CHEMOTHERAPY OF BACTERIAL INFECTIONS

Part VIII. Synthesis of Carboxylic Acid Derivatives of 2-Sulphanilamidothiazole

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In Part V of this series, many alkyl derivatives of 2-sulphanilamidothiazole were described. In continuation of this, herein is reported the synthesis of some typical carboxylic acid derivatives with the acid grouping attached directly or through alkyl radicals to the thiazole ring in the positions 4 or 5. The synthesis of such acid derivatives has another object also. The exhaustive studies carried out hitherto with the various sulphanilamide derivatives have led to a novel application of these drugs for purposes wherein only their \textit{in vitro} bacteriostatic and bactericidal effects are of prime importance. For one of such purposes are required solutions of these drugs in concentrations of the order of 1 to 30\% at about 0\° C. with the pH of the solution being as near as possible to 7.4. In the cases of 2-sulphanilamidopyridine and 2-sulphanilamidothiazole, such concentrations are possible only with their sodium salts and the pH of these solutions is about 10 to 11. We anticipate the sodium salts of the acid derivatives described here to satisfy our requirements.

The sulphanilamido derivatives herein reported were all synthesised by the usual method of condensing the 2-aminothiazole derivative with acet-sulphanilic chloride and hydrolysing the resulting product. The hydrolysis was carried out in alcoholic hydrochloric acid or sodium hydroxide. When the conditions were more drastic, decarboxylation was also effected. For example, the hydrolysis of 2-acetsulphanilamido-4-methyl-5-carbethoxythiazole or 2-acetsulphanilamido-4-carbethoxymethylthiazole with about 5 N hydrochloric acid, yielded 2-sulphanilamido-4-methylthiazole. Similarly, 2-acetsulphanilamido-4-methyl-5-carbethoxymethylthiazole furnished 2-sulphanilamido-4:5-dimethylthiazole. We are adopting this method to synthesise some alkyl and other derivatives of 2-sulphanilamidothiazole, the preparation of which by the usual methods are more involved.

The starting aminothiazole derivatives are all known excepting ethyl 2-aminothiazole-5-carboxylate and ethyl \textit{a-}(2-aminothiazolyl)caproate. The
former was prepared by condensing thiourea with ethyl chloroformylacetate and the latter, which was not isolated, by the action of thiourea on the \( \gamma \)-bromination product of ethyl \( \alpha \)-butylacetocacetate.

The compounds obtained are listed in the following table.

<table>
<thead>
<tr>
<th>Serial No.</th>
<th>Name of Compound</th>
<th>M.P. (^\circ)C.</th>
<th>Molecular Formula</th>
<th>% Nitrogen Found</th>
<th>% Nitrogen Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>96</td>
<td>2-Sulphanilamido-5-carbethoxythiazole</td>
<td>227-28</td>
<td>C(<em>{12})H(</em>{13})N(_2)O(_4)S (_2)</td>
<td>13.4</td>
<td>12.8</td>
</tr>
<tr>
<td>47</td>
<td>2-Acetsulphanilamido-5-carbethoxythiazole</td>
<td>228-29</td>
<td>C(<em>{14})H(</em>{15})N(_2)O(_4)S (_2)</td>
<td>12.0</td>
<td>11.4</td>
</tr>
<tr>
<td>48</td>
<td>2-Sulphanilamido-4-carboxymethylthiazole</td>
<td>195</td>
<td>C(<em>{11})H(</em>{11})N(_2)O(_4)S (_2)</td>
<td>12.9</td>
<td>13.4</td>
</tr>
<tr>
<td>49</td>
<td>2-Acetsulphanilamido-4-carboxymethylthiazole</td>
<td>154(^\circ)</td>
<td>C(<em>{12})H(</em>{13})N(_2)O(_4)S (_2)</td>
<td>11.4</td>
<td>11.0</td>
</tr>
<tr>
<td>97</td>
<td>( \alpha )-(2-Sulphanilamido-(4)-thiazolyl) caproic acid</td>
<td>170-71</td>
<td>C(<em>{12})H(</em>{13})N(_2)O(_4)S (_2)</td>
<td>11.3</td>
<td>11.0</td>
</tr>
<tr>
<td>98</td>
<td>( \alpha )-(2-Sulphanilamido-(4)-thiazolyl) tert.-butyric acid</td>
<td>183-84</td>
<td>C(<em>{14})H(</em>{17})N(_2)O(_4)S (_2)</td>
<td>11.7</td>
<td>11.8</td>
</tr>
<tr>
<td>99</td>
<td>Ethyl ( \alpha )-(2-acetsulphanilamido-(4)-thiazolyl) tert.-butyrate</td>
<td>203-04</td>
<td>C(<em>{14})H(</em>{17})N(_2)O(_4)S (_2)</td>
<td>10.6</td>
<td>10.6</td>
</tr>
<tr>
<td>33</td>
<td>2-Sulphanilamido-4-methylthiazole</td>
<td>236-37</td>
<td>C(<em>{10})H(</em>{12})N(_2)O(_4)S (_2)</td>
<td>15.0</td>
<td>15.1</td>
</tr>
<tr>
<td>81</td>
<td>2-Sulphanilamido-4 : 5-dimethylthiazole</td>
<td>243-44</td>
<td>C(<em>{11})H(</em>{12})N(_2)O(_4)S (_2)</td>
<td>14.7</td>
<td>14.8</td>
</tr>
</tbody>
</table>

