Synthesis, Conformational Analysis, and Antiarrhythmic Properties of 7-Benzyl-3-thia-7-azabicyclo[3.3.1]nonan-9-one, 7-Benzyl-3-thia-7-azabicyclo[3.3.1]nonane Hydroperchlorate, and 7-Benzyl-9-phenyl-3-thia-7-azabicyclo[3.3.1]nonan-9-ol Hydroperchlorate and Derivatives: Single-Crystal X-ray Diffraction Analysis and Evidence for Chair–Chair and Chair–Boat Conformers in the Solid State

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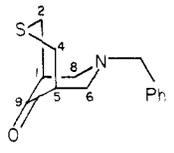
The synthesis of the title ketone has been completed via a type of Mannich reaction starting from 4-thianone. An X-ray diffraction analysis has revealed that the solid system is a *chair–boat* conformer with the sulfur atom in the *boat* portion of the bicyclic ring compound. Wolff–Kishner reduction of the ketone group gave 7-benzyl-3-thia-7-azabicyclo[3.3.1]nonane, which was isolated as the hydroperchlorate. However, X-ray diffraction analysis of the salt showed this solid to be a *chair–chair* conformer. Addition of phenylmagnesium bromide to the ketone gave a tertiary alcohol with the C–C_6H_5 bond being equatorial with respect to the thiane ring and axial with respect to the piperidine ring. The reaction of the Grignard reagent with the ketone to give this alcohol seems to be very stereospecific. An X-ray analysis of the hydroperchlorate of the alcohol confirmed the system to be a chair–chair form in the solid. The title compounds were screened for antiarrhythmic activity in anesthetized mongrel dogs in which myocardial infarctions had been created when the left anterior descending coronary artery was ligated. Vagal-induced slowing of the sinus mode firing rate was used to determine the underlying ventricular automaticity in the dogs, which averaged 164 ± 27 beats/min. Ventricular pacing was initiated to rates between 240 and 390/min. This technique resulted in the induction of rapid and sustained ventricular tachycardia. At doses of 3 and 6 mg/kg of body weight, 7-benzyl-3-thia-7-azabicyclo[3.3.1]nonane hydroperchlorate in alcohol (the solution was administered intravenously) was able to suppress markedly the induced ventricular tachycardia in five of six dogs. The compound also caused a 10–15% *increase* in blood pressure within a few minutes. The antiarrhythmic properties of this compound and others of related structure are discussed, and some comparison is made with the action of lidocaine in similar dog preparations.

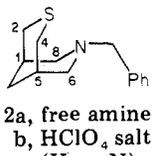
Bicyclo[3.3.1]nonanes (BCN)[1] and 3,7-diheterobicyclo-[3.3.1]nonanes (HBCN)[2,3] have novel stereochemical aspects as well as potentially useful medicinal properties. Indeed, several citations are available in the recent review[3] on the effects of certain 3,7-diazabicyclo[3.3.1]nonanes (DBCN) on the cardiovascular system. We now report the synthesis, conformational analysis, and action of the title compounds on induced arrhythmias in dogs. In addition, single-crystal X-ray diffraction analysis for each of these compounds is also recorded.

Results and Discussion

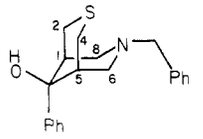
Chemistry. Although a Mannich-type condensation of 1-hetera-4-cyclohexanones with an amine and an aldehyde appears at this time to be one of the better approaches to 3,7-diheterobicyclo[3.3.1]nonan-9-ones (HBCNO),[3] yields are commonly quite modest.[2-6] The title ketone **1a** was



1a, free amine
b, $HClO_4$ salt
(H on N)



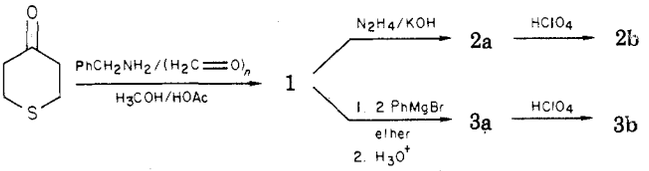
2a, free amine
b, $HClO_4$ salt
(H on N)



3a, free amine
b, $HClO_4$ salt
(H on N)

obtained via this technique, but to obtain the maximum yield (38%) required care, including control of such parameters as the order of addition of reagents, the pH of the reaction mixture, the solvent employed, and the rate of addition of 4-thianone.

Reduction (Wolff–Kishner) of **1a** gave **2a** in good yield



but as an oil, which was converted to perchlorate **2b** (82%). Recrystallization of crude **2b** from ethanol gave a product of high purity, which produced consistent biological screening data. Alcohol **3a** was prepared (81%) by the addition of 2 equiv of phenylmagnesium bromide to ketone **1** in ether in approximately 2 h. Recrystallization of crude **3a** from ethanol gave only one pure isomer. Consequently, the addition appeared to be very stereoselective.

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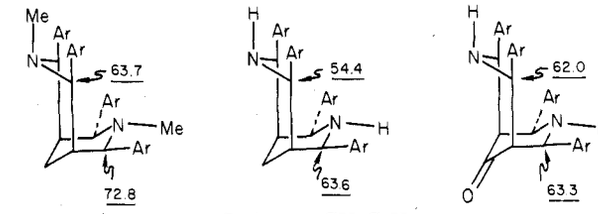
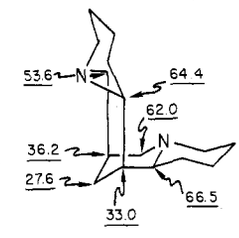
Analysis of a single crystal of free amine **1a** revealed a chair–boat (CB) form in the solid state, and this will be discussed shortly. In contrast, such analyses of salts **2b** (from free amine **2a**) and **3b** (from free amine **3a**) revealed that both are chair–chair (CC) forms in the solid state. If one assumes a BC form for **1a** in solution, intuitively one might expect the addition of the phenyl group to occur from the side on which the S atom resides if coordination between the Grignard reagent and the S and O (of the C=O group) atoms developed. Since this direction of addition was not observed as part of the major pathway for the reaction, possibly coordination involving the S atom is weak and/or S may simply block attack of the Grignard aggregate from the S side of the carbonyl face. At this time there does not appear to be another obvious argument that is tenable to explain the results, since the yield of **3b** (and therefore presumably **3a**) from **1a** is greater than 80%. Eliel and co-workers[6] have noted that attack of a nucleophilic type occurred from the least hindered side of *cis*-2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ones,[6] which, however, contained the chair–boat forms.

Infrared analysis of **1a** revealed a band at 1720 cm^{-1} for the C=O group; however, this type of peak was surprisingly absent from the spectrum of perchlorate **1b**. This is reminiscent of the behavior of 7-benzyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-one, which formed a hydrate when treated with perchloric acid.[4] Indeed, hydration of the carbonyl group has been noted in certain quaternary salts of piperidones[7] and 4-phosphorinanones.[8] The perchlorate **2b** had absorption at 3400 cm^{-1} (N–H) while alcohol perchlorate **3b** displayed a band at 3490 cm^{-1} (OH). Both salts had a common absorption at 1100 cm^{-1} for perchlorate ion.[9]

^1H NMR analyses of compounds **1–3** were relatively uninformative, except for the obvious signals for protons of the CH_2 group bonded to the phenyl. However, in all cases, the ^{13}C NMR spectra clearly showed that the carbons adjacent to the more electronegative nitrogen atom were downfield from the carbons attached to sulfur (see Experimental Section), as is reasonable.[10] Although known, ^{13}C NMR data for these types of HBCN are relatively rare,[4-6,10,11] but some analogies exist with the shifts in simple 1-heteracyclohexanes[12] and 1-hetera-4-cyclohexanones.[13] It is interesting that the C(α) in **1a** (α to sulfur in the boat conformer) is *deshielded* by nearly 4.6 ppm compared to the corresponding shift (30.0 ppm) in 4-thianone.[13] In contrast, the chemical-shift *difference* for C(α) in **2a** and thiane (29.1 ppm) is 2.3 ppm.[12] The origin of the greater deshielding of C(α) in **1a** compared to that in 4-thianone is speculative but may be due to an alteration in hybridization on the carbon because of ring flattening near the sulfur end of the molecule, as revealed in the X-ray analysis. There is also the hint of interaction between S and C(9) in the solid state, which may affect the shielding of C(α) in **1a**. Of course, 4-thianone is a mobile system, and the shift for C(α) is an average value. Surprisingly, very little change was observed in the chemical shift of C(6,8) [C(α) to N] in **1a**, **2a**, and **3a** [the axial phenyl group at C(9) in the piperidine ring of **3a** does shield C(6,8) to a small extent compared to the same carbon shifts in **1a** and **2a**]. It is interesting that in compounds **4–7** and **7a**, the benzylic carbon in the boat con-



4, Ar = p-$CH_3C_6H_4$ 5, Ar = p-$CH_3C_6H_4$ 6, Ar = p-$CH_3C_6H_4$



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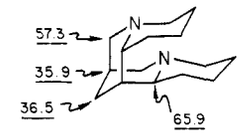

7a

former was always at higher field in **4–6**[11] and for similar carbons in sparteine (**7**)[14] compared to the chemical shift for the benzylic carbon in the chair conformer. This is noteworthy since the heteroatoms are identical in these four systems. Another curious observation is the *downfield* shift (5.6 ppm) of C(6,8) in **1a** compared to the C(α) in *N*-benzyl-4-piperidone,[13] which may be due to the fact that in the latter mobile system, C(α) experiences an averaging effect by the *N*-benzyl group, which is inverting rapidly on the nitrogen atom while, in addition, ring reversal is in operation.

