

ORGANOGERMANIUM COMPOUNDS. SYNTHESIS AND PROPERTIES OF BIOACTIVE  
GERMANIUM SESQUISULFIDES

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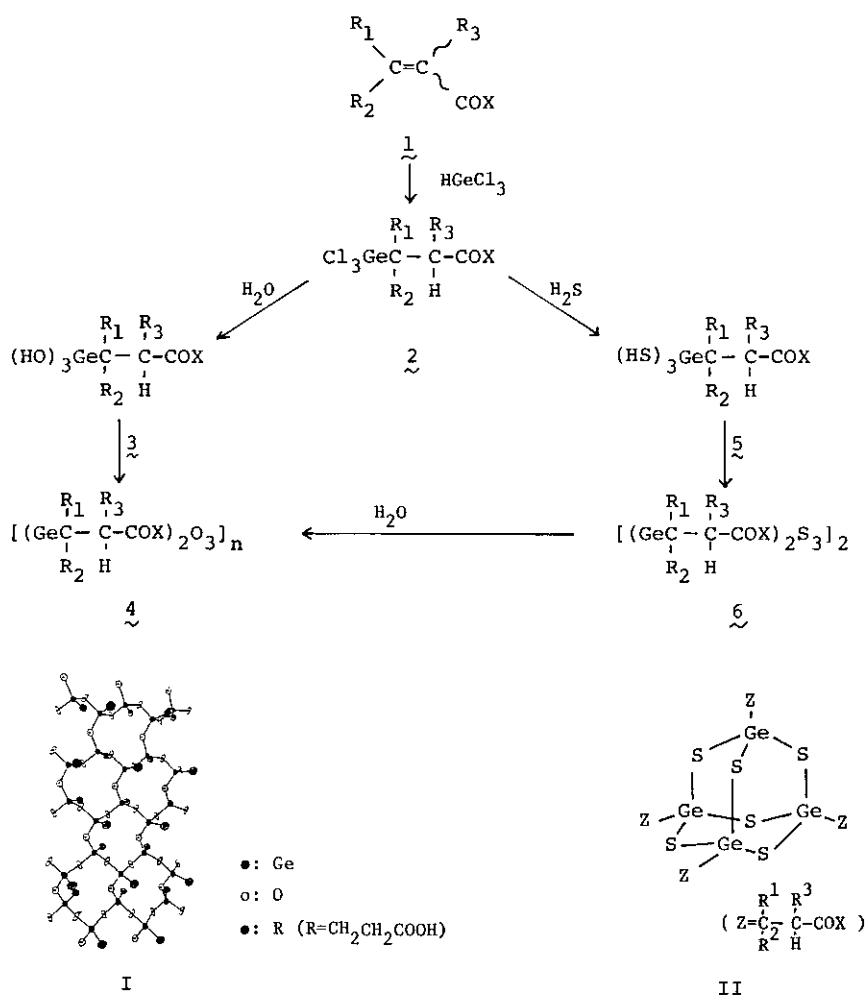
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Abstract — The synthesis, structure, and properties of bioactive germanium sesquisulfides (6) were investigated. Compound (6) prepared from the substitution reaction of trichlorogermyl adducts (2) with hydrogen sulfide seems to have the thiogermaadamantane structure from mass spectral data. It was found to have the unique bioactivities, such as those of an antitumor and antioxidant, and inhibitory activity towards enkephalin hydrogenase.

For many years, silicon has been considered biologically inactive. However, the development in the field of organosilicon compounds has shown it to be an essential element to metabolism. This has spurred a considerable interest in recent years to the synthetic chemistry of bioactive silicon compounds having unique structures and termed silapharmaca<sup>1</sup>. Only a few reports<sup>2</sup> have appeared on the synthesis of bioactive organic germanium compounds with chemical and physical properties similar to those of silicon. We recently observed that carboxyethylgermanium sesquioxide<sup>3</sup> (4:  $R_1=R_2=R_3=H$ ,  $X=OH$ ) (Ge-132) and related compounds formed via (3) from the hydrolysis of  $\beta$ -trichlorogermylpropionic acid and germyl adducts (2)<sup>4</sup> obtained from the reaction of readily available  $\alpha,\beta$ -unsaturated carboxylic acids (1) with trichlorogermane, have unique chemical structures, antitumor activity<sup>5</sup>, and the major function of an inducer of interferon<sup>6</sup>.

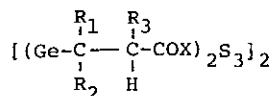
This report presents a general method for the synthesis of novel functionalized germanium sesquisulfides (6) by replacement of trichloro moiety on germyl adducts

(2) with hydrogen sulfide instead of water, for a comparison of Ge-132 related compounds (4) in regard to their chemical properties and biological activity. The synthetic process is shown in Scheme 1. Germyl adducts (2) were prepared regio-selectively from the reaction of trichlorogermane with  $\alpha,\beta$ -unsaturated compounds (1) in high yields<sup>4</sup>. The reaction of (2) with hydrogen sulfide in the presence of pyridine gave the unstable trimercaptogermyl products (5) which immediately underwent self-dehydrosulfidation to yield germanium sesquisulfides (6) in good yields. The structures of (6) were confirmed by spectral (ir, nmr ( $^1\text{H}$  and  $^{13}\text{C}$ )) and analytical data. The results of the preparation of (6) are summarized in Table I.



