Studies on Spiro Azetidinones and Spiro Thiazolidinones, III

Synthesis of Some New Spiro Azetidinones, Spiro Thiazolidinones, Bis-azetidinones and Bis-thiazolidinones

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Cyclocondensation Reaction, Spiro Azetidinones, Spiro Thiazolidinones

Cyclocondensation reaction of 3-isatylideneoxime \((1a)\), -hydrazone \((1b)\), -phenylhydrazone \((1c)\), semicarbazone \((1d)\) and -thiosemicarbazone \((1e)\) with chloroacetyl chloride (and thioglycolic acid) gave the corresponding spiro azetidinones \((2)\) and spiro thiazolidinones \((3)\). 3-Isatylidenehydrazone \((1b)\) was condensed easily with aromatic aldehydes afforded a new 3-isatylidene azomethines \((4)\) which submitted for cyclocondensation reaction with chloroacetyl chloride (and thioglycolic acid) giving bis-azetidinones \((5)\) and bis-thiazolidinones \((6)\), respectively.

In previous articles \([1, 2]\) of this series it was shown that the cyclocondensation reaction of chloroacetyl chloride (and thioglycolic acid) on 3-isatylidene anils gave spiro azetidinones (and thiazolidinones). In view of the antibiotic activity of the azetidinone moiety and the antimicrobial activity of the thiazolidine nucleus it was anticipated that the new spiro isatylidene azetidinones (and thiazolidinones) would possess interesting biological activity. This has led us to extend this work to cover other classes of amino compounds to prepare a wide variety of substituted spiro isatylidene azetidinones (and thiazolidinones). Moreover, we have synthesized a new series of substituted isatylidene bis-azetidinones and bis-thiazolidinones, respectively.

Thus, isatin was condensed easily with amines, namely hydroxylamine, hydrazine, phenylhydrazine, semicarbazide and thiosemicarbazide in boiling ethanol giving the corresponding oxime \((1a)\), hydrazone \((1b)\), phenylhydrazine \((1c)\), semicarbazide \((1d)\) and thiosemicarbazide \((1e)\) \([3-5]\).

\[ \begin{array}{c}
\text{1} \quad R \\
a \quad \text{OH} \\
b \quad \text{NH}_3 \\
c \quad \text{NHCH}_3\text{H}_5 \\
d \quad \text{NH-CO-NH}_2 \\
e \quad \text{NH-CS-NH}_2 
\end{array} \]

Cyclocondensation reaction of chloroacetyl chloride (or thioglycolic acid) on isatylidene anils \((1a-e)\) according to the methods reported for the general synthesis of azetidinones \([6]\) and thiazolidinones \([7]\) yielded the corresponding new substituted spiro[indoline-3,4'-azetidine]-3'-chloro-2,2'-dions \((2)\) and spiro[indoline-3,2'-thiazolidine]-2,4'-diones \((3)\).

The structure of compounds \((2)\) and \((3)\) was established from the microanalytical data and the IR spectra, which showed an absorption band at about 1750–1743 cm\(^{-1}\) \(\nu\text{C}=\text{O}\) (monocyclic \(\beta\)-lactams) \([8]\) and at 1698 cm\(^{-1}\) for \(\nu\text{C}=\text{O}\) group (compound \((3)\) \([9]\)).

3-Isatylidene hydrazone \((1b)\) as a typical aromatic amine, containing a free amino group was subjected for a condensation reaction with aromatic aldehydes in boiling ethanol in presence of piperidine as a catalyst, giving the corresponding unsymmetrical Schiff bases \((4)\).

The structure of these compounds \((4)\) was identified from the correct analytical data and the IR spectra, which showed and absorption band at 1640 cm\(^{-1}\) (\(\text{C}=\text{N}\)) and the absence of the bands due to the \(\text{NH}_2\) group \([8]\).
Hence, the unsymmetrical bis-anils (4) were prepared, it seems of interest to synthesized the unreported bis-azetidinones and bis-thiazolidinones. Thus, cyclocondensation reaction of chloroacetyl chloride (or thiaglycolic acid) on bis-anils (4), giving bis-azetidinones (5) and bis-thiazolidinones (6), respectively.

