SYNTHESIS OF SOME NEW PRODRUGS OF SULPHONAMIDES AND STUDIES ON THEIR ANTIMICROBIAL AND ANTI-INFLAMMATORY ACTION

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Various amide-based prodrugs of sulphonamides have been synthesised by condensing appropriate sulphonamide moiety with different β-aroyl propionic acids. All the compounds have been evaluated for their antimicrobial and anti-inflammatory activities. Their structures were established on the basis of elemental analysis, $^1$H NMR and Mass spectral data. Some of these compounds were found to have significant activity.

Key words: Sulphonamides, prodrugs, amides, anti-inflammatory, antimicrobial.

Introduction

The sulphonamides are one of the least expensive chemotherapeutic agents and this factor largely accounts for their greater extent of use in developing countries. They are used in urinary tract infections, meningitis, streptococcal pharyngitis, bacillary dysentery, trachoma, chancroid, malaria, toxoplasmosis, nocardiasis and conjunctivitis$^{1-3}$. Dapsone still remains the drug of
choice for all forms of leprosy. They are generally taken orally in higher doses which cause nausea, vomiting and epigastric pain\(^4,5\). \(\beta\)-Aroyl propionic acids are well known anti-inflammatory drugs and some of them are available in the market (fenbufen, buclocic acid, furobufen etc.)\(^3,6\), they owe their activity to in-vivo metabolism to the corresponding phenyl acetic acid and have been reported to have comparatively more gastrointestinal side effects as compared to other NSAIDs\(^7,9\). In view of these facts, it was considered worthwhile to study various amide-based prodrugs of sulphonamides with \(\beta\)-aeryl propionic acids in order to improve their efficacy and to decrease the side effects. Some times inflammation is caused by microbial infections also and a combination of the antiinflammatory drugs with sulphur drugs will naturally be useful for such conditions. Different \(\beta\)-aeryl propionic acids were therefore condensed with appropriate sulphonamides and their structures were established on the basis of elemental analysis, \(^1\)H NMR and Mass spectral data. These compounds were evaluated for their anti-inflammatory and antimicrobial activity.

**Results and Discussion**

Fourteen new amide-based prodrugs (7-20) were synthesized by condensing \(\beta\)-aeryl propionic acid (1-6) with appropriate sulphonamide moiety in molar ratio in dry pyridine in presence of phosphorous oxychloride as condensing agent. The required \(\beta\)-aeryl propionic acids were prepared by condensing aromatic hydrocarbons or their derivatives with succinic anhydride in presence of anhydrous aluminium chloride following Friedel-Craft’s acylation reaction conditions. The physical and analytical data are recorded in Tables-I & II.
**Table-I: Physical data of the β-acyl propionic acids 1-6**

![Diagram of β-acyl propionic acids]

<table>
<thead>
<tr>
<th>Compd</th>
<th>Ar</th>
<th>Melting point (°C)</th>
<th>PMR chemical shifts in δ Values</th>
<th>Ar protons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Protons of two methylene groups</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>118</td>
<td>2.80 &amp; 3.36 (t each, 2x-CH$_2$-)</td>
<td>7.46 (m, 3H, H-3,4,5), 7.84 (m, 2H, H-2,6)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>180</td>
<td>2.82 &amp; 3.37 (t each, 2x-CH$_2$-)</td>
<td>7.45 (m, 3H, H-3,4,5), 7.64 (m, 2H, H-2,6), 7.7 &amp; 8.07 (d each, 2xA$_2$B$_2$, p-substituted phenyl)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>172</td>
<td>2.8 &amp; 3.27 (t each, 2x-CH$_2$-)</td>
<td>7.17 (m, 3H, H-3,4,5), 7.41 (m, 2H, H-2,6), 7.7 &amp; 7.97 (d each, 2xA$_2$B$_2$, p-substituted phenyl)</td>
</tr>
<tr>
<td>4</td>
<td>H$_2$C</td>
<td>106</td>
<td>2.65 &amp; 3.26 (t each, 2x-CH$_2$-)</td>
<td>2.37 (s, 3H, -CH$_3$), 7.27 &amp; 7.85 (d each, 2xA$_2$B$_2$, p-substituted phenyl)</td>
</tr>
<tr>
<td>5</td>
<td>H$_3$C</td>
<td>110</td>
<td>2.80 &amp; 3.30 (t each, 2x-CH$_2$-)</td>
<td>1.25 (t, 3H, CH$_3$CH$_2$), 2.69 (q, 2H, CH$_3$CH$_2$), 7.27 &amp; 7.90 (d each, 2xA$_2$B$_2$, p-substituted phenyl)</td>
</tr>
<tr>
<td>6</td>
<td>Cl</td>
<td>124</td>
<td>2.81 &amp; 3.38 (t each, 2x-CH$_2$-)</td>
<td>7.45 &amp; 7.92 (d each, 2xA$_2$B$_2$, p-substituted phenyl)</td>
</tr>
</tbody>
</table>

