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Chemical Transformation of Pyrido[2,3-d]Pyrimidin-4-ONES. 2. Selective Reduction of 2,3-Trimethylenepyrido[2,3-d]Pyrimidin-4-one by Sodium Borohydride

Kh.U. Khodjaniyazov[1*], A.A. Mamadrakhimov[2], Kh.S. Tadjimukhamedov[3], M.G. Levkovich[1]

[1]S.Yunusov Institute of the Chemistry of Plant Substances AS of the Republic of Uzbekistan, 100170, Tashkent, M.Ulugbek st., 77
[2]A.S. Sadikov Institute of Biorganic Chemistry AS Uzbekistan
[3]Mirza Ulugbek National university of Uzbekistan

*corresponding author: hamidkhodjaniyazov@yandex.ru

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Abstract: Reduction of 2,3-trimethylenepyrido[2,3-d]pyrimidin-4-one by sodium borohydride was investigated in an alcohol solution. Selective reduction of only a N1=C2 double bound of the initial compound was shown. The isomeric 2,3-trimethylene-1,2,3,4-tetrahydropyrido[2,3-d]-pyrimidin-4-ones are formed and quantitatively separated on HPLC with chiral adsorbent column. Theoretically formation of four optical isomers of 2,3-trimethylene-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidin-4-ones are discussed.

INTRODUCTION

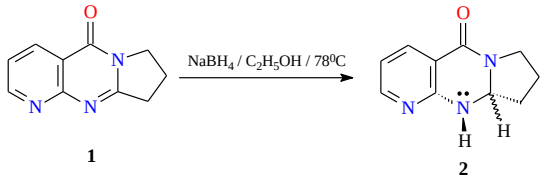
Interest to pyrido[2,3-d]pyrimidine moiety is gradually increasing because that there are many pharmaceutical preparations containing pyridopyrimidine core. Therefore, they are useful building blocks in synthetic organic chemistry. Pyridopyrimidines derivatives are used in various branches of medicine as anti-cancer, antimicrobial, antibacterial, fungicides, and for treatment of CNS disorders such as neuropsychiatric disorders (Buron, Merour, Akssira, Guillaumet and Routier, 2015; Yang et al., 2015; DeMichele et al., 2015; Verma, 2007; Geffken, Soliman, Soliman, Abdel-Khalek, and Issa, 2011; Abdel-Aziem, El-Gendy, and Abdelhamid, 2012; Ibrahim, Behbehani, and Elnagdi, 2013; Hanafy, 2011; Campbell, Duron, Vollrath, and Wade, 2011).

In the previous reports we have described the results of the reaction of 2,3-trimethylenepyrido[2,3-d]pyrimidin-4-one with aromatic aldehydes in acidic media and structure of a product which (E)-9-(4-nitrobenzylidene)-8,9-dihydropyrido[2,3-d]pyrrolo[1,2-a]pyrimidin-5(7H)-one was confirmed by X-ray analysis (Khodjaniyazov, 2015; Khodjaniyazov and Ashurov, 2016). In this current paper we present the results of a selective reduction of a N1 = C2 double bond in pyrimidine ring of 2,3-trimethylenepyrido[2,3-d] pyrimidin-4-one with sodium borohydride.

MATERIALS AND METHODS

The research object is a nitrogen-containing heterocyclic system with three fused nuclei such as pyridine, pyrimidine, and pyrrolidine, i.e. 2,3-trimethylenepyrido[2,3-d]pyrimidin-4-one (**1**), sodium borohydride is used as a selective reducing agent. Research methods are methods of organic synthesis, analysis of the structure of the synthesized compounds by IR, ^{1}H and ^{13}C NMR spectra, qualitative separation of optical isomers by HPLC using a column packed with a chiral adsorbent of selective reduction reaction of a N1 = C2 double bond. It is a theoretical approach in terms of the optical activity of the products of the reaction. The reaction progress was monitored by TLC. The reaction proceeds as following scheme 1.
The results of Electro Spray Ionization Mass Spectrometry (ESI-MS) were recorded using 6420 TripleQuadLC/MS (Agilent Technologies, USA) mass spectrometer. The measurements were carried out in positive-ion mode. Mass spectrometer parameters were chosen as follows: scan range m/z 15-2200, gas consumption N_2 dehumidifier 10L/min, 300^0C temperature of the gas on the needle atomiser 20 psi gas pressure evaporator temperature 300^0C, the voltage across the capillary 4000V.

