

Thematic course: Physico-chemical studies of transformations in the series of 2,4-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide. Part 1.

Synthesis and X-ray diffraction of derivatives 2,4-dimethyl-6-oxo-1,6-dihydropyridin-3-carboxamide

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Abstract

Based on the synthesized starting 2,4-dimethyl-6-oxo-1,6-dihydropyridin-3-carboxamide crystallizing as a dihydrate, 9 derivatives of it including *O*- and *N*-phenacyl substituted products were obtained through original rearrangements and cyclizations. The corresponding oxazolopyridinium perchlorate was obtained from the latter preparation in the presence of acid, from which indolysin was obtained under the action of a nitrogenous base.

The obtained molecular and crystal structures of all the compounds were studied by single crystal diffraction: 2,4-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide dihydrate, 6-hydroxy-2,4-dimethyl-3-carbamoyl-pyridinium chloride monohydrate, 2,4-dimethyl-6-methoxypyridine-3-carboxamide, 1-[2-(4-methylphenyl)-2-oxoethyl]-2,4-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide, 2,4-dimethyl-6-oxo-1-[2-(4-chlorophenyl)-2-oxoethyl]-1,6-dihydropyridine-3-carboxamide, 2,4-dimethyl-6-[2-(4-methylphenyl)-2-oxoethoxy]pyridin-3-carboxamide, 2,4-dimethyl-6-[2-(4-chlorophenyl)-2-oxoethoxy] pyridin-3-carboxamide, 6-carbamoyl-2-(4-chlorophenyl)-5,7-dimethyl[1,3]oxazolo[3,2-a]pyridin-4 perchlorate, 7-methyl-5-morpholin-4-yl-2-(4-chlorophenyl) indolysin-8-carboxamide. A structural analysis of the by-products of 1,4-bis(4-methylphenyl) butane-1,4-dione and 1,4-bis(4-chlorophenyl) butane-1,4-dione was also carried out. The synthesis methods of each of them are given.

A comparative analysis of bond lengths, valence and torsion angles in similar fragments of molecules is carried out. Hydrogen bonds were revealed in the structures and their influence on the strength of molecular packing in crystals was shown.

All structures of the studied compounds, in addition to XRD, are characterized by ¹H NMR spectra.

References

- [1] V.B. Rybakov, S.G. Zhukov, E.V. Babaev, O.S. Mazina, L.A. Aslanov. X-ray mapping in heterocyclic design. 1. Diffractometric study of crystalline 1,2-dihydro-2-imino-1-carboxymethylpyridine monohydrate: structural evidence for the zwitterionic character of the molecule. *Crystallography Reports*. **1999**. Vol.44. No.6. P.997-999. (russian)
- [2] V.B. Rybakov, E.V. Babaev, E.G. Paronikyan. X-ray mapping in heterocyclic design. 18. X-Ray diffraction study of series of derivatives of 3-cyanopyridine-2-one with annealed heptanes and octane cycles. *Crystallography Reports*. **2017**. Vol.62. No.2. P.219-231. DOI:10.1134/S1063774517020249

