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Synthesis and Antiarrhythmic Properties of Novel 3-Selena-7-azabicyclo[3.3.1]nonanes and Derivatives. Single-Crystal X-ray Diffraction Analysis of 7-Benzyl-3-selena-7-azabicyclo[3.3.1]nonan-9-one and 7-Benzyl-3-selena-7-azabicyclo[3.3.1]nonane Hydroperchlorate

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Several members of the heterocyclic family 3-selena-7-azabicyclo[3.3.1]nonane have been synthesized and characterized via IR, ¹H, ¹³C, ¹⁵N, and ⁷⁷Se NMR spectroscopy and, in some cases, by X-ray diffraction analysis. Select members, namely the hydroperchlorates of the amines, were examined for antiarrhythmic properties in anesthetized dogs in which myocardial infarctions were induced by techniques previously described. In the predrug, or control state, sustained ventricular tachycardia were induced by ventricular paced beats at rates above 300/min. When 7-benzyl-3-selena-7-azabicyclo[3.3.1]nonane hydroperchlorate was administered at 3 and 6 mg/kg, the sustained ventricular tachycardia could no longer be induced. Similar doses of lidocaine, a commonly used antiarrhythmic, caused slowing of the sustained ventricular tachycardia below 300/min but did not abolish their inducibility. In addition, select members of the hydroperchlorates caused a moderate 10–20% increase in mean blood pressure whereas lidocaine caused either no change in or slightly reduced mean blood pressure. Some general conclusions are delineated concerning the structural requirements that appear to be necessary for activity in this family of heterocycles and that have not been reported previously.

In the course of our investigations for new antiarrhythmic properties in 3,7-diheterabicyclo[3.3.1]nonanes and derivatives, several 3-thia-7-azabicyclo[3.3.1]nonanes were synthesized and were found to be active in certain dog models.¹ Since selenium may bioisosterically replace sulfur² and since ⁷⁵Se is radioactive,³ we reasoned that such Se relatives might have similar antiarrhythmic activity and might offer a vehicle by which they could serve as part of imaging agents to define an infarcted zone in the heart, the latter being a long-term goal. This paper reveals our synthesis of members of 1 and 2 both of which came from methodology starting from the recently prepared 4-selenanone (3).⁴ Earlier studies¹ had indicated that such reduced amines as 4, and more often the salts like 5, showed the most significant antiarrhythmic action and thus these were prepared from 1 and 2. Antiarrhythmic effectiveness was assessed in dog models and reported in terms of ac-

tivity as compared with lidocaine as the standard.

Results and Discussion

Chemistry. Ketones 1 were prepared via a Mannich reaction previously outlined¹ but starting with 4-selenanone (3).³ Reduction of the carbonyl groups under Wolff–Kishner conditions gave the corresponding amines

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(1) Bailey, B. R., III; Berlin, K. D.; Holt, E. M.; Scherlag, B. J.; Lazzara, R.; Brachmann, J.; van der Helm, D.; Powell, D. R.; Pantaleo, N. S.; Ruenitz, P. C. *J. Med. Chem.* 1984, *27*, 758–767.
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(4) Thompson, M. D.; Holt, E. M.; Berlin, K. D.; Scherlag, B. J. *J. Org. Chem.* 1985, *50*, 2580.

4, which were converted to hydroperchlorates **5**. The salts

1a, R = C$_6$H$_5$CH$_2$
　b, R = C$_6$H$_5$CH$_2$CH$_2$

Table I. ^{13}C NMR Signals for Members of 1, 2, 5, 6, 8–10a (ppm)

compd	C(1,5)	C(2,4)	C(6,8)	C(9)	other aliphatic carbons
1a	46.2	25.5	59.0	213.8	Ar*C*H$_2$, 61.5
1b	46.2	25.4	59.1	213.5	Ar*C*H$_2$, 33.7; ArCH$_2$*C*H$_2$, 58.3
2	54.0	29.2	64.2	207.3	
5a	25.2	22.0	56.6	28.5	Ar*C*H$_2$, 60.5
5b	25.3	21.9	46.7	28.5^b	Ar*C*H$_2$, 29.9;^{b} ArCH$_2$*C*H$_2$, 58.8
6	34.7	21.1	54.9	92.5	Ar*C*H$_2$, 60.1
8	31.2	23.5	61.5	26.6	
9^a	47.1	34.6	58.4	212.8	Ar*C*H$_2$, 60.4
10^a	24.9	29.9	55.6	27.7	Ar*C*H$_2$, 59.9

^{a} ^{13}C signals for aromatic carbons are in the Experimental Section. ^{b} Signals may be reversed.

were the most easily purified by recrystallization techniques. Attempts to prepare a hydroperchlorate of ketone 1 resulted in the formation of the *gem*-diol salt **6**. Such diols of systems containing the 1-hetera-4-cyclohexanone unit are documented[5] but are rare. The overall reactions are outlined below for the generation of members of **5–8**.

Treatment of **2** under the usual Wolff–Kishner conditions gave **7**, which was best isolated as the hydroperchlorate **8**. The rationale for the synthesis of **8** was based upon
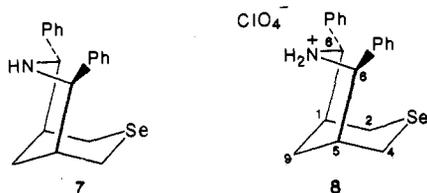
the premise that steric effects around the nitrogen atom might well influence the antiarrhythmic properties of the compound and this was found to be substantiated.

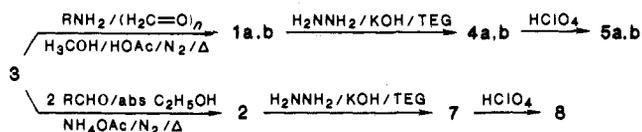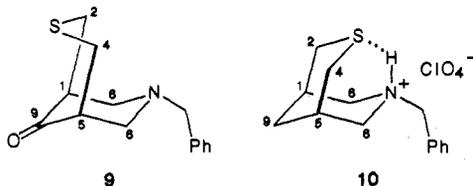In view of our previous observations that the sulfur counterpart **9**[1] of **1a** and the corresponding reduced salt **10**[1] (sulfur analogue of **5a**) were found to exist in a chair–boat (CB) and chair–boat (CC) conformer, respectively, it was reasoned that the geometry would be replicated in **1a** and **5a**. However, the lack of adequate model

compounds in the six-membered, selenium-containing ring system mandated that X-ray analyses of these compounds be performed to determine structures of the solids. These data should prove useful to others in the field as well as aid in correlating structures with activity for our work. That a CB form was present in **1a** and a CC form in **5a** was confirmed by the X-ray diffraction analysis on single crystals. In **1a**, the selenium atom is in the boat ring while it is in a flattened chair ring in **5a**. This again parallels the situation found in the sulfur analogues.[1]

The infrared spectra of members of **1a,b** and **2a** revealed absorption for the C=O group in the range of 1710–1730 cm^{-1}. Attempted preparation of a hydroperchlorate from **1a** resulted in the formation of **6**, which gave an infrared spectrum devoid of a band for a C=O group. This appears very typical of many diols obtained from 1-hetera-4-cyclohexanone systems.[1,5] The hydroperchlorate **5** and the diol **6** displayed absorption for the N–H stretch near 3400 cm^{-1} and a band near 1100 cm^{-1} for the perchlorate ion.[5,6] A band near 610 cm^{-1} was noted in the spectra of salts **5**, which might arise form a C–Se stretch,[2b] but this is tentative.

Proton NMR analyses of ketones **1** and **2**, as well as of the perchlorate **5** and the diol **6**, were quite complex due to high signal density in certain areas. In contrast, ^{13}C NMR analysis proved useful for identification purposes and again parallels that found for the sulfur models **9** and **10**.[1,5,7] However, signals for C(2,4) α to the selenium atom are at *higher* field than in the sulfur counterpart.[1] Presumably this is the result of selenium being slightly less electronegative than sulfur. One noteworthy feature is that C(2,4) resonances are more shielded in ketones **1a,b**, which we believe[8] have a selenium atom in a boat conformation, than in ketones **2**, which, in our opinion, have the selenium ring in a chair conformation.

