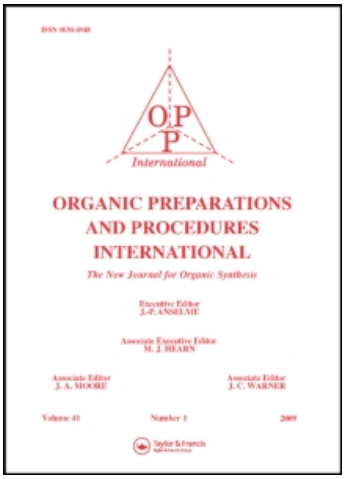

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SYNTHESIS AND SINGLE CRYSTAL X-RAY DIFFRACTION CHARACTERIZATION OF [2-AMINO-N-(2,6-DIMETHYLPHENYL)-ACETAMIDATO-N²] DICHLOROETHYLSELENIUM, A SELENIUM-CONTAINING LIDOCAINE MIMIC

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SYNTHESIS AND SINGLE CRYSTAL X-RAY DIFFRACTION CHARACTERIZATION OF [2-AMINO-N-(2, 6-DIMETHYLPHENYL)-ACETAMIDATO-N2] DICHLOROETHYLSELENIUM, A SELENIUM-CONTAINING LIDOCAINE MIMIC

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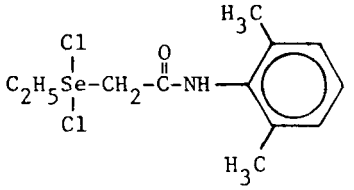
Lidocaine is an antiarrhythmic drug and one of the most clinically employed for the treatment of arrhythmias especially in cases of sudden cardiac disorders.[1] Since ^{75}Se is radioactive, it is conceivable that lidocaine mimic containing such a label might be potentially useful for tracer studies.[2,3] Therefore, we report herein the first synthesis of such a model system, namely [2-amino-*N*-(2,6-dimethylphenyl) acetamidato-*N*2]-chloroethylselenium (**1**). Mimic **1** resembles lidocaine (**2**) except for the fact that the former only has one ethyl group and is a salt which enhances aqueous solubility. The synthesis is outlined below. In general, the procedure is relatively easy to perform but, of course, all precautions were



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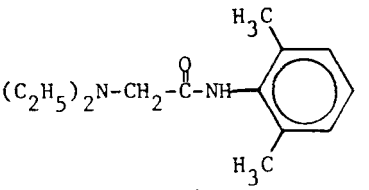

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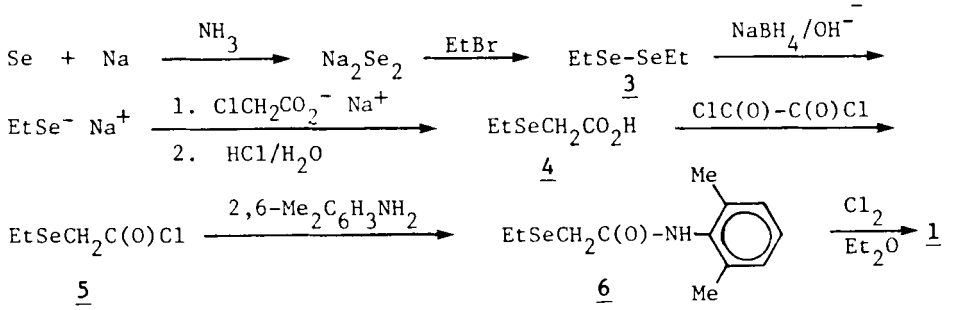
utilized for safety since it was presumed all compounds produced were potentially hazardous to some degree. The mimic **1** is a beautifully crystalline solid.



In view of the scarcity of selenium-containing relatives of **1**, it was deemed useful to obtain an X-ray diffraction analysis of the crystal in order to confirm the structure and to serve as a reference source for others.[4] The coordination about the selenium atom in **1** is trigonal bipyramidal in which the free electron pair occupies one of the positions in the basal plane. This seems to agree with previously found structures of selenium bound with chlorine[5-9] and with bromine[10-12] with a coordination number of four. Bond distances, bond angles, and torsion angles are given in Tables 1 and 2. The deviation of the C-Se-C angle from the ideal value of 180° is only 1.1°. The C-Se-C angles differ from 90° by less than 2°. The C-Se-C angle was found to be 104.4(4)° which compares with 106.5° and 108° for di-p-tolylselenium dichloride and dibromide, respectively.[6] The Se-C distances of 2.359(2) Å and 2.389(2) Å agree with those previously found.[6,9] The Se-C distances were found to be 1.972(9) Å [Se(1)-C(16)] and 1.942(7) Å [Se(1)-C(15)]. The latter seems somewhat short compared to the distances in similar compounds[6,9] as well as the weighted average distance in related non-aromatic compounds [1.98(2) Å].[13] The on-planarity of the amide group is described according to Winkler and Dunitz[14] χ_C = -0.5(10)°, τ = 174(4)°, χ_N = -21(4)°. Intermolecular hydrogen bonding occurs between O(5) and N(4) in separate molecules. The O...N distance is 2.949(10) Å and the O...H distance is 1.98(11) Å while the O-H-N angle is 165(7)°. There seems to be some strain in the molecule caused by the tendency of the amide group to align itself to allow for the best H-bonding on one hand and by the packing forces on the other hand. The angle between the plane of the C-Se-C bonds and the amide group is 21°, and the angle between the amide group and the plane of the six-membered ring is 60°.

