SYNTHESIS AND STRUCTURE OF NEW N-ALKOXY-N-(1-PYRIDINIUM)UREA CHLORIDES


Keywords: N-alkoxy-N-(1-pyridinium)urea salts, 1-N-alkoxyaminoypyridinium salts, N-alkoxy-N-chloroureas, synthesis, structure.

New N-[(4-amino)pyridinium]-N-methoxyurea chloride, N-[(2-aminopyridinium]-N-methoxyurea chloride and their analogs were synthesized by N-alkoxy-N-chloroureas reaction with the proper pyridines in acetonitrile or ether solution by improved procedure. XRD study of N-[(4-amino)pyridinium]-N-methoxypea and N-[(2-aminopyridinium]-N-methoxyurea revealed the elongation of N-N+ bonds and some shortening of MeO-N bonds, quinonoid deformation of pyridine rings compare to it unsubstituted analog. The substantial pyramidality of central nitrogen atom in O-N-N+ moiety and N-C carbamoyl bonds difference were established too. The structure summary of N-alkoxy-N-(1-pyridinium)urea salts and other derivatives of 1-(N-alkoxyamino)pyridinium salts has been done.

Introduction

1-(N-alkoxyamino)pyridinium salts were first synthesized by the interaction of N-chloro-N-methoxy-N-tert-alkylamines with pyridine. The hygroscopic 1-(N-alkoxyamino)pyridinium chlorides are easily converted in the unhygroscopic perchlorates. These compounds may be regarded as a kind of N-alkoxyhydrazines. Usually such N-alkoxyhydrazines are labile due to destabilization by nO(Me)→σ*(O,Me) orbital interaction or anomeric effect. But the 1-(N-alkoxyamino)pyridinium chlorides are relatively stable compounds due to impossibility of the orbital interaction caused by the absence of lone electron pair (LP) on nitrogen N+.

XRD study of the structure of perchlorate of 1-(N-methoxy-N-tert.alkyl)amino-4-pyridinium revealed a high degree of pyramidality of central nitrogen atom in the O-N=O geminal system. The sum of bond angles centered on this nitrogen atom (∑B) is 322.8°. But the pyramidality of O-N-O central nitrogen atom in acyclic N,N-dialkoxypyr when in perhydro-1,3,2-dioxazine is somewhat higher. However, it was found by an XRD study that in 1-(N-methoxy-N-tert.alkyl)amino-4-dimethylamino-pyridinium perchlorate, LP of central nitrogen is situated in pyridine plane (TaLPy is 18°), its ∑B is 325.7°, the N−N+ (1.445(2) Å) is shorter, and the N−OMe bond (1.425(2) Å) is longer. These structure changes reflect decreasing of action of nO(Me)→σ*(O,Me) anomeric effect and stabilization of N-N+ bond, respectively. These data are consistent with observed “quinonoid” deformation of pyridine ring in this compound. This phenomenon causes some difference in chemical properties of these classes of compounds. But reported structural data of N-alkoxy-N-(1-pyridinium)urea salts are not sufficient for the complete understanding of this novel kind of anumeric urea salts. So, this work was undertaken to synthesize new N-alkoxy-N-(1-pyridinium)urea salts and to study of their structure.

Experiments

1H and 13C NMR spectra were recorded on Varian VXP-300 spectrometer (300 and 75 MHz, respectively) and Varian JEMINI 2000 (400 and 100 MHz, respectively). Solvents were DMSO and CD3OD with TMS as internal standard and expressed as δ ppm. IR spectra were recorded on UR-20 in KBr pellets. Mass spectra were recorded on VG 70-70EQ mass spectrometer in fast atom bombardment (FAB) mode. XRD structural study was performed on Xcalibur 3 automatic four-circle diffractometer (MoKα-radiation, graphite monochromator, Sapphire-3 CCD-detector, Scanning). Elemental analysis for C, H and N was performed on Carlo Erba analyzer.

4-Dimethylaminopyridine (DMAP), 4-aminopyridine and 2-aminopyridine were sublimated under vacuum (3 Torr). The solvents were purified and dried according to standard procedures.

