Novel 3,7-Diheterabicyclo[3.3.1]nonanes That Possess Predominant Class III Antiarrhythmic Activity in 1-4 Day Post Infarction Dog Models: X-ray Diffraction Analysis of 3-[4-(1*H*-Imidazol-1-yl)benzoyl]-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane Dihydroperchlorate

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Several 3,7-diheterabicyclo[3.3.1]nonanes (DHBCNs) were prepared and screened in the Harris dog model for their ability to abolish pace-induced and sustained ventricular tachycardia (SVT) or prevent induction of ventricular tachycardia. In addition, an electrophysiological examination was made in the infarcted hearts of each animal to determine if more than one class activity was present. The examples exhibited predominately class III antiarrhythmic activity via a prolongation of the ventricular effective refractory period (VERP) in the models, although there may well be an underlying class Ib action present as exemplified by the ability of several of the agents to slow conduction in the myocardial infarcted dog hearts. 3-[4-(1*H*-Imidazol-1-yl)benzoyl]-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane dihydroperchlorate displayed powerful class III activity in the model systems while several other DHBCNs exhibited various degrees of class III action. An X-ray diffraction analysis revealed that this compound has a 3,7-diazabicyclo[3.3.1]nonane bicyclic unit in a chair−chair conformation.

Introduction

Sudden cardiac death (SCD) is a leading cause of mortality in which ventricular arrhythmias are believed to play a major role.[1] Prevention and control of ventricular tachycardias (VT)/ventricular fibrillation (VF) have very significant therapeutic importance. Patients who suffer from ischemic heart disease or congestive heart failure experience the majority of potentially lethal arrhythmias. Clinical evidence and many individual studies have concluded that most life-threatening arrhythmias are due to reentry.[2]

In the last decade, new antiarrhythmic agents (AAA) have been prepared which differed greatly in activity. Such agents have been designated as having class I−IV activity.[3] These classifications were assigned somewhat arbitrarily, but they are commonly associated with the following properties.[3] A class I agent must slow conduction of the cardiac impulse by blocking the fast Na^+ channel, as evidenced by a significant reduction of the upstroke of the transmembrane action potential (V_{max}).[3] Side effects with class I agents are proarrhythmia and negative inotropism along with certain gastrointestinal and CNS difficulties. Class II agents (β-blockers) antagonize the effects of catecholamines on cardiac tissue. A reduction in SCD has also been associated with some class II agents. Side effects include negative inotropic and chronotropic properties that severely restrict their useage.[3] Class III agents prolong transmembrane action potential duration (APD) and refractoriness without affecting cardiac conduction, i.e., V_{max}.[4] APD prolongation can result from a block of outward K^+ current or from an increase of the inward ion current.[4,5] Class IV agents are calcium channel antagonists and usually have minimal or no class I−III actions.[3] Several derivatives of the 3,7-diheterabicyclo-[3.3.1]nonane (DHBCN) family, such as **1** in Chart 1, have class I activity (i.e., class Ib).[6]

Lidocaine (**2**) has been the agent of choice in the treatment of lethal arrhythmias.[7] Several agents possess class II and class III activity such as propranolol (**3**) and sematilide (**4**), respectively, as shown in Chart 1.[8] Tedisamil (**5**) is related to **1** and is a recently reported antiarrhythmic agent possessing class III activity.[9]

Class I AAA, as mentioned earlier, are prescribed worldwide for the prevention of arrhythmias. These agents often reduce the frequency of premature ventricular contractions (PVC) but are rather poor in controlling life-threatening VT and VF. Results of the cardiac arrhythmia suppression trials (CAST) have clearly shown that the negative side effects can outweigh the clinical benefit of certain potent class I agents.[10] One recent approach for the development of new antiarrhythmic agents has been to introduce properties into a single molecule which induce actions in at least two different classes. For example, it was reported[11] that when certain features of propranolol (**3**) and sematilide (**4**) were combined to give **6**, an increased therapeutic index was realized compared to **3** and **4** individually in terms of preventing programmed, electrical stimulation-induced reentrant ventricular tachycardia (PES-VT) in dogs (Chart 2).[11] (±)-Sotatol (**7**) exhibits both class II and class III activity.[12] An

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Chart 1. Selected Antiarrhythmic Agents

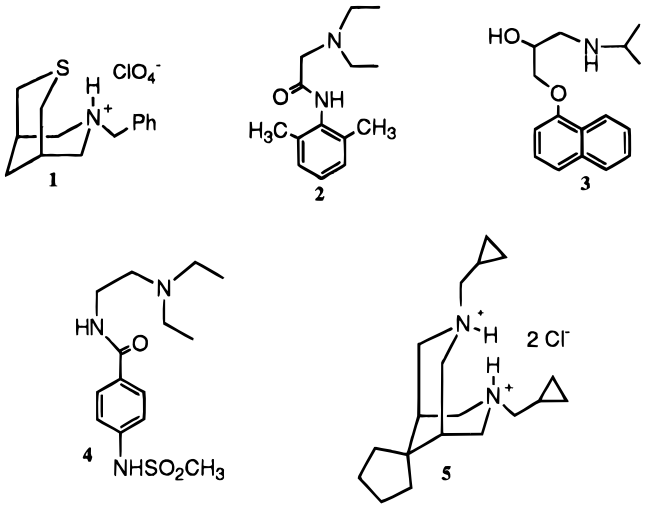
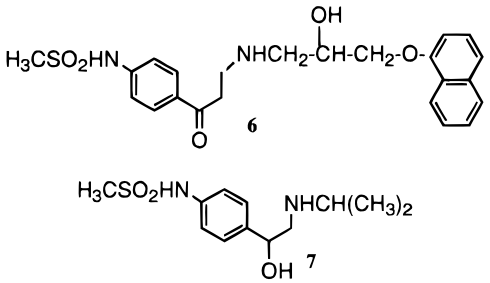
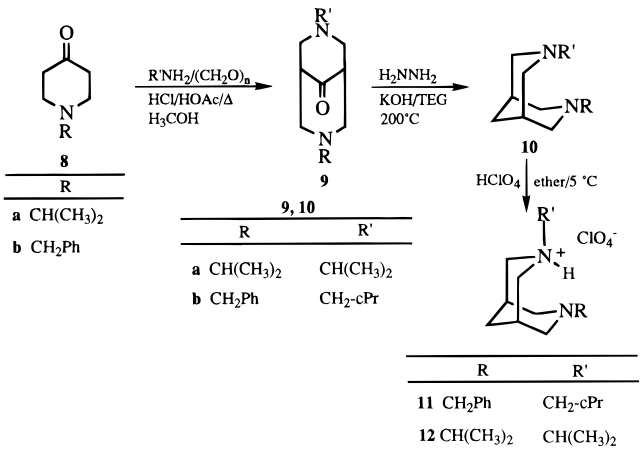


Chart 2. Antiarrhythmics with Combined Class Actions



Scheme 1

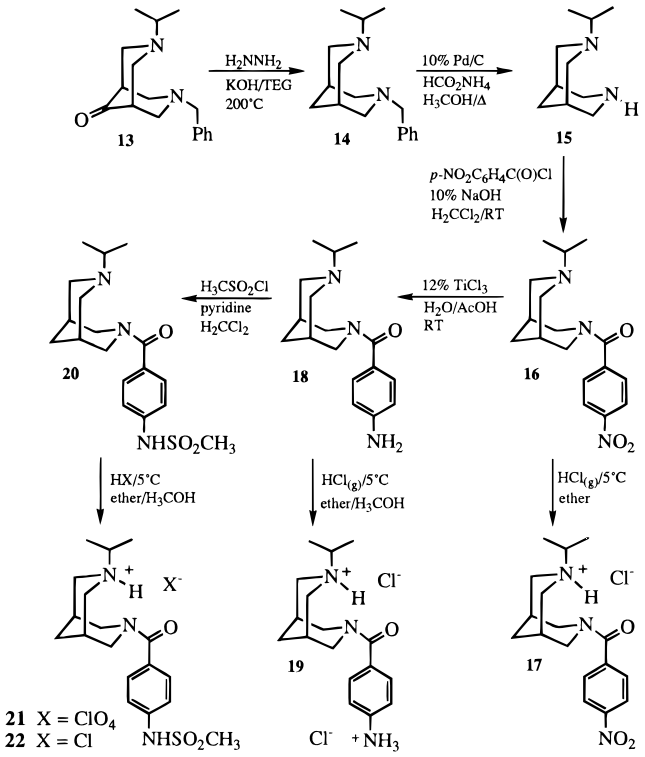


objective of the present work was to determine if multiclass antiarrhythmic action could be induced into certain members of 3,7-diheterabicyclo[3.3.1]nonanes (DHBCNs).

Chemistry

The preparation of several novel 3,7-diheterabicyclo-[3.3.1]nonanes has been achieved by the methods outlined below in Schemes 1−6. A modified double-Mannich condensation (Scheme 1) using piperidin-4-ones **8a** nd **8b** in the presence of HCl, glacial acetic acid, paraformaldehyde, and the appropriate primary amine led to ketones **9a** and **9b**. It has been observed[6a,b] that an additional equivalent of paraformaldehyde added during the reaction can increase the yields of product to above 70%. Wolff−Kishner reduction of ketones **9a** and **9b** gave amines **10a** and **10b**, respectively, in high

Scheme 2



yields. The corresponding solid hydroperchlorates **11** and **12** were easily prepared using perchloric acid. In all of our work to date, we have only isolated monosalts of members of the family of 3,7-diheterabicyclo[3.3.1]-nonanes. Tedisamil (**5**) is a dihydrochloride, but the exact conditions for its preparation have not been published to the best of our knowledge. We have no explanation for the formation of the monosalts in our present work, although space-filling models imply that the "bite" area between the heteroatoms is highly congested when one nitrogen is protonated.

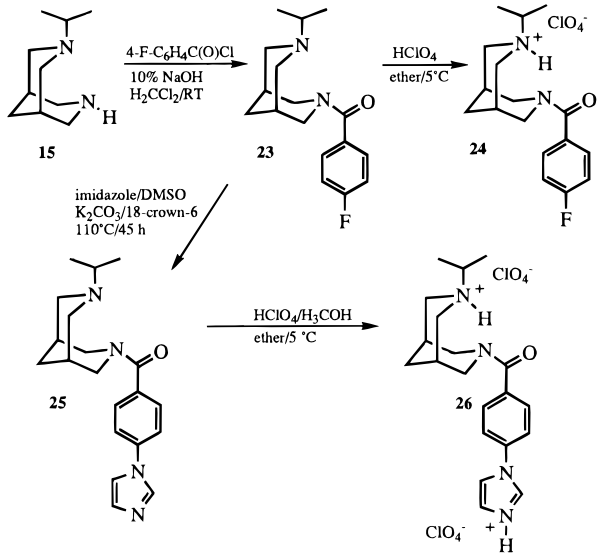
It had been noted earlier that certain *N*-aroyl derivatives of DHBCNs exhibited inhibitory activity with guinea pig myocardial Na^+,K^+-ATPase.[6i] It was rationalized that selected N-substituents on such systems might induce more than one class action in the antiarrhythmic agent. Reduction of ketone **13**[6] (Scheme 2) to amine **14**,[6] followed by debenzylation of the latter, gave key intermediate **15**.[6c,13] Using modified Schotten−Baumann conditions, the reaction of amine **15** with 4-nitrobenzoyl chloride produced benzamide **16** (97%).

Acidification of a solution of **16** with HCl(g) generated hydrochloride **17**. Conversion of the nitro group in **16** to an amino function using $TiCl_3$ gave benzamide **18** which was treated with HCl(g) to give the corresponding hydrochloride **19**. Sulfonylation of benzamide **18** with methanesulfonyl chloride/pyridine led to sulfonamide **20** which was converted to the hydroperchlorate and the hydrochlorides **21** and **22**, respectively.

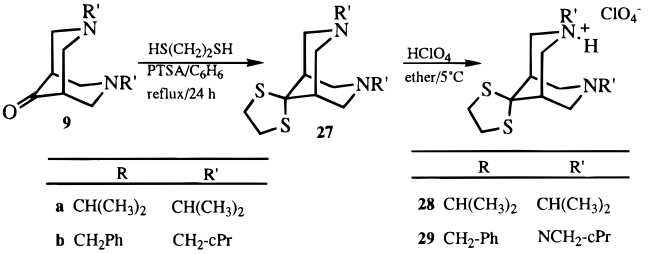
Amidation of **15** in aqueous methylene chloride produced benzamide **23** (Scheme 3) which was converted to its corresponding hydroperchlorate **24**. Nucleophilic aromatic substitution of **24** using imidazole, K_2CO_3, DMSO, and 18-C-6 gave amide **25** containing an imidazole moiety in the para position of the phenyl ring. Acidification of benzamide **25** with perchloric acid gave dihydroperchlorate **26**.

