SYNTHESIS AND ANTICONVULSANT ACTIVITY OF SOME NEW N-[p-(SUBSTITUTED BENZAMIDO) BENZOYL] HYDRAZONES

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ABSTRACT

A series of N-[p-(substituted benzamido) benzoyl] hydrazones was synthesized by refluxing N-[p-(substituted benzamido) benzoyl] hydrazines with various araldehydes in ethanol in the presence of a few drops of glacial acetic acid. Some of these compounds when screened for anticonvulsant activity provided protection against pentylentetrazole-induced convulsions in mice.

INTRODUCTION

Hydrazine derivatives have been found to be potent inhibitors of MAO enzyme and inhibitors of this enzyme have displayed pronounced anticonvulsant activity. Various substituted phenyl hydrazone derivatives have also shown an appreciable anticonvulsant activity. Furthermore, the presence of 3,4,5-trimethoxybenzene nucleus in reserpine was shown to be responsible for CNS depressant and hypotensive properties. These findings led us to synthesise the title hydrazones with a view to assessing their anticonvulsant activity.

Substituted benzoyl chloride was allowed to react with ethyl p-aminobenzoate to give ethyl p-(substituted benzamido) benzoate which, on reaction with hydrazine hydrate, yielded N-[p-(substituted benzamido) benzoyl] hydrazines. The latter on being refluxed with various araldehydes afforded the title hydrazones.

EXPERIMENTAL

All melting points were taken in open capillaries and are uncorrected. The purity of the compounds was checked by T.L.C. on silica gel-G using iodine vapours as visualising agent. The IR spectra were recorded on perkin-Elmer infracord spectrometer. The PMR spectra were taken on varian EM-360 spectrometer using TMS as an internal reference.

Ethyl p-aminobenzoate (I)

Ethyl p-aminobenzoate was prepared by esterification of p-aminobenzoic acid by the method reported earlier.

Ethyl p-(R-substituted benzamido) benzoates (II)

To a solution of ethyl p-aminobenzoate (0.02 mole) in anhydrous tetrahydrofuran (30 ml) was slowly added substituted benzoyl chloride (0.03 mole) slowly in small portions with shaking, the temperature of the mixture being maintained at 0–10°C. The resulting mixture was stirred for one hour and allowed to stand overnight in a fridge. The solvent was removed by distillation under reduced pressure. The solid residue filtered and washed with 5% hydrochloric acid and 5% sodium carbonate and then with water. The product was recrystallised from benzene-petroleum ether and characterised by I.R. (KBr) spectral bands at 1680 cm⁻¹ (N–C str.), 1710–1720 cm⁻¹ (COOC₂H₅ str.) and 3350 cm⁻¹ (–NH str.). The esters thus prepared are as follows:

(a) 4 = 4-Chloro, m.p. 180°C, yield –73%. Found: C, 62.78; H, 4.47 and N, 4.35%. C₁₆H₁₄NO₃Cl requires C, 63.26; H, 4.61 and N, 4.61%.
(b) R = 4-Methoxy, m.p. 175°C, yield –70%. Found: C, 68.53; H, 5.32 and N, 4.92%. C₁₅H₁₅NO₄ requires C, 68.22; H, 5.68 and N, 4.68%. PMR (DMSO-d₆): δ 1.24 (t, 3H, COOCH₂CH₃), 3.75 (s, 3H, OCH₃), 4.29 (q, 2H, COOCH₂CH₃).
(c) R = 3,4,5-Trimethoxy, m.p. 113°C (Lit² 114°C), yield –65%. Found: N, 4.23%. C₁₅H₁₃NO₄ requires N, 3.89%.

N-[p-(R-substituted benzamido)benzoyl] hydrazones (III)

A mixture of II (0.02 mole) and hydrazine hydrate (0.02 mole) in absolute ethanol (25 cc) was refluxed on a steambath for 16 hr. The excess ethanol was distilled off and the solid that separated on cooling was filtered, dried and recrystallised from ethanol. The IR (KBr) spectra of the products showed peaks at
1680-1700 cm⁻¹ (N–C str.) and 3360–3380 cm⁻¹ (CONH NH₂ str.). The hydrazines thus prepared are as follows:

(I) R = 4-Chloro, m.p. 160 °C, yield 68 %. Found: C, 57.62; H, 4.47 and N, 14.27 %. C₁₄H₁₂N₂O₂Cl requires C, 58.03; H, 4.14 and N, 14.50 %.

