SYNTHESIS OF 4-AMINO-6-(HETARYL)PYRIDAZIN-3-ONES AS ANALOGS OF PYRIDAZINE-BASED CARDIOTONIC AGENTS

N. N. Smolyar,[1] Yu. M. Yutilov,[1] and S. V. Gres'ko[1]

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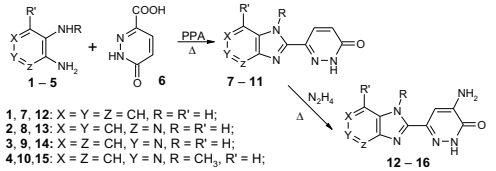
A series of 4-amino-6-(hetaryl)pyridazin-3-ones were synthesized for screening purposes. The target compounds were obtained on heating hydrazine hydrate with 6-(hetaryl)pyridazin-3-ones, which had been prepared via the reaction of *o*-diaminohetaryls with 3-pyridazine-6-carboxylic acid.

Key words: pyridazine, *o*-phenylenediamine, diaminopyridine, benzimidazole, imidazo[4,5-*b*]pyridine, imidazo[4,5-*c*]pyridine, imidazo[4, 5-*d*]pyridazine

Derivatives of 6-(pyridyl-4)pyridazin-3-one and 4-amino-6-(pyridyl-3 or -4)pyridazin-3-one with significant cardiotonic activity have been reported [1, 2]. It seemed interesting to us to synthesize 4-amino-6-(hetaryl)pyridazin-3-ones containing benzimidazole, imidazo[4,5-*b*]pyridine, imidazo[4,5-*c*]pyridine, and imidazo[4, 5-*d*]pyridazine as the hetaryl moieties in order to advance research in this area. It was expected that this combination of condensed nitrogenous heterocyclic fragments and pyridazine in the structures of the newly synthesized compounds would potentiate their cardiovascular properties. Hetaryl-substituted benzimidazole and imidazo[4, 5-*d*]pyridazine are known to have cardiovascular properties [3 – 5] whereas imidazo[4,5-*b*]pyridine and imidazo[4,5-*c*]pyridine are used as starting material for preparing compounds with cardiovascular activity [6 – 8].

Reaction of *o*-phenylenediamine (**1**), 2,3-diaminopyridine (**2**), 3,4-diaminopyridine (**3**), 4-methylamino-3-aminopyridine (**4**), and 6-methyl-4,5-diaminopyridazin-3-one (**5**) with 3-pyridazinone-6-carboxylic acid (**6**) in orthophosphoric acid at 170 – 180°C produced the 6-(hetaryl)pyridazin-3-one derivatives (**7 – 11**) (Table 1).



The structures of **7 – 11** were confirmed by PMR and IR spectra; the compositions, by elemental analyses. IR spectra of **7 – 11** contained absorption bands in the range 1645 – 1670 cm^{-1} that were characteristic of the pyridazine carbonyl.

The PMR spectrum of **9** as an example contained resonances for 5′-H (7.41 ppm) and 4′-H (8.47) with SSCC 9.9 Hz of the pyridazine ring and two doublets for 7-H (8.28) and 6-H (8.70) with SSCC 6.7 Hz and a singlet for 4-H (9.44) of the pyridine ring (Table 2).

Heating **7 – 11** with an excess of hydrazine hydrate according to the literature method [9] under conditions analogous to those used before [10] formed 4-amino-6-hetarylpyridazin-3-ones (**12 – 16**) in 65 – 90% yields. The structures of **12 – 16** were confirmed by PMR and IR spectra (Table 2).

Both 4-amino-6-(hetaryl)pyridazin-3-ones (**12 – 16**) and 6-(hetaryl)pyridazin-3-ones (**7 – 11**) are definitely interesting for research on their pharmacological properties because they are analogs of 6-(pyridyl)pyridazin-3-ones and their 4-amino derivatives, which are highly active cardiovascular agents [1, 2].

EXPERIMENTAL PART

The purity of the synthesized compounds and the course of reactions were monitored by TLC on Silufol UV-254 plates (alcohol, iodine vapor detection in UV light).

Elemental analyses of prepared compounds agreed with the empirical formulas. Table 1 gives the melting points of synthesized compounds. PMR spectra were recorded on Tesla BS-487 C (operating frequency 80 MHz, CF_3COOH) and Gemini-200 (operating frequency 200 MHz, CD_3COOD) instruments. IR spectra in mineral oil were obtained on a UR-20 instrument. Table 2 lists the spectral properties of the synthesized compounds. The synthesis of starting **2 – 6** has been reported [10 – 14].