Masking of the carbonyl groups in ketones **9a** and **9b**

Scheme 3



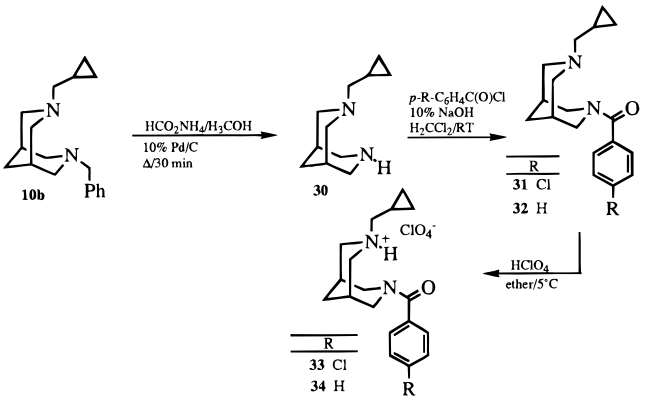
Scheme 4



	R	R'
a	$CH(CH_3)_2$	$CH(CH_3)_2$
b	CH_2Ph	CH_2-cPr

	R	R'
28	$CH(CH_3)_2$	$CH(CH_3)_2$
29	CH_2-Ph	NCH_2-cPr

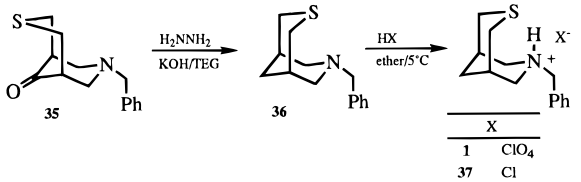
Scheme 5



with 1,2-ethanedithiol and *p*-tolunenesulfonic acid (PTSA in Scheme 4) led to thioketals **27a** and **27b** in good yields. The respective hydroperchlorates **28** and **29** were then prepared with perchloric acid in standard fashion.

Debenzylation of amine **10b** gave the key secondary amine **30** which, with an appropriate aroyl chloride, led to benzamides **31** and **32** (Scheme 5). Treatment of these compounds with perchloric acid resulted in formation of salts **33** and **34**, respectively. In addition to and because of the strong antiarrhythmic activity displayed by **1**,[6a,f] an evaluation of the activity of the corresponding hydrochloride **37** was deemed worthwhile since no study has been reported in this family of heterocyclic salts with respect to the influence of the anion on antiarrhythmic action. Known ketone **35**[6a,b] and amine **36**[6a,b] were prepared, and **36** with HCl(g) gave salt **37** (Scheme 6). Highly purified salt **37** did not appear to be

Scheme 6



hygroscopic as might be expected.

X-ray Crystallographic Analysis of 26

In view of the paucity of simple model systems in the family of DHBCNs[14] and the fact that **26** exhibited such powerful class III activity, it was deemed of value to subject crystals of **26** to an X-ray diffraction analysis. An ORTEP plot of the molecule is shown in Figure 1. The bicyclo[3.3.1]nonane system of **26** assumes a chair−chair (CC) conformation (Figure 3) as found in **1**[6a] and other related structures.[13b,15] It was observed that hydrogen atoms were bonded to N(3) and N(22) in **26**. Both hydrogens refined with normal temperature factors. The molecule is therefore a dication, and the positive charges are neutralized by two perchlorate anions in the crystal structure. The geometry of N(3) is near tetrahedral (the average of the three C−N−C angles is 112.8°). The configuration of N(7) is approximately planar.

Despite the large R groups attached to the nitrogen atoms, the bicyclo[3.3.1]nonane system assumes a chair−chair (CC) conformation in the solid state. As seen in Figure 2, however, both chairs are significantly flattened due to the repulsion of the two nitrogen atoms and the large R groups. The interplanar angles 2/3 and 4/5 are 137.9° and 133.1° (Figure 3), respectively, and are much larger than the ideal angle of 120°. This suggests considerable strain within the system. It is clearly noticeable that the plane containing the N(7) adopts a smaller angle than that containing N(3). This observation indicates that the group on N(7) requires less space in the bicyclo[3.3.1]nonane unit than the atoms attached to N(3). The chair−chair arrangement may be critical for maximum antiarrhythmic activity in DHBCNs as illustrated in the one published work in this area.[6g]

Although the N(3)−N(7) distance of 2.91 Å is slightly shorter than the 3.0 Å observed for a (CC) system with a CH_2 group at the 3-position and an NH_2 group at the 7-position,[16] there are several indications that no intramolecular hydrogen bonding occurs between H(3) and N(7) (see Figures 1−3). The relevant N(7)−HN(3) bond angle is only 121.7° and clearly bent instead of being linear or close to linear as expected for a hydrogen bond. For comparison, the corresponding angle in 7-hydroxy-*β*-isosparteine is 163°.[17] Furthermore, the nonbonded N(7)···H(3) distance in **26** is 2.39 Å, which is much longer than the counterpart (1.84 Å) found in the sparteine derivative. One reason for the "apparent lack of a hydrogen bond" might lie in the involvement of the lone pair on N(7) via delocalization into the N−C(O) linkage of the amide bond, resulting in a very short N(7)−C(13) bond distance of 1.357(3) Å as compared with a "normal C−N bond". Moreover, the increased double bond character of the N(7)−C(13) bond likely flattens the ring with a simultaneous increase in the H(3)···N(7) distance. A similar effect was observed in

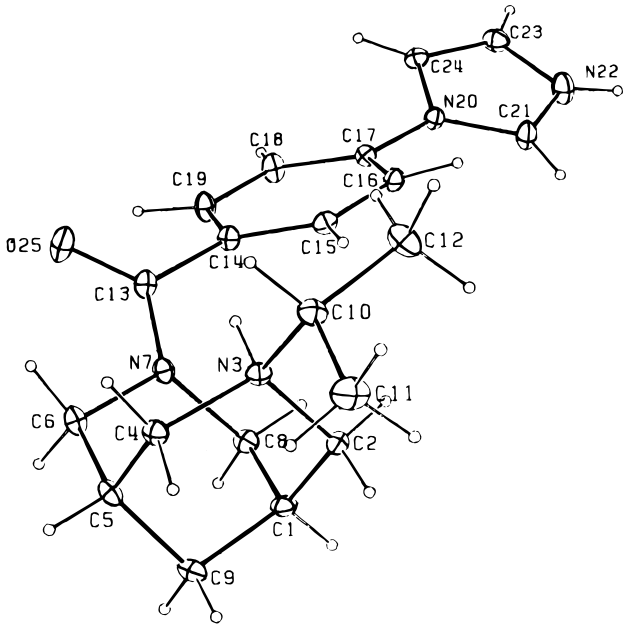


Figure 1. ORTEP drawing of **26**.

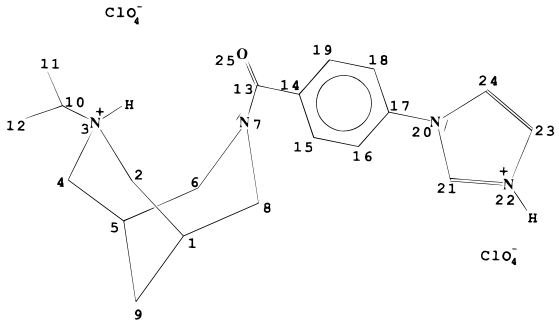


Figure 2. Schematic drawing of **26**.

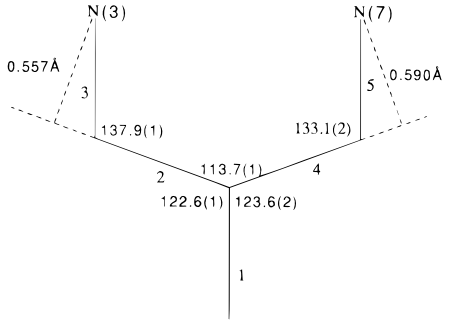


Figure 3. Interplanar angles in the bicyclo[3.3.1]nonane system **26**.

the X-ray crystal structure of anhydrous (+)-lupanine perchlorate with a length of 1.362 (5) Å for the corresponding bond.[18] This implies that the slightly shortened N(3)···N(7) distance merely results from ring strain imposed on the structure by angles within the bicyclic unit.

The N(3)H group, however, forms a hydrogen bond to O(P2) of one perchlorate group. No further hydrogen bonding of atoms in **26** with perchlorate groups was observed. The N(22)−H(22) group, which is where the second positive charge is located, forms a strong intermolecular hydrogen bond with O(25).

Bond distances in the bicyclo[3.3.1]nonane portion of **26** agree well with those reported for anhydrous lupanine perchlorate,[18] the monohydrate of (+)-lupanine perchlorate,[19] (+)-lupanine hydrochloride dihydrate,[18] 15-oxasparteine perchlorate hemihydrate,[20] and two other sparteine derivatives.[16,21] All C−C bonds in **26** lie between 1.52 and 1.53 Å. The C(6)−N(7) bond [1.477 (4) Å] and the N(7)−C(8) bond [1.484 (3) Å] are markedly shorter than the C(2)−N(3) and N(3)−C(4) bonds with respective values of 1.520 (4) and 1.495 (4) Å. This is due to the positive charge on N(3). Similar results have been noted for the other compounds cited above.

The substituent on N(7) consists of three noninteracting π-systems, namely the C=O group, the phenyl ring, and the imidazolium ion. These π systems do *not* lie in a common plane and thus do not interact. Indeed, the C=O plane and the phenyl ring are rotated from one another around the common bond by 45.6 (1)°. The plane of the imidazolium ring is rotated by an angle of 28.2 (2)° from the plane of the phenyl ring.

The imidazolium ring is linked to the phenyl ring by N(20). Both N(20) and N(22) are completely planar coordinated since the sum of the three bond angles around them is 360.0° and 359.8°, respectively. Such angles imply that the lone pairs on the two nitrogen atoms participate in the ring bonding, but several bond distances suggest that the six available π-electrons are not entirely delocalized. The C−N bonds range from 1.310 (4) Å for the C(21)−N(22) bond to 1.387 (3) Å for the N(20)−C(24) bond. In addition, the C(23)−C(24) bond distance of 1.330 (4) Å is comparatively short, suggesting an almost completely localized double bond. A comparable situation has been found with the corresponding bond in imidazolium sulfate (1.335 Å)[22] and in 1,3-diphenylimidazolium perchlorate (1.339 Å).[23] In the reported deuterated imidazolium hydrogen maleate, the similar bond seems unusually long at 1.358 Å and may be due to the fact that the measurement was done by neutron diffraction.[24]

The present work supports our previous prediction[6g] that the chair−chair form of selected members of the DHBCN family could well exhibit useful antiarrhythmic activity. Confirmation of the chair−chair form in **26** is exemplary in this respect, although the exact mechanism by which antiarrhythmic effects occur remains to be uncovered.

