

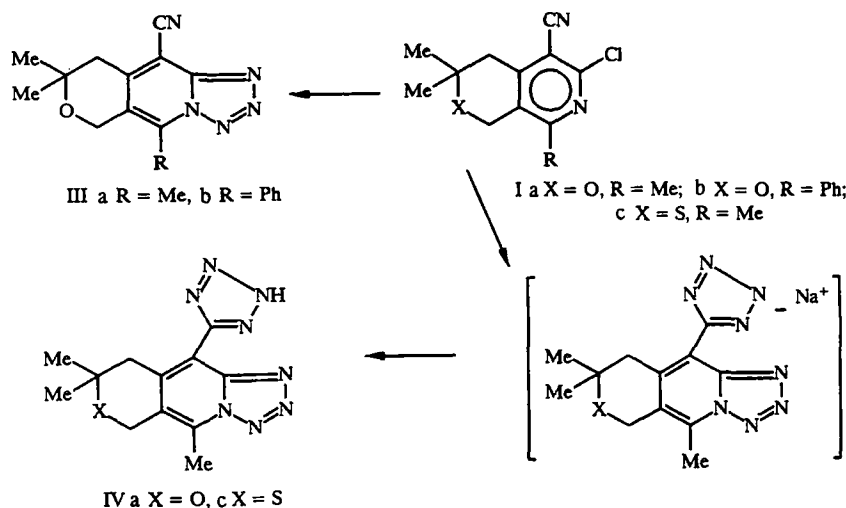
# SYNTHESIS OF DERIVATIVES OF TETRAZOLO[1,5-*a*]- AND OXAZOLO[4,5-*b*]PYRANO(THIOPYRANO)[3,4-*c*]PYRIDINES

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*Tetrazolo[1,5-*a*]- and oxazolo[4,5-*b*]pyrano(thiopyrano)[3,4-*c*]pyridines, which are new heterocyclic systems, have been synthesized from pyrano[3,4-*c*]pyridine derivatives.*

The development of methods of obtaining tetrazolo[1,5-*a*]- and oxazolo[4,5-*b*]pyrano(thiopyrano)[3,4-*c*]pyridines is reported in the present paper. This work is a continuation of our investigations on the synthesis of new condensed heterocycles containing a pyridine ring [1, 2]. These compounds are of interest as potentially biologically active substances.

3-Chloro and 3-oxo derivatives of pyrano(thiopyrano)[3,4-*c*]pyridines (I) and (II), obtained by us previously [3, 5], were used as starting materials for synthesis. Tetrazolo[1,5-*a*]pyrano[3,4-*c*]pyridines (III) were obtained by the reaction of chloronitriles (Ia-d) with sodium azide. On carrying out the reaction in the presence of ammonium chloride the sodium azide reacts with the nitrile group instead of condensing to form system (III). The 4-tetrazolyl derivatives (IVa, c) were obtained as a result.

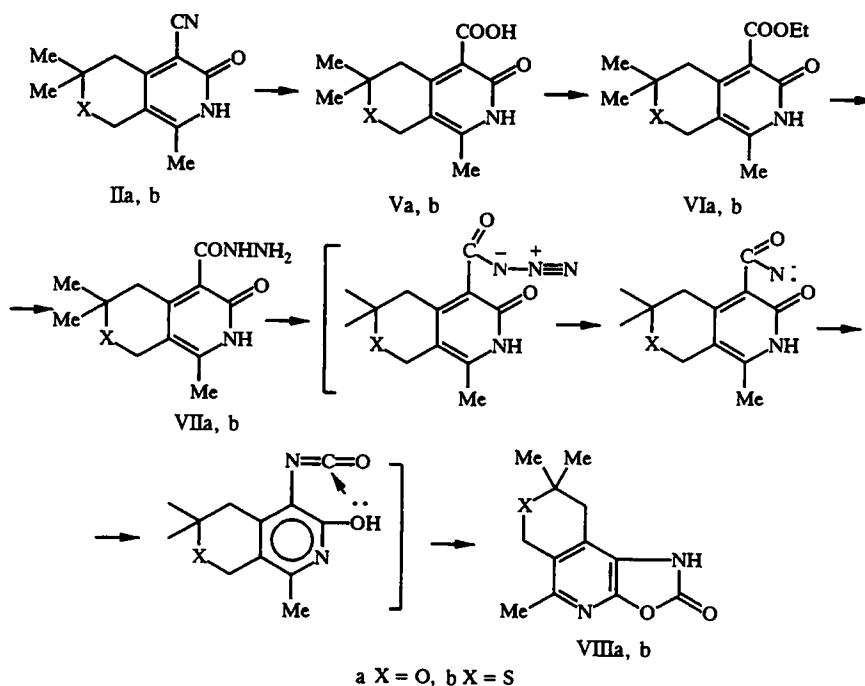


Absorption bands for a nitrile group were absent from the IR spectra of compounds (IVa, c). The presence of two tetrazole rings was confirmed by mass spectroscopy.

