Tuberculostatic Derivatives of \( p \)-Aminobenzoic Acid

V. 4-Aminosalicyloyl Derivatives of Sulfanilamide and Related Compounds

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With the purpose of investigating their tuberculostatic activity some compounds which at the same time are derivatives of \( p \)-aminosalicylic acid (PAS) and sulfonamides or sulfones were prepared.

From the reaction of \( p \)-nitrosalicyloyl chloride with aniline a well defined product could more easily be obtained than from the reaction of this acid chloride with heterocyclic amines (cf. the preceding paper\(^1\)). Analogously \( p \)-nitrosalicyloyl derivatives of sulfanilamide, sulfathiazole etc. were obtained without difficulty and generally in good yields. The nitro compounds form intensely yellow powders which are very slightly soluble in most solvents. The following compounds were prepared (\( R = O_2N\text{\textsuperscript{\(\circ\})} \)):

\[
\begin{align*}
\text{I} & \quad \text{RNH} \text{\textsuperscript{\(\circ\})} \text{SO}_2\text{NH}_2 \\
\text{II} & \quad \text{RNH} \text{\textsuperscript{\(\circ\})} \text{SO}_2\text{NH} \text{\textsuperscript{\(\circ\})} \text{CH} \\
\text{III} & \quad \text{RNH} \text{\textsuperscript{\(\circ\})} \text{SO}_2\text{NH} \text{\textsuperscript{\(\circ\})} \text{CH} \\
\text{IV} & \quad \text{RNH} \text{\textsuperscript{\(\circ\})} \text{SO}_2\text{NH} \text{\textsuperscript{\(\circ\})} \text{CH}_3 \\
\text{V} & \quad \text{RNH} \text{\textsuperscript{\(\circ\})} \text{SO}_2\text{NH} \text{\textsuperscript{\(\circ\})} \text{CH}_3 \\
\text{VI} & \quad \text{RNH} \text{\textsuperscript{\(\circ\})} \text{SO}_2\text{NH} \text{\textsuperscript{\(\circ\})} \text{CH}_3 \\
\end{align*}
\]

PNS-Derivative of:

Sulfanilamide
Sulfapyridine
Sulfathiazole
SulfamethyHzol
Sulfadiazine
Sulfamerazine
In addition to the compounds of this type we also prepared p-nitrosalicyloyl derivatives of 4,4'-diamino-diphenylsulfone (VII), p-aminomethylbenzene-sulfonamide (Marfanil, Sulfamylon. VIII) and β-alanine (IX):

\[
\text{VII} \quad \text{VIII} \quad \text{IX}
\]

The nitro compounds were reduced to the corresponding amino compounds with tin and hydrochloric acid in acetic acid solution. The following compounds were isolated and characterized (R' = H₂N<CO—):

\[
\text{PAS-Derivative of:}
\]

\[
\text{X} \quad \text{XI} \quad \text{XII} \quad \text{XIII} \quad \text{XIV}
\]

Sulfanilamide
Sulfathiazole
Sulfamethylizole
4,4'-Diamino-diphenylsulfone
Marfanil

EXPERIMENTAL

p-Nitrosalicylanilide (2-Hydroxy-4-nitrobenzanilide). p-Nitrosalicyloyl chloride (2 g) was added with cooling to aniline (5 ml) and the reaction product recrystallized from benzene. Yield 2.1 g (80 %). M. p. 238°.

\[
\text{C}_{13}\text{H}_{10}\text{O}_4\text{N}_2 \quad (258.2) \quad \text{Calc. N} \quad 10.85 \quad \text{Found} \quad 10.65
\]

By catalytic hydrogenation at room temperature and atmospheric pressure (cf. Jensen, Rosdahl and Ingvorsen) this compound was transformed into p-aminosalicylanilide (m. p. 143°) identical with the product prepared by Jensen and Ingvorsen.

\[
\text{N}^4-(p\text{-Nitrosalicyloyl})-\text{sulfanilamide (I). Sulfanilamide (0.005 mole; 0.85 g) dissolved in 10 ml of pyridine was added to p-nitrosalicyloyl chloride (1 g) and the solution heated for ½ hour at 120°. The mixture was diluted with water and the precipitate filtered and washed thoroughly with water. Yield of crude product 1.55 g (89%). Recrystal-}
\]
lized from ethanol it formed orange-yellow crystals which turned almost white at 200° and melted at 249—50°.

\[ \text{C}_{13}\text{H}_{11}\text{O}_6\text{N}_5\text{S} \] (337.3) Calc. N 12.46 Found N 12.54

In a similar way the other nitro compounds (Table I) were prepared. In preparing the comp. no. VIII the hydrochloride of Marfanil instead of the free amine was used. Yields in most cases were 70—90%. The crude products were recrystallized from ethanol or acetic acid. The derivatives of the heterocyclic sulfonamides and comp. no. VII are very slightly soluble in the common solvents, whereas the other compounds were rather soluble in hot ethanol. The compounds form light yellow crystals.

