A new synthesis of 4-oxo-4,5-dihydro-1,3-oxazolium perchlorates from D-pantoamide

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Abstract: The reaction of D-(−)-pantolactone with ammonia leads to the formation of D-pantoamide, which reacts with Ac₂O and HClO₄ to give 5-[2-(acetoxy)-1,1-dimethylethyl]-2-methyl-4-oxo-4,5-dihydro-1,3-oxazolium perchlorate. The obtained 2-methyl-1,3-oxazolium perchlorate readily reacts with aromatic aldehydes to afford 2-(2-arylvinyl)-1,3-oxazolium perchlorates. The plant protecting properties of the obtained compounds were studied. We found that 2-(2-arylvinyl)-4-oxo-4,5-dihydro-1,3-oxazolium perchlorates are effective as antidotes towards herbicide 2,4-D but have no plant growth activity.

Keywords: D-(−)-pantolactone, D-pantoamide, 4-oxo-4,5-dihydro-1,3-oxazolium perchlorates, antidote activity, plant growth activity.

Due to the wide range of useful properties, 4(5H)-oxazolones and their salts, 4-oxo-4,5-dihydro-1,3-oxazolium, have occupied the attention of chemists (for reviews see [1-3]).
The aim of this work was to synthesize new 2-methyl-4-oxo-4,5-dihydro-1,3-oxazolium salts, starting from D-(-)-pantolactone, to study the reactions with aldehydes and the biological effects of the resulting products.

D-Pantoic acid amide (D-2,4-dihydroxy-3,3-dimethylbutyramid) 2 was synthesized by a modified procedure [4] by passing ammonia stream through a solution of D-(-)-pantolactone in wet methylene chloride. However, all the attempts to obtain N-methylamide 3 by the analogous method described in the PhD thesis [5] were unsuccessful. Instead of the product which was reported to be readily crystallized from ether, a viscous colorless oil readily soluble in ether was obtained. According to IR, NMR and GC-MS data, the resulting product is a mixture of starting D-(-)-pantolactone, N-methylamide 3 and N-methyl butyrolactam 4. We failed to separate the mixture by column chromatography on a silica gel or Al₂O₃. Probably, the spontaneous cyclization of N-methyl amide 3 into the butyrolactam 4 occurs during the chromatography step. The IR spectrum of the product reveals two bands of carbonyl groups at 1770 cm⁻¹ (νC=O lactone or lactam) and 1651 cm⁻¹ (amide νC=O). Increasing the duration of methylamine passing resulted in disappearance of ν 1770 cm⁻¹ band, but during the storage for a few hours the band at ν = 1770 cm⁻¹ appears again, so we concluded that N-methyl amide 3 is relatively instable and tends to cyclize. GC-MS detects two peaks, one of which corresponds to the starting mixture of pantolactone and butyrolactam 4 (M = 130 and 143), and the second to N-methylpantoamide 3 (M = 161).

Synthesis of oxazolonium perchlorate 1a was performed by heating in Ac₂O in the presence of 70% HClO₄. The mixture of compounds 3 and 4 under the same
conditions yielded a crystalline perchlorate 6 in 49% yield. Compound 1a was obtained as colorless crystals, which are readily soluble in Me_{2}CO, AcOEt and AcOH. The IR spectrum of perchlorate 1a revealed two absorption bands of C=O groups: at ν 1753 cm^{-1} (acetate) and ν 1778 cm^{-1} (oxazolonium). \(^1\)H NMR spectrum of 1a showed a singlet at δ 5.83 ppm. Signals of the diastereotopic gem-methyl groups were observed as a pair of singlets at δ 1.04 and 1.25 ppm.

Oxazolonium perchlorate 1a reacts with aromatic aldehydes to give 2-(β-arylvinyl)oxazolonium perchlorates 7a-c (Method A). Compounds 7 can also be obtained in lower yields by direct reaction of D-pantoamide 2 with aromatic aldehydes in boiling Ac_{2}O in the presence of 70% HClO₄ (Method B). Compounds 7a, b are yellow crystals, 7c - red crystals, all have sharp melting points, readily soluble in AcOEt, EtOH and Me_{2}CO. It is known that the reaction of salts of 2-alkylsubstituted heterocycles (like indoleninium, 1,3-benzoazinum salts, etc.) with ortho-hydroxy benzaldehydes gives 2-spiro-condensed chromenes. These spirochromenes have photochromic properties and are of interest to construct smart materials, molecular controllers and nanotransistors etc. A survey of literature revealed that syntheses of such spiro compounds based on 4-oxo-4,5-dihydro-1,3-oxazolium perchlorates 1 or 7 were not described to date. We tried to obtain 2-spiro-condensed chromenes by reaction of 1a with salicylaldehyde. However, the sole product we obtained was perchlorate 7d, similar to the condensation products with another aromatic aldehydes. Upon treatment with bases (NaHCO₃, Et₃N) perchlorates 7 afforded 2-(arylvinyl)oxazoles 8 (Fig 1).

7a Ar = Ph; b Ar = 4-BrC₆H₄; c Ar = 4-Me₂NC₆H₄.
Figure 1. $^1$H and $^{13}$C NMR spectra (300/75 MHz, DMSO-d$_6$) of 5-(2-acetoxy-1,1-dimethylethyl)-2-[(E)-2-(2-hydroxyphenyl) vinyl]-4-oxo-4,5-dihydrooxazole 8d.

Due to good solubility in water, synthesized perchlorates 7a,b,d are of interest for their use in agricultural chemistry. We have estimated the activity of 7a,b,d as herbicide antidots and studied plant growth regulating activity on sunflower seedlings in a laboratory experiment.
The compounds 7a,b,d were screened for antidotal activity towards the widely used herbicide 2,4-D on the sunflower culture. We found that all the organic salts 7a,b,d have the protective effect. They are capable of reducing by 10-70% the negative effects of 2,4-D. At the concentrations of 10⁻⁵ mol%, the antidote effect of 7a and 7b is maximal (56% and 50%, estimated by the length of hypocotyl for the systems “pure herbicide” (reference) and «herbicide + antidote”).

Experimental

5-(2-Acetoxy-1,1-dimethylethyl)-2-((E)-2-arylvinyl)-4-oxo-4,5-dihydrooxazolium perchlorates (7a-d). A solution of perchlorate 1a (3.13 g, 0.01 mol) and 0.011 mol of the corresponding aromatic aldehyde in 4.0 mL of AcOH was heated to the boiling point (in the case of salicylaldehyde - heated for 15-20 minutes at 60 °C). After cooling, the mixture was diluted with ether (10 mL). The precipitated product was filtered and washed with Et₂O.

5-(2-Acetoxy-1,1-dimethylethyl)-2-((E)-2-phenylvinyl)-4-oxo-4,5-dihydrooxazolium perchlorate 7a. Bright yellow crystals, yield 50%, mp 171 °C. IR spectrum (KBr), v/cm⁻¹: 3443 (N–H), 2979 (C–H), 1798, 1739 (2 C=O), 1633 (C=C), 1550 (O–C=N), 1114 (ClO₄⁻). NMR ¹H (400 MHz, acetone-d₆, δ, ppm, J/Hz): 1.00 (s, 3 H, CH₃); 1.16 (s, 3 H, CH₃); 1.95 (s, 3 H, CH₃CO₂); 4.16 (br.s, 2 H, CH₂); 5.64 (s, 1 H, CH); 6.68 (d, 1 H, –CH=, ³J = 16.0); 7.28 (m, 5 H, Ph); 7.41 (d, 1 H, –CH=, ³J = 16.0). The signal of NH⁺ was not observed, probably due to deuterium exchange. UV-spectrum (AcOH, c = 1·10⁻⁴ M), λmax/nm (lg ε): 318 (2.3). Microanalysis was not performed due to the risk of explosion.

References