Table 1. Bond Distances (λ and Bond Angles (°) in 1

Se(1) - Cl (2)	2.359(2)	Se(1) - C(15) - C(14)	106.2(6)
Se(1) - Cl(3)	2.389(2)	Se(1) - C(16) - C(17)	109.3(8)
Se(1) - C(15)	1.942(7)	Cl(2) - Se(1) - C(15)	89.3(2)
Se(1) - C(16)	1.972(9)	Cl(2) - Se(1) - C(16)	90.2(2)
N(4) - C(6)	1.445(9)	Cl(3) - Se(1) - C(15)	91.8(2)
N(4) - C(14)	1.342(10)	Cl(3) - Se(1) - C(16)	89.4(2)
0(5) - C(14)	1.216(12)	N(4) - C(6) - C(7)	129.7(5)
C(6) - C(7)	1.413(9)	N(4) - C(6) -(11)	117.1(6)
C(6) - C(11)	1.400(9)	N(4) - C(14) - 0(5)	126.0(8)
C(7) - C(8)	1.396(10)	N(4) - C(14) - C(15)	113.5(8)
C(7) - C(13)	1.499(10)	0(5) - C(14) - C(15)	120.5(7)
C(8) - C(9)	1.384(10)	C(6) - N(4) - C(14)	120.9(7)
C(9) - C(10)	1.367(11)	C(6) - C(7) - C(8)	116.5(6)
C(10) - C(11)	1.404(10)	C(6) - C(7) - C(13)	122.2(6)
C(11) - C(12)	1.487(11)	C(6) - C(11) - C(10)	117.4(6)
C(14) - C(15)	1.517(11)	C(6) - C(11) - C(12)	121.7(7)
C(16) - C(17)	1.488 (13)	C(7) - C(8) - C(9)	120.9(7)
		C(8) - C(7) - C(13)	121.2(6)
		C(8) - (C(9) -C(10)	121.7(7)
		C(9) - C(10) - C(11)	120.3(7)
		C(10 - C(11) - C(12)	120.9(7)

Table 2. Torsion Angles in 1

Se(1) - C(15) - C(14) - N(4)	158.1(5)
C(6) - N(4) - C(14) - C(15)	-175.5(5)
C(7) - C(6) - N(4) - C(14)	-67.8(8)
C(11) - C(6) - N(4) - C(14)	110.3(8)
C(14) - C(15) - Se(1) - C(16)	-169.9(5)
C(15) - Se(1) - C(16) - C(17)	-176.7(6)

Crystallographic Data for 1

Mol formula:	$C_{12}H_{17}NCSl_2OSe$	radiation:	MoKα
M_r:	351	standards:	3 measured every 200 reflections
Linear Absorp. Coeff:	28.26		
space group:	$P2_1$	structure soln:	Patterson synthesis
cell dimensions:		final refinement:	Full matrix
a, Å	13.622(10)	wt scheme:	$\omega = \sigma (F)^{-2}$
b, Å	4.733(3)		
c, Å	12.284(8)	temp data coll:	138 ± 2 K
α, deg	90.	no. reflect meas:	1688
β, deg	113.36(4)	no. reflect obs:	1388
γ deg	90.		
volume, A^3 :	727	criteria for obs:	I>2θ (I)
cell detern proced:	48 reflections	final R	0.038
		Rω	0.039
Z	2	refine. of hydro:	isotropic
density(Calcd), g/cm^3:	1.56	final diff.. Four. map max density	
recsryst solvent:	ether	e/$Å^3$:	0.5
data collect range, deg:	0<2θ< 53		
scan, scan time:	θ–2θ 90 s		

