



from the reaction mixture. Similar results have been observed previously with the sulfur analogue diphenyl disulfide (9). Whether or not this deactivation of the aromatic ring toward the electrophilic substitution by the hydroxy compound **2** can be attributed to the partial double bond nature of the Se-Se (and S-S) bond in these compounds (including the consequences implied) is still an open question.

The successful use of the barium hydroxide hydrolysis method to obtain the final desired free amino acid **4** from **3** is of particular importance: the classic method for the amino-blocking group removal (*i.e.*, hydrolysis with concentrated hydrohalide solution) is not applicable for many acid-sensitive selenium-containing amino acids such as **3a**. This limitation dictates the use of benzyl carbamate rather than benzyl amide (or other primary amides) in preparing the appropriate **2**, to be used in turn, for the preparation of **3**. The final amino acids **3** were easily obtained by crystallization from aqueous solutions.

Finally, based on the nmr spectrum, the heterocyclic part of the benzoselenophene system **3b** assumed to be in the  $\alpha$ -position in accord with theoretical considerations and with analogy to similar known cases in the literature (11).

The results described in this paper represent an efficient straightforward synthesis of *C*-substituted  $\alpha$ -amino acetic acid derivatives from readily available starting materials. We believe this approach is of general use for the preparation of a wide variety of selenium-containing  $\alpha$ -amino acids. The biological distribution and the organ-scanning usefulness of this class of compounds are now under investigation and the results will be reported elsewhere.

## EXPERIMENTAL

### Phenyl Methyl Selenide (1a).

Diphenyl diselenide (15.6 g, 0.05 mole) was dissolved in 96% ethanol (200 ml). The pH of this solution was brought to pH = 10 by adding dropwise 10% sodium hydroxide solution. To this mixture, sodium borohydride was added in small portions, until the yellow color of the diselenide was discharged and hydrogen evolution ceased. Then, methyl iodide (14.2 g, 0.1 mole) was added in one portion whilst swirling the mixture which was previously cooled with ice. After 15 minutes, the reaction mixture was diluted with 300 ml of water and extracted with ether. Excess ethanol was removed by washing the ether extract with saturated sodium chloride solution. The ether extract was dried (magnesium sulfate), filtered, and the ether was distilled off. The residue of phenyl methyl selenide (15.5 g, 90% yield) was pure enough for subsequent use.

### *N*-Benzyloxycarbonyl(4-methylseleno)phenylglycine (3a).

To a stirred solution of phenyl methyl selenide (8.6 g, 0.05 mole) in glacial acetic acid (100 ml) containing 3 g of concentrated sulfuric acid, was added  $\alpha$ -hydroxy-*N*-benzyloxycarbonyl glycine (**2**) (8) (11.3 g, 0.05 mole) and the stirring continued at ambient temperatures until the mixture became homogenous. After 48 hours the mixture was poured into cold water (about 1 liter) and filtered off. The crude precipitate was taken up in 1*N* sodium hydroxide solution and filtered off from small amounts

of difficultly soluble bis(benzyloxycarbonyl-amino)acetic acid sodium salt. The clear solution was extracted with ether to remove additional impurities and subsequently was brought to pH 2 with 1*N* hydrochloric acid. The crystalline precipitate obtained was filtered off, washed thoroughly with cold water and air-dried. Additional purification was affected by dissolving the precipitate in ether, filtering from any insoluble material, concentrating the solution to half volume, and adding pentane until incipient crystallization. The material was recrystallized from ethyl acetate-pentane to give 10.2 g of **3a** (54%), mp 104°; ir (nujol): 3305 (m), 1687 (s), 1598, 1495, 1257 (m), 1062 (m), 758, 702 (m) cm<sup>-1</sup>.

*Anal.* Calcd. for C<sub>17</sub>H<sub>17</sub>NO<sub>2</sub>Se: C, 53.98; H, 4.53; N, 3.70. Found: C, 54.22; H, 4.54; N, 3.79.

### (4-Methylseleno)phenylglycine (4a).

Compound **3a** (7.6 g, 0.02 mole) was refluxed for 4 hours in ethanol-water solution (150 ml, 2:1 V/V) containing hydrated crystalline barium hydroxide (19 g, 0.06 mole) until precipitation of barium carbonate was completed. The mixture was filtered and the filtrate carefully acidified with 1*N* sulfuric acid to pH 5.5. By additional filtration barium sulfate was removed.

The combined precipitates of barium carbonate and barium sulfate were treated with 1*N* perchloric acid followed by filtration to remove some insoluble impurities. The purified solution thus obtained was combined with the filtrate previously obtained. The pH of this combined solution was again adjusted to 5.5 with barium hydroxide solution, and the aqueous solution was concentrated until incipient crystallization. The crystals were filtered off. The mother-liquor yielded additional crops of the product by careful concentration. The crude combined yield of **4a** was 2.6 g (52%), mp 216-218° dec; ir (Nujol): 1583 (s), 1150, 908, 770 (m).

*Anal.* Calcd. for C<sub>8</sub>H<sub>11</sub>NO<sub>2</sub>Se: C, 44.27; H, 4.54; N, 5.74. Found: C, 44.00; H, 4.65; N, 5.57.

### *N*-Benzyloxycarbonyl 2-[3-benzoselenophenyl]glycine (3b).

Benzoselenophene (3.6 g, 0.02 mole) was condensed with **2** (4.5 g, 0.02 mole) using the procedure already described for **3a**. The cold water-quenched mixture was filtered to give a crude precipitate. The latter was dissolved in dilute sodium hydroxide, filtered from any unreacted material and the aqueous filtrate was further washed with ether. Acidification (pH = 2) afforded crude **3b**. The product thus obtained was further purified by dissolving it in ether, filtering off from any bis(benzyloxycarbonylamino)acetic acid, concentrating the solution and causing crystallization by adding pentane. Recrystallization from ethyl acetate-pentane afforded 4.9 g of **3b** 63% mp 148°; ir (Nujol): 3300 (m), 1708, 1682 (s), 1538, 1249, 1222 (m), 1064 (w), 783, 723, 700 (m); nmr (DMSO-d<sub>6</sub> + deuteriochloroform):  $\delta$ , 7.79 (m, 2H), 7.26 (m, 3H), 7.17 (s, 5H), 6.54 (broad, 1H), 5.57 (d, 1H).

*Anal.* Calcd. for C<sub>16</sub>H<sub>13</sub>NO<sub>2</sub>Se: C, 55.68; H, 3.89; N, 3.60. Found: C, 55.56; H, 3.98; N, 3.32.

### Benzoselenophenylglycine (4b).

This seleno-amino acid was obtained in 70% yield from 0.01 mole of **3b** using the same procedure as for **4a** except that dilute ammonia was used for adjusting the pH of the aqueous solution to 5.5 before the final crystallization of the ammonium salt, mp 199-200° dec; ir (Nujol): 3440, 3100 (m), 1593 (s), 1534, 1500, 1428, 1333 (m), 1247, 801 (w), 761 (s), 737 (m).

*Anal.* Calcd. for C<sub>10</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>Se: C, 44.29; H, 4.46; N, 10.33. Found: C, 44.20; H, 4.25; N, 10.45.

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