Tetrahedron Vol. 42, No. 18, pp. 4983 to 4990, 1986
Printed in Great Britain.

0040-4020/86 $3.00+.00

CONCISE SYNTHESES OF L-SELENOMETHIONINE AND OF L-SELENOCYSTINE USING RADICAL CHAIN REACTIONS

Derek H.R. Barton, Dominique Bridon, Yolande Hervé, Pierre Potier, Josiane Thierry and Samir Z. Zard*

Institut de Chimie des Substances Naturelles, C.N.R.S.
91190 Gif-sur-Yvette, France.

(*Received in France* 23 *June* 1986)

Abstract : L-Selenomethionine and L-selenocystine were prepared in high overall yields from protected L-glutamic and L-aspartic acid derivatives respectively. Irradiation of the mixed anhydrides (esters) derived from 4 *(e.g.* 15*) in the presence of dimethyldiselenide provided the protected L-selenomethionine* 16 *directly. We have shown that triselenocyanide* $Se_3(CN)_2$ *can serve as an efficient selenocyanating agent for radicals; the selenocyanide group is a good precursor for the diselenide moiety of L-selenocystine.*

Selenium analogues of sulfur containing aminoacids are acquiring increasing importance. They are used as tools in the study of selenium poisoning of grazing animals ("alkali disease"; "blind staggers", etc.) and the various detoxification processes involved.[1] More recently, the finding that some important enzymatic systems such as glutathione peroxidase, actually require selenium at their active site has spurred further interest in these substances.[1] In this paper we describe concise syntheses of the two most important members of this group : selenomethionine 1 and selenocystine 2.

As with most organoselenium compounds, previous syntheses of 1 and 2 have relied on ionic reactions involving a selenium nucleophile and various activated derivatives of alanine, serine or homoserine.[2,3,4] Our synthetic scheme, in contrast, is based on a novel radical decarboxylation process we have recently described.[5]

Mixed anhydrides 3 derived from aliphatic or alicyclic carboxylic acids and a suitable thiohydroxamic acid such as 4, undergo a smooth decarboxylation leading to sulphides 5 upon heating or irradiation with visible light from a tungsten lamp. The reaction follows the simple chain mechanism expressed in Scheme 1, path A. The experimental conditions are gentle enough to allow the modification of amino acids and even peptides.[6] Furthermore, the inclusion of external radical traps into the system leads to a variety of synthetically useful modifications of the basic process. Specifically, we had shown that in the presence of diphenyldiselenide, an efficient S_H2 reaction takes place to give the corresponding phenylselenide, R-SePh, in excellent yield[7] (Scheme 1, path B; X-Y = PhSeSePh). If this reaction could be extended to the somewhat less reactive dimethyldiselenide, the synthesis of selenomethionine 1 from a suitably protected glutamic acid derivative such as 8 would be straightforward.

We first established the feasibility of the reaction on the bisnorcholic acid derivative 9 and acetylated hederagenin 10. The corresponding mixed anhydrides 11 and 12 were prepared from the respective acid chlorides and irradiated *in situ* in the presence of excess dimethyldiselenide. Indeed, a smooth reaction occured to give methylselenides 13 and 14 in 71 and 72% yield respectively.

As in the earlier work on the modification of amino acids and peptides,[6] we chose the method employing isobutylchloroformate for the preparation of the requisite mixed anhydride 15 from the protected glutamic acid 8. The acid chloride route used above is not appropriate in this case. Irradiation of 15 for a few minutes in the presence of excess dimethyldiselenide gave the expected selenomethionine derivative 16 cleanly in 78% yield. Deprotection to selenomethionine 1 was effected by the literature method. Thus saponification gave acid 17 quantitatively which was best characterised as its dicyclohexylammonium salt. Exposure to trifluoroacetic acid in dichloromethane removed the BOC- group and afforded L-selenomethionine 1 (96%, $[\alpha]_D^{20}$ = +23.6°).

For work on a larger scale we employed a less direct but more convenient modification of the above scheme which avoids the use of an excess of the evil smelling dimethyldiselenide. Irradiation of mixed anhydride 15 in bromotrichloromethane afforded the bromo derivative 18 in 82% yield (X-Y = Br-CCl_3 in Scheme 1). This Hunsdiecker type reaction is exceptionally efficient.[5b] Displacement of the bromine with sodium methylselenide produced 16 in 93% yield. After deprotection as above, selenomethionine is obtained in an overall yield of about 70% from the commercially available L-glutamic acid derivative 8.

