Piperazine Compounds Containing a 2,6-Dimethylphenyl Residue

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A number of piperazine compounds containing a 2,6-dimethylphenyl residue were prepared and tested for local anesthetic, ataractic and sedative properties. No appreciable effects were found.

In connection with investigations on local anesthetics of the aminoacylanilide type a series of compounds were prepared using an N-substituted piperazine as the amine component (type I, \(X = -\text{NHCOC}_2\text{H}_5\) or \(-\text{NHCOC}(\text{C}_2\text{H}_5)_2\)). As an extension of this work a number of compounds were prepared in which the 2,6-dimethylphenyl and piperazine residues were joined by a carbamoyl (II, \(X = -\text{NHCO-}\)) or a carbonyl (III, \(X = -\text{CO-}\)) group.

\[
\begin{align*}
\text{I, } X &= -\text{NHCOC}_2\text{H}_5, \\
&\quad -\text{NHCOC}(\text{C}_2\text{H}_5)_2 \\
R &= \text{CH}_3, \ -\text{CH}_2\text{CH} = \text{CH}_2, \\
&\quad -\text{CH}_3\text{C}_2\text{H}_5, \ -\text{CH}_2\text{CH}_2\text{OH}, \\
&\quad -\text{COOC}_2\text{H}_5, \ -\text{CH}_2\text{COOC}_2\text{H}_5 \\
\text{II, } X &= -\text{NHCO-} \\
\text{III, } X &= -\text{CO-}
\end{align*}
\]

The new compounds were synthesized by treating an N-substituted piperazine derivative with the following: halogenoacetyl-2,6-dimethylaniline (method A); 2,6-dimethylphenylisocyanate (method B); or 2,6-dimethylbenzoyl chloride (method C).

The N-methylpiperazine derivatives (\(R = -\text{CH}_3\)) could also be smoothly prepared from the corresponding urethanes (\(R = -\text{COOC}_2\text{H}_5\)) according to

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Table 1. Piperazines containing a 2,6-dimethylphenyl group.

<table>
<thead>
<tr>
<th>No.</th>
<th>X</th>
<th>R</th>
<th>Method</th>
<th>Yield %</th>
<th>Derivative</th>
<th>M.p. °C</th>
<th>Recryst. Solvent a</th>
<th>Formula</th>
<th>Calc. %</th>
<th>Found %</th>
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<td>1</td>
<td>—NHCOCH₃—</td>
<td>—COOC₂H₅</td>
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<td>92</td>
<td>Base</td>
<td>94—95</td>
<td>L</td>
<td>C₁₇H₂₉N₂O₃</td>
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<td>7.89</td>
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<td>2</td>
<td>—CH₃</td>
<td>—CH₃</td>
<td>A</td>
<td>70</td>
<td>2 HCl</td>
<td>267—268</td>
<td>E-Aq</td>
<td>C₁₅H₂₃N₂O·2 HCl</td>
<td>53.9</td>
<td>7.54</td>
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<td></td>
<td></td>
<td></td>
<td>D</td>
<td>66</td>
<td>2 HCl</td>
<td>267—268</td>
<td>E-Aq</td>
<td></td>
<td>54.0</td>
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<td>3</td>
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<td>73</td>
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<td>145—146</td>
<td>M</td>
<td>C₂₁H₂₇N₅O</td>
<td>74.7</td>
<td>8.07</td>
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<td>4</td>
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<td>Base</td>
<td>83—84</td>
<td>L</td>
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<td>8.16</td>
<td>12.6</td>
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<td>5</td>
<td>—CH₃CH₂OH</td>
<td>D</td>
<td>99</td>
<td>Base</td>
<td>111—112</td>
<td>L-B</td>
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<td>65.9</td>
<td>8.65</td>
<td>14.4</td>
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<td>6</td>
<td>—CH₃CH=CH₂</td>
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<td>84</td>
<td>Base</td>
<td>88—89</td>
<td>L</td>
<td>C₁₉H₂₃N₅O</td>
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<td>7</td>
<td>—NHCOCH₃—</td>
<td>—COOC₂H₅</td>
<td>A</td>
<td>45</td>
<td>Base</td>
<td>127—128</td>
<td>L-B</td>
<td>C₁₉H₂ₙN₅O₂</td>
<td>65.6</td>
<td>8.41</td>
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<td>8</td>
<td>—CH₃COOC₂H₅</td>
<td>A</td>
<td>31</td>
<td>Base</td>
<td>91—92</td>
<td>L</td>
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<td>8.64</td>
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<td>9</td>
<td>—NHCO—</td>
<td>—COOC₂H₅</td>
<td>B</td>
<td>98</td>
<td>Base</td>
<td>231—232</td>
<td>M</td>
<td>C₁₉H₂ₙN₅O₂</td>
<td>62.9</td>
<td>7.59</td>
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<td>—CH₃</td>
<td>—CH₃</td>
<td>B</td>
<td>86</td>
<td>Base</td>
<td>198—199</td>
<td>B</td>
<td>C₁₉H₂ₙN₅O</td>
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<tr>
<td>11</td>
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<td>B</td>
<td>97</td>
<td>Base</td>
<td>235—236</td>
<td>M</td>
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<td>74.3</td>
<td>7.79</td>
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<td>B</td>
<td>91</td>
<td>Base</td>
<td>132—134</td>
<td>M</td>
<td>C₂₁H₂₇N₅O₂</td>
<td>63.9</td>
<td>7.89</td>
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<td>13</td>
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<td>D</td>
<td>63</td>
<td>Base</td>
<td>164—165</td>
<td>B</td>
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<td>64.9</td>
<td>8.36</td>
<td>15.2</td>
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<tr>
<td>14</td>
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<td>B</td>
<td>89</td>
<td>Base</td>
<td>171—172</td>
<td>E-Aq</td>
<td>C₁₉H₂ₙN₅O</td>
<td>70.3</td>
<td>8.48</td>
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<td>15</td>
<td>—CO—</td>
<td>—CH₃</td>
<td>D</td>
<td>92</td>
<td>HCl</td>
<td>267—268</td>
<td>E</td>
<td>C₁₉H₂ₙN₅O·HCl</td>
<td>62.6</td>
<td>7.88</td>
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<td>16</td>
<td>—CH₃C₆H₅</td>
<td>C</td>
<td>56</td>
<td>HCl</td>
<td>257—259</td>
<td>E</td>
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<td>69.6</td>
<td>7.30</td>
<td>8.12</td>
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<td>17</td>
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<td>C</td>
<td>93</td>
<td>HCl</td>
<td>206—207</td>
<td>E-Et</td>
<td>C₁₉H₂ₙN₅O₂·HCl</td>
<td>60.5</td>
<td>7.78</td>
<td>9.41</td>
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<td>18</td>
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<td>D</td>
<td>90</td>
<td>HCl</td>
<td>184—185</td>
<td>E-Et</td>
<td>C₁₉H₂ₙN₅O₂·HCl</td>
<td>60.8</td>
<td>7.59</td>
<td>9.69</td>
</tr>
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<td>19</td>
<td>—CH₃CH=CH₂</td>
<td>C</td>
<td>69</td>
<td>HCl</td>
<td>222—224</td>
<td>E-Et</td>
<td>C₁₉H₂ₙN₅O₂·HCl</td>
<td>65.2</td>
<td>7.86</td>
<td>9.50</td>
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</tbody>
</table>