EXPERIMENTAL SECTION

All reactions were performed under nitrogen and in a good hood. Residues from all reactions were destroyed by adding bleach. All effluents from reactions were trapped via the use of alcoholic KOH. *CAUTION; GLOVES SHOULD BE WORN AT ALL TIMES IN HANDLING THE SELENIUM COMPOUNDS AND ALL MATERIALS SHOULD BE CONSIDERED POTENTIALLY TOXIC.* No danger was encountered when the above technique was applied and no odors could be detected. All melting points were taken on a Thomas-Hoover apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer 681 as KBr pellets or films. All ^{1}H, ^{13}C and ^{77}Se NMR spectra were recorded on a Varian XL-300 spectrometer at 299.99, 75.4, and 57.22 MHz, respectively. A few ^{13}C NMR spectra were also recorded on a Varian XL-100 (15) unit at 25.20 MHz. Chemical shifts are measured in ppm downfield for ^{13}C (from TMS) and for ^{77}Se [from $(H_3C)_2Se$ (0 ppm) using $(C_6H_5Se)_2$ (481.0 ppm) as the external, secondary reference][15] Chemical shifts for ^{1}H were δ values (from TMS). Elemental analyses were performed by Galbraith Labs, Knoxville, TN.

Diethyl Diselenide (3).- Ammonia (500 mL) was condensed into a 1-ℓ, round-bottomed flask equipped with a gas inlet and a Dry Ice condenser. Freshly-cut sodium metal (8.0 g, 348 mmol) was added to the ammonia in small pieces over a 30-min period to give a dark blue solution. After 30 min, selenium metal (27.7 g, 350 mmol) was then added slowly in 5-g portions over 1 hr. During the addition, the dark blue color of the solution turned progres-sively to purple, light pink, light brown, and finally to a very dark green; at that point, the mixture was stirred for an additional hour. Ethyl bromide (90 g, 830 mmol) was added drop-wise over 1 hr. The ammonia was allowed to evaporate overnight, and the residue was taken up in ether (350 mL). The ethereal solution was washed with water (50 mL) and dried (K_2CO_3). Evaporation and distillation of the residue gave **3** as an orange oil (36.0 g, 48%), bp. 60-70°C/5 mm Hg, lit.[16] bp. 75°C/14 mm Hg:
^{1}H NMR ($DCCl_3$): δ 1.46 [t, 6 H, H(2), J = 7.5 Hz], 2.90 [q, 4 H, H(1), J = 7.43 Hz];
^{13}C NMR ($DCCl_3$): ppm 16.4 [C(2)], 23.0 [t, C(1)].

3-Selenavaleric Acid (4). - A solution of diethyl diselenide (**3**, 25.0 g, 115 mmol) in 95% ethanol (35 mL) was placed in a flask equipped with a condenser and two addition funnels

with one carrying a nitrogen inlet. A solution on NaOH (5.0 g, 217 mmol) and $NaBH_4$ (10.0 g, 265 mmol) in water (80 mL) was added dropwise. The resulting solution was heated to boiling and then stirred at reflux until the orange color disappeared (1 hr). After cooling to at 0°C in an ice bath, a solution of $ClCH_2CO_2H$ (21.8 g, 229 mmol) and Na_2CO_3 (12.2 g, 114 mmol) in water (75 mL) was added dropwise. After stirring at room temp for 18 hrs, the mixture was cooled to 0°C, acidified with conc. HCl (ca 40 mL), and extracted with ether (4 x 50 mL). The combined extracts were washed with water (50 mL) and dried (Na_2SO_4). Evaporation of the ether gave a light yellow oil and a white solid. The solid was removed by filtration and the oil was distilled to give acid **4** as a light yellow oil (29.2 g, 76%), bp: 89-94°C/1.0 mm Hg, lit [17] bp. 85-86°C/0.6 mm Hg: ^{1}H NMR ($DCCl_3$): δ 1.43 [t, 3 H, H(5), J = 7.5 Hz], 2.80 [q, 2 H, H(4), J = 7.5 Hz]. 3.19 [s, 2 H, H(2)], 11.77 [s, 1 H, CO_2H]; ^{13}C NMR ($DCCl_3$): ppm 15.1 [C(5)], 19.3 [C(4)], 21.4 [C(2)], 178.4 [C(1)]; ^{77}Se NMR ($DCCl_3$): ppm 96.29 [Se(3)].

3-Selenavaleryl Chloride (5).- A two-necked flask equipped with a magnetic stirrer unit and condenser was charged with oxalyl chloride (7.30 g, 56.7 mmol). 3-Selenavaleric acid (**4**, 4.75 g, 28.3 mmol) was added cautiously with cooling. Once the initial, vigorous reaction had subsided, the solution was heated to reflux and stirred at this temp for 4 hrs. The flask was then altered for vacuum distillation and excess oxalyl chloride was distilled under aspirator vacuum. The residual oil was distilled under high vacuum to give 5 as a light yellow oil (4.0 g, 76%), bp. 25-33°C/0.25 mm Hg, lit[17] bp. 75-76 °C/15 mm Hg: ^{1}H NMR ($DCCl_3$): δ 1.44 [t, 3 H, H(5), J = 6 Hz], 2.83 [q, 2 H, H(4), J = 6 Hz], 3.64 [s, 2 H, H(2)]; ^{13}C NMR ($DCCl_3$): ppm 14.9 [C5)], 19.7 [C(4)], 33.1 [C(2)], 169.8 [C(1)]; ^{77}Se NMR ($DCCl_3$): ppm 5.06 [Se(3)].

