

**Studies on the Methods of Preparation of Di- and Tri-selena-
straight-chain Fatty Acids and the Corresponding Amides,
with Some Remarks on the Infrared Spectra of the
Mono-, Di- and Tri-selena-fatty Acids**

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In this work, (a) a simple method for the preparation of haloalkyl selenides is introduced; (b) two different methods of synthesizing 12,16-di-selena-stearic acid are presented; (c) the number of methylene groups replaced by selenium atoms in an acid with constant chain length have been increased to three, thus 12,16,20-tri-selena-behenic acid has been prepared; (d) the preparation of ω,ω' -di-selena-di-fatty acid amide, ω,ω' -di-selena-di-selena-fatty acid amide and di- and tri-selena-fatty acid amides are described, and (e) the effect of the increase in the number of selenium atoms incorporated in the chain of fatty acids in relation to their infrared spectra and some of their physical properties have been investigated.

In a previous paper¹ a method of preparation of di-selena-straight-chain fatty acids has been introduced. The results presented in this paper constitute an extension of the work and describe various synthetic approaches for the preparation of di- and tri-selena-fatty acids and their amides.

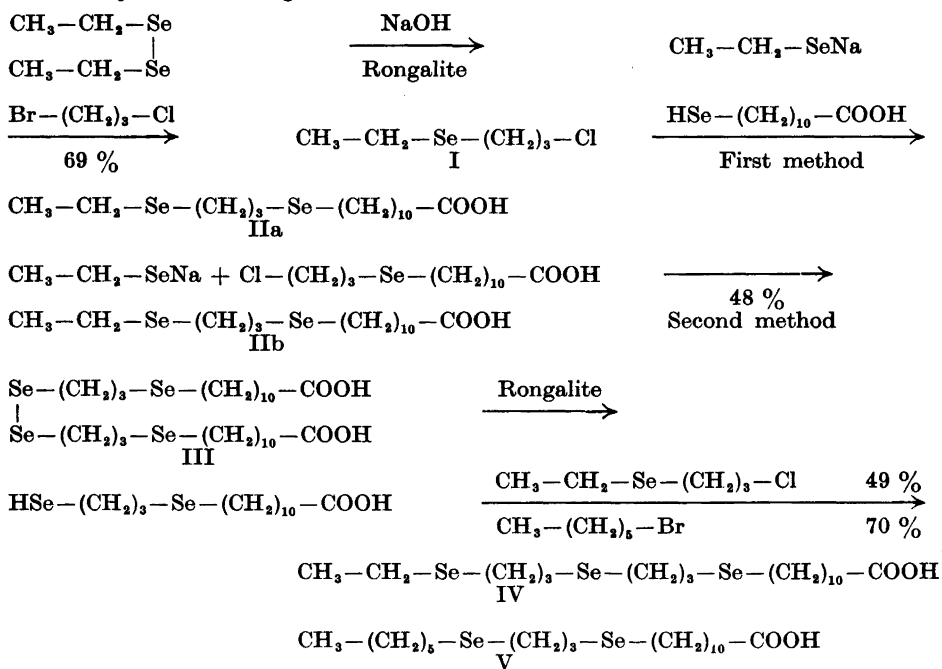
In addition to the interest in the biological evaluation of this type of compounds in regard to the Factor-3-activity, a regular increase in the number of selenium atoms in the chain of a specific acid with constant chain length should present a series of convenient molecules for comparative studies on the intrinsic changes in the nature of the acid caused by the incorporation of selenium atoms. An investigation into the crystal structure of long-chain selena-aliphatic carboxylic acids has shown that there is a bend of the chain at the position of the selenium atom.² This phenomenon and the effect of the position and number of this heavy element on the chain, as well as on the end polar group may call for X-ray studies. The investigation of their surface-film behaviour might also be of interest.

As a preliminary step some infrared spectra studies of the acids both in solution and in the solid state have been carried out. The results of these studies and the methods of the preparation of di- and tri-selena-fatty acids and their corresponding amides are presented below.