*a* E, ethanol; Et, ether; Aq, water; B, benzene; M, methanol; L, ligroin.

*b* The starting material for this reduction, 1-(2,6-dimethylbenzoyl)-4-ethoxycarbonylpiperazine, was prepared by method C but could not be obtained in crystalline form. Therefore it was used without further purification.
Table 2. Piperazinoacylbenzhydrylamines and phenothiazines.

\[
\begin{array}{|c|c|c|c|c|c|c|c|c|c|c|c|}
\hline
\text{No.} & \text{X} & \text{Y} & \text{R} & \text{Method} & \text{Yield \%} & \text{Derivative} & \text{M.p. \ ^\circ C} & \text{Reccryst. Solvents} & \text{Formula} & \text{Calc. \ %} & \text{Found \ %} \\
\hline
20 & \text{Cl} & \text{CHNH} & \text{H} & \text{COOC}_2\text{H}_4 & \text{A} & 90 & \text{HClO}_4 & 214 - 216 (d) & \text{E-Aq} & \text{C}_{22}\text{H}_{26}\text{ClN}_3\text{O}_4\cdot\text{HClO}_4 & 51.2 & 5.27 & 8.14 & 51.4 & 5.34 & 8.02 \\
21 & \text{CH} & \text{CH}_2 & \text{CH}_3 & \text{CH}_2 & \text{A} & 73 & \text{Base} & 143 - 144 & \text{M-Aq} & \text{C}_{22}\text{H}_{26}\text{ClN}_3\text{O} & 67.1 & 6.76 & 11.7 & 66.8 & 6.84 & 11.4 \\
22 & \text{CH} & \text{CH}_2 & \text{CH}_2 & \text{CHCOOC}_2\text{H}_4 & \text{A} & 77 & 2 \text{HCl} & 201 - 203 (d) & \text{E} & \text{C}_{22}\text{H}_{26}\text{ClN}_3\text{O}_2 \cdot 2 \text{HCl} & 54.9 & 6.01 & 8.36 & 55.2 & 6.13 & 8.11 \\
23 & \text{CH} & \text{CH}_2 & \text{CH}_2 & \text{CH}_2 \text{CH}_2 \text{OH} & \text{A} & 69 & 2 \text{HCl} & 254 - 256 (d) & \text{E-Aq} & \text{C}_{22}\text{H}_{26}\text{ClN}_3\text{O}_2 \cdot 2 \text{HCl} & 54.7 & 6.12 & 9.12 & 54.5 & 6.32 & 9.07 \\
24 & \text{CH} & \text{CH}_2 & \text{CH}_2 & \text{CH}_2 \text{CH}_2 \text{H}_5 & \text{A} & 72 & \text{Base} & 141 - 142 & \text{E-Aq} & \text{C}_{22}\text{H}_{26}\text{N}_2\text{OS} & 72.3 & 6.06 & 10.1 & 72.4 & 6.06 & 10.0 \\
25 & \text{H} & \text{CH}_2 & \text{CH}_2 & \text{H}_5 & \text{A} & 80 & \text{Base} & 213 - 214 & \text{E-Aq} & \text{C}_{22}\text{H}_{26}\text{N}_2\text{OS} \cdot 2 \text{HCl} & 62.1 & 5.82 & 8.36 & 61.9 & 6.06 & 8.22 \\
\hline
\end{array}
\]