Several experiments were performed to assess the conformational integrity of **1a** and **2a** in solution. A variable-temperature study of **1a** (from room temperature to −120 °C) showed only the spectrum changing from the pattern given in the Experimental Section to a broad singlet at −120 °C. A similar ^{13}C NMR analysis revealed essentially no change in the spectrum down to −85 °C. However, from −90 to −120 °C, small additional signals began to emerge, the shifts of which were relatively close to those observed at room temperature. These data from both experiments suggest to us that the nitrogen inversion barrier is of such magnitude that two nitrogen invertomers are visible on the NMR time scale within this low-temperature range, and the ^{13}C NMR shifts for each N-invertomer are visible. Heating **1a** at 150 °C for 24 h under N_2 resulted in the compound being recovered unchanged. In addition, an examination and comparison of the ^{13}C NMR spectrum of **1a** with that of 3-azabicyclo[3.3.1]nonan-9-one (**8**) supports the variable-temperature data, which suggests that **1a** is a CB in solution. Comparison of similar shifts in models cyclohexanone and 4-thianone showed sharp differences. Interestingly, all shifts in **1a** are *upfield* from those in **8**, but the *differences* are small compared to the differences in the model compounds.

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(12) Lambert, J. B.; Netzel, D. A.; Sun, H. N.; Lilianstrom, K. K. *J. Am. Chem. Soc.* **1976**, *98*, 3778.
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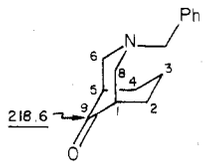
(14) (a) Bohlmann, F.; Zeisberg, R. *Chem. Ber.* **1975**, *108*, 1043. (b) Private communication from Professor Bohlmann.



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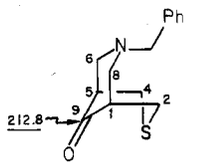
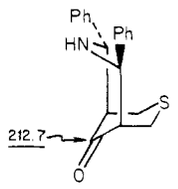


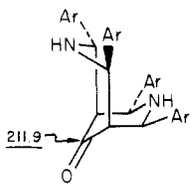
1a

	C(1,5)	C(2,4)	C(6,8)	C(9)
8 – 1a	−0.8 ppm	−1.0 ppm	−0.1 ppm	−5.8 ppm
cyclohexanone – 4-thianone	+2.1		+2.9	−0.8

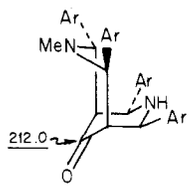
Moreover, we have noted that the shifts for C(9) in certain systems believed to be CB forms in solution are at *higher field* than in related systems considered to be in CC forms. For example, CB ketones **1a** and **9–13** have shifts in the



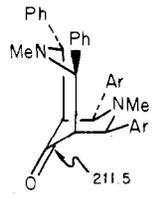
9,[11]



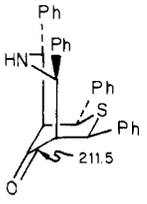
10,[11] Ar = 4-ClC$_6$H$_4$



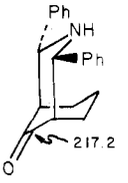
11,[11] Ar = 4-ClC$_6$H$_4$



12,[11] Ar = 4-CH$_3$C$_6$H$_4$



13[5]



14[6b]

range of 211.5–212.8 ppm, while ketones 8 and 14[6b] (believed to be CC forms in solution) exhibit shifts for C(9) that are 5–6 ppm further *downfield*. The increased shielding for C(9) in **1a** and in **9–13** may result from a shielding effect caused by the heteroatom being in a syn-periplanar arrangement with the C=O group. More specifically, a lone pair of electrons on the nitrogen or sulfur atom is likely directed toward C(9). We tentatively conclude that in a 3,7-diheterabicyclo[3.3.1]nonan-9-one system, a CB form can be diagnosed if the chemical shift for C(9) is at *higher field* than in a corresponding 3-heterabicyclo[3.3.1]nonan-9-one analogue. Large substituents on either ring, especially at the 3,7-positions or α to the heteroatom, might well cause a CB to form.[13c] Thus, our postulate seems best reserved for systems with small or no substituents, except hydrogen, in these positions. It should be added that the X-ray analysis of solids **1a** and **13**[5] indicate that C(9) leans toward the S and N atoms, respectively. Moreover, this hypothesis finds additional support in the comparison of the related models sparteine (**7**) and isosparteine (**7a**), which are two stable isomers.[14] The ^{13}C NMR chemical shifts for carbons α to nitrogen in the boat ring and at the bridge of the CB **7** are *upfield* compared to the counterparts in CC **7a**. Unfortunately, the resonances for the carbonyl carbon were not recorded for precursor analogues with a C=O bridge.[14b]

Further evidence available stems from a comparison of the ^{15}N NMR shifts for sparteine, which occur at 48.6 and 49.1 ppm (*downfield* from anhydrous liquid ammonia).[15] The nitrogen in the boat form was suggested to give the

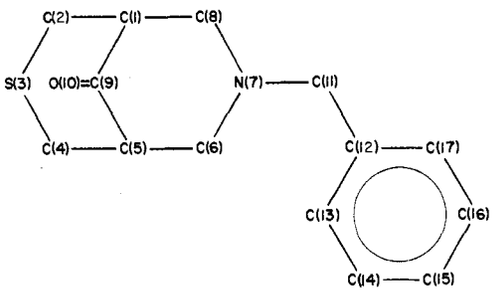
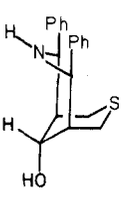


Figure 1. Schematic diagram of **1a**. Compound **2b** has no atom O(1). Compound **3b** has a hydroxyl and a phenyl group attached at C(9).

^{15}N signal at higher field. We have noted a large upfield shift for the ^{15}N signal [37.3 ppm from NH_3 (l)] for **1a** compared to that (49.1 ppm) in the model *N*-benzyl-4-piperidone. The shift in biased **1a** is presumably due also to a large syn-periplanar effect. We also tentatively conclude that in the rigid systems **1–3** there exists a γ-shielding effect from C(2,4) on nitrogen, which is a reported phenomenon from γ-oriented heteroatoms.[16] Protonation of the nitrogen of **1a** results in a large deshielding of the ^{15}N signal in **1b**, a situation already well known with protonated amines.[16] We note in passing that the ^{15}N signal for 2,4,6,8-tetraphenyl-3-thia-7-azabicyclo[3.3.1]-nonan-9-one[5] (59.73 ppm) (**13**) is at higher field compared to the similarly biased system *cis*-2,6-diphenyl-4-piperidone (66.4 ppm) and tentatively conclude that the carbonyl group [C(9)=O] may shield the nitrogen atom in the boat form of **13**. Muller and co-workers also detected a difference in the ^{15}N resonances for members of **4** and a few related compounds.[11] The latter and our examples appear to be the sole representatives for ^{15}N NMR analysis of HBCN, since even a recent review of the field did not include such a citation.[3] Taken as a whole, the ^{15}N and ^{13}C NMR data seem to support a CB form for **1a** in solution.

