Synthesis of Some N-Alkylamino-N-vanillylpropionamides

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Z. Naturforsch. 38 b, 997–999 (1983); received April 11, 1983

N-Alkylamino-N-vanillylpropionamides, Synthesis, $^1$H NMR Spectra, $^{13}$C NMR Spectra

Following a general method N,N-dimethyl, N,N-diethyl, N-isopropyl and N-piperidinyl-amino-N-vanillylpropionamide were synthesized. Their spectroscopic ($^1$H and $^{13}$C NMR, MS) properties are reported.

Several and diverse pharmacological properties have been associated with vanillylamine derivatives, including stimulating agents acting on chemogenic pain detectors [1–4] on peripheral and central warmth detectors [5, 6], on baroreceptors [7–9] as well as in metabolic [10] and motor [11] modifications on the gastrointestinal system. Moreover, earlier studies with capsaicin, the pungent principle in red pepper and the responsible of the pungent action on the tongue taste-receptors [12], demonstrated that the active portion of the whole molecule was its vanillylamine moiety.

These observations prompted us to prepare a series of compounds structurally related to capsaicin – replacing the alkyl chain by alkylamino groups – in order to test their pharmacological activity. The various N-alkylamino-N-vanillylpropionamides were synthesized according to the steps shown in Fig. 1.

The 3-chloro-N-vanillylpropionamide (1) was prepared by condensation of vanillylamine with 3-chloropropionyl chloride following known procedures [13, 14]. Reaction of compound 1 with dimethyl, diethyl and isopropylamine and with piperidine [15] was performed as indicated in Experimental leading to the substitution compounds 2 (a, b, c, d) which were isolated as the respective hydrochlorides. Although these compounds could not be induced to crystallize, they showed in each case a 99.8% purity by GLC and their structures were confirmed by IR, MS, $^1$H NMR and $^{13}$C NMR analysis as presented in Tables I and II.

In the case of the $^{13}$C NMR spectra the assignments for the aromatic carbons were done by correlations with the published values for vanillin [16, 17] and those obtained from the spectrum of vanillylamine hydrochloride which was registered for this purpose. The absorptions for the methylene carbons were assigned taking into account the known effects of the different substituents in the molecule [18, 19].

Preliminary experiments in vitro with compounds 1 and 2 (a, b, c) on different rat isolated organs showed appreciable biological activity, characteristic of structures of this kind. The biological tests are being carried out in our laboratories.

Experimental

Melting points were registered with a Fisher-Johns hot plate and are uncorrected. GLC analysis were performed with a Hewlett-Packard model 5840 chromatograph using glass columns (1.80 m × 2 mm i.d.) packed with 3.25% Silar 10 C on Chromosorb W–AW–DMCS. The IR spectra were registered in Nujol dispersions using a Perkin-Elmer 421 spectrophotometer. $^1$H and $^{13}$C FT NMR were recorded.

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0340–5087/83/0800–0997/$ 01.00/0
Table I. \(^1\)H NMR spectral data of compounds 1 and 2 (a, b, c, d). Solvents are indicated into brackets in each case.

<table>
<thead>
<tr>
<th>Proton (CDCl(_3))</th>
<th>(^1)H NMR spectral data of compounds 1 and 2 (a, b, c, d)</th>
<th>(^1)H NMR spectral data of compounds 1 and 2 (a, b, c, d)</th>
<th>(^1)H NMR spectral data of compounds 1 and 2 (a, b, c, d)</th>
<th>(^1)H NMR spectral data of compounds 1 and 2 (a, b, c, d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(_2)</td>
<td>6.82–6.88 (m)</td>
<td>6.88–6.96 (m)</td>
<td>6.86–6.98 (m)</td>
<td>6.84–6.96 (m)</td>
</tr>
<tr>
<td>H(_{10})</td>
<td>4.42 (d)</td>
<td>3.0</td>
<td>4.44 (s)</td>
<td>4.30 (s)</td>
</tr>
<tr>
<td>H(_9)</td>
<td>2.66 (t)</td>
<td>3.5</td>
<td>2.82 (t)</td>
<td>3.5</td>
</tr>
<tr>
<td>H(_{11})</td>
<td>3.71 (t)</td>
<td>3.5</td>
<td>3.48 (t)</td>
<td>3.5</td>
</tr>
<tr>
<td>H(_{12})</td>
<td>3.87 (s)</td>
<td>3.88 (s)</td>
<td>3.85 (s)</td>
<td>3.88 (s)</td>
</tr>
<tr>
<td>H(_{13})</td>
<td>4.44 (s)</td>
<td>3.82 (s)</td>
<td>4.30 (s)</td>
<td>3.78 (s)</td>
</tr>
<tr>
<td>OH</td>
<td>5.93 (br.s.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NH</td>
<td>5.90 (br.s.)</td>
<td></td>
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</tr>
</tbody>
</table>

\(\delta\) = values are in ppm downfield from TMS.

Table II. \(^13\)C NMR spectral data of compounds 1, 2 (a, b, c, d) and vanillylamine hydrochloride. Solvents are indicated into brackets in each case.