N-[1-(4-Dimethylamino)pyridinium]-N-methoxyurea chloride (I)

A solution of DMAP (327 mg, 2.674 mmol) in Et2O (30 mL) was added to a solution of N-chloro-N-methoxyurea (2) (350 mg, 2.868 mmol) in Et2O (5 mL) at -10 °C, the reaction mixture was maintained for 10 min at -10 °C, then 70 h at 5°C. The white precipitate was filtered off, washed with Et2O (10 mL), then dried for 2 h under
vacuum (2 Torr), yielding 1 as white crystals (607 mg, 92 %). m.p. 168–169 °C (decomp.), which was identified by 1H NMR spectroscopy and mass spectrometry. 2H NMR (300 MHz, CD3OD) δ = 3.35 (6H, s, NMe3), 3.88 (3H, s, NOMe) 7.07 (2H, d, 3J = 7.8, H Py), 8.30 (2H, d, 3J = 7.8, H Py). 1H NMR (400 MHz, (CD3)2SO) δ = 3.28 (6H, s, NMe3), 3.78 (3H, s, NOMe), 7.06 (2H, d, 3J = 7.8, H Py), 7.96 (2H, br.s, C(O)NH2). 8.44 (2H, d, 3J = 7.8, H Py). 13C NMR (100 MHz, (CD3)2SO) δ = 40.4 (NOMe), 63.1 (NOMe), 107.5, 142.1, 156.6, 157.0 (C-2, C-3, C-4, C-5, C-6 Py), 255.8 (C=O), IR 1628 (C=N), 1725 (C-4 Py), 158.0 (C-4 Py), 232.1 (C=O). MS, m/z (%) = 225 M+ (100), 180 (27), 168 (8), 122 (14).

N-[1-(4-Amino)pyridinium]-N-methoxyurea chloride (3)

A solution of 4-aminopyridine (186 mg, 1.976 mmol) in MeCN (16 mL) was added to a solution of 2 (242 mg, 1.947 mmol) in MeCN (5 mL) at 30 °C. The reaction mixture was heated to 18 °C during 18 h, maintained for 2 h at 18 °C, the precipitate was filtered off, washed with MeCN (4 mL), then CH2Cl2 (5 mL), dried under vacuum (5 mmHg), yielding 3 as yellowish-white hygroscopic crystals (408 mg, 95 %). m.p. 124–125 °C (decomp.) (i-PrOH). 1H NMR (300 MHz, CD3OD) δ = 3.09 (3H, s, Me), 3.34 (6H, s, NMe2), 3.89 (3H, s, NMe2), 6.93 (2H, d, 3J = 7.5, H Py), 8.25 (2H, d, 3J = 7.5, H Py). 13C NMR (75 MHz, CD3OD) δ = 64.2 (NOMe), 110.7 (C-3, C-5 Py), 144.5 (C-2, C-6 Py), 162.5 (C-4 Py), 232.1 (C=O). IR 1628 (C=N), 1747 (C=O), 3310 (N–H) cm−1. MS, m/z (%) = 183 M+ (100). Anal. Calcd. for C10H16ClN4O3: C 47.09, H 6.33, N 23.32. Found: C 47.09, H 6.31, N 23.36.

N-[1-(4-Dimethylamino)pyridinium]-N-methoxyurea chloride (6a)

A solution of 2-amino-1-pyridinium chloride (30 mg, 0.225 mmol) in MeCN (6 mL) was added to a solution of 2 (253 mg, 2.035 mmol) in MeCN (6 mL) at -22 °C, the reaction mixture was heated to 9 °C for 18 h, maintained for 1 h at 18 °C, the precipitate was filtered off, washed with MeCN (5 mL), dried under vacuum (2 mmHg), yielding 6a as colourless crystals (288 mg, 65 %). m.p. 167–168 °C (decomp.). 1H NMR (300 MHz, CD3OD) δ = 3.58 (3H, s, Me), 4.02 (2H, q, 3J = 7.8, CH2CH3), 6.93 (1H, t, 3J = 7.2, H Py), 7.30 (1H, t, 3J = 7.2, H Py), 7.37 (1H, t, 3J = 7.2, H Py). 13C NMR (75 MHz, CD3OD) δ = 225 M+ (100), 180 (41), 164 (6). MS, m/z (%) = 225 M+ (100). Anal. Calcd. for C10H16ClN4O3: C 47.09, H 6.33, N 23.36. Found: C 47.09, H 6.31, N 23.36.