\( ^a \) Messrs. May and Baker's patent\(^a\) records m.p. 190\(^\circ\). Jensen and Thorsteinsson\(^b\) record m.p. 193\(^\circ\).

\( ^b \) Messrs. May and Baker's patent\(^a\) records m.p. 249\(^\circ\). Jensen and Thorsteinsson\(^b\) record m.p. 152-53\(^\circ\).

\( ^c \) Jensen and Thorsteinsson\(^b\) record m.p. 185\(^\circ\).

\( ^d \) Jensen and Thorsteinsson\(^b\) record m.p. 172-73\(^\circ\).

\( ^e \) Obtained by the hydrolysis of the acetyl derivative of compounds 47 and 48.

\( ^f \) Obtained by the hydrolysis of the acetyl derivative of compound 49.

\( ^g \) Mels at 154\(^\circ\), then solidifies and melts again at 248\(^\circ\).

These compounds are being tested in some experimental bacterial infections in mice and the results obtained will be reported in due course.

**Experimental**

*Ethyl 2-aminothiazole-5-carboxylate.*—To powdered sodium (4·6 gm.) suspended in dry ether (200 c.c.) was added gradually with stirring a mixture
of ethyl chloracetate (25 gm.) and ethyl formate (14·8 gm.). The reaction mixture was cooled with ice-water, the stirring continued for some hours and then allowed to stand overnight. Sufficient water (about 50 c.c.) was added to dissolve the sodium salt. The aqueous layer was separated, extracted with ether to remove any unchanged substance, neutralised and treated with thiourea (15·2 gm.). The mixture was allowed to stand overnight at the room temperature, then extracted with ether, and the acidic aqueous solution basified with ammonia whereby 2-amino-5-carbethoxythiazole separated. This was filtered and crystallised from water; m.p. 160–61°. (Found: N, 16·8; C₈H₇N₂O₄S requires N, 16·3%). Yield, 7 gm.

2-Sulphanilamidothiazole Derivatives.—These compounds were prepared according to the usual process. The condensation of the aminothiazole derivatives with acetsulphanilylchloride was carried out in the presence of pyridine. It was found to be advantageous to employ the esters themselves rather than the acid derivatives of the aminothiazoles. The hydrolysis of the acetsulphanilamido derivatives was carried by boiling with 6 times the amount of about 5 N hydrochloric acid with an equal volume of alcohol for one to one and a half hours. In many cases, this hydrolysed only the acetamino group, leaving the ester group intact which was then hydrolysed by boiling with alcoholic potash. If the hydrolysis was carried out with hydrochloric acid or 2·5 N sodium hydroxide and especially the boiling continued for about one hour, decarboxylation also took place furnishing the alkyl derivatives.

We express our grateful thanks to Lt.-Col. S. S. Sokhey, Director, Haffkine Institute, Parel, Bombay, for his kind interest in these investigations.

Summary

A number of carboxylic acid derivatives of 2-sulphanilamidothiazole with the acid grouping attached directly or through alkyl radicals to the thiazole ring at the positions 4 or 5, are described.

REFERENCES