Single-Crystal X-ray Diffraction Analysis. In view of the possibility the 3-thia-7-azabicyclo[3.3.1]nonanes and derivatives in this study might exist as CB rather than CC systems and since differences in antiarrhythmic activity were observed, a single-crystal X-ray analysis was performed on **1a**, **2b**, and **3b**. Although **13**[5] and **15**[6] exist as



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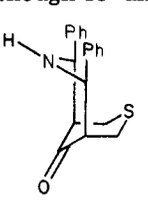

16

CB molecules in the solid state, ^{13}C NMR analysis was interpreted to favor a CB arrangement for **16** in which the S atom was in the chair portion.[6a] In comparison, we have found that **1a**, **2b**, and **3b** exist as CB, CC and CC forms, respectively, in the crystal state. In **1a**, the S atom resides in the *boat* part of the ring system. This suggests that perhaps in **16** the large phenyl groups α to the nitrogen atom force the N atom into the boat conformer. It should be pointed out that the related compounds **6**,[11] **13**,[5] and **15**[6] were prepared by synthetic routes that involved a Mannich-type of reaction with NH_4OAc and an aryl aldehyde with the appropriate ketone. This has, in all re-

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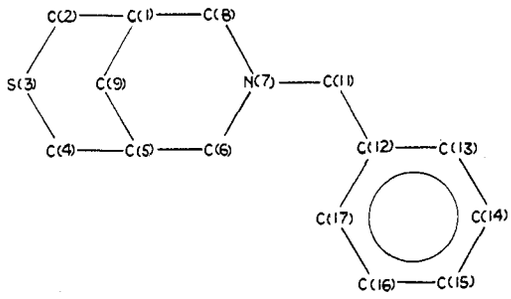

Figure 2. Schematic diagram of **2b**.

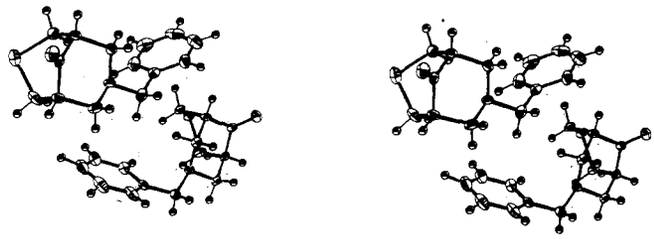

Figure 3. A stereo drawing of an asymmetric unit of 7-benzyl-3-thia-7-azabicyclo[3.3.1]nonan-9-one (**1a**).

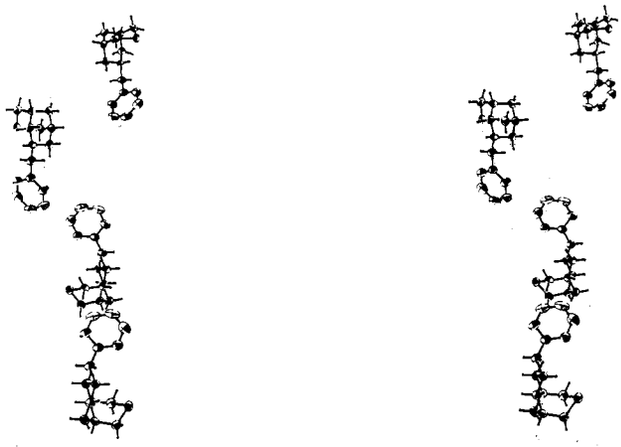

Figure 4. A stereo drawing of 7-benzyl-3-thia-7-azabicyclo-[3.3.1]nonane hydroperchlorate (**2b**).

ported cases, led to a nitrogen-containing ring, which was a boat conformer. While our work was being drafted for publication, this conclusion was reached in two other instances.[6a,b,11] Table I contains all pertinent crystal data for **1a**, **2b**, and **3b**, respectively. Bond distances, angles, and selected torsion angles are given in Tables II–IV, respectively. Schematic diagrams of **1a** and **2a** are shown in Figures 1 and 2, respectively. ORTEP[17] drawings of **1a**, **2b**, and **3b** are shown in Figures 3–5, respectively.

In the solid state, ketone **1a** is in a chair–boat (CB) conformation, with the sulfur-containing ring in a boat conformation and the nitrogen-containing ring in a chair conformation. The compound crystallizes in the space group $P\bar{1}$ with two molecules in the asymmetric unit (1A and 1B). The fused ring portion of the two molecules is virtually identical. The structure of **1a** contrasts with that of **13**, which, while also a CB conformation, has the sulfur-containing ring in a chair and the nitrogen-containing ring in a boat.[5]

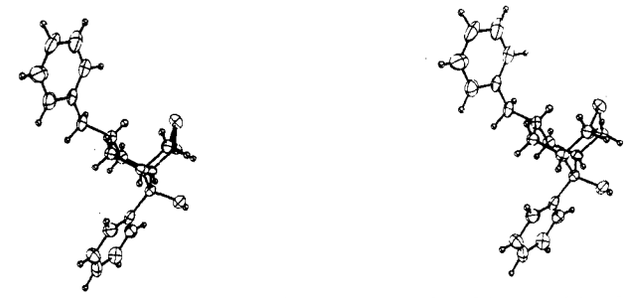

Figure 5. A stereo drawing of 7-benzyl-3-thia-7-azabicyclo-[3.3.1]nonan-9-ol hydroperchlorate (**3b**).

The hydroperchlorate **2b** exists in a CC conformation. The hydrogen from the perchloric acid is transferred to the nitrogen. An intramolecular hydrogen bond is formed between the nitrogen and sulfur. The S–N distance [3.038 (4) Å] is quite small compared to the average intermolecular hydrogen-bonded S–N distance (3.42 Å) found by Kuleshova and Zorkii.[20] However, the geometry around the sulfur is not ideal for forming hydrogen bonds [C(2)–S···H, C(4)–S···H, and S···H–N are 82.5 (9), 86.1 (10), and 128.8 (29)°]. The distances for N–H and S···H are 0.94 (4) and 2.42 (4) Å, respectively.

Solid **3b** is in a CC conformation. As in **2b**, a hydrogen from the perchloric acid is bonded to the nitrogen and forms an intramolecular hydrogen bond to sulfur [S–N, N–H, S···H, C(2)–S···H, C(4)–S···H and S···H–N are 3.047 (3), 0.87 (4), 2.38 (4) Å, 80.8 (7), 85.5 (7), and 134 (3)°, respectively]. A phenyl and hydroxyl group are bonded at C(9) with the C–C_6H_5 bond being equatorial with respect to the thiane ring and axial with respect to the piperidine ring.

The average C–S bond lengths found in **1a**, **2b**, and **3b** are 1.811 (5), 1.826 (4) and 1.821 (4) Å, respectively. These values are within 2 standard deviations of the mean paraffinic C–S bond length [1.817 (5) Å] given by Sutton[21] and within the range of C–S bond lengths found in other sulfur-containing, six-membered rings (1.811–1.840 Å).[22,23] The C–S length observed in **1a** is slightly shorter than the average C–S bonds in **13** [1.819 (2) Å].[5] The lengthening of the C–S bonds in **2b** and **3b** is probably due to the formation of the S···H–N hydrogen bond, which withdraws electron density from around the sulfur. Average C–N bond lengths for compounds **1a**, **2b**, and **3b** are 1.463 (4), 1.509 (4) and 1.511 (5) Å, respectively. The C–N bonds for **2b** and **3b** are lengthened because of the protonation of the nitrogen. A similar lengthening of C–N bonds has been reported by Skrzypczak-Jankun et al.,[24] by Speck,[25] and by Singh and Ahmed.[26] The average C–N bond in **1a** is somewhat smaller than the average found in **13** [1.472 (4) Å].[5]

In both **1a** and **13**, the C(1)–C(9)–C(5) angle is smaller (113.3°) than ideal geometry (116°) for bicyclo[3.3.1]no-

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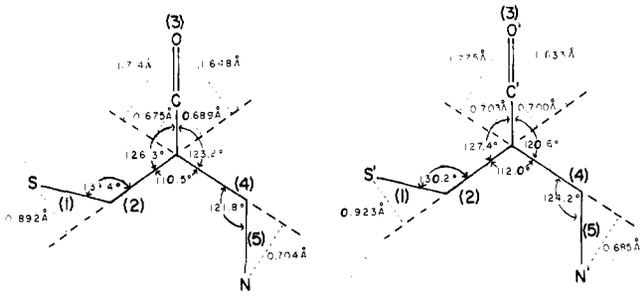

Figure 6. Angles between planes in **1a**. Dotted lines are perpendicular distances between the atoms and the indicated planes.

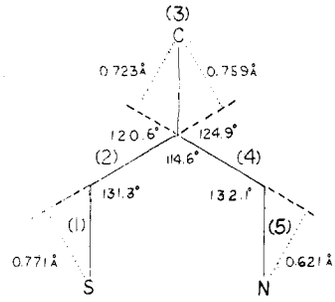

Figure 7. Angles between planes in **2b**. Dotted lines are perpendicular distances between the atoms and the indicated planes.

