1-(N-ETHOXYCARBONYL-N-ISOPROPYOXY)AMINO-4-DIMETHYLAMINOXYCARBONYL-N-PYRIDINUM CHLORIDE. SYNTHESIS AND STRUCTURE


Keywords: N-alkoxy-N-chlorocarbamates, 1-(N-alkoxy-N-alkoxycarbonyl)aminopyridinium salts, 1-(N-ethoxycarbonyl-N-isoproxyloxy)amino-4-dimethylaminopyridinium chloride, synthesis, structure.

Stable 1-(N-alkoxy-N-alkoxycarbonyl)amino-4-dimethylaminopyridinium salt, 1-(N-ethoxycarbonyl-N-isoproxyloxy)amino-4-dimethylaminopyridinium chloride, has been synthesized for the first time. Its structure has been studied by XRD method.

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INTRODUCTION

It has been found earlier[1,2] that an interaction of methyl N-alkoxy-N-chlorocarbamates (1a-f) with 4-dimethylaminopyridine (DMAP) is a route to unknown 1-(N-alkoxyamino-4-dimethylaminopyridinium chlorides (3a-f) which was presumably realized via initial formation of unstable 1-(N-alkoxy-N-methoxyxcarbonyl)amino-4-dimethylaminopyridinium chlorides (2a-f) as the reaction intermediates (Scheme 1). Evidently the decomposition of unstable compounds 2a-f yields 1-N-alkoxyamino-4-dimethylaminopyridinium chlorides (3a-f). Compounds 3a, b exist as structure (3a,b (b)) and “quinonoid” deformation of the pyridine ring take place.[3]

In this article synthesis of stable 1-(N-alkoxy-N-alkoxycarbonylamino-4-dimethylaminopyridinium chloride and XRD study of its structure have been described.

EXPERIMENTAL

1H and 13C NMR spectra were recorded on VARIAN JEMINI 400 spectrometer (400 and 100 MHz, respectively) in DMSO-d6 and CDCl3 as solvents with TMS as internal standard. Mass spectrum was 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, oscanning). DMAP was sublimated under vacuum (3 mm Hg). The solvents were purified and dried according to standard procedures.

Scheme 1. Reported synthesis of 1-N-alkoxyamino-4-dimethylaminopyridinium chlorides.

Synthesis of 1-(N-ethoxycarbonyl-N-isoproxyloxy)amino-4-dimethylaminopyridinium chloride (5)

A solution of DMAP (166 mg, 1.357 mmol) in MeCN (13 mL) was added to a solution of ethyl N-chloro-N-isoproxyloxy carbamate (4)[4] (245 mg, 1.347 mmol) in MeCN (6 mL) at 8 °C. The reaction solution was maintained at 8 °C for 46 h, then it was evaporated under vacuum (20 mm Hg), dried under vacuum (4 mm Hg), washed with benzene (12 mL), dried under vacuum (4 mm Hg), giving 5 as colorless hygroscopic crystals (399 mg, 97 %), m.p. 103-104 °C (with decomp.), after crystallization (CH3Cl2-EtOAc) m.p. 104-105 °C (with decomp.). 1H NMR (400 MHz, CDCl3) δ = 1.18 (6H, d, J = 6.0, NOCHMe2), 1.26 (3H, t, J = 7.2, CO2CH2Me), 3.36 (6H, s, NMe2), 4.23 (H, sept, J = 6.0, NOCHMe2), 4.28 (2H, q, J = 7.2, CO2CH2Me), 7.39 (2H, d, J = 8.0, H Py), 8.17 (2H, d, J = 8.0, H Py).
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I-(EtO2C)(iPr)N-4-MeN-pyridinium chloride

8.0, HPy). 1H (400 MHz, (CD3)2SO) δ = 1.23 (6H, d, J' = 6.4, NOCHMe2), 1.26 (3H, t, J' = 7.0, CO2CH2Me). 3.29 (6H, s, NMe2); 4.29 (H, sept, J' = 6.4, NOCHMe2), 4.30 (2H, q, J' = 7.0, CO2CH2Me), 7.11 (2H, d, J' = 8.0, HPy), 8.68 (2H, d, J' = 8.0, HPy). 13C NMR (100 MHz, CDCl3) δ = 13.9 (CO2CH2Me), 20.5 (NOCHMe2), 41.2(NMe2), 65.7(NOCHMe2), 79.2 (CO2CH2Me), 155.6, 156.8 (C-3, C-5, C-2, C-6 Py), 166.7 (C-4 Py), 185.5 (C=O). Mass spectrum, m/z, (Irel %): 268 M+ (100). Anal. Calcd. for C13H26Cl2N3O2: N 13.83; Found: N 13.65.