For the synthesis of selenocystine 2, we envisaged introducing a benzylseleno group starting from a protected L-aspartic acid derivative. The removal of the benzyl group by reductive cleavage with sodium in ammonia producing eventually the required diselenide moiety has been reported for closely related systems.

The two protected aspartic acid derivatives 19 and 20 were converted to the corresponding mixed anhydrides with thiohydroxamic acid 4 by the same method used in the selenomethionine 1 synthesis. Irradiation in the presence of dibenzyldiselenide (X-Y = $PhCH_2Se$-$SeCH_2Ph$) afforded the respective benzylselenocysteine derivatives 21 (70%) and 22 (64%). Although the cleavage of the benzyl group to produce eventually a diselenide could in principle be accomplished by sodium in liquid ammonia, it appeared, however, that a simpler and perhaps more general route to diselenides from carboxylic acids was desirable. We thus considered using selenocyanogen as the radical trap (X-Y = NCSe-SeCN). This would have led to a selenocyanate, R-SeCN, which can be transformed into a diselenide by a variety of reagents under very mild conditions.[2] Selenocyanogen, however, is reactive and difficult to handle,[2,8] so we turned to a similar and, *a priori*, more convenient substance, dicyanogen triselenide 23. This nicely crystalline compound is prepared by treating potassium selenocyanate with bromine.[9] Since the S_H2 attack of the carbon radical can take place either on the middle or on one of the outer selenium atoms, we undertook a brief exploratory study using simple models.

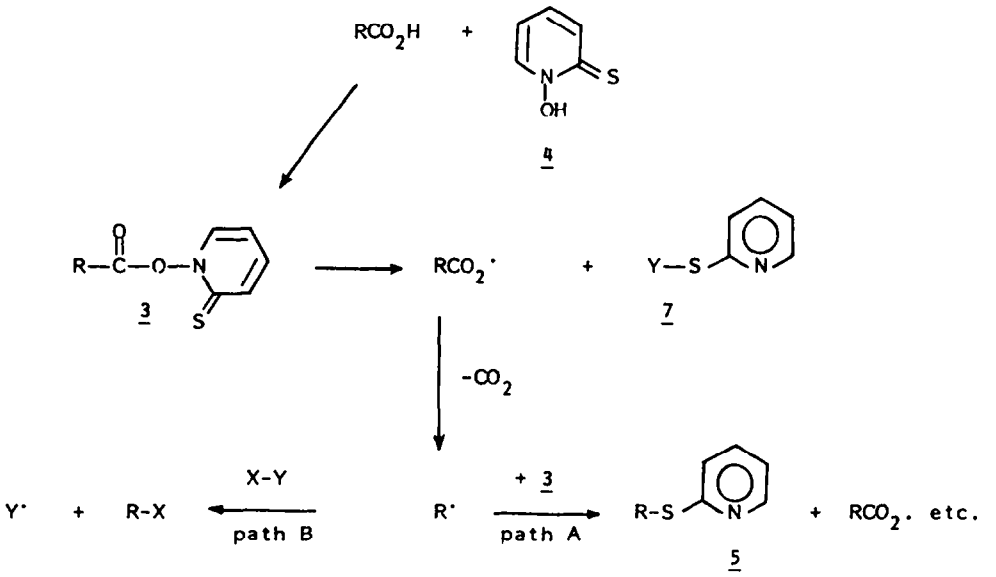
Irradiation of mixed anhydride 24 derived from palmitic acid in the presence of the triselenide 24 gave indeed the selenocyanate 25 in 87% yield. Selenium metal was also produced. These observations suggest that the substitution takes place on the outer selenium to give the selenocyanate and a diselenide radical NCSeSe$^{\cdot}$. The latter extrudes selenium with the concomitant formation of a selenocyanate radical which propagates the chain. Incidentally, the selenosulphide 7 (Y = SeCN) co-produced, but which could not be isolated, is also a potential selenocyanating agent. 2,2'-Dipyridyldisulphide is pratically the only product derived from the heterocyclic moiety of the anhydride 24.

The reaction also proceeded smoothly in the case of anhydrides 26 and 27 affording high yields of the respective selenocyanate 28 (89%) and 29 (77%).

