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Original paper

A study of the synthesis and antiarrhythmic properties of selected 3,7-diheterabicyclo[3.3.1]nonanes with substituents at the 2,4-positions and at the 9-position

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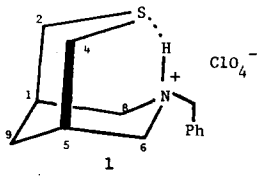
Summary – Some members of the family of 3,7-diheterabicyclo[3.3.1]nonanes with substituents at the 2-, 4- and 9-positions were synthesized *via* a Mannich reaction. Hearts of anesthetized dogs with myocardial infarctions were subjected to ventricular tachycardia (VT). Heterocyclics with [S, NR] or [RN, NR] at the 3- or 7-positions exhibited ability to abolish VT [or prevent the VT from being sustained] or reduce the rate of VT. A CH_2 group at the 9-position or the methyl ketal group [$(H_3CO)_2C(9)$] enhanced the antiarrhythmic activity regardless of whether sulfur or nitrogen was at the 3-position. Compounds with aryl groups alpha to the heteroatoms were less effective in controlling VT. Lidocaine was the standard.

Résumé – **Une étude de la synthèse et des propriétés antiarythmiques de 3,7-dihétérabicyclo[3.3.1]nonanes substitués en position 2, 4 et 9.** *Certains membres de la famille des 3,7-dihétérabicyclo[3.3.1]nonanes substitués en position -2, -4 et -9 ont été synthétisés au moyen d'une réaction de Mannich. Des cœurs de chiens anesthésiés atteints d'infarctus du myocarde ont été assujetis à une tachycardie ventriculaire (VT). Les hétérocycles ayant [S, NR] ou [RN, NR] en position -3 ou -7 se sont montrés capables d'abolir la TV [ou empêcher la TV de se maintenir] ou de réduire le taux de TV. Un groupe de CH_2 en position -9 ou le groupe [$(H_3CO)_2C(9)$] ont augmenté l'activité anti-arythmique avec ou sans la présence de soufre ou d'azote en position -3. Les composés avec des groupes aryles, en alpha par rapport aux hétéroatomes étaient moins efficaces pour limiter la TV. De la lidocaïne a été utilisée comme produit de référence.*

3,7-diheterabicyclo[3.3.1]nonanes / antiarrhythmic activity / lidocaine / X-ray / ^{15}N NMR

Introduction

The search for new antiarrhythmic agents remains a viable goal. In a continuing effort to determine the structural features which convey optimum antiarrhythmic properties on 3,7-diheterabicyclo[3.3.1]nonanes and derivatives [1], we synthesized several substituted systems. Previous results [2, 3] have indicated that perhaps certain groups at C(2,4) [or C(6,8)] and at C(9) might influence activity. Salts **1** [2] and **2** [3] exhibited excellent ability to reduce the rates of ventricular tachycardia (VT) or to abolish them as compared to lidocaine in dog models. Salts **3**–**7** were considered the candidates of choice to assess both polar groups at C(9) and aryl groups at the 2,4-positions as well as different conformers, in terms of control exerted on VT.



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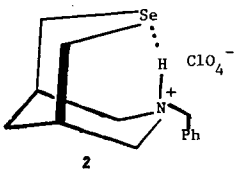

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It was recognized that diastereomeric salts, such as **6** and **7**, are conceivable, but rarely recorded, from a Mannich condensation of 1-hetera-4 cylclohexanones with the appropriate aldehyde and amine. We report herein the synthesis of isomers **6** and **7** and a study of the antiarrhythmic properties thereof. While our work was in

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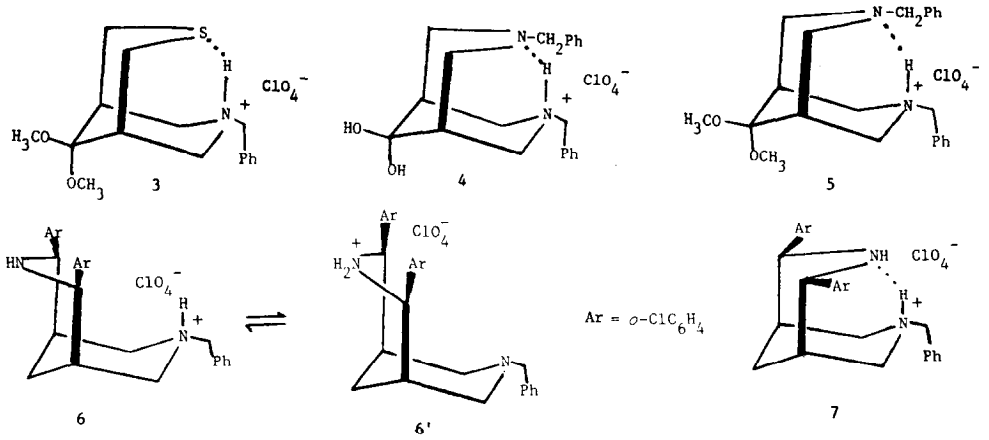
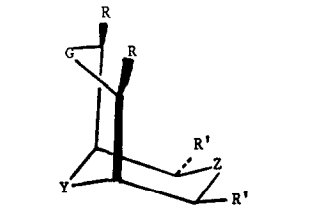
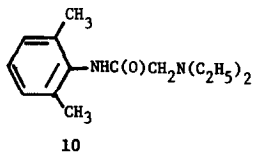


progress, two somewhat related amines appeared in the literature, namely **8** and **9** [4–6].



8 R = H, R' = p-$H_3CC_6H_4$, Z = NCH_3
G = NCH_3, Y = CH_2

9 R = H, R' = p-$H_3CC_6H_4$, Z= NH
G = NCH_3, Y = CH_2



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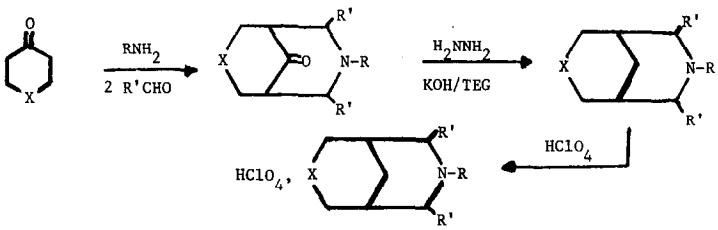
Antiarrhythmic activity in the dog models was determined for **3–7,** the target compounds. It had been determined previously that ketone and amine precursors of a few 3,7-diheterabicyclo[3.3.1]nonanes [2, 3] only displayed marginal activity, and thus these were not screened in the present work. Lidocaine **(10)** was the standard by which all samples were measured in terms of ability to reduce the rates of or eliminate induced VT in dog models previously described [2, 3].

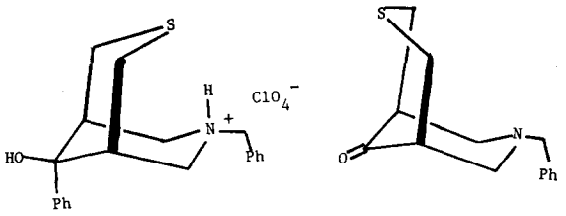
Chemistry

The chemistry involved in this work utilized a Mannich condensation of 1-hetera-4-cyclohexanones with appropriate amines in the presence of an aldehyde to yield a 3,7-diheterabