Unusual Ambident Behavior and Novel Ring Transformation of Oxazolo[3,2-*a*]pyridinium Salts

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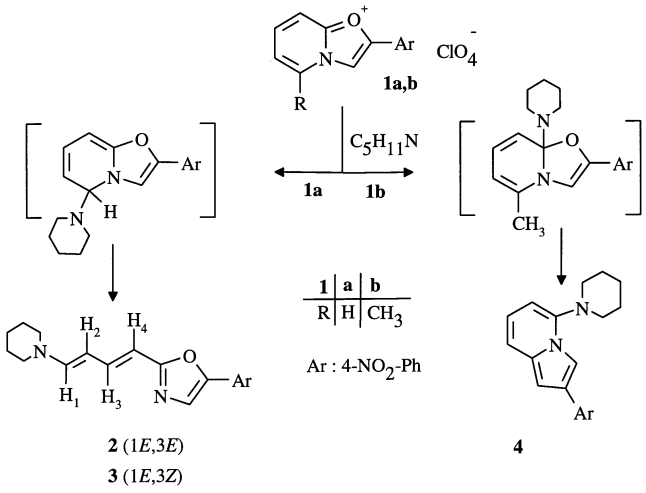
2-Aryloxazolo[3,2-*a*]pyridinium perchlorate, **1a**, and its 5-methyl homologue, **1b**, undergo quite different ring transformations when reacting with piperidine. For **1a** the opening of the pyridine fragment occurs with formation of the isomeric aminobutadienes **2** [with (1*E*,3*E*)-configuration] or **3** [(1*E*,3*Z*)-isomer], depending on the temperature, whereas **1b** undergoes an unexpected recyclization of the oxazolium ring involving the methyl group to form the 5-aminoindolizine **4**. **1a** and **1b** undergo an opening of the 5-membered ring when reacting with alkali. These results are explained by quantum chemical SINDO1 calculations, which give the energies of the isomeric C-5 and C-8a adducts with NMe_2 and HO groups.

The reactivity of the bicyclic heteroaromatic system oxazolo[3,2-*a*]-pyridinium perchlorate **1** with a bridgehead nitrogen (first prepared in 1960's[1]) is still poorly investigated, and there are only few examples given in the literature of its reaction with nucleophiles. Such a cation undergoes an opening of the oxazolium ring in alkaline solution,[2] and it transforms the same ring in the reaction with primary aliphatic[3] (but not aromatic[4]) amines, or some other nucleophiles from the 5th main group.[5] Recently it was found that carbanions can also be used to transform the cations **1** to indolizines.[6] Although the data reviewed indicate that only the 5-membered ring opens, the closely related heteroanalog, the thiazolo[3,2-*a*]pyridinium cation, undergoes an opening of the 6-membered ring in reactions with secondary amines.[7] No data on the reactions of the cation **1** with secondary amines is available.

We report here that 2-aryloxazolo[3,2-*a*]pyridinium perchlorate, **1a**, and its 5-methyl homologue, **1b**, undergo quite different ring transformations with piperidine. For **1a** the opening of the six-membered fragment (previously unknown for this ring system) occurs with formation of the isomeric aminobutadienes **2** and **3**, whereas the 5-methyl homologue **1b** reacts with the same amine to give 5-piperidylindolizine **4** (Scheme 1).