s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet
Table II: Physical data of the compounds 7-20

![Chemical structure](image-url)

<table>
<thead>
<tr>
<th>Compd</th>
<th>R</th>
<th>R'</th>
<th>Molecular Formula; Mass spectral data (m/z)</th>
<th>M.P.</th>
<th>% Yield</th>
<th>Value</th>
<th>$^1$H NMR (δ ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>H</td>
<td></td>
<td>$\text{C}<em>{20}\text{H}</em>{19}\text{O}<em>{3}\text{N}</em>{3}\text{S}$ 413(M$^+$), 316, 161, 105, 77</td>
<td>188-90</td>
<td>70</td>
<td>0.74</td>
<td>2.3(s,3H,CH$_3$), 2.73&amp;3.36 (t each,2x-CH$_2$-), 6.2 (s,1H, oxazole ring), 7.7 (m, 3H,H-3,4,5 phenyl ring), 7.82 (s,1H, -SO$_2$NH-), 7.62&amp;7.92 (d each, A$_2$B$_2$,4H, sulphanilamide ring), 8.0 (m,2H,H-2,6 phenyl ring), 9.98 (s,1H,-CONH-)</td>
</tr>
<tr>
<td>8</td>
<td>H</td>
<td></td>
<td>$\text{C}<em>{32}\text{H}</em>{28}\text{O}<em>{6}\text{N}</em>{2}$ Not recorded</td>
<td>204</td>
<td>42</td>
<td>0.6</td>
<td>2.9&amp;3.6 (t each,2x-CH$_2$-CH$_2$-), 7.5 (m,6H,2xH-3,4,5 2x phenyl ring), 7.69 (d,4H, 2x hydrogens ortho to the amino group), 7.98 (d,4H, 2x hydrogens ortho to SO$_2$ group), 7.88 (m,4H,2xH-2,6 2x phenyl ring)</td>
</tr>
<tr>
<td>9</td>
<td>H</td>
<td>-NH$_2$</td>
<td>$\text{C}<em>{16}\text{H}</em>{16}\text{O}<em>{4}\text{N}</em>{2}$ 322(M$^+$), 161, 105, 77</td>
<td>194</td>
<td>50</td>
<td>0.68</td>
<td>2.76&amp;3.4 (t each,2x-CH$_2$-), 6.74 (s,2H,-SO$_2$NH$_2$), 7.27 (m,3H,H-3,4,5 phenyl ring), 8.0 (m,2H,H-2,6 phenyl ring), 7.7&amp;7.92 (d each, A$_2$B$_2$, 4H, sulphanilamide ring), 10.08 (s,1H,-CONH-)</td>
</tr>
<tr>
<td>10</td>
<td>H</td>
<td>-NH</td>
<td>$\text{C}<em>{19}\text{H}</em>{16}\text{O}<em>{4}\text{N}</em>{2}$ 396(M$^+$), 234, 161, 105</td>
<td>144-46</td>
<td>46</td>
<td>0.71</td>
<td>2.8&amp;3.48 (t each,2x-CH$_2$-), 7.4 (t,1H,H-4, diazine ring), 7.6 (m,3H,H-3,4,5 phenyl ring), 7.68&amp;7.96(d, A$_2$B$_2$, 4H, sulphanilamide ring), 7.8 (s,1H,-SO$_2$NH-), 8.2 (m,2H,H-2,6 phenyl ring), 8.5 (d,2H,H-3,5, diazine ring), 9.88 (s,1H, -CONH-)</td>
</tr>
</tbody>
</table>
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\[
\begin{align*}
&\text{\text{C}_2\text{H}_2\text{O}_3\text{N}_3\text{S} \quad 212 \quad 48} \\
&\text{488(M\textsuperscript{+}), 470, 236, 180, 152}
\end{align*}
\]