- [3] E.M. Okul', V.B. Rybakov, E.V. Babaev. The structure of products of phenacylation and subsequent (re)cyclizations of 3-acetyl-4,6-dimethylpyridin-2(1H)-one. *Chemistry of Heterocyclic Compounds*. **2017**. Vol.53. No.9. P.997-1002. DOI: 10.1007/S10593-017-2161-2
- [4] V.B. Rybakov, E.V. Babaev. Transformations of substituted oxazolo-[3,2-*a*]pyridines to 5,6-disubstituted indolizines: synthesis and X-ray structural mapping. *Chemistry of Heterocyclic Compounds*. **2014**. Vol.50. No.2. P.225-236. DOI: 10.1007/S10593-014-1465-8
- [5] D.V. Al'bov, O.S. Mazina, V.B. Rybakov, E.V. Babaev, V.V. Chernyshev, L.A. Aslanov. X-ray mapping in heterocyclic design: XII. X-ray diffraction study of 2-pyridones containing cycloalkane fragments annelated to the C(5)-C(6) bond. *Crystallography Reports*. **2004**. Vol.49. No.2. P.158-168. DOI: 10.1134/1.1690408
- [6] D.V. Albov, E.I. Turubanova, V.B. Rybakov, E.V. Babaev, L.A. Aslanov. 2-(4-Bromophenyl)-8-cyano-5,7-dimethyloxazolo[3,2-*a*]pyridine-1-ylum perchlorate. *Acta Crystallographica*. **2004**. Vol.E60. P.o1303-o1304. DOI: 10.1107/S1600536804015995.
- [7] D.V. Albov, E.I. Turubanova, V.B. Rybakov, E.V. Babaev, L.A. Aslanov. *N*-(4-bromophenacyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-2-carbonitrile. *Acta Crystallographica*. **2004**. Vol.E60. P.o1222-o1223. DOI: 10.1107/S1600536804014175.
- [8] O.S. Mazina, V.B. Rybakov, V.V. Chernyshev, E.V. Babaev, L.A. Aslanov. X-ray mapping in heterocyclic design. 14. Tricyclic heterocyclic based on 2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile. *Crystallography Reports*. **2004**. Vol.49. No.6. P.998-1009. DOI: 10.1134/1.1828145
- [9] O.S. Mazina, V.B. Rybakov, S.I. Troyanov, E.V. Babaev, L.A. Aslanov. X-ray mapping in heterocyclic design. 15. Tricyclic heterocyclic based on 2-oxo-2,5,6,7-tetrahydro-1H-cyclopenta[*b*]pyridine-3-carbonitrile. *Crystallography Reports*. **2005**. Vol.50. No.1. P.61-71. (russian)
- [10] E.V. Babaev, O.S. Mazina, V.B. Rybakov. The structure of the tricycles on the basis of the nitriles cycloalkanones. *LAMBERT Academic Publishing RU Bahnhofstrasse 28, 66111 Saarbrücken, Deutschland*, ISBN 978-3-659-94026-4. **2016**. 188c. (russian)
- [11] Ya.I. Koval', E.M. Okul', A.V. Yatsenko, E.V. Babaev, I.N. Polyakova, V.B. Rybakov. Theoretical and experimental study of the transformation of 2-pyridone-5-amide into nitrile. *Russian Journal of Physical Chemistry A*. **2017**. Vol.91. No.2. P.247-252. DOI: 10.1134/S0036024417020182
- [12] F. Neese. The ORCA program system. *Wiley Interdisc. Rev. Comp. Mol. Sci.* **2012**. Vol.2. No.1. P.73-78. DOI: 10.1002/wcms.81.
- [13] M. Breugst, H. Mayr. Ambident reactivities of pyridine anions. *J. Amer. Chem. Soc.* **2010**. Vol.132. No.43. P.15380-15389. DOI: 10.1021/ja106962u.
- [14] G. Hopkins, J. Jonak, H. Minnemeyer, H. Tieckelmann. Alkylations of heterocyclic ambident anions. II. Alkylation of 2-pyridone salts. *J. Org. Chem.* **1967**. Vol.32. No.12. P.4040-4044. DOI:10.1021/jo01287a600.
- [15] K. Gevald, H.J. Jänsch. 3-Amino-furo[2,3-*b*]pyridine. *J. für Prakt. Chemie*. **1976**. Vol.318. No.2. P.313-320. DOI: 10.1002/prac.19763180216.
- [16] Stoe & Cie (2015). *X-AREA & X-RED32*. Stoe & Cie, Darmstadt, German.
- [17] Enraf-Nonius CAD-4 Software. Version 5.0. *Enraf-Nonius, Delft, The Netherlands*. **1989**.
- [18] Bruker (2015). APEX2, SAINT. *Bruker AXS Inc., Madison, Wisconsin, USA*.
- [19] G.M. Sheldrick. A short history of *SHELX*. *Acta Cryst.* **2008**. Vol.A64. No.1. P.112-122. DOI: 10.1107/S0108767307043930.
- [20] G.M. Sheldrick. Crystal structure refinement with *SHELXL*. *Acta Cryst.* **2015**. Vol.C71. P.3-8. DOI: 10.1107/S2053229614024218.
- [21] A.L. Spek. Structure validation in chemical crystallography. *Acta Cryst.* **2009**. Vol.D65. P.148-155. DOI: 10.1107/S090744490804362X.
- [22] C.R. Groom, F.H. Allen. The Cambridge structural database in retrospect and prospect. *Angew. Chem. Int. Ed.* **2014**. Vol.53. P.662-671. DOI: 10.1002/anie.201306438.