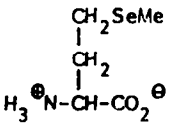
When we attempted the reaction on the protected aspartic derivative 20, we found that it was necessary to semi-purify the intermediate mixed anhydride by precipitation before irradiation. Unlike the other diselenides used in this study, triselenide 23 is destroyed by N-methylmorpholine, the base employed to scavenge the hydrogen chloride in the activated ester method. Notwithstanding this minor complication, the decarboxylative selenocyanation itself proceeded cleanly providing 30 in 73% yield. The conversion of the latter into protected selenocystine 31 was achieved most simply by exposure for 1 min. to sodium borohydride in ethanol (94%). This operation could be, in principle, effected without isolation of intermediate selenocyanate.

Finally, treatment with hydrobromic acid removed the protecting groups to give optically pure L-selenocystine 2 in an overall yield of ~60% ($[\alpha]_D^{20}$ -160°; lit. $[\alpha]_D^{20}$ -162°).

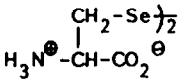
In conclusion, the application of the radical decarboxylation reaction has provided a simple high yielding synthesis of two of the most important seleno-amino acids starting from commercially available glutamic and aspartic acid derivatives. Furthermore, the conditions are sufficiently mild as to avoid any racemisation. The advantages of a radical process are perhaps best appreciated in the synthesis of selenocystine. Previous routes have relied on β-chloroalananine or O-tosyl serine derivatives where β-elimination, and therefore racemisation, is a serious problem requiring delicate experimental conditions especially with regard to pH control. Reproducibility is hence difficult to achieve as we have learnt to our cost in the course of the present study.



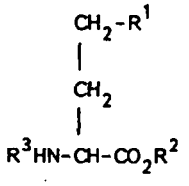
Scheme 1



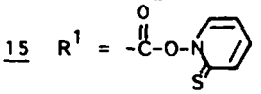
1



2



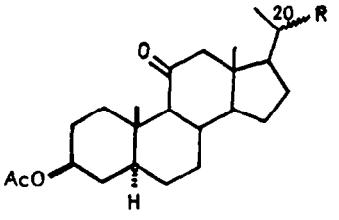
8 $R^1 = CO_2H$; $R^2 = PhCH_2$- ; $R^3 =$ 

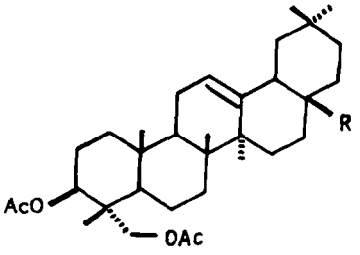
15 $R^1 =$  ; $R^2 = PhCH_2$; $R^3 =$ 

16 $R^1 = SeMe$; $R^2 = PhCH_2$- ; $R^3 =$ 

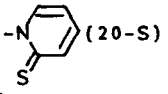
17 $R^1 = SeMe$; $R^2 = H$; $R^3 =$ 

18 $R^1 = Br$; $R^2 = PhCH_2$- ; $R^3 =$ 



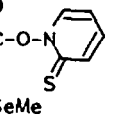


9 R = CO_2H (20-S)

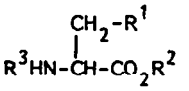
11 R = CO_2-  (20-S)

13 R = SeMe

10 R = CO_2H

12 R = 

14 R = -SeMe



19 $R^1 = CO_2H$; $R^2 = CH_2Ph$; $R^3 =$ 

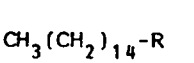
20 $R^1 = CO_2H$; $R^2 = CH_2Ph$; $R^3 = PhCH_2OCO$-

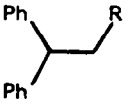
21 $R^1 = -SeCH_2Ph$; $R^2 = -CH_2Ph$; $R^3 =$

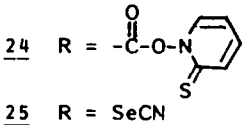
22 $R^1 = -SeCH_2Ph$; $R^2 = -CH_2Ph$; $R^3 = PhCH_2OCO$-