DI- AND TRI-SELENA-MONO CARBOXYLIC ACIDS

In this paper the preparation of 12,16-di-selena-stearic acid (IIa, IIb) and 12,16,20-tri-selena-behenic acid are presented. Although the synthesis of 12,16-di-selena-stearic acid has been described by the author previously,¹ it has now been prepared through two other methods, which are similar in character. In the first method 3-ethylselenopropyl chloride (I) which seems to be the first compound of this class, has been prepared and reacted with ω,ω' -di-selena-di-undecanoic acid.³ For the preparation of (I) diethyl diselenide was reduced with sodium formaldehyde-sulfoxylate (Rongalite C) in an alkaline solution and was added in portions to trimethylene chlorobromide. The difference in the halide activities of the mixed halide, *i.e.* the ease of reaction of the bromine atom with ethyl selenolate furnished the desired product with a good yield (69 %). In the second method the reverse approach has been made and a neutralized solution of 15-chloro-12-selena-pentadecanoic acid¹ was reacted with ethyl selenolate. Acidification of the solution gave 12,16-di-selena-stearic acid with nearly the same yield as that of the first method. 12,16,20-Tri-selena-behenic acid (IV) was prepared by the interaction of 3-ethylselenopropyl chloride (I) and reduced ω,ω' -di-selena-di-12-selena-pentadecanoic acid¹ (III). For the comparison of the infrared spectra and some of the physical properties, 12,16-di-selena-behenic acid (V) was also prepared from (III) and hexyl bromide.

The syntheses are given in scheme 1:

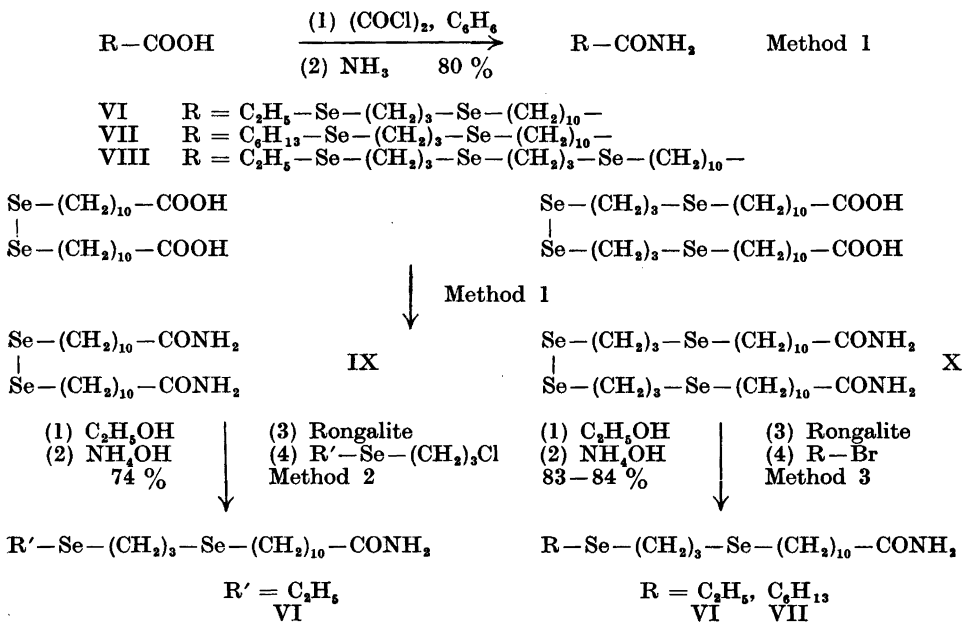


Scheme 1.

DI- AND TRISELENA-, DISELENO- AND
DISELENODI-SELENA-FATTY ACID AMIDES

The reaction of normal fatty acids with thionyl chloride to form acid chlorides and then with ammonia, is a widely applicable way of preparing amides. It has been found experimentally that this reagent is very aggressive when reacting with selenium-containing fatty acids, and in many cases causes the formation of elemental selenium. Bergson and Delin^{4,5} observed the severe decomposition of 3-selena-valeric acid by thionyl chloride while attempting to prepare the corresponding amide. Thus they used oxalyl chloride instead and added ammonia to the acid chloride in ether. Fredga⁶ prepared a series of amides of this type having a moderate chain length by two other methods; *via* interaction of di-selena-di-nitril with ammonia or di-selena-di-ester with ammonia and subsequent addition of alkyl halide to the reduced diselenide.

It has been found that the conversion of long-chain di- and tri-selena-, di-selena- and di-selena-di-selena-fatty acids to the corresponding amides can be effected by reaction with oxalyl chloride and ammonia. The acids were dissolved in benzene, oxalyl chloride was added gradually, and the mixture refluxed for 2–3 h. The excess oxalyl chloride and the benzene were removed. Ice-cold conc. ammonium hydroxide was added to the undistilled acid chlorides which gave the amides in about 80 % yield. Thus 12,16-diselena-stearamide (VI), 12,16-di-selena- and 12,16,20-tri-selena-behenamides (VII, VIII), ω,ω' -di-selena-di-undecanamide (IX), and ω,ω' -di-selena-di-12-selena-pentadecanamide (X) were prepared in this way (Method 1).



