent ($R_{int} = 0.000$). The structure was solved by direct methods (G. M. Sheldrick, SHELXS-93, Program for Crystal Structure Determination, University of Göttingen, 1993) and refined against $F^2(hkl)$ with full-matrix least-squares (G. M. Sheldrick, SHELXL-93, Program for Crystal Structure Refinement, University of Göttingen, 1993). Hydrogen atoms were included in the refinement at their calculated positions. The final residuals were $R_1 = 0.0755$, $wR_2 = 0.1496$ ($R$ indicates for all data: $R_1 = 0.0755$, $wR_2 = 0.1496$). Bond lengths, angles and torsions are given in Table 5. Other parameters are available on request.

## RESULTS AND DISCUSSION

The compounds studied are presented in Fig. 2. The spectra were measured under different conditions, *i.e.* at ambient and low temperatures and in protic and aprotic solvents. The ^{1}H, ^{13}C, ^{15}N and ^{17}O NMR data are given in Tables 1, 2, 3 and 4, respectively. An assignment of the signals in the ^{13}C NMR spectra was made unequivocally on the basis of corresponding INADEQATE spectra which were measured for compounds **1**, **4**, **6** and **7** (Table 2).

In order to determine whether **I** or **II** is the major form present in acetone solution, we followed the approach of Boulton *et al.*[5] and analysed the chemical shifts for the C3a and C7a carbon atoms in compound **1**. Fortunately, we observed in the low-temperature ^{13}C spectrum of this compound two pairs of signals of different intensity. By considering the chemical shifts of these nuclei in benzofuroxan, which are 153.0 and 114.7 ppm for C3a and C7a, respectively,[8] and using additivity rules for the introduction of the nitrogen atom in the benzene ring one can predict the chemical shift values in **I** and **II**. The additivity increments are deduced from a comparison of the relevant carbon chemical shifts of naphthalene and quinoline. This shows that the introduction of the nitrogen atom in quinoline results in a chemical shift increase of 16.1 ppm for the $\alpha$-carbon (C3a) and a decrease of 4.4 ppm for the $\beta$-carbon (C7a). The predicted values for **I** are 170 and 110 ppm for C3a and C7a, respectively. These values are in close agreement with the observed chemical shifts at 160 and 110 ppm. Following the same reasoning one obtains 136 and 144 ppm for C3a and C7a, respectively in form **II**. The observed signals at 126 and 148 ppm are in reasonable agreement with this prediction. Since the pair of signals at 160 and 110 ppm are significantly stronger than those at 126 and 148 ppm we conclude that form **I** is present to a larger extent than is form **II** in acetone solution.

As shown in Fig. 2, the present investigations involved 10 compounds, the majority of which are found to exhibit equilibrium. Those which do not are compounds **7**, **9** and **10**. For those compounds which do exhibit equilibrium in solution the predominant form is **I** with the exception of compound **8**, where form **II** predominates. X-ray diffraction data (Table 5) on crystals of compound **7**

**Table 2.** $^{13}C$ NMR chemical shifts (ppm) and $^{13}C$–$^1H$ and $^{13}C$–$^{13}C$ coupling constants (Hz) of the compounds studied in acetone-$d_6$ solution at $T = 233$ K

|  | 1 I | 1 II | 2 I | 2 II | 3 I | 3 II | 4 I | 4 II | 5 I |
|---|---|---|---|---|---|---|---|---|---|
| C7a | 109.6 | 148.4 | 108.3 | —[a] | 108.9 | 148.4 | 109.7 | 149.3 | 107.0 |
| C3a | 160.4 | 126.2 | 160.2 | —[a] | 160.0 | 124.6 | 160.2 | 125.3 | 157.7 |
| C5 | 161.7 | 157.3 | 171.5 | —[a] | 164.5 | 160.0 | 161.0 | 156.9 | 153.7 |
| C6 | 125.8 | 129.2 | 127.6 | —[a] | 136.6 | 140.0 | 124.4 | 127.3 | 141.4 |
| C7 | 123.3 | 127.7 | 122.4 | —[a] | 119.0 | 123.8 | 137.1 | 139.8 | 122.0 |
| CH$_3$ | — | — | 26.1 | 25.7 | 19.0 | 19.2 | 15.5 | 15.4 | — |
| C5–H5 | 185.7 | 187.9 | — | — | 183.7 | 185.0 | 183.8 | 186.3 | —[a] |
| C6–H6 | 172.1 | 170.0 | 170.5 | —[a] | — | — | 168.8 | 167.3 | —[a] |
| C7–H7 | 179.2 | 176.7 | 174.3 | —[a] | 176.4 | 173.5 | — | — | —[a] |
| C7a–C3a | 65.5 | —[a] | —[b] | —[b] | —[b] | —[b] | —[a] | —[a] | —[b] |
| C5–C6 | 48.8 | 49.6 | —[b] | —[b] | —[b] | —[b] | 49.6 | 50.6 | —[b] |
| C6–C7 | 61.4 | 61.1 | —[b] | —[b] | —[b] | —[b] | 62.9 | —[a] | —[b] |
| C7–C7a | 64.1 | 62.8 | —[b] | —[b] | —[b] | —[b] | 64.0 | —[a] | —[b] |