(II) R = 4-Methoxy, m.p. 140 °C, yield 65 %. Found: C, 62.73; H, 5.43 and N, 14.49 %. C₁₃H₁₅N₂O₃ requires C, 63.15; H, 5.26 and N, 14.73 %. PMR (DMSO-D₆) δ: 3.72 (s, 3H, OCH₃), 4.38 (b, 2H, CONHNH₂), 7.25–7.80 (m, 8H, aromatic), 9.87 (b, 1H, CONNH₂), 10.46 (b, 1H, CONH).

(III) R = 3,4,5-Trimethoxy, m.p. 198 °C [Lit 202 °C]. Found: N, 11.82 %. C₁₃H₁₅N₃O₅ requires N, 12.17 %.

N-(p-substituted benzamido) benzoyl) hydrazones (IV)

A mixture of (III) (0.002 mole), an appropriate aldehyde (0.02 mole), ethanol (15 ml) and a few drops of glacial acetic acid was refluxed on a steam bath for 4 to 5 hr. Excess ethanol was distilled off. The solid mass thus obtained was washed with water and recrystallised from ethanol (table 1).

**Table 1** N-(p-Substituted benzamido) benzoyl) hydrazones

<table>
<thead>
<tr>
<th>S. No.</th>
<th>R</th>
<th>AR</th>
<th>M.P. °C</th>
<th>Molecular formula</th>
<th>% Nitrogen Found</th>
<th>% Nitrogen Calcd.</th>
</tr>
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<td>1.</td>
<td>4-Chloro</td>
<td>2-Hydroxyphenyl</td>
<td>153</td>
<td>C₂₁H₁₈N₂O₅Cl</td>
<td>10.94</td>
<td>10.67</td>
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<td>2.</td>
<td>&quot;</td>
<td>4-Methoxyphenyl</td>
<td>162</td>
<td>C₂₂H₁₉N₂O₃Cl</td>
<td>9.97</td>
<td>10.30</td>
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<td>3.</td>
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<td>4-Hydroxy-3-methoxyphenyl</td>
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<td>C₂₂H₁₈O₅Cl</td>
<td>9.64</td>
<td>9.92</td>
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<td>4.</td>
<td>4-Methoxy</td>
<td>Styryl</td>
<td>165</td>
<td>C₂₂H₁₈N₂O₅</td>
<td>10.21</td>
<td>10.52</td>
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<tr>
<td>6.</td>
<td>&quot;</td>
<td>Furfury</td>
<td>166</td>
<td>C₂₀H₁₇N₂O₄</td>
<td>11.19</td>
<td>11.57</td>
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<td>7.</td>
<td>3,4,5-Trimethoxy</td>
<td>4-Methoxyphenyl</td>
<td>110</td>
<td>C₂₂H₂₁N₂O₆</td>
<td>8.74</td>
<td>9.07</td>
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<td>8.</td>
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<td>4-N,N-Dimethylaminophenyl</td>
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<td>C₂₆H₂₆N₂O₅</td>
<td>11.43</td>
<td>11.76</td>
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<td>10.*</td>
<td>4-Chloro</td>
<td>3,4-Dimethoxyphenyl</td>
<td>157</td>
<td>C₂₃H₂₁N₂O₅Cl</td>
<td>9.32</td>
<td>9.60</td>
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<td>11.</td>
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<td>4-Tolyl</td>
<td>159</td>
<td>C₂₂H₁₈N₂O₅</td>
<td>10.41</td>
<td>10.72</td>
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<td>12.</td>
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<td>4-N,N-Dimethylaminophenyl</td>
<td>154</td>
<td>C₂₃H₂₁N₂O₅</td>
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<td>13.</td>
<td>4-Methoxy</td>
<td>4-Hydroxy-3-methoxyphenyl</td>
<td>155</td>
<td>C₂₃H₂₁N₂O₅</td>
<td>10.32</td>
<td>10.02</td>
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<td>15.</td>
<td>&quot;</td>
<td>3,4-Dimethoxyphenyl</td>
<td>153</td>
<td>C₂₃H₂₁N₂O₅</td>
<td>9.32</td>
<td>9.69</td>
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<td>16.*</td>
<td>3,4,5-Trimethoxy</td>
<td>4-Tolyl</td>
<td>140</td>
<td>C₂₃H₂₁N₂O₅</td>
<td>9.72</td>
<td>9.39</td>
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<td>17.</td>
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<td>2-Nitrophenyl</td>
<td>85</td>
<td>C₂₂H₁₈N₂O₇</td>
<td>11.73</td>
<td>11.71</td>
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<td>18.</td>
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<td>Styryl</td>
<td>181</td>
<td>C₂₀H₁₉N₂O₅</td>
<td>8.74</td>
<td>9.15</td>
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<td>19.</td>
<td>4-Chloro</td>
<td>Furfury</td>
<td>168</td>
<td>C₁₉H₁₈N₂O₅Cl</td>
<td>11.36</td>
<td>11.42</td>
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<td>20.</td>
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<td>3-Nitrophenyl</td>
<td>95</td>
<td>C₂₁H₁₈N₂O₅Cl</td>
<td>12.87</td>
<td>13.25</td>
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<td>22.*</td>
<td>4-Methoxy</td>
<td>4-Methoxyphenyl</td>
<td>118</td>
<td>C₂₃H₂₁N₂O₄</td>
<td>13.06</td>
<td>13.42</td>
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<td>23.</td>
<td>&quot;</td>
<td>4-N,N-Dimethylaminophenyl</td>
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<td>C₂₃H₂₁N₂O₅</td>
<td>13.12</td>
<td>13.46</td>
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<td>24.</td>
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<td>4-Tolyl</td>
<td>137</td>
<td>C₂₂H₁₈N₂O₄</td>
<td>10.43</td>
<td>10.85</td>
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<td>25.</td>
<td>3,4,5-Trimethoxy</td>
<td>2-Hydroxyphenyl</td>
<td>186</td>
<td>C₂₂H₁₈N₂O₆</td>
<td>9.12</td>
<td>9.35</td>
</tr>
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<td>26.*</td>
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<td>4-Hydroxy-3-methoxyphenyl</td>
<td>210</td>
<td>C₂₃H₂₁N₂O₅</td>
<td>8.48</td>
<td>8.76</td>
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<tr>
<td>27.</td>
<td>&quot;</td>
<td>3,4-Dimethoxyphenyl</td>
<td>189</td>
<td>C₂₉H₂₆N₂O₇</td>
<td>8.21</td>
<td>8.52</td>
</tr>
</tbody>
</table>