Scheme 2.

As (IX) and (X) could be easily reduced in alcoholic ammoniacal solution with Rongalite, 12,16-di-selena-stearamide was obtained from the addition of 3-ethylselenopropyl chloride (I) to reduced (IX) (Method 2), and by the addition of ethyl bromide to reduced (X) (Method 3). 12,16-Di-selena-behenamide was also prepared by the reaction of hexyl bromide and reduced (X) (Method 3).

Scheme 2 illustrates the methods of synthesis involved in the preparation of the amides.

12-Selena-stearic and behenic acids and their amides have been used for comparative studies. The preparation of these will be reported in another paper.⁷

All the acids and amides are waxy crystalline compounds and resemble very much the normal fatty acids and amides. A comparison between melting points of mono- and di-selena-stearic acids and of mono-, di- and tri-selena-behenic acids show that with an increase in the number of selenium atoms in the chain a decrease in the melting points of the acids takes place. The case is similar for the amides. This might not always be so, as the position of the selenium atom in the chain also has an important effect on melting points.

IR-SPECTRA

There is little to be found concerning infrared spectral studies of selenium-containing fatty acids. In this work a brief comparison of infrared absorption spectra of these acids and the corresponding normal acids has been made. The effect of the increase in the number of selenium atoms in the chain has been especially discussed.

There is a close similarity in the spectra of mono-, di- and tri-selena-fatty acids with that of the normal acids. In carbon disulphide solution all the acids exhibit a broad absorption band between 670 and 1500 cm^{-1} . The methylene rocking vibration and the symmetrical and antisymmetrical methylene stretching vibrations appear at 720, 2850 and 2920 cm^{-1} , respectively.

There is no indication of free hydroxyl absorption which shows that the presence of even as many as three selenium atoms in the chain has no marked effect on the hydrogen bond of the strongly bonded hydroxyl of the carboxylic group. The band positions of the carboxy-group in the spectra of selenium-containing acids are fairly normal: A strong C=O stretching vibration band appears at 1725 cm^{-1} and a very weak band, probably due to the carboxyl group of the monomer at 1760 cm^{-1} .⁸ The other bands associated with the carboxyl groups⁹ are a broad band at 940 cm^{-1} and a weak band near 2700 cm^{-1} both of which appear at their expected regions. The band at 1420 cm^{-1} is obscured by carbon disulphide absorption.

There is a doublet absorption at about 1290 and 1250 cm^{-1} in Figs. 1 and 2 which in normal fatty acids has been tentatively related to vibrations involving the C—O linkage in COOH.¹⁰ In Fig. 1 the spectra of normal mono- and di-selena-stearic acids and in Fig. 2 the spectra of mono-, di- and tri-selena-behenic acids in the regions of 1100 and 1400 cm^{-1} have been compared. It is interesting to note that the intensity of the absorption bands at 1250 cm^{-1}

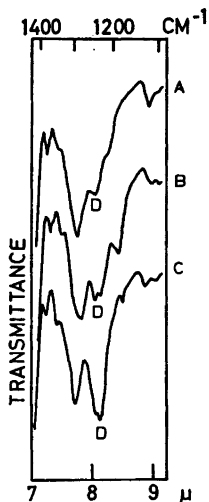


Fig. 1. IR-Spectra of normal stearic acid and mono- and di-selena-stearic acids in carbon disulphide solution at 1400–1100 cm^{-1} ; cell thickness 0.2 mm; molar conc. 0.1. A. Stearic acid. B. 12-Selena-stearic acid. C. 12,16-Di-selena-stearic acid.

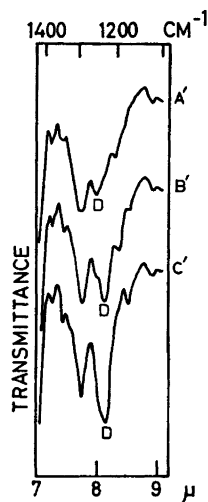


Fig. 2. IR-Spectra of mono-, di- and tri-selena-behenic acids in carbon disulphide solution at 1400–1100 cm^{-1} ; cell thickness 0.2 mm; molar conc. 0.1. A'. 12-Selena-behenic acid. B'. 12,16-Di-selena-behenic acid. C'. 12,16,20-Tri-selena-behenic acid.