|  | 5 II | 6 I | 6 II | 7 I[c] | 8 I | 8 II | 9 I[a] | 10 I A[c,d] | 10 I T[c,d] |
|---|---|---|---|---|---|---|---|---|---|
| C7a | —[a] | 109.2 | 148.0 | 107.9 | 108.3 | 147.5 | 106.9 | 107.5 | 107.0 |
| C3a | —[a] | 158.4 | 124.4 | 159.6 | 160.8 | 127.3 | 160.4 | 157.8 | 144.1 |
| C5 | —[a] | 160.9 | 156.3 | 168.8 | 160.8 | 156.2 | 167.7 | 162.9 | 149.9 |
| C6 | —[a] | 131.6 | 135.3 | 121.1 | 125.0 | 128.3 | 129.6 | 120.6 | 116.1 |
| C7 | —[a] | 121.0 | 125.3 | 125.2 | 131.2 | 134.8 | 119.7 | 124.7 | 119.3 |
| CH$_3$ | —[a] | — | — | 55.5 | — | — | — | — | — |
| C5–H5 | —[a] | 193.6 | 196.1 | — | 188.7 | 191.3 | —[a] | — | — |
| C6–H6 | —[a] | — | — | 175.3 | 175.4 | 173.6 | —[a] | 174.8 | 181.5 |
| C7–H7 | —[a] | 183.0 | 180.8 | 174.9 | — | — | —[a] | 178.5 | 181.3 |

[a] Not determined because of low concentration.
[b] Not recorded.
[c] Measured at 303 K.
[d] **T** = tetrazole form of and **A** = azide form of **10 I**.

(Fig. 3) show that in the solid state this compound exists entirely in form **I**, thus supporting the finding of the $^{13}C$ NMR measurements, especially for the assignment of the C3a and C7a signals which are typical of the *N1*-oxide form **I**.

The pyridofuroxan molecule is almost planar (Table 5). The bond lengths and bond angles of the furoxan portion are similar to the values mentioned previously,[6,9,10] although some differences caused by the introduction of a nitrogen atom and methoxy group in the benzofuroxan molecule are also discernible. The pyridine ring has typical bonds reflecting the presence of double bonds and thus the presence of furoxan functionality. The C5–N4 bond is shorter than the reported mean of 1.337 Å for pyridine C—N bonds,[6] whereas the C5—C6 and C7—C7a bonds are both long and C6—C7 is short compared with the aromatic C—C bond length of 1.380 Å found in other pyridines.

**Table 3.** $^{15}N$ NMR chemical shifts (ppm) of the compounds studied in acetone-$d_6$ solution at $T = 233$ K

|  | 1 I | 1 II | 2 I | 2 II | 3 I | 3 II | 4 I | 4 II | 5 I |
|---|---|---|---|---|---|---|---|---|---|
| N1 | −19.4 | −4.4 | —[a] | —[a] | −20.7 | —[a] | −18.6 | −6.0 | −16.5 |
| N3 | −6.4 | −20.0 | —[a] | —[a] | —[a] | —[a] | −7.5 | −19.5 | —[a] |
| N4 | −90.8 | −98.0 | —[a] | —[a] | −91.3 | −99.5 | −98.6 | −106.1 | −87.9 |
| N4–H5 | 12.2 | 12.5 | — | — | 12.0 | 12.6 | 13.0 | 13.5 | 11.4 |

|  | 5 II | 6 I | 6 II | 7 I[b] | 8 I | 8 II | 9 I[b] | 10 IA[b,c] | 10 IT[b,c] |
|---|---|---|---|---|---|---|---|---|---|
| N1 | —[a] | −20.2 | —[a] | −24.9 | −17.8 | −6.5 | −31.2 | —[a] | −22.3 |
| N3 | —[a] | −5.0 | —[a] | −17.3 | −7.3 | −19.0 | −27.6 | −13.9 | −29.8 |
| N4 | −92.1 | −86.1 | −93.8 | −163.4 | −94.5 | −101.3 | −160.5 | −140.4 | −158.8 |
| N4–H5 | 11.8 | 11.8 | 12.0 | — | 13.1 | 13.3 | — | — | — |