XRD structural study of compound (5)

Crystals of 5 suitable for X-ray structural analysis were grown from a solution in CH3Cl2-EtOAc mixture at 6 °C. Triclinic, C13H26NO3Cl2·H2O, at 100 K, α = 9.2359(8) Å, b = 13.2566(8) Å, c = 13.8685(9) Å, α = 75.552(5)°, β = 89.534(7)°, γ = 89.291(6)°, V = 1644.2(2) Å3, M = 321.80, Z = 4, space group P T, dcalc = 1.30 g cm–3, μ(MoKα) = 0.25 mm–1, F(000) = 688. Cell parameters and intensities of 11451 reflections (5737 independent reflections, Rint = 0.068) were measured using Xcalibur 3o diffractometer (graphite-monochromated MoKα radiation, CCD detector, 2 θ range = 50°)

The structure solved by direct method using SHELX-2016 program package. 4 Positions of hydrogen atoms were located geometrically and refined using the riding model with Uiso=Ueq(2) of the carrier atom (n=1.5 for methyl moieties and n=1.2 for other hydrogen atoms). Full-matrix least-squares refinement against F2 in anisotropic approximation for non-hydrogen atoms to wR2 = 0.2844 for 5737 reflections (Rw = 0.108 for 4016 reflections with F>4σ(F), S = 1.389). The final atomic coordinates, molecular geometry parameters, and crystallographic data of compound 5 were deposited in the Cambridge Crystallographic Data Center, 12 Union Road, CB2, 1EZ, UK (fax:+44-1223-336033, e-mail: deposit@cdcc.cam.ac.uk) and is available on request quoting the deposition number CCDC 1565981).

RESULTS AND DISCUSSION

We have found that ethyl N-chloro-N-isopropylxycarbamate (4)3 reacted with DMAP in acetonitril yielding relatively stable 1-(N-ethoxy carbonyl-N-isopropylxylamino-4(dimethylaminopyridinium chloride (5) (Scheme 2). The reaction must be carried out in mild condition at 8 °C, because under certain conditions compound (5) may be spontaneously converted to 1-N-isopropylxylamino-4(dimethylaminopyridinium chloride (3e), for example if the reaction time is increased to 93 h.

Compound (5) is the first example of stable 1-(N-alkoxy-N-alkoxy carbonyl)amino-4(dimethylaminopyridinium chloride, a novel kind of N-alkoxy hydrizines. 1,2,5-10 Earlier it was regarded that 1-(N-alkoxy-N-alkoxy carbonyl)amino-4(dimethylaminopyridinium chlorides were very labile and cannot exist, for example compounds 2a-2f. The structure of 1-(N-ethoxy carbonyl-N-isopropylxylamino-4(dimethylaminopyridinium chloride (5) has been confirmed by data of 1H and 13C NMR spectra and mass spectrum. Also XRD study of N-alkoxy hydrizine (5) has been done (Figure 1, Tables 1 and 2).

It was found that in independent part of the unit cell of crystal of compound 5 there were two organic cations of forms 5a and 5b, two Cl- anions and two molecules of water. Cations 5a and 5b differ by some geometric parameters.

Evidently, the positive charge is localized mainly on N(3) atom of Me2N-group conjugate to the pyridine ring, which is confirmed by shortening of the N(3)–C(3) bond as in cation 5a and 5b (Table 1) in comparison with average value of 1.371 Å for N–C atom bond. 11 The lengths of the N(3)–C(3) bonds are close to mean value of N=C bond (1.316 Å). 11 Thus 1-(N-ethoxy carbonyl-N-isopropylxylamino-4-di-3-methylaminopyridinium chloride (5) structure is more closed to “quinonoid” structure 5b (Scheme 2).

The observed altering of pyridine bonds conforms to this assumption: the C(2)–C(3) and C(3)–C(4) bonds are elongated in cation 5a and 5b, the N(2)–C(1) and N(2)–C(5) bond are elongated in both the cations 5a and 5b (Table 1), whereas the C(1)–C(2) and C(4)–C(5) bonds are shortened in both the cations in comparison with average bond lengths of pyridine 11 (Table 1).

In Table 1 the parameters of “quinonoid” deformation of pyridine ring are given in comparison 7 with those of 1-(N-methoxyamino)pyridinium perchlorate (6) with unsubstituted on 4-site as reference etalon and 1-(N-alkoxyamino)–4(dimethylaminopyridinium salts (3a), 3b, 3c (Scheme 3). The corresponding bond lengths of compounds 2a, 3a, 5a, 5b, 7 and 8 are similar in contrast to those in 4-unsubstituted 6. Evidently, the nature of the substituent (H, CO2Et, C(O)NH2, C(O)NMe2) at nitrogen atom, which are bound with alkyl group, causes slight influence on “quinonoid” deformation of pyridine ring.

