CONDENSED PYRIDOPYRIMIDINES.

6*. SYNTHESIS OF NOVEL PYRANO-[3',4':6,7]PYRIDO[2,3-d]PYRIMIDINES

A. Sh. Oganisyan, A. S. Noravyan, and M. Zh. Grigoryan

The previously unreported pyrano[3',4':6,7]pyrido[2,3-d]pyrimidines have been synthesized from 2-ethyl-2-methyltetrahydropyran-4-one.

Keywords: pyranopyridine, pyranopyridopyrimidine, pyridine, pyrimidine, pyridopyrimidine, tetrahydropyran, synthesis.

Condensed pyranopyridine derivatives are of great interest as the basis for the preparation of novel condensed heterocyclic systems [2].

This work concerns the synthesis of novel condensed pyrido[2,3-d]pyrimidines starting from 2-ethyl-2-methyltetrahydropyran-4-one. The reaction of the pyrrolidinyl enamine of ketone 1 with ethyl ethoxymethylenecyanoacetate gave the ethyl ester of 3-(6-ethyl-6-methyl-4-pyrrolidino-5,6-dihydro-2H-pyran-3-yl)-2-cyanoacrylic acid (2) which was cyclized in the presence of aqueous ammonia solution to 2-amino-3-carbethoxypyran[4,3-b]pyridine (3). Refluxing an alcohol solution of the latter with phenyl- and benzylisothiocyanates gave the corresponding 2-N'-thioureido derivatives 4a,b which underwent heterocyclization to the 2-thio-3-substituted pyranopyrido[2,3-d]pyrimidines 5a,b (Scheme 1).

Compounds 5a,b were also prepared in a single stage from the pyranopyridine 3 and the indicated isothiocyanates at a temperature of 130-140°C. The reaction of the thiopyranopyridopyrimidines 5a,b with ethyl chloroacetate or with phenacyl bromide gave the corresponding S-alkyl derivatives 6a-d.

EXPERIMENTAL

1H NMR spectra were recorded on a Varian Mercury 300 (300 MHz) instrument using chloroform-d$_1$ (compounds 1-3, 5a,b) or DMSO-d$_6$ (compounds 4a,b, 6a,b). TLC was carried out using Silufol UV-254 plates and revealed using iodine vapor.

The characteristics for the compounds synthesized are given in Table 1.

Pyrrolidinyl Enamine of 2-Ethyl-2-methyltetrahydropyran-4-one (1). A mixture of pyrrolidine (7.1 g), ketone (14.2 g, 0.1 mol) and p-toluenesulfonic acid (0.01 g) in absolute toluene (30 ml) was refluxed using a Dean–Stark apparatus until the calculated amount of water had collected. After evaporation of solvent

* For Communication 5 see [1].
Scheme 1

\[
\begin{align*}
\text{NH} + \text{EtO–CH=C–COOEt} \rightarrow \text{EtO–CH=C–COOEt} + \text{NH}_2 \\
\text{RNCS} \quad \text{130–140 °C} \\
\text{RNCS} \\
\text{NH} \quad \text{N} \\
\text{O} \\
\text{O} \\
\text{O} \\
\text{CN} \\
\text{NH}_3 \\
\text{21} \\
\text{O} \\
\text{N} \\
\text{N} \\
\text{O} \\
\text{S} \\
\text{RNCS} \\
\text{130–140 °C} \\
\text{KOH} \\
\text{5a,b} \\
\text{R} = \text{Ph}, \text{b} = \text{CH}_2\text{Ph}; \text{a, b} \quad \text{R} = \text{CH}_2\text{Ph}; \text{a, b} \quad \text{R} = \text{CH}_2\text{COOEt}, \text{c, d} \quad \text{R} = \text{CH}_2\text{COPh}
\end{align*}
\]

4, 5 a R = Ph, b R = CH2Ph; 6 a, c R = Ph, b, d R = CH2Ph; a, b R1 = CH2COOEt, c, d R1 = CH2COPh

**TABLE 1. Characteristics of Compounds 1-6**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Empirical formula</th>
<th>C</th>
<th>H</th>
<th>N</th>
<th>S</th>
<th>mp, °C</th>
<th>Rf *2</th>
<th>Yield, % (method)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C12H21NO</td>
<td>74.25</td>
<td>9.87</td>
<td>7.59</td>
<td></td>
<td></td>
<td>0.61</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>C18H26N2O3</td>
<td>67.28</td>
<td>8.3</td>
<td>7.9</td>
<td></td>
<td></td>
<td>103-106</td>
<td>0.62</td>
</tr>
<tr>
<td>3</td>
<td>C14H20N3O3</td>
<td>62.87</td>
<td>8.02</td>
<td>10.3</td>
<td></td>
<td></td>
<td>125-127</td>
<td>0.56</td>
</tr>
<tr>
<td>4a</td>
<td>C21H22N3O3S6</td>
<td>63.63</td>
<td>7.58</td>
<td>10.6</td>
<td></td>
<td></td>
<td>194-196</td>
<td>0.57</td>
</tr>
<tr>
<td>4b</td>
<td>C22H24N3O3S</td>
<td>65.08</td>
<td>5.10</td>
<td>9.11</td>
<td>8.3</td>
<td>157-159</td>
<td>0.59</td>
<td>60</td>
</tr>
<tr>
<td>5a</td>
<td>C19H19N3O2S</td>
<td>62.6</td>
<td>6.03</td>
<td>9.58</td>
<td>8.15</td>
<td>194-196</td>
<td>0.65</td>
<td>80 (A), 92 (B)</td>
</tr>
<tr>
<td>5b</td>
<td>C20H21N3O2S</td>
<td>65.4</td>
<td>5.85</td>
<td>10.24</td>
<td>7.8</td>
<td>194-196</td>
<td>0.63</td>
<td>82 (A), 91 (B)</td>
</tr>
<tr>
<td>6a</td>
<td>C23H25N3O4S6</td>
<td>65.10</td>
<td>6.05</td>
<td>12.20</td>
<td>9.81</td>
<td>290</td>
<td>0.65</td>
<td>80 (A), 92 (B)</td>
</tr>
<tr>
<td>6b</td>
<td>C24H27N3O4S6</td>
<td>64.75</td>
<td>6.25</td>
<td>12.08</td>
<td>8.12</td>
<td>300</td>
<td>0.63</td>
<td>82 (A), 91 (B)</td>
</tr>
<tr>
<td>6c</td>
<td>C27H25N3O3S</td>
<td>68.72</td>
<td>6.22</td>
<td>8.12</td>
<td>7.23</td>
<td>168-170</td>
<td>0.65</td>
<td>77</td>
</tr>
<tr>
<td>6d</td>
<td>C28H27N3O3S</td>
<td>68.72</td>
<td>6.22</td>
<td>8.12</td>
<td>7.23</td>
<td>168-170</td>
<td>0.65</td>
<td>77</td>
</tr>
</tbody>
</table>

* Compound 1, bp 110-112°C (3 mm Hg)
*2 Solvent systems: chloroform–ether, 2:1 (1); benzene–ether–methanol, 1:1:1 (2); benzene–ether, 1:3 (3); chloroform–ether, 1:2 (4a,b); chloroform–benzene–ether, 1:1:1 (5a,b); chloroform–ether–heptane, 1:1:2 (6a,b); benzene–ether–heptane, 1:1:1 (6c,d).