0.76 2.3(s,3H,CH\textsubscript{3}), 2.86&3.44 (t each, 2x-CH\textsubscript{2}-), 6.06 (s,1H, oxazole ring), 7.7&7.78 (d each,A\textsubscript{1}B\textsubscript{2},4H, p-substituted phenyl ring), 7.8 &8.07(d each, A\textsubscript{1}B\textsubscript{2}, 4H, sulphanilamide ring), 7.4-7.62 (m,5H, phenyl ring hydrogens), 7.82 (s,1H, -SO\textsubscript{2}NH-), 9.97(s,1H,-CONH-)

12

\[
\begin{align*}
&\text{\text{C}_2\text{H}_2\text{O}_3\text{N}_3\text{S} \quad 198 \quad 60} \\
&\text{408(M\textsuperscript{+}), 390, 236, 152, 77}
\end{align*}
\]

0.78 2.82&3.34 (t each,2x-CH\textsubscript{2}-), 7.26&7.7 (d each, A\textsubscript{1}B\textsubscript{2},4H, p-substituted phenyl ring), 7.77&7.94 (d each, A\textsubscript{1}B\textsubscript{2}, sulphanilamide ring), 7.07-7.2 (m,5H, phenyl ring hydrogens), 7.62 (s, 2H, -SO\textsubscript{2}NH\textsubscript{2}), 10.04 (s, 1H, -CONH-)

13

\[
\begin{align*}
&\text{\text{C}_2\text{H}_2\text{O}_6\text{N}_3\text{S} \quad 208 \quad 56} \\
&\text{505(M\textsuperscript{+}), 487, 253, 197, 169}
\end{align*}
\]

0.62 2.3(s,3H,CH\textsubscript{3}), 2.79&3.34 (t each, 2x-CH\textsubscript{2}-), 6.04 (s,1H, oxazole ring), 7.1&7.7 (d each, A\textsubscript{1}B\textsubscript{2}, sulphanilamide ring), 7.77&7.94 (d each, A\textsubscript{1}B\textsubscript{2}, sulphanilamide ring) 7.07-7.2 (m,5H, phenyl ring hydrogens), 7.6 (s,1H, -SO\textsubscript{2}NH-), 10.11 (s,1H, -CONH-)

14

\[
\begin{align*}
&\text{\text{C}_2\text{H}_2\text{O}_6\text{N}_4\text{S} \quad 168 \quad 51} \\
&\text{488(M\textsuperscript{+}), 424, 253, 234, 197}
\end{align*}
\]

0.66 2.8&3.42(t each,2x-CH\textsubscript{2}-), 6.97 &7.6 (d each, A\textsubscript{1}B\textsubscript{2}, 4H, p-substituted phenyl ring), 7.94 &7.97 (d each, A\textsubscript{1}B\textsubscript{2}, sulphanilamide ring), 6.8-7.2 (m,5H, phenyl ring hydrogens), 7.4 (t,1H,H-4,diazine ring), 8.5 (d,2H,H-3,5,diazine ring), 7.8 (s,1H,SO\textsubscript{2}NH-), 10.12 (s,1H, -CONH-)