In 5 atom N(2) has planar configuration. The sum of bond angles centered at this nitrogen atom (∑β) is 359.9° as in 5a as in 5b. But amide nitrogen atom N(1), the central atom of geminal systems O-N-N+, has pyramidal configuration. Its ∑β is equal 335.6° in (5a) and 335.4° in 5b. Among anomic structures 12,13 the existing in two or more forms differing by the pyramidal degree of the amide nitrogen atom is known for N-ethoxy-N-chlorourea 14 and N-chloro-N-methoxy-N’-(4-nitrophenoxy)urea. 15 Also, N-[benzoyl]hydroxymethyl]-N-benzyloxy-N’-(2-bromo-phenyl)-urea exists in two forms which vary in a different degree of pyramidalism of the same nitrogen atom. 16

Scheme 2. Formation of (5).
Scheme 3. Structure of 6, 7, 8 and 9.

Figure 1. Molecular structure of 5A monohydrate.

Table 1. Pyridine ring deformation in 1-(N-alkoxyamino)pyridinium salts (3a), (5A), (5B), (6), (7) and (8).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Bond lengths, Å</th>
<th>N2-C1</th>
<th>C1-C2</th>
<th>C4-C5</th>
<th>C2-C3</th>
<th>C3-C4</th>
<th>C3-NMe2</th>
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<tbody>
<tr>
<td>6</td>
<td></td>
<td>1.341(2)</td>
<td>1.385(3)</td>
<td>1.349(5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5A</td>
<td></td>
<td>1.348(7)</td>
<td>1.360(7)</td>
<td>1.432(7)</td>
<td>1.337(7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5B</td>
<td></td>
<td>1.356(7)</td>
<td>1.352(7)</td>
<td>1.429(7)</td>
<td>1.326(7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3a</td>
<td></td>
<td>1.349(2)</td>
<td>1.351(2)</td>
<td>1.414(2)</td>
<td>1.337(2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>1.354(2)</td>
<td>1.355(2)</td>
<td>1.416(2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>1.361(2)</td>
<td>1.353(3)</td>
<td>1.425(2)</td>
<td>1.324(2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Py</td>
<td></td>
<td>1.337</td>
<td>1.380</td>
<td>1.379</td>
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</tr>
</tbody>
</table>

Numbering of pyridine ring shown Figure 1 has been used

In compound 5 the $\Sigma \beta$ is more in comparison to those in known 1-(N-alkoxyamino)pyridinium salts (3a, b), (6), (7) and (8) (Table 1).

Probably it is caused by higher electron withdrawing capacity of EtO-C-substituent compare to hydrogen (3a, 3b), carbamoyl (6, 7) and dimethylcarbamoyl (8) substituents. In anomic amides the presence of electron withdrawing substituent at pyridinal amide nitrogen atom diminishes it pyramidalness degree.12,13

The lone pair (LP) of the N(1) atom is almost coplanar to the pyridine plane (the LPN(1)−N(1)−N(2)−C(1) torsion angle (TaLPPy) is -10.40° in cation 5A and 14.60° in cation 5B. The conjugation between LP(N(1) and π-system of pyridine is impossible. The same type of LP(N(1) orientation was revealed for other 1-(N-alkoxyamino)pyridinium salts 3a, 3b, 6, 7, 8 and 8 (Table 2).

In compound 5 the N−N' bond is elongated compare to the N−N bond in hydrazides of carboxylic acids (1.400 Å).17 Probably, this N=N' bond elongation has been caused by $n_{(\text{OMe})}$→$\sigma^*_{N,N'}$ anomeric effect action as in cases of 1-(N-alkoxyamino)pyridinium salts 3a, 3b, 6, 7, 8 and 8.5

The lengths of the amide N−C bond in compound 5 is close to that in methyl N-(4-chlorobenzoyloxy)-N-methoxycarbamate 9 (1.423(2) Å). The degrees of the nitrogen pyramidalness in compounds 5 and 9 ($\Sigma \beta$ 334.1) are also close.18 There is some elongation of the amide N−C bond in compound 5 compare to that in amides19 (1.359 Å). It is caused by different degrees of C=O conjugation with sp$^3$ hybridized nitrogen atom in compounds 5, 9 and sp$^2$ hybridized nitrogen atom in usual amides.12,13

In compound 5 ester moiety adopts +sc- and -sc-conformations relatively to the N(1)−N(2) bond, respectively. The C(11)−O(1)−N(1)−N(2) torsion angle is 77.8(5)° in 5A and -81.4(5)° in 5B. Ethoxy moiety has -sc-conformation toward to the C(8)−O(3) bond, the C(8)−O(3)−C(9)−C(10) torsion angle is -77.1(7)° in (5A) and -84.8(8)° in 5B.