[a] Not recorded or not observed in $^1H$–$^{15}N$ GHMBC experiment.
[b] Measured at 303 K. **9 I**: —$N$=P = −255.6 ppm.
[c] **T** = tetrazole form and **A** = azide form of **10 I**, **10 I A**: N1′ = −261.7 ppm, N2′ = −146.7 ppm, N3′ = −136.6 ppm. **10 I T**: N1′ = −56.9 ppm, N2′ = +23.2 ppm, N3′ = −28.6 ppm.

**Table 4.** $^{17}O$ NMR chemical shifts (ppm) in acetone-$d_6$ solution at $T = 303$ K for some of the compounds studied

| | 1 | 4 | 5 | 6 | 7 | 10 I T[a] |
|---|---|---|---|---|---|---|
| $O_{exo}$ | 406 (230) | 409 (260) | 433 (310) | 411 (290) | 388 (290) | 406 (300) |
| O2 | 509 (270) | 506 (290) | 526 (390) | 518 (340) | 492 (350) | 502 (500) |
| $NO_2/OCH_3$ | — | — | —[b] | — | 100 (250) | — |

[a] **T** = tetrazole form of **10 I**.
[b] Invisible because overlapping with acetone signal.

The $^{15}N$ NMR spectra of the compounds which undergo the equilibrium consist of two sets of signals of different intensity, three resonances each. Their assignment was made in the following way using compound **1** as an example. The $^{15}N$ NMR spectrum of
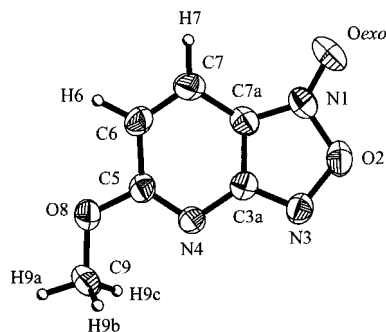


**Figure 3.** Crystallographic structure (ORTP projection) of 5-methoxypyridofuroxan (**7**)

this compound has three signals at $-6.4$, $-19.4$ and $-90.8$ ppm, which, owing to their intensity, obviously belong to the form **I**. Their assignment was made as follows. The signal at $-90.8$ ppm is fairly typical of the pyridine-type nitrogen atom[11] and is assigned to N4 of structure **I**. In order to distinguish between the other two signals we also recorded the $^{14}N$ NMR spectrum. The signal appearing at $-19.4$ ppm is much sharper in the $^{14}N$ NMR spectrum than that at $-6.4$ ppm. The *N*-oxide nitrogen atoms invariably give a fairly sharp $^{14}N$ NMR signal due to the presence of the residual charge on the nitrogen atom producing a fairly small electric field gradient at the site of quadrupolar nuclei.[12] Consequently, the signal at $-19.4$ ppm is attributed to N1 in structure **I** and the signal at $-6.4$ ppm to N3. In the case of structure **II** the signal at $-98.0$ ppm must be assigned to N4, whereas the signals at $-4.4$ ppm and $-20.0$ ppm are assigned to N1 and N3, respectively.