30 $R^1 = SeCN$; $R^2 = -CH_2Ph$; $R^3 = PhCH_2OCO$-

23 31

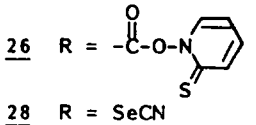






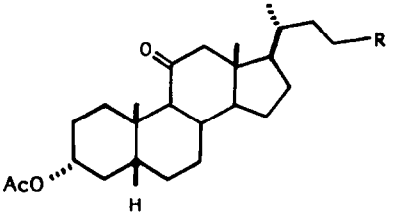
24 R =

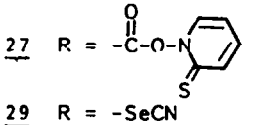
25 R = SeCN



26 R =

28 R = SeCN





27 R =

29 R = -SeCN

Experimental

M.p's were determined with a Kofler hot stage apparatus. ^{1}H-NMR spectra are for deuterated chloroform solutions with tetramethylsilane as internal standard, unless otherwise stated. IR spectra are of nujol mulls for solid samples or neat in the case of liquids unless otherwise specified. Irradiations were performed with either two 100 W tungsten lamps or a 300 W projector lamp placed near the reaction vessel. Normal work-up consisted in washing the organic phase with water, then with brine followed by drying with sodium sulphate which was used throughout as a drying agent for organic layers.

DMF is N,N-dimethylformamide, THF is tetrahydrofuran and DMAP is 4-dimethylaminopyridine.

Dimethyldiselenide

We have used a slightly improved modification of the method of Syper and Myochowski.[10] To an ice cold suspension of metallic selenium (7.9 g, 100 mmoles) and powdered sodium hydroxide (6 g, 15 mmoles) in water (30 ml) was added dropwise over 30 min. hydrazine hydrate (5.05 ml, 105 mmoles) under an inert atmosphere. The mixture was stirred for 6 hours at room temperature then treated with an aqueous solution of trimethylsulphonium iodide (30.6 g, 150 mmoles in 50 ml warm water), added dropwise. After stirring overnight at room temperature and extraction with dichloromethane (3 x 30 ml), the organic phase was washed with water, brine and dried. Concentration and purification by distillation afforded pure dimethyldiselenide as an evil smelling orange liquid (7.3 g, 78%); b.p. 156-157°C; δ_H 2.26 (6H, s).

3β-Acetoxy-20-methylselenopregnan-11-one 13

To a stirred solution of steroid acid 9 (202 mg, 0.5 mmole) in anhydrous toluene (5 ml) was added oxalyl chloride (0.5 ml) and DMF (1 drop). After stirring for 3 hours at room temperature under argon, the solution was concentrated, and the residue redissolved in fresh anhydrous toluene (5 ml). This solution was then poured onto a solution of thiohydroxamic acid 4 (76 mg) containing triethylamine (0.08 ml) and a little DMAP (6 mg). After stirring at room temperature in the dark and under argon for 1.5 hours, dimethyldiselenide (960 mg) was added and the resulting solution irradiated for 20 min. Normal work-up and purification by chromatography on silica (dichloromethane) afforded selenide 13 as a white solid (162 mg, 72%); m.p. 154-156°C (ether-hexane); ν_{max} 1730, 1705 cm^{-1}; δ_H 4.66 (1H, broad, 3α-H); 2.02 (3H, s, -OAc), 1.96 (3H, s, -Se-Me); 1.03 (3H, s, 19-Me), 0.66 (3H, s, -18-Me); m/e 452 (M^+). (Found: C, 63.91; H. 8.41. Calc. for $C_{24}H_{37}O_3Se$: C, 63.70; H, 8.24%).

3β,23-Diacetoxy-17β-methylseleno-28-nor-4α-Olean-12-ene 14

The methylselenide 14 was obtained as above (212 mg, 71%) from hederagenin diacetate (330 mg) after purification by chromatography on silica (dichloromethane-hexane 2:1 then 3:1). It had m.p. 168-170°C (ether-hexane); ν_{max} 1750 cm^{-1}; δ_H (400 MHz) 5.23 (1H, m), 4.79 (1H, m), 3.89 (1H, d, J = 11 Hz); 3.70 (1H, d, J = 11 Hz), 2.45 (1H, m), 2.07, 2.02, 1.83, 1.14, 1.08, 1.01, 0.93, 0.88, 0.85 (nine singlets representing 3 hydrogens each); m/e 606 (M^+). (Found: C, 67.03; H, 9.02. Calc. for $C_{34}H_{55}O_4Se$: C, 67.30; H, 9.14).