Our rationale that members of **1** have selenium in a boat conformer in solution are based, in part, on an X-ray diffraction analysis of a single crystal of **1a**, which clearly demonstrated that the CB arrangement was present in the solid state which was true for crystalline **9** as well as in solution.[1] Regarding the conformation of members of **2**, it was not possible to obtain a useful crystal for an X-ray study from any member of the family. However, we do note that **11** has been examined by NMR analysis[9] and exists in solution as shown. The ^{13}C NMR analysis for **11** revealed signals for C(1,5) at 55.0 ppm and that for C(6,8) at 63.5 ppm.[9] Carbon-13 resonances for C(2,4) next to sulfur were at 37.4 ppm (compared to 29.2 ppm in **2**; see Table I). Significant features in the comparison are that the signals for C(1,5) and C(6,8) are very close in both compounds and that a CB is supported for **11** by NMR

(5) Bailey, B. R., III; Berlin, K. D.; Holt, E. M. *Phosphorus Sulfur* **1984**, *20*, 131–137.

(6) (a) Conley, R. T. *Infrared Spectroscopy*; Allyn & Bacon: Boston, 1966; Chapter 6. (b) Nakanishi, K.; Solomon, P. H. *Infrared Adsorption Spectroscopy*, 2nd ed.; Holden-Day: San Francisco, 1977; Chapter 2.

(7) Bailey, B. R., III; Berlin, K. D.; Powell, D. R.; van der Helm, D. *Phosphorus Sulfur* **1984**, *21*, 121–133.

(8) The average for several ketones related to 9[7] for the C(2,4) resonance was 34.6 ppm and that for 10[7] and related systems was 30.5 ppm.

(9) Jeyaraman, R.; Jawaharsingh, C. B.; Avila, S.; Sanapathy, K.; Eliel, E. L.; Manoharan, M.; Morris-Natscke, S. *Heterocycl. Chem.* **1982**, *19*, 449–458.

11   **12**   **13**
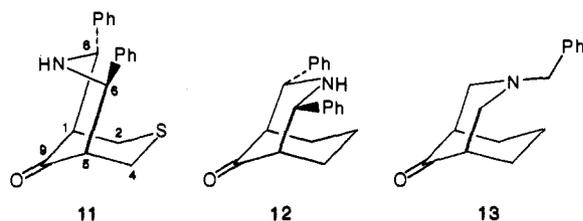
analysis.[9] The last piece of evidence to support our conjecture concerning a CB conformer for 2 was that C(9),[1] the bridgehead carbon, had a signal at 207.2 ppm while in 12[10] and 13[1] the shifts were at 217.2 and 218.6 ppm, respectively. In our opinion, which we have elaborated upon previously,[11] this is strong evidence for a CB form in 2 and a CC form in 12 and in 13 since one might expect an increased *shielding* for C(9) in the boat conformation in 2 due to a syn-periplanar effect[10] between C(9) and N. The shift for C(9) in 11 was 212.7 ppm.[9]

Since ketone 2 proved difficult to purify, it was reduced to 7, which in turn was converted to salt 8, the latter being easy to obtain in pure form. The major differences in chemical shifts for 8 and that of the sulfur analogue 10 (and relatives)[1,7] were observed in the resonances for C(2,4), which averaged 30.4 ppm for 10 and several related systems. In contrast, the corresponding signal in 8 was 23.5 ppm. Again it appears that Se, being less electronegative than sulfur, may, in part, cause *less* deshielding at C(2,4). However, the effect seems larger than this explanation can defend alone. Data for 9 and 10 are in Table I for completeness. The nearest relative to 8 was 14,[9] which had a signal for C(2,4) at 34.1 ppm. Unfortunately, the salt 15, a more appropriate model, was not reported.

14   **15**
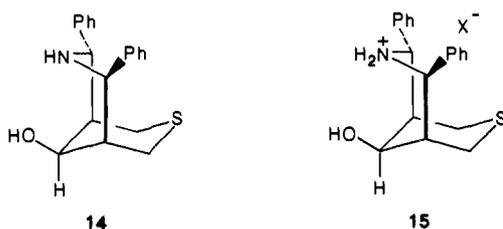
The ability of ^{15}N NMR analysis to provide stereochemical insight into the structure of a member of the families 1 and 5 has been recognized[1] but to a limited extent. With *N*-benzyl-4-piperidone, a signal was found at 49.1 ppm [from NH$_3$(l)] while that of members of 1 ranged from 35.2 to 38.3 ppm (see Experimental Section). In our opinion, this increased shielding is a result of the nitrogen atom being in a chair conformation in a biased system with a γ-shielding effect operating.[12] A γ-shielding effect on ^{15}N by C(2,4) has been known for γ-oriented heteroatoms.[13] Slightly impure 2 showed a signal at 63.2 ppm, which is comparable to those found in the sulfur analogues.[1] The amines 5a,b had signals at 51.56 and 58.54 ppm, respectively, and, on the basis of the results of the X-ray diffraction analysis, the ^{15}N signal almost surely arose from nitrogen atom in a boat conformer. Salt 8 displayed an ^{15}N signal at 57.9 ppm, which was expected since a protonated nitrogen atom in a salt is nearly always deshielded compared to that in the free amine[1,13] although little information has been available on this point in this

Table II. Crystal Data for 7-Benzyl-3-selena-7-azabicyclo[3.3.1]nonan-9-one (1a) and 7-Benzyl-3-selena-7-azabicyclo[3.3.1]nonane Hydroperchlorate (5a)

	1a	5a
mol formula	$C_{14}H_{17}NOSe$	$C_{14}H_{20}NClO_4Se$
M_r	294.1	380.7
linear absorption coefficient, cm^{-1}	27.72	44.56
space group	$P\bar{1}$	$P2_12_12_1$
cell dimensions		
a, Å	12.298 (3)	14.692 (4)
b, Å	10.070 (2)	15.950 (1)
c, Å	11.156 (4)	6.646 (1)
α, deg	85.10 (3)	90.0
β, deg	92.10 (3)	90.0
γ, deg	104.81 (2)	90.0
volume, Å^3	1332.1 (7)	1557.4
cell determination proced	15 refl (15 < 2θ < 25)	36 refl (0 < 2θ < 60)
Z, g cm^{-3}	4	4
density (calcd), g cm^{-3}	1.466	1.63
recrystn solvent	95% ethanol	methanol
data collection range, deg	0 < 2θ < 60	0 < 2θ < 150
scan, scan time	θ–2θ, variable	θ–2θ, 90 s
radiation	Mo Kα	Cu Kα
standards	3, remeasured every 97 refl	3, remeasured every 200 refl
structure solution	MULTAN 80[19]	Patterson synthesis
final refinement	full matrix	full matrix
wt scheme	$\omega = \sigma(F_o)^{-1}$	$\omega = \sigma(F_o)^{-2}$
temp of data collection, K	298 ± 2	135 ± 2
no. reflections measd	7756	1842
no. reflections obsd	2207	1766
criteria for observation	$I > 3.0\sigma(I)$	$I > 2\sigma(I)$
final R	0.065	0.052
final Rω	0.068	0.061
refinement of hydrogens	not refined	isotropic
final difference Fourier map		
max density, e/Å^3	0.38	2.3

family of heterocycles. Purification of amine 7 was accomplished to a limited degree and gave an ^{15}N signal at 55.7 ppm. Arguments for the CB form for *sulfur analogues of* 8 have been made previously[1,8-10] that we feel remain valid for the latter 8 since the aryl rings likely induce formation of the boat conformer that is formed via a Mannich-type reaction mechanism operating in the synthesis.[1,9,10,14] To date, most related systems with aryl groups geminal to a nitrogen atom appear to have the nitrogen in a boat comformer in the family of 3,7-diheterabicyclo[3.3.1]nonanes where one heteroatom is a nitrogen. Efforts to obtain suitable crystals of 7 or 8 have not proven fruitful. Nevertheless, the structures of 7 and 8 are believed to be of the CB type on the basis of NMR analysis and a correlation with such data from the sulfur counterparts.

Single-Crystal X-ray Diffraction Analysis. Single crystals could be grown and were subjected to X-ray diffraction analysis for 1a and 5a since no members in this selenium heterocyclic family have been reported heretofore. Conformations in the solid state were determined

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(11) See ref 1 for a discussion on this point.

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(13) Levy, G. C.; Richter, R. L. *Nitrogen in Nuclear Magnetic Resonance Spectroscopy*; Wiley-Interscience: New York, 1979.

