SYNTHESIS AND ALKYLATION OF CYCLIC AZOMETHINES —  
3-SPIRO- AND 3,3-DIMETHYL-3,4-DIHYDROISOQUINOLINES

A. G. Mikhailovskii, V. S. Shklyaev, and E. V. Feshina

The cyclic imines 3,3-dimethyl-, 3-spiro-3,4-dihydro-, and benzo[f]isoquinolines were synthesized, and their quaternary salts were obtained.

Earlier we obtained and investigated cyclic imines of the 3,3-dimethyl-3,4-dihydroisoquinoline series [1-3]. The method for the production of these compounds based on the Ritter reaction has wide possibilities. In particular, it makes it possible to obtain spiroannelated [4, 5] and benzo[f]isoquinolines [6], which are of undoubted interest as biologically active compounds. Until now, 3,4-dihydroisoquinolines with such structures have been unknown. The aim of the present work was to study the possibility of synthesizing these compounds.

Cyclization to an isoquinoline ring by the Ritter reaction with hydrocyanic acid as nitrile component was first realized by Wollweber and Hiltmann [7]. In [1] we proposed a method of cyclization suitable for preparative purposes. Here the alcohols (Ia) (R' = H, R^2 = Me) and (Ib) (R^1 = OMe, R^2 = Me), which give the respective isoquinolines (IIa, b) during cyclization, were used as starting compounds.

Investigations showed that the reaction of the tertiary carbinols (Ia-c) with potassium cyanide in the presence of sulfuric acid also leads to the corresponding isoquinolines (IIc-f).

The characteristics of the compounds obtained for the first time are given in Table 1. As seen from the data in the table, the yield of the cyclization product depends on the nature of the aromatic ring; in the case of activation by methoxy groups [carbinols (Ic, f)] the yield is increased by approximately 1.5 times compared with the inactivated ring [carbinols (Ic, e)].

As expected, analogous cyclization with the naphthalene-containing carbinols (IIa, b) takes place smoothly with the formation of benzo[f]isoquinolines (IVa, b) (Table 1). The yields of the products reflect the increased activity of the naphthalene ring compared with the activated benzene ring [compounds (IIc, e)] in substitution reactions.

It should be noted that in the case of an inactivated aromatic ring the reactions of the respective carbinols with other nitrile components, such as benzyl cyanides [8, 9] and the esters [10] or amides [5, 11] of cyanoacetic acid, lead to larger preparative yields than in the case of hydrocyanic acid, where lesser stabilization of the nitrile intermediate evidently occurs [12].
TABLE 1. Characteristics of the Synthesized Compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>( x^1 )</th>
<th>( C(\text{H}_2)_2 )</th>
<th>Found, %</th>
<th>Molecular formula</th>
<th>Calculated, %</th>
<th>mp, °C</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>C</td>
<td>H</td>
<td>N</td>
<td>C(S)</td>
<td>C</td>
</tr>
<tr>
<td>IIc</td>
<td>H</td>
<td>C(\text{H}_2)_2</td>
<td>70.3</td>
<td>7.1</td>
<td>5.6</td>
<td>15.8</td>
<td>C_{15}H_{16}N \cdot HCl</td>
</tr>
<tr>
<td>IIId</td>
<td>OCH(_3)</td>
<td>C(\text{H}_2)_2</td>
<td>71.1</td>
<td>7.6</td>
<td>6.0</td>
<td>14.8</td>
<td>C_{15}H_{16}NO \cdot HCl</td>
</tr>
<tr>
<td>IIe</td>
<td>H</td>
<td>C(\text{H}_2)_2</td>
<td>64.8</td>
<td>7.8</td>
<td>4.8</td>
<td>11.8</td>
<td>C_{16}H_{17}N \cdot HCl</td>
</tr>
<tr>
<td>IIIf</td>
<td>OCH(_3)</td>
<td>C(\text{H}_2)_2</td>
<td>58.5</td>
<td>5.5</td>
<td>4.6</td>
<td>10.3</td>
<td>C_{15}H_{13}N \cdot H_2SO_4</td>
</tr>
<tr>
<td>IVa</td>
<td>-</td>
<td>C(\text{CH}_3)_2</td>
<td>75.0</td>
<td>6.6</td>
<td>5.3</td>
<td>12.9</td>
<td>C_{15}H_{13}N \cdot HCl</td>
</tr>
<tr>
<td>IVb</td>
<td>-</td>
<td>C(\text{CH}_2)_2</td>
<td>47.7</td>
<td>5.3</td>
<td>4.8</td>
<td>-</td>
<td>C_{12}H_{16}N</td>
</tr>
<tr>
<td>Va</td>
<td>H</td>
<td>C(\text{CH}_3)_2</td>
<td>46.5</td>
<td>5.4</td>
<td>3.8</td>
<td>-</td>
<td>C_{16}H_{16}NO_2</td>
</tr>
<tr>
<td>Vb</td>
<td>OCH(_3)</td>
<td>C(\text{CH}_3)_2</td>
<td>51.2</td>
<td>5.3</td>
<td>3.8</td>
<td>-</td>
<td>C_{16}H_{16}N</td>
</tr>
<tr>
<td>Vc</td>
<td>H</td>
<td>C(\text{CH}_2)_2</td>
<td>52.7</td>
<td>5.8</td>
<td>3.9</td>
<td>-</td>
<td>C_{15}H_{20}N</td>
</tr>
<tr>
<td>Vd</td>
<td>H</td>
<td>C(\text{CH}_3)_2</td>
<td>45.6</td>
<td>5.1</td>
<td>3.5</td>
<td>-</td>
<td>C_{16}H_{16}NO_4</td>
</tr>
</tbody>
</table>

(decomp.)