Pharmacological Results

Only a few antiarrhythmic properties of a small number of DHBCNs have appeared in the literature.[6,13a,b,15,25] The compounds (Table 1) in the current study were examined in anesthetized mongrel dogs 24−96 h following the occlusion of the left anterior descending coronary artery. This occusion results in a myocardial infarction with a surviving rim of epicardium that serves as the substrate for inducible, sustained ventricular tachycardia (SVT). A 12-lead electrocardiogram (ECG) was monitored throughout. Induction of SVT (SVT is defined as a series of ventricular beats which are usually uniform and at a rate of 250 beats/min or more and lasting 30 s or more) was initiated using programmed electrical stimulation (PES) in the baseline state followed with the test agents at doses of 3 and 6 mg/kg administered intravenously (iv). The agent's ability to terminate or prevent the induction of SVT was measured in all experiments. Lidocaine (**2**) (Table 1) was used as the standard for comparison purposes since it is currently the agent of

Table 1. Selected Antiarrhythmic Properties of **2**, **26**, **28**, **31**, and **34**

	HR[b]		MBP[c]		QT interval[d]		AH interval[e]		HV interval[f]		VERP[g]	
compd[a]	pre[h]	post[i]	pre	post	pre	post	pre	post	pre	post	pre	post
2 (lidocaine)	NE[j]	NE	105	84	NE	NE	NE	NE	NE	NE	142	167
26	148	110	94	84	196	288	57	66	32	37	144	187
28	154	105	61	76	236	270	56	75	30	40	140	180
31	125	105	88	98	215	250	60	68	NE	NE	170	220
34	120	111	92	83	NE	NE	65	70	NE	NE	170	190

[a] Antiarrhythmic properties are compared to lidocaine (**2**) using doses (3 and 6 mg/kg) in which SVT was noninducible in the DHBCN system while lidocaine only reduced the rate of the VT. The limits on the above values were ±5%. [b] HR = heart rate (beats/min). [c] MBP = mean blood pressure (mmHg). [d] QT interval = time (ms) required for the ventricular myocardium to undergo depolarization and repolarization. [e] AH interval = (ms) measures A−V nodal conduction time. [f] HV interval = (ms) measures His−Purkinje conduction time. [g] VERP = (ms) ventricular effective refractory period. [h] Pre = drug free; measurements before administration of agent. [i] Post = post drug; measurements after the administration of agent. [j] NE = no effect.

Table 2. Certain Antiarrhythmic Properties of Selected Agents **1**, **11**, **17**, **19**, **21**, **22**, **29**, and **37**

	HR[b]		MBP[c]		OT interval[d]		AH interval[e]		HV interval[f]		VERP[g]		NSVT,[h]
compd[a]	pre[h]	post[i]	pre	post	pre	post	pre	post	pre	post	pre	post	mg/kg
1	162	162	98	120	NE[i]	NE	NE	NE	30	40	142	163	3
11	130	110	130	37	220	260	NM[j]		35	50	160	230	3
17	130	100	95	75	220	260	60	75	NM		160	230	6
19	130	115	100	77	210	220	55	65	NM		180	220	6
21	150	150	70	50	NE		NE		NE		NE		6
22	150	150	95	95	NE		NE		NE		NE		6
29	148	148	105	105	NE		NE		NE		NE		3
37	162	165	99	105	NE		NE		30	35	NE		3

[a] Antiarrhythmic properties of test compounds were compared to lidocaine (3 and 6 mg/kg iv) in that lidocaine (**2**) only reduced the rate of the VT and possessed only class Ib. The limits on the above values were ±5%. [b] HR = heart rate (beats/min). [c] MBP = mean blood pressure (mmHg). [d] QT interval = time (ms) elapsed for the ventricular myocardium to undergo depolarization and repolarization. [e] AH interval = (ms) measures A−V nodal conduction time. [f] HV interval = (ms) measures His−Purkinje conduction time. [g] VERP = (ms) ventricular effective refractory period. [h] NSVT = nonsustained ventricular tachycardia; SVT not inducible at indicated dosage. [i] NE = no effect. [j] NM = not measured.

choice for the treatment of SVT[26] in acute stages of myocardial infarction.

The DHBCN agents tested in the present study possess class III antiarrhythmic activity in these dog models (Table 1). The effects on the class III parameters varied between agents nearly all of which abolished the VT at doses of 3 and 6 mg/kg. Specifically, four compounds (**26**, **28**, **31**, and **34**) exhibited the most significant antiarrhythmic activity. The most active compound was dihydroperchlorate **26**. This agent slightly reduced the MBP, but the effect was short lasting. However, salt **26** markedly reduced the HR and prolonged the VERP, AH, HV, and the QT intervals. From the data obtained, it was tentatively concluded that this agent possessed predominately class III antiarrhythmic activity.[15c]

Tedisamil (**5**), a known K^+ current blocker,[9] and thioketal **28** show some structural similarities. However, **28** *cannot* be considered a close analogue of tedisamil due to the observed activity differences from those reported for **5**.[9] For example, after administration of **28**, the MBP increased while the HR was reduced with a prolongation of the VERP, HV, and QT interval (Table 1). SMVT was found to be noninducible after 3 and 6 mg/kg doses of **28**, and SVT was terminated with 6 mg/kg iv. These studies suggested that **28** is not only capable of preventing but also capable of terminating PES-induced SMVT.

Two other compounds (**31** and **34**) were found to exhibit excellent antiarrhythmic activity. Both amides possess similar activities with some variation in the degree of effectiveness in terms of the class III parameters measured. One interesting property of **34** is the simultaneous lowering of the HR and the MBP which suggests that these agents may possess Ca^{2+} channel blocking action (class IV AAA).[9]

The other eight agents examined showed good class Ib antiarrhythmic activity while their effects on the class III parameters were modest to weak (Table 2). After the administration (3 mg/kg iv) of **11**, a marked drop in the MBP and the HR was observed. This agent had no effect on any of the class III parameters measured. Interestingly, compounds **17** and **19** possessed similar action (decreased MBP and HR; class IV action) but with varying degrees of effect on the class III action parameters (Table 2). It should be noted that the hydroperchlorate **1** increased the VERP while the corresponding hydrochloride **37** had no effect. Interestingly, the hydroperchlorate **21** produced a decrease in MBP while the hydrochloride **22** had no effect. These are the first examples of two different salts of single DHBCNs which have demonstrated ability to exert varying degrees of influence on such cardiovascular parameters.

Agents **17** and **19** abolished SVT at the 6 mg/kg dose level with no pronounced effect seen at 3 mg/kg. Compound **17** decreased the MBP (95 to 70 mmHg) with fast recovery and induced a lowering of HR (130 to 110 beats/min) which had a lasting effect of 2 h. Amide **17** also prolonged HV (35−50 ms), VERP (160−230 ms), and QT (220−260 ms). Similar properties were observed with dihydroperchlorate **19,** but the effects were less pronounced.

Discussion and Conclusions

A comparison of hydroperchlorate **1** and hydrochloride **37** revealed related activities but not identical. Salt **1** induced a significant prolongation of the HV interval (30−40 ms) and the VERP (142−163 ms) while prolongation by **37** of the HV interval (30−35 ms) was less pronounced and there was no effect on the VERP. Agent **1** prevented electrically induced sustained mono-

morphic ventricular tachycardia (SMVT) in two of the six dogs tested. Salt **1**, however, did markedly slow the rate of SMVT in the other four dogs while **37** had no effect. These slight differences in activities may be due to an effect by the different anions, namely chloride versus perchlorate. Only very slight differences were noted in activity between **21** and **22**.

Most of the agents tested in Tables 1 and 2 demonstrate physiological properties which are consistent with a predominant class III antiarrhythmic action. Some evidence for class I action was also observed, especially in the significant prolongation of the HV intervals (slowing of conduction in the His−Purkinje system) by **26**, **28**, and **37**.

The underlying feature of these agents, however, is a class Ib antiarrhythmic action which may well be associated with the heterobicyclic unit present in these molecules. Indeed, such class Ib activity was shown previously to be the major antiarrhythmic property of agent BRB-I-28 (**1**) in dog models as well as in tissues.[6a,f] The fact that a chair−chair form exhibited improved antiarrhythmic activity over a chair−boat form with two isomeric DHBCN systems previously reported[6g] may also be an important parameter as could be the nature of the heteroatom and substituent(s) attached thereto. Moreover, polar, geminal hydroxyl groups at C(9) resulted in a near lack of any antiarrhythmic activity in certain systems previously investigated.[6a,b] Consequently, it appears that hydrophobic groups may be preferred at C(9) as well as on the heteroatoms for optimum antiarrhythmic activity. This is reminiscent of the structure in tedisamil (**5**) which has a nonpolar five-membered ring fused in a spiro arrangement at the 9-position.[9] It is interesting to note that the torsional angle of C(6)−N(7)−C(13)−C(14) is 177.1 (2)° in **26** while in the sulfur relative **1** the angle is 169.7 (4)°. It should be recalled that the 3-position in **1** is comparable to the 7-position in **26**, both rings containing these positions being slightly flattened. One might speculate that the nature of the group attached to nitrogen might be quite variable, and yet the system could retain good antiarrhythmic properties if a certain conformation around nitrogen were maintained.[6] This supposition has support from the observation that the selenium analog[13] of **1** clearly possesses strong antiarrhythmic activity. The corresponding selenium system is also flattened at the end of the molecule holding the selenium atom. Consequently, manipulation of selected N-substituted groups at the 3- or 7-position of the DHBCN unit may well be the key to multiclass antiarrhythmic activity in these systems. Work is continuing to explore the biological properties of these heterocyclics.

Experimental Section

Materials and Methods. Chemistry. Melting points were obtained on a Thomas-Hoover melting point apparatus or on an Electrothermal IA9100 digital melting point apparatus and were uncorrected. IR spectra were recorded on a Perkin-Elmer 681 (KBr pellets or films). All NMR spectra were taken either on a Varian XL-300 NMR spectrometer with ^{1}H and ^{13}C being observed at 299.94 and 75.43 MHz, respectively, or on a XL-400 NMR unit with ^{1}H, ^{13}C, and ^{15}N being observed at 399.99, 100.6, and 41.2 MHz, respectively. Chemical shifts for ^{1}H and ^{13}C NMR spectra were reported in δ or ppm downfield from TMS [$(CH_3)_4Si$)] for ^{1}H and ^{13}C and from NH_3(l) for ^{15}N. Mass spectral data were recorded on a VG analytical instrument model ZAB-2SE. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN 37921.

Syntheses were performed under an atmosphere of N_2 at room temperature (RT) unless otherwise specified. The following compounds required distillation prior to use: benzoyl chloride (bp 46 °C/1.0 mmHg, Eastman), benzylamine (bp 57−59 °C/4.25 mmHg, Lancaster), 4-chlorobenzoyl chloride (bp 40 °C/10 mmHg, Aldrich), 1,2-ethanedithiol (bp 144−146 °C, Aldrich), 4-fluorobenzoyl chloride (82 °C/20 mmHg, Aldrich), *N*-benzyl-4-piperidinone (bp 134 °C/7.0 mmHg, Aldrich), *N*-isopropyl-4-piperidinone (bp 100−101 °C/27 mmHg, Lancaster), and pyridine (114 °C, Fisher). Precursors **13**−**15** were prepared by procedures reported previously.[6c] Reagent grade solvents were used without further purification, and chromatographic separations were performed on silica gel (Davisil 62, 60−200 mesh, Davison Chemical) and alumina (neutral, 70−230 mesh, Merck). *CAUTION: Although no difficulties were encountered with the hydroperchlorates, careful precautions should always be exercised in all handling operations.*

3,7-Diisopropyl-3,7-diazabicyclo[3.3.1]nonan-9-one (9a). A mixture of isopropylamine (8.87 g, 150.0 mmol), HCl (37%, 7.39 g, 75.0 mmol), glacial acetic acid (9.01 g, 150.0 mmol), and paraformaldehyde (9.46 g, 315.0 mmol) in deoxygenated (dry N_2 was bubbled through the solvent for 2 h) H_3COH (125 mL) was stirred at reflux (15 min) under N_2. A solution of *N*-isopropyl-4-piperidinone (**8a**, 21.18 g, 150.0 mmol) in glacial acetic acid (9.01 g, 150.0 mmol) was added dropwise over 1.5 h, and this was followed by a period of boiling (23 h). After the initial 10 h of heating, another equivalent of paraformaldehyde (9.46 g, 315.0 mmol) was added in one portion to the mixture after which reflux was continued (13 h). After cooling to RT, the solution was concentrated under vacuum and gave an orange oil which was redissolved in H_2O (150 mL). Extracts (ether, 2 × 100 mL) thereof were discarded. The aqueous layer was chilled (5 °C) and made basic (pH ∼12, NaOH pellets). Extraction (H_2CCl_2, 3 × 75 mL) gave a solution which was dried (Na_2SO_4), filtered, and concentrated to give a viscous, reddish-orange oil. Distillation of the oil on a molecular still (110−120 °C/10^{-5} mmHg) gave 22.53 g (67.3%) of a light yellow oil, **9a**: IR (film) 1735 (C═O) cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 1.02 (d, J = 6.5 Hz, 12 H, CH_3 isopropyl), 2.58 [m, 2 H, H(1,5)], 2.87 [m, 6 H, H(2,4,6,8)$_{ax}$, C-*H* isopropyl], 3.04 [dd, J = 10.1 Hz, 4 H, H(2,4,6,8)$_{eq}$]; ^{13}C NMR ($DCCl_3$) ppm 17.90, 18.02 (*C*H$_3$, isopropyl), 46.82 [C(1,5)], 53.17 (*C*-H isopropyl), 53.27, 53.36 [C(2,4,6,8)], 215.18 [C(9)]. Anal. ($C_{13}H_{24}N_2O$) C, H, N.