(bands D) is selenium dependent. A progressive increase in the intensity of the absorption band in this region together with a displacement of the band toward lower frequency is observed when the number of selenium atoms in the chain is increased. There is also a change in the solid state spectra of the acids about this region, (Figs. 3 and 4, peaks E). It can be seen that the transmittance peak decreases when the number of selenium atoms is increased. The solid state spectra of the amides of the acids show the same effect (unpublished). Sinclair *et al.*⁸ have demonstrated that the relative intensity of the methylene rocking vibration at 720 cm^{-1} in the spectra of solution increases as the chain lengthens. This cannot be fully recognized from the spectra of the acids with the same molar concentration when the number of methylene groups is decreased and replaced by selenium atoms. However, there is a definite broadening effect on the higher frequency side of the absorption band when the number of selenium atoms in the chain is increased.

The solid film spectra of the normal fatty acids offer better prospects for their identification but the effect of polymorphism on the infrared spectra of the acids is quite large.⁸ This effect can be minimized and more detail obtained by using potassium bromide discs.¹¹ Thus in the study of infrared spectra of mono-, di- and tri-selena-fatty acids in the solid state the latter method was used, and the spectra obtained were compared with spectra of the corresponding normal acids available in the literature.¹¹ While the IR-spectra of the selenium-containing acids show some marked differences com-

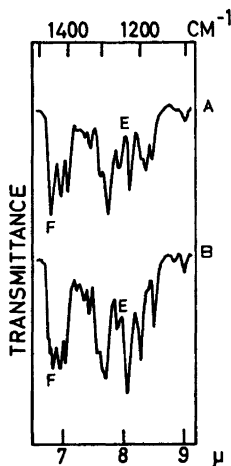


Fig. 3. IR-Spectra of mono- and di-selena-stearic acids in KBr at 1500–1100 cm^{-1} . A. 12-Selena-stearic acid. B. 12,16-Di-selena-stearic acid.

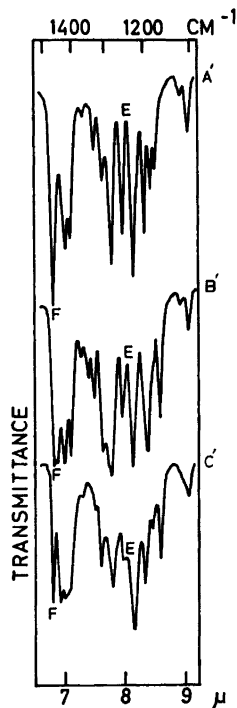


Fig. 4. IR-Spectra of mono-, di- and tri-selena-behenic acids in KBr at 1500–1100 cm^{-1} . A'. 12-Selena-behenic acid. B'. 12,16-Di-selena-behenic acid. C'. 12,16,20-Tri-selena-behenic acid.

pared with the normal ones, their general appearance remains unchanged. The splitting of the 720 cm^{-1} rocking band into two components in the spectra of the normal stearic and behenic acids disappears in the spectra of analogous selenium-containing acids. Jones *et al.*¹² called attention to a remarkable spectral feature of fatty acids between 1180 and 1350 cm^{-1} . In this region a progression of absorption bands with uniform spacing and intensity attributable to CH_2 wagging^{13,14} is observed. Further spectral studies, by Meiklejohn *et al.*,¹¹ in this region revealed the "rule of two" relationship; *i.e.* each band represents two carbons in the chain. It can be seen from the spectra of selenium-containing acids (Figs. 3 and 4) that the introduction of selenium atom or atoms has considerable effect on the "rule of two", and to some extent on the uniformity of spacing and intensities. The other effect of increasing the number of selenium atoms can be observed in the bending methylene vibration band at $1460\text{--}1465\text{ cm}^{-1}$ ⁸ (bands F). Here also the decrease in the number of methylene groups will decrease the intensity of the band. As previously mentioned the relative disappearance of the transmittance peaks near

1250 cm^{-1} (peaks E) occurs when the number of selenium atoms decreases, and it should be remembered that this is the region in the solution spectra at which the increase of selenium atoms has marked effect on the increasing intensity of the absorption band. There is also a weak absorption band at 680 cm^{-1} in the spectra of mono-selena-acids which in the spectra of di- and tri-selena-acids shifts to 690 and 698 cm^{-1} , respectively. The OH out-of-plane bands in this series lie within the range 935–955 cm^{-1} varying from compound to compound.