Heating of the salt **1a** with piperidine results in formation of the 1:1 adduct (**2**) of the starting materials; the composition of the product is confirmed by the MS and elemental analysis data. The aliphatic carbon atom signals in the ^{13}C-

Scheme 1. Ring transformations of the fused oxazolopyridinium perchlorates



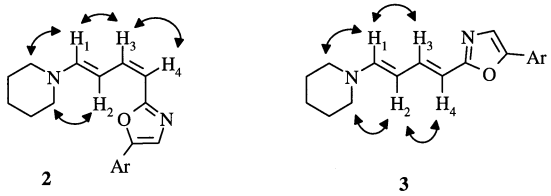
NMR spectra correspond only to the piperidyl group; the absence of other aliphatic carbon atom peaks (expected for any of the addition products) is supporting evidence for the presence of the open-chain structure. The intense bands in the UV spectra of **2** (λ_{max} = 350 nm and 462 nm), typical for conjugated dienes with intramolecular charge transfer, and the diene band (ν = 1625 cm^{-1}) in its IR spectra, also confirm that the opening occurs at the six-membered ring. In the MS of **2** the observed peak M = 241 (loss of the

  1434–193X/98/0101–0193 $ 17.50+.50/0

piperidine fragment) may be associated with the probable reversed cyclization of **2** to the cation **1a**. The coupling constants in the ^{1}H-NMR spectra of **2** (J_{23} = 12.9 Hz, J_{23} = 11.3 Hz, J_{34} = 15.2 Hz) support the *all-(E)* configuration of the butadiene structure of **2**.

The reaction of the salt **1a** with piperidine at room temp. leads to the isomeric aminobutadiene **3**. The spectral data (UV, IR, and MS) and chromatographic behavior of the isomers **2** and **3** are quite similar, and the main difference is manifested in their ^{1}H-NMR spectra in benzene. The final assignment of the (1*E*,3*Z*) configuration to isomer **3** and (1*E*,3*E*) configuration to isomer **2** was confirmed by NOESY (Scheme 2). The ring opening reactions of **1a** to **2** and **3** occur smoothly, and open an easy route to the unknown α-amino-ω-(oxazolyl-2)-butadienes which have a high asymmetry in their π-electron density.

Scheme 2. NOESY data and configuration of the aminobutadienes **2** and **3**



The salt **1b,** in the same reaction with piperidine, yields the red product **4**, with properties quite different from those expected from either an adduct or a ring-opening product. Absence of the signal of methyl group in its ^{1}H-NMR spectra, and appearance of two singlets in the aromatic region, confirm the closure of the new pyrrole ring via transformation of the oxazolium fragment and involving the methyl group. Indeed, the ^{1}H-NMR spectra of **4** is similar to the spectra of the reference structure 2-(*p*-nitrophenyl)indolizine, and the absence of a downfield signal of 5-H is compensated by appearance of 5-piperidyl group signals. The multiplet of 7-H (unresolved in $CDCl_3$) can be resolved in $(CD_3)_2CO$. The doublets for protons 6-H (δ = 6.09, J_{67} = 7.3 Hz) and 8-H (δ = 7.17, J_{78} = 8.8 Hz), that are separated from 7-H by a single and a double C−C bond, respectively, have been assigned according to the known trend for ^2J in the cyclic polyenes.[8] Assignment of the structure **4** to the still unknown class of 5-aminoindolizine[9] is also supported by the fact that it forms a deep blue dye with *p*-dimethylaminobenzaldehyde (the classical Ehrlich test), typical for indolizines.[10] In CF_3COOH indolizine **4** undergoes protonation at C-3 (a singlet at δ = 5.62 is usual for CH_2 protons of 3H-indolizinium cations).[11]

The unusual shift of the ring-opening selectivity from the cation **1a** to **1b** may be connected with either the sterical effect of the 5-methyl group, or its possible deprotonation. It should be also mentioned that both homologues **1a** and **1b** undergo the expected opening of 5-membered ring when reacting with alkali to form *N*-(β-oxoalkyl)pyridones-2. In order to clarify the complex influence of the 5-methyl group, and the nature of the attacking nucleophile on the selectivity of ring opening, we performed quantum chemical SINDO1[12] calculations for the adducts formed from cations **1a** and **1b** and hydroxyl and dimethylamino groups.

Since there are a few electron deficient positions in the bicyclic ring system **1** the isomeric C-5-, C-8a-, C-7-, and C-2-adducts with nucleophiles are taken for comparison for every homolog. The structures of the adducts were fully optimized by SINDO1. The total energy (see Table 1) was, in all cases, lowest for the C-8a-adduct (favorable for 5-membered-ring opening). This can explain the observed results of the reactions of the cations **1a** and **1b** with alkali, as well as the initial step of the recyclization **1b** → **4** (see Scheme 1). The question arises of how to explain the reactions **1a** → **2** (**1a** → **3**), where the initial step of the pyridine-ring opening requires the nucleophilic attack of the amine at position C_5. The answer can be found in Table 2, where the relative energies of the isomeric adducts are given with respect to the most stable case. As one can conclude, just in the unique case of C-5 and C-8a adducts of cation **1a** with amine the difference in energy between these two adducts is negligible. Hence, the driving force for the experimentally observed 6-membered-ring opening may not be the initial nucleophilic attack, but the next step of ring cleavage (5- or 6-membered). One can assume that formation of the dieneamines **2** and **3** (via the 6-membered-ring opening) may be much more preferable than the formation of the zwitterionic adduct that would result in the case of 5-membered-ring cleavage.

Table 1. Total energy (Hartree)[a] of adducts between the cations **1a**,**b** and nucleophiles

Oxazolopyridine **1**	**1a** (5-H)		**1b** (5-Me)	
Nucleophile/Place of addition	OH	NMe_2	OH	NMe_2
8a	−86.621	−95.196	−93.548	−102.124
5	−86.613	−95.194	3.527	−102.099
7	−86.601	−95.184	−93.530	−102.113
2	−86.604	−95.183	−93.534	−102.115

[a] 1 Hartree = 627.5 kcal/mol.

Table 2. Relative energies (kcal/mol) of isomeric adducts in respect to the most stable C-5-adduct

Oxazolopyridine **1**	**1a** (5-H)		**1b** (5-Me)	
Nucleophile/Place of addition	OH	NMe_2	OH	NMe_2
8a	0	0	0	0
5	4.46	0.82	13.13	15.80
7	12.37	7.57	11.12	7.28
2	10.31	8.03	8.28	5.96

The previously unreported opening of 6-membered ring in **1a**, is somewhat similar to the behavior of the related bridgehead nitrogen heterocycles,[7][13][14] and is the first proof of the ambident properties of the cation **1**. The second transformation discovered, **1b** → **4**, which opens a

route to unknown 5-aminoindolizines, is quite unusual, even when one considers the entire family of bridgehead azoloazines.[14] It should be mentioned that this novel disconnection scheme for the construction of the indolizine ring was recently predicted[15] using the computer program GREH.[16]

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Experimental Section

2-(p-Nitrophenyl)oxazolo[3,2-a]pyridinium Perchlorate (**1a**): 1.0 g (3.87 mmol) of *N*-(*p*-nitrophenacyl)pyridone-2[17] was dissolved in 2 ml of H_2SO_4 and kept for about 12 h. The solution was diluted by 150 ml of water, heated to 90°C, and 70% $HClO_4$ (10 ml) was then added to the hot filtered solution, giving **1a** as a white solid (0.93 g, 70%, m.p. 190−191°C, H_2O/EtOH, 1:1). − $C_{13}H_9ClN_2O_7$ (340.5): calcd C 45.83, H 2.66, N 8.22; found C 45.74, H 2.70, N 8.02. − ^{1}H NMR (CF_3COOH, 400 MHz, TMS): δ = 9.05 (d, 1 H, H-5), 8.92 (s, 1 H, H-3), 8.5−8.6 (m, 3 H, H-7, *p*-NO_2Ph), 8.2−8.3 (m, 3 H, H-8, *p*-NO_2Ph), 8.00 (t, 1 H; H-6).

