A Facile Synthesis of 2- and 3-Hydroxyalkylseleno Compounds

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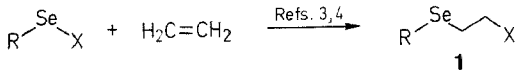
2-Hydroxyethylseleno and 3-hydroxypropylseleno compounds (selenides **6**–**9**) have been prepared in good yields employing 2-hydroxyethyl and 3-hydroxypropyl selenocyanates (**4** and **5**). Several types of electrophilic substrates that reacted with the selenolate anions generated from **4** and **5** *in situ* in the presence of sodium borohydride included alkyl, benzylic, activated aromatic, benzoyl, and picolinyl halides.

2-Hydroxyalkyl selenides are useful intermediates for the synthesis of a variety of functionalized molecules, such as allyl alcohols, epoxides, olefins, and α,β-unsaturated carbonyl compounds. Methods of preparing 2-hydroxyalkyl selenides and their reactions have been reviewed.[1,2] Our interest in 2-hydroxyalkyl selenides, specifically 2-hydroxyethyl selenides, is associated with development of organoselenium alkylating agents as antineoplastics, analogues of nitrogen and sulfur mustards.

We have recently reported kinetic studies and cytotoxicities of 2-haloethyl aryl selenides and bis(2-chloroethyl) selenides.[3] 2-Hydroxyethyl selenides are immediate precursors to organoselenium alkylating agents $RSeCH_2CH_2X$ (**1**) where R is an organic carrier and X a leaving group. Although 2-haloethyl selenides can be prepared by organoselenenyl halides (RSeX) with



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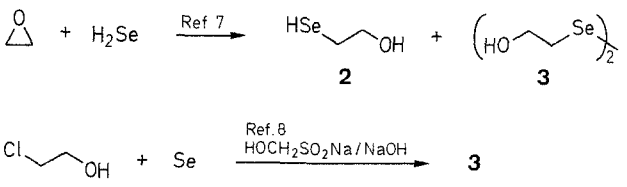
Scheme **A**

ethylene (Scheme **A**)[3,4] without involving the corresponding hydroxy intermediates, this approach has limitations. In particular, the choice of leaving group for the selenenyl halides is limited to bromide and chloride, and the organic carriers (R) are mostly restricted to aromatic moieties. Another drawback is that the reaction may result in diselenide by-products, which are known to be cytotoxic,[3,5] due to a further reaction of 2-haloethyl selenide with RSeX.[6] In addition, we were unsuccessful in an attempt to prepare 2-chloroethyl benzyl selenide by this reaction (dibenzyl diselenide was treated with sulfuryl chloride and then ethylene gas at room temperature). These considerations prompted us to develop a more general method of synthesizing 2-hydroxyethyl selenides, which then can be easily converted into organoselenium alkylating agents.

The present report describes a facile method of preparing 2-hydroxyethyl selenides utilizing 2-hydroxyethyl selenocyanate. The versatility of this approach is shown by the analogous synthesis of the homologs, 3-hydroxypropyl selenides, employing 3-hydroxypropyl selenocyanate.

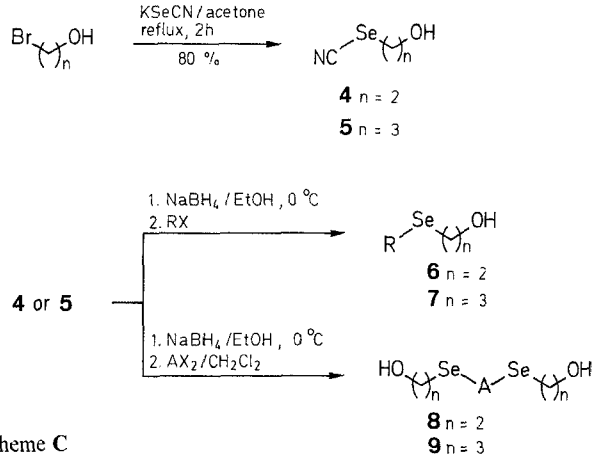
Two previous communications (Scheme **B**)[7,8] have dealt with 2-hydroxyethylseleno compounds; 2-hydroxyethylselenol $HOCH_2CH_2SeH$ (**2**) and its corresponding diselenide $HOCH_2CH_2Se\text{-}SeCH_2CH_2OH$ (**3**). The 2-hydroxyethyl selenolate anion, a key intermediate for nucleophilic substitution reactions with electrophilic substrates to give 2-hydroxyethyl selenides, can be generated by treatment of **2** with a base or **3** with sodium borohydride. The method[7] using ethylene oxide and hydrogen selenide involves reaction in a sealed ampoule at room temperature for 100 h; this reaction gives only 38% of **2** and 12% of **3**. The second method[8] amalgamates sodium hydroxymethanesulfinate, sodium hydroxide, elemental selenium and 2-chloroethanol at room temperature for 5 h, and yields only 39% of **3** after distillation.



