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Amides of Aliphatic Selena-carboxylic Acids

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Thirteen amides of fatty acids, having a selenium atom incorporated in the chain, have been prepared. The methods of preparation are discussed.

In the course of current work on organoselenium compounds of potential biological interest, the author and his collaborators have prepared a number of long-chain selena-carboxylic acids of the general formula I[1–3]. The acids are beautifully crystallising compounds, very similar to ordinary fatty acids. Their biological and physico-chemical properties are being investigated. Most of the acids have rather good Factor 3 activity, but the effect varies in an interesting way with the position of the selenium in the chain[4]. The presence of the heavy selenium atom in the molecule is favourable for X-ray studies of the crystal structure.

C_mH_{2m+1}–Se–$(CH_2)_n$–COOH (I) CH_3–CH_2–Se–CH_2–$CONH_2$ (II)

The work has now been extended to amides of such acids and in the present paper thirteen amides of moderate chain length are described. The 3-selena-valeramide (ethylseleno-acetamide) (II) has earlier been prepared by Bergson, who obtained it in the conventional way from the corresponding acid chloride and ammonia[5]. As ω-bromo esters and ω-bromo nitriles are often the best starting materials for preparing selenosubstituted acids, the author has tried to find a more direct way to the selena amides without isolating the acids.

Starting from the ω-bromo-nitriles, the following sequence of reactions was found convenient:

$$Br\text{–}(CH_2)_n\text{–}CN \xrightarrow[\text{Water}]{Na_2Se_2} [\text{–}Se\text{–}(CH_2)_n\text{–}CN]_2 \xrightarrow[\text{Ether}]{HCl,\ H_2O}$$

$$[\text{–}Se\text{–}(CH_2)_n\text{–}CONH_2]_2 \xrightarrow[NH_3,\ aq]{\text{Rongalite}} HSe\text{–}(CH_2)_n\text{–}CONH_2 \xrightarrow{C_mH_{2m+1}Br}$$

$$C_mH_{2m+1}\text{–}Se\text{–}(CH_2)_n\text{–}CONH_2$$

A solution of sodium diselenide is obtained by shaking calculated amounts of sodium hydroxide, Rongalite and elemental selenium with water in a closed bottle. The ω-bromo nitrile is then added and the mixture shaken until the deep red-brown colour has disappeared and the nitrile layer is purely yellow. The diseleno-dinitrile is then taken up in ether and the ether solution, which contains the necessary amount of water, is saturated with hydrogen chloride. On standing, the amide separates as a yellow crystalline precipitate. After 4–5 days, it is filtered off, washed with ether and treated with sodium carbonate solution to remove all hydrogen chloride. In most cases, the alkaline water layer remains colourless, indicating that no carboxylic acid has been formed. Finally the amide is recrystallised several times from methanol.

The crude product is often contaminated with monoseleno and polyseleno diamides. Probably the sodium diselenide solution, the stoichiometric composition of which corresponds to the formula Na_2Se_2, contains an equilibrium mixture of HSe-ion and various polyselenide ions. According to Schwarzenbach and Fischer, such complex equilibria exist in the solutions of alkali polysulphides[6].

The diseleno diamide is suspended in aqueous ammonia and shaken with Rongalite in a closed bottle until a colourless solution is obtained (the selenol amide formed is soluble in ammonia owing to the acid properties of the selenol group). Finally, alkyl bromide, dissolved in a little ethanol, is added and the shaking is continued for some hours.

In most cases, the selena-amide separates as a crystalline precipitate during the shaking. If the yield of crude amide is not satisfactory, a second crop may be obtained by concentrating the mother liquor. The lowest homologues are, however, rather soluble in water and do not separate. They can be isolated by exhaustive extraction with ether or by evaporating the reaction mixture to dryness and subsequent extraction of the residue with boiling carbon tetrachloride. The product is recrystallised two or three times from carbon tetrachloride (once with charcoal).