5-Methyl-2-(p-nitrophenyl)oxazolo[3,2-a]pyridinium Perchlorate (**1b**) was prepared, by the method described for **1a,** from 6-methyl-*N*-(*p*-nitrophenacyl)pyridone-2; 69%, m.p. 255°C. − $C_{14}H_{11}ClN_2O_7$ (354.5): calcd. C 47.41, H 3.13, N 7.90; found C 47.14, H 3.09, N 7.89. − ^{1}H NMR (CF_3COOH, 400 MHz, TMS): δ = 8.86 (s, 1 H, H-3), 8.53 (m, 2 H, *p*-NO_2Ph), 8.45 (dd, 1 H, H-7), 8.27 (m, 2 H, *p*-NO_2Ph), 8.10 (d, 1 H, H-8), 7.78 (d, 1 H, H-6), 3.07 (s, 3 H, CH_3).

4-[5-(p-Nitrophenyl)oxazolyl-2]-1-piperidylbutadiene-(1E,3E) (**2**): To a solution of 0.2 g (0.59 mmol) of the salt **1a** in 5 ml of CH_3CN 0.5 ml of piperidine was added, and the mixture was refluxed for 1 h. The cooled solution was poured into 30 ml of water, yielding a dark-red solid (0.157 g, 88%, m.p. 179−180°C). − $C_{18}H_{19}N_3O_3$ (325.1): calcd. C 66.45, H 5.88, N 12.91; found C 66.59, H 5.95, N 12.35. − ^{1}H NMR ([D$_6$]benzene, 200 MHz, TMS): δ = 7.93 (m, 2 H, *p*-NO_2Ph), 7.12 (m, 2 H, *p*-NO_2Ph), 7.60 (dd, *J* = 11.3/15.2 Hz, 1 H, H-3), 7.30 (s, 1 H; H in oxazole), 6.35 (d, *J* = 15.2 Hz, 1 H; H-4), 6.12 (d, *J* = 12.9 Hz, 1 H; H-1), 5.23 (dd, *J* = 11.3/12.9 Hz, 1 H, H-2), 2.7 (m, 4 H, piperidyl), 1.1 (m, 6 H, piperidyl). − MS; *m/z* (%): 325 (60) [M^+], 241 (100) [$C_{13}H_9N_2O^3_+$], 195 (70) [$C_{13}H_9NO^+$], 122 (10) [*p*-NO_2Ph], 84 (6) [piperidyl]. − UV/Vis ($CHCl_3$): λ_{max} (lg ε) = 259 nm (3.80), 287 (3.80), 350 (4.32), 462 (4.36).

4-[5-(p-Nitrophenyl)oxazolyl-2]-1-piperidylbutadiene-(1E,3Z) (**3**): A solution of 0.2 g (0.59 mmol) of the salt **1a** in 1 ml of piperidine was kept for 2 h at 20°C. The solution was poured into 50 ml of water, giving a dark-red solid (0.155 g, 81%, m.p. 160−161°C). ^{1}H NMR ([D$_6$]benzene, 200 MHz, TMS): δ = 7.90 (m, 2 H, *p*-NO_2Ph), 7.09 (m, 2 H, *p*-NO_2Ph), 7.40 (s, 1 H, H in oxazole), 7.03 (dd, *J* = 9.0/12.9 Hz, 1 H, H-2), 6.55 (dd, *J* = 9.0/10.7 Hz, 1 H, H-3), 6.22 (d, *J* = 12.9 Hz, 1 H, H-1), 5.97 (d, *J* = 10.7 Hz,1 H, H-4), 2.8 (m, 4 H, piperidyl), 1.2 (m, 6 H, piperidyl). − MS; *m/z* (%): 325 (63) [M^+], 241 (100) [$C_{13}H_9N_2O^+_3$], 195 (66) [$C_{13}H_9NO^+$], 122 (15) [*p*-NO_2Ph], 84 (8) [piperidyl]. − UV/Vis ($CHCl_3$): λ_{max} (lg ε) = 259 nm (4.46), 287 (4.41), 346 (4.88), 464 (4.88). Whilst in the NMR tube (solvent C_6D_6 or $CDCl_3$) **2** slowly isomerized to **3**.