Benzyl N-t-Butoxycarbonylselenomethioninate 16

To a stirred solution of the protected glutamic acid derivative 8 (337 mg, 1 mmole) in dry THF were added, with cooling to -15°C and under nitrogen, N-methylmorpholine (0.11 ml) and isobutylchloroformate (0.14 ml). After 5 min. at this temperature a cooled solution of thiohydroxamic acid 4 (152 mg) and triethylamine (0.17 ml) in dry THF was added. The mixture was stirred in the dark for 20 min. then filtered rapidly. To the filtrate, containing derivative 15, was added dimethyldiselenide (1.86 g) and the mixture irradiated for 20 min. under nitrogen. Normal work-up after dilution with ether and chromatography on silica (dichloromethane-hexane 1:1 then dichloromethane) afforded the title compound 16, a pale yellow oil (300 mg, 78%); $[\alpha]_D^{20}$ -34° (c = 1.1 in methanol); ν_{max} 3350, 1750, 1710 cm^{-1}; δ_H 7.32 (5H, 6s, aromatic H); 5.42 (1H, broad d), 5.14 (2H, s), 4.32 (1H, m), 2.45 (2H, t, J = 7 Hz), 2.12 (2H, m), 1.89 (3H, s), 1.40 (9H, s); m/e 387 (M^+), 386 (M^+ -100). (Found: C, 52.86; H, 6.44; N, 3.74. Calc. for $C_{13}H_{24}NO_4Se$: C, 52.85; H, 6.52; N, 3.63%).

Selenomethionine 1

The benzyl ester 16 (470 mg) was stirred with dilute aqueous sodium hydroxide (0.5 N, 3 ml) in dioxane (5 ml) for 30 min. at room temperature. The dioxane was evaporated and the benzyl alcohol eliminated by extraction with ether. The aqueous phase was acidified with hydrochloric acid (1N) until pH 3 and then extracted with ethyl acetate. The organic phase was washed with brine, dried and concentrated to give acid 17 as an oil (360 mg, 100%) which was kept in a dessicator containing KOH overnight.

This acid was best characterised as its dicyclohexylammonium salt; m.p. 127-129°C; $[\alpha]_D^{20}$ 20.9° (c = 1.1 in DMF) (lit.[3e], m.p. 128.5-130.5°C; $[\alpha]_D^{20}$ 18.0°).

Acid 17 (100 mg) was dissolved in dichloromethane (0.5 ml) and trifluoroacetic acid (0.26 ml). After keeping at room temperature for 30 min., the solution was concentrated in vacuo and the trifluoroacetate salt precipitated with dry ether. The solid was filtered, washed with dry ether then dissolved in a minimum of water and the pH adjusted with ammonia to 5.5. The water was removed in vacuo and the residual solid filtered, washed with absolute ethanol and dried in a vacuum dessicator. It consisted of pure L-selenomethionine (65 mg, 96%); m.p. 275°C (starts decomp. at 253°C); $[\alpha]_D^{20}$ +23.6° (c = 0.5 in 2N HCl); $[\alpha]_D^{20}$ +18.6° (c = 1, 1N HCl); (lit. $[\alpha]_D^{22}$ +17.5° (c = 17.5; 2N HCl)) (Found: C, 30.44; H, 5.45; N, 6.94. Calc. for $C_5H_{11}NO_2Se$: C, 30.62; H, 5.65; N, 7.14%).

S-Benzyl N-t-Butyloxy-2-amino-4-bromobutyrate 18

The preparation of derivative 15 from 8 (3.37 g) followed the procedure described above for the synthesis of the protected selenomethionine 16. After filtration, the solvent was evaporated in vacuo in the dark without heating and replaced by bromotrichloromethane (100 ml). Irradiation for 45 minutes under an inert atmosphere followed by concentration and purification by chromatography on silica (dichloromethane-hexane 1:1, then dichloromethane) gave the bromo derivative 18 as white crystals (3.05 g, 82%); m.p. (from pentane) 53°C; $[\alpha]_D^{20}$ -34° (c = 1 in methanol); ν_{max} 3370, 1770, 1685 cm^{-1}; δ_H 7.42 (5H, broad s); 5.22 (2H, s), 5.1 (1H, broad), 4.47 (1H, m), 3.4 (2H, t, J = 7 Hz), 2.32 (2H, m), 1.45 (9H, s) (Found: C, 51.53; H, 5.96; Br, 21.61; N, 3.85. Calc. for $C_{16}H_{22}BrNO_4$: C, 51.62; H, 5.96; Br, 21.47; N, 3.76%).

