The Preparation of Selenium-Containing Aromatic and Heterocyclic *C*-Substituted α-Amino Acetic Acid Derivatives of Potential Biomedical Application

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Model selenium-containing aromatic and heterocyclic *C*-substituted αamino acid compounds have been synthesized as potential biomedical organ scanning application (external imaging) agents. The synthesis is based on the amidoalkylation of aromatic and heterocyclic compounds with αhydroxyglyoxylic acid-primary amide adducts (**2**). The procedure is simple and straightforward, the overall yields are good, and the method appears to be of general use for the preparation of a wide variety of selenium-containing amino acids (**4**).

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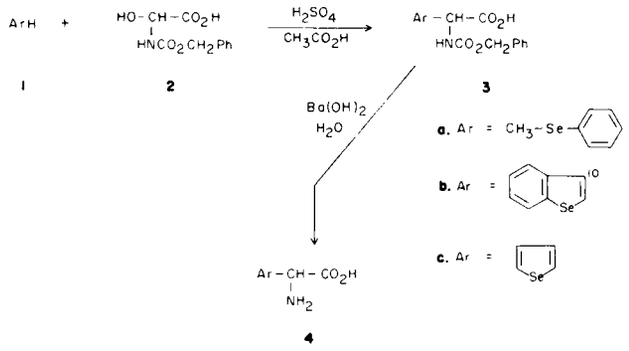
Amino acids of compact structure show favorable organ specificity and good selective absorption if employed in pancreatic scanning as external imaging agents (1). Amino acids for imaging purposes incorporating the radiation of selenium-73 or selenium-75 would permit external visualization of the organ with a γ-scintillation camera, and a pathological lesion would be detected as a negative or "cold area" within the organ (2). Based on the experience gained with ^{35}S-labeled amino acids for this purpose, a promising approach has been the substitution of selenium (3) or tellurium (4) for the sulfur, amino acids. Compact amino acids such as these containing aromatic or heterocyclic moieties are expected to be localized in the pancreas (2), including those where the selenium atom is incorporated within the aromatic system (5). Bearing all the above in mind, the preparation of selected selenium-containing aromatic and heterocyclic *C*-substituted α-amino acetic acid derivatives was undertaken within our current project investigating new radiopharmaceuticals for organ imaging.

The general field of organoselenium chemistry is well-documented (6). However, the application of new synthetic methods to prepare selenium-containing species is less common. Our approach was the adaptation of the new synthetic method of Ben Ishai, *et al.*, (7) for the preparation of substituted αamino acids based on the amidoalkylation of aromatic and heterocyclic compounds with αhydroxyhippuric acid and other glyoxylic acid-primary amide adducts. This method has been successfully applied in preparing sulfur-containing αamino acetic acid derivatives (8).

Following the successful application of this method for the preparation of sulfur-containing aromatic and heterocyclic glycine derivatives of potential medical interest (9) to be employed as model compounds, we describe here the successful application of this approach to the synthesis of selenium-containing aromatic and heterocyclic *C*-substituted α-aminoacetic acids (and derivatives). These are currently under investigation for their intended biomedical organ scanning application (external imaging).

Our synthetic procedure is given below:



Results and Discussion.

Phenyl methyl selenide (**1a**) was prepared *in situ* in high yield from diphenyl diselenide by sodium borohydride reduction and subseqent methylation with methyl iodide in ethanol.

The sulfuric acid-catalized procedure (8) was used for the amidoalkylation of the selenium-containing aromatic compounds (**1a-c**). The condensation proceeded smoothly affording high yields of **3** (see experimental). We encountered difficulties, however, in the preparation of the pure parent selenophene derivative (**3c**).

The reason for this is not yet clear, particularly in light of the straightforward synthesis of the thiophene analogue (**7a**). Interestingly, all attempts to amidoalkylate diphenyl diselenide failed and the latter was recovered unchanged

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 α-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 α-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 α-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 *p*H of this solution was brought to *p*H = 10 by adding dropwise 10% sodium hydroxide solution. To this mixture, sodium borohydride was added in small portions, until the yellow color of the diselinide 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 α-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 *p*H 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 insolubale 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^{-1}.

Anal. Calcd. for $C_{17}H_{17}NO_4Se$: 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 1N sulfuric acid to *p*H 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 *p*H 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 $C_9H_{11}NO_2Se$: 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 (*p*H = 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_6 + deuteriochloroform): δ, 7.79 (m, 2H), 7.26 (m, 3H), 7.17 (s, 5H), 6.54 (broad, 1H), 5.57 (d, 1H).

Anal. Calcd. for $C_{18}H_{15}NO_4Se$: 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 *p*H 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 $C_{10}H_{12}N_2O_2Se$: C. 44.29; H, 4.46; N, 10.33. Found: C, 44.20; H, 4.25; N, 10.45.

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