EXPERIMENTAL

The infrared spectra were recorded on a Perkin-Elmer Model 137 infracord spectrophotometer. For the solid phase spectra the crystalline substances were mixed into pellets with dried potassium bromide (ca. 2 mg substance and 250 mg KBr, pellet diameter 13 mm).

The melting points are uncorrected. Mixed melting point tests were carried out for the substances which have been prepared by various methods.

Trimethylene chlorobromide was prepared according to Cloke *et al.*¹⁵

Diethyl diselenide was prepared from diethyl sulphate and sodium diselenide according to Bird and Challenger¹⁶ and from ethyl bromide and sodium diselenide. B.p. 85–86° (21 mm); n_D^{20} 1.5830.

3-Ethylselenopropyl chloride (I) 21.6 g diethyl diselenide (0.1 mole) were reduced with 17 g excess Rongalite C in 12 g sodium hydroxide dissolved in a mixture of 120 ml water and 100 ml ethanol. This mixture was shaken until the yellow colour of the diselenide disappeared. Half of this solution was added to 35 g (0.22 mole) trimethylene chlorobromide dissolved in 250 ml ethanol. This mixture was shaken for 6 h. Then the remaining portion of the reduced diselenide was added and it was shaken over-night. During this process a milky solution and some salt appeared. After standing for a day the oily selena-alkyl chloride remained at the bottom of the flask. This oily material was separated and the rest of the solution was diluted with water. The remaining material in the solution was extracted twice with ether and it was added to the oily material. After drying over MgSO_4 and removal of ether, the product was fractionated through a short Vigreux column. *3-Ethylselenopropyl chloride*, an oily colourless substance with a poignant smell, was obtained in 69 % yield (26 g). It boiled at 77° (14 mm); n_D^{20} 1.5142. (Found: Se 42.43. Calc. for $\text{C}_5\text{H}_{11}\text{ClSe}$: Se 42.56).

ω,ω' -Diselena-diundecanoic acid was prepared according to Fredga and Lindgren.³

12,16-Di-selena-stearic acid (IIa), Method 1. 1.58 g (0.003 mole) of ω,ω' -diselena-diundecanoic acid were dissolved in 20 ml of 2 N aqueous ammonia and 30 ml of ethanol. Excess Rongalite was added to this solution which was shaken for 10 min until the yellow colour disappeared. 1.2 g (excess) *3-ethylselenopropyl chloride* in 30 ml of ethanol was added to the solution, which was shaken over-night. The solution was diluted with water to four times its volume and acidified with 2 N hydrochloric acid. The oily product was precipitated in the refrigerator and filtered off. It was recrystallized three times from petroleum ether (b.p. 30–65°) and yielded 1.3 g (52 %) pure substance; m.p. 42–43.5°. (Found: Se 38.14; equiv. wt. 412.3. Calc. for $\text{C}_{16}\text{H}_{32}\text{O}_2\text{Se}_2$: Se 38.11; equiv. wt. 414.3).

12,16-Di-selena-stearic acid (IIb), Method 2. To 1.08 g (0.005 mole) diethyl diselenide in a 100 ml flask were added 10 ml ethanol, 25 ml water, 1 g Rongalite and 0.7 g sodium hydroxide. The mixture was shaken until its yellow colour disappeared. 3.42 g 15-chloro-12-selena-pentadecanoic acid¹ were neutralized with 2 N aqueous ammonia and added to the flask. The solution was shaken for 12 h. Acidification of a small sample showed that the reaction had not taken place and most of the 15-chloro-12-selena-pentadecanoic acid could be recovered. Then the solution was stirred while refluxing on a water bath for 2 h. After cooling it was diluted with water and acidified with 2 N hydrochloric acid. The pale yellowish product was recrystallized twice from petroleum ether using active charcoal once, yielding 2 g (48.3 %) of glistening crystals; m.p. 42–43.5°. (Found: Se 38.20; equiv. wt. 412.2. Calc. for $\text{C}_{16}\text{H}_{32}\text{O}_2\text{Se}_2$: Se 38.11; equiv. wt. 414.3).