XRD structural study of compounds 3 and 4

Crystals, suitable for X-ray structural analysis, were grown from a solution in i-PrOH–MeOH mixture of 3 and from a solution of 4 in i-PrOH. The structure was solved by conjugate gradient technique with the SHELX8 software and refined by full matrix method of least squares in anisotropic approximation for non-hydrogen atoms using the SHELXL8 software. The atomic coordinates, molecular geometry parameters, and crystallographic data of compounds 3 and 4 have been deposited in the Cambridge Crystallographic Data Center (deposits CCDC 1457353 (3) and 1457354 (4)).
Results and Discussion

We have synthesized novel amino-substituted pyridinium derivatives 3 and 4 by an interaction of 2 with 4-aminopyridine and 2-aminopyridine, respectively (Scheme 1).

Scheme 1. Synthesis of compounds 3 and 4.

This reaction has been carried out in MeCN solution, in which the products 3 and 4 are insoluble. In ether solution, 2 reacts with 4-methylpyridylurea to give 5. N-alkoxy-N-chlorourea 7 and 8 yield 6a and 6b with DMAP (Scheme 2). Products 5, 6a and 6b are insoluble in ether and appear as precipitates. As it analog 1 is sensitive to the presence of base, 11 N-alkoxy-N-chlorourea, 7 and 8 were used in excess in the syntheses of 6a and 6b. This procedure avoids partial decomposition of the products. The known compound 1 can also be synthesized by this method.

Scheme 2. Synthesis of compounds 6a and 6b. R = Et (6a, 7), Bu (6b, 8).

The structure of N-alkoxy-N-(1-pyridinium)urea chlorides 3, 4, 5, 6a and 6b was confirmed by 1H and 13C NMR spectroscopy, MS, and in the case of compounds 3 and 4 by XRD study also (Figure 1).

In the crystal, cations of compound 3 are linked in centrally symmetric dimmers by hydrogen bonds N1-H1a…O1i [i: -x,-y,-z] (H…O 2.09(2) Å, N-H…O 173.0(19)°). The dimmers are linked by intermolecular hydrogen bonds with Cl- anions participating N1-H1b…Cl1iv [x-y,-z] (H…Cl 2.74(3) Å, A-N-H…Cl 158(2)°), N4-H4a…Cl1iv [iii: 1/2+x,1/2-y,1/2+z] (H…Cl 2.39(3) Å, A-N-H…Cl 159(2)°), N4-H4b…Cl1iv [iv: 1-x,-y,-z] (H…Cl 2.33(3) Å, A-N-H…Cl 170(2)°), C3-H3…Cl1v [v: 1/2-x,1/2+y,-1/2-z] (H…Cl 2.68 Å, C-H…Cl 139°) and C7-H7…Cl1 (H…Cl 2.63 Å, A-C-H…Cl 155°). In compound 4 all intermolecular hydrogen bonds are formed with the participation of water and Cl- anions: N1-H1b…O3i [i: x,1/2-y,1/2+z] (H…O 1.96(3) Å, A-N-H…O 173(2)°), O3-H3b…O1 (H…O 2.06(3) Å, O-H…O 162(3)°), N1-H1a…Cl1 (H…Cl 2.51(2) Å, A-N-H…Cl 157(2)°), O3-H3a…Cl1iv [ii: -1+x,1/2-y,1/2+z] (H…Cl 2.28(4) Å, O-H…Cl 176(3)°), N4-H4a…Cl1iv [iii: x,y,1+z] (H…Cl 2.34(2) Å, A-N-H…Cl 165(2)°), N4-H4b…Cl1iv [iv: x,1/2-y,1/2+z] (H…Cl 2.53(3) Å, A-N-H…Cl 161(3)°) and C5-H5…O1v [v: 1-x,-y,2-z] (H…O 2.55 Å, A-C-H…Cl 146°).

