ISSN 1070-4280, Russian Journal of Organic Chemistry, 2018, Vol. 54, No. 3, pp. 426–430. © Pleiades Publishing, Ltd., 2018.
Original Russian Text © R.M. Khaziev, N.V. Shtyrlin, O.A. Lodochnikova, N.V. Volobueva, R.V. Chestnova, A.P. Alekseev, E.I. Romanova, K.V. Balakin, Yu.G. Shtyrlin, 2018, published in Zhurnal Organicheskoi Khimii, 2018, Vol. 54, No. 3, pp. 421–425.

Dedicated to Full Member of the Russian Academy of Sciences I.P. Beletskaya on her jubilee

Synthesis and Antimycobacterial Activity of Hydrazides Based on Pyridoxine Derivatives

R. M. Khaziev[a], N. V. Shtyrlin[a], O. A. Lodochnikova[b], N. V. Volobueva[c], R. V. Chestnova[c], A. P. Alekseev[c], E. I. Romanova[a], K. V. Balakin[a, d], and Yu. G. Shtyrlin[a]*

[a] *Scientific Educational Center of Pharmaceutics, Kazan (Volga Region) Federal University, ul. Kremlevskaya 18, Kazan, 420008 Tatarstan, Russia*
**e-mail: Yurii.Shtyrlin@gmail.com*

[b] *Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Center, Russian Academy of Sciences, ul. Arbuzova 8, Kazan, 420088 Tatarstan, Russia*

[c] *Republican Clinical Antitubercular Dispensary, Ministry of Health Protection of Tatarstan Republic, ul. Shalyapina 20, Kazan, 420049 Tatarstan, Russia*

[d] *Sechenov First Moscow State Medical University, Bol'shaya Pirogovskaya ul. 2-4, Moscow, 119991 Russia*

Received July 12, 2017

Abstract—Pyridoxine derivatives, 3-hydroxy-2-methylpyridine-4- and -5-carbohydrazides, were synthesized according to optimized known procedures, and a method for the synthesis of 5-(hydroxymethyl)-2,2,8-trimethyl-4*H*-[1,3]dioxino[4,5-*c*]pyridine-6-carbohydrazide was developed. The hydroxymethyl groups in positions *5* and *6* of 2,2,8-trimethyl-4*H*-[1,3]dioxino[4,5-*c*]pyridine showed different reactivities, and only the 6-hydroxymethyl group was selectively oxidized to aldehyde under mild conditions. The lactone ring in 5,6-dihydrofuro[3,4-*b*]pyridin-7(5*H*)-one was found to be stable to nucleophiles. The synthesized hydrazides showed no antimycobacterial activity.

DOI: 10.1134/S1070428018030090

We previously reported the synthesis of a pyridoxine derivative, 6-hydroxymethyl ketal **1** [1], as an important intermediate product for the preparation of biologically active compounds [2–4]. In this work we studied new ways of chemical modification of pyridoxine and ketal **1** with the goal of obtaining hydrazides **2** [5, 6], **3** [7, 8], and **4** that are bioisosteres of the antitubercular drug isoniazid (Scheme 1).

Isoniazid is one of the most efficient and widely used antitubercular drugs. However, besides high activity, it is characterized by significant toxicity toward central and peripheral nervous systems (neurotoxicity) and liver (hepatotoxicity) [9]. The main factor responsible for hepatotoxicity of isoniazid, especially for immunocompromised patients, is its metabolism to acetylisoniazid and acetylhydrazine [9]. In some cases, damage to liver (drug-induced hepatitis) can be avoided by using analogs and derivatives of isoniazid.

Possible modifications of isoniazid imply introduction of substituents into the pyridine ring and change of the position of the hydrazide fragment with respect to the pyridine nitrogen atom [5, 10–13]. However, among these structures there are no compounds sufficiently active against *M. tuberculosis* strains. Nicotinic acid hydrazide, which is isomeric to isoniazid, exhibits almost no antitubercular activity [10], whereas another isomer, picolinic acid hydrazide, is highly toxic [11]. Antitubercular activity has been found *in vivo* (in mice) for isonicotinic acid hydrazide analogs containing substituents in the *ortho* and *meta* positions with respect to the pyridine nitrogen atom [5]. Derivatives with alkyl substituents displayed the highest antitubercular activity which however did not exceed the activity of isoniazid. Their antitubercular activity decreased as the length of the alkyl chain increased (*ortho*-substituted derivatives): H > Me > Et > CH_2=CH > Pr > *i*-Bu. Increase of the size of the *ortho* substituent