* Showed I.R. (KBr) spectral bands at 1650–1670 cm⁻¹ (C = NH str), 1680–1710 cm⁻¹ (N–C str), 2900 cm⁻¹ (CH₂ str), 3200–3300 cm⁻¹ (–NH str).

Satisfactory analysis for C and H were obtained.

Compounds No. 2, 8, 10, 17, 21, 22, 24, 25, 27 afforded 0, 40, 20, 20, 0, 0, 0, 20 °, protection respectively against pentylenetetrazole-induced seizures in mice where diazepam afforded 100 ° protection.
BIO ASSAY

(1) \( ALD_{50} \) and gross behavioural effects

\( ALD_{50} \) was determined following the method of Horn\(^9\). Different doses of compounds including 1/5th of \( ALD_{50} \) were administered i.p. in groups of animals, which were then observed for 6 hr and 24 hr for any effect on gross behaviour\(^10\).

(2) Anticonvulsant activity

Anticonvulsant activity was determined by the method of Swinyard et al\(^11\). The compounds were tested against pentyleneetetrazole-induced seizures in albino mice of either sex weighing between 15-20 g. Groups of 5 mice, pretreated with 1/5th \( ALD_{50} \) dose of compounds i.p. were injected pentyleneetetrazole (80 mg/kg) subcutaneously after one hour. Animals were observed for a period of 60 min for the occurrence of clonic convulsions. Animals not exhibiting threshold convulsions during this period of observations were considered protected. The number of animals protected in each group was recorded and the anticonvulsant activity of the compounds expressed in terms of percentage protection.

RESULTS AND DISCUSSION

The approximate \( LD_{50} \) values of the compounds ranged from 562 to 1000 mg/kg. The maximum value was exhibited by compounds no. 2, 17 and 22. However, the compounds No. 8, 10, 21, 24, 25, 27 exhibited \( ALD_{50} \) (mg/kg) values as 681, 825, 681, 562, 825, 681 respectively. The \( ALD_{50} \) value of diazepam was found to be 121 mg/kg.

The depressant feature was common among these compounds with the exception of no. 21. The compounds reduced the rate of respiration in mice and decreased in reactivity to body and limbs. Loss of righting reflex and ataxia were observed in experimental animals. Reactivity towards sound and touch was also decreased. The compounds (vide footnote table 1) exhibited anticonvulsant activity ranging from 20 to 40\( \% \) which was considerably less than that of diazepam. The compounds having \( R = 3,4,5 \)-trimethoxy and \( Ar = 3,4 \)-dimethoxyphenyl showed moderate activity. Compounds having \( R = p-\text{OCH}_3 \) or \( CI \) and \( Ar = p \)-tolyl, styryl and \( p \)-methoxy phenyl were inactive. The maximum protection (40\( \% \)) was exhibited by the compound 8 having \( R = 3,4,5 \)-trimethoxy and \( Ar = p \)-N,N-dimethylaminophenyl. It appears therefore, that the presence of 3,4,5-trimethoxyphenyl moiety in these compounds is essential for conferring the anticonvulsant activity on them.

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