To assist in the assignment of the $^{15}N$ signals, a sample

**Table 5.** Bond lengths and angles of compound **7**

| Bond | Bond length (Å) | Bond | Bond angle (°) | Bond | Torsion (°) |
|---|---|---|---|---|---|
| N1–$O_{exo}$ | 1.215(4) | C5–N4–C3a | 113.5(4) | C3a–N4–C5–O8 | −176.7(1) |
| N1–O2 | 1.446(5) | C5–O8–C9 | 117.6(4) | C3a–N4–C5–C6 | −2(2) |
| O2–N3 | 1.389(6) | O8–C9–H9a | 109.7(1) | C9–O8–C5–N4 | 0(2) |
| N3–C3a | 1.318(5) | O8–C9–H9b | 105.5(1) | C9–O8–C5–C6 | −176.0(1) |
| C3a–N4 | 1.364(5) | O8–C9–H9c | 103.4(1) | O2–N3–C3a–N4 | 179.5(1) |
| N4–C5 | 1.294(6) | H9a–C9–C9b | 112.4(6) | O2–N3–C3a–C7a | −1(2) |
| C5–C6 | 1.461(6) | H9a–C9–H9b | 144.8(1) | C5–N4–C3a–N3 | −177.3(1) |
| C6–C7 | 1.328(6) | C3a–N3–O2 | 105.4(4) | C5–N4–C3a–C7a | 3(2) |
| C7–C7a | 1.422(7) | $O_{exo}$–N1–C7a | 135.1(5) | C3a–N3–O2–N1 | −3(2) |
| C7a–C3a | 1.418(6) | $O_{exo}$–N1–O2 | 118.2(4) | $O_{exo}$–N1–O2–N3 | −180.0(1) |
| N1–C7a | 1.330(6) | C7a–N1–O2 | 106.4(4) | C7a–N1–O2–N3 | 5(2) |
| C6–H6 | 1.00 | N4–C5–O8 | 120.8(4) | $O_{exo}$–N1–C7a–C3a | −179(2) |
| C7–H7 | 1.00 | N4–C5–C6 | 126.3(4) | O2–N1–C7a–C3a | −5(2) |
| C5–O8 | 1.325(5) | O8–C5–C6 | 112.7(4) | O1–N1–C7a–C7 | 15(3) |
| O8–C9 | 1.453(6) | N3–C3a–N4 | 124.0(4) | O2–N1–C7a–C7 | −170.8(1) |
| C9–H9a | 1.07(3) | N3–C3a–C7a | 112.3(4) | N3–C3a–C7a–N1 | 4(2) |
| C9–H9b | 1.13(3) | N4–C3a–C7a | 123.7(4) | N4–C3a–C7a–N1 | −177(2) |
| C9–H9c | 1.05(2) | N3–O2–N1 | 108.8(3) | N3–C3a–C7a–C7 | 171.4(1) |
| | | C6–C7–C7a | 114.5(4) | N4–C3a–C7a–C7 | −9(2) |
| | | C6–C7–H7 | 122.8(3) | C6–C7–C7a–N1 | 177(2) |
| | | C7a–C7–H7 | 122.7(3) | C6–C7–C7a–C3a | 13(2) |
| | | N1–C7a–C3a | 106.9(5) | C7a–C7–C6–C5 | −11(3) |
| | | N1–C7a–C7 | 131.3(5) | N4–C5–C6–C7 | 7(3) |
| | | C3a–C7a–C7 | 120.4(4) | O8–C5–C6–C7 | −178(2) |
| | | C7–C6–C5 | 120.3(4) | | |
| | | C7–C6–H6 | 119.8(2) | | |
| | | C5–C6–H6 | 119.8(2) | | |
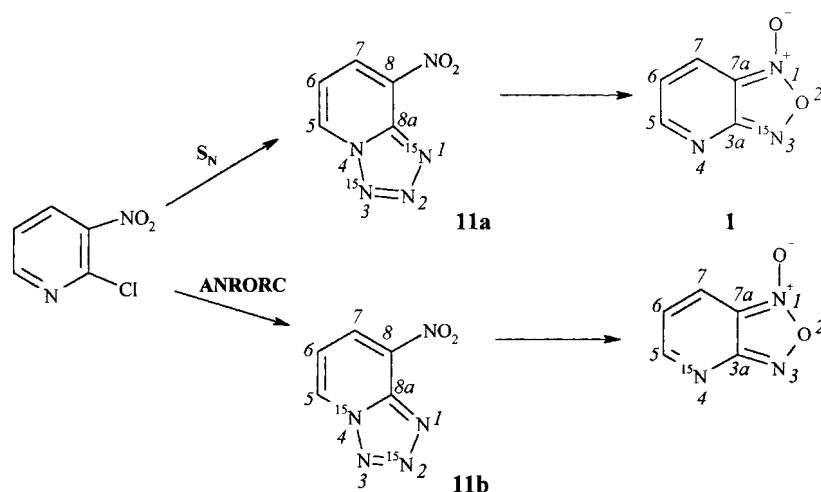
**Figure 4.** Two possible mechanisms for the reaction between 2-chloro-3-nitropyridine and selectively labelled potassium azide, $K^{15}NN^{15}N$

individually enriched at N3 and N4 was prepared as shown in Fig. 4 and its spectrum analysed. The synthesis of selectively 3- and 4-^{15}N-labelled pyridofuroxan, **1**, proceeds according to the following steps.