[1] Litvinenko Institute of Physical and Organic Chemistry and Carbochemistry, National Academy of Sciences of Ukraine, Donetsk, Ukraine.

TABLE 1. Physicochemical Properties and Yields of **7 – 16**

Compound	Starting compound	Empirical formula	Yield, %	mp, °C (crystallization solvent)
7	**1**	$C_{11}HgN_4O$	76	> 320 (CH_3COOH)
8	**2**	$C_{10}H_7N_5O$	80	> 330 (ethanol-water)
9	**3**	$C_{10}H_7N_5O$	70	> 330 (CH_3COOH)
10	**4**	$C_{11}H_9N_5O$	93	> 310 (ethanol-water)
11	**5**	$C_{10}H_8N_6O_2$	87	> 340 (CH_3COOH)
12	**7**	$C_{11}H_9N_5O$	90	> 340 (CH_3COOH)
13	**8**	$C_{10}H_8N_6O$	75	> 320 (water)
14	**9**	$C_{10}H_8N_6O$	65	> 340 (DMF)
15	**10**	$C_{11}H_{10}N_6O$	78	> 350 (ethanol-water)
16	**11**	$C_{10}H_9N_7O_2$	83	> 340 (ethanol-water)

TABLE 2. Spectral Properties of **7 – 16**

Compound	PMR spectrum, δ, ppm	IR spectrum, ν(CO), cm^{-1}
7	7.78 (s, 5H, 4-H, 5-H, 6-H, 7-H, 5′-H), 8.60 (d, 1H, 4′-H)	1645
8	7.67 (d, 1H, 5′-H, J = 9.0 Hz), 8.03 (m, 1H, 6-H), 8.55 (d, 1H, 4′-H, J = 9.0 Hz), 8.85 – 9.00 (m, 2H, 5-H, 7-H)	1660
9	7.41 (d, 1H, 5′-H, J = 9.9 Hz), 8.28 (d, 1H, 7-H, J = 6.7 Hz), 8.47 (d, 1H, 4′-H, J = 9.9 Hz), 8.70 (d, 1H, 6-H, J = 6.7 Hz)	1665
10	4.40 (s, 3H, N-CH_3), 7.67 (d, 1H, 5′-H, J = 8.0 Hz), 8.28 (d, 1H, 7-H, J = 6.0 Hz), 8.60 (d, 1H, 4′-H, J = 8.0 Hz), 8.77 (d, 1H, 6-H, J = 6.0 Hz)	1660
11	2.87 (s, 3H, Z-CH_3), 7.62 (d, 1H, 5′-H, J = 8.0 Hz), 8.58 (d, 1H, 4′-H, J = 8.0 Hz)	1670
12	7.45 (s, 1H, 5′-H), 7.80 (s, 4H, 4-H, 5-H, 6-H, 7-H)	1650
13	7.58 (s, 1H, 5′-H), 8.08 (m, 1H, 6-H), 8.81 – 9.05 (m, 2H, 5-H, 7-H)	1660
14	7.52 (s, 1H, 5′-H), 8.18 (d, 1H, 7-H, J = 6.5 Hz), 8.74 (d, 1H, 6-H, J = 6.5 Hz), 9.45 (s, 1H, 4-H)	1655
15	4.33 (s, 3H, N-CH_3), 7.40 (c, 1H, 5′-H), 8.20 (d, 1H, 7-H, J = 6.0 Hz), 8.73 (d, 1H, 6-H, J = 6.0 Hz), 9.73 (s, 1H, 4-H)	1665
16	2.85 (s, 3H, Z-CH_3), 7.50 (c, 1H, 5′-H)	1670

Note. PMR spectra of **7**, **8**, **10 – 13**, **15**, and **16** were recorded in CF_3COOH; **9** and **14**, in CD_3COOD.

6-(Hetaryl)pyridazin-3-ones (7 – 11). A mixture of *o*-diaminohetaryl compound (**1 – 5**, 30 mmol) and 3-pyridazinone-6-carboxylic acid (**6**, 30 mmol) in orthophosphoric acid (85%, 30 mL) was heated at 170 – 180°C for 4 – 5 h, cooled, poured onto ice, and neutralized with K_2CO_3. The resulting precipitate was filtered off, washed with icewater, dried, and recrystallized from a suitable solvent (Table 1).

4-Amino-6-(hetaryl)pyridazin-3-ones (12 – 16). 6-(Hetaryl)pyridazin-3-one (**7 – 11**, 10 mmol) was mixed with hydrazine hydrate (20 mL), heated at 140 – 160°C for 10 – 14 h, and cooled. The resulting precipitate was filtered off, washed with icewater, dried, and recrystallized from a suitable solvent (Table 1).

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