\* See Table 1.
the excellent method of Dannley et al.¹ (method D). (This method involves preparation of methylyamines from urethanes by reduction with lithium aluminium hydride). The β-hydroxyethyl compounds (R = \( -\text{CH}_2\text{CH}_3\text{OH} \)) were alternatively prepared by reduction of the corresponding ethoxy carbonylmethyl derivative (R = \( -\text{CH}_2\text{COOC}_2\text{H}_5 \)).

The compounds and their properties are listed in Table 1. The new compounds were tested for local anesthetic action on rabbit cornea, using Xylocaine as standard. The observed effects were slight and it is evident that the piperazine residue decreases the anesthetic potency in the aminoacylanilide type of local anesthetics.

Toxicity tests showed some compounds to have a sedative effect; attempts were therefore made to enhance this effect by replacing the 2,6-dimethylphenyl group by a p-chlorobenzylidryl or a phenothiazine residue (compounds 20—25 in Table 2). However, these compounds had little or no ataractic and sedative properties in pharmacological tests.

**EXPERIMENTAL**

The melting points were determined in an electrically heated metal block using calibrated Anschütz thermometers.

All compounds were dried at 50°/0.01 mm for 4 h before analysis.

1-Methylpiperazine and 1-(β-hydroxyethyl)-piperazine are commercially available. 1- (Ethoxycarbonyl)-piperazine, 1-benzylpiperazine, and ethyl 1-piperazineacetate were prepared by published methods. 1-Allylpiperazine was prepared in 35%, yield from allyl chloride and piperazine hexahydrate following the method for preparation of 1-benzylpiperazine given by Baltzy et al., b.p. 62—64°/11 mm.

a-Chloro-2,6-dimethylacetanilide, a-bromo-2,6-dimethylbutyranilide, 10-chloroacetylphenothiazine, 10-(a-bromopropionylphenothiazine), 2,6-dimethylphenylisocyanate, and 2,6-dimethylbenzylicloride were prepared according to procedures described in the literature.

N-(Chloroacetyl)-p-chlorobenzylidrylamine was prepared from chloroacetyl chloride and p-chlorobenzylidrylamine in 64%, yield according to the method of Löfgren for the chloroacetylation of amines. M.p. 116—117° after recrystallisation from ligroin-benzene. (Found: C 61.7; H 4.66; N 4.99. Calc. for C₁₅H₁₃ClN₂O: C 61.2; H 4.48; N 4.76).

Piperazinoacrylamines (Method A). A solution of the appropriate piperazine compound (0.125 mole) and a halogenoacylamine (0.05 mole) in benzene (50 ml) was refluxed. The reflux time was 2 h for compounds 1—4 and 5—6 h for compounds 5—8 and 20—25. Toluen was used as solvent in the preparation of compounds 24 and 25. After cooling to room temperature the amine hydrochloride was filtered and the filtrate extracted thoroughly with 2 N hydrochloric acid. The extract was made alkaline with 5 N sodium hydroxide. The reaction product usually separated as an oil which soon crystallised and was purified by recrystallisation. When the base failed to crystallise, it was extracted with ether and converted to the hydrochloride by the addition of an ethereal solution of hydrogen chloride.

2,6-Dimethylphenylcarbamoylpiperazines (Method B). A solution of 2,6-dimethylphenylisocyanate (0.1 mole) and the appropriate piperazine derivative (0.12 mole) in benzene (50 ml) was refluxed for 2 h. On cooling, the reaction product separated in practically pure form.

2,6-Dimethylbenzoylpiperazines (Method C). A solution of 2,6-dimethylbenzoyl chloride (0.05 mole) and the appropriate piperazine derivative (0.12 mole) in benzene (100 ml) was refluxed for 2 h. The reaction mixture was then worked up as described for method A.

Reductions of ethoxycarbonyl- and ethoxycarbonylmethylpiperazines by lithium aluminium hydride (Method D). The piperazine compound (0.02 mole) was added in small portions to a solution of lithium aluminium hydride (0.05 mole) in ether (200 ml). The mixture was

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refluxed for 2 h and 2 N sodium hydroxide (10 ml) was added. The ether layer was separated, dried over sodium sulphate and evaporated. The residue was recrystallised or converted to the hydrochloride.

Physical constants and analytical data are collected in Tables 1 and 2.

REFERENCES


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