\[
\begin{align*}
\text{R} & \quad \text{m.p.} & \quad \text{Yield} & \quad \text{Molecular formula} & \quad \text{Analyses [\%]} & \quad \text{N} & \quad \text{S} \\
2a & \text{NHC}_{6}\text{H}_{3} & 210-212 & 26 & \text{C}_{16}\text{H}_{12}\text{N}_{3}\text{O}_{2}\text{Cl} & 13.39 & - \\
2b & \text{NH} \cdot \text{CO} \cdot \text{NH}_{2} & 208-209 & 30 & \text{C}_{11}\text{H}_{9}\text{N}_{4}\text{O}_{3}\text{Cl} & 19.96 & - \\
2c & \text{NH} \cdot \text{CS} \cdot \text{NH}_{2} & 178-179 & 40 & \text{C}_{11}\text{H}_{9}\text{N}_{4}\text{Cl} & 18.88 & 10.79 \\
3a & \text{OH} & 256-258 & 18 & \text{C}_{10}\text{H}_{8}\text{N}_{2}\text{S}_{2} & 11.86 & 13.55 \\
3b & \text{NHC}_{6}\text{H}_{5} & 211-212 & 16 & \text{C}_{15}\text{H}_{12}\text{N}_{3}\text{O}_{3} & 13.50 & 10.28 \\
3c & \text{NH} \cdot \text{CO} \cdot \text{NH}_{2} & 269-270 & 21 & \text{C}_{15}\text{H}_{10}\text{N}_{3}\text{O}_{3} & 20.97 & 11.98 \\
3d & \text{NH} \cdot \text{CS} \cdot \text{NH}_{2} & 236-238 & 20 & \text{C}_{15}\text{H}_{10}\text{N}_{3}\text{S}_{2} & 19.78 & 22.61 \\
4a & \text{H} & 188-189 & 70 & \text{C}_{16}\text{H}_{11}\text{N}_{3} & 16.86 & - \\
4b & \text{o-OH} & 227-229 & 75 & \text{C}_{15}\text{H}_{11}\text{N}_{3} & 15.84 & - \\
4c & \text{p-OCH}_{3} & 180-182 & 79 & \text{C}_{15}\text{H}_{12}\text{N}_{3} & 15.05 & - \\
4d & \text{p-Cl} & 270-271 & 69 & \text{C}_{15}\text{H}_{11}\text{N}_{3}\text{O} & 14.81 & - \\
4e & \text{p-NO}_{2} & 283-284 & 71 & \text{C}_{15}\text{H}_{10}\text{N}_{3} & 19.04 & - \\
4f & \text{p-N(CH}_{3})_{2} & 248-249 & 68 & \text{C}_{17}\text{H}_{16}\text{N}_{4} & 19.17 & - \\
4g & \text{O}_{2}\text{CH}_{2} & 220-222 & 60 & \text{C}_{16}\text{H}_{11}\text{N}_{3} & 14.33 & - \\
\end{align*}
\]

All compounds gave satisfactory C,H analyses.
Table III. Bis-azetidinones (5) and bis-thiazolidinones (6).

<table>
<thead>
<tr>
<th>Compound R</th>
<th>m.p. [°C]</th>
<th>Yield [%]</th>
<th>Molecular formula</th>
<th>Analysis [%]</th>
<th>calcd (found)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a H</td>
<td>143-144</td>
<td>12</td>
<td>C₁₉H₁₉N₃O₂Cl₂</td>
<td>10.44 -</td>
<td>—</td>
</tr>
<tr>
<td>5b o-OH</td>
<td>126-127</td>
<td>10</td>
<td>C₁₉H₁₉N₃O₂Cl₂</td>
<td>9.90 -</td>
<td>(10.00) -</td>
</tr>
<tr>
<td>5c p-OCH₃</td>
<td>167-168</td>
<td>14</td>
<td>C₂₀H₁₅N₃O₄Cl₂</td>
<td>18.10 -</td>
<td>(18.30) -</td>
</tr>
<tr>
<td>5d p-N(CH₃)₂</td>
<td>190-191</td>
<td>15</td>
<td>C₂₁H₁₉N₄O₃Cl₂</td>
<td>22.85 -</td>
<td>(23.02) -</td>
</tr>
<tr>
<td>6a o-OH</td>
<td>215-216</td>
<td>11</td>
<td>C₁₉H₁₅N₃S₂O₄</td>
<td>10.16 15.49</td>
<td>(10.21) 15.53</td>
</tr>
<tr>
<td>6b p-Cl</td>
<td>228-230</td>
<td>16</td>
<td>C₁₉H₁₅N₃S₂O₃Cl</td>
<td>9.73 14.83</td>
<td>(10.01) 15.01</td>
</tr>
<tr>
<td>6c p-N(CH₃)₂</td>
<td>219-220</td>
<td>18</td>
<td>C₂₁H₂₀N₃S₂O₃</td>
<td>12.72 14.54</td>
<td>(12.90) 14.73</td>
</tr>
</tbody>
</table>

All compounds gave satisfactory C,H analyses.

Synthesis of spiro thiazolidinones (4)

Spiro[indoline-3,2'-thiazolidine]-2,4'-diones (3) were prepared according to the literature [2]. The results are given in Table I.

Preparation of the unsymmetrical anils (4)

Equimolecular amounts of isatin-3-hydrazone (1b) and the corresponding aldehyde and few drops of piperidine in 50 ml alcohol were refluxed for 5 h. The mixture was concentrated and cooled. The formed precipitate was filtered off and crystallized from alcohol. The results are cited in Table II.

Preparation of bis-azetidinones (5)

To a well stirred solution of (0.01 mole) of Schiff bases (4) and (0.04 mole) of NEt₃ in dry dioxane added (0.04 mole) of monochloroacetyl chloride dropwise at room temperature. After all the quantity of the chloroacetyl chloride was added, the mixture stirred for 5 h and left at room temperature for 3 d. The formed precipitate (triethylamine hydrochloride) was filtered off, washed thoroughly with the same solvent. The combined solvent and filtrate was evaporated to a minimum volume then cooled, and poured into the acidified water. The precipitate was collected and crystallized from benzene/dioxane (1/1). The results are summarized in Table III.

Synthesis of bis-thiazolidinones (6)

A mixture of (0.02 mole) of Schiff bases (4) and (0.04 mole) of mercaptoacetic acid in 100 c.c. dry benzene was refluxed with water separator connected to the apparatus until the theoretical amount of water had been collected. After most of the benzene had been removed the residue was dissolved in ether and seeded. The results are listed in Table III.