Synthesis and bioactivities of chlorodiphenylgermanium heterocyclic carboxylates

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The eight chlorodiphenylgermanium heterocyclic carboxylates, Ph₂Ge(CI)O₂CR (R=2-furanyl, 2-furanvinyl, 2-thiophenyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 3-indolymethyl, 3-indolylpropyl) have been synthesized by the reaction of corresponding diphenylgermanium dichloride with heterocyclic carboxylates in 1:1 molar ratio. Their structures are characterized by elemental analysis, IR, 'H NMR and MS. The IR data indicate that the carboxyl groups are monodentate ligands. The biological activity of the products have been tested and the compounds show high antitumour activities in vitro.

In recent years, the chemistry of organotin and organogermanium compounds were extensively studied due to their biological activities. In our recent work, the organotin heterocyclic carboxylates, dithiocarbamates, alkynyl phosphonates and organogermanium carboxylates, dithiocarbamates, alkynyl phosphonates were synthesized, and their structures and biological activities were studied. Up to now, the chlorodiphenylgermanium carboxylates have not been reported.

In this note, the synthesis of chlorodiphenylgermanium heterocyclic carboxylates by the reaction of diphenylgermanium dichloride with sodium carboxylates has been reported. Their structures were characterized by elemental analysis, IR, 'H NMR, and MS. The synthetic procedure is shown in Scheme 1.

Experimental Section
Melting points were determined with Kofler micro melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet-460 spectrometer in KBr. 'H NMR spectra were measured on a AC-P200 spectrometer using TMS as internal standard and CDCl₃ as solvent. Elemental analysis were performed on a Carlo-Erba 1106 element- analyzer. The mass spectrum were recorded on a HP-5988A spectrometer operating at 70 eV. The samples of antitumour activity tests were prepared by dissolving the compounds in DMSO, and by diluting the solution obtained with water. The cell lines were maintained in a continuous logarithmic culture in Dulbecco’s medium supplemented with 10% foetal calf serum, penicillin (100 IU cm⁻³) and streptomycin (100 μg cm⁻³). The cells were mildly trypsinized for passage and for use in experiments. Stock solutions of the compounds to be tested were prepared in DMSO and full growth medium.

The preparation of compounds was carried out under nitrogen atmosphere, Ph₂GeCl₂ (1.0 mmole) and anhydrous sodium carboxylates (1.0 mmole) were added to 20 mL of dry dichloromethane and stirred for 8 hr at 30°C. The precipitated salts were removed by filtration and the filtrate was concentrated to 5 mL under reduced pressure. Hexane(5 mL) was added to this solution. Immediately a precipitate was formed. The product was recrystallized from dichloromethane-hexane to give a colourless crystals.

Results and Discussion
The compounds are soluble in organic solvents such as benzene, methylene chloride, chloroform. Because diphenylgermanium dichloride are water sensitive, they must be prepared under water-free conditions. Otherwise, no germanium-containing heterocyclic carboxylates are formed, but diphenylgermanium oxide (Ph₃GeO)₃ can be detected. The analytical and physical data of compounds 1-8 are given in Table I.

The title compounds adopt three type of structures A, B and C in the solid state. A monomeric structure A. can be 4-coordinate, whereas a polymeric structure C contains 5-coordinate germanium atoms. Five coordinate compounds which adopt structure type B...
Table I — The analytical and physical data of the title compounds

<table>
<thead>
<tr>
<th>Compd</th>
<th>Mol. formula</th>
<th>m.p. °C</th>
<th>Yield (%)</th>
<th>Found % (Calcd)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>(Mol wt)</td>
<td></td>
<td>C</td>
<td>H</td>
</tr>
<tr>
<td>1</td>
<td>C₁₇H₁₃ClGeO₂</td>
<td>106-08</td>
<td>88.2</td>
<td>54.47</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>(54.69 3.51)</td>
</tr>
<tr>
<td>2</td>
<td>C₁₉H₁₄ClGeO₃</td>
<td>120-22</td>
<td>75.9</td>
<td>57.40</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>(57.14 3.79)</td>
</tr>
<tr>
<td>3</td>
<td>C₁₇H₁₃GeO₂S</td>
<td>117-19</td>
<td>81.5</td>
<td>52.58</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>(52.43 3.36)</td>
</tr>
<tr>
<td>4</td>
<td>C₁₈H₁₄ClGeN</td>
<td>154-55</td>
<td>87.6</td>
<td>56.03</td>
</tr>
<tr>
<td></td>
<td>(384.38)</td>
<td></td>
<td></td>
<td>(56.25 3.67)</td>
</tr>
<tr>
<td>5</td>
<td>C₁₉H₁₄ClGeN</td>
<td>172-74</td>
<td>75.9</td>
<td>56.42</td>
</tr>
<tr>
<td></td>
<td>(384.38)</td>
<td></td>
<td></td>
<td>(56.25 3.67)</td>
</tr>
<tr>
<td>6</td>
<td>C₁₈H₁₄ClGeN</td>
<td>190-92</td>
<td>70.4</td>
<td>56.55</td>
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<td></td>
<td>(384.38)</td>
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<td></td>
<td>(56.25 3.67)</td>
</tr>
<tr>
<td>7</td>
<td>C₂₂H₁₈ClGeN</td>
<td>158-60</td>
<td>77.5</td>
<td>60.80</td>
</tr>
<tr>
<td></td>
<td>(436.45)</td>
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<td></td>
<td>(60.54 4.16)</td>
</tr>
<tr>
<td>8</td>
<td>C₂₄H₂₂ClGeN</td>
<td>116-18</td>
<td>64.7</td>
<td>62.11</td>
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<tr>
<td></td>
<td>(464.51)</td>
<td></td>
<td></td>
<td>(62.06 4.77)</td>
</tr>
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</table>

inevitably occur when the carboxylate acts as a chelating ligand.