Benzyl N-t-Butoxycarbonylselenomethionate 16

To a solution of dimethyldiselenide (531 mg) in ice-cold absolute ethanol (15 ml) was added portionwise, under an inert atmosphere, sodium borohydride (134 mg). The pale yellow solution was stirred for 15 min. at room temperature followed by addition of the bromobutyric acid derivative 18 (876 mg) in a little ethanol. After 30 min., the mixture was diluted with

ether (80 ml) then washed successively with dilute sodium bicarbonate (0.1 N), water and brine. Drying and concentration of the organic phase gave the selenomethionine derivative 16 (844 mg, 93%) identical with the previously prepared sample.

Benzyl N-t-Butoxycarbonyl-3-benzylselenoalaninate 21

To a stirred solution of the protected aspartic acid derivative 19 (323 mg, 1 mmole) in dry THF (5 ml) cooled to -15°C were added, under argon, N-methylmorpholine (0.11 ml) and isobutylchloroformate (0.14 ml). The mixture was stirred for 5 min. then treated dropwise with a cooled solution of thiohydroxamic acid 4 (152 mg) and triethylamine (0.17 ml) in dry THF (3 ml). After 30 min. at -15°C, the precipitated solid was filtered and dibenzyldiselenide[10] (1 g) added to the filtrate which was then irradiated for 30 min. at room temperature under argon. Dilution with ether followed by normal work-up and purification by chromatography on silica (ether-cyclohexane 1:4) gave selenide 21 (300 mg, 70%); m.p. (from ether-pentane) 84.5C°; $[\alpha]_D^{20}$ -45.5° (c = 1 in methanol); ν_{max} 3380, 1760, 1695, 1530 cm^{-1}; δ_H 7.21 (5H, broad s), 7.32 (5H, broad s), 5.32 (1H, broad d), 5.16 (2H, s), 4.62 (1H, m), 3.72 (2H, s), 2.90 (2H, d, J = 5Hz), 1.42 (9H, s) (Found: C, 59.12; H, 6.10; N, 3.19. Calc. for $C_{22}H_{27}NO_4Se$: C, 58.92; H, 6.07; N, 3.12%).

Benzyl N-Benzyloxycarbonyl-3-benzylselenoalaninate 22

This compound was obtained from 20 by the same procedure as for 21 above, in 64% yield. It had a m.p. of 83.5°C (ether-pentane); $[\alpha]_D^{20}$ -42° (c = 1.0 in DMF) (lit.[4d], m.p. 84°C; $[\alpha]_D^{20}$ -39.2°).

General Method for the Preparation of Mixed Anhydrides 24, 26, and 27

A mixture of the acid chloride (10 mmoles) and the sodium salt of N-hydroxy-2-pyridinethione (10.5 mmoles) in dichloromethane (50 ml) were stirred under an inert atmosphere, in the dark (covered with aluminium foil) for 1-2 hrs. A little dry ether was added, the precipitated sodium chloride filtered and the filtrate concentrated in vacuo, in the dark without heating.

The yellow residue was purified by flash chromatography (column wrapped with aluminium foil) eluting with dichloromethane-pentane 1:1 in the case of compounds 24 and 26. Derivative 27 was eluted with ether and obtained as an oil (81%) which was used without further purification.

N-Palmitoxy-2-pyridinethione 24

This was obtained in 82% yield; m.p. 48-55°C dec. (dichloromethane-pentane), $\nu_{max.}$ 1810, 1610 cm^{-1}; δ_H 6.40-8.40 (4H, m), 2.68 (2H, t); m/e 365 (M^+), 321 ($M^+ - CO_2$) (Found: C, 68.96; H, 9.63; N, 4.13; S, 8.58. Calc. for $C_{21}H_{35}NO_2S$: C, 68.99; H, 9.65; N, 3.83; S, 8.77%).

(3,3-Diphenylpropanoyloxy)-2-pyridinethione 26

This was obtained in 77% yield; m.p. (from dichloromethane-pentane) 118-120°C dec.; $\nu_{max.}$ ($CHCl_3$) 1790, 1600 cm^{-1}; δ_H 7.75-6.35 (4H, m), 7.40 (10H, broad s), 4.68 (1H, t, J = 8 Hz), 3.46 (2H, d, J = 8 Hz); m/e 335 (M^+), 291 ($M^+ - CO_2$) (Found: C, 71.40; H, 5.17; N, 4.42; S, 9.84. Calc. for $C_{20}H_{17}NO_2S$: C, 71.61; H, 5.11; N, 4.18; S, 9.56%).