In the first step the reaction between 2-chloro-3-nitropyridine and the doubly labelled potassium azide $K^{15}NN^{15}N$ takes place, leading to compound **11**, whose labelling depends on the mechanism involved: the 1,3-di-^{15}N-8-nitrotetrazolo[1,5-a]pyridine isotopomer, **11a** (45%), is formed as the result of an $S_N$ nucleophilic substitution mechanism and 2,4-di-^{15}N-8-nitrotetrazolo[1,5-a]pyridine isotopomer, **11b** (55%), is obtained when the ANRORC (addition of nucleophile, ring opening and ring closure) mechanism takes place (Fig. 4). The ratio of these two isotopomers (45:55) can be easily estimated from the integration of the signals in the ^{15}N NMR spectrum (in DMSO) of the compound **11**. Two signals at −67.3 and −30.0 ppm are characteristic of the tetrazole nitrogens N1 and N3, respectively, which correspond to isotopomer **11a**, and two signals at +20.7 and −122.9 ppm are due to the N2 and N4 atoms of the isotopomer **11b**.[13] After thermolysis of labelled compound **11**, two isotopomers of compound **1** are formed: 3-[15]N (45%) and 4-[15]N (55%).

On lowering the temperature of the mixture of isotopomers of **1** in acetone solution, two sets of signals are observed. The stronger signals at −6.4 (N3) and −90.8 ppm (N4) are characteristic of the *N1*-oxide form **I**, whereas two weaker signals at −20.0 and −98.0 ppm correspond to atoms N3 and N4, respectively, of form **II**. These observations support the nitrogen signal assignments based on the ^{14}N NMR relative linewidths and [1]H–[15]N correlation measurements.

An assignment of the signals in the ^{17}O NMR spectrum presents some problems. From an ^{17}O NMR study on benzofuroxan it is reported that the exocyclic oxygen is deshielded with respect to the ring oxygen atom.[14]

However, as was shown in our recent study on this class of compounds, this assignment should be reversed.[15] It is therefore reasonable to assume that also in the case of pyridofuroxans the exocyclic oxygen is shielded with respect to the ring oxygen atom (see also the section where the relevant ^{17}O NMR DFT calculations are discussed).

