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

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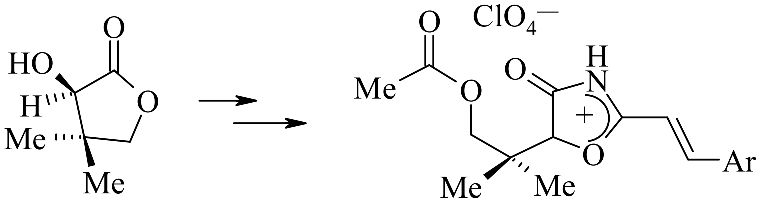
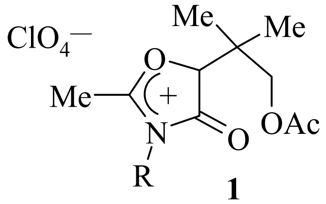
Abstract: The reaction of *D*-(–)-pantolactone with ammonia leads to the formation of *D*-pantoamide, which reacts with Ac_2O and $HClO_4$ to give 5-[2-(acetoxy)-1,1-dimethylethyl]-2-methyl-4-oxo-4,5-dihydro-1,3-oxazolium perchlorate. The obtained 2-methyl-1,3-oxazolium perchlorate readily reacts with 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 **1**, starting from D-(–)-pantolactone, to study the reactions with aldehydes and the biological effects of the resulting products.



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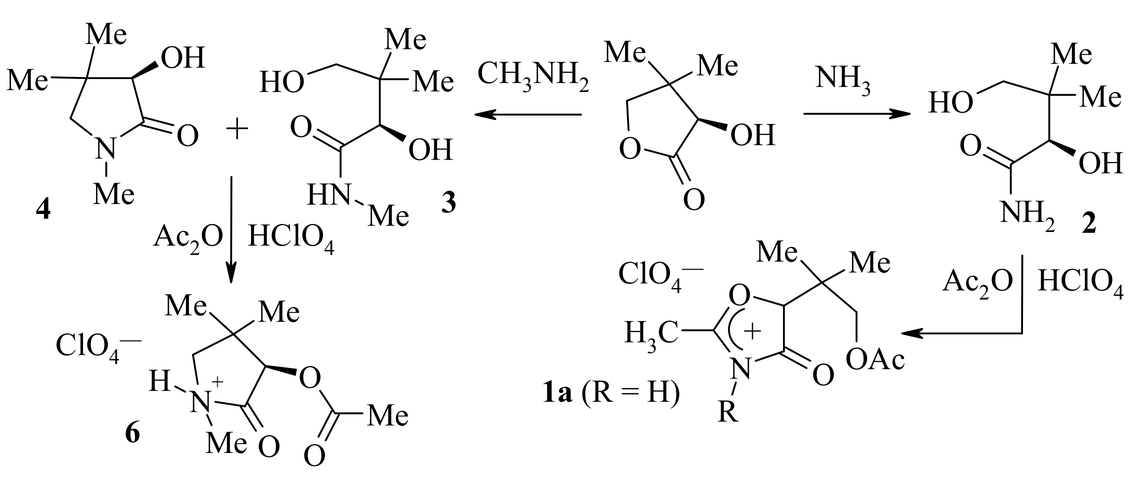
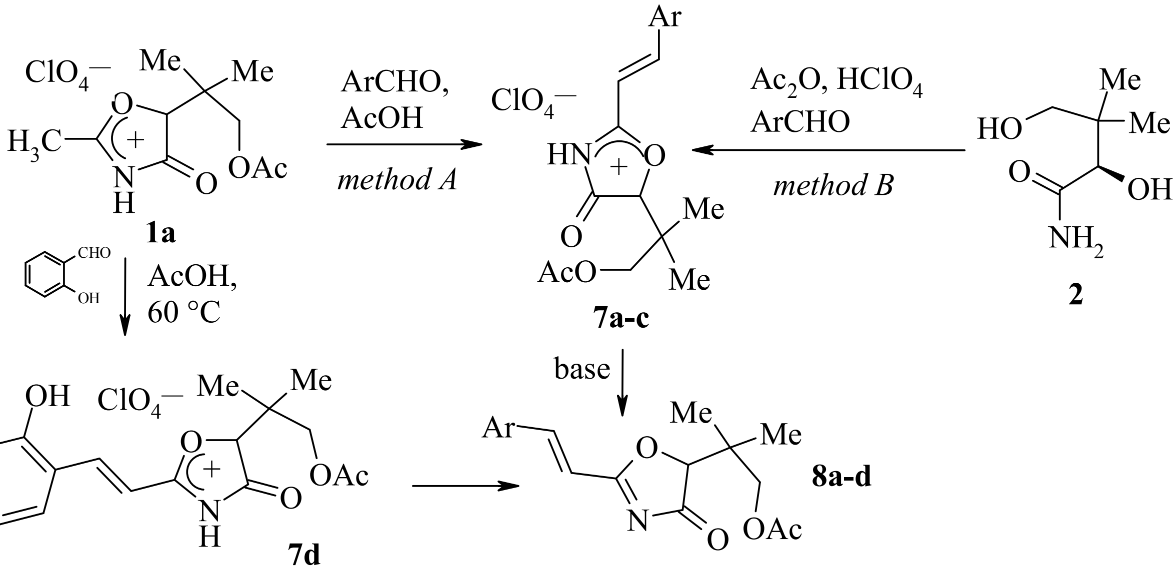
D-Pantoic acid amide (D-2,4-dihydroxy-3,3-dimethylbutyramide) **2** was synthesized by a modified procedure [4] by passing ammonia stream through a solution of D-(–)-pantolactone in wet methylene chloride. However, all the attempts to obtain N-methylamide **3** by the analogous method described in the 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 Al_2O_3. 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} ($\nu_{C=O}$ lactone or lactam) and 1651 cm^{-1} (amide $\nu_{C=O}$). 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 Ac_2O in the presence of 70% $HClO_4$. 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_2CO, 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). ^1H 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_2O in the presence of 70% $HClO_4$ (Method B). Compounds **7a, b** are yellow crystals, **7c** - red crystals, all have sharp melting points, readily soluble in AcOEt, EtOH and Me_2CO. It is known that the reaction of salts of 2-alkylsubstituted heterocycles (like indoleninium, 1,3-benzoxazinium 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 ($NaHCO_3$, Et_3N) perchlorates **7** afforded 2-(arylvinyl)oxazoles **8** (Fig 1).