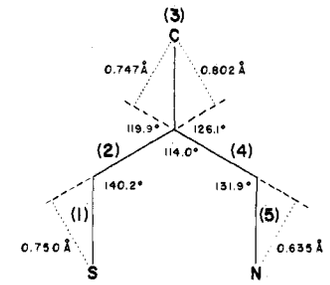

Figure 8. Angles between planes in **3b**. Dotted lines are perpendicular distances between the atoms and the indicated planes.

nan-9-one,[27] suggesting some strain in the carbonyl groups. The carbonyl groups of the two unique molecules of **1a** are relatively planar, as indicated by the sum of the angles around C(9) of 359.8 and 359.6° for **1a**, A, and **1a**, B, respectively. In both molecules, C(9) is displaced slightly (0.027 and 0.037 Å) from the plane formed by C(1), C(5), and O(10) in the direction of the sulfur atom. In **13** C(9) was displaced slightly toward the nitrogen by 0.026 Å.[5] Thus, these data suggest that in both **1a** and **13** there is some small interaction between C(9) and the heteroatom at the opposite end of the boat conformation.

The angles between various planes in the fused ring systems of **1a**, **2b**, and **3b**, displayed in Figures 6–8, show the major strains in the fused ring systems. In the ideal diamond structure, the angle between a three-membered plane and a four-membered plane would be 125.25°,[28] suggesting an ideal angle of 109.5° between adjacent four-membered planes. The angle between planes (2) and (4) has an average value of 111.3° in **1a** but increases to 114.6 and 114.0° in **2b** and **3b**, respectively. Plane (3) leans toward the sulfur ring in **2b** and **3b** and toward the nitrogen (chair) ring in **1a**, as shown by the angles between plane (3) and planes (2) and (4) in the respective structures. The nitrogen end of the piperidine ring in **1a** is puckered with an average angle between planes of 123.0 (12)° and an average torsion angle of 62.9 (12)°. The ideal

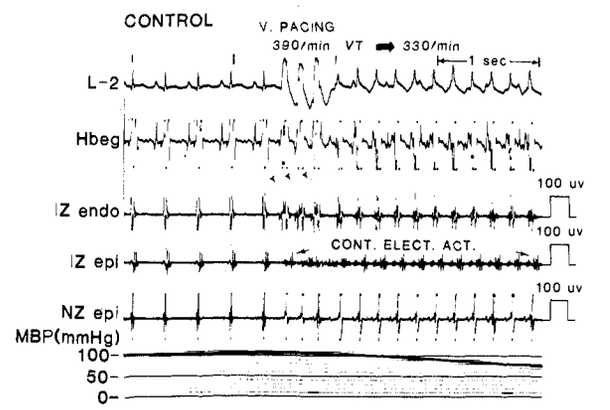

Figure 9. The induction of sustained ventricular tachycardia in the 24- infarcted dog heart. Traces from above are Lead II (L-2) electrocardiograms, His bundle electrogram (Hbeg), electrode catheter recording from the endocardial surface of the infarct zone (IZ endo), a composite electrode recording from the epicardial surface overlying the infarct zone (IZ epi), and a similar composite electrode recording from the noninfarcted or normal epicardial surface on the posterior left ventricle (NZ epi). The calibrated blood pressure tracing is shown at the bottom. See text for details.

chair conformation in cyclohexane has torsion angles of 56°. In contrast, both the nitrogen and sulfur ends of the rings in **2b** and **3b** are decidedly flattened. The average torsion angles around sulfur and nitrogen are, respectively, 45.6 (4) and 52.9 (4)° in **2b** and 44.5 (3) and 52.6 (4)° in **3b**. The angles between planes (1) and (2) and between planes (4) and (5) are 131.3° and 132.1° in **2b**. However, the angles between the corresponding planes are 140.2 (11) and 131.9 (9)° in **3b**. The greater flattening of the sulfur end of the ring is **3b** is probably due to the inherent flexibility of the bicyclo[3.3.1]nonane system and to steric interactions between the hydroxyl group at C(9) and the axial hydrogens on C(2) and C(4).

Biology. Antiarrhythmic properties of the compounds were assessed with 12 mongrel dogs, which were examined 24 h after ligation of the left anterior descending coronary artery.[29] At this time, multifocal, accelerated idioventricular rhythms are commonly seen interspersed with normal beats of sinus node origin.

Comparative Effects of the Title Compounds and Lidocaine. Six dogs were studied with compound **2b** at doses of 3 and 6 mg/kg, administered intravenously in a bolus of compound dissolved in 50% ethanol solution. For comparative purposes, six other dogs (also with 24-h myocardial infarction) were studied with a standard antiarrhythmic agent, lidocaine, at doses of 2, 4, and 6 mg/kg, administered intravenously. In the comparable clinical setting of acute myocardial infarction, lidocaine is the drug of choice for ventricular tachycardia.[30] The results are shown in Table V.

Compound **2b** caused a 10–15% *increase* in blood pressure at 2 min. Moreover, the induction of ventricular tachycardia by ventricular paced beats was completely inhibited in three dogs (see control in Figure 9; see test in Figure 10) even at rates of pacing 30–60 beats higher than the rate required to cause the arrhythmia before drug administration and 40 min (duration of action of **2b**) after the drug had been given. In two dogs, 3 and 6 mg/kg of **2b** simply slowed the rate of the ventricular tachycardia (induced by pacing) by an average of 100 beats/min.

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Table I. Crystal Data for 7-Benzyl-3-thia-7-azabicyclo[3.3.1]nonan-9-one (1a), 7-Benzyl-3-thia-7-azabicyclo[3.3.1]nonane Hydroperchlorate (2b), and 7-Benzyl-9-phenyl-3-thia-7-azabicyclo[3.3.1]nonan-9-ol Hydroperchlorate (3b)

	1a	2b	3b
mol formula	$C_{14}H_{17}SNO$	$C_{14}H_{20}SN{\cdot}HClO_4$	$C_{20}H_{23}NOS{\cdot}HClO_4$
M_r	247.4	334.7	425.9 g mol^{-1}
linear absorption coefficient	1.94	4.07	2.84 cm^{-1} (Mo Kα)
space group	$P\bar{1}$	$P2_12_12_1$	$Pna2_1$
cell dimensions:			
a, Å	11.105 (7)	6.604 (3)	10.046 (3)
b, Å	12.033 (6)	14.742 (9)	14.858 (6)
c, Å	9.899 (4)	16.177 (5)	13.084 (5)
α, deg	104.64 (4)	90.0	90.0
β, deg	85.40 (5)	90.0	90.0
γ, deg	92.39 (4)	90.0	90.0
volume, Å^3	1275	1569	1953
cell determination proced	50 reflections (Mo Kα_1 0.70926)	15 reflections ($15° < 2\theta < 30°$)	48 reflections (Mo Kα_1 0.70926)
Z, g cm^{-3}	4	4	4
density (calcd)	1.289	1.416	1.407
recrystn solvent	Skelly B	ethanol	ethanol
data collection range, deg	$1 < 2\theta < 53$	$2 < 2\theta < 80.2$	$1 < 2\theta < 50$
scan range	1.0 + 0.2 tan θ (θ-2θ scan)	+1.2 above Kα_2 (θ-2θ scan) −1.2 below Kα_1	0.86 ± 0.2 tan θ (θ-2θ scan)
standards	3 remeas after every 5000 scans	3 remeas every 97 reflections	3 remeas every 120 min
structure solution	SHELX[a]	MULTAN 80[b]	Patterson synthesis
final refinement	Blocked full matrix	full matrix	full matrix
wt scheme	ref 15	unit weights	$w = \sigma(F_o)^{-2}$
temp of data collection	138 ± 2	298 ± 2	138 ± 2K
no. of reflections meas	4721	4077	1776
no. of reflections obserd	3317	1764	1621
criteria for observation	$F > 2.5\sigma(F)$	$I > 3.0\sigma(I)$	$I > 2.0\sigma(I)$ [I(unobsd) assigned 1.40(I)]
final R	0.0762	0.037	0.033
Rw	0.0813		0.034
refinement of hydrogens	isotropic	only H of NH refined (isotropically)	isotropic
final difference Fourier map			
max density, e/Å^3	0.41	0.3	0.24

[a] Reference 18. [b] Reference 19.