In order to obtain some independent proof of the assignments of the signals in the spectra of the compounds studied, we performed DFT calculations of the nuclear shieldings for the parent compound **1** (in both forms **I** and **II**) and compound **7**. The results are presented in Figs 5, 6 and 7 where, respectively, plots of observed ^{13}C, ^{15}N and ^{17}O NMR chemical shifts against nuclear shieldings calculated by the density functional method (DFT)[7] are presented. In the DFT calculations we employed the PW91 functional and the IGLO III basis set. The correlation coefficients and standard deviations for the least-squares data fitting are given in Figs 5–7 and are very satisfactory in each case. These results support our assignments of the ^{13}C, ^{15}N and ^{17}O NMR spectra. It is also worth mentioning that not only are the trends reproduced correctly but also agreement between the calculated and experimental data is satisfactory.
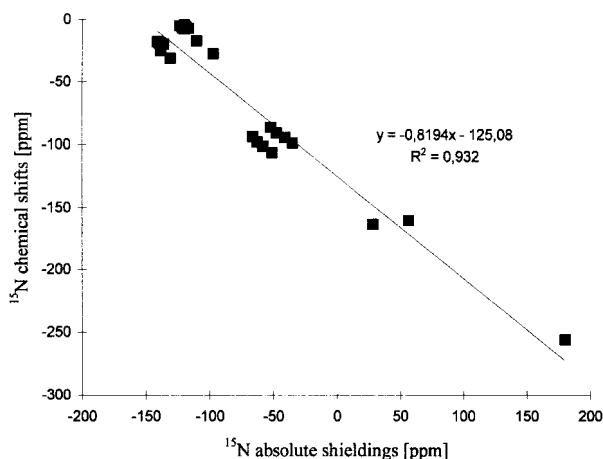
Inspection of the data in Table 6 reveals that compounds **1–6** and **8** exist in acetone solution in the form of two tautomers, and for compounds **1–6** the equilibrium between these tautomers is strongly shifted towards the *N1*-oxide form, **I**. The compounds in question are the parent pyridofuroxan **1**, its 5-, 6- and 7-methyl derivatives, **2–4**, the 6-nitro derivative, **5**, and the 6-chloro derivative, **6**. In the case of the 7-chloro derivative (**8**), the equilibrium is displaced in the opposite direction with form **II** being favoured. The $K_{I/II}$ values vary from 0.05 in compound **5**, where the strong electron-withdrawing $NO_2$ group is attached to carbon 6, to 0.15
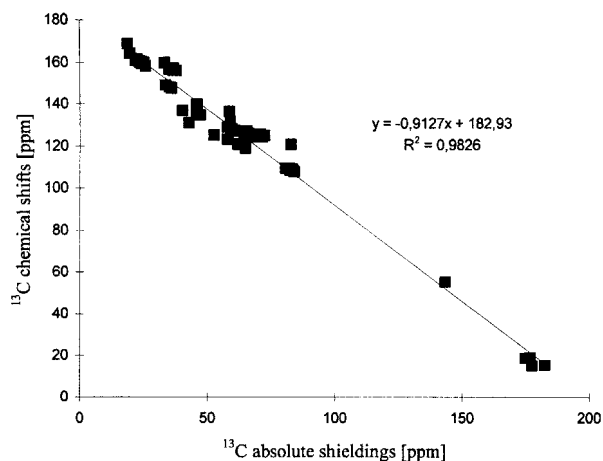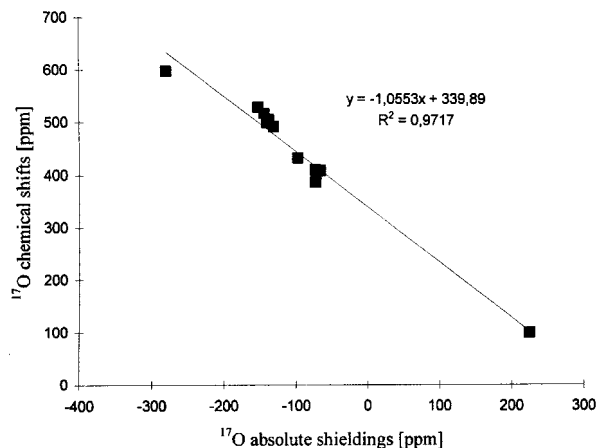
**Figure 5.** Plot of calculated $^{13}$C absolute shieldings against experimental $^{13}$C NMR chemical shifts



**Figure 7.** Plot of calculated $^{17}$O absolute shieldings against experimental $^{17}$O NMR chemical shifts

for compound **6**, where the electron-donating chlorine atom is present in position 6. These results show that the substituents at position 6 have a relatively small influence regardless of their nature on the position of the equilibrium. This is in agreement with the previously published data.[16]

In the case of compounds with a substituent in position 5, both forms **I** and **II** were observed only in the case of the methyl derivative **2**. The presence of substituents containing electronegative atoms leads most obviously to destabilization of the *N3*-oxide form and, as a result, only form **I** is found in the case of compounds **7**, **9** and **10**. It should be mentioned that in the case of compound **10**, owing to the presence of the azide group, a more complex equilibrium may exist.[13] As shown in Table 6, the $K_{I/II}$ data for compounds **4** and **8** are significantly different (0.18 and 1.22, respectively). This difference arises from a change in the substituent at position 7 from a methyl group to a chlorine atom. The change in $K_{I/II}$ is

undoubtedly not due to steric effects but rather to electronic differences between these two substituents. As suggested by Boulton *et al.*,[5] weak hydrogen bonding and thus accentuation of hyperconjugation of the 7-methyl group with the aza-nitrogen are of small importance because there is no meaningful change in the $^{17}$O NMR chemical shifts for compound **4** (Table 4).

Finally, we have also become interested in the effects of protonation on the compounds studied. The $^1$H, $^{13}$C and $^{15}$N NMR spectra of compounds **1**, **3**, **4**, **6**, **7** and **10** were measured in the presence of excess trifluoroacetic acid (TFA) and the results are shown in Table 7. The main conclusion which can be drawn from an analysis of the data is that under acidic conditions the equilibrium is totally shifted towards isomer **I**. First, only one set of the signals is observed in the spectra of all compounds studied when measured at 269 K. Second, the signal corresponding to carbon C7a appears in the $^{13}$C NMR spectra of all protonated samples at *ca*. 110 ppm, which is very close to the position of this signal in the spectra of non-protonated compounds, *ca*. 108 ppm. These results provide unquestionable evidence that, as mentioned above, the protonated compounds exist exclusively in the form **I**. Additionally, according to the mesomeric structures given in Fig. 8, protonation of the molecules under consideration should strongly stabilize the *N1*-oxide (form **I**). It is worth noting again at this point that