ω,ω' -Di-seleno-di-12-selena-pentadecanoic acid (III) was prepared according to Golmohammadi.¹

12,16,20-Tri-selena-behenic acid (IV). Following the procedure already described for the preparation of 12,16-di-selena-stearic acid (Method 1), 12,16,20-tri-selena-behenic acid was prepared from ω,ω' -di-seleno-di-12-selena-pentadecanoic acid and 3-ethylselenopropyl chloride in 49 % yield of glistening crystals. It melted at 46–47°. (Found: Se 44.09; equiv. wt. 535.9. Calc. for $C_{19}H_{38}O_2Se_3$: Se 44.24; equiv. wt. 535.4).

12,16-Di-selena-behenic acid (V). This acid was prepared from ω,ω' -di-seleno-di-12-selena-pentadecanoic acid and hexyl bromide in 70 % yield according to the procedure used for the preparation of 12,16-di-selena-octadecanoic acid. It melted at 48–49.5°. (Found: Se 33.54; equiv. wt. 471.2. Calc. for $C_{20}H_{40}O_2Se_2$: Se 33.57; equiv. wt. 470.4).

Amides

ω,ω' -Di-selena-di-undecanamide (IX). 6 g ω,ω' -di-seleno-di-undecanoic acid were dissolved in 60 ml warm dry benzene. 20 ml oxalyl chloride were added drop-wise at such a rate that a gentle reflux was maintained during the addition. It was refluxed for 3 h. The excess oxalyl chloride and benzene were removed. 100 ml of cold conc. ammonia were added to the remaining material and it was shaken for 5 min. The yellowish precipitate was filtered off, washed with water, and dried. It was recrystallized five times from methanol and gave 4.8 g (80 %) of yellowish crystalline material; m.p. 130–132°. (Found: Se 30.07. Calc. for $C_{22}H_{44}N_2O_2Se_2$: Se 29.99).

ω,ω' -Di-selena-di-12-selena-pentadecanamide (X). This amide was prepared from ω,ω' -di-seleno-di-12-selena-pentadecanoic acid according to the above procedure. As many attempts to purify it through recrystallization failed, it was used in its impure form.

12,16-Di-selena-stearamide (VI), Method 1. Following the procedure for the preparation of ω,ω' -di-seleno-di-undecanamide, 1 g acid was dissolved in 25 ml dry benzene and 5 ml oxalyl chloride were added drop-wise. The mixture was refluxed for 2 h. The oxalyl chloride and benzene were removed and 30 ml cold conc. ammonia were added. The amide was recrystallized three times from carbon tetrachloride and gave 0.8 g (yield 80 %) of glistening crystals; m.p. 85.5–86.5°. (Found: Se 38.22. Calc. for $C_{16}H_{31}NOSe_2$: Se 38.39).

Method 2. 0.6 g ω,ω' -diseleno-di-undecanamide were dissolved in 40 ml of warm ethanol, then 10 ml of conc. ammonia were added to the solution. Rongalite C was added up to the disappearance of the yellowish colour, which took about 3 min. Excess 3-ethylselenopropyl chloride was added. The solution was warmed to 60° for an hour and allowed to stand over-night. It was diluted with water to 10 times its volume. The precipitation was filtered off, washed with water and dried. It was recrystallized three times from carbon tetrachloride and gave 0.7 g (74 % yield); m.p. 86–87°. (Found: Se 38.42. Calc. for $C_{16}H_{31}NOSe_2$: Se 38.39).

Method 3. Following the above procedure, omitting warming the solution to 60° for an hour, this amide was prepared from ω,ω' -di-seleno-di-12-selena-pentadecanamide and ethyl bromide, in 83 % yield; m.p. 85.5–87°. (Found: Se 38.47. Calc. for $C_{16}H_{31}NOSe_2$: Se 38.39).

12,16-Di-selena-behenamide (VII). Following the procedures of Methods 1 and 3 described for the preparation of 12,16-di-selena-stearamide, this amide was prepared in 80 and 84 % yield, respectively. In Method 1 the corresponding acid, and in Method 3 ω,ω' -di-seleno-di-12-selena-pentadecanamide and hexyl bromide were used. The products of both methods melted at 89.5–90.5°. (Found: Method 1: Se 33.61; Method 3: Se 33.55. Calc. for $C_{20}H_{41}NOSe_2$: Se 33.64).

12,16,20-Tri-selena-behenamide (VIII). This amide was prepared from its corresponding acid according to Method 1, in 80 % yield; m.p. 84.5–85.5°. (Found: Se 44.15. Calc. for $C_{19}H_{39}NOSe_3$: Se 44.33).

The selenium analyses were carried out according to Fredga.¹⁷

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