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# Synthesis of 3,5-dinitro-1,4,5,6-tetrahydropyridine-2-amine

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## Abstract

Tetrahydropyridine derivatives possess antimicrobial, antioxidant, anti-inflammatory, analgesic effect. Therefore, the expansion of the range of these compounds and studying their properties is important. There are published data on various approaches to the formation of tetrahydropyridine structure: mild oxidation of piperidine and its derivatives, condensation of nitriles, primary amines, etc. Previously, we have implemented a selective dearomatization 6-tizanidine 3,5-dinitropyridine and 2-hydroxy-3,5-dinitropyridine under the action of tetrahydroborate sodium, followed by C-protonation of hydride adducts with the formation of tetrahydropyridine derivatives.

This article describes the two-step method of obtaining *N*-*R*-3,5-dinitro-1,4,5,6-tetrahydropyridine-2-amines based on *N*-substituted 3,5-dinitropyridine-2-amines. In the first stage under the action of a substrate, tetrahydroborate sodium as a result of dearomatization the selective joining of the hydride ion at the positions 4 and 6 of the pyridine ring with the formation of doubly charged intermediate σ-adduct. The target 3,5-dinitro-1,4,5,6-tetrahydropyridine-2-amines obtained by the action on σ-adducts diluted orthophosphoric acid. The transition to the soft conditions from the activated nitro groups by the pyridine system to anionic σ-adductum, and from them to the appropriate tetrahydropyridine allows obtaining products with high yields. The proposed method is applicable for obtaining new polyfunctional derivatives of $\Delta^2$-piperideine. In addition, further functionalization of amino-, nitro-, carboxyl groups opens up opportunities for a variety of compounds with presumably high biological activity.

The structure of the obtained compounds were proved by IR spectroscopy method, data of two-dimensional homo- (COSY) and heteronuclear (HMBC, HSQC) correlation NMR spectroscopy, and elemental analysis data. Final proof of the structure of the synthesized tetrahydropyridine was derived from RSA data of the crystal of the *N*-cycloheptyl-3,5-dinitro-1,4,5,6-tetrahydropyridine-2-amine. In the analyzed crystal tetrahydropyridine fragment is characterized by the conformation of the distorted elbow, with axial location of the nitro group in the 5-position. The oxygen atom of one of the nitro groups forms a strong intramolecular hydrogen bond with the proton of the amino group substituents, which leads to a reduction of the neighboring relations, in comparison with the average values from the Cambridge structural database.

## References

[1] S. Prachayasittikul, A. Worachartcheewan, R. Lawung, S. Ruchirawat, V. Prachayasittikul. Activities of tetrahydropyridines as antioxidantand antimicrobialagents. *EXCLI Journal.* **2009**. Vol.8. P.107.
[2] B. Mochona, T. Wilson, K. Redda. Synthesis and anti-inflammatory activites of N-benzoylamino-1,2,3,6-tetrahydrpyridine analogs. *Drugs Under Experimental and Clinical Res.* **2003**. Vol.29. P.131.
[3] S. Modi, D.E. Gilham, M.J. Sutcliffe, L.Y. Lian, W.U. Primrose, C.R. Wolf, G.C. Roberts. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine as a substrate of cytochrome P450 2D6: Allosteric effects of NADPH-cytochrome P450 reductase. *Biochemistry*. **1997**. Vol.36. P.4461.
[4] H. Lin, Y. Tan, W.-J. Liu, Z.-C. Zhang, X.-W. Sun, G.-Q. Lin. A highly efficient access to enantiopure tetrahydropyridines: dual-organocatalyst-promoted asymmetric cascade reaction. *Chem. Commun*. **2013**. Vol.49. P.4024-4026. DOI: 10.1039/C3CC40690C

[5] V.D. Dyachenko, D.A. Krasnikov, M.V. Horik. Synthesis and alkylation of 6-amino-N(3)-aryl-4-aryl(raran-2-yl)-N(5)-phenyl-2-thioxo-l,2,3,4-tetrahydropyridine-3,5-dicarboxamides. *HGS*. **2008**. Vol.7. P.1018-1023. (russian)
[6] L. Huo, A. Ma, Y. Zhang, D. Ma. Assembly of 4-Substituted 3-Nitro-1,2,3,4-tetrahydropyridines via Organocatalytic Michael Addition. *Adv.Synth. Catal*. **2012**. Vol.354. P.991. DOI: 10.1002/adsc.201100903
[7] Yu.M. Atroshchenko, I.V. Blokhin, E.V. Ivanova, I.V. Kovtun. Experimental and theoretical investigation of physical-chemical properties of the hydride adducts based on 2-hydroxy-3,5-dinitropyridine. *Izvestiya of the Tula state University. Science*. **2013**. Vol.3. P.244. (russian)
[8] I.I. Surova, E.V. Ivanova, I.V. Blokhin, I.V. Shahkeldyan, Yu.M. Atroshchenko, K.I. Kobrakov, D.N. Kuznetsov, I.V. Fedyanin. Synthesis 6-thiosubstituted 3,5-dinitro-1,2,3,4-tetrahydropyridines. *Butlerov Communications.* **2015**. Vol.42. No.4. P.91. DOI: 10.37952/ROI-jbc-01/15-42-4-91
[9] G.M. Sheldrick. A short history of SHELX. *Acta Crystallog. A: Found. Crystallogr.* **2007**. A64. P.112.
[10] F.H. Allen. The Cambridge Structural Database: a quarter of a million crystal structures and rising. *Acta Crystallog. B: Struct. Sci.* **2002**. Vol.B 58. P.380.
[11] *Methods of obtaining of chemical reagents and drugs, ed.* by R. P. Lastovsky. *Moscow: IREA*. **1971**. Vol.23. P.150. (russian)
[12] S.X. Cai, J.-Ch. Huang, S.A. Espitia, M. Tran, V.I. Ilyin, et al. 5-(*N*-oxyaza)-7-substituted-1,4-dihydroquinoxaline-2,3-diones: novel, systemically active and broad spectrum antagonists for NMDA/glycine, AMPA, and kainate receptors. *J. Med. Chem*. **1997**. Vol.40. P.3679.
[13] E.C.S. Brenelli, P.J.S. Moran. The reactivity of some primary amines $SN_{2AR}$ reactions with 2-chloro-3,5-dinitropyridine. *J. Chem. Res. Miniprint*. **1989**. Vol.12. P.2816.
[14] G. Gilli, F. Bellucci, V. Ferretti, V. Bertolasi. Evidence for resonance-assisted hydrogen bonding from crystal-structure correlations on the enol form of the beta-diketone fragment. *JACS*. **1989**. Vol.111. P.1023.