Table II. Bond Distances for Compounds 1a, 2b, and 3b[a]

	1a, A	1a, B	2b	3b
C(1)-C(2)	1.559 (5)	1.537 (5)	1.503 (7)	1.533 (5)
C(2)-S(3)	1.814 (3)	1.813 (4)	1.831 (5)	1.817 (4)
S(3)-C(4)	1.813 (4)	1.802 (4)	1.820 (4)	1.825 (4)
C(4)-C(5)	1.550 (5)	1.545 (6)	1.505 (6)	1.524 (5)
C(5)-C(6)	1.543 (4)	1.533 (5)	1.533 (6)	1.535 (5)
C(6)-N(7)	1.459 (4)	1.464 (4)	1.506 (5)	1.502 (4)
N(7)-C(8)	1.459 (4)	1.458 (4)	1.512 (5)	1.510 (4)
C(8)-C(1)	1.543 (4)	1.538 (5)	1.538 (5)	1.518 (5)
C(1)-C(9)	1.512 (5)	1.516 (4)	1.510 (6)	1.552 (4)
C(5)-C(9)	1.505 (4)	1.513 (5)	1.547 (6)	1.547 (4)
C(9)-O(10)	1.218 (4)	1.216 (4)		1.433 (4)
N(7)-C(11)	1.467 (4)	1.469 (4)	1.516 (5)	1.521 (5)
C(11)-C(12)	1.512 (5)	1.511 (5)	1.522 (6)	1.517 (5)
C(12)-C(13)	1.390 (5)	1.392 (5)	1.363 (7)	1.385 (5)
C(13)-C(14)	1.388 (6)	1.368 (6)	1.404 (7)	1.384 (6)
C(14)-C(15)	1.385 (7)	1.392 (6)	1.365 (9)	1.366 (7)
C(15)-C(16)	1.383 (8)	1.359 (8)	1.356 (10)	1.386 (6)
C(16)-C(17)	1.382 (6)	1.390 (6)	1.396 (7)	1.391 (6)
C(17)-C(12)	1.398 (5)	1.388 (5)	1.398 (7)	1.391 (5)
C(9)-C(18)				1.542 (5)
C(18)-C(19)				1.401 (5)
C(19)-C(20)				1.387 (6)
C(20)-C(21)				1.369 (6)
C(21)-C(22)				1.379 (6)
C(22)-C(23)				1.391 (6)
C(23)-C(18)				1.374 (5)

[a] Values in parentheses are the estimated standard deviations (ESD) in the significant digits.

However, one dog, which did not show an inducible ventricular tachycardia prior to the administration of the drug, exhibited an inducible ventricular tachycardia/fibrillation after **2b** was given.

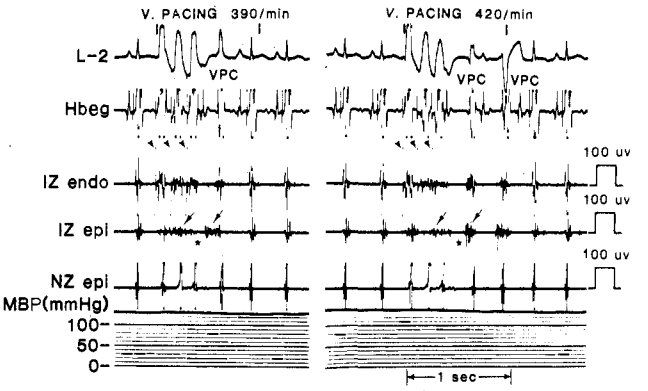

Figure 10. Inhibition of induced tachycardia after intravenous administration of **2b** (6 mg/kg). After drug administration, several attempts were made to induce sustained ventricular tachycardia (as in Figure 9) with three-beat ventricular pacing at rates up to 420/min. Note that with both 390 and 420/min, continuous activity is interrupted after the paced beats (asterisks) and only single or multiple premature ventricular contractions (VPC) occur.

Lidocaine caused a 5–10% *decrease* in blood pressure and slowed the rate of induced ventricular tachycardia in three dogs by an average of 40 beats/min. In one dog, no change in the inducible ventricular tachycardia was seen before and after the administration of lidocaine. In two dogs, ventricular tachycardias were induced only after the administration of lidocaine. In no dog was the induction of ventricular tachycardia completely abolished as was the case in three instances with compound **2b**.

The effects of compound **2b** and lidocaine were comparable on cardiac conduction through normal tissues,

Table III. Bond Angles for Compounds 1a, 2b and 3b[a]

	1a, A	1a, B	2b	3b
C(1)-C(2)-S(3)	111.9 (2)	112.8 (2)	114.7 (3)	115.5 (2)
C(2)-S(3)-C(4)	98.0 (2)	96.2 (2)	99.3 (2)	99.8 (2)
S(3)-C(4)-C(5)	112.9 (2)	112.8 (3)	114.5 (3)	113.8 (2)
C(4)-C(5)-C(6)	110.5 (3)	112.0 (3)	114.2 (3)	113.2 (3)
C(5)-C(6)-N(7)	109.3 (3)	110.6 (3)	111.8 (3)	113.1 (3)
C(6)-N(7)-C(8)	110.8 (3)	110.9 (3)	112.6 (3)	110.9 (2)
N(7)-C(8)-C(1)	109.3 (2)	110.0 (3)	111.4 (3)	111.6 (3)
C(8)-C(1)-C(2)	110.7 (3)	112.1 (3)	114.6 (4)	114.6 (3)
C(2)-C(1)-C(9)	111.7 (2)	111.2 (3)	111.9 (4)	111.7 (3)
C(4)-C(5)-C(9)	111.0 (3)	111.2 (3)	111.4 (3)	112.4 (3)
C(8)-C(1)-C(9)	106.4 (3)	106.5 (3)	109.4 (3)	110.1 (3)
C(6)-C(5)-C(9)	107.0 (2)	106.4 (3)	109.6 (3)	110.9 (3)
C(1)-C(9)-C(5)	113.3 (3)	112.1 (3)	109.6 (3)	106.7 (2)
C(1)-C(9)-O(10)	123.2 (3)	123.7 (3)		110.4 (3)
C(5)-C(9)-O(10)	123.3 (3)	123.8 (3)		105.3 (3)
C(6)-N(7)-C(11)	112.7 (2)	110.3 (3)	111.9 (3)	112.6 (3)
C(8)-N(7)-C(11)	111.7 (2)	111.5 (3)	110.0 (3)	110.6 (3)
N(7)-C(11)-C(12)	112.0 (2)	112.2 (3)	110.8 (3)	111.1 (3)
C(11)-C(12)-C(13)	120.7 (3)	120.9 (3)	120.7 (4)	119.5 (3)
C(11)-C(12)-C(17)	120.9 (3)	120.6 (3)	119.3 (4)	120.6 (3)
C(12)-C(13)-C(14)	120.6 (4)	120.9 (4)	119.2 (4)	119.8 (4)
C(13)-C(14)-C(15)	120.2 (4)	120.1 (4)	120.8 (5)	120.6 (4)
C(14)-C(15)-C(16)	119.9 (4)	119.8 (4)	119.8 (5)	120.4 (4)
C(15)-C(16)-C(17)	119.8 (4)	120.6 (4)	120.2 (5)	119.7 (4)
C(16)-C(17)-C(12)	121.1 (4)	120.2 (4)	120.0 (5)	119.7 (4)
C(17)-C(12)-C(13)	118.3 (3)	118.5 (3)	120.0 (4)	119.9 (3)
C(1)-C(9)-C(18)				112.2 (3)
C(5)-C(9)-C(18)				113.9 (3)
O(10)-C(9)-C(18)				108.2 (2)
C(9)-C(18)-C(19)				118.4 (3)
C(9)-C(18)-C(23)				123.7 (3)
C(18)-C(19)-C(20)				121.0 (3)
C(19)-C(20)-C(21)				120.4 (3)
C(20)-C(21)-C(22)				119.3 (4)
C(21)-C(22)-C(23)				120.4 (4)
C(22)-C(23)-C(18)				121.2 (3)
C(23)-C(18)-C(19)				117.6 (3)

[a] Values in parentheses are the estimated standard deviations (ESD) in the significant digits.