3-Selenavalero-o-xylide (6). - The acid chloride **5** (4.00 g, 21.6 mmol) was dissolved in anhydrous ether (70 mL). The solution was cooled (0°C, ice bath) and 2,6-dimethylaniline (5.30 g, 43.8 mmol) was added dropwise with swirling. A dense, white precipitate formed immediately and the resulting mixture was allowed to stand at room temp with occasional swirling for 1 hr. Solid 2,6-dimethylaniline hydrochloride was filtered and ice-water (100

mL) was added cautiously. Two layers separated and the aqueous layer was extracted (ether, 2 x 75 mL). The combined ether portions were dried (K_2CO_3) and then evaporated to give **6** as white needles (4.12 g, 71%), mp. 93.0-94.0°C:
^{1}H NMR ($DCCl_3$): δ 1.38 [t, 3 H, H(5), J = 8.5 Hz], 2.13 [s, 6 H, ArC<u>H</u>$_3$] 2.70 [q, 2 H, H(4), J = 7.5 Hz], 3.28 [s, 2 H, H(2)], 6.97 [m, 3 H, ArH], 7.90 [b s, 1 H, N-<u>H</u>]; ^{13}C NMR ($DCCl_3$): ppm 15.3 [C(5)], 18.3 [Ar<u>C</u>H$_3$], 19.2 [C(4)], 25.5 [C(2)], 127.2 [C(4')], 128.1 [C 3', 5')], 133.6 [C(2',6')], 135.1 [C (1')], 168.2 [C(1)].

<u>Anal</u>. Calcd. for $C_{12}H_{17}NOSe$: C, 53.31; H, 6.34; N, 5.19; Se, 29.23
Found: C, 53.06; H, 6.45; N, 5.10; Se, 29.44

<u>[α-Amino-*N*-(2,6-dimethylphenyl) acetamidato-*N*^{2}]dichloroethylselenium (1).</u> - The amide **6** (0.5 g, 1.80 mmol) in anhydrous ether (100 mL) was placed in a standard flask. Chlorine gas was bubbled through the solution and a precipitate formed immediately. The addition was continued until precipitation of solid ceased. Filtration of the solid gave the dichloride **1** as a white crystalline material (0.48 g, 78%), mp. 142.0-143.0°C (dec);
^{1}H NMR ($DCCl_3$): δ 1.74 [t, 3 H, H(5)], 2.50 [s, 6 H, ArC<u>H</u>$_3$], 3.98 [q, 2 H, H(4)], 4.36 [b s, 2 H, H(2)], 7.40 [m, 3 H, Ar<u>H</u>], 9.98 [b s, 1 H, N-<u>H</u>]; ^{13}C NMR ($DCCl_3$): ppm 10.2 [C(5)], 18.3 [Ar<u>C</u>H$_3$], 53.9 [C(4)], 62.8 [C(2)], 126.8 [C(4')], 127.7 [C(3',5')], 133.9 [C(1')], 134.9 [C(2',6')], 161.9 [C(1)]; ^{77}Se NMR ($DCCl_3$): ppm 390.06 [Se(3)].

<u>Anal</u>. Calcd. for $C_{12}H_{17}Cl_2NOSe$: C, 42.22; H, 5.01; N, 4.11; Cl, 20.79; Se, 23.15
Found: C, 42.26; H, 4.96; N, 4.06; Cl, 20.68; Se, 22.99

<u>Experimental for X-ray Data Collection for **1**.</u> - A crystal of **1** with approximate dimensions of 0.08 x 0.09 x 0.31 mm was used for the data collection. The reflections were measured on a Nonius CAD-4 automatic diffractometer with liquid N_2 device using MoK_α radiation (l = 0.7169 Å). The position of the Se atom was determined using a Patterson synthesis with the y coordinate arbitrarily assigned. Positions of other atoms including all of the hydrogen atoms were determined by difference Fourier syntheses and subsequently refined with

anisotropic thermal parameters by full matrix least-squares with the SHELX program.[18] The final difference Fourier map had a maximum density of 0.52 e Å^{-3} close to the Se atom. The final R factor was 0.038. The space group is polar and centrosymmetrically related coordinates refined to a large R-value (0.042). Scattering factor for the Se atom was taken from the International Tables for X-ray crystallography.[19]

Supplementary Material Available. May be obtained from the senior author.

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