(14) (a) Jackman, L. M.; Dunne, T. S.; Muller, B. *Chem. Ber.* 1982, 115, 2872. (b) Quast, H.; Muller, B.; Peters, E. M.; Peters, K.; von Schnering, H. G. *Chem. Ber.* 1982, 115, 3631. (c) Quast, H.; Muller, B.; Peters, K.; von Schnering, H. G. *Chem. Ber.* 1983, 116, 424. (d) Pantaleo, N.; van der Helm, D.; Ramarajan, K.; Bailey, B. R., III; Berlin, K. D. *J. Org. Chem.* 1981, 46, 4199.

Table III. Bond Angles (deg) and Distances (Å) for $C_{14}H_{17}NOSe$ (1a)

	molecule A	molecule b		molecule A	molecule b
			Bond Distances		
C(1)–C(2)	1.53 (2)	1.51 (3)	C(9)–O(10)	1.19 (2)	1.22 (2)
C(2)–Se(3)	1.93 (1)	1.95 (2)	N(7)–C(11)	1.45 (2)	1.48 (2)
Se(3)–C(4)	1.97 (1)	1.91 (1)	C(11)–C(12)	1.50 (2)	1.50 (2)
C(4)–C(5)	1.53 (2)	1.49 (2)	C(12)–C(13)	1.41 (3)	1.35 (2)
C(5)–C(6)	1.53 (2)	1.53 (2)	C(13)–C(14)	1.37 (2)	1.37 (2)
C(6)–N(7)	1.45 (2)	1.44 (2)	C(14)–C(15)	1.34 (4)	1.40 (3)
N(7)–C(8)	1.45 (2)	1.46 (2)	C(15)–C(16)	1.36 (3)	1.36 (4)
C(8)–C(1)	1.55 (2)	1.57 (2)	C(16)–C(17)	1.37 (2)	1.35 (2)
C(1)–C(9)	1.50 (2)	1.49 (2)	C(17)–C(12)	1.37 (2)	1.37 (2)
C(5)–C(9)	1.52 (2)	1.51 (2)			
			Bond Angles		
C(1)–C(2)–Se(3)	113.0 (9)	112.1 (12)	C(1)–C(9)–O(10)	123.4 (12)	123.6 (11)
C(2)–Se(3)–C(4)	95.3 (5)	90.5 (6)	C(5)–C(9)–O(10)	123.5 (13)	122.8 (13)
Se(3)–C(4)–C(5)	111.0 (8)	114.4 (9)	C(6)–N(7)–C(11)	113.7 (11)	113.8 (10)
C(4)–C(5)–C(6)	111.3 (10)	112.2 (12)	C(8)–N(7)–C(11)	110.9 (9)	110.7 (9)
C(5)–C(6)–N(7)	108.9 (11)	112.3 (11)	N(7)–C(11)–C(12)	111.3 (10)	111.8 (10)
C(6)–N(7)–C(8)	110.8 (10)	110.1 (11)	C(11)–C(12)–C(13)	119.7 (13)	120.2 (13)
N(7)–C(8)–C(1)	109.6 (9)	110.3 (10)	C(11)–C(12)–C(17)	123.2 (13)	118.6 (13)
C(8)–C(1)–C(2)	111.0 (11)	108.6 (12)	C(12)–C(13)–C(14)	118.8 (16)	120.2 (14)
C(2)–C(1)–C(9)	113.3 (9)	113.4 (11)	C(13)–C(14)–C(15)	123.2 (19)	118.6 (18)
C(4)–C(5)–C(9)	114.6 (11)	112.6 (11)	C(14)–C(15)–C(16)	118.0 (19)	119.8 (16)
C(8)–C(1)–C(9)	105.5 (11)	106.1 (11)	C(15)–C(16)–C(17)	121.5 (18)	120.9 (18)
C(6)–C(5)–C(9)	106.6 (9)	105.3 (9)	C(16)–C(17)–C(12)	121.3 (15)	119.3 (17)
C(1)–C(9)–C(5)	113.0 (19)	113.4 (12)	C(17)–C(12)–C(13)	117.2 (13)	121.2 (13)

Table IV. Torsion Angles (deg) for $C_{14}H_{17}NOSe$ (1a)

	molecule A	molecule B		molecule A	molecule B
C(1)–C(2)–Se(3)–C(4)	57.9	60.0	Se(3)–C(4)–C(5)–C(9)	45.5	47.2
C(2)–Se(3)–C(4)–C(5)	55.8	58.5	N(7)–C(8)–C(1)–C(9)	67.8	67.7
Se(3)–C(4)–C(5)–C(6)	126.2	128.2	N(7)–C(6)–C(5)–C(9)	68.2	68.8
C(4)–C(5)–C(6)–N(7)	76.5	76.5	C(2)–C(1)–C(9)–O(10)	126.7	131.4
C(5)–C(6)–N(7)–C(8)	74.9	73.7	C(4)–C(5)–C(9)–O(10)	126.3	128.0
C(6)–N(7)–C(8)–C(1)	75.4	71.4	C(8)–C(1)–C(9)–O(10)	122.2	119.9
N(7)–C(8)–C(1)–C(2)	74.6	73.9	C(6)–C(5)–C(9)–O(10)	122.1	119.6
C(8)–C(1)–C(2)–Se(3)	125.9	130.5	C(1)–C(8)–N(7)–C(11)	168.3	173.5
C(1)–C(9)–C(5)–C(4)	78.6	76.4	C(5)–C(6)–N(7)–C(11)	169.1	173.6
C(5)–C(9)–C(1)–C(2)	77.1	74.1	C(8)–N(7)–C(11)–C(12)	168.7	174.5
C(1)–C(9)–C(5)–C(6)	70.0	70.1	C(6)–N(7)–C(11)–C(12)	78.8	74.9
C(5)–C(9)–C(1)–C(8)	68.8	70.6	N(7)–C(11)–C(12)–C(13)	140.3	72.3
Se(3)–C(2)–C(1)–C(9)	46.3	46.5	N(7)–C(11)–C(12)–C(17)	68.5	134.0

to be a CB (1a) and a CC (5a) form. Table II contains all pertinent crystal data for the systems. Bond distances and bond angles are in Table III for 1a and selected torsion angles are in Table IV. Ketone 1a crystallizes with two molecules per asymmetric unit, both of which display CB conformations with selenium in the boat ring and nitrogen in the chair ring. Figure 1 contains a stereo drawing of 1a that is reminiscent of that for the sulfur relative 9.[1] Differences between the sulfur 9 and selenium 1a analogues may be interpreted in light of the larger covalent radius of selenium (1.16 Å as compared to 1.04 Å for sulfur) and the resulting longer bond lengths [Se–C av 1.94 (1) Å as compared to S–C av 1.810 (4) Å]. This difference manifests itself most prominently in the torsion angles [C(9)–C(1)–C(2)–Se(3), C(9)–C(5)–C(4)–Se(3)] relating the conformation of the two ends of the boat (Table IV). In the sulfur analogue 9, these torsion angles are small in magnitude (2.6–3.9°) whereas in 1a the comparable torsion angles are significantly greater (45.5–47.2°), indicating a flattening of the selenium end of the boat in 1a compared to the sulfur-containing boat of 9.[1] This flattening also manifests itself in the Se–C(9) distance [2.901 (13), 2.886 (13) Å], which is larger than the S(3)–C(9) distance [2.831 (4), 2.802 (4) Å] in 9 by an amount approximately equal to the difference in covalent radii.[1]

The nitrogen-containing ring in 1a displays larger [C-(9)–C(5)–C(6)–N(7), C(9)–C(1)–C(8)–N(7)] torsion angles (67.7–68.8°) as compared to 58.7–59.1° for the previously

reported sulfur molecule 9,[1] indicating a greater downward bend of the C(6)–N(7)–C(8) plane of the nitrogen-containing chair in the selenium structure 1a. Thus, substitution of Se for S has resulted in flattening of the Se-containing ring and a greater deviation from planarity for the N-containing ring.

The single-crystal X-ray diffraction analysis of 7-benzyl-3-selena-7-azabicyclo[3.3.1]nonane hydroperchlorate (5a) indicates the proton from perchloric acid is attached to nitrogen and intramolecular hydrogen bonding occurs between hydrogen and selenium on the basis of interatomic distances. Bond angles, bond distances, and selected torsion angles are found in Tables V and VI, respectively.

