AMINOACETYLENIC CARBONYL COMPOUNDS.

I. 2-SUBSTITUTED 2-(6-AMINOBUTYNYL)-1,3-INDANDIONES

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Aminoacetylenic carbonyl compounds have been little studied [1]. They merit attention for their polyfunctionality, as well as for their potential pharmacological activity. Many observations have been accumulated on the pharmacological activity of aminoacetylenes [2-5]. On the other hand, aminocarboxylic and dicarboxylic compounds are also characterized by a wide spectrum of activity on the central nervous system [6].

In the present investigation we studied the possibility of synthesizing aminoacetylenic derivatives of the indandione series. Alkylation of 2-substituted indan-1,3-diones (Ia-Ic) with propargyl bromide (best in the presence of sodium iodide) yielded 2-substituted 2-propargylindan-1,3-diones (IIa-IIc). The structures of IIa-IIc were confirmed by IR spectra (Table 1) and by study of their chemical properties. In the IR spectra of IIa-IIc one finds the characteristic twin absorption maxima for the dicarbonyl grouping in the 1707-1754 cm⁻¹ interval [7] and absorption maxima at the frequencies of monosubstituted acetylenes: ν = C-H 3258-3295 cm⁻¹, ν C = C 2120-2127 cm⁻¹ [8].

Compounds IIa-IIc, as monosubstituted acetylenes, are aminomethylated with paraformaldehyde and secondary amines in dioxane solution in the presence of cuprous acetate:

\[ \text{IIa-IIc} \rightarrow \text{IIIa-IIIc} \]

The structures of the resulting 2-substituted 2-(6-aminobutynyl)indan-1,3-diones (IIIa-IIIc) were confirmed by IR absorption spectra (Table 2), in which one observes the frequencies characteristic of β-dicarbonyl groups, and of the C=C bond in disubstituted acetylenes.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mp (°C)</th>
<th>Yield (%)</th>
<th>Empirical formula</th>
<th>Found (%) Calc. (%)</th>
<th>νC-O</th>
<th>νC=O</th>
<th>νC=H</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>80</td>
<td>136-7</td>
<td>C₁₅H₁₂O₂</td>
<td>83,46 4,71</td>
<td>1741(67) 1707(75)</td>
<td>2127(57) 3295(70)</td>
<td></td>
</tr>
<tr>
<td>IIb</td>
<td>76</td>
<td>123-124.5</td>
<td>C₁₅H₁₂O₂</td>
<td>83,49 5,22</td>
<td>1748(68) 1709(60)</td>
<td>2130(34) 3292(63)</td>
<td></td>
</tr>
<tr>
<td>IIc</td>
<td>44</td>
<td>91-2</td>
<td>C₁₅H₁₄O₂</td>
<td>78,72 4,92</td>
<td>1754(71) 1713(93)</td>
<td>2126(30) 3258(75)</td>
<td></td>
</tr>
</tbody>
</table>

The pharmacological activity of 2-substituted 2-(δ-aminobutyryl)indan-1,3-diones (IIIa-IIIm) was studied in white mice. In all experiments the compound under study was introduced intraperitoneally about 30 min before testing. We studied anti-convulsive activity in relation to maximum electric shock and tranquilizer activity by the rotating rod test. We studied the ability of each substance to intensify hexenal narcosis (hexenal was introduced intravenously in 70 mg/kg doses). We also studied the effect of these compounds on animal behavior and on acute toxicity.

The experimental material was treated statistically by the method of Litchfield and Wilcoxon [9]. In all cases we calculated the median lethal dose (LD₅₀) and the median effective dose (ED₅₀) in proportion to the maximum electric shock and disturbance of coordination of movement, and also the index of intensification of hexenal narcosis (the ratio of narcosis duration in experimental animals to that in the control animals). See Table 3.

From the data in Table 3, it follows that the anticonvulsive activity is most evident in compounds containing the phenyl group (IIIa-IIIg). When the phenyl radical is replaced by benzyl (IIIg-IIIk) or methyl (IIIi-IIIm), some anticonvulsive activity is observed only in compounds containing the morpholine ring (IIIk- and IIIl). The remaining compounds have anticonvulsive activity only in doses which exceed one-third of the lethal dose.

All the substances studied have tranquilizer properties; they show disturbance in coordination of movement, and intensify hexenal narcosis. The tranquilizer properties are intensified with increasing chain length of the aliphatic radicals.

It was shown that, in small doses, all the substances studied depress spontaneous motor activity, and at toxic concentrations show motor excitation and tonic-clonic spasms which sometimes terminate in death. Increase in the length of the aliphatic chain on the nitrogen atom reduces toxicity. Reduction in