**Figure 6.** Plot of calculated $^{15}$N absolute shieldings against experimental $^{15}$N NMR chemical shifts

**Table 6.** Equilibrium constants for the *N1-N3*-oxide rearrangement

| Compound | Constant | Compound | Constant |
|---|---|---|---|
| **1** | $0.10 \pm 0.005$ | **6** | $0.15 \pm 0.005$ |
| **2** | $0.08 \pm 0.005$ | **7** | 0.00 |
| **3** | $0.12 \pm 0.005$ | **8** | $1.22 \pm 0.005$ |
| **4** | $0.18 \pm 0.005$ | **9** | 0.00 |
| **5** | $0.05 \pm 0.005$ | **10** | 0.00 |

**Table 7.** $^1$H, $^{13}$C and $^{15}$N NMR chemical shifts for some protonated (in TFA) and alkylated (in acetone, $T = 269$ K) compounds

|                 | 1      | 1[a]   | 1 et[b] | 3      | 4      | 4 et[b] | 6      | 7      | 10 T[c] |
|-----------------|--------|--------|---------|--------|--------|---------|--------|--------|---------|
| H5              | 8.65   | 8.56   | 9.78    | 8.46   | 8.44   | 9.50    | 8.02   | —      | —       |
| H6              | 7.09   | 7.04   | 8.11    | —      | 6.92   | 7.87    | —      | 6.42   | 7.34    |
| H7              | 7.69   | 7.81   | 9.11    | 7.59   | —      | —       | 7.15   | 7.30   | 7.43    |
| CH$_3$          | —      | —      | —       | 1.98   | 2.29   | 1.64    | —      | 3.66   | —       |
| C7a             | 111.2  | 111.0  | 114.2   | 110.9  | —[d]   | 114.4   | 109.6  | 109.1  | 107.5   |
| C3a             | 151.0  | 152.7  | 150.9   | 150.7  | —[d]   | 150.7   | 155.2  | 157.3  | 144.1   |
| C5              | 158.7  | 158.2  | 161.4   | 161.1  | —[d]   | 159.2   | 160.7  | 169.7  | 150.3   |
| C6              | 123.3  | 123.1  | 125.1   | 136.4  | —[d]   | 123.7   | 132.6  | 121.8  | 114.3   |
| C7              | 133.0  | 129.7  | 136.5   | 129.0  | —[d]   | 154.5   | 122.1  | 124.9  | 121.4   |
| N1              | −18.2  | —[e]   | −17.2   | −21.2  | −17.6  | —[f]    | −23.1  | −30.7  | −21.8   |
| N3              | −17.0  | −13.6  | —[e]    | —[e]   | −21.7  | —[f]    | —[e]   | −30.0  | −30.4   |
| N4              | −175.2 | −150.5 | −188.9  | −173.6 | −212.0 | —[f]    | −116.1 | −191.9 | −158.2  |

[a] At 303 K

[b] ethylated form of compounds **1** and **4**.

[c] $^{15}$N NMR chemical shifts of remaining nitrogen nuclei of tetrazole form (**T**) of compound **10**: N1′ = −78.6 ppm, N2′ = +7.4 ppm, N3′ = −31.2 ppm.

[d] Not recorded.

[e] Not observed in $^1$H–$^{15}$N GHMBC experiment.

[f] Not recorded because of instability of the ethylated derivative.

the C7a signals in the spectra of isomer **II** appear in the region of 148 ppm. A further comparison of the data obtained for the protonated compounds with those derived for the non-protonated compounds shows that the protonation takes place on the nitrogen atom of the pyridine ring, *i.e.* on N4. This results in very strong shielding of this atom in comparison with the non-protonated molecule. Its magnitude depends dramatically on the substituents attached to the pyridine ring and varies from 30 ppm in compound **6** up to 110 ppm in compound **4**. In the first case the chlorine atom in position 6 probably strongly decreases the electron density at N4, weakening the protonation effect considerably, and the methyl group at position 7, in contrast, increases the electron density at N4, strengthening the shielding effect caused by protonation of this atom. The changes occurring at N4 are accompanied by shielding of carbon C3a and deshielding of C7, −9 and 10 ppm, respectively. All these values are very close to the protonation effects in pyridine itself and its corresponding derivatives. Thus, for example the corresponding $\Delta(\delta)$ values in unsubstituted pyridine are −115.6 ppm, −7.7 ppm and +12.4 ppm for N4, C2 and C4, respectively (J Wiench, P Cmoch, L Stefaniak and GA Webb. *J. Mol. Struct.* in preparation). Also, an increase of $^1J_{C5C6}$ and $^1J_{C3aC7a}$ couplings of 5 Hz observed in the spectrum of **1** recorded