The theoretical van der Waals distance between selenium and nitrogen should be about 3.5 Å.[15] It was determined that this distance in 5a was 3.130 (5) Å, which was significantly shorter than the calculated van der Waals distance. The geometry around selenium is not ideal for hydrogen bonding since the Se(3)···H(7)–N(7) angle is 119° rather than the expected 180°. On the other hand, the Se(3)···H(7) distance of 2.567 Å was much shorter than expected from the sum of the van der Waals radii of 3.2 Å for selenium and hydrogen. Thus, it appears the Se-(3)···H(7)–N(7) bond may be stronger than that between

(15) Pauling, L. *The Nature of the Chemical Bond*, 3rd ed.; Cornell University: Ithaca, NY, 1972.
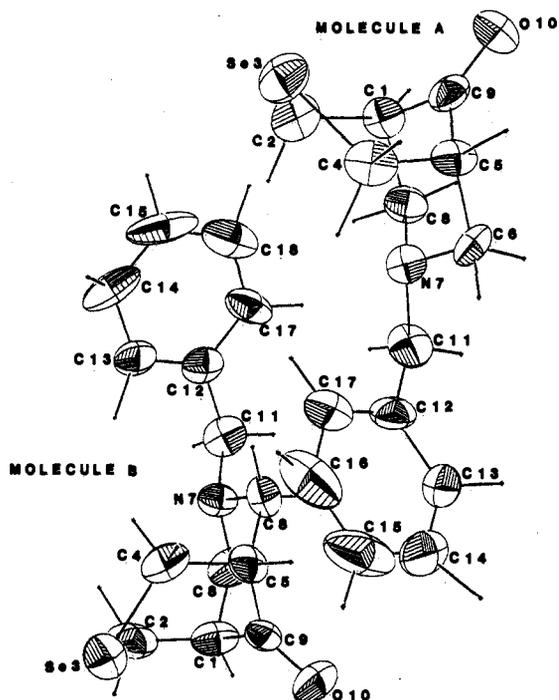
Figure 1. A view of **1a**.

Table V. Bond Distances (Å) and Bond Angles (deg) for $C_{14}H_{20}ClNO_4Se$ (**5a**)

Bond Distances			
C(1)–C(2)	1.529 (9)	C(5)–C(9)	1.518 (9)
C(2)–Se(3)	1.971 (7)	N(7)–C(10)	1.509 (8)
Se(3)–C(4)	1.962 (7)	C(10)–C(11)	1.510 (9)
C(4)–C(5)	1.524 (9)	C(11)–C(12)	1.388 (10)
C(5)–C(6)	1.528 (8)	C(12)–C(13)	1.398 (10)
C(6)–N(7)	1.517 (8)	C(13)–C(14)	1.374 (13)
N(7)–C(8)	1.514 (8)	C(14)–C(15)	1.394 (12)
C(8)–C(1)	1.531 (8)	C(15)–C(16)	1.401 (10)
C(1)–C(9)	1.530 (8)	C(16)–C(11)	1.392 (10)

Bond Angles			
C(1)–C(2)–Se(3)	113.5 (4)	C(1)–C(9)–C(5)	111.7 (5)
C(2)–Se(3)–C(4)	96.6 (3)	C(6)–N(7)–C(10)	110.4 (5)
Se(3)–C(4)–C(5)	115.1 (5)	N(7)–C(10)–C(11)	111.3 (5)
C(4)–C(5)–C(6)	114.7 (5)	C(10)–C(11)–C(12)	120.0 (6)
C(5)–C(6)–N(7)	111.9 (5)	C(10)–C(11)–C(16)	119.4 (6)
C(6)–N(7)–C(8)	111.5 (5)	C(11)–C(12)–C(13)	120.2 (7)
N(7)–C(8)–C(1)	112.5 (5)	C(12)–C(13)–C(14)	119.5 (7)
C(8)–C(1)–C(2)	114.2 (5)	C(13)–C(14)–C(15)	120.7 (7)
C(2)–C(1)–C(9)	112.3 (5)	C(14)–C(15)–C(16)	120.0 (8)
C(4)–C(5)–C(9)	112.0 (5)	C(15)–C(16)–C(11)	118.9 (6)
C(8)–C(1)–C(9)	109.8 (5)	C(16)–C(11)–C(12)	120.6 (6)
C(6)–C(5)–C(9)	109.1 (5)		

sulfur and the corresponding hydrogen in **10**.[1] The C–Se bond lengths in **5a** are 1.971 (7) Å and 1.962 (7) Å and are close to the values [1.98 (3) Å] given by Sutton.[16] The comparable C–S lengths in **10**[1] were 0.14 Å shorter.

The angles between planes 1, 2, 3, 4, and 5 (Figure 2) in **5a** were similar to those found in **10** except for the angle between planes 1 and 2, which is 10° larger in **5a**. Thus, there is an increased ring flattening in the selenium-containing ring of **5a** compared to the sulfur-containing ring in **10**.[1] Figure 3 is a stereo drawing of **5a** and substantiates that the system is a CC conformer in the solid state.

Biology. Antiarrhythmic properties of targeted compounds, namely **5a**, **5b**, **6**, **8**, and lidocaine (**16**), were examined with anesthetized mongrel dogs via the techniques

(16) Sutton, C. E. *Tables of Interatomic Distances*; The Chemical Society: London, 1965.

Table VI. Torsion Angles (deg) for **5a**

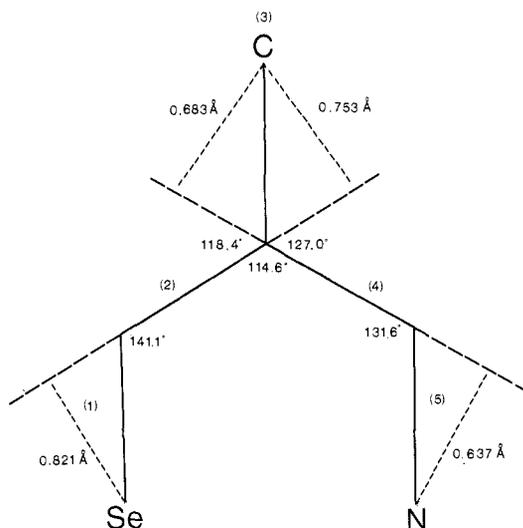|	
C(1)–C(2)–Se(3)–C(4)	−43.2 (5)
C(2)–Se(3)–C(4)–C(5)	42.9 (5)
Se(3)–C(4)–C(5)–C(6)	66.3 (6)
C(4)–C(5)–C(6)–N(7)	−69.6 (7)
C(5)–C(6)–N(7)–C(8)	−54.7 (7)
C(6)–N(7)–C(8)–C(1)	53.1 (7)
N(7)–C(8)–C(1)–C(2)	73.2 (7)
C(8)–C(1)–C(2)–Se(3)	−65.6 (6)
C(1)–C(9)–C(5)–C(4)	69.4 (6)
C(5)–C(9)–C(1)–C(2)	−70.9 (6)
C(1)–C(9)–C(5)–C(6)	−58.7 (7)
C(5)–C(9)–C(1)–C(8)	57.2 (6)
Se(3)–C(2)–C(1)–C(9)	60.1 (6)
Se(3)–C(4)–C(5)–C(9)	−58.8 (6)
N(7)–C(8)–C(1)–C(9)	−53.8 (6)
N(7)–C(6)–C(5)–C(9)	57.0 (7)
C(1)–C(8)–N(7)–C(10)	177.1 (5)
C(5)–C(6)–N(7)–C(10)	−179.4 (7)
C(8)–N(7)–C(10)–C(11)	64.1 (7)
C(6)–N(7)–C(10)–C(11)	−171.3 (5)
N(7)–C(10)–C(11)–C(12)	−116.7 (7)
N(7)–C(10)–C(11)–C(16)	62.4 (8)

Figure 2. Angles between planes in **5a**. Dotted lines are perpendicular distances between the atoms and the indicated planes. The planes are as follows: plane 1, Se(3)–C(2)–C(4); plane 2, C(1)–C(2)–C(4)–C(5); plane 3, C(1)–C(5)–C(9); plane 4, C(1)–C(8)–C(5)–C(6); plane 5, C(6)–N(7)–C(8).
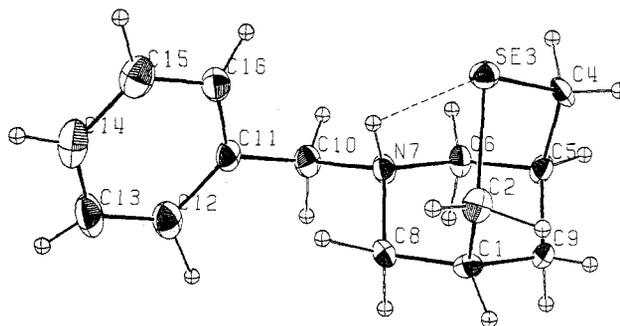

Figure 3. A view of **5a**.

described previously.[1] Lidocaine was employed as a standard by which comparisons could be determined. The dogs were examined 24 h after ligation of the left anterior descending coronary artery.[1] Tabulation of the results can be found in Table VII.