By reaction of \( p \)-nitrosalicyloyl chloride with 4,4'-diaminodiphenylsulfone a bis-\( p \)-nitrosalicyloyl derivative was obtained. With 4-aminophenyl-5'-amino-2'-thiazoylsulfone (Promizole) on the other hand a product was obtained which apparently is a mono-\( p \)-nitrosalicyloyl derivative (calc. 13.34% N, found 13.10%). Other preparations, however, gave lower nitrogen values and the compound was not examined further.

The derivative of \( \beta \)-alanine was prepared by using a Schotten-Bauman procedure in the same way as salicyloyl-\( \beta \)-alanine (Moss et al.4).

Reduction was performed with tin and hydrochloric acid in acetic acid solution in the same way as described in the preceding paper.

\( N^4 \)-(\( p \)-Aminosalicyloyl)-sulfanilamide. On recrystallizing from dilute ethanol (70%) the compound separated as white shiny plates. Slightly soluble in hot ethanol, easily soluble in acetone. M. p.: decomposes gradually at 270—300°.

\[ \text{C}_{13}\text{H}_{13}\text{O}_4\text{N}_5\text{S} \] (307.3) Calc. N 13.74 S 10.64 Found N 13.70 S 10.64

In a similar way the other amino compounds (Table 2) were prepared.

<table>
<thead>
<tr>
<th>No.</th>
<th>Empirical formula</th>
<th>M. p.</th>
<th>calc.</th>
<th>% N</th>
<th>found</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>( \text{C}<em>{12}\text{H}</em>{11}\text{O}_6\text{N}_5\text{S} )</td>
<td>250°</td>
<td>12.46</td>
<td>12.50</td>
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<tr>
<td>II</td>
<td>( \text{C}<em>{13}\text{H}</em>{14}\text{O}_6\text{N}_4\text{S} )</td>
<td>205° (dec.)</td>
<td>13.52</td>
<td>13.45</td>
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<tr>
<td>III</td>
<td>( \text{C}<em>{16}\text{H}</em>{12}\text{O}_6\text{N}_4\text{S}_2 )</td>
<td>290° (dec.)</td>
<td>13.36</td>
<td>13.80</td>
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<td>IV</td>
<td>( \text{C}<em>{16}\text{H}</em>{13}\text{O}_6\text{N}_5\text{S}_2 )</td>
<td>296° (dec.)</td>
<td>16.08</td>
<td>16.60</td>
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<tr>
<td>V</td>
<td>( \text{C}<em>{17}\text{H}</em>{13}\text{O}_6\text{N}_5\text{S} )</td>
<td>295° (dec.)</td>
<td>16.86</td>
<td>16.63</td>
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<tr>
<td>VI</td>
<td>( \text{C}<em>{18}\text{H}</em>{15}\text{O}_6\text{N}_5\text{S} )</td>
<td>270° (dec.)</td>
<td>16.31</td>
<td>16.45</td>
<td></td>
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<tr>
<td>VII</td>
<td>( \text{C}<em>{26}\text{H}</em>{18}\text{O}_{10}\text{N}_4\text{S} )</td>
<td>245° (dec.)</td>
<td>9.68</td>
<td>9.97</td>
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<tr>
<td>VIII</td>
<td>( \text{C}<em>{14}\text{H}</em>{13}\text{O}_6\text{N}_5\text{S} )</td>
<td>254°</td>
<td>11.94</td>
<td>11.96</td>
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<tr>
<td>IX</td>
<td>( \text{C}<em>{10}\text{H}</em>{10}\text{O}_6\text{N}_2\text{S} )</td>
<td>212—13°</td>
<td>11.03</td>
<td>11.15</td>
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</table>
Nos. III and IV were recrystallized from acetic acid, the others from ethanol. No. VI melts first at ca. 160° but solidifies again.

Table 2. p-Aminosalicyloyl derivatives of sulfanilamide etc.

<table>
<thead>
<tr>
<th>No.</th>
<th>Empirical formula</th>
<th>M. p.</th>
<th>% N</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
<td>calc.</td>
<td>found</td>
</tr>
<tr>
<td>X</td>
<td>C₁₃H₁₂O₄N₃S</td>
<td>dec.</td>
<td>13.74</td>
</tr>
<tr>
<td>XI</td>
<td>C₁₆H₁₄O₄N₄S₂</td>
<td>270° (dec.)</td>
<td>14.35</td>
</tr>
<tr>
<td>XII</td>
<td>C₁₆H₁₆O₄N₅S₂</td>
<td>280° (dec.)</td>
<td>17.50</td>
</tr>
<tr>
<td>XIII</td>
<td>C₂₈H₂₀O₅N₄S</td>
<td>264°</td>
<td>10.81</td>
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<tr>
<td>XIV</td>
<td>C₁₄H₁₆O₄N₃S</td>
<td>219°</td>
<td>13.08</td>
</tr>
</tbody>
</table>

SUMMARY

p-Nitrosalicylic acid derivatives of sulfanilamide and substituted sulfanilamides, of diaminodiphenylsulfone and p-aminomethylbenzenesulfonamide (Marfanil, Sulfamylon) were prepared by the reaction of p-nitrosalicyloyl chloride with the appropriate amino compound in pyridine solution. The corresponding p-amino derivatives were obtained by reduction of the nitro compounds with tin and hydrochloric acid in acetic acid solution.

REFERENCES


Received August 18, 1951.