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\[
\begin{align*}
&\text{\text{H}_3\text{C}- \quad \text{C}_2\text{H}_18\text{O}_4\text{N}_4\text{S} \quad 206-8} \\
&\text{424(M\textsuperscript{+}), 360, 342, 175, 119, 91, 77}
\end{align*}
\]

0.40 2.41 (s,3H,CH\textsubscript{3}), 2.8&3.34 (t each, 2x-CH\textsubscript{2}-), 6.9 (t,1H,H-4,diazine ring), 7.27 (m,2H,H-3,5, diazine ring), 7.62 (s,1H, -SO\textsubscript{2}NH-), 7.75&8.4 (d each, A\textsubscript{1}B\textsubscript{2}, sulphanilamide ring), 7.89 &7.9 (d each, A\textsubscript{1}B\textsubscript{2}, sulphanilamide ring), 10.16 (s,1H, -CONH-)
| 16 | H₃C− | −NH₂ | C₁₇H₁₈O₂N₂S | 176-78 | 56 | 0.44 | 2.46(s,3H,CH₃), 2.82&3.37 (t each, 2x-CH₂−), 6.85 (s, 2H, -SO₂NH₂), 7.71 &8.1 (d each, A₁B₂, 4H, p-substituted phenyl ring), 7.74&7.78 (d each, A₁B₂, 4H, p-substituted toluene ring), 10.06 (s,1H,-CONH−) |
| 17 | H₃C− | −NH₂ | C₁₈H₂₀O₂N₂S | 166 | 52 | 0.38 | 1.26 (t,3H,CH₃), 2.58 (q, 2H, -CH₂−), 2.83 & 3.37 (t each, 2x-CH₂−), 6.75 (s,2H,-SO₂NH₂), 7.29 &7.91 (d each, A₁B₂, 4H, p-substituted ethylbenzene ring), 7.74 & 7.78 (d each, A₁B₂, 4H, sulphanilamide ring), 10.06 (s,1H,-CONH−) |
| 18 | H₃C− | −NH− | C₂₁H₂₀O₂N₄S | 204 | 42 | 0.68 | 1.25 (t,3H,CH₃), 2.72 (q, 2H, -CH₂−), 2.78 & 3.34(t each,2x-CH₂−), 6.94(t,1H, H-4,diazine ring), 7.28 (m, 2H, H-3,5, diazine ring), 7.6 (s,1H, -SO₂NH₂), 7.7 &8.4 (d each,A₁B₂, 4H, p-substituted phenyl ring), 7.86&7.97 (d each,A₁B₂, 4H, p-substituted ethyl benzene ring), 10.16 (s,1H,-CONH−) |
| 19 | H₃C− | −NH− | C₂₂H₂₂O₂N₃S | 192 | 46 | 0.60 | 1.25 (t,3H,CH₃), 2.71 (q, 2H, -CH₂−), 2.37 (s, CH₃, oxazole ring), 2.84 & 3.5 (t each, 2x-CH₂−), 6.26 (s,1H, oxazole ring), 7.29 & 7.95 (d each, A₁B₂,p-substituted phenyl ring), 7.49&7.6 (d each,A₁B₂, 4H, p-substituted ethylbenzene ring), 7.68 (s,1H, -SO₂NH₂), 9.19 (s, 1H, -NH−) |
| 20 | Cl− | −NH₂ | C₁₇H₁₈O₂N₂SCl | 200 | 50 | 0.52 | 2.83&3.37 (t each, 2x-CH₂−), 6.92 (s,2H, -SO₂NH₂), 7.48 &7.75 (d each, A₁B₂, 4H, p-substituted phenyl ring), 7.8 &7.98 (d each, A₁B₂, 4H, sulphanilamide ring), 10.16 (s,1H,-CONH−) |

s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet
Anti-inflammatory activity