Starting from the ω-bromo esters, the synthesis may be performed as follows:

$$Br{-}(CH_2)_n{-}COOC_2H_5 \xrightarrow[NH_3,\ aq]{(NH_4)_2Se_2} [{-}Se{-}(CH_2)_n{-}COOC_2H_5]_2 \xrightarrow[NH_3,\ aq]{Rongalite}$$

$$HSe{-}(CH_2)_n{-}COOC_2H_5 \xrightarrow{NH_3,\ aq} HSe{-}(CH_2)_n{-}CONH_2 \xrightarrow{C_mH_{2m+1}Br}$$

$$C_mH_{2m+1}{-}Se{-}(CH_2)_n{-}CONH_2$$

A solution of ammonium diselenide is prepared by shaking calculated amounts of selenium and Rongalite with concentrated ammonia in a closed bottle. ω-Bromo ester is added and the shaking continued until the colour is purely yellow. More Rongalite and more concentrated ammonia (which should be present in considerable excess) are then added and the mixture is shaken until the ester layer has dissolved and the yellow colour of the diselenide has dis-

Table 1. 4-Selena-amides.

	m. p. °C	Se calc. %	Se found %
4-Selena-valeramide	87–88	47.53	47.37
4-Selena-capronamide	77–79	43.84	43.63
4-Selena-oenanthamide	88.5–89.5	40.68	40.56
4-Selena-caprylamide	88–89	37.93	38.04
4-Selena-pelargonamide	89.5–90.5	35.53	35.48
4-Selena-capramide	90.5–91.5	33.43	33.18
4-Selena-undecanamide	93–94	31.55	31.40

appeared. On standing for 4–6 days, the selenol ester is converted into the selenol amide, which stays in solution. Alkyl bromide is then added and the reaction is performed as described above.

In some cases, the diseleno ester is contaminated by monoseleno ester, which is of course not reduced to selenol ester. Instead it is converted into monoseleno diamide, which may separate as a crystalline precipitate. This should be filtered off before adding the alkyl bromide. If the solution turns yellow during the filtration (oxidation to diselenide), it is decolourised by adding some Rongalite.

It may also be desired to prepare and purify the diseleno diamide. The oxidation of the selenol amide is easily performed by evaporating the solution by a current of air. The diselenide separates as a yellow crystalline precipitate (sometimes discoloured by elemental selenium) and is purified by recrystallisation from methanol.

Direct treatment of esters of diseleno-dicarboxylic acids or selena-carboxylic acids with concentrated ammonia is practicable only for the lowest homologues. The diseleno-dipropionic amide could thus be prepared from the corresponding methyl ester. The higher members of the series react very slowly at room temperature. On heating, undesired side reactions take place.

Table 2. Selena-capramides.

	m. p. °C	Se calc. %	Se found %
3-Selena-capramide	66.5–68	33.43	33.20
4- „ „	90.5–91.5	„	33.18
5- „ „	81–82	„	33.26
6- „ „	89.5–90.5	„	33.22
7- „ „	95.5–96.5	„	33.23
8- „ „	85–86	„	33.25
9- „ „	86.5–88.5	„	33.21

If a halogenosubstituted amide is accessible, it may of course be used as starting material. Thus the 3-selena-capramide was prepared from chloroacetamide via the diseleno diamide.

Two series of amides have been prepared, one with the selenium in position 4 and various chain lengths and one with constant chain length and the selenium atom in various positions. The data are given in Tables 1 and 2 (the 4-selena-capramide is common to both series). The compounds crystallise very readily, the 3-selena-capramide in needles and the others in glistening scales or flakes.

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REFERENCES

1. Fredga, A. and Lindgren, A. *Acta Chem. Scand.* **15** (1961) 938.
2. Rebane, E. *Arkiv Kemi* **20** (1962) 205.
3. Fredga, A. *11 Nord. Kemistmötet, Helsingfors 1962, Berättelse och föredrag,* Helsingfors 1963.
4. Schwarz, K. and Fredga, A. *To be published.*
5. Bergson, G. and Delin, A.-L. *Arkiv Kemi* **18** (1961) 441.
6. Schwarzenbach, G. and Fischer, A. *Helv. Chim. Acta* **43** (1960) 1365.

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