General Procedure for the Synthesis of Selenocyanates 25, 28 and 29

A solution of the mixed anhydride (0.5 mmole) and triselenium cyanide (1 mmol) in dry degassed dichloromethane (10 ml) was irradiated ca. 30 min. under argon. The solvent was then evaporated and the residue purified by chromatography, eluting with dichloromethane- pentane (2:3) in the case of 25 and 28 and dichloromethane in the case of 29.

1-Palmitylselenocyanate 25

This was obtained in 87% yield as a low melting solid; $\nu_{max.}$ ($CHCl_3$) 2150 cm^{-1}; δ_H 3.02 (2H, t); m/e 315, 317 (M^+); 288, 290 ($M^+ - CN$) (Found: C, 60.99; H, 9.98; N, 4.41. Calc. for $C_{16}H_{31}NSe$: C, 60.74; H, 9.88; N, 4.43%).

2,2-Diphenylethylselenocyanate 28

This was obtained in 89% yield as a white crystalline solid; m.p. (from methanol) 70°C; $\nu_{max.}$ ($CHCl_3$) 2155 cm^{-1}; δ_H 7.25 (10H, broad s), 4.33 (1H, broad t, J = 8 Hz), 3.64 (2H, d, J = 8 Hz); m/e 285, 287 (M^+), 167 (Found: C, 62.87; H, 4.76; N, 5.00. Calc. for $C_{15}H_{13}NSe$: C, 62.94; H, 4.58; N, 4.89%).

3β-Acetoxy-11-oxo-23-Selenocyanato-24-norcholane 29

This was obtained in 77% yield as a white crystalline solid; m.p. 138-140°C (hexane); $\nu_{max.}$ ($CHCl_3$) 2155, 1720 cm^{-1}; δ_H 4.65 (1H, m, 3β-H), 2.94 (2H, t, 23-H), 0.95 (3H, s, 19-Me), 0.66 (3H, s, 18-Me); m/e 491, 493 (M^+) (Found: C, 63.69; H, 8.09. Calc. for $C_{26}H_{39}NO_3Se$: C, 63.40; H. 7.98%).

Benzyl N-Benzyloxycarbonyl-3-selenocyanatoalaninate 30

To a solution of aspartic acid derivative 20 (1.07 g) in dry THF cooled to -15°C was added, under argon, N-methylmorpholine (0.33 ml) and isobutylchloroformate (0.42 ml). After 5 min. at this temperature the sodium salt of 4 (536 mg) was added and the mixture stirred at -15°C for 1 hour in the dark. The suspension was then filtered, and the filtrate concentrated in vacuo without heating. The residue was taken up in a little dichloromethane (~ 2ml) and then excess pentane was added to precipitate the crude mixed anhydride. After cooling, the solid was filtered, washed with pentane and used directly for the next step (1.31 g, 94%).

The mixed anhydride (538 mg) in dry, degassed dichloromethane (4 ml) was added to a solution of triselenium cyanide (693 mg) in the same solvent (80 ml). The solution was irradiated for 7 min. at room temperature under argon, concentrated and the residue purified by flash chromatography on silica (dichloromethane) to give the selenocyanate 30 (665 mg, 73%); m.p. 68°C (ether-pentane); $[\alpha]_D^{20}$ -6.4° (c = 0.5 in MeOH); ν_{max} 3320, 2150, 1720 cm^{-1}; δ_H 7.34 (5H, broad s), 7.28 (5H, broad s), 5.92 (1H, broad d), 5.18 (2H, s), 5.08 (2H, s), 4.75 (1H, m), 3.45 (2H, d, J = 6 Hz) (Found: C, 54.69; H, 4.35; N, 6.51. Calc. for $C_{19}H_{18}N_2O_4Se$: C, 54.66; H, 4.34; N, 6.74%).