Carrageenan induced rat paw oedema method was employed for evaluating the anti-inflammatory activity of the compounds at a dose level of 20 mg/kg b.w. in albino rats (weighing 100-120 gm) using indomethacin as a standard drug for comparison. The rat paw oedema was produced by the method of Winter et al.\textsuperscript{10}. The percentage inhibition of inflammation was calculated by applying Newbould formula\textsuperscript{11}. In this test, the most active compounds were 13 and 14 which showed 58.06\% and 54.83\% inhibition respectively and their activity was comparable with the standard drug indomethacin (61.30\%) at a dose of 20 mg/kg body weight. Results are presented in Table-III. It is significant that none of these compounds showed ulcerogenic activity, which is a common feature with NSAIDs. The ulcerogenic activity was carried out by the reported method\textsuperscript{12}.

Antibacterial activity

The bacterial strains gram positive (\textit{Staphylococcus aureus}) and gram negative (\textit{Escherichia coli}) were used. The test was carried out according to the turbidity method\textsuperscript{13}. A solution of the compounds was prepared in dimethylformamide (DMF) and a series of doubling dilutions prepared with sterile pipettes. To each of a series of sterile stoppered test tubes a standard volume of nutrient broth medium was added. A control tube containing no antimicrobial agent was included. The inoculum consisting of an overnight broth culture of microorganisms was added to separate tubes. The tubes were incubated at 37\degree C for 24 hours and examined for turbidity. The tubes with highest dilution showing no turbidity was the MIC. Compound 9
showed excellent activity against *Staphylococcus aureus* (MIC-5 μg/ml) while compound 20 was highly active against *Escherichia coli* (MIC-10 μg/ml). Results are presented in Table-III.

### Table-III: Biological activity

<table>
<thead>
<tr>
<th>Compd</th>
<th>Antibacterial Activity</th>
<th>Anti-inflammatory Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>S. aureus</em></td>
<td><em>E. coli</em></td>
</tr>
<tr>
<td>6</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
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</tr>
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<td>8</td>
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<td>&gt;100</td>
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<tr>
<td>19</td>
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<td>-</td>
</tr>
<tr>
<td>20</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>0.73±0.03</td>
<td>0.85±0.03</td>
</tr>
<tr>
<td>Control</td>
<td>0.68±0.02 (y)</td>
<td>0.99±0.03 (b)</td>
</tr>
</tbody>
</table>

* = in μg/ml; - = insignificant activity

**EXPERIMENTAL.**

Melting points were taken in open capillary tubes and are uncorrected. Analytical data of C, H, O, N, and S were within ± 0.4% of the theoretical values. $^1$H NMR spectra were recorded on Varian E-360 MHz or Bruker spectropsin DPX-300MHz with tetramethylsilane as internal
standard in solvent CDCl₃. Mass spectra of the compounds were recorded on a JEOL-DX 303 instrument. TLC were carried out using silica gel (Merck No. 5554). Dry solvents were used throughout.

**β-Aroyl propionic acids 1-6**

Succinic anhydride (0.1mole) was condensed in presence of anhydrous aluminium chloride (0.1125 mole) with appropriate aromatic compounds in equimolar ratio. The reactions were carried out in dry solvents (nitrobenzene or 1,1,2,2-tetrachloroethane). In case of aromatic compounds which were liquid in nature, no solvent was used and they were taken in excess. The reaction mixture was refluxed for two hours and excess solvent was removed by steam distillation. It was purified by dissolving in sodium hydroxide solution, filtering, followed by addition of hydrochloric acid. A solid mass so obtained was filtered, washed with cold water, dried and crystallized from methanol to give 1-6 (Table-I).

**Amides 7-20**

Amides were synthesized by dissolving β-aroyl propionic acid and sulphonamide (equimolar: 3mmole) in minimum quantity of dry pyridine separately. The two solutions were then mixed together and stirred magnetically followed by the addition of phosphorous oxychloride (0.9ml) dropwise while maintaining the temperature below 5°. The contents were stirred for another half-hour and left overnight. The reaction mixture was then poured into ice cold water and a solid mass, which separated out, was filtered, washed, dried and crystallized from ethanol to give 7-20 (Table-II).
References


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