7-Benzyl-3-(cyclopropylmethyl)-3,7-diazabicyclo[3.3.1]nonan-9-one (9b). A mixture of (aminomethyl)cyclopropane (4.44 g, 62.4 mmol), HCl (37%, 3.07 g, 31.2 mmol), glacial acetic acid (3.75 g, 62.4 mmol), and paraformaldehyde (3.94 g, 131.04 mmol) in deoxygenated (N_2 bubbled in for 2 h) CH_3OH (125 mL) was stirred at reflux for 15 min under N_2. A solution of *N*-benzyl-4-piperidinone (**8b**, 11.8 g, 62.4 mmol) and glacial acetic acid (3.75 g, 62.4 mmol) was added dropwise over 1.5 h. After 10 h at reflux, the mixture was treated with additional paraformaldehyde (3.94 g, 131.04 mmol) in one portion. Heating at reflux was continued (19 h). Upon cooling to RT, the solution was concentrated under vacuum and gave a orange oil which was dissolved in H_2O (100 mL). Extracts (ether, 2 × 75 mL) of the aqueous solution were discarded. The aqueous layer was cooled (5 °C) and made basic (pH ∼12, NaOH pellets). Extraction (H_2CCl_2, 3 × 75 mL) gave a solution which was dried (Na_2SO_4), filtered, and concentrated to a viscous, reddish-orange oil. Distillation of the oil (175−190 °C/10^{-5} mmHg) gave 13.54 g (76.3%) of **9b** as an light yellow oil which solidified upon standing at −10 °C, mp 56.0−57.5 °C. A portion of this solid was recrystallized (pentane) to give an analytical sample: mp 58.5−59.5 °C; IR (KBr) 3005 (C-H, cyclopropyl), 1740 (C═O), 1495 (ArC═C), cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 0.12 [m, 2 H, cyclopropyl], 0.51 [m, 2 H, cyclopropyl], 0.89 [m, 1 H, (C-*H*), cyclopropyl], 2.32 (d, J = 9.8 Hz, 2 H, CH_2-cyclopropyl), 2.59 [m, 2 H, H(1,5)], 2.81 [dd, J = 10.8 Hz, J = 5.6 Hz, 2 H, H(6,8)$_{ax}$], 2.94 [dd, J = 10.8 Hz, J = 6.8 Hz, 2 H, H(2,4)$_{ax}$], 3.04 [dd, J = 10.8 Hz, J = 3.2 Hz, 2 H, H(6,8)$_{eq}$], 3.12 [dd, J = 10.8 Hz, J = 3.2 Hz, 2 H, H(2,4)$_{eq}$], 3.57 (s, 2 H, CH_2Ph), 7.38−7.22 (m, 5 H, Ar-*H*); ^{13}C NMR ($DCCl_3$) ppm 3.76

(CH_2, cyclopropyl), 8.53 (*C*H, cyclopropyl), 46.76 [C(1,5)], 58.19 [C(2,4)], 58.36 [C(6,8)], 61.11 (CH_2Ph), 61.85 (CH_2-cyclopropyl), 127.08, 128.22, 128.66, 138.54 (Ar-*C*), 214.85 (*C*═O); ^{15}N NMR ($DCCl_3$) ppm 36.17 [N(7)], 37.74 [N(3)]; MS (EI) data calcd $C_{18}H_{24}N_2O$ *m*/*z* (M^+) 284.1188, found 284.1190. Anal. ($C_{18}H_{24}N_2O$) C, H, N.

3,7-Diisopropyl-3,7-diazabicyclo[3.3.1]nonane (10a). To a solution of ketone **9a** (5.90 g, 20.3 mmol) in triethylene glycol (60 mL) was added KOH pellets (85%, 13.89 g, 210.9 mmol) and anhydrous hydrazine (95%, 3.55 g, 105.19 mmol). The stirred mixture was heated at 160−170 °C for 4 h under N_2 via the use of a jacketed flask containing boiling tetralin (bp 207 °C). Cooling of the solution to RT (1 h) was followed by addition of ice-cold H_2O (100 mL). Extraction (ether, 4 × 50 mL) was followed by washing of the combined extracts with 10% NaOH (100 mL) and saturated NaCl (100 mL) and then drying (Na_2SO_4). Filtration and concentration of the solution gave a light yellow oil **10a** (4.48 g, 81.1%) which was placed on a vacuum pump overnight (RT/0.2 mmHg). IR analysis of the compound showed no carbonyl absorption as present in the starting material **9a**, and thus the crude product **10a** was used without further purification to prepare salt **12**.

7-Benzyl-3-(cyclopropylmethyl)-3,7-diazabicyclo[3.3.1]nonane (10b). To a solution of ketone **9b** (9.53 g, 33.51 mmol) in triethylene glycol (100 mL) were added KOH pellets (85%, 17.7 g, 268.08 mmol) and hydrazine (95%, 4.52 g, 134.04 mmol). The stirred mixture was heated at 160−170 °C for 4 h under N_2 in a jacketed flask containing boiling tetralin (bp 207 °C). Cooling of the solution to RT (1 h) was followed by addition of ice-cold H_2O (100 mL). Combined extracts (ether, 4 × 80 mL) of the suspension were first washed with 10% NaOH (80 mL) and saturated NaCl (80 mL) and then dried (Na_2SO_4). Filtration and concentration under vacuum gave a light yellow oil **10b** (8.99 g, 98.2%) which was placed on a vacuum pump overnight (RT/0.2 mmHg): IR (film) 3090 (Ar-H) 735 and 700 (monophenyl) cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 0.14 [m, 2 H, cyclopropyl], 0.51 [m, 2 H, cyclopropyl], 0.94 [m, 1 H, (C*H*), cyclopropyl], 1.52 [dd, J = 19.8 Hz, 2 H, H(9)], 1.91 [m, 2 H, H(1,5)], 2.20 (d, J = 6.6 Hz, 2 H, CH_2-cyclopropyl), 2.33 [dd, J = 10.7 Hz, J = 3.6 Hz, 2 H, $H(6,8)_{ax}$], 2.41 [dd, J = 10.8 Hz, J = 4.8 Hz, 2 H, $H(2,4)_{ax}$], 2.76 [d, J = 10.5 Hz, 2 H, $H(6,8)_{eq}$], 2.85 [d, J = 10.5 Hz, 2 H, $H(2,4)_{eq}$], 3.49 (s, 2 H, Ar-CH_2), 7.21−7.45 (m, 5 H, Ar-*H*); ^{13}C NMR ($DCCl_3$) ppm 3.90 (CH_2, cyclopropyl), 8.72 (*C*H, cyclopropyl), 29.43 [C(9)], 30.22 [C(1,5)], 57.68 [C(2,4)], 57.90 [C(6,8)], 62.75 (Ar-CH_2), 64.04 (CH_2-cyclopropyl), 126.38, 127.92, 128.62, 139.74 (Ar-*C*). IR and ^{13}C NMR spectra confirmed the absence of the carbonyl group, and thus the oil was used without further purification to prepare salt **11** and secondary amine **30**.

7-Benzyl-3-(cyclopropylmethyl)-3,7-diazabicyclo[3.3.1]nonane Hydroperchlorate (11). To a chilled (5 °C) solution of amine **10b** (4.41 g, 16.3 mmol) in dry ether (150 mL) was added $HClO_4$ (60%, 3.41 g, 20.4 mmol) dropwise over a period of 15 min. The mixture was allowed to stir (15 min) at 0−5 °C. A white precipitate formed and was filtered and washed (cold ether, 30 mL). The solid was recrystallized (H_3COH, 30 mL), and the resulting white needles were collected and washed with cold H_3COH (25 mL) and dried (80 °C/0.2 mmHg) to give 4.3 g (71.1%) of salt **11**: mp 190−191 °C; IR (KBr) 3060 (Ar-H), 1100 (Cl-O), 735 and 710 (monophenyl) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.46 [m, 2 H, cyclopropyl], 0.62 [m, 2 H, cyclopropyl], 1.07 [m, 1 H, (C*H*), cyclopropyl], 1.64 [d, J = 11.4 Hz, 1 H, $H(9)_{ax}$], 1.77 [d, J = 11.4 Hz, 1 H, $H(9)_{eq}$], 2.42 [d, J = 11.1 Hz, 2 H, $H(6,8)_{ax}$], 2.85 (d, J = 7.2 Hz, 2 H, CH_2-cyclopropyl), 3.09 [m, 4 H, $H(2,4)_{ax}$, $H(6,8)_{eq}$], 3.54 [bs, 4 H, CH_2-Ar, $H(2,4)_{eq}$], 7.31−7.43 (m, 5 H, Ar-*H*); ^{13}C NMR (DMSO-d_6) ppm 3.87 (CH_2, cyclopropyl), 6.07 (*C*H, cyclopropyl), 27.46 [C(6)], 29.58 [C(1,5)], 57.01, 56.84 [C(2,4,6,8)], 60.56 (CH_2-Ar), 61.49 (NCH_2-cyclopropyl), 127.57, 128.39, 129.32, 136.49 (Ar-*C*); ^{15}N NMR (DMSO-d_6) ppm 49.22 [N(7)], 55.18 [N(3)]; MS (EI) data calcd $C_{18}H_{26}N_2$ ($HClO_4$) *m*/*z* (M^+) 270.2096 (−$HClO_4$), found 270.2093. Anal. ($C_{18}H_{27}ClN_2O_4$) C, H.

3,7-Diisopropyl-3,7-diazabicyclo[3.3.1]nonane Hydroperchlorate (12). To a chilled (5 °C) solution of amine **10a** (3.4 g, 16.16 mmol) in dry ether (50 mL) was added $HClO_4$ (60%, 3.4 g, 20.2 mmol) dropwise over a period of 15 min. The mixture was allowed to stir (15 min) at 0−5 °C. A white precipitate formed and was filtered and washed (cold ether, 30 mL). The solid was recrystallized (H_3COH, 30 mL), and the resulting white needles were collected, washed (cold H_3COH, 25 mL), and dried (80 °C/0.2 mmHg) to give 3.63 g (72.3%) of salt **12**: mp 211−212 °C; IR (KBr) 3560 (O-H), 3400 (N-H), 1090 (Cl-O) cm^{-1}; ^{1}H NMR (D_3CCN) δ 1.14 (d, J = 6.2 Hz, 12 H, CH_3 isopropyl), 1.80 [bs, 2 H, H(1,5)], 2.21 [bs, 2 H, H(9)], 2.97 (d, J = 11.9 Hz, 4 H, ring protons), 3.19 (m, 2 H, C-*H* isopropyl), 3.28 (d, J = 12.2 Hz, 4 H, ring protons); ^{13}C NMR (D_3CCN) ppm 17.11 (CH_3 isopropyl), 28.56 [C(1,5)], 31.41 [C(9)], 54.26 [C(2,4 6,8)], 56.13 (*C*-H isopropyl); the compound proved slightly hygroscopic; MS (EI) data calcd $C_{13}H_{27}N_2ClO_4$ *m*/*z* (M^+) 210.2096, found 210.2096. Anal. Calcd for $C_{13}H_{27}N_2O_4Cl$: C, 50.24; H, 8.76; N, 9.01. Anal. Calcd for $C_{13}H_{27}N_2O_4Cl{\cdot}0.2H_2O$: C, 49.66; H, 8.78; N, 8.91. Found: C, 49.33; H, 8.52; N, 9.31.