Scheme 1

Table I. The Germanium Sesquisulfides (6)\*



| 6 | R <sub>1</sub>  | R <sub>2</sub>  | R <sub>3</sub>  | X                              | Yield (%) | Mp (°C) | IR (cm <sup>-1</sup> ) |      | Molecular formula                                                                            | MS m/e (M <sup>+</sup> ) |
|---|-----------------|-----------------|-----------------|--------------------------------|-----------|---------|------------------------|------|----------------------------------------------------------------------------------------------|--------------------------|
|   |                 |                 |                 |                                |           |         | C=O,                   | Ge-S |                                                                                              |                          |
| a | H               | H               | H               | OH                             | 87        | 200     | 1705,                  | 420  | C <sub>12</sub> H <sub>20</sub> Ge <sub>4</sub> O <sub>8</sub> S <sub>6</sub>                | 780                      |
| b | CH <sub>3</sub> | H               | H               | OH                             | 58        | 185     | 1705,                  | 425  | C <sub>16</sub> H <sub>28</sub> Ge <sub>4</sub> O <sub>8</sub> S <sub>6</sub>                | 836                      |
| c | H               | CH <sub>3</sub> | CH <sub>3</sub> | OH                             | 90        | 198     | 1705,                  | 425  | C <sub>16</sub> H <sub>28</sub> Ge <sub>4</sub> O <sub>8</sub> S <sub>6</sub>                | 836                      |
| d | CH <sub>3</sub> | CH <sub>3</sub> | H               | OH                             | 80        | 191     | 1705,                  | 425  | C <sub>20</sub> H <sub>36</sub> Ge <sub>4</sub> O <sub>8</sub> S <sub>6</sub>                | 892                      |
| e | CH <sub>3</sub> | H               | CH <sub>3</sub> | OH                             | 93        | 200     | 1705,                  | 425  | C <sub>20</sub> H <sub>36</sub> Ge <sub>4</sub> O <sub>8</sub> S <sub>6</sub>                | 892                      |
| f | ph              | H               | H               | OH                             | 94        | 210     | 1710,                  | 425  | C <sub>36</sub> H <sub>36</sub> Ge <sub>4</sub> O <sub>8</sub> S <sub>6</sub>                | 1084                     |
| g | ph              | H               | CH <sub>3</sub> | OH                             | 86        | 185     | 1705,                  | 420  | C <sub>40</sub> H <sub>44</sub> Ge <sub>4</sub> O <sub>8</sub> S <sub>6</sub>                | 1140                     |
| h | H               | H               | H               | OCH <sub>3</sub>               | 77        | 159-160 | 1725,                  | 420  | C <sub>16</sub> H <sub>28</sub> Ge <sub>4</sub> O <sub>8</sub> S <sub>6</sub>                | 836                      |
| i | CH <sub>3</sub> | H               | H               | OCH <sub>3</sub>               | 91        | 70-72   | 1735,                  | 420  | C <sub>20</sub> H <sub>36</sub> Ge <sub>4</sub> O <sub>8</sub> S <sub>6</sub>                | 892                      |
| j | H               | H               | CH <sub>3</sub> | OCH <sub>3</sub>               | 88        | 87-88   | 1735,                  | 420  | C <sub>20</sub> H <sub>36</sub> Ge <sub>4</sub> O <sub>8</sub> S <sub>6</sub>                | 892                      |
| k | CH <sub>3</sub> | CH <sub>3</sub> | H               | OCH <sub>3</sub>               | 80        | 179-181 | 1735,                  | 400  | C <sub>24</sub> H <sub>44</sub> Ge <sub>4</sub> O <sub>8</sub> S <sub>6</sub>                | 948                      |
| l | ph              | H               | H               | OCH <sub>3</sub>               | 90        | 174-175 | 1735,                  | 420  | C <sub>40</sub> H <sub>44</sub> Ge <sub>4</sub> O <sub>8</sub> S <sub>6</sub>                | 1140                     |
| m | H               | H               | H               | OC <sub>2</sub> H <sub>5</sub> | 88        | 82.5-84 | 1725,                  | 420  | C <sub>20</sub> H <sub>36</sub> Ge <sub>4</sub> O <sub>8</sub> S <sub>6</sub>                | 892                      |
| n | CH <sub>3</sub> | CH <sub>3</sub> | H               | OC <sub>2</sub> H <sub>5</sub> | 88        | 115-118 | 1725,                  | 400  | C <sub>28</sub> H <sub>52</sub> Ge <sub>4</sub> O <sub>8</sub> S <sub>6</sub>                | 1004                     |
| o | ph              | H               | H               | OC <sub>2</sub> H <sub>5</sub> | 88        | 175-176 | 1735,                  | 400  | C <sub>44</sub> H <sub>52</sub> Ge <sub>4</sub> O <sub>8</sub> S <sub>6</sub>                | 1196                     |
| p | H               | H               | H               | CH <sub>3</sub>                | 58        | 225     | 1715,                  | 425  | C <sub>16</sub> H <sub>28</sub> Ge <sub>4</sub> O <sub>4</sub> S <sub>6</sub>                | 772                      |
| q | CH <sub>3</sub> | H               | H               | CH <sub>3</sub>                | 85        | 112-113 | 1715,                  | 425  | C <sub>20</sub> H <sub>36</sub> Ge <sub>4</sub> O <sub>4</sub> S <sub>6</sub>                | 828                      |
| r | H               | H               | CH <sub>3</sub> | CH <sub>3</sub>                | 82        | 86-91   | 1710,                  | 420  | C <sub>20</sub> H <sub>36</sub> Ge <sub>4</sub> O <sub>4</sub> S <sub>6</sub>                | 828                      |
| s | CH <sub>3</sub> | CH <sub>3</sub> | H               | CH <sub>3</sub>                | 63        | 195-196 | 1720,                  | 420  | C <sub>24</sub> H <sub>44</sub> Ge <sub>4</sub> O <sub>4</sub> S <sub>6</sub>                | 884                      |
| t | ph              | H               | H               | CH <sub>3</sub>                | 45        | 198-200 | 1715,                  | 420  | C <sub>40</sub> H <sub>44</sub> Ge <sub>4</sub> O <sub>4</sub> S <sub>6</sub>                | 1076                     |
| u | H               | H               | H               | C <sub>2</sub> H <sub>5</sub>  | 95        | 138-140 | 1715,                  | 420  | C <sub>20</sub> H <sub>36</sub> Ge <sub>4</sub> O <sub>4</sub> S <sub>6</sub>                | 828                      |
| v | H               | H               | H               | NH <sub>2</sub>                | 60        | 203     | 1665,                  | 425  | C <sub>12</sub> H <sub>24</sub> Ge <sub>4</sub> N <sub>4</sub> O <sub>4</sub> S <sub>6</sub> | 776                      |
| w | CH <sub>3</sub> | H               | H               | NH <sub>2</sub>                | 84        | 206     | 1660,                  | 425  | C <sub>16</sub> H <sub>32</sub> Ge <sub>4</sub> N <sub>4</sub> O <sub>4</sub> S <sub>6</sub> | 832                      |
| x | H               | H               | CH <sub>3</sub> | NH <sub>2</sub>                | 88        | 248     | 1650,                  | 420  | C <sub>16</sub> H <sub>32</sub> Ge <sub>4</sub> N <sub>4</sub> O <sub>4</sub> S <sub>6</sub> | 832                      |
| y | CH <sub>3</sub> | CH <sub>3</sub> | H               | NH <sub>2</sub>                | 71        | 264     | 1655,                  | 410  | C <sub>20</sub> H <sub>40</sub> Ge <sub>4</sub> N <sub>4</sub> O <sub>4</sub> S <sub>6</sub> | 888                      |
| z | CH <sub>3</sub> | H               | CH <sub>3</sub> | NH <sub>2</sub>                | 88        | 220     | 1665,                  | 420  | C <sub>20</sub> H <sub>40</sub> Ge <sub>4</sub> N <sub>4</sub> O <sub>4</sub> S <sub>6</sub> | 888                      |