Table IV. Selected Torsion Angles for Compounds 1a, 2b and 3b[a]

	1a, A	1a, B	2b	3b
C(1)-C(2)-S(3)-C(4)	-53.8 (3)	-55.9 (3)	-45.4 (4)	44.2 (3)
C(2)-S(3)-C(4)-C(5)	54.1 (3)	55.7 (3)	45.8 (4)	-44.8 (3)
S(3)-C(4)-C(5)-C(6)	-121.2 (3)	-122.7 (3)	64.9 (4)	-66.4 (3)
C(4)-C(5)-C(6)-N(7)	62.8 (3)	62.9 (3)	-70.6 (4)	71.8 (4)
C(5)-C(6)-N(7)-C(8)	63.8 (3)	61.8 (3)	-52.6 (4)	52.3 (4)
C(6)-N(7)-C(8)-C(1)	-64.4 (3)	-61.7 (3)	53.3 (5)	-54.9 (4)
N(7)-C(8)-C(1)-C(2)	-62.6 (3)	-62.7 (3)	69.0 (5)	-66.1 (4)
C(8)-C(1)-C(2)-S(3)	121.4 (3)	123.0 (3)	-65.4 (4)	66.5 (3)
C(1)-C(9)-C(5)-C(4)	-67.7 (3)	-62.4 (4)	67.4 (4)	-69.7 (3)
C(5)-C(9)-C(1)-C(2)	62.8 (4)	62.3 (3)	-67.2 (4)	67.4 (3)
C(1)-C(9)-C(5)-C(6)	58.0 (3)	59.7 (4)	-60.0 (4)	58.1 (4)
C(5)-C(9)-C(1)-C(8)	-58.2 (4)	-60.0 (3)	60.9 (4)	-61.1 (4)
S(3)-C(2)-C(1)-C(9)	2.9 (3)	3.9 (3)	59.9 (4)	-59.6 (3)
S(3)-C(4)-C(5)-C(9)	-2.6 (3)	-3.9 (4)	-60.1 (4)	62.2 (3)
N(7)-C(8)-C(1)-C(9)	58.9 (3)	59.1 (3)	-57.5 (5)	60.8 (4)
N(7)-C(6)-C(5)-C(9)	-58.2 (3)	-58.7 (3)	55.3 (4)	-55.5 (3)
C(2)-C(1)-C(9)-O(10)	-122.2 (3)	-124.6 (3)		-46.5 (3)
C(4)-C(5)-C(9)-O(10)	122.2 (3)	124.5 (4)		47.6 (3)
C(8)-C(1)-C(9)-O(10)	116.9 (3)	113.0 (3)		-175.0 (3)
C(6)-C(5)-C(9)-O(10)	-117.1 (3)	-134.4 (4)		175.4 (3)
C(1)-C(8)-N(7)-C(11)	169.0 (3)	174.9 (3)	178.9 (4)	179.5 (3)
C(5)-C(6)-N(7)-C(11)	-170.1 (3)	-174.2 (3)	-177.1 (3)	176.7 (3)
C(8)-N(7)-C(11)-C(12)	-168.3 (3)	-61.0 (3)	169.7 (4)	-170.3 (3)
C(6)-N(7)-C(11)-C(12)	66.2 (3)	175.3 (3)	-64.3 (5)	65.0 (4)
N(7)-C(11)-C(12)-C(13)	39.6 (4)	-49.8 (4)	-62.8 (5)	80.3 (4)
N(7)-C(11)-C(12)-C(17)	-140.2 (3)	130.0 (3)	118.4 (4)	-100.7 (4)
C(2)-C(1)-C(9)-C(18)				-167.2 (3)
C(4)-C(5)-C(9)-C(18)				165.9 (3)
C(8)-C(1)-C(9)-C(18)				64.3 (3)
C(6)-C(5)-C(9)-C(18)				-66.3 (3)
C(1)-C(9)-C(18)-C(19)				44.9 (4)
C(1)-C(9)-C(18)-C(23)				-141.9 (3)
C(5)-C(9)-C(18)-C(19)				166.3 (3)
C(5)-C(9)-C(18)-C(23)				-20.5 (4)

[a] Values in parentheses are the estimated standard deviations (ESD) in the significant digits.

Table V. Comparative Effects of Compound 2b and Lidocaine on Induced Ventricular Tachycardia (VT)

	rate of VT[a]	abolition of VT: no./total	mean BP, mm
control	354 ± 22		98 ± 11
2b	250 ± 18	3/6	112 ± 9
control	345 ± 17		106 ± 14
lidocaine	315 ± 26	0/6	95 ± 12

[a] Values are means plus or minus standard deviation.

showing no significant change in intratrial, A-V nodal, His-Purkinje, and ventricular muscle conduction. However, lidocaine significantly slowed the spontaneous idioventricular rhythms. Other reports have indicated that these rhythms are the result of automatic[31] or triggered[32] mechanisms. Compound **2b** did not significantly affect the underlying idioventricular rate. It should be pointed out that these arrhythmias seldom produce severe hemodynamic impairment of the heart or fatal arrhythmia, i.e., ventricular fibrillation, in contrast to the lethal consequences of the induced, reentrant ventricular tachycardia (Figure 9).

Fifty percent ethanol solution (H_2O) was injected into the dogs in order to determine if some or any of the effects of **2b** were due to the solvent. Ethanol injected intravenously in appropriate volumes produced a small but consistent decrease in arterial blood pressure and no appreciable changes in ventricular ectopic activity either of the reentrant or nonreentrant types. There were no other

(31) Scherlag, B. J.; El-Sherif, N.; Hope, R.; Lazzara, R. *Circ. Res.* **1974**, *35*, 372.
(32) El-Sherif, N.; Mehra, R.; Gough, W. B.; Zeiler, R. H. *Circ. Res.* **1982**, *51*, 152.

Table VI. Relative Effects of Compounds 1a, 1b, and 3b[a]

		myocardial conduction		
no.	mean BP	normal (A-V, I-V)	abnormal	abolition of VT
1a	SL ↑ <10%	NC	NC	
1b	↑ 15%	NC	↓++	+
3b	SL ↑ <10%	↓++	↓+++	+

[a] Abbreviations used are as follows: VT, ventricular tachycardia; SL, slight; ↑, increase; ↓, decrease; NC, no change; +, slight degree; ++, moderate degree; +++, marked degree as compared with control.

remarkable responses to ethanol injections.

Similar studies have been carried out with compounds **1a**, **1b**, and **3b** in order to determine their antiarrhythmic properties. Table VI summarizes our preliminary findings. Compound **1a** showed a slight positive pressor effect but little antiarrhythmic efficacy. On the other hand, compound **1b** had properties similar to compound **2b**. Compound **3b** had a slight augmenting effect on blood pressure but, compared to **2b**, did exhibit a markedly depressed conduction not only in abnormal myocardium but also in normal myocardium, as well as depressing conduction in A-V nodal and His-Purkinje tissue. It is worthy of notation that some antiarrhythmic properties of **7** are known, as are those of 3,7-diazabicyclo[3.3.1]nonanes and related systems.[3] However, no examples have been reported in which screening data were obtained on live anesthetized dogs.

Summary

The three title compounds **1a**, **2b**, and **3b**, as well as **1b**, were screened in mongrel dogs for antiarrhythmic activity via the mechanism described previously. There was strong

evidence that **2b** had the best overall activity in that it prevented induction of ventricular tachycardias and increased blood pressure slightly. Since **2b** is a CC form, at least in the solid state, it is probable that this conformation alone is not wholly responsible for the activity observed, since **3b** is also a CC form. Thus, the nature of the group at C(9) must play a significant role as well. Interestingly, both **1a** and **1b** showed antiarrhythmic activity, but **1b** more closely resembled **2b** in characteristics of activity. Since **1b** is possibly a CB form, it seems reasonable that the type of conformations present may not be as important as might seem intuitively obvious from only considerations of steric factors.