3-(4-Nitrobenzoyl)-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane (16). To a mixture of amine **15**[6c] (3.82 g, 22.70 mmol) in H_2CCl_2 (25 mL) and 10% NaOH (22.76 g, 56.80 mmol) was added dropwise 4-nitrobenzoyl chloride (4.63 g, 24.90 mmol) in H_2CCl_2 (15 mL) over a period of 15 min. Stirring of the mixture was continued for 3 h under N_2. To the heterogeneous mixture was added H_2O (100 mL) in one portion, and two layers were separated. Further extracts (H_2CCl_2, 3 × 50 mL) of the aqueous layer were combined, dried (Na_2SO_4), filtered, and concentrated under vacuum to give a viscous yellow oil which solidified. This yellow solid was dissolved in ether, and the solution was filtered. The filtrate was concentrated under vacuum and then placed on vacuum pump overnight (RT/0.2 mmHg) to give 6.79 g (94.3%) of a light yellow solid **16**: mp 119−120 °C; IR (KBr) 3090, (Ar-H), 1635 (NC═O) cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 0.56 (d, J = 6.7 Hz, 3 H, CH_3 isopropyl), 0.69 (d, J = 6.7 Hz, 3 H, CH_3 isopropyl), 1.34 [m, 2 H, $H(9)_{ax}$, H(5)], 1.61 [bs, 1 H, H(1)], 2.04−2.32 [m, 3 H, ring protons], 2.67 (dd, J = 11.2 Hz, 2 H, ring protons), 2.94 (dd, J = 12.9 Hz, 1 H, ring proton), 3.20 (d, J = 12.9 Hz, 1 H, ring proton), 3.39 (d, J = 11.2 Hz, 1 H, ring proton), 7.13 (d, 2 H, Ar-*H*), 7.85 (d, 2 H, Ar-*H*); ^{13}C NMR ($DCCl_3$) ppm 15.89, 19.46 (CH_3 isopropyl), 28.81 29.57 [C(1,5)], 32.04 [C(9)], 46.55 [C(2)], 51.79, 52.31, 54.26, 54.85 [C(4,6,8), *C*-H isopropyl], 123.52, 127.60, 143.91, 147.62 (Ar-*C*), 167.58 (N*C*═O); MS (EI) data calcd $C_{17}H_{23}N_3O_3$ *m*/*z* (M^+) 317.1739, found 317.1750. Anal. ($C_{17}H_{23}N_3O_3$) C, H, N.

3-(4-Nitrobenzoyl)-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane Hydrochloride (17). Gaseous HCl was generated in a standard setup with a collection flask containing solid NaCl. The H_2SO_4 (∼15 mL) was added dropwise (1 mL/min), and the HCl gas generated was passed through a $CaCl_2$ drying tube. Into a flask equipped with a magnetic stirrer and an ice bath was bubbled HCl(g) to a chilled (5 °C) solution of amide **16** (2.5 g, 7.88 mmol) in ether (75 mL) over a 15 min period. The mixture was allowed to stir (15 min) at 0−5 °C. A white precipitate formed and was filtered and washed (cold ether-30 mL). The solid was recrystallized (H_3COH/ether, 1:1, 60 mL), and the white needles were washed (cold ether, 25 mL) and dried (80 °C/0.2 mmHg) to give 2.09 g (74.9%) of salt **17**: mp 258−259 °C; IR (KBr) 3400 (N-H), 1660 (NC═O) cm^{-1}; ^{1}H NMR (D_2O) δ 1.44 (d, J = 6.1 Hz, 6 H, CH_3 isopropyl), 2.03 [bs, 2 H, H(9)], 2.52 [bs, 2 H, H(1,5)], 3.39−3.67 (m, 9 H, ring protons, C-*H* isopropyl), 4.45 (s, 1 H, N-*H*), 7.71 (d, 2 H, Ar-*H*), 8.36 (d, 2 H, Ar-*H*); ^{13}C NMR (D_2O) ppm 19.82 (bs, CH_3 isopropyl), 29.36 [bs, C(1,5,9)], 49.42, 54.01 [bs, C(2,4,6,8)], 63.38 (*C*-H isopropyl), 126.89, 130.73, 143.84, 151.10 (Ar-*C*), 175.77 (N*C*═O); MS (EI) data calcd $C_{17}H_{23}N_3O_3$ (HCl) *m*/*z* (M^+) 317.1739 (−HCl), found 317.1734. Anal. ($C_{17}H_{24}N_3O_3$-Cl) C, H, N.

3-(4-Aminobenzoyl)-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane (18). To amide **16** (9.17 g, 28.90 mmol) in AcOH/H_2O (1:1, 100 mL) was added in one portion $TiCl_3$ (12% in HCl, 195.0 g, 202.3 mmol), and the mixture was stirred at RT (7 min). The deep purple solution was basified (pH ∼12−20%, NaOH) until a dark blue color persisted. Extractions (H_2CCl_2, 4 × 90 mL) were washed with H_2O (2 × 100 mL) and brine (100 mL). After drying (Na_2SO_4), the solution was filtered and concentrated to give 7.34 g (86.2%) of an off-white solid **18**:

mp 149−150 °C; IR (KBr) 3220 (N-H), 1640 (NC═O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.98 (bs, 6 H, C*H*$_3$ isopropyl), 1.67 [m, 3 H, H(5), H(9)], 1.91 [s, 1 H, H(1)], 2.41 (bs, 2 H, ring proton), 2.59 (m, 1 H, C-*H* isopropyl), 2.72 (s, 1 H, ring proton), 3.02 (bs, 2 H, ring protons), 3.31 (d, 1 H, ring proton), 3.83 (bs, 3 H, N*H*$_2$, ring proton), 4.70 (bd, 1 H, ring proton), 6.62 (d, 2 H, Ar-*H*), 7.19 (d, 2 H, Ar-*H*); ^{13}C NMR ($DCCl_3$) ppm 16.81, 18.79 (*C*H$_3$ isopropyl), 29.15, 29.79 [C(1,5)], 32.25 [C(9)], 46.61 [C(2)], 52.59, 54.22 [C(4,6,8), *C*-H isopropyl], 114.10, 127.21, 128.68, 147.18 (Ar-*C*), 170.47 (N*C*═O). Anal. ($C_{17}H_{25}N_3O$) C, H, N.

3-(4-Aminobenzoyl)-7-isopropyl-3,7-diazabicyclo[3.3.1]-nonane Dihydrochloride (19). Amide **18** (2.0 g, 6.96 mmol) in ether (75 mL) was chilled (5 °C). HCl gas (generated as described for **17**) was bubbled into the system (10 min). The resulting white precipitate was filtered and washed with cold ether (10 mL). Recrystallization (H_3COH/ether, 1:1, 20 mL) was followed by filtering and drying (80 °C/0.2 mmHg) to afford salt **19** (1.58 g, 70.2%): mp 209−210 °C; IR (KBr) 3560 (O-H), 3400 (N-H), 3160 (NH_2), 1630 (NC═O) cm^{-1}; ^1H NMR (D_2O) δ 1.45 (d, J = 6.0 Hz, 6 H, C*H*$_3$ isopropyl), 2.03 [bs, 2 H, H(9)], 2.49 [bs, 2 H, H(1,5)], 3.40−3.67 (m, 9 H, ring protons, C-*H* isopropyl), 4.63 (s, 2 H, N-*H*), 7.62 (m, 4 H, Ar-*H*); ^{13}C NMR (D_2O) ppm 18.83 (bs, *C*H$_3$ isopropyl), 29.84 [C(1,5)], 30.14 [C(9)], 52.19, 55.26 [bs, C(2,4,6,8)], 63.65 (*C*-H isopropyl), 124.20, 131.59, 135.29, 139.39 (Ar-*C*), 177.42 (N*C*═O); MS (EI) calcd $C_{17}H_{25}N_3O$ (2 HCl) m/z (M^+) 287.1998 (−2HCl), found 287.2013. Anal. Calcd ($C_{17}H_{27}Cl_2N_3O$): C, 63.05; H, 8.09. Anal. Calcd ($C_{17}H_{27}Cl_2N_3O{\cdot}0.9H_2O$): C, 54.23; H, 7.71. Found: C, 54.56; H, 7.62.

3-[4-[(Methylsulfonyl)amino]benzoyl]-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane (20). To a chilled (5 °C) solution of amide **18** (3.0 g, 10.44 mmol) and pyridine (0.87 g, 10.96 mmol) in H_2CCl_2 (20 mL) was added dropwise methanesulfonyl chloride (1.18 g, 10.34 mmol) in H_2CCl_2 (10 mL) over a 15-min period. When the addition was complete, the mixture was allowed to stir at RT overnight. Filtration of the mixture removed pyridine hydrochloride, and the filtrate was transferred to a separatory funnel. Extraction (1 N NaOH, 4 × 40 mL) was followed by neutralization (pH ∼7, HOAc) of the aqueous phase, and the remaining organic layer was discarded. This neutral solution was extracted (H_2CCl_2, 4 × 40 mL), dried (Na_2SO_4), and filtered. After concentration *in vacuo*, there was obtained 3.46 g (90.6%) of an off-white solid **20**: mp 89−91 °C; IR (KBr) 3140 (N-H), 1610 (NC═O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.97 (d, J = 6.1 Hz, 3 H, C*H*$_3$ isopropyl), 1.08 (d, J = 6.1 Hz, 3 H, C*H*$_3$ isopropyl), 1.69 [bs, 1 H, H(5)], 1.79 [bd, 2 H, H(9)], 1.98 [bs, 1 H, H(1)], 2.42 (d, J = 11.3 Hz, 1 H, ring proton), 2.51 (d, J = 11.3 Hz, 1 H, ring proton), 2.60 (m, 1 H, C-*H* isopropyl), 2.74 (d, J = 11.3 Hz, 1 H, ring proton), 3.03 (m, 5 H, ring protons, SO_2CH_3), 3.32 (d, J = 13.0 Hz, 1 H, ring proton), 3.78 (d, J = 13.0 Hz, 1 H, ring proton), 4.76 (d, J = 13.0 Hz, 1 H, ring proton), 7.21−7.30 (q, 4 H, Ar-*H*); ^{13}C NMR ($DCCl_3$) ppm 16.26, 1916 (*C*H$_3$ isopropyl), 28.89, 29.55 [C(1,5)], 32.05 [C(9)], 39.18 (SO_2CH_3), 46.76 [C(2)], 52.11, 52.52, 54.19, 54.54 [C(4,6,8), *C*-H isopropyl], 119.80, 128.05, 128.16, 133.22, 138.21 (Ar-*C*), 169.63 (N*C*═O). Sulfonamide **20** was used without further purification to prepare salts **21** and **22**.

3-[4-[(Methylsulfonyl)amino]benzoyl]-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane Hydroperchlorate (21). Sulfonamide **20** (3.1 g, 8.48 mmol) was dissolved in EtOH (95%, 50 mL), and the resulting solution was chilled (5 °C). With stirring, $HClO_4$ (60%, 1.77 g, 10.60 mmol) in EtOH (5 mL) was added dropwise over a period of 15 min, and stirring was continued (10 min). The white precipitate formed was filtered and recrystallized (warm H_2O, 25 mL) to give 1.97 g (49.9%) of white platelets of **21**: mp 267−268 °C; IR (KBr) 3120 (N-H), 1630 (NC═O), 1100 (Cl-O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.32 (dd, J = 6.1 Hz, 2 H, C*H*$_3$ isopropyl), 1.69−1.87 [dd, 2 H, H(9)], 2.24 [m, 2 H, H(1,5)], 3.06 (s, 3 H, SO_2CH_3), 3.18−3.55 (m, 9 H, ring protons, C-*H* isopropyl), 7.24 (bd, 2 H, Ar-*H*), 7.37 (bd, 2 H, Ar-*H*), 7.93 (bs, 1 H, N-*H*), 10.05 (s, 1 H, CH_3SO_2N-*H*); ^{13}C NMR (DMSO-d_6) ppm 26.48 (*C*H$_3$ isopropyl), 27.59 [C(1,5,9)], 59.53 [bs, *C*-H isopropyl, C(2,4,6,8), CH_3SO_2], 118.12, 128.81, 130.60, 139.53 (Ar-*C*), 172.62 (N*C*═O); MS (EI) data $C_{18}H_{27}N_3SO_3$ ($HClO_4$) m/z (M^+) 365.1773 (−$HClO_4$), found 365.1775. Anal. ($C_{18}H_{28}ClN_3SO_7$) C, H, N, S.