Synthesized compounds were screened by HPLC (Agilent 1100 Series, USA) using a column with chiral adsorbent - amylose *tris*-[(*S*)-α-methylbenzylcarbamate] coated on 10μm silica-gel (ChiralPak® AS 0.46cm ϕ x25cm, DAIC 20025, Daicel Chemical Industries, LTD, France), and mobile phase A - ACN, and B - i-PrOH in gradient mode: 0-10min B2% to 10% and 10-15min B10%.



1 **2**

Scheme 1

Table 1. IR- and UV-spectral characteristics of compounds **1** and **2**.

Compound	IR spectrum		UV spectrum	
	C=O	C=N	Neutral condition	Acidic condition
1	1718	1625	**268.93 (C=N)** 301.93	269.36 302.68
2	1654	-	**239.6 (C-N)** 337.01	- 336.95

^{1}H NMR spectra of 2,3-trimethylenepyrido[2,3-d]pyrimidin-4-one and the isomeric 2,3-trimethylene-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidin-4-ones taken in $CDCl_3$ solution on Unity 400plus spectrometer (Varian) with an operating frequency of 400 MHz for ^{1}H. Chemical shifts are reported on a scale δ. HMDS is used as the internal standard. IR spectra were recorded on a PERKIN ELMER System unit 2000 FT-IR tablets with KBr.

Reduction method

In a round bottom flask with reflux condenser was placed 2,3-trimethylenepyrido[2,3-d]-pyrimidin-4-one (0.191 g, 0.001 mol), sodium borohydride $NaBH_4$ (0.754 g, 0.02 mol) and ethanol (5 ml) . The reaction mixture was heated in a water bath at 78^{0}C for 2.5 hours. After completion of the reaction (TLC monitoring), water was poured into the flask, extracted with chloroform, the organic layer was dried over Na_2SO_4. The chloroform removed and residue recrystallized from cyclohexane.

It should be noted that the starting material and the product have the same spot in TLC (with R_f 0.52 values, chloroform-methanol, 11: 1), but unlike the parent compound, the reduction product gives fluorescence under UV light.

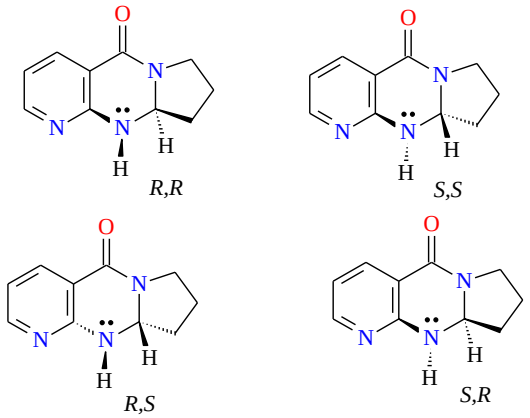
RESULTS AND DISCUSSION

The initial compound **1** was first synthesized by condensing of a 2-aminonicotinic acid with γ-butyrolactam (Khodjaniyazov, 2015). Interaction of 2,3-trimethylenepyrido[2,3-d]pyrimidin-4-one with sodium borohydride in ethanol was held at reflux on the steam bath. On the basis of spectral data showed that the selective reduction of a N1 = C2 double bond proceeded. The formation of product recovery for this bound show the spectral data.

For example, ESI-MS spectrum of a product gave a strong $[M+H]^+$ peak at m/z 190, indicating the molecular weight of 189 for this compound, which in conjunction with NMR data suggested the molecular formula of $C_{10}H_{11}N_3O$. The MSMS experiment on m/z 190 resulted in three peaks at 121, 93, and 70 due to fragmentation of the molecule.

Moreover, at the reduction with sodium borohydride of a N1 = C2 double bond of 2,3-trimethylenepyrido[2,3-d]pyrimidin-4-one an absorption band at 1625 cm^{-1} (C = N) disappears in the IR spectrum of the reaction product. The absorption band of the carbonyl group at C4, observed at 1718 cm^{-1} (CO) is shifted to lower frequencies (1654 cm^{-1}). As a result of the reaction product obtained by selective reduction with saturated N1-C2 bond (**2**). Some spectral characteristics of compounds **1** and **2** are shown in the table 1.