In 3 and 4 central nitrogen atom of O—N—N+ geminal group is oriented to LP of N2 atom and forms a weak intramolecular hydrogen bond O-Nm…N (O-H…N 2.34(2) Å, N-H…N 101(2)°). In compound 4 the weak intramolecular hydrogen bond N1-H1b…O2 takes place (H…O 2.09(2) Å, A-H…O 173.0(19)°). The dimmers are linked by intermolecular hydrogen bonds with Cl- anions participating N1-H1b…Cl1iv [x,y,-z] (H…Cl 2.74(3) Å, A-N-H…Cl 158(2)°), N4-H4a…Cl1iv [iii: 1/2+x,1/2-y,1/2+z] (H…Cl 2.39(3) Å, A-N-H…Cl 159(2)°), N4-H4b…Cl1iv [iv: 1-x,-y,-z] (H…Cl 2.33(3) Å, A-N-H…Cl 170(2)°), C3-H3…Cl1v [v: 1/2-x,1/2+y,-1/2-z] (H…Cl 2.68 Å, C-H…Cl 139°) and C7-H7…Cl1 (H…Cl 2.63 Å, A-C-H…Cl 155°). In compound 4 all intermolecular hydrogen bonds are formed with the participation of water and Cl- anions: N1-H1b…O3i [i: x,1/2-y,1/2+z] (H…O 1.96(3) Å, A-N-H…O 173(2)°), O3-H3b…O1 (H…O 2.06(3) Å, O-H…O 162(3)°), N1-H1a…Cl1 (H…Cl 2.51(2) Å, A-N-H…Cl 157(2)°), O3-H3a…Cl1iv [ii: -1+x,1/2-y,1/2+z] (H…Cl 2.28(4) Å, O-H…Cl 176(3)°), N4-H4a…Cl1iv [iii: x,y,1+z] (H…Cl 2.34(2) Å, A-N-H…Cl 165(2)°), N4-H4b…Cl1iv [iv: x,1/2-y,1/2+z] (H…Cl 2.53(3) Å, A-N-H…Cl 161(3)°) and C5-H5…O1v [v: 1-x,-y,2-z] (H…O 2.55 Å, A-C-H…Cl 146°).
In the family of N-alkoxy-N-(1-pyridinium)ureas 1, 3, 4, 9 and 10 the largest degree of pyramidality of central nitrogen atom in O−N−N' germinal system is observed in compound 10. Probably, it is caused by the presence of weak electronegative dimethylcarbamoyl substituent at the nitrogen in contrast with the carbamoyl moiety present in other compounds. In compounds 1 and 3, the nitrogen pyramidality degrees are similar (Table 1).

It must be noted that quinonoid deformation of pyridine ring relatively to compound 9^* matches (Table 2). The (AlkO)N−C bond elongation and any N−C−N bond shortening relatively to compound 9 (Table 1) and the known quinonoid deformation of pyridine ring relatively to pyridine^16 and compound 9^* establishes (Table 2). Thus it may be supposed that resonance form 3B (Scheme 3) makes certain contribution to the structure of compound 14. In form 3B n_{N−C(O)}→σ^{*}_{N−C(O)} anomic effect becomes possible. Its action is opposite to that of n_{N−C(O)}→σ^{*}_{N−C(O)} anomic effect, which dominate in resonance form 3A.

In compound 4 a quinonoid deformation of pyridine ring is somewhat different, C4−C5 bond is shortened, C3−C4 bond is elongated, that is correspond with quinonoid form 4B (Scheme 4).

Note: 9 = 1-(N-methoxy-N-carbamoyl)aminopyridinium perchlorate, 10 = 1-(N-propoxy-N-dimethylcarbamoyl)amino-4-dimethylaminopyridinium perchlorate.

**Table 1. Structural parameters in N-alkoxy-N-(1-pyridinium)urea salts.**

<table>
<thead>
<tr>
<th>Compounds</th>
<th>N−N^*</th>
<th>N−OMe</th>
<th>N−C(O)</th>
<th>R^*_{N−C(O)}</th>
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</thead>
<tbody>
<tr>
<td>9^*</td>
<td>1.425(2)</td>
<td>1.400(2)</td>
<td>1.452(2)</td>
<td>1.323(2)</td>
</tr>
<tr>
<td>1^5</td>
<td>1.413(2)</td>
<td>1.411(2)</td>
<td>1.450(2)</td>
<td>1.310(2)</td>
</tr>
<tr>
<td>10^*</td>
<td>1.425(3)</td>
<td>1.429(3)(Pr)</td>
<td>1.465(3)</td>
<td>1.324(3)</td>
</tr>
<tr>
<td>3</td>
<td>1.410(2)</td>
<td>1.413(2)</td>
<td>1.438(2)</td>
<td>1.315(3)</td>
</tr>
<tr>
<td>4</td>
<td>1.415(2)</td>
<td>1.408(2)</td>
<td>1.432(2)</td>
<td>1.313(2)</td>
</tr>
</tbody>
</table>

*Standard numeration of pyridine ring atoms has been used.