Sequential reactions of the nitrile group in compounds (IIa, b) led to carboxyl (Va, b), ester (VIa, b), and carbohydrazide (VIIa, b) groups.

A Curtius rearrangement occurs on treating compounds (VIIa, b) with aqueous sodium nitrile solution in the presence of 20% acetic acid. This followed by intramolecular cyclization leading to the formation of oxazolo[4,5-*b*]pyrano(thiopyrano)[3,4-*c*]pyridines (VIIIa, b).

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Vibrations of a carbonyl group at  $1760\text{ cm}^{-1}$  were observed in the IR spectra of compounds (VIIIa, b). Several characteristic fragment peaks were present in the mass spectra of (VIIIa, b) in addition to the peaks for the molecular ions.

## EXPERIMENTAL

The IR spectra were taken on a UR 20 instrument in Nujol. The PMR spectra were described on a Varian T 60 instrument in DMSO- $D_6$ , internal standard was TMS. The mass spectra were obtained on an MX 1303 mass spectrometer with direct insertion of samples. The purity of compounds obtained was checked by TLC on Silufol UV 254 plates using the systems: pyridine–ethanol, 1:1 for (III), (IVa), (Vb); chloroform–ether, 1:1 (Va); ethanol–water, 1:2 (VIa, b); butanol–acetic acid–water, 4:2:5 (VII), (VIIIa, b).

**4-Carboxy(ethoxycarbonyl,carbohydrazide)-1,6,6-trimethyl-3-oxo-5,6-dihydro-8H-pyrano[3,4-c]pyridines (Va), (VIa), (VIIa)** were synthesized in the same way as their thiopyran analogues (Vb), (VIb), (VIIb), the preparation of which was described in [4]. The characteristics of the new compounds are given in Table 1.

**10-Cyano-8,8-dimethyl-5-phenyl-8,9-dihydro-6H-tetrazolo[1,5-a]pyrano[3,4-c]pyridine (IIIb).** A solution of sodium azide (0.8 g, 0.012 mole) in water (4 ml) was added to a solution of chloronitrile (Ib) (3.0 g; 0.01 mole) in DMF (20 ml). The mixture was heated at  $120\text{--}125^\circ\text{C}$  for 2 h. The DMF was distilled off and water (20 ml) was added to the residue. The resulting crystals were filtered off, washed with water, dried, and recrystallized from nitromethane. Yield was 1.3 g. IR spectrum: 1120 (tetrazole); 1580, 1620 ( $\text{C}=\text{C}$ ,  $\text{C}=\text{N}$ );  $2230\text{ cm}^{-1}$  (CN). PMR spectrum: 1.21 (6H, s,  $2\text{CH}_3$ ); 2.76 (2H, t, 5- $\text{CH}_2$ ); 4.28 (2H, t, 8- $\text{CH}_2$ ); 7.51 ppm (5H, s,  $\text{C}_6\text{H}_5$ ). Mass spectrum,  $m/z$  (I, %):  $\text{M}^+$  305 (100), 290 (10), 277 (39), 248 (52), 219 (56).

**10-Cyano-5,8,8-trimethyl-8,9-dihydro-6H-tetrazolo[1,5-a]pyrano[3,4-c]pyridine (IIIa)** was obtained analogously (Table 1).