Scheme **B**

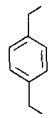
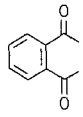
Our present method involves reaction of 2-bromoethanol with potassium selenocyanate in boiling acetone for 2 h to give 2-hydroxyethyl selenocyanate (**4**) in 80% yield. A similar yield of 3-hydroxypropyl selenocyanate (**5**) is obtained from the reaction of 3-bromo-1-propanol with potassium selenocyanate under the same conditions as for **4**. The selenocyanates **4** and **5** are converted *in situ* in the presence of sodium borohydride to

the corresponding selenolate anions, which react with electrophilic substrates to yield 2-hydroxyethyl and 3-hydroxypropyl selenides, respectively, as shown in Scheme **C**.



Scheme **C**

6	R	X	7	R	X
a	C_2H_5	Br	a	$C_6H_5CH_2$	Cl
b	2,4-$(NO_2)_2C_6H_3$	F	b	3-pyridyl-CH_2	Cl
c	$C_6H_5CH_2$	Cl			
d	$C_2H_5O_2CCH_2$	Br			
e	C_6H_5CO	Cl			

	A	X		A	X
8a		Br	9a		Br
8b		Cl			
8c		Cl			

The isolated yields of more than 70% for the hydroxyalkyseleno compounds, except for **6b** and **8c** indicate that the reactions of the selenocyanates **4** and **5** with electrophilic substrates in the presence of sodium borohydride give almost quantitative formation of the products in a 30 min reaction period. The relatively low yield of **6b**, obtained from 2,4-dinitrofluorobenzene and **4**, was partly due to formation of the by-product bis(2,4-dinitrophenyl) diselenide (10%).[9]

It should be mentioned that the carbonyl stretching absorption of the selenoester **6e** is observed at 1665 cm^{-1}, ca. 60 cm^{-1} low that (1727 cm^{-1}) of ethyl benzoate.[10] The low carbonyl frequency of **6e** is expected, because replacement of the more electronegative oxygen atom of a carboxylic ester by sulfur reduces the carbonyl frequency by ca. 40 cm^{-1}.[11] The measured value of **6e** is in reasonable agreement with the carbonyl frequency (1675 cm^{-1}) of *n*-butyl selenobenzoate.[12] In the ^{1}H-NMR of the *para*-substituted diol **8b**, which has poor solubility in chloroform and acetone, the alcoholic protons exhibit a triplet at 4.72 ppm in DMSO-d_6, somewhat downfield compared to that (3.00 ppm) of the *ortho*-substituted isomer **8a** taken in $CDCl_3$.[13] This suggests that the hydroxylic protons on **8b** hydrogen-bond with dimethyl sulfoxide. Also the protons on the CH_2 groups carrying the hydroxy moieties in **8b** display an unsymmetrical triplet compared with the *ortho*-isomer **8a**, which may be a combined effect of the AA'BB' splitting pattern and a slow exchange of OH protons in dimethyl sulfoxide.

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR4240 or IR4210 spectrophotometer, and ^{1}H-NMR spectra were obtained with a Hitachi Perkin-Elmer high resolution 60 MHz R 24 NMR spectrometer using TMS as internal standard. Mass spectral data were taken at 200 eV with a Hewlett Packard GC/MS 5985 A equipped with dual EI/CI. The elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN, and MicAnal Organic Analysis, Tucson, AZ.

2-Hydroxyethyl Selenocyanate (4):
Potassium selenocyanate (1.44 g, 10 mmol) dissolved in acetone (20 mL) is added dropwise to a solution of 2-bromoethanol (Aldrich, 95% purity; 0.9 mL, 12 mmol) at room temperature. The mixture is gently refluxed for 2 h yielding a white precipitate. After filtering off the solid, the filtrate is concentrated and distilled at reduced pressure to give **4** as a slightly pale yellow liquid; yield: 1.2 g (80%); bp 102–105 °C/0.6–0.8 Torr.