in TFA in comparison with those determined for the non-protonated compound may be considered as a result typical of protonation of the pyridine ring.[17]

For labelled compound **1** we were also able to measure the $^{15}$N NMR spectrum in TFA at 303 K. At this temperature the N3 and N4 signals are shifted to higher frequencies, by 3.4 and 22.0 ppm, respectively, which indicates that the proton–nitrogen interaction is, as expected, weaker at higher than at lower temperatures.

It is also of interest that similar effects to those described above are observed upon N4 alkylation of the compounds studied. Thus, a nitrogen shielding increase of about 100 ppm has been observed in the *N4*-ethyl derivatives of compounds **1** and **4** for nitrogen N4 and deshielding of carbon C7 by 10 ppm (see Table 7).

In order to obtain a deeper insight into the electron distribution in pyridofuroxans, we measured also $^1J_{CC}$ couplings for compound **1** and its protonated form, and for the compounds which are pyridofuroxan precursors, **11**, **12** and **13**. These results are given in Table 8. Thermolysis of compound **11** and oxidation of compounds **12** and **13** (Fig. 2) provide a change in electron distribution and result in bond localization. The most sensitive NMR parameters to these changes are $^1J_{CC}$ and nitrogen chemical shifts (Table 8). Especially visible are the changes of coupling constants (C5–C6) between
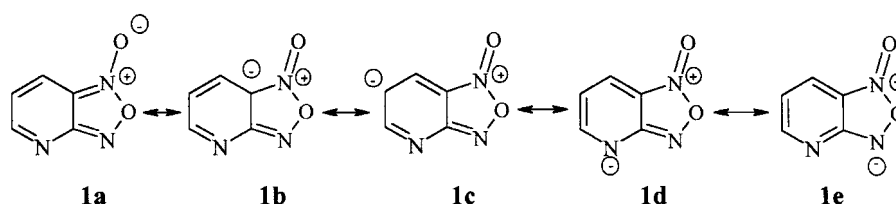


**Figure 8.** Mesomeric structures of pyridofuroxan

**Table 8.** $^1J_{CC}$ coupling constants for compounds **1**, **11**, **12**, **13** and the protonated form of **1**

|       | **1** | **1**[a] | **11**[b] | **12** | **13** |
|-------|-------|----------|-----------|--------|--------|
| C7a–C3a | 65.5 | 71.2 | —[c] | 71.2 | 76.2 |
| C5–C6 | 48.8 | 53.7 | 65.5 | 51.4 | 50.5 |
| C6–C7 | 61.4 | 58.8 | 52.7 | 56.0 | 59.5 |
| C7–C7a | 64.1 | 65.8 | 71.9 | 67.8 | 55.8 |

[a] For protonated form.
[b] Numbering of atoms for compounds **11**, **12** and **13** in Fig. 2; for compound **11**, corresponding couplings: C8–C8a = C7a–C3a, C5–C6 = C5–C6, C6–C7 = C6–C7 and C7–C8 = C7–C7a.
[c] Not observed.

compounds **11** and **1**. The value of $^1J_{C5C6}$ is 65.5 Hz for **11** and 48.8 Hz for **1**, showing the changes in bond localization for these two different compounds.

## CONCLUSIONS

We conclude that $^1$H, $^{13}$C and $^{15}$N NMR parameters are very well placed to provide information on the furoxan type of equilibrium and also on possible mechanism of furoxan formation. By means of these data it is possible to distinguish between the two structures (*N1*-oxide and *N3*-oxide) in equilibrium. A significant shielding increase by more 100 ppm for N4 reveals that this atom is the site of protonation and alkylation. Changes in $^1J_{CC}$ values and nitrogen chemical shifts can be used to show that bond localization between pyridofuroxans and their precursors is completely different. X-ray results and DFT molecular orbital calculations can be useful in supporting NMR signal assignments.

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