In compound 3, the presence of 4-amino group causes some N−OMe bond elongation and some N−N' bond shortening relatively to compound 9 (Table 1) and the known quinonoid deformation of pyridine ring relatively to pyridine^16 and compound 9^* is established (Table 2). Thus it may be supposed that resonance form 3B (Scheme 3) makes certain contribution to the structure of compound 14. In form 3B n_{N−C(O)}→σ^{*}_{N−C(O)} anomic effect becomes possible. Its action is opposite to that of n_{N−C(O)}→σ^{*}_{N−C(O)} anomic effect, which dominate in resonance form 3A.

In compound 4 a quinonoid deformation of pyridine ring is somewhat different, C4−C5 bond is shortened, C3−C4 bond is elongated, that is correspond with quinonoid form 4B (Scheme 4).

**Table 2. Pyridinium ring deformation in N-alkoxy-N-(1-pyridinium)urea salts 1, 3, 4 and 10.**

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Bond lengths, Å</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N1-C2, N1-C6</td>
</tr>
<tr>
<td>9^*</td>
<td>1.341(2), 1.341(2)</td>
</tr>
<tr>
<td>1^5</td>
<td>1.361(2), 1.345(2)</td>
</tr>
<tr>
<td>10^*</td>
<td>1.366(3), 1.346(3)</td>
</tr>
<tr>
<td>3</td>
<td>1.353(2), 1.356(2)</td>
</tr>
<tr>
<td>4</td>
<td>1.357(2), 1.374(3)</td>
</tr>
<tr>
<td>PyN^*</td>
<td>1.337</td>
</tr>
</tbody>
</table>

In the family of N-alkoxy-N-(1-pyridinium)ureas 1, 3, 4, 9 and 10 the largest degree of pyramidality of central nitrogen atom in O−N−N’ germinal system is observed in compound 10. Probably, it is caused by the presence of weak electronegative dimethylcarbamoyl substituent at the nitrogen in contrast with the carbamoyl moiety present in other compounds. In compounds 1 and 3, the nitrogen pyramidality degrees are similar (Table 1).

It must be noted that quinonoid deformation of pyridine ring relatively to compound 9 (Table 1) and the known quinonoid deformation of pyridine ring relatively to pyridine^16 and compound 9^* is established (Table 2). Thus it may be supposed that resonance form 3B (Scheme 3) makes certain contribution to the structure of compound 14. In form 3B n_{N−C(O)}→σ^{*}_{N−C(O)} anomic effect becomes possible. Its action is opposite to that of n_{N−C(O)}→σ^{*}_{N−C(O)} anomic effect, which dominate in resonance form 3A.

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**Scheme 3. Resonance in compound 3.**

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Presence of 2-amino group in the pyridinium moiety causes some N−OMe elongation and any N−N’ shortening relatively to compound 9 (Table 1). Probably, it is the concurrence of the sequence of n N−O(Me) affects and n_{OMe}→σ^{*}_{N−OMe} anomic effects.

In the case of both 3 and 4 C−NH2 bond is shortened and its length is close to length of C=N−H2 bond.

It must be noted that quinonoid deformation of pyridine ring, similar to that observed in compound 3, also takes place in 1-N-alkoxyamino-4-dimethylaminopyridinium salts^11 (Scheme 5).

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New alkoxy-N-(1-pyridinium)urea chlorides

Scheme 5. Quininoid deformation in 1-N-alkoxyamino-4-dimethylaminopyridinium salts.

Conclusion

New N-[1-(4-amino)pyridinium]-N-methoxyurea chloride 3, N-[1-(2-amino)pyridinium]-N-methoxyurea chloride 4 and their analogs were synthesized by an improved procedure. XRD study of N-[1-(4-amino)pyridinium]-N-methoxyurea and N-[1-(2-amino)pyridinium]-N-methoxyurea revealed the elongation of N-N+ bonds and some shortening of MeO-N bonds, quinonoid deformation of pyridine rings compare to it unsubstituted analog. The substantial pyramidality of central nitrogen atom in O-N-N+ moiety and N-C carbamoyl bonds difference was also established. The structural features of N-alkoxy-N-(1-pyridinium)urea salts and other derivatives of 1-(N-alkoxyamino)pyridinium salts has been summarized.

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