Comparative Effects of the Title Compounds with Lidocaine (16). The electrocardiograms are shown in Figure 4 in a typical experiment in which a severe arrhythmia, i.e., sustained ventricular tachycardia (VT),

Table VII. Biological Data for Targeted Organoselenium Compounds[a]

| control[b] | | | | compd | 3 mg/kg | | | | 6 mg/kg | | | |
NSR[c]	MBP[d]	Sus VT[e]	VT MBP		NSR	Sus VT	MBP (no VT)	MBP (VT)	NSR	Sus VT	MBP (no VT)	MBP (VT)
	125		50	5a	160		126		160		125	
170	114	330	50	5b	168		128		165		125	
165	110	340	50	16	165	270	110	40	160	360	112	40
150	125	340	70	5b	150		150		150		150	
160	125	330	70	8	150		125		145		125	
150	125	330	70	6	150	280	125		155	320	125	70
150	130	290	80	6	155	300	130	40	150	255	130	60
140	100	330	55	8	150	270	82	30	140	280	80	20
150	70	300	65	5b	155		85		155		85	
150	70	310	70	16	150	210	70	75	150	330	72	52

[a] Each division represents tests performed on separate dogs. [b] Data recorded before the administration of the test compound. [c] Norman sinus rhythm. [d] Mean blood pressure. [e] Sustained ventricular tachycardia.
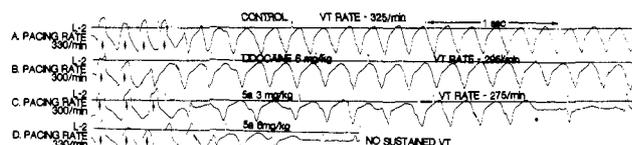

Figure 4. Electrocardiographic tracings (L-2) from an experiment in which lidocaine (16) and various doses of 5a were administered to an anesthetized dog with a 24-h myocardial infarction. Panel A: ventricular paced beats (arrows) induced a sustained ventricular tachycardia (VT) at a rate of 325 beats/min in the control state. Panel B: after intravenous administration of lidocaine (6 mg/kg), ventricular paced beats (arrows) induced a slower VT (295 beats/min). In panels C and D, after lidocaine dissipation and return to control conditions, 5a (3 and 6 mg/kg) was administered intravenously. Not only was the induced VT slowed (275/min) but the VT could not be sustained (*), indicating that 5a was more effective in the abolition of sustained ventricular tachycardia than lidocaine at similar dose levels.

could be induced in the control state. In order to induce the tachycardia, rapid bursts (2–4 beats) of ventricular pacing were delivered to the heart (arrows). In panel A, such a burst at a rate of 330 beats/min initiated a run of sustained ventricular tachycardia (spontaneous rate = 325 beats/min). After electrical conversion to a normal rate and rhythm, followed by a period of recovery, the same provocative test was repeated. However, on this occasion, a dose of lidocaine (cumulative dose of 6 mg/kg) was administered intravenously prior to ventricular burst pacing.
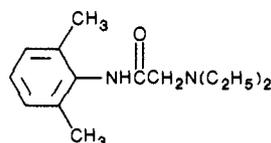
16
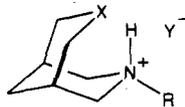
17: X = S, Se

In panel B, at a pacing rate 30 beats lower than in the control state, sustained ventricular tachycardia was again induced. However, the spontaneous rate of this tachycardia was slower than in the control state (295 beats/min). This slowing effect of lidocaine is consistent with its antiarrhythmic action and relates to the slowing of conduction in the reentry circuit that sustained the arrhythmia.[1]

After a lapse of sufficient time to permit the effects of the lidocaine to dissipate (about 20 min), ventricular pacing induced the same ventricular tachycardia as in panel A. This confirmed the loss of action by the drug and the reproducibility of the arrhythmia. Salt 5a was then administered intravenously in a dose of 3 mg/kg as a solution in a minimum of 50% alcohol. This alcohol–water solution, devoid of a drug, was previously[1] screened for activity

in the same arrhythmia model and was found to be without any antiarrhythmic effect.

At a ventricular pacing rate of 300 beats/min (panel C), a similar tachycardia was induced but at a rate of 275 beats/min. However, the ventricular tachycardia were not sustained as was true also over several trials. Consequently, the greater slowing of the tachycardia and its inability to persist at half the dose of lidocaine (panel B) indicate the greater antiarrhythmic efficacy of 5a compared to that of 16. A similar difference in efficacy was noted between the sulfur analogue 10 and 16.[1]

It was likewise observed that when the dose of 5a was increased (cumulative dose of 6 mg/kg), no sustained tachycardia could be induced even if the ventricular pacing was increased to 330/min (panel D). The results further suggest that 5a on a milligram/kilogram basis is more effective in exhibiting a potent inhibitory effect on ventricular tachycardia than 16. Data obtained from the dog models using 5, 6, 8, and 16 have also been provided in Table VII.

Table VII clearly shows that salt 5b (a close relative of 5a) also exhibits a marked ability to prevent the induction of sustained VT at both the 3 and 6 mg/kg dosage. The ventricular tachycardia induced after administration of 5b was *not* sustained but reverted to normal sinus rhythm. Moreover, 5b also caused a blood pressure increase at both dose levels. Diol 6, although active, exhibited a proarrhythmic effect (generation of a new arrhythmia at a faster rate of 320 beats/min) at a dose of 6 mg/kg. In addition, there was a decrease in the blood pressure during the ventricular tachycardia compared with the blood pressure observed during the VT in the control state.

The diaryl-substituted salt 8 had similar properties to those of 5a and 5b, but the blood pressure fell or was unaffected. It appears that 8 did not inhibit the sustained VT as well as did members of 5. This situation to some degree parallels that found in certain sulfur analogues[1] in which those derivatives with aryl groups attached at α positions to the heteroatom had a boat ring that may be a critical factor for the loss of antiarrhythmic activity. Table VIII is a summary of the relative limits of action of these compounds compared to the action of lidocaine in the dog models.

It appears that replacement of nitrogen[17] by selenium or sulfur in these heterocycles does not diminish the antiarrhythmic properties. The presence of a CC form in

(17) Jeyaraman, R.; Avila, S. *Chem. Rev.* 1981, *31*, 149. This review contains references to previous work concerning antiarrhythmic properties of 3,7-diheterabicyclo[3.3.1]nonanes and derivatives.

Table VIII. Relative Effects of **5a**, **5b**, **6**, **8**, and **16** on Heart Rate, Blood Pressure and VT[a]

compd	NSR	mean BP	abolition of VT	slowing of VT	exacerbation of VT
5a	NC	SL ↑ 8%	+	NA	−
5b	NC	mod ↑ 16%	+	NA	−
6	NC	NC	−	+	+
8	SL ↓, SL ↑	NC, mod ↓	±	+	+
16	NC	NC	−	+	+

[a] VT = ventricular tachycardia; BP = blood pressure; NSR = normal sinus rate. mod = moderate, 10–20%. SL = slight, 5–10%. ↑ = increase. ↓ = decrease. NC = no change. + = yes. − = no. NA = not applicable.

these salts appears to be mandatory for maximum activity although a variety of substituents in **17** at nitrogen (R) have not yet been screened to determine which might well enhance such action. The existence of aryl groups on carbon attached to the nitrogen does alter the antiarrhythmic property of the compound, but the effect is much less pronounced than the systems devoid of these groups. This was also observed in the sulfur counterparts.[1] Consequently, steric effects are likely very important, particularly around the heteroatom. Although antiarrhythmic action has been reported in bispidine derivatives,[17] a stereochemical study has not been previously recorded. It is noteworthy that lengthening the chain of the group attached to nitrogen by one methylene group (as in **5b**) did *not* alter antiarrhythmic activity and, in fact, resulted in a derivative that inhibited the induction of sustained ventricular tachycardia. Consequently, study is continuing in this family in order to determine the structure–activity profile in terms of stereochemical aspects of groups around the heteroatoms and possible imaging qualities of the Se materials.