7 a Ar = Ph; **b** Ar = 4-BrC_6H_4; **c** Ar = 4-$Me_2NC_6H_4$.

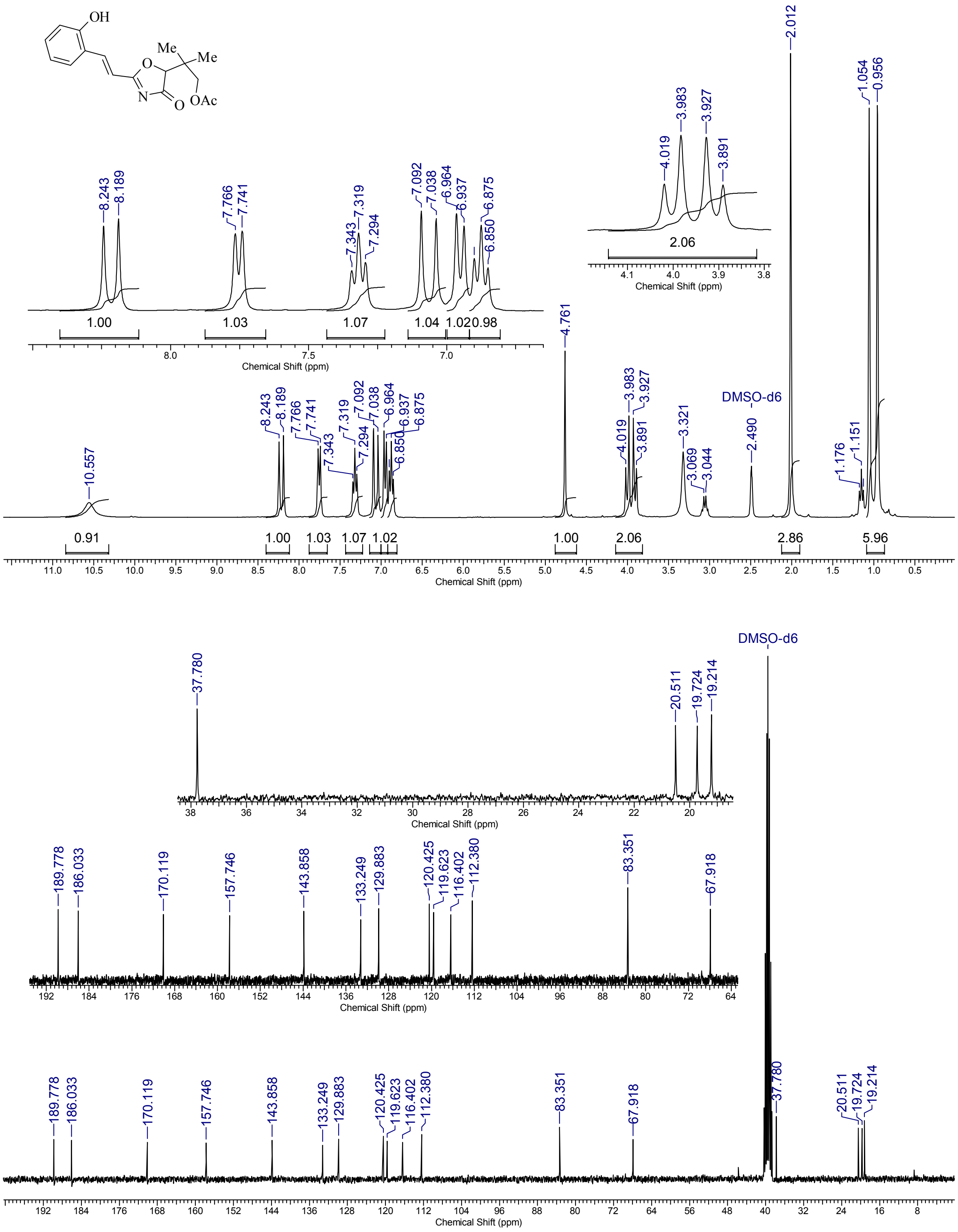


Figure 1. ^{1}H and ^{13}C NMR spectra (300/75 MHz, DMSO-d_6) of 5-(2-acetoxy-1,1-dimethylethyl)-2-[(E)-2-(2-hydroxyphenyl) vinyl]- 4-oxo-4,5-dihydrooxazole **8d**.

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 Et_2O.

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), ν/cm^{-1}: 3443 (N–H), 2979 (C–H), 1798, 1739 (2 C=O), 1633 (C=C), 1550 ($O–C^+–N$), 1114 (ClO_4^-). NMR ^1H (400 MHz, acetone-d_6, δ, ppm, J/Hz): 1.00 (s, 3 H, CH3); 1.16 (s, 3 H, CH3); 1.95 (s, 3 H, CH_3CO_2); 4.16 (br.s, 2 H, CH_2); 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, $c = 1\cdot10^{-4}$ M), λ_{max}/nm (lg ε): 318 (2.3). Microanalysis was not performed due to the risk of explosion.

References

1. D. C. Palmer, in *Oxazoles: Synthesis, Reactions, and Spectroscopy, Part B, Volume 60*, Ed. D. C. Palmer, John Wiley & Sons Inc., Hoboken, USA, 2004, pp. 53-128.
2. Y. S. Rao, R. Filler, In *Oxazoles, Vol. 45, The Chemistry of Heterocyclic Compounds*, Ed. I. J. Turchi, John Wiley & Sons Inc., New York, 1986, pp. 363-691.
3. Yu. L. Ryabukhin, L. N. Faleeva, T. P. Kosulina, V. G. Kul’nevich, *Chem. Heterocycl. Compd.*, 1991, **27**, 563.
4. S. G. Tishshenko, V. P. Chekhun, R. S. Gavrilov, V. A. Papanov. USSR Patent 360340 (1972).
5. F.-U. Lyubke, PhD thesis, Krasnodar, 1980, 147 pp.