3-[4-[(Methylsulfonyl)amino]benzoyl]-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane Hydrochloride (22). Into a chilled (5 °C) solution of sulfonamide **20** (3.18 g, 8.70 mmol) in H_3COH (75 mL) was bubbled HCl gas over a period of 15 min, and the resulting mixture was stirred for an additional 15 min. Filtration of the precipitate was followed by dissolving in H_3COH (10 mL). To this solution was added ether (∼35 mL) to reach the cloud point, and the resulting solution was allowed to cool to RT. The precipitate was filtered and dried (80 °C/0.2 mmHg) to give 1.13 g (33.8%) of **22**: mp 203−204 °C; IR (KBr) 3575 (O-H), 3420 (N-H), 3240 (N-H), 1720 (NC═O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.43 (d, J = 6.5 Hz, 6 H, C*H*$_3$ isopropyl), 1.82 [m, 2 H, H(9)], 2.36 [bs, 2 H, H(1,5)], 3.11 (s, 3 H, SO_2CH_3), 3.29 (m, 5 H, ring protons, C-*H* isopropyl), 3.35 (d, J = 13.1 Hz, 2 H, ring protons), 3.60 (d, J = 13.1 Hz, 2 H, ring protons), 7.32 (d, 2 H, Ar-*H*), 7.94 (d, 2 H, Ar-*H*), 9.72 (bs, 1 H, N-*H*); ^{13}C NMR (DMSO-d_6) ppm 16.92 (*C*H$_3$ isopropyl), 25.21 [C(1,5 9)], 43.81 (SO_2CH_3), 50.65, 51.72 [C(2,4,6,8)], 61.09 (*C*-H isopropyl), 117.56, 123.77, 130.62, 143.01 (Ar-*C*), 165.66 (N*C*═O); MS (EI) data $C_{18}H_{27}N_3O_3S$ (HCl) m/z (M^+) 365.1773 (−HCl), found 365.1754. Anal. Calcd ($C_{18}H_{28}ClN_3O_3S$): C, 53.79; H, 7.02. Anal. Calcd ($C_{18}H_{28}ClN_3O_3S{\cdot}2.5H_2O$): C, 48.37; H, 7.44. Found: C, 48.46; H, 7.37.

3-(4-Fluorobenzoyl)-7-isopropyl-3,7-diazabicyclo[3.3.1]-nonane (23). To amine **15** (2.53 g, 15.03 mmol) and NaOH (10% aqueous, 15.07 g, 37.58 mmol) in H_2CCl_2 (25 mL) was added a solution of 4-fluorobenzoyl chloride (2.62 g, 16.54 mmol) in H_2CCl_2 (15 mL) dropwise over a period of 0.5 h under N_2. The mixture was stirred (3 h). Addition of H_2O (50 mL) was followed by extraction with H_2CCl_2 (3 × 50 mL). Combined extracts were dried (Na_2SO_4), filtered, and concentrated under vacuum to give a light yellow oil, which was flash chromatographed on neutral alumina (50 g) with hexane/ethyl acetate (60:40) as the eluent. The filtrate was concentrated under vacuum and placed on a vacuum pump overnight (RT/0.2 mmHg) to give 3.88 g (89.0%) of amide **23** as a white solid: mp 87−88 °C; IR (KBr) 1630 (NC═O), 750 cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.96 (d, J = 5.9 Hz, 3 H, C*H*$_3$ isopropyl), 1.07 (d, J = 5.9 Hz, 3 H, C*H*$_3$ isopropyl), 1.71 [m, 3 H, H(9), H(5)], 1.95 [s, 1 H, H(1)], 2.41−2.72 (m, 4 H, ring protons, C-H isopropyl), 3.03 (d, J = 12.7 Hz, 2 H, ring protons), 3.31 (d, J = 12.7 Hz, 1 H, ring proton), 3.72 (d, J = 12.7 Hz, 1 H, ring proton), 4.74 (d, J = 12.7 Hz, 1 H, ring proton), 7.08 (m, 2 H, Ar-*H*), 7.36 (m, 2 H, Ar-*H*); ^{13}C NMR ($DCCl_3$) ppm 16.26, 19.18 (*C*H$_3$ isopropyl), 28.97, 29.69 [C(1,5)], 32.16 [C(9)], 46.59 [C(2)], 52.12, 52.49, 54.65 [C(4,6,8), *C*-H isopropyl], 114.96, 115.25, 128.77, 128.88, 133.60, 133.64 (Ar-*C*), 161.04, 164.33 (J = 248.2 Hz, Ar*C*-F), 169.07 (N*C*═O); ^{15}N NMR ($DCCl_3$) ppm 40.78 [N(7)], 119.65 [N(3)]; MS (EI) data $C_{17}H_{23}N_2OF$ m/z (M^+) 290.1794, found 290.1790. Anal. Calcd ($C_{17}H_{23}N_2OF$) C, H, N.

3-(4-Fluorobenzoyl)-7-isopropyl-3,7-diazabicyclo[3.3.1]-nonane Hydroperchlorate (24). To a chilled (5 °C) solution of amide **23** (1.0 g, 3.44 mmol) in ether (25 mL) was added dropwise $HClO_4$ (60%, 0.72 g, 4.30 mmol) over a period of 5 min. The precipitate was filtered and washed (cold ether). Recrystallization (H_3COH) of the precipitate was followed by filtration and drying (80 °C/0.2 mmHg) to give 1.03 g (76.3%) of salt **24** as white platelets: mp 246−247 °C; IR (KBr) 3120 (N-H), 1625 (NC═O) cm^{-1}; ^1H NMR (D_3CCN) δ 1.38 (d, J = 6.5 Hz, 6 H, C*H*$_3$ isopropyl), 1.81 [bd, 1 H, H(5)], 2.29 [bd, 3 H, H(5,9)], 3.34 (m, 5 H, ring protons, C-*H* isopropyl), 3.52 (bd, 4 H, ring protons), 7.17 (t, 2 H, Ar-*H*), 7.38 (m, 2 H, Ar-*H*); ^{13}C NMR (D_3CCN) ppm 16.72 (*C*H$_3$ isopropyl), 27.89 [C(1,5)], 28.99 [C(9)], 50.34, 53.52 [bs, C(2,4,6,8)], 60.96 (*C*-H isopropyl), 116.29, 116.59, 118.01, 118.36, 130.65, 130.77, 132.78, 132.82 (Ar-*C*), 162.59, 165.88 (J = 247.6 Hz, Ar*C*-F), 174.13 (N*C*═O); MS (EI) data $C_{17}H_{23}N_2OF$ ($HClO_4$) m/z (M^+) 290.1855 (−$HClO_4$), found 290.1853. Anal. ($C_{17}H_{24}ClN_2O_5F$) C, H.

3-[4-(1*H*-Imidazol-1-yl)benzoyl]-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane (25). To a solution of amide **23** (3.35 g, 11.54 mmol) in DMSO (15 mL) was added imidazole (1.18 g, 17.30 mmol), potassium carbonate (anhydrous,1.67 g, 12.12 mmol), and 18-crown-6 (100 mg). The stirred mixture was heated at 110 °C for 45 h under N_2 in a jacketed flask

containing boiling toluene. Cooling the solution to RT was followed by the addition of chilled H_2O. Combined extracts (H_2CCl_2, 4 × 40 mL) of the suspension were washed with H_2O (80 mL) and saturated NaCl (80 mL); the solution was then dried (Na_2SO_4). Filtration and concentration gave a light yellow solid [dried overnight at RT/0.2 mmHg]. Flash chromatography (neutral alumina) of the crude solid in solution using ethyl acetate/hexane (2:3) caused the starting material to be eluted first. With a more polar solvent system [EtOAc/H_3COH (30:1)], product **25** was isolated (1.35 g, 35.1%) as an off white solid. This solid was sensitive to air and became gummy when exposed to the atmosphere: IR(film) 3400 (N-H), 1620 (NC═O) cm^{-1}; ^1H ($DCCl_3$) δ 0.96−1.14 (dd, J = 5.9 Hz, 6 H, CH_3 isopropyl), 1.68 [bd, 1 H, H(9)], 1.81 [bs, 2 H, H(1,5)], 2.02 [bs, 1 H, H(9)], 2.45 (d, J = 10.8 Hz, 1 H, ring proton), 2.57 (d, J = 10.8 Hz, 1 H, ring proton), 2.63 (m, 1 H, C-*H* isopropyl), 2.77 (d, J = 10.8 Hz, 1 H, ring proton), 3.09 (d, J = 12.4 Hz, 2 H, ring protons), 3.38 (d, J = 12.4 Hz, 1 H, ring proton), 3.76 (d, J = 12.4 Hz, 1 H, ring proton), 4.79 (d, J = 12.4 Hz, 1 H, ring proton), 7.22 (s, 1 H, C-*H* imidazole), 7.32 (s, 1 H, C-*H* imidazole), 7.41−7.54 (dd, 4 H, Ar-*H*), 7.89 (s, 1 H, C-*H* imidazole); ^{13}C NMR ($DCCl_3$) ppm 16.33, 19.41 (*C*H_3 isopropyl), 29.03, 29.78 [C(1,5)], 32.26 [C(9)], 46.72 [C(2)], 52.15, 52.61, 54.38, 54.82 [C(4,6,8), *C*-H isopropyl], 118.07 (*C*-H imidazole), 121.15, 128.54 (Ar-C), 130.60, 135.44 (*C*-H imidazole), 136.91, 137.43 (Ar-*C*), 168.80 (N*C*═O). Due to its extreme hygroscopic nature, benzamide **25** was converted directly to the dihydroperchlorate **26**.

3-[4-(1*H*-Imidazol-1-yl)benzoyl]-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane Dihydroperchlorate (26). To a flask was added amide **25** (1.44 g, 4.25 mmol) in 40 mL of ether/H_3COH (50:50) which was chilled (5 °C). To this new solution was added perchloric acid (60%, 1.56 g, 9.56 mmol), and immediately a white precipitate formed. The heterogeneous mixture was stirred an additional 15 min at 5 °C. After filtering, the solid was recrystallized (H_3COH, 35 mL), and this solution was allowed to stand at room temperature. The solid which formed was filtered and dried (80 °C/0.2 mmHg) to give white needles (1.14 g, 60.9%) of **26**: mp 262−263 °C; IR (KBr) 3200 (N-*H*), 1645 (NC═O), 1100 (Cl-O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.33 (d, J = 5.8 Hz, 6 H, CH_3 isopropyl), 1.71−1.92 [bd, 2 H, H(9)], 2.34−2.41 [bs, 2 H, H(1,5)], 3.23 [m, 5 H, $H(2,4,6,8)_{ax}$, C-*H* isopropyl], 3.23−3.97 [m, 4 H, $H(2,4,6,8)_{eq}$], 3.94 (bs, 1 H, N-*H*), 7.66 (d, 2 H, Ar-*H*), 7.94 (s, 1 H, C-*H* imidazole), 7.96 (d, 2 H, Ar-*H*), 8.32 (s, 1 H, C-*H* imidazole), 9.20 (s, 1 H, C-*H* imidazole); ^{13}C NMR (DMSO-d_6) ppm 26.42 [C(1,5)], 27.36 [C(9)], 59.64 [C(2,4,6,8), *C*-H isopropyl], 120.63, 121.35, 122.01, 128.74, 135.27, 137.49 (Ar-*C*), 171.49 (N*C*═O); MS (EI) data $C_{20}H_6N_4O$ ($2HClO_4$) m/z (M^+) 338.2106 (−2HClO_4), found 338.2099. Anal. ($C_{20}H_{28}Cl_2N_4O_9$) C, H, N.

3,7-Diisopropyl-9,9-(1,3-dithiolan-2-yl)-3,7-diazabicyclo[3.3.1]nonane (27a). A flask was equipped with a magnetic stirrer, a condenser with a N_2 inlet, a Dean−Stark trap, and a heating mantle. After addition of ketone **9a** (8.0 g, 35.66 mmol), 1,2-ethanedithiol (33.59 g, 356.6 mmol), *p*-toluenesulfonic acid (16.28 g, 85.58 mmol), and benzene (200 mL), the resulting mixture was heated at reflux (40 h). Benzene was then removed through the Dean−Stark trap, and the resulting oil was dissolved in H_2O (100 mL). The aqueous layer was extracted (ether, 2 × 100 mL), the extracts being discarded. Basification (pH ∼12, 10% NaOH) was followed by extraction (ether, 4 × 75 mL) and washing with NaOH (1 N, 90 mL) and then with brine (90 mL). After the solution was dried (Na_2SO_4), evaporation under vacuum afforded 8.06 g (75.2%) of a light yellow oil **27a**: IR (film) 2905 and 2800 (aliphatic C-H) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.03 (d, J = 12.5 Hz, 12 H, CH_3 isopropyl), 2.26 [bs, 2 H, H(1,5)], 2.62 (d, 4 H, ring protons), 2.77 (m, 2 H, C-*H* isopropyl), 2.89 (d, J = 12.7 Hz, 4 H, ring protons), 3.08 (s, 4 H, S-CH_2); ^{13}C NMR ($DCCl_3$) ppm 17.97 (*C*H_3 isopropyl), 37.39 [C(1,5)], 43.11 (S-*C*H_2), 51.20 [C(2,4,6,8)], 53.21 (*C*-H isopropyl), 70.89 [C(9)]. Spectral analyses (IR and ^{13}C NMR) of the oil did not show the presence of a carbonyl group as present in **9a**, and thus the thioketal was used without purification to prepare **28**.