**5,8,8-Trimethyl-10-(5-2H-tetrazolyl)-8,9-dihydro-6H-tetrazolo[1,5-a]-6H-pyrano[3,4-c]pyridine (IVa).** A mixture of chloronitrile (Ia) (2.4 g, 0.01 mole), sodium azide (1.4 g, 0.021 mole), ammonium chloride (1.2 g, 0.022 mole), and DMF (30 ml) was heated at  $120\text{--}125^\circ\text{C}$  for 6 h. The DMF was distilled off, water (50 ml) was added to the residue, and the solution acidified with hydrochloric acid to pH 2. The precipitated crystals were filtered off, washed with water, dried, and recrystallized from ethanol. Yield was 2.0 g. IR spectrum: 1100 (tetrazole); 1580, 1630 ( $\text{C}=\text{C}$ ,  $\text{C}=\text{N}$ );  $3150\text{ cm}^{-1}$  (NH). PMR spectrum: 1.25 (6H, s,  $2\text{CH}_3$ ); 2.85 (3H, s,  $\text{CH}_3$ ); 3.11 (2H, t, 5- $\text{CH}_2$ ); 4.91 (2H, t, 8- $\text{CH}_2$ ); 6.40 ppm (1H, s, NH). Mass spectrum,  $m/z$  (I, %):  $\text{M}^+$  286 (44), 271 (15), 258 (17), 243 (87), 174 (100).

TABLE 1. Characteristics of Compounds (III)-(VIII)

Compound	Empirical formula	Found, %/Calculated, %			mp, °C	$R_f$	Yield, %
		C	H	N			
IIIa	C <sub>12</sub> H <sub>13</sub> N <sub>5</sub> O	<u>59.21</u> 59.25	<u>5.42</u> 5.38	<u>28.81</u> 28.79	259...260	0,62	45,6
IIIb	C <sub>17</sub> H <sub>15</sub> N <sub>5</sub> O	<u>66.94</u> 66,87	<u>5.07</u> 4,95	<u>22.99</u> 22,93	267...268	0,69	43,0
IVa	C <sub>12</sub> H <sub>14</sub> N <sub>8</sub> O	<u>50.26</u> 50,34	<u>4.72</u> 4,90	<u>39.21</u> 39,10	235...236	0,59	70,2
IVc	C <sub>12</sub> H <sub>14</sub> N <sub>8</sub> S	<u>47.54</u> 47,67	<u>4.51</u> 4,66	<u>37.12</u> 37,09	236...237	0,67	63,1
Va	C <sub>12</sub> H <sub>15</sub> NO <sub>4</sub>	<u>60.84</u> 60,74	<u>6.42</u> 6,37	<u>5.97</u> 5,90	285...286	0,53	71,5
VIa	C <sub>14</sub> H <sub>19</sub> NO <sub>4</sub>	<u>63.44</u> 63,38	<u>7.34</u> 7,21	<u>5.35</u> 5,27	222...223	0,60	72,6
VIIa	C <sub>12</sub> H <sub>17</sub> N <sub>3</sub> O <sub>3</sub>	<u>57.45</u> 57,36	<u>6.94</u> 6,81	<u>16.83</u> 16,72	244...245	0,71	75,7
VIIIa	C <sub>12</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub>	<u>61.48</u> 61,52	<u>5.89</u> 6,02	<u>11.81</u> 11,59	256...257	0,57	61,7
VIIIb	C <sub>12</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub> S	<u>57.64</u> 57,59	<u>5.76</u> 5,63	<u>11.23</u> 11,19	247...248	0,64	63,9

**5,8,8-Trimethyl-10-(5-2H-tetrazolyl)-8,9-dihydro-tetrazolo[1,5-*a*]-8H-thiopyrano[3,4-*c*]pyridine (IVc)** was obtained analogously.

**5,8,8-Trimethyl-2-oxo-8,9-dihydro(1H,6H)oxazolo[4,5-*b*]pyrano[3,4-*c*]pyridine (VIIIa).** Sodium nitrite (0.7 g, 0.01 mole) dissolved in water (5 ml) was added with stirring to a solution of hydrazide (VIIa) (2.5 g, 0.01 mole) in 20% acetic acid (20 ml) maintaining the temperature at 0°C. The mixture was then left at 20-22°C for 16 h. The resulting crystals were filtered off, o-xylene (20 ml) was added, and the mixture boiled for 20 min. After cooling, the obtained crystals were filtered off, washed with ethanol, dried, and recrystallized from nitromethane. Yield was 1.45 g. IR spectrum: 1590 (C=C); 1760 (C=O); 3450 cm<sup>-1</sup> (NH). Mass spectrum, m/z (I, %): M<sup>+</sup> 234 (40), 219 (14), 191 (12), 176 (100).

**5,8,8-Trimethyl-2-oxo-8,9-dihydro(1H,6H)oxazolo[4,5-*b*]thiopyrano[3,4-*c*]pyridine (VIIIb)** was obtained analogously. Mass spectrum, m/z (I, %): M<sup>+</sup> 250 (100), 235 (35), 217 (33), 202 (10), 176 (95).

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