2-(p-Nitrophenyl)-5-piperidylindolizine (**4**): 0.1 g (0.282 mmol) of the salt **1b** in 1 ml of piperidine was refluxed for 15 min. The cooled mixture was poured into water, and the resulting solid was filtered and purified by column chromatography (Silpearl, $CHCl_3$), giving **3** (0.06 g, 66%, m.p. 174°C, EtOH). − $C_{19}H_{19}N_3O_2$ (321.2): calcd. C 71.01, H 5.90, N 13.08; found C 70.87, H 5.98, N 13.17. − ^{1}H NMR ($CDCl_3$, 200 MHz, TMS): δ = 8.23−7.80 (m, 4 H, *p*-NO_2Ph), 7.70 (s, 1 H, H-3), 7.17 (d, *J* = 8.8 Hz, 1 H, H-8), 6.77 (s, 1 H, H-1), 6.77 (dd, *J* = 8.8/7.3 Hz, 1 H, H-7), 6.09 (d, *J* = 7.3 Hz, 1 H, H-6), 3.1 (m, 4 H, piperidyl), 1.6 (m, 6 H, piperidyl). − ^{1}H NMR (CF_3COOH, 400 MHz): δ = 8.43 (m, 2 H, *p*-NO_2Ph), 8.29 (m, 1 H, H-7), 7.93 (m, 2 H; *p*-NO_2Ph), 7.58 (d, *J* = 7.9 Hz, 1 H, H-8), 7.55 (s, 1 H, H-1), 7.32 (d, *J* = 8.5 Hz, 1 H, H-6), 5.62 (s, 2 H, H-3), 3.53 (s, 4 H, piperidyl), 1.91 (s, 6 H, piperidyl). − MS; *m/z* (%): 321 (100) [M^+], 292 (71), 238 (79), 192 (33), 96 (24).

2-(p-Nitrophenyl)indolizine:[18] ^{1}H NMR ($CDCl_3$, 400 MHz, TMS): δ = 8.25 (m, 2 H, *p*-NO_2Ph), 7.91 (d, *J* = 7.0 Hz, 1 H, H-5), 7.77 (m, 2 H, *p*-NO_2Ph), 7.66 (s, 1 H, H-3), 7.38 (d, *J* = 9.0 Hz, 1 H, H-8), 6.74 (s, 1 H, H-1), 6.7 (dd, *J* = 6.8 Hz, *J* = 9.0 Hz, 1 H, H-7), 6.52 (t, *J* = 7.0/6.8 Hz, 1 H, H-6).

6-Methyl-N-(p-nitrophenacyl)pyridone-2: A mixture of 6.0 g (24.6 mmol) of *p*-nitrophenacyl bromide, and 3.0 g (24.4 mmol) of 2-methoxy-6-methylpyridine in 20 ml of CH_3CN, was refluxed for 11 h yielding a solid (2.5 g, 39%, m.p. 186°C, PrOH). − $C_{14}H_{12}N_2O_4$ (272.3): calcd. C 61.76, H 4.44; found C 61.78, H 4.68. − IR (nujol): ν = 1700 cm^{-1}(COPh), 1670 (CON). − ^{1}H NMR ($CDCl_3$, 200 MHz, TMS): δ = 8.3 (m, 4 H, *p*-NO_2Ph), 7.33 (dd, *J* = 6.8/9.2 Hz, 1 H, H-4), 6.5 (d, *J* = 9.2 Hz, 1 H, H-3), 6.15 (d, *J* = 6.8 Hz, 1 H, H-5), 5.49 (s, 2 H, CH_2), 2.29 (s, 3 H, CH_3). − MS; *m/z* (%): calcd. 272 (97) [M^+].

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