C_3H_5NOSe calc. C 24.01 H 3.36
(150.0) found 23.80 3.45

IR (neat): ν = 3600–3100 (broad, OH), 2160 cm^{-1} (SeCN).

^{1}H-NMR ($CDCl_3$): δ = 3.23 (t, 2 H, J = 9 Hz, CH_2SeCN); 3.63 (s, 1 H, OH); 3.98 (t, 2 H, J = 9 Hz, $C\underline{H}_2OH$).

3-Hydroxypropyl Selenocyanate (5):
The same procedure as for **4** is followed: the reaction of potassium selenocyanate (1.44 g, 10 mmol) with 3-bromo-1-propanol (Eastman, practical grade; 1.13 mL, 12 mmol, based on 95% purity) yields **5** as a pale yellow liquid; yield: 1.32 g (80%); bp 110–116 °C/0.5–0.8 Torr.

C_4H_7NOSe calc. C 29.28 H 4.30
(164.1) found 29.50 4.11

IR (neat): ν = 3650–3100 (broad, OH), 2157 cm^{-1} (SeCN).

^{1}H-NMR ($CDCl_3$): δ = 2.08 (quint., 2 H, J = 9 Hz, $CH_2C\underline{H}_2CH_2$); 3.17 (t, 2 H, J = 10 Hz, CH_2SeCN); 3.37 (s, 1 H, OH); 3.65 (t, 2 H, J = 9 Hz, $C\underline{H}_2OH$).

2-Hydroxyethylseleno Compounds 6a–e; General Procedure:
To a solution of 2-hydroxyethyl selenocyanate (**4**; 153 mg, 1 mmol) in absolute EtOH at 0 °C is added $NaBH_4$ (2 mmol or more) in a nitrogen atmosphere until the solution is colorless. Immediately after the ethanolic mixture turns colorless the appropriate electrophile (1.25 mmol) is added at 0 °C through a dropping funnel. In all cases the reaction time is no longer than 30 min. The reaction is stopped by addition of (1.0 mL) water. The solution is then concentrated at reduced pressure. The residue is transferred into a separatory funnel with the aid of brine and CH_2Cl_2 and then extracted with CH_2Cl_2 (5 × 10 mL). The combined organic layer is dried (Na_2SO_4) and concentrated to dryness at reduced pressure. The residue is purified by a column chromatograph of silica gel (25 cm × 1.1 cm; 60–200 mesh) using $CHCl_3$/EtOAc as eluent except for dinitro compound **6b**, which is recrystallized from EtOAc/*n*-hexane based on the literature method.[9]

Ethyl 2-hydroxyethyl selenide (**6a**) is obtained as a colorless and malodorous liquid; yield: 118 mg (77%).

$C_4H_{10}OSe$ calc. C 31.38 H 6.58
(153.1) found 31.30 6.59

^{1}H-NMR ($CDCl_3$): δ = 1.42 (t, 3 H, J = 10 Hz, CH_3); 2.40–2.90 [m, 4 H, overlapping between 2.54 (q, 2 H, J = 10 Hz, $CH_3C\underline{H}_2Se$) and 2.75 (t, 2 H, J = 9 Hz, $SeC\underline{H}_2CH_2OH$)]; 3.08 (s, 1 H, OH); 3.78 (t, 2 H, J = 10 Hz, $HOC\underline{H}_2$).

2,4-Dinitrophenyl 2-hydroxyethyl selenide (**6b**) is obtained as an orange solid; yield: 140 mg (48%); mp 102.5–104 °C (Lit.[9] mp 104–104.5 °C).

^{1}H-NMR (acetone-d_6): δ = 3.32 (t, 2 H, J = 10 Hz, CH_2Se); 4.02 (t, 2 H, J = 10 Hz, $C\underline{H}_2OH$); 4.25 (s, 1 H, OH); 7.90–8.20 (d, 1 H, J = 12 Hz, H-6); 8.20–8.50 (dd, 1 H, J = 12, 4 Hz, H-5); 8.85 (d, 1 H, J = 3 Hz, H between NO_2 groups).

Benzyl 2-hydroxyethyl selenide **(6c)** is obtained as a colorless liquid; yield: 194 mg (90%).

$C_9H_{12}OSe$ (215.2) calc. C 50.24 H 5.62 found 49.90 5.40

MS (CI): m/z = 216 (Se^{80}, M^+, 63.6%), 199 ($M^+ - 17$, 100%).