7-Benzyl-3-(cyclopropylmethyl)-9,9-(1,3-dithiolan-2-yl)-3,7-diazabicyclo[3.3.1]nonane (27b). An identical setup was used as was done for **27a**. After addition of ketone **9b** (6.0 g, 21.09 mmol), 1,2-ethanedithiol (19.87 g, 210.9 mmol), *p*-toluenesulfonic acid (9.63 g, 50.6 mmol), and benzene (120 mL), the resulting mixture was heated at reflux (30 h). Benzene was removed through the Dean−Stark trap, and the resulting oil was dissolved in H_2O (100 mL). The aqueous layer was extracted (ether, 2 × 50 mL), and these extracts were discarded. Basification of the aqueous solution (pH ∼12, aqueous 10% NaOH) followed. This new solution was extracted (ether, 4 × 75 mL), and the extracts were then washed with NaOH (1 N, 90 mL) and saturated NaCl (90 mL). After drying (Na_2SO_4), the organic solution was evaporated *in vacuo* to afford 6.44 g (84.7%) of **27b**, a light yellow oil: IR (film) 3010 (Ar-H) cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.14 [m, 2 H, cyclopropyl], 0.51 [m, 2 H, cyclopropyl], 0.92 [m, 1 H, (C*H*), cyclopropyl], 2.15 [m, 2 H, H(1,5)], 2.27 (d, J = 5.5 Hz, 2 H, CH_2-cyclopropyl), 2.73−2.84 (m, 8 H, ring protons), 3.14 (s, 4 H, SCH_2), 3.53 (s, 2 H, Ar-CH_2), 7.24−7.46 (m, 5 H, Ar-*H*); ^{13}C NMR ($DCCl_3$) ppm 3.83 (*C*H_2, cyclopropyl ring), 8.60 (*C*H, cyclopropyl ring), 37.93, 37.98 [C(1,5)], 43.51 (S*C*H_2), 56.56 [C(2,4)], 56.67 [C(6,8)], 61.68 (*C*H_2-Ar), 62.49 (*C*H_2-cyclopropyl), 71.91 [C(9)], 126.60, 128.02, 128.62, 139.34 (Ar-*C*). Thioketal **27b** was used without further purification to prepare salt **29**.

3,7-Diisopropyl-9,9-(1,3-dithiolan-2-yl)-3,7-diazabicyclo[3.3.1]nonane Hydroperchlorate (28). Thioketal **27a** (8.06 g, 26.82 mmol) in dry ether (100 mL) was cooled (0−5 °C). To the stirred solution was added $HClO_4$ (60%, 5.61 g, 33.52 mmol) dropwise over a period of 15 min. After an additional 15 min of stirring at 5 °C, the solution deposited a white precipitate which was filtered and washed with cold ether (25 mL). Recrystallization (H_3COH, 50 mL) afforded, after drying (80 °C/0.2 mmHg, P_2O_5), hydroperchlorate **28** as white needles (3.15 g, 29.3%): mp 222.0−223.0 °C; IR (KBr) 2980 and 2920 (aliphatic C-H) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.18 (d, J = 6.4 Hz, 12 H, CH_3 isopropyl), 2.31 [bs, 2 H, H(1,5)], 3.32−3.57 [m, 15 H, N-*H*, $H(2,4,6,8)_{ax-eq}$, C-*H* isopropyl, S-CH_2]; ^{13}C NMR ($DCCl_3$) ppm 16.78 (*C*H_3 isopropyl), 39.29 [C(1,5)], 41.23 (S-*C*H_2), 52.29 [C(2,4,6,8)], 54.64 (*C*-H isopropyl), 70.22 [C(9)]. Anal. ($C_{15}H_{29}ClN_2S_2O_4$) C, H, N, S.

7-Benzyl-3-(cyclopropylmethyl)-9,9-(1,3-dithiolan-2-yl)-3,7-diazabicyclo[3.3.1]nonane Hydroperchlorate (29). Thioketal **27b** (6.44 g, 17.86 mmol) was dissolved in dry ether (100 mL), and the solution was cooled (0−5 °C). To the stirred mixture was added dropwise perchloric acid (60%, 3.73 g, 22.32 mmol) over a period of 15 min. After an additional 15 min of stirring at 5 °C, a white precipitate formed and was filtered and washed with cold ether (25 mL). Recrystallization (H_3COH, 50 mL) afforded, after drying (80 °C, 0.2 mmHg, P_2O_5), hydroperchlorate **29** (3.34 g, 40.6%) as white needles: mp 147.5−149.0 °C; IR (KBr) 3010 (Ar-H), 1100 (Cl-O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.59 [m, 2 H, cyclopropyl ring], 0.68 [m, 2 H, cyclopropyl], 0.98 (m, 1 H, C-*H* cyclopropyl), 2.26 [bs, 2 H, H(1,5)], 3.01 [m, 4 H, $H(2,4)_{ax}$, CH_2-cyclopropyl], 3.31−3.46 [m, 8 H, $H(6,8)_{ax}$, $H(2,4)_{eq}$, SCH_2], 3.73 (s, 2 H, Ar-CH_2), 3.92 [d, J = 13.1 Hz, 2 H, $H(6,8)_{eq}$], 7.28−7.45 (m, 5 H, Ar-*H*); ^{13}C NMR ($DCCl_3$) ppm 4.29 (*C*H_2, cyclopropyl), 6.10 (*C*H, cyclopropyl), 39.19, 39.35 (S*C*H_2), 41.73 [C(1,5)], 56.12 [C(2,4)], 56.92 [C(6,8)], 60.96 (Ar-*C*H_2), 60.99 (*C*H_2-cyclopropyl), 69.42 [C(9)], 128.04, 128.57, 129.89, 135.09 (Ar-*C*); MS (EI) data $C_{20}H_{28}N_2S_2$ ($HClO_4$) m/z (M^+) 360.1694 (−$HClO_4$), found 360.1703. Anal. ($C_{20}H_{29}ClN_2O_4S_2$) C, H, N, S.

3-(Cyclopropylmethyl)-3,7-diazabicyclo[3.3.1]nonane (30). The system was initially flushed with N_2 for a period of 15 min. Palladium-on-carbon (Alfa, 10%, 0.997 g, 30 mg of catalyst/mmol of the amine) was added in one portion, and the system was flushed with N_2. Dry and deoxygenated H_3COH (90 mL) was slowly poured over the catalyst (*CAUTION*: catalyst can ignite in the presence of air). To the stirred solution were added amine **10b** (8.99 g, 33.24 mmol) and anhydrous HCO_2NH_4 (5.24 g, 83.1 mmol), and the resulting mixture was boiled under N_2 (30 min). Cooling of the mixture to RT and filtering through a Celite pad was followed by concentration of the resulting solution to give an off-white, viscous oil. The oil was dissolved in H_2O (100 mL) and made basic (pH ∼12, 10% NaOH pellets). Combined extracts (CCl_4, 4 × 60 mL) of the aqueous solution were dried (Na_2SO_4),

filtered, and concentrated *in vacuo* to give a yellow oil **30** (5.50 g, 91.8%): IR (film) 3300 (N-H), 3010 (C*H*$_2$ cyclopropyl) cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 0.13 [m, 2 H, cyclopropyl], 0.52 [m, 2 H, cyclopropyl], 0.87 [m, 1 H, (C*H*), cyclopropyl], 1.64 [m, 2 H, H(1,5)], 1.82 [m, 2 H, H(9)], 2.07 (d, J = 6.6 Hz, 2 H, CH_2-cyclopropyl), 2.31 [d, J = 11.1 Hz, 2 H, H(6,8)$_{ax}$], 2.94 [d, J = 13.8 Hz, 2 H, H(2,4)$_{ax}$], 3.09 [d, J = 13.2 Hz, 2 H, H(6,8)$_{eq}$], 3.17 [d, J = 11.1 Hz, 2 H, H(2,4)$_{eq}$], 4.09 [bs, 1 H, (N-*H*)]; ^{13}C NMR ($DCCl_3$) ppm 3.76 (*C*H$_2$, cyclopropyl), 8.76 (*C*H, cyclopropyl), 29.87 [C(9)], 33.23 [C(1,5)], 52.45 [C(6,8)], 59.51 [C(2,4)], 64.32 (*C*H$_2$-cyclopropyl). The ^{1}H NMR spectrum was devoid of aromatic protons, and thus the oil was used without further purification to prepare amides **31** and **32**.

3-(4-Chlorobenzoyl)-7-(cyclopropylmethyl)-3,7-diazabicyclo[3.3.1]nonane (31). To a mixture of amine **30** (4.03 g, 22.35 mmol) in H_2CCl_2 (25 mL) and 10% NaOH (22.41 g, 55.88 mmol) was added dropwise a solution of 4-chlorobenzoyl chloride (4.30 g, 24.59 mmol) in H_2CCl_2 (15 mL) over a period of 30 min. Stirring of the mixture was continued for an additional 3 h under N_2. To the heterogeneous mixture was added H_2O (100 mL), and two layers were separarated. Extracts (H_2CCl_2, 3 × 50 mL) of the aqueous layer were combined, dried (Na_2SO_4), filtered, and concentrated under vacuum to give a viscous yellow oil. Flash chromatography of the oil was accomplished on neutral alumina (50 g) using hexanes/ethyl acetate (60:40) as the eluent. The filtrate was concentrated and then placed under vacuum overnight (RT/0.2 mmHg) to give 4.18 g (83.1%) of an off-white solid **31**: mp 67−68 °C; IR (KBr) 3005 (Ar-H), 1635 (NC═O) cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 0.12 [m, 2 H, cyclopropyl], 0.54 [m, 2 H, cyclopropyl], 0.91 [m, 1 H, (C*H*), cyclopropyl], 1.73 [m, 3 H, H(5), H(9)], 2.02 [m, 2 H, H(1), CH_2-cyclopropyl], 2.24 [m, 3 H, H(4)$_{ax}$, H(6)$_{ax}$, CH_2-cyclopropyl], 2.96 [d, J = 10.5 Hz, 1 H, H(6)$_{eq}$], 3.03 [d, J = 13.2 Hz, 1 H, H(2)$_{ax}$], 3.28 [m, 2 H, H(8)$_{ax}$, H(4)$_{eq}$], 3.75 [d, J = 13.2 Hz, 1 H, H(8)$_{eq}$], 4.83 [d, J = 13.2 Hz, 1 H, H(2)$_{eq}$], 7.39 (s, 4 H, Ar-*H*); ^{13}C NMR ($DCCl_3$) ppm 3.21, 4.43 (*C*H$_2$ cyclopropyl), 8.29 (*C*H cyclopropyl), 29.01 [C(1)], 29.41 [C(5)], 32.10 [C(9)], 46.59 [C(2)], 52.16, 58.10, 58.38 [C(4,6,8)], 64.25 (N*C*H$_2$-cyclopropyl), 128.15, 128.28, 134.40, 135.90 (Ar-*C*), 169.06 (N*C*═O); ^{15}N NMR ($DCCl_3$) ppm 40.55 [N(7)], 119.74 [N(3)]; MS (EI) data ($C_{18}H_{23}ClN_2O$) m/z (M^+) 318.1499, found 318.1498. Anal. ($C_{18}H_{23}ClN_2O$) C, H, N.