The isopropoxy substituent is situated in sp-conformation toward to the N(1)−N(2) bond. The N(2)−N(1)−C(8)−O(2) torsion angle is -23.3(8)° in 5A and 20.3(10)° in 5B. This orientation of substituent is stabilized by attractive intramolecular shortening contact N(2)···H(11) 2.65 Å in 5A and 2.63 Å in 5B, the van der Waals radii sum is 2.66 Å.20

Table 2. Some structure parameters in 1-(N-alkoxyamino)pyridinium salts

<table>
<thead>
<tr>
<th>Compound</th>
<th>Σβ, °</th>
<th>Bond lengths, Å</th>
<th>Tal.LPP, °</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N–N*</td>
<td>N–OR</td>
</tr>
<tr>
<td>5A</td>
<td>335.6</td>
<td>1.418(6)</td>
<td>1.411(6)</td>
</tr>
<tr>
<td>5B</td>
<td>335.4</td>
<td>1.421(6)</td>
<td>1.414(6)</td>
</tr>
<tr>
<td>3a (ref.1)</td>
<td>312</td>
<td>1.428(2)</td>
<td>1.431(2)</td>
</tr>
<tr>
<td>3b (ref.1)</td>
<td>312</td>
<td>1.426(1)</td>
<td>1.440(1)</td>
</tr>
<tr>
<td>6 (ref.7)</td>
<td>333.9(3)</td>
<td>1.4254(18)</td>
<td>1.3999(17)</td>
</tr>
<tr>
<td>7 (ref.8)</td>
<td>332.7</td>
<td>1.413(2)</td>
<td>1.411(2)</td>
</tr>
<tr>
<td>8 (ref.8)</td>
<td>324.22</td>
<td>1.425(3)</td>
<td>1.429(3)</td>
</tr>
</tbody>
</table>

In crystal of 5 due to system of intramolecular hydrogen bonds with participating of chlorine anions and bridging molecules of water three-dimensional network takes place:

O(4WA)–H(4WA)…Cl(1A)’  (x,y,z) H…Cl’  2.50 Å, O–H…Cl’  142°;
O(4WA)–H(4WB)…Cl(1A)’  (2-x,1-y,1-z) H…Cl’  2.46 Å, O–H…Cl’  157°;
O(4WB)–H(4WC)…Cl(1B)’  (x,y,z) H…Cl’  2.37 Å, O–H…Cl’  165°;
O(4WB)–H(4WD)…Cl(1B)’  (1-x,1-y,1-z) H…Cl’  2.58 Å, O–H…Cl’  143°;
C(1A)–H(1A)…Cl(1B)’  (1-x,1-y,1-z) H…Cl  2.90 Å, C–H…Cl  125°;
C(1B)–H(1B)…Cl(1A)’  (1-x,1-y,1-z)H…Cl  2.58 Å, C–H…Cl  143°;
C(2A)–H(2A)…Cl(1B)’  (1-x,1-y,1-z) H…Cl  2.87 Å, C–H…Cl  127°;
C(4B)–H(4B)…Cl(1A)’  (2-x,1-y,1-z) H…Cl  2.76 Å, C–H…Cl  134°;
C(5A)–H(5A)…Cl(1B)’  (2-x,1-y,1-z) H…Cl  2.68 Å, C–H…Cl  138°;
C(7A)–H(7AC)…Cl(1A)’  (x,y,z) H…Cl  2.81 Å, C–H…Cl  143°;
C(7A)–H(7AC)…Cl(1A)’  (x,y,z) H…Cl  2.81 Å, C–H…Cl  143°;
C(7A)–H(7AB)…O(2A)’  (2-x,1-y,1-z) H…O  2.40 Å, C–H…O  176°;
C(7B)–H(7BC)…C(5A)’  (π) (2-x,1-y,1-z) H…C  2.73 Å, C–H…C  148°

Conclusion
The first stable 1-(N-alkoxy-N-alkoxycarbonyl)amino-4-dimethylaminopyridinium salt, 1-(N-ethoxycarbonyl-N-isoproplxy)amino-4-dimethylaminopyridinium chloride, has been synthesized. XRD study of it structure has been done.

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References


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