Dibenzyl N,N'-di(Benzyloxycarbonyl)selenocystinate 31

The above selenocyanate 30 (250 mg) was dissolved in absolute ethanol (10 ml) and treated with excess sodium borohydride. After stirring for ca. 1 min. at room temperature, the mixture was diluted with ether and washed with dilute (0.1 N) aqueous sodium bicarbonate, then with brine. Drying and concentration of the organic phase gave pure diselenide 31 (220 mg, 94%); m.p. (from ether-pentane) 84°C; $[\alpha]_D^{20}$ -62° (c = 1 in methanol), ν_{max} 3320, 1725 cm^{-1}; δ_H 7.37 (5H, broad s), 7.29 (5H, broad s), 5.7 (1H, broad d), 5.14 (2H, s), 5.09 (2H, s), 4.71 (1H, m, J = 6 Hz), 3.35 (2H, d, J = 6 Hz) (Found: C, 55.39; H, 4.78; N, 3.83. Calc. for $C_{36}H_{36}N_2O_8Se_2$: C, 55,24; H, 4.64; N, 3.60%).

Selenocystine 2

The above diselenide 31 (108 mg) was dissolved in 4N hydrobromic acid in acetic acid (0.7 ml). After 2 hours at room temperature, the solution was concentrated in vacuo and the residual solid hydrobromide salt washed with ether. The solid was then taken up in the minimum of water (0.4 ml) and the pH adjusted to 5 with 2N ammonia. The yellow solid produced was filtered and dried by lyophilisation to give selenocystine (36 mg, 84%); m.p. 192°C; $[\alpha]_D^{20}$ -160° (c = 0.5 in 2N HCl) (lit.[4e], m.p. 218°C, $[\alpha]_D^{25}$ -162°).

References

1. T. Stadtman, Adv. in Enzymology, 48, 1 (1979) and references there cited.
2. "Organic Selenium Compounds : Their Chemistry and Biology", ed. D.L. Klayman and W.H.H. Günther, Wiley-Interscience, 1973.
3. a) E.P. Painter, J. Am. Chem. Soc., 69, 232 (1947); b) H. Plieninger, Chem. Ber., 83, 265 (1950); c) G. Zdansky, Ark. Kemi., 19, 559 (1962); d) F. Pan and H. Tarver, Arch. Biochem. Biophys., 119, 429 (1967); e) H.D. Jakubke, J. Fischer, K. Jost and J. Rudinger, Coll. Czech. Chem. Commun., 33, 3910 (1968); f) G.F. Pande, R. Rudick and R. Walter, J. Org. Chem., 35, 1440 (1970).
4. a) E.P. Painter, J. Am. Chem. Soc., 69, 229 (1947); b) L.R. Williams and A. Rauve, J. Am. Chem. Soc., 70, 1244 (1948); c) G. Zdansky, Ark. Kemi., 17, 273 (1961); 29, 443 (1968); d) D. Theodoroupoulos, I.L. Schartz and R. Walter, Tetrahedron Letts., 25, 2411 (1967); e) J. Roy, W. Gordon and R. Walter, J. Org. Chem., 35, 510 (1970).
5. D.H.R. Barton, D. Crich and W.B. Motherwell, J. Chem. Soc., Chem. Commun., 939 (1983); b) D.H.R. Barton, D. Crich and W.B. Motherwell, Tetrahedron Letts., 4979 (1983); c) D.H.R. Barton, D. Crich and G. Kretzschmar, J. Chem. Soc., Perkin Trans 1, 39 (1986) and references there cited; d) D.H.R. Barton, D. Bridon and S.Z. Zard, J. Chem. Soc., Chem. Commun., 1066 (1985); e) D.H.R. Barton, H. Togo and S.Z. Zard, Tetrahedron, 41, 5507 (1985).
6. D.H.R. Barton, Y. Hervé, P. Potier and J. Thierry, J. Chem. Soc., Chem. Commun., 1298 (1984); D.H.R. Barton, D. Crich, Y. Hervé, P. Potier and J. Thierry, Tetrahedron, 41, 4347 (1985).
7. D.H.R. Barton, D. Bridon and S.Z. Zard, Tetrahedron Letts., 25, 5777 (1984); idem, Heterocycles, submitted for publication.
8. L.B. Agenäs, Acta Chem. Scand., 17, 268 (1963); H.P. Kaufmann and F. Kogler, Chem. Ber., 59, 178, 185 (1926).
9. S. Hange, Acta Chem. Scand., 25, 3081 (1971).
10. L. Syper and J. Myochowski, Synthesis, 439 (1984).