Isomeric reaction products were 2,3-trimethylene-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidin-4-ones. These compounds appear on TLC by a single peak, although theoretically they can be in the form of four optical isomers (Scheme 2).



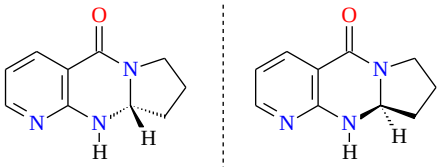
Scheme 2

The similar reactions were carried out in a series of benzene analogues of the abovementioned compounds, i.e. quinazolines (Shakhidoyatov, 1988; Shakhidoyatov and Khodjaniyazov, 2010; Samarov, 2010; Oripov, 1980). However, the

presence of two optically active centers in the reactions of the products and the possibility of formation of isomeric products did not discuss in these reports. The works (Girreser, Heber, and Schütt, 2001; Mayo, 1936) described only reduction of pyridine ring.

It is known that a nitrogen atom having three different substituent, as well as a lone electron pair becomes optically active. Such nitrogen atom in the case of 2,3-trimethylenepyrido[2,3-d]pyrimidin-4-one is N1. In addition, the composition of the reaction product has an asymmetric carbon atom in position 2. The relative arrangement of substitutents around these two optical centers makes it possible presence of four optical isomers. They are pairs of *threo* (*R,R; S S*) and the *erythro* (*R,S; S,R*) isomers.

Using HPLC equipped with a chiral column, we were able to separate qualitatively two optical isomers with RT 8.567 (46.5041%) and 9.108 (53.4959%), respectively. Since optical isomers occurring at the expense of the nitrogen atoms are unstable due to the rapid conversion, the data can easily be explained as a result of isomerism around one optical center - C2 atom, i.e. actually there are two enantiomers (Scheme 3).



Scheme 3

UV spectrum 2,3-trimethylene-1,2,3,4-tetrahydropyrido[2,3-d] pyrimidin-4-ones removed in neutral alcoholic solution has absorption bands at 239.62 (C-N), and 337.01. The first band disappears, and the second is almost unchanged and appeared at 336.95 in an acidic condition.

IR spectrum of 2,3-trimethylene-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidin-4-ones (KBr, ν, cm-1): 3431.39, 3213.31, 3100.28 (aromatic CH), 3008.40 , 2964.06 (aliphatic CH), 2924.36, 2879.55, 1654.17 (CO), 1610.38, 1539.43, 1474.30, 1442.62, 1353.87, 1258.72, 1211.42, 1086.17, 918.61, 900.73, 775.44, 713.83, 613.31, 582.61, 538.39, 520.95, 421.20.

The IR spectrum (KBr, ν, cm-1) **2,3-trimethylenepyrido[2,3-d]pyrimidin-4-one** has the following absorption bands: 3409 (weak), 3221, 2921, 2862, 1718 (CO) , 1625 (C = N), 1491, 1457, 1400, 1307, 1257.

UV spectrum of 2,3-trimethylenepyrido[2,3-d]pyrimidin-4-one, neutral medium: 210.43, 268.93 (C = N), 301.93; acidic medium: 269.36, 302.68, 316.01; alkaline medium: 267.61, 301.58.

^{1}H NMR spectrum of 2,3-trimethylene-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidin-4-ones: 1.85-2.40 (4H, m, α- and β-CH2), 3.59 (1H , td, J = 8.6; 2.9, γ_a-CH2), 3.70 (1H, m, γ_e-CH_2), 5.10 (1H, dd, J = 7.1; 5.3, at asymmetric carbon C_2-H), 5.74 (1H, brs , NH), 6.74 (1H, dd, J = 7.6; 5.0, C_6-H), 8.06 (1H, dd, J = 7.4; 1.8, C_5-H), 8.10 (1H, dd, J = 5.0; 1.8, C_7-H).

CONCLUSION

Selective reduction of a N1 = C2 double bond of 2,3-trimethylenepyrido [2, 3-d]- pyrimidin - 4 -one with sodium borohydride in an alcoholic solution was carried out at the first time. The reaction products are optically active isomers of 2,3-trimethylene-1, 2, 3, 4 -tetrahydropyrido [2,3-d]pyrimidin-4-one, which are qualitatively separated by HPLC.

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