Experimental Section

All reactions were performed under nitrogen and in an efficient hood unless otherwise specified. Residues from all reactions involving a selenium compound were destroyed by adding bleach. Trapping of any effluents was efficient via the use of alcoholic KOH. **CAUTION:** Gloves should be worn in the handling of all selenium compounds, which should be considered toxic.

Melting points were determined with a Thomas-Hoover apparatus and were uncorrected. Infrared spectra were recorded on a Perkin-Elmer 681 IR spectrometer as KBr pellets or as films. All ^{1}H, ^{15}N, and ^{77}Se NMR signals were recorded on a Varian XL-300 NMR spectrometer operating at 299.99, 30.41, and 57.22 MHz, respectively. All ^{13}C NMR signals were observed on either a Varian XL-100(15) spectrometer at 25.20 MHz or a Varian XL-300 MHz spectrometer at 75.4 MHz. Chemical shifts were measured in ppm downfield for ^{13}C (from Me$_4$Si), for ^{15}N [from NH$_3$(l) with ^{15}NH$_4$NO$_3$ as an external reference], and for ^{77}Se [from (H$_3$C)$_2$Se (0 ppm) with (H$_5$C$_6$Se)$_2$ (481.0 ppm) as an external, secondary reference]. Chemical shifts for ^{1}H signals were measured in δ values downfield from Me$_4$Si. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. 4-Selenanone (**3**) was prepared by the method reported.[4] Ketones **1a,b** proved difficult to purify, although a few individual crystals could be hand-picked for X-ray analysis or for obtaining spectral data (multiple scans were required). It became more efficient to reduce the carbonyl group at C(9) to a CH$_2$ in members of **4**, which in turn were converted to hydroperchlorates **5** that gave very satisfactory analyses.

7-Benzyl-3-selena-7-azabicyclo[3.3.1]nonan-9-one (1a). Benzylamine (0.687 g, 6.26 mmol) and glacial acetic acid (0.38 g, 6.33 mmol) were dissolved in dry methanol (30 mL). Paraformaldehyde (1.5 g, 50 mmol) was added and the resulting mixture was brought to reflux under an atmosphere of nitrogen. 4-Selenanone (**3**; 1.00 g, 6.13 mmol) was then added in one portion, which quickly turned the solution yellow. Boiling was continued

under nitrogen in the dark for 5 h. The resulting deep red solution was then allowed to cool to room temperature and was stirred for an additional 18 h. The methanol was evaporated and the orange residual oil was partitioned between ether (50 mL) and water (50 mL). The ether layer was discarded and the aqueous layer was made basic with KOH (85%, 1.2 g, 18.2 mmol). This solution was extracted with ether (5 × 40 mL). The combined extracts were dried (K$_2$CO$_3$) and evaporated to give an oil, which was digested on a steam bath with Skelly B (50 mL). Evaporation gave a light yellow oil, which solidified upon standing. This solid was recrystallized (95% ethanol) to give **1a** (0.78 g, 43%) as white needles: mp 155.5–157.0 °C dec; IR (KBr) cm^{-1} 1726 (C=O); ^{1}H NMR (DCCl$_3$) δ 2.71 [d, 2 H, H(6,8$_{ax}$), J = 9 Hz], 2.73 [br s, 2 H, H(1,5)], 3.10 [d, 2 H, H(6,8$_{eq}$), J = 9 Hz], 3.21 [d, 2 H, H(2,4$_{eq}$), J = 5 Hz], 3.23 [br s, 2 H, H(2,4$_{ax}$)], 3.58 [s, 2 H, H(11-ArCH$_2$], 7.32 [m, 5 H, ArH]; ^{13}C NMR (DCCl$_3$) ppm 25.5 [t, C(2,4)], 46.2 [d, C(1,5)], 59.0 [t, C(6,8)], 61.5 [t, C(11-ArCH$_2$)], 127.1 [d, C(4')], 128.2 [d, and 128.6 (d) C(2', 3', 5', 6')], 138.0 [s, C(1')], 213.8 [s, C(9)]; ^{15}N NMR (DCCl$_3$) ppm 38.31 [N(7)]; ^{77}Se NMR (DCCl$_3$) ppm 84.68 [Se(3)]. The above proton signals could be partially resolved by a HETCOR 2D experiment.[18] A satisfactory elemental analysis proved very difficult for **1a** and thus it was converted to **5a** without further purification. Since HETCOR 2D capability was not previously available to us and since the proton signals of **1a** were compared to those of **9**,[1] a HETCOR experiment was performed on **9**, which gave the following results with corrections for a few previously erroneous assignments[1] for only a few protons. For **9**: ^{1}H NMR (DCCl$_3$) δ 2.71 [dd, 2 H, H(6,8$_{ax}$), J = 11.2 Hz, J = 5.0 Hz], 2.80 [m, 2 H, H(1,5)], 3.08 [dd, 2 H, H(6,8$_{eq}$), J = 11.2 Hz, J = 1.3 Hz], 3.12 [dd, 2 H, H(2,4$_{ax}$), J = 13.5 Hz, J = 7.3 Hz], 3.23 [dd, 2 H, H(2,4$_{eq}$), J = 13.5 Hz, J = 4.0 Hz], 3.57 [s, 2 H, H(10-NCH$_2$)], 7.26–7.34 [m, 5 H, ArH]. The ^{13}C signals for **9** are correct as given earlier.[1] This downfield shift for the protons α to the selenium (in **1a**) and to the sulfur counterpart (in **9**) compared to signals for protons α to nitrogen is unusual. The X-ray analysis indicates the solid forms have greatly flattened ends where the heteroatom resides. This may mean that the presumably increased s character to the C–H bonds on the α carbon (to Se or S) results in a greater deshielding of the protons than expected.

7-Phenethyl-3-selena-7-azabicyclo[3.3.1]nonan-9-one (1b). A solution was made of 2-phenethylamine (1.48 g, 12.3 mmol) and glacial acetic acid (0.85 g, 14.2 mmol) in methanol (60 mL). Paraformaldehyde (3.0 g, 100 mmol) was added and the resulting mixture was heated to reflux with magnetic stirring under an atmosphere of nitrogen. Ketone **3** (2.00 g, 12.3 mmol) was added and boiling was continued for 5 h, resulting in an orange solution. Methanol was evaporated and the residual orange oil was mixed with water (200 mL). This aqueous mixture was made basic by addition of NaOH (2.0 g, 50 mmol) and was then extracted with ether (5 × 40 mL). The combined extracts were washed with saturated brine and dried (K$_2$CO$_3$). Evaporation gave a brown residue, which was digested in boiling Skelly B (150 mL). Evaporation of the Skelly B gave a solid, which was recrystallized (ethanol) to give 0.82 g (22%) of **1b** as a light tan solid: mp 91–92 °C; IR (KBr) cm^{-1} 1710 (C=O); ^{1}H NMR (DCCl$_3$) δ 2.62–2.83 [m, 8 H, H(1,5; 6,8; 10-ArCH$_2$), 11-NCH$_2$] 3.02–3.20 [m, 6 H, H(6,8; 2,4)], 7.16–7.38 [m, 5 H, ArH]; ^{13}C NMR (DCCl$_3$) ppm 25.4 [s C(2,4)], 33.7 [s, C(10-ArCH$_2$)], 46.2 [d, C(1,5)], 58.3 [t, C(11-NCH$_2$)], 59.1 [t, C(6,8)], 125.9 [s, C(4')], 128.1 [d, C(2',6') or C(3',5')], 128.4 [d, C(3',5') or C(2',6')], 139.7 [s, C(1')], 213.5 [s, C(9)]; ^{15}N NMR (DCCl$_3$) ppm 35.44 [N(7)]; ^{77}Se NMR (DCCl$_3$) ppm 79.51 [Se(3)]. Ketone **1b** was converted to **5b** without further purification. A HETCOR 2D experiment partially resolved the proton spectra of **1b** as in **1a**.

6,8-Diphenyl-3-selena-7-azabicyclo[3.3.1]nonan-9-one (2). A jacketed flask was charged with a solution of dry ammonium acetate (2.31 g, 30.0 mmol) in absolute ethanol (30 mL), which was warmed to 65 °C by boiling methanol in the jacket. A solution of ketone **3** (2.45 g, 15.0 mmol) and benzaldehyde (3.18 g, 30.0 mmol) in absolute ethanol (15 mL) was added in one portion. The resulting solution was stirred under nitrogen at 65 °C for 45 min.