\* Elemental analyses of these compounds were within acceptable limits.

It should be noted that (6) obtained here were found to be tetramer from mass spectroscopic data. Their mass spectra generally showed parent-ion peaks along with relative strong peaks corresponding to fragments produced by the loss of one bridge head substituent. This characteristic phenomena in the mass spectrum have been also exhibited in substituted adamantane hydrocarbons and silicon analogs<sup>7</sup>. The <sup>1</sup>H and

$^{13}\text{C}$  nmr spectra showed the typical symmetrical signals of the expected intensity. The ir spectrum was relatively simple. The germanium sesquisulfide is thus considered to be a bridgehead compound with highly symmetrical and stable adamantane structure (II) containing four germanium and six sulfur atoms in a molecule, since Benno<sup>8</sup> confirmed the structure for tetra(methylgermanium)hexasulfide from X-ray crystallographic analysis. It should be noted that the structure of (6) differs from that<sup>3</sup> of (4) which was obtained from hydrolysis of the same germyl adducts (2) and was found by X-ray crystallographic analysis to be polymer (I) with a twelve-size ring. When refluxed in aqueous ethanol, (6) was converted to (4) in a quantitative yield. We also observed that the germanium sesquisulfides generally exhibit the following unique bioactivity. a) more efficacious antitumor activity in mice at a dose lower than Ge-132 and related sesquioxides. b) stronger action as a pain reliever (inhibitory<sup>9</sup> toward dipeptidyl carboxypeptidase and dipeptidyl aminopeptidase of enkephalin hydrogenase) than Ge-132 and related sesquioxides. c) antioxidant activity (the antioxidant activity of (6c) is almost the same with that of vitamin E).

A study on the relationship between structure and the biological activity of the newly prepared germanium sesquisulfides is now being carried out and the results will appear in a future publication.

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