Some important IR spectral data of the title compounds are given in Table II. In the IR spectra, the most important bands due to $ν(CO_2)_{\text{asy}}$ and $ν(CO_2)_{\text{sym}}$ are observed at 1666-1697 cm$^{-1}$ and 1395-1436 cm$^{-1}$, respectively. The $Δν [ν(CO_2)_{\text{sym}} - ν(CO_2)_{\text{sym}}]$ value has been used to predict the mode of carboxylate interaction$^{10}$. In Table II, the $Δν$ value in the range of 243-286 cm$^{-1}$ strongly indicates that these carboxylate groups are monodentate ligands, so the possible structure for the title compounds are four-coordinated configuration A. In addition, a new absorption band appears at 928-933 cm$^{-1}$ which is the characteristic of vibrations of Ge-O band formed$^{11}$.

The $^1$H NMR spectral of the title compounds are given in Table III. It is observed that the values of the $^1$H NMR chemical shift, 7.32-7.55 ppm for the Ge-C$_2$H$_5$ protons shift upfield as compared to that of diphenylgermanium dichloride. It is possible that the carboxylate groups are more electronegative than the chlorine atom, and this leads to the decrease of circulating and deshielding effects of the benzene ring. In addition, the value of the chemical shift for the protons of heteroaromatic ring in compounds are close to that corresponding free acids. It is seen that the S, O, or N hetero atom in carboxylate ligands do not coordinate to germanium atom.

The important mass spectral data of compounds 1-8 are listed in Table II. Parent molecular ions in low abundance were detected for all compounds. So these compounds are monomeric in structure. The most abundant ion in these spectra is germanium-containing fragment at m/z 288, which could be assigned to Ph$_2$Ge$, M^+−Cl$ and $M^+−O_2$-CR peaks are main germanium-containing fragments in all the compounds.

The compounds 1-8 were tested in vitro against two human tumor cell lines, MCF-7 a mammary
<table>
<thead>
<tr>
<th>Compd</th>
<th>IH NMR (δ, ppm)</th>
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<tbody>
<tr>
<td>1</td>
<td>6.56 (1H, q, 4-furan-H), 7.32 (1H, t, 3-furan-H), 7.43-7.55 (10H, m, GeC₆H₅), 7.72 (1H, m, 5-furan-H)</td>
</tr>
<tr>
<td>2</td>
<td>6.48-6.70 (3H, m, 4-furan-H, -CH=CH-), 7.36 (1H, m, 3-furan-H), 7.41-7.67 (1H, GeC₆H₅, 5-furan-H)</td>
</tr>
<tr>
<td>3</td>
<td>7.01 (1H, m, 4-thiophene-H), 7.40-7.66 (1H, m, GeC₆H₅, 3-thiophene-H), 7.88 (1H, m, 5-thiophene-H)</td>
</tr>
<tr>
<td>4</td>
<td>7.32-7.52 (10H, m, GeC₆H₅, 5-pyridine-H), 7.62 (1H, br, 4-pyridine-H), 7.82 (1H, d, 6-pyridine-H), 8.62 (1H, d, 4-pyridine-H), 9.01 (1H, br, 2-pyridine-H)</td>
</tr>
<tr>
<td>5</td>
<td>7.34-7.52 (10H, m, GeC₆H₅), 7.64 (1H, d, 5-pyridine-H), 7.82 (1H, d, 4-pyridine-H), 8.62 (1H, d, 6-pyridine-H)</td>
</tr>
<tr>
<td>6</td>
<td>7.31-7.56 (10H, m, GeC₆H₅), 7.60 (2H, d, 3, 3'-pyridine-H), 8.01 (2H, d, 2, 2'-pyridine-H)</td>
</tr>
<tr>
<td>7</td>
<td>2.95 (2H, s, ArCH₂CO₂), 3.83 (1H, s, N-H), 6.91-7.65 (15H, m, GeC₆H₅, indole-H)</td>
</tr>
<tr>
<td>8</td>
<td>2.05 (2H, m, CH₂), 2.76 (2H, t, ArCH₂), 2.95 (2H, t, O₂CH₂), 4.05 (1H, s, N-H), 6.91-7.54 (15H, m, GeC₆H₅, indole-H)</td>
</tr>
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**Table IV** — The inhibition rate of compounds against tumor (%)

<table>
<thead>
<tr>
<th>Compd</th>
<th>MCF-7</th>
<th>WiDr</th>
</tr>
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<tr>
<td>1</td>
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<td>64</td>
</tr>
<tr>
<td>2</td>
<td>63</td>
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<td>6</td>
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<td>7</td>
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</tr>
<tr>
<td>8</td>
<td>74</td>
<td>71</td>
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**Acknowledgement**

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**References**