(18) Gray, G. A. *Varian Instrument Appl.* **1982**, *16*, 11. Gray, G. A. *Org. Magn. Reson.* **1983**, *21*, 111 and references therein.

After the reaction mixture was cooled to about 30–40 °C, ether (15 mL) was added and stirring was continued for 10 min. Cooling (5 °C) overnight resulted in the formation of a yellow solid, which was filtered and recrystallized (ethanol) to give 0.89 g (17%) of ketone 2 as white needles: mp 207.0–208.5 °C dec; IR (KBr) cm⁻¹ 3320 (N–H), 1730 (C═O); ¹N NMR (DCCl₃) δ 1.77 [br s, 1 H, H(7)], 2.84 [br d, 4 H, H(2,4), *J* = 8 Hz], 3.59 [m, 2 H, H (1,5)], 5.04 [m, 2 H, H(6,8)], 7.20–7.50 [m, 10 H, ArH]; ¹³C NMR (DCCl₃) ppm 29.2 [C(2,4)], 54.0 [C(1,5)], 64.2 [C(6,8)], 144.4 [C(1')], 127.0 [C(3',5') or C(2',6')], 127.9 [C(4')], 128.7 [C(2',6') or C(3',5)], 207.2 [C(9)]; ¹⁵N NMR (DCCl₃) ppm 63.28 [N(7)]; ⁷⁷Se NMR (DCCl₃) ppm 25.38 [Se(3)]. Anal. (C₁₉H₁₉NOSe) C, H, N, Se.

7-Benzyl-3-selena-7-azabicyclo[3.3.1]nonane Hydroperchlorate (5a). A solution was made of 1a (2.0 g, 6.8 mmol) and hydrazine (95%, 5.0 g, 148 mmol) in triethylene glycol (40 mL). Potassium hydroxide (85%, 10.0 g, 152 mmol) was added and the resulting mixture was heated to 140 °C in an oil bath under a nitrogen atmosphere for 12 h. After cooling to room temperature, the solution was poured into water (200 mL) and the resulting suspension was extracted with ether (5 × 40 mL). The combined extracts were dried overnight (K₂CO₃) and cooled to 0 °C. Perchloric acid (60%, 2.0 g, 11.9 mmol) was added dropwise. The yellow orange solid that formed was filtered and recrystallized (methanol) to give 5a (1.94 g, 75%) as white needles: mp 161.0–162.0 °C dec; IR (KBr) cm⁻¹ 3440, 1105; ¹H NMR (Me₂SO-d₆) δ 1.75 [d, 1 H, H(9), *J* = 13.7 Hz], 1.88 [d, 1 H, H(9), *J* = 13.6 Hz], 2.41 [br s, 2 H, H(1,5)], 2.64 [d, 2 H, H(2,4)ₐₓ, *J* = 12.2 Hz], 3.19 [d, 2 H, H(2,4)ₑq, *J* = 12.1 Hz], 3.42 [m, 2 H, H(6,8)ₐₓ], 3.61 [d, 2 H, H(6,8)ₑq, *J* = 11.8 Hz], 4.32 [d, 2 H, H(10-NCH₂), *J* = 5.75 Hz]; ¹³C NMR (Me₂SO-d₆) ppm 22.0 [C-(2,4)], 25.2 [C(1,5)], 28.5 [C(9)], 56.6 [C(6,8)], 60.5 [C(10-NCH₂)], 128.9, 129.3, 129.8, 130.0 [ArC]; ¹⁵N NMR (Me₂SO-d₆) ppm 51.56 [N(7)]; ⁷⁷Se NMR (Me₂SO-d₆) ppm 96.61 [Se(3)]. Anal. (C₁₄-H₂₀ClNO₄Se), C, H, N, Se, Cl.

7-Phenethyl-3-selena-7-azabicyclo[3.3.1]nonane Hydroperchlorate (5b). A jacketed flask was charged with a mixture of ketone 1b (1.3 g, 4.2 mmol), N₂H₄ (95%, 2.0 g, 59 mmol), and KOH (85%, 6.0 g, 91 mmol) in triethylene glycol (40 mL). The flask was equipped for simple distillation under a rapid stream of nitrogen. The reaction mixture was heated to 140–145 °C by boiling xylene contained in the jacket. Heating was continued under a nitrogen stream for 5 h. During this time, a small amount of water and hydrazine distilled out. The resulting clear, light brown solution was cooled in a water bath to room temperature and was then poured into ice–water (200 mL). The white suspension that formed was extracted with ether (5 × 40 mL). The combined ether extracts were washed with brine (30 mL) and dried (K₂CO₃) overnight. After the desiccant was filtered out, this ether solution was cooled to 0–5 °C in an ice bath and 60% HClO₄ (1.0 g, 6.0 mmol) was added dropwise *very slowly*. After the mixture was stirred overnight, the resulting orange precipitate was filtered and recrystallized (methanol, decolorizing carbon) to give 0.67 g (40%) of 5b as white plates: mp 249–250 °C dec; IR (KBr) cm⁻¹ 3400, 1140; ¹H NMR (Me₂SO-d₆) δ 1.73 [br d, 1 H, H(9), *J* = 14.0 Hz], 1.89 [br d, 1 H, H(9), *J* = 13.8 Hz], 2.41 [br s, 2 H, H(1,5)], 2.64 [d, 2 H, H(2,4)ₐₓ, *J* = 12.1 Hz], 3.07 [t, 2 H, H(11-ArCH₂), *J* = 7.9 Hz], 3.20 [d, 2 H, H(2,4)ₑq, *J* = 12.2 Hz], 3.33 [m, 4 H, H(10-NCH₂), (6,8)ₐₓ], 3.86 [d, 2 H, H(6,8)ₑq, *J* = 12.3 Hz], 7.28–7.50 [m, 5 H, ArH], 8.89 [br s, 1 H, H(7)]; ¹³C NMR (Me₂SO-d₆) ppm 21.9 [t, C(2,4)], 25.3 [d, C(1,5)], 28.5 [t, C(9) or C(11-ArCH₂)], 29.9 [t, C(11-ArCH₂) or C(9)], 56.7 [t, C(6,8)], 58.8 [t, C(10-NCH₂)], 126.8 [d, C(4')], 128.5 [d, C(2',6',3',5')], 136.2 [s, C(1')]; ¹⁵N NMR (Me₂SO-d₆) ppm 48.25 [N(7)]; ⁷⁷Se NMR (Me₂SO-d₆) ppm 88.42 [Se(3)]. Anal. (C₁₅H₂₂ClNO₄Se) C, H, N, Se.

7-Benzyl-3-selena-7-azabicyclo[3.3.1]nonane-9,9-diol Hydroperchlorate (6). Ketone 1a (0.65 g, 2.2 mmol) was dissolved in dry benzene (250 mL). Perchloric acid (60%, 1.0 g, 6.0 mmol) was added dropwise very slowly with cooling and swirling. This precipitated an orange solid, which adhered to the sides of the flask. The benzene was decanted and the solid was recrystallized (95% ethanol) to give the diol hydroperchlorate 6 (0.62 g, 68.3%) as white needles: mp 214.0–216.0 °C dec; IR (KBr) cm⁻¹ 3430, 1080; ¹H NMR (Me₂SO-d₆) δ 2.43 [br s, 2 H, H(2,4)ₐₓ], 2.72 [br d, 2 H, H(2,4)ₑq], 3.22–3.50 [m, 6 H, H(6,8)ₐₓ, H(1,5), O*H*], 3.50–3.64 [m, 2 H, H(6,8)ₑq], 4.35 [d, 2 H, H(10-NC*H₂*)], 7.40–7.70 [m, 5 H, ArH], 9.20 [br s, 1 H, H(7)]; ¹³C NMR (Me₂SO-d₆) ppm 21.1

[C(2,4)], 34.7 [C(1,5)], 54.9 [C(6,8)], 60.1 [C(10-NCH₂)], 92.5 [C(9)], 129.2, 129.7, 130.0, 130.5 [ArC]; ¹⁵N NMR (Me₂SO-d₆) ppm 51.88 [N(7)]; ⁷⁷Se NMR (Me₂SO-d₆) ppm 62.39 [Se(3)]. Anal. (C₁₄-H₂₀ClNSeO₆) N, Se.