^{1}H-NMR ($CDCl_3$): δ = 2.40 (s, 1H, OH); 2.65 (t, 2H, J = 9 Hz, $OCH_2C\underline{H}_2Se$); 3.53–3.83 (m, 4H, benzylic CH_2 overlapped with the downfield peak of CH_2O triplet); 7.23 (s, 5 H_{arom}).

Ethyl (2-hydroxyethylseleno)acetate **(6d)** is obtained as a colorless liquid; yield: 158 mg (75%).

$C_6H_{12}O_3Se$ (211.1) calc. C 34.13 H 5.73 found 34.01 5.79

MS (CI): m/z = 213 (Se^{80}, $M^+ + 1$, 18%), 195 ($M^+ - 17$, 100%).

IR (neat): ν = 3600–3060 (broad, OH), 1722 cm^{-1} (C=O).

^{1}H-NMR ($CDCl_{13}$): δ = 1.27 (t, 3H, J = 11 Hz, CH_3); 2.85 (t, 2H, J = 10 Hz, $SeC\underline{H}_2CH_2OH$); 3.18 (s, 2H, $SeCH_2CO$); 3.70–4.00 (m, 3H, singlet of OH overlapped with triplet of CH_2O protons); 4.16 (q, 2H, J = 11 Hz, CO_2CH_2).

Se-(2-Hydroxyethyl) selenobenzoate **(6e)** is obtained as a colorless viscous liquid; yield: 179 mg (78%).

$C_9H_{10}O_2Se$ (229.1) calc. C 47.17 H 4.40 found 47.48 4.34

MS (CI): m/z = 231 (Se^{80}, $M^+ + 1$, 6.0%), 105 [$M^+ - 125$ ($SeCH_2CH_2OH$), 100%].

IR (neat): ν = 3650–3000 (OH), 1665 cm^{-1} (Se–C=O).

^{1}H-NMR ($CDCl_3$): δ = 3.16 (t, 2H, J = 10 Hz, $OCSeCH_2$); 3.50 (s, 1H, OH); 3.79 (t, 2H, J = 10 Hz, $SeCH_2C\underline{H}_2OH$); 7.00–7.85 (m, 5 H_{arom}).

3-Hydroxypropyl Selenides 7a, b:

General Procedure above is followed, replacing **4** with 3-hydroxypropyl selenocyanate (**5**; 165 mg, 1 mmol).

Benzyl 3-hydroxypropyl selenide **(7a)** is obtained as a colorless viscous liquid; yield: 186 mg (81%).

$C_{10}H_{14}OSe$ (229.2) calc. C 52.41 H 6.16 found 52.25 6.06

MS (CI): m/z = 230 (Se^{80}, M^-, 74.1%) 121 ($M^+ - 109$, 100%).

^{1}H-NMR ($CDCl_3$): δ = 1.75 (quint, 2H, J = 10 Hz, $CH_2C\underline{H}_2CH_2OH$); 2.47 (t, 2H, J = 10 Hz, $SeC\underline{H}_2CH_2CH_2$); 3.00 (s, 1H, OH); 3.56 (t, 2H, $SeCH_2CH_2C\underline{H}_2OH$); 3.71 (s, 2H, $C_6H_5C\underline{H}_2Se$); 7.19 (s, 5 H_{arom}).

3-(3-Hydroxypropylseleno)methylpyridine **(7b)**: The reaction of 3-chloromethylpyridinium chloride,[14] prepared from 3-pyridylmethanol and thionyl chloride, with **5** in EtOH in the presence of $NaBH_4$ gives **7b** as a pale yellow viscous liquid; yield: 184 mg (80%).

$C_9H_{13}NOSe$ (230.2) calc. C 46.97 H 5.69 found 46.69 5.60

^{1}H-NMR ($CDCl_3$): δ = 1.90 (quint, 2H, J = 10 Hz, $CH_2C\underline{H}_2CH_2OH$); 2.61 (t, 2H, J = 10 Hz, $SeC\underline{H}_2CH_2CH_2OH$); 3.51–3.92 (m, 4H, $C\underline{H}_2OH$ and $PyCH_2Se$); 4.69 (s, 1H, OH) 7.01–8.58 (m, 4 H_{arom}).