<table>
<thead>
<tr>
<th>Carbon (Pyd(_6))</th>
<th>(^13)C NMR spectral data of compounds 1, 2 (a, b, c, d)</th>
<th>(^13)C NMR spectral data of compounds 1, 2 (a, b, c, d)</th>
<th>(^13)C NMR spectral data of compounds 1, 2 (a, b, c, d)</th>
<th>(^13)C NMR spectral data of compounds 1, 2 (a, b, c, d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(_1)</td>
<td>120.6</td>
<td>121.2</td>
<td>121.4</td>
<td>121.2</td>
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<tr>
<td>C(_2)</td>
<td>110.6</td>
<td>112.7</td>
<td>113.0</td>
<td>112.7</td>
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<tr>
<td>C(_3)</td>
<td>145.1</td>
<td>144.8</td>
<td>145.8</td>
<td>145.0</td>
</tr>
<tr>
<td>C(_4)</td>
<td>146.7</td>
<td>148.1</td>
<td>146.9</td>
<td>148.3</td>
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<td>C(_5)</td>
<td>114.3</td>
<td>114.6</td>
<td>114.7</td>
<td>116.5</td>
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<tr>
<td>C(_6)</td>
<td>129.6</td>
<td>131.3</td>
<td>128.1</td>
<td>131.3</td>
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<tr>
<td>C(_7)</td>
<td>43.7</td>
<td>42.2</td>
<td>43.7</td>
<td>43.9</td>
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<tr>
<td>C(_8)</td>
<td>173.6</td>
<td>171.0</td>
<td>169.4</td>
<td>171.0</td>
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<tr>
<td>C(_9)</td>
<td>38.8</td>
<td>35.5</td>
<td>30.3</td>
<td>32.3</td>
</tr>
<tr>
<td>C(_10)</td>
<td>40.4</td>
<td>43.7</td>
<td>43.1</td>
<td>43.8</td>
</tr>
<tr>
<td>C(_11)</td>
<td>55.9</td>
<td>54.3</td>
<td>56.9</td>
<td>57.1</td>
</tr>
<tr>
<td>C(_12)</td>
<td>30.7</td>
<td>48.4</td>
<td>41.7</td>
<td>56.7</td>
</tr>
<tr>
<td>C(_13)</td>
<td>9.1</td>
<td>19.2</td>
<td>23.5</td>
<td></td>
</tr>
<tr>
<td>C(_14)</td>
<td></td>
<td></td>
<td></td>
<td>21.7</td>
</tr>
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</table>

\(\delta\) = values are in ppm downfield from TMS.
with a Varian XL-100-15 spectrometer; solvents are indicated in each case. Mass spectra were performed at 70 eV (direct inlet) with a Varian-Mat CH7-A spectrometer interfaced to a Varian-Mat Data System 166 computer.

3-Chloro-N-vanillylpropionamide (1)

To a solution of vanillylamine (153 mg) in dry acetone (50 ml), a solution of pyridine (0.2 ml) and 3-chloropropionyl chloride (0.2 ml) in acetone (3 ml) was added dropwise. The reaction mixture was refluxed for 5 h. The salts were filtered off and the solvent was removed. The residue was dissolved in methylene chloride and washed with 2 N hydrochloric acid, saturated sodium hydrogen carbonate solution and water and dried over sodium sulphate. Evaporation of the solvent afforded an oily residue which showed a 90.8% purity by GLC and characterized from benzene yielding pure compound 1 (100 mg, 78%) of m.p. 77-78 °C. IR (cm⁻¹) 3250 (broad, OH), 1680 (C=O), 1670 (C=O), 860, 810 and 740 (aromatic CH). MS: m/e (%): 245(5) (M++2), 243(15) (M+), 207(78), 152(40), 137(58), 122(15), 113(11), 98(100), 86(45), 30(45).

(3-N,N-Dimethylamino)-N-vanillylpropionamide (2a)

Compound 1 (243 mg, 1 mmol) dissolved in absolute ethanol (5 ml) was treated with dimethylamine (5 mmol) and the mixture was kept at room temp. for 17 h. The solvent was removed and the residue was purified by column chromatography (Silica gel G eluted with methylene chloride: methanol 94:6), and the pure compound (GLC) was transformed into its hydrochloride by treatment with conc. hydrochloric acid and lyophylized yielding 210 mg of 2a. IR: (film) (cm⁻¹) 3240 (OH), 3120 (NH), 1670 (C=O), 860, 790 and 750 (aromatic CH). MS: m/e (%): 252(18) (M+−HCl), 207(4), 152(4), 137(11), 58(100).

(3-N,N-Diethylamino)-N-vanillylpropionamide (2b)

This was prepared as indicated for 2a except that the reaction mixture was refluxed for 3 h. The yield of 2b as its hydrochloride was 248 mg. IR (film) (cm⁻¹) 3250 (OH), 3110 (NH), 1670 (C=O), 860, 810 and 740 (aromatic CH). MS: m/e (%): 280(11) (M+−HCl), 207(16), 152(9), 137(40), 86(100), 58(88), 30(45).

(3-N-Isopropylamino)-N-vanillylpropionamide (2c)

This was prepared as indicated for 2a except that the reaction mixture was refluxed for 18 h. The yield of 2c as its hydrochloride was 242 mg. IR (film) (cm⁻¹) 3240 (OH), 3110 (NH), 1670 (C=O), 860, 790 and 730 (aromatic CH). MS: m/e (%): 266(15) (M+−HCl), 207(8), 152(8), 137(28), 72(100), 44(39), 30(85).

(3-N-Piperidinylamino)-N-vanillylpropionamide (2d)

It was prepared as indicated for 2a except that the reaction mixture was refluxed for 24 h. The yield of 2d as its hydrochloride was 198 mg. IR (film) (cm⁻¹) 3250 (OH), 3110 (NH), 1680 (C=O), 860, 790 and 730 (aromatic CH). MS: m/e (%): 292(12) (M+−HCl), 152(24), 137(23), 98(100), 30(42).

We thank CONICET and The Organization of the American States for financial support.