Experimental Section

Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 681 or a Beckman IR 33. ^1H and ^{13}C NMR spectra were recorded on a Varian XL-100 (15) spectrometer equipped with a Nicolet TT-100 PFT accessory operating at 100.1 MHz for proton and 25.2 MHz for carbon (Me_3Si as internal standard). The ^{13}C NMR spectra were obtained operating in the FT mode utilizing broad-band proton decoupling and off-resonance decoupling where necessary. The ^{15}N spectra were recorded on a Varian XL-300 multinuclear, superconducting NMR system operating at 30.4 MHz, with formamide as an external standard (112.4-ppm downfield from liquid ammonia). All ^{15}N chemical shifts are recorded as referenced from the standard ^{15}N signal of liquid ammonia. The ^1H spectrum of **8** was recorded on a Hitachi X20A unit at 60 MHz at the University Georgia. Mass spectral data were obtained on a CEC Model 21-110B HR spectrometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN, or by Atlantic Microlab, Inc., Atlanta, GA. The ^{13}C NMR spectrum of *N*-benzyl-4-piperidone has been recorded.[13]

7-Benzyl-3-thia-7-azabicyclo[3.3.1]nonan-9-one (1a). A solution containing 0.40 g (0.0043 mol) of benzylamine and 1.0 g (0.033 mol) of paraformaldehyde in 15 mL of CH_3OH was made acidic with acetic acid (0.38 g, 0.0064 mol). To this solution was added 0.5 g (0.0043 mol) of tetrahydrothiopyran-4-one (4-thianone)[33] (Aldrich Chemical Co.) all at once, and the resulting solution was heated at reflux for 4–5 h. Evaporation of nearly all of the solvent produced an oily residue, which was partitioned between H_2O and ether (30 mL each). The aqueous layer was separated, washed twice with ether, and made basic with NaOH pellets (0.3 g, 0.0075 mol) at ice-bath temperature. Extraction of the resulting solution with ether (4 × 30 mL) gave, after combining extracts, a light yellow solution, which was dried (Na_2SO_4) for 30 min. Evaporation of the ether gave a red oil, which crystallized upon standing overnight. Skelly B (200 mL; bp 60–68 °C) was added to the solid, and the mixture was boiled on a steam bath for 30 min. The solution was filtered hot. Evaporation of the solvent gave a solid (0.5 g), which was sublimed at 80 °C (0.025 mm): yield 0.4 g (38%). The melting point of pure **1a** was 91–92 °C: IR (KBr) 1720 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 2.25–3.25 (m, 10 H, ring CH_2 and CH), 3.5 (s, 2 H, $C_6H_5CH_2$), 7.25 (m, 5 H, Ar H); ^{13}C NMR ($DCCl_3$) 34.6 [C(2,4)], 47.1 [C(1,5)], 58.4 [C(6,8)], 61.4 [C(1)], 212.8 [C(9)], 127.3, 128.2, 128.6, 137.9 (Ar C) ppm; ^{15}N NMR ($DCCl_3$) 37.36 ppm. Anal. ($C_{14}H_{17}NOS$) C, H, N, S.

A sample of **1a** (0.30 g, 0.001 mol) was placed in 15 mL of water and 15 mL of ethanol. To this was added dropwise 1 mL of 60% $HClO_4$ (Baker) over a 5-min period. A white solid precipitated but redissolved upon heating for 1 min. This solution was treated with decolorizing carbon and filtered hot. The solution was cooled to −20 °C, and the solid that formed, **1b**, was filtered: yield 0.32 g (76%); mp 214–215 °C; IR (KBr) 3460, 3280 (O–H, N–H), 1100 (ClO_4) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.4–2.8 (m, 6 H, ring CH_2 and CH), 3.1–3.65 (m, 6 H, ring CH_2 and CH and OH), 7.5–7.62 (m, 5 H, Ar H), 9.25 (s, 1 H, NH); ^{13}C NMR (Me_2SO-d_6) 29.0 [C(2,4)], 37.3 [C(1,5)], 54.7 [C(6,8)], 59.9 [C(1′)], 88.5 [C(9)], 129.0, 129.4, 129.9, 130.3 [Ar *C*] ppm; ^{15}N NMR (Me_2SO-d_6) 54.02 ppm. MS ($C_{14}H_{17}NOS{\cdot}HClO_4{\cdot}H_2O$) calcd, 365.0770, 247.1031 ($M^+ - HClO_4{\cdot}H_2O$); found, 247.1028 ($M^+ - HClO_4{\cdot}H_2O$).

7-Benzyl-3-thia-7-azabicyclo[3.3.1]nonane (2a) and the Hydroperchlorate (2b). Ketone **1a** (0.5 g, 0.002 mol) was added to a solution of 2 g (0.062 mol) of hydrazine hydrate (Fischer Scientific Co.) in 10 mL of triethylene glycol (Aldrich Chemical Co.). Potassium hydroxide pellets (3.5 g, Mallinkrodt) were added at once, and the resulting solution was heated at 145–150 °C for 4 h under nitrogen. Approximately 1.5 mL of distillate was removed during the heating via the use of fractional take-off. After cooling to room temperature, the solution was diluted (H_2O; 30 mL) and then extracted with ether (3 × 30 mL). The ether extracts were combined to give, after evaporation, a clear, moderately viscous oil, which did not crystallize with chilling. Refrigeration for long periods also did not induce crystallization. Mass spectral analysis of the oil gave the following results: MS ($C_{14}H_{19}NS$) calcd, 233.1128; found, 233.1232. IR and ^1H and ^{13}C NMR analyses were performed on the oil (crude **2a**): IR (film) 3100, 3075, 3040, 2920, 1620, 700 cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.50–3.00 (m, 12 H, ring H), 3.35 (s, 2 H, $C_6H_5CH_2$), 7.1–7.45 (m, 5 H, Ar *H*); ^{13}C NMR ($DCCl_3$) 27.1 [C(1,5)], 29.7 [C(9)], 31.4 [C(2,4)] ppm; ^{15}N NMR ($DCCl_3$) 36.99 ppm. If the ether extracts, cooled with ice and containing **2a** as described above, were treated slowly with 2 mL of $HClO_4$ solution (60% Baker), small white needles formed and were filtered and washed with dry ether. After drying at 25 °C (10 mm) for 20 min, the solid was recrystallized (ethanol) to give 0.55 g (82%) of **2b**: mp 155–156 °C. IR (KBr) 3400 (NH), 1100 (ClO_4) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.0–3.1 (m, 12 H, ring H), 4.27 (d, 2 H, $C_6H_5CH_2$), 7.5 (m, 5 H, Ar H), 9.25 (s, 1 H, NH); ^{13}C NMR (Me_2SO-d_6) 29.9 [C(2,4)], 24.9 [C(1,5)], 27.7 [C(9)], 55.65 [C(6,8)], 59.9 [C(1′)], 128.2, 128.6, 129.0, 129.45 (Ar *C*) ppm; ^{15}N NMR (Me_2SO-d_6) 54.16 ppm; MS, M^+ calcd, 233.1238; found, 233.1228. Anal. ($C_{14}H_{19}NS{\cdot}HClO_4$) C, H, N, S.

7-Benzyl-9-phenyl-3-thia-7-azabicyclo[3.3.1]nonan-9-ol (3a). To an ether solution of phenylmagnesium bromide [prepared from 0.94 g (0.006 mol) of C_6H_5Br, 0.2 g (0.0084 g at) of Mg, and 40 mL of dry ether] was added slowly a solution of ketone **1a** (0.5 g, 0.002 mol) in dry ether (25 mL). After the addition (15 min), the solution was stirred at room temperature for 1 h. To the new solution was added slowly, with cooling (ice bath), 20 mL of 9 M H_2SO_4 with stirring. After 1 h, the water layer was separated, cooled in an ice bath, and made basic via addition of KOH pellets. Dilution of this solution was achieved with 100 mL of H_2O. The mixture was extracted with ether (3 × 20 mL), and after combining the extracts, a new solution was obtained and dried (KOH). The solution was decanted and treated dropwise with $HClO_4$ (60%), with stirring, which resulted in the formation of a white precipitate, which was washed with ether. Recrystallization (twice from ethanol) gave 1.37 g (81%) of **3b**, mp 249–250 °C. Anal. ($C_{20}H_{23}NOS{\cdot}HClO_4$) C, H, Cl, N, S. A similar reaction of 1 equiv of **1a** with 1 equiv of phenylmagnesium bromide gave **3b** (81%) after 1 h: IR (KBr) 3490 (OH and NH) 1100 (ClO_4^-) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.5–3.15 (m, 10 H, ring H), 3.3 (s, 2 H, $C_6H_5CH_2$), 3.6 (s, 1 H, OH), 7.2–7.45 (m, 10 H, Ar H); ^{13}C NMR (Me_2SO-d_6) 27.3 [C(2,4)], 33.4 [C(1,5)], 55.1 [C(6,8)], 59.6 (Ar C), 67.42 [C(9)], 125.2, 127.8, 128.7, 128.9, 129.4, 129.9, 130.1, 141.8 (Ar C) ppm; ^{15}N NMR (Me_2SO-d_6) 54.35 ppm.