6,8-Diphenyl-3-selena-7-azabicyclo[3.3.1]nonane (7). Ketone 2 (0.189 g, 2.5 mmol) and hydrazine (95%, 3.0 g, 89 mmol) were dissolved in triethylene glycol (40 mL). This solution was placed in a jacketed flask equipped for simple distillation under a rapid stream of nitrogen. Water was boiled in the jacket at about 100 °C with stirring for 2 h. Potassium hydroxide (85%, 1.0 g, 15 mmol) was added and the temperature was increased to about 207 °C by boiling tetralin in the jacket. As the temperature increased, a gas evolved, presumably nitrogen. After stirring at this temperature for 4 h, 3 mL of water and excess hydrazine had distilled out. The reaction mixture was cooled to 60–70 °C and was then poured into ice–water (200 mL). The filtered solid was recrystallized (ether, decolorized carbon) to give 0.63 g (74%) of amine 7 as white needles: mp 193.5–195.0 °C dec; IR (KBr) cm⁻¹ 3250 (N–H); ¹H NMR (C₆D₆) δ 0.83 [dt, 1 H, H(9), *J* = 12.0, 1.5 Hz], 1.34 [m, 1 H, H(7)], 1.78 [m, 2 H, H(1,5)], 2.00 [dd, 2 H, H(2,4)ₐₓ, *J* = 12.0, 1.4 Hz], 2.33 [m, 1 H, H(9)], 2.84 [dd, 2 H, H(2,4)ₑq, *J* = 12.0, 2.0 Hz], 4.34 [d, 2 H, H(6,8), *J* = 2.0 Hz], 7.1–7.4 [m, 10 H, ArH]; ¹³C NMR (C₆D₆ @ 50 °C) ppm 25.1 [C(2,4)], 27.2 [C(9)], 34.5 [C(1,5)], 62.0 [C(6,8)], 126.9 [C(2') or C(3')], 127.2 [C(4')], 128.7 [C(3') or C(2')], 151.9 [C(1')]; ¹⁵N NMR (C₆D₆) ppm 55.68 [N(7)]; ⁷⁷Se NMR (C₆D₆ @ 50 °C) ppm 2.38 [Se(3)]. Anal. (C₁₉H₂₁NSe) C, H, N, Se.

6,8-Diphenyl-3-selena-7-azabicyclo[3.3.1]nonane Hydroperchlorate (8). A solution was made of amine 7 (0.63 g, 1.8 mmol) in benzene (100 mL). Perchloric acid (60%, 1.0 g, 6.0 mmol) was added dropwise *very slowly* with swirling. The resulting mixture was allowed to stand at room temperature with occasional swirling for 3 h. The orange solid that formed was filtered and recrystallized (methanol) to give 0.62 g (78%) of salt 8 as white needles: mp 288.0–289.0 °C dec, sealed tube); ¹H NMR (Me₂SO-d₆) δ 1.78 [br d, 1 H, H(9), *J* = 13.0 Hz], 2.36 [br d, 2 H, H(2,4)ₐₓ, *J* = 12.0, 2.0 Hz], 4.73 [br d, H, H(6,8), *J* = 3.0 Hz], 7.19–7.70 [m, 10 H, ArH], 8.72 [m, 1 H, H(7)ₐₓ], 9.67 [m, 1 H, H(7)ₑq]; ¹³C NMR (Me₂SO-d₆) ppm 23.5 [C(2,4)], 26.6 [C(9)], 31.2 [C(1,5)], 61.5 [C(6,8)], 128.5, 128.6, 128.7, 137.0 [C(1')]; ¹⁵N NMR (Me₂SO-d₆) ppm 57.91 [N(7)]; ⁷⁷Se NMR (Me₂SO-d₆) ppm 1.16 [Se(3)]. Anal. (C₁₉H₂₂ClNO₄Se) C, H, N, Se.

Experimental for X-ray Data Collection for 7-Benzyl-3-selena-7-azabicyclo[3.3.1]nonan-9-one (1a). A crystal of 7-benzyl-3-selena-7-azabicyclo[3.3.1]nonan-9-one (1a) was sealed in a capillary and mounted on a Syntex P3 automated diffractometer. Unit cell dimensions (Table II) were determined by least-squares refinement of the best angular positions for 15 independent reflections (2θ > 15°) during normal alignment procedures with molybdenum radiation (λ = 0.710 69 Å). The intensities of three standard reflections were remeasured after every 97 reflections, and since the intensities of these reflections showed less than 6% variation, corrections for decomposition were deemed unnecessary. Data were corrected for Lorentz, polarization, and background effects. Refinement of scale factor, positional, and anisotropic thermal parameters for all non-hydrogen atoms was carried out to convergence. Hydrogen atom positions were determined from a difference Fourier synthesis. These positions were included in the final cycles of refinement but were held invariant.[20] Anomalous dispersion corrections were made for selenium. Scattering factors were taken from Cromer and Mann.[21] Unit weights were used until the final cycles of refinement when a weight = 1/σ(F) was introduced.

Experimental for X-ray Data Collection for 7-Benzyl-3-selena-7-azabicyclo[3.3.1]nonane Hydroperchlorate (5a).

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Preliminary investigations indicated that the crystal system of **5a** was orthorhombic. Lattice parameter and intensity data were collected on an Enraf-Nonius CAD-4 automatic X-ray diffractometer fitted with a liquid N_2 low-temperature device. The receiving aperture, which had a variable width of $(4.0 + 0.86\theta)$ mm and a constant height of 5 mm, was located 173 mm from the crystal. The intensities of three reflections, remeasured after every 200 reflections, showed no significant variation during the time of data collection.

Positions of the non-hydrogen atoms were refined by a full-matrix least-squares routine using anisotropic thermal parameters for the non-hydrogen atoms.[22] Scattering factors were obtained from *International Tables for X-ray Crystallography*.[23] An analysis of the variance, after refinement of the data, revealed no systematic variance of $\sum \omega ||F_o| - |F_c||^2$ with either $\sin \theta$ or F.[24]

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Flavones. 1. Synthesis and Antihypertensive Activity of (3-Phenylflavonoxy)propanolamines without β-Adrenoceptor Antagonism[1]

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The synthesis of a series of (3-phenylflavonoxy)propanolamines is described. These compounds were evaluated for potential antihypertensive activity in spontaneously hypertensive rats, as well as for in vivo and in vitro evidence of β-adrenoceptor antagonism. Some of the compounds of this series exhibited effective antihypertensive properties but did not antagonize β-adrenergic receptors. These active compounds represent a unique series of effective antihypertensive agents that, despite possessing structural characteristics typical of β-blockers, does not have β-adrenergic receptor blocking activity.

Ahlquist's concept of classifying adrenergic receptors into two distinct groups, α and β,[2] provided the basis for the emergence of a new class of drugs, β-adrenergic blocking agents, which have made a substantial impact on the understanding and the treatment of a variety of disease states. Propranolol, a well-known β-adrenergic blocking drug, was first introduced for the treatment of angina and later was observed to show significant antihypertensive activity in patients.[3,4] The discovery of this antihypertensive activity has led to the use of β-blockers as primary or secondary drugs in the treatment of hypertension.[5-8]

Despite the considerable attractiveness of β-adrenoceptor antagonists for treatment of hypertension, there is good rationale to attempt to extend the utility of β-adrenergic antagonists by incorporating desirable ancillary antihypertensive properties. For instance, prizidilol has been developed as a β-adrenoceptor antagonist having additional vasodilatory properties.[9] Also noteworthy has been the realization of labetalol, a new class of antihypertensive agent having both α- and β-adrenoceptor blocking properties,[10,11] whose antihypertensive efficacy is greater than that of simple β-adrenergic antagonists.[12] Based on these encouraging findings, our research efforts focused on developing a class of agents having both β-adrenoceptor antagonist and vasodilatory properties.

Scheme I
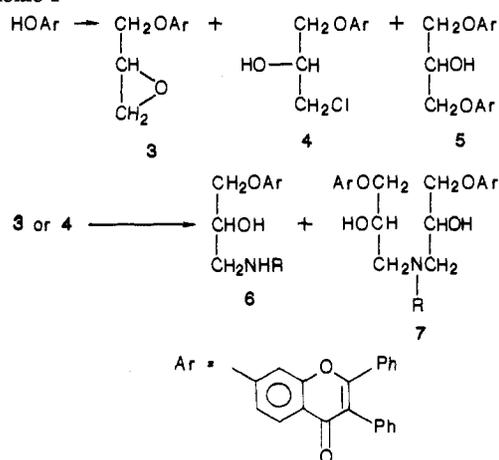
Our rationale for the design of compound **1** and its analogues was based on recordil (**2**), a chromone derivative,

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