Bis(2-hydroxyethylseleno) Compounds 8a–c:

α,α-Dibromo-*o*-xylene (264 mg, 1 mmol) in CH_2Cl_2 (3 mL) for **8a**, α,α'-dichloro-*p*-xylene (175 mg, 1 mmol) in CH_2Cl_2 (3 mL) for **8b**, or phthaloyl dichloride (203 mg, 1 mmol) in dichloromethane (5 mL) for **8c** is added dropwise into a solution of **4** (322 mg, 2.1 mmol) treated with $NaBH_4$ (3 mmol or more) in EtOH (10 mL) at 10°C. After 30 min of stirring, the reaction is quenched by addition of water (1 mL). The reaction mixture is concentrated at reduced pressure, and then the residue is extracted with $CHCl_3$ (5 × 10 mL) in the presence of water (10 mL) and brine (10 mL). The combined $CHCl_3$ extracts are dried (Na_2SO_4) and concentrated at reduced pressure.

α,α-Bis(2-hydroxyethylseleno)-o-xylene **(8a)** is obtained as a waxy solid by a silica gel column chromatography (25 cm × 1.1 cm; 60–200 mesh) using $CHCl_3$/EtOAc (1:2, v/v) as eluent; yield: 300 mg (85%); mp 35.5–37.0°C.

$C_{12}H_{18}O_2Se_2$ (352.18) calc. C 40.92 H 5.15 found 41.01 5.08

^{1}H-NMR ($CDCl_3$): δ = 2.73 (t, 4H, J = 10 Hz, $SeC\underline{H}_2CH_2OH$); 3.00 (s, 2H, OH); 3.75 (t, 4H, J = 10 Hz, $SeCH_2C\underline{H}_2OH$); 3.98 (s, 4H, $C\underline{H}_2SeCH_2CH_2OH$); 7.23 (5, 4 H_{arom}).

α,α'-Bis(2-hydroxyethylseleno)-p-xylene **(8b)** is obtained as a fluffy white solid by recrystallization from *n*-hexane/EtOAc (1:3, v/v): yield: 303 mg (86%); mp 101–103°C.

$C_{12}H_{18}O_2Se_2$ (352.18) calc. C 40.92 H 5.15 found 40.99 5.09

^{1}H-NMR (DMSO-d_6): δ = 2.53 (t, 4H, J = 10 Hz, $SeC\underline{H}_2CH_2OH$); 3.50 (t, 4H, J = 10 Hz, $SeCH_2C\underline{H}_2OH$); 3.76 (s, 4H, $C\underline{H}_2SeCH_2CH_2OH$); 4.72 (t, 2H, J = 8 Hz, OH); 7.17 (s, 4 H_{arom}).

Se,Se-Bis(2-hydroxyethyl) diselenophthalate **(8c)** is obtained as a white solid by recrystallization from $CHCl_3$/*n*-hexane (2:1, v/v); yield: 209 mg (55%); mp 86–87°C.

$C_{12}H_{14}O_4Se_2$ (380.15) calc. C 37.91 H 3.71 found 37.64 3.59

^{1}H-NMR (acetone-d_6): δ = 3.19 (t, 4H, J = 10 Hz, $SeCH_2$); 3.85 (t, 4H, J = 10 Hz, $C\underline{H}_2OH$); 4.04, (s, 2H, OH); 7.73 (s, 4 H_{arom}).

α,α'-Bis(3-hydroxypropylseleno)-*o*-xylene (9a):

The same procedure as for **8a** is applied except that the selenocyanate **4** is replaced by 3-hydroxypropyl selenocyanate (**5**; 165 mg, 1 mmol). Silica gel column chromatography (2.5 cm × 1.1 cm; 60–200 mesh) of the crude product eluted with EtOAc/$CHCl_3$ (1:1, v/v) gives **9a** as a viscous liquid; yield: 327 mg (86%).

$C_{14}H_{22}O_2Se_2$ (380.24) calc. C 44.22 H 5.83 found 43.97 5.78

^{1}H-NMR ($CDCl_3$): δ = 1.87 (quint, 4H, J = 10 Hz, $CH_2C\underline{H}_2CH_2OH$); 2.61 (t, 4H, J = 10 Hz, $SeC\underline{H}_2CH_2CH_2OH$); 3.08 (s, 2H, OH); 3.59 (t, 4H, J = 9 Hz, $C\underline{H}_2OH$); 3.90 (s, 4H, $C_6H_4C\underline{H}_2Se$); 7.08 (s, 4 H_{arom}).

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