An aqueous solution of **3b** [0.150 g (0.35 mmol) in 50 mL of H_2O] was made basic with NaOH pellets. Extraction of the solution with ether (3 × 50 mL) gave a solution, which was dried (Na_2SO_4) and then evaporated. A white solid was obtained and was recrystallized (ether–petroleum ether, 1:1) to give 0.113 g (quantitative) of **3a**: mp 112–113 °C; IR (KBr) 3370 (OH and NH) cm^{-1}; ^1H NMR ($DCCl_3$) δ 2.2 (s, 1 H, OH), 2.4–3.0 (m, 8 H, ring H), 3.3 (s, 2 H, $C_6H_5CH_2$), 3.65–3.75 (dd, 2 H, ring H), 7.15–7.4 (m, 10 H, Ar H); ^{13}C NMR ($DCCl_3$) 29.2 [C(2,4)], 35.6 [C(1,5)], 55.5 [C(6,8)], 62.1 [C(1′)], 71.2 [C(9)], 125.2, 126.3, 127.4, 127.8, 128.1, 128.4, 139.0, 144.5 (Ar C) ppm; ^{15}N NMR ($DCCl_3$) 35.45 ppm. MS ($C_{20}H_{23}NOS$) calcd, 325.1500; found, 325.1505.

3-Benzyl-3-azabicyclo[3.3.1]nonan-9-one (8). A mixture of 4.9 g (50 mmol) of cyclohexanone, 12 g of paraformaldehyde, 5.4 g (50 mmol) of benzylamine, 3.0 g (50 mmol) of acetic acid, and 220 mL of methanol was stirred at room temperature for 15 days. The mixture was concentrated in vacuo, and the orange residue

(33) (a) Johnson, P. Y.; Berchtold, G. A. *J. Org. Chem.* **1970**, *35*, 584. (b) Garst, M. E.; McBride, B. J.; Johnson, A. T. *Ibid.* **1983**, *48*, 8.

was partitioned between 50 mL of chloroform and 50 mL of 5% aqueous hydrochloric acid. The lower phase was withdrawn, and the aqueous phase was further extracted with two, 40-mL portions of chloroform. The aqueous extracts were discarded. The aqueous phase was cooled at 0 °C, and 4 g of sodium hydroxide pellets was added. The suspension was extracted with two, 50-mL portions of petroleum ether (bp 30–60 °C). The combined extracts were dried (Na_2SO_4) and the filtrate was filtered, and concentrated in vacuo to give 3.5 g of a yellow oil. This was chromatographed on 97 g of 60–200 mesh silica gel. Elution with 150 mL of chloroform gave 1.9 g (17%) of a colorless oil after removal of solvent in vacuo. The product solidified during storage at 8 °C for several months. Trituration on a porous plate removed a small amount of liquid and left a white crystalline solid: mp 48–50 °C; IR (0.2 M in CCl_4, 0.1-mm path length) 1735 cm^{-1}, shoulder at 1715 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 1.80–2.50 (m, 8 H, CCH_2 and bridgehead CH), 2.55 (d, J = 10.5 Hz, 2 H, exo NCH), 3.10 (d, J = 10.5 Hz, 2 H, exo NCH), 3.10 (d, J = 10.5 Hz, 2 H, endo NCH), 3.45 (s, 2 H, $C_6H_5CH_2$), 7.35 (s, 5 H, Ar H). Anal. ($C_{15}H_{19}NO$) C, H, N.

Crystallography. Crystals of **1a**, **2b**, and **3b** were prepared by recrystallization from suitable solvents (Table I), and unit cell parameters of each were determined during normal alignment procedures for the automated diffractometers used. Data were collected by variable scan procedures and molybdenum radiation (Mo $K\alpha$, λ = 0.71069 Å). All data were corrected for background, Lorentz, and polarization effects. Hydrogen positional parameters were determined from a difference Fourier synthesis. Details of the final refinements are given in Table I. Tables of positional parameters, anisotropic thermal parameters, and F_{obsd}/F_{calcd} are available as supplementary material. Scattering factors were taken from ref 36.

Data for **1a** were collected on a Enraf-Nonius CAD-4 diffractometer fitted with a low-temperature apparatus. A receiving aperture with a variable width of (3.50 + 0.86 tan θ) mm and a constant height of 6 mm was located at a distance of 173 mm from the crystal. The maximum scan time for a reflection was 60 s. For each reflection, two-thirds of the scan time was spent scanning the peak and one-sixth of the scan time was spent scanning each of the two backgrounds.

The phases of 576 reflections, having a normalized structure factor (E) greater than 1.4, were used to construct E maps. The map with the highest reliability factor (parachor = 3.06) gave both structures among the top 38 peaks, with the exception of three carbon atoms. After isotropic refinement of the non-hydrogen atoms found in the initial E map, the remaining three atoms of the structures were located in difference maps. The non-hydrogen atoms were refined by least-squares methods in stages with isotropic and anisotropic thermal parameters.

An analysis of the variance in terms of the parity of the reflection indices, sin θ, and $[F_0/F_{max}]^{1/2}$, showed no significant variation of v for various ranges of the functions tested. Refinement was terminated when all parameter shifts were less than 10% of their corresponding standard deviations.

Data for perchlorate **2b** was collected on a Syntex-Nicolet P3 automated diffractometer equipped with a 1-mm collimator using a variable scan width. Backgrounds were counted for 10 s at positions 1.2° above $K\alpha_2$ and 1.2° below $K\alpha_1$. The structure was solved by MULTAN 80 utilizing normal computational procedures.[19] The final cycle of least squares showed all shifts and parameters to be less than 2% of their calculated values.

Lattice parameter data and intensity data for **3b** were measured on an Enraf-Nonius CAD-4 diffractometer. The receiving aperature with a variable width of (4.0 + 0.86 tan θ) mm and a constant height of 4 mm was located 173 mm from the crystal. The maximum scan time for a reflection was 90 s, with two-thirds of the time spent scanning the peak and the remaining time spent divided equally between the high- and low-θ backgrounds. The positions of the sulfur and chlorine atoms in **3b** were determined from an analysis of a Patterson map. Subsequent structure factor and electron density calculations revealed the positions of all remaining non-hydrogen atoms. The final structure analysis showed that $\sum\omega\Delta F^2$ did not vary significantly with either $\sin^2\theta$ or $|F_o|$, thus validating the weighting scheme used.

Biology. In anesthetized dog (30 mg/kg sodium pentobarbital given intravenously), the heart was exposed via a left thoracotomy, and the following electrical recordings were made: standard lead II of the electrocardiogram, His bundle electrogram from an electrode catheter in the aortic root, another electrode catheter in the left ventricle in contact with the endocardium bordering the infarct, a special composite electrode on the left ventricular epicardial surface overlying the infarct, and another composite electrode on the noninfarcted posterior epicardium of the left ventricle to serve as a control or reference.[34] Mean arterial blood pressure was monitored continuously. Two silver wires were inserted into the left vagosympathetic trunk. The sinus rhythm could be slowed sufficiently to unmask the underlying idioventricular rhythm, without interference from a competing sinus pacemaker, by delivering 20-Hz square wave pulse to the nerve trunk. Other pairs of wires were inserted into the right atrium for atrial pacing and right ventricle for ventricular pacing.

Vagal stimulation was applied to determine the underlying ventricular automaticity in 12 dogs (as described above), which, in these preparations, averaged 164 ± 27 beats/min, similar to the values described in previous studies.[31,35] Atrial pacing at rates from 180/min up to the rate at which second degree A-V block was induced (average: 300/min) was performed before and after drug administration in order to determine the effects of the compound on intra-atrial, A-V nodal, His-Purkinje, and ventricular muscle conduction properties. Ventricular pacing was then instituted by introducing three ventricular paced beats at rates between 240 and 390/min. The detailed methodology for inducing the tachycardia has been described elsewhere.[34,35] It was found that this method resulted in the induction of rapid and sustained ventricular tachycardia (averaging 340 ± 17 beats/min; see Figure 9). If rapid pacing or DC cardioversion was not instituted to "break" this tachycardia within 2 min, it would commonly degenerate into ventricular fibrillation. During sustained tachycardia, recording of continuous electrical activity from the epicardial area overlying the infarct (Figure 9) suggested a reentrant mechanism for these arrhythmias.

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Registry No. **1a**, 89398-04-9; **1b**, 89398-05-0; **2a**, 89398-06-1; **2b**, 89398-07-2; **3a**, 89398-08-3; **3b**, 89460-81-1; **8**, 81879-64-3; 4-thianone, 1072-72-6; benzylamine, 100-46-9; cyclohexanone, 108-94-1.

Supplementary Material Available: Structure factor amplitudes, atomic coordinates, and anisotropic factors for **1a**, **2b**, and **3b** (55 pages). Ordering information is given on any current masthead page.

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