3-Benzoyl-7-(cyclopropylmethyl)-3,7-diazabicyclo[3.3.1]nonane (32). In flask were placed the amine **30** (5.50 g, 30.51 mmol) and NaOH (10%, 30.60 g, 76.28 mmol) in H_2CCl_2 (25 mL). A solution of benzoyl chloride (4.72 g, 33.56 mmol) in H_2CCl_2 (15 mL) was added dropwise over a period of 0.5 h under N_2. The mixture was allowed to stir an additional 3 h. Addition of H_2O (50 mL) was followed by extraction with H_2CCl_2 (3 × 50 mL). Combined extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give a yellow oil. Flash chromatography of the oil was performed on neutral alumina (50 g) with ethyl acetate as the eluent. The filtrate was concentrated under vacuum and then dried under vacuum overnight (RT/0.2 mmHg) to give 7.15 g (82.4%) of amide **32** as an oil: IR (film) 3005 (Ar-H), 1630 (NC═O) cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 0.11 [bd, 2 H, cyclopropyl], 0.49 [m, 2 H, cyclopropyl], 0.92 (m, 2 H, cyclopropyl C-*H*), 1.74 [m, 3 H, H(5,9)], 1.98 [bs, 2 H, H(1), CH_2 cyclopropyl], 2.23 [bs, 3 H, H(4,6)$_{ax}$, CH_2 cyclopropyl], 2.94 [d, 1 H, H(6)$_{eq}$], 3.01 [d, 1 H, H(2)$_{ax}$], 3.28 [m, 2 H, H(8)$_{ax}$, H(4)$_{eq}$], 3.78 [d, J = 12.2 Hz, 1 H, H(8)$_{eq}$], 4.79 [d, J = 12.1 Hz, 1 H, H(2)$_{eq}$], 7.38 (m, 5 H, Ar-*H*); ^{13}C NMR ($DCCl_3$) ppm 2.85, 4.11 (cyclopropyl *C*H$_2$), 7.95 (cyclopropyl *C*-H), 28.64, 29.01 [C(1,5)], 31.72 [C(9)], 46.02 [C(2)], 51.74, 57.71, 57.98 [C(4,6,8)], 63.84 (*C*H$_2$ cyclopropyl), 126.13, 127.64, 128.07, 137.20 (Ar-*C*), 169.68 (N*C*═O). Benzamide **32** was used without further purification to prepare salt **34**.

3-(4-Chlorobenzoyl)-7-(methylcyclopropyl)-3,7-diazabicyclo[3.3.1]nonane Hydroperchlorate (33). To a cooled (5 °C, ice bath) solution of amide **31** (1.0 g, 3.14 mmol) in ether (30 mL) was added $HClO_4$ (60%, 0.66 g, 3.92 mmol) dropwise over a period of 15 min. The suspension was stirred an additional 10 min at this temperature followed by filtration. A white solid produced was recrystallized (H_3COH, 25 mL) and dried (80 °C/0.2 mmHg) to give 0.93 g (70.9%) **33** as white needles: mp 231−232 °C; IR (KBr) 3180 (N-H), 1620 (NC═O), 1090 (Cl-O) cm^{-1}; ^{1}H NMR (D_3CCN) δ 0.51 [d, J = 3.2 Hz, 2 H, cyclopropyl], 0.82 [d, J = 3.6 Hz, 2 H, cyclopropyl], 1.18 (m, 1 H, C-*H* cyclopropyl), 1.85 [bd, 1 H, H(9)], 2.33 [bs, 3 H, H(1,5,9)], 3.03 (d, J = 6.2 Hz, 2 H, CH_2 cyclopropyl), 3.29 (m, 4 H, ring protons), 3.74 (bs, 2 H, ring protons), 4.09 (bs, 2 H, ring protons), 7.36 (d, 2 H, Ar-*H*), 7.48 (d, 2 H, Ar-*H*); ^{13}C NMR (D_3CCN) ppm 4.94, 6.40 (cyclopropyl *C*H$_2$), 27.89 [C(1,5)], 29.05 [C(9)], 57.42, 63.98, 64.08 [C(2,4,6,8), *C*H$_2$-cyclopropyl], 118.37, 129.67, 129.79, 129.95, 135.08, 136.29 (Ar-*C*), 173.85 (N*C*═O); MS (EI) data $C_{18}H_{23}ClN_2O$ ($HClO_4$) m/z (M^+) 318.1499 (−$HClO_4$), found 318.1500. Anal. ($C_{18}H_{24}Cl_2N_2O_5$) C, H.

3-Benzoyl-7-(cyclopropylmethyl)-3,7-diazabicyclo[3.3.1]nonane Hydroperchlorate (34). To a cooled (5 °C), stirred solution of amide **32** (7.15 g, 25.14 mmol) in dry ether (120 mL) was added dropwise a solution of $HClO_4$ (60%, 5.26 g, 31.43 mmol) over a 10-min period, followed by stirring for an additional 10 min. Filtered salt **34** (a white solid) was washed with dry, cold ether (60 mL). The white solid was dissolved (H_3COH, 160 mL) and filtered hot and then allowed to cool to RT. Filtration and drying (0.2 mmHg/80 °C) afforded 6.30 g (65.1%) of pure salt **34**: mp 236.0−237.0 °C; IR (KBr) 3150 (N-H), 1630 (NC═O), 1095 (Cl-O) cm^{-1}; ^{1}H NMR (D_3CCN) δ 0.52 [d, J = 3.1 Hz, 2 H, cyclopropyl], 0.81 [d, J = 2.7 Hz, 2 H, cyclopropyl], 1.19 (m, 1 H, cyclopropyl C-*H*), 1.83 [bd, 1 H, H(1)], 2.24 [bd, 3 H, H(5,9)], 2.98 (d, J = 6.2 Hz, 2 H, CH_2 cyclopropyl), 3.21 (m, 4 H, ring protons), 3.71 (bs, 2 H, ring protons), 4.08 (bs, 2 H, ring protons), 7.41 (m, 5 H, Ar-*H*); ^{13}C NMR (D_3CCN) ppm 5.27 (cyclopropyl *C*H$_2$), 26.45 [C(1,5)], 27.76 [C(9)], 62.56 [C(2,4,6,8), *C*H$_2$-cyclopropyl], 126.95, 128.22, 129.33, 136.98 (Ar-*C*), 172.69 (N*C*═O); ^{15}N NMR (DMSO-d_6) ppm 50.05 [N(7)], 108.49 [N(3)]; MS (EI) data $C_{18}H_{24}N_2O$ ($HClO_4$) m/z (M^+) 284.1888 (−$HClO_4$), found 284.1888. Anal. ($C_{18}H_{25}ClN_2O_5$) C, H.

7-Benzyl-3-thia-7-azabicyclo[3.3.1]nonane Hydrochloride (37). Gaseous HCl was generated in a collection flask from solid NaCl as described for **17**. The HCl(g) generated was bubbled into a cooled (5 °C, ice bath) solution of amine **36** (5.00 g, 20.20 mmol) in ether (150 mL) over a 15 min period. The mixture was allowed to stir an additional 15 min at 0−5 °C. A white precipitate formed and was filtered and washed with cold ether (30 mL). The solid was recrystallized (H_3COH/ether, 1:1, 60 mL), and the white solid collected was washed with cold ether (25 mL) and dried (80 °C/0.2 mmHg) to give 3.31 g (60.7%) of salt **37**: mp 246.0−247.0 °C; IR (KBr) 3040 (Ar-H) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.84 [m, 2 H, H(9)], 2.38 [m, 2 H, H(1,5)], 2.71 [d, J = 11.9 Hz, 2 H, H(6,8)$_{ax}$], 3.13 [d, J = 11.9 Hz, 2 H, H(2,4)$_{ax}$], 3.36 [bs, 2 H, H(6,8)$_{eq}$], 3.60 [d, J = 10.3 Hz, 2 H, H(2,4)$_{eq}$], 4.29 (d, 2 H, CH_2Ph), 7.61−7.49 (Ar-*H*), 9.25 (bs, 1 H, N-*H*); ^{13}C NMR (DMSO-d_6) ppm 25.96 [C(1,5)], 28.65 [C(9)], 30.91 [C(2,4)], 56.41 [C(6,8)], 60.82 (*C*H$_2$-Ph), 129.21, 129.82, 130.19, 130.43 (Ar-*C*); MS (EI) data $C_{14}H_{20}$-NSCl m/z (M^+) 233.1238, found 233.1239. Anal. ($C_{14}H_{20}NSC$) C, H, N.

Electrophysiology. The techniques and overall approach have been previously described in detail.[6g] For the sake of completeness, a summary of the methodology follows. Mongrel dogs, weighing about 12−25 kg, were anesthetized with sodium pentobarbital (~30 mg/kg), after which a full 12 lead electocardiogram (ECG) was recorded for baseline establishment. A left thoracotomy was performed at the 4th intercostal space, and the heart was exposed through an opening in the pericardium. Dissection followed of the left anterior descending coronary artery approximately 5−8 mm from its origin, and a silk ligature was employed to interupt flow partially. After 20 min, the vessel was completely ligated in order to produce an anteroseptal myocardial infarction. After repair of the thoracotomy, the animal was allowed to recover for 24−96 h.

After the period of recovery and after induction of anesthesia with sodium pentobarbital, standard ECG leads V_2−V_6 revealed QS patterns indicative of an anterior wall myocardial infarction. The heart was exposed through the original thoracotomy incision. Composite electrodes were secured to the area overlying the infarct zone (anterior wall) and a normal zone (posterior wall) to obtain local electrical recordings during induced ventricular arrhythmias. One His bundle electrogram

Table 3. Crystal Data, Data Collection, and Refinement Parameters for **26**

formula	$C_{20}H_{28}O_9N_4Cl_2$
M_r	539.1
space group	$P2_1/a$
cell dimensions	
a (Å)	10.796(4)
b	12.842(9)
c	17.475(8)
β	97.10(4)
V (Å^3)	2404.2
z	4
D_x (gm cm^{-3})	1.488
radiation	Cu Kα
μ, cm^{-1}	28.10
temperature	163 K
$2\theta_{max}$ (deg)	150
h range	−13 to +13
k	0 to 16
l	0 to 22
scan width (deg)	$(1.30 + 0.20) \tan \theta$
aperature	$(4.50 + 0.86) \tan \theta$
T_{max} (s)	75
monitors	2 h
max variation	7.4%
total reflections	4909
no. of obsd	3802
reflections ($I > 2\sigma(I)$)	
R	0.048
$R\omega$	0.055
$(\Delta/\sigma)_{max}$	0.02
S	1.73
no. of parameters	429
max density (e/Å^3)	0.49
(diff. map)	
min density	−0.38

from the aortic root and central aortic blood pressure were continuously monitored during the experiments as were Lead II and V_2.

Ventricular pacing was initiated via pacing pulses from an electrical stimulator (S-88 Grass Stimulator) to the right ventricle. Three-beat bursts, at rates of 240−390/min, were employed to induce ventricular arrhythmias. The generation of ventricular ecotopic beats lasting at least 30 s, or more than 100 consecutive ectopic beats, was accepted as having created sustained ventricular tachycardia.

Both lidocaine (**2**) and the agents were administered intravenously in doses of 3 and 6 mg/kg.

Approximately 2−5 min after the administration of each agent, control testing, i.e., provocative ventricular pacing was used to determine the inducibility of lack thereof. Thirty minutes after administration of the agent, the same pacing procedure was utilized to ascertain the dissipation of the effect of the agent. All agents were dissolved in 1:1 water/ethanol. Previous work[6a] revealed the tests were unaffected by the use of ethanol alone.

Crystallographic Experimental Data for 26. The bicyclo-[3.3.1]nonane **26** was recrystallized by means of slow vapor diffusion in an ethanol/water solution. The crystals were monoclinic, space group $P2_1/a$. More complete information about data collection and cell parameters are given in Table 3. Data collection was accomplished with a Nonius CAD-4 diffractometer equipped with a nitrogen low-temperatrure device. The cell dimensions were determined by a least square fit to $\pm 2\theta$ of 48 reflections. The structure was solved by direct methods using the program SHELXS.[27] No absorption correction was performed.

The structure was refined with least squares in the SHELX76 program[28] that minimized the quantity $\sum(F_o - F_c)^2$. Hydrogen atoms were located from a difference Fourier map and refined. The structure refined to a final R factor of 0.048. The disorder displayed by one of the two perchlorate anions, which was reflected in the high anisotropic temperature factors, was responsible for and prevented the achievement of a better fit.

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Supporting Information Available: Complete tables of crystallographic data, atom coordinates, anisotropic thermal parameters, bond lengths, angles, and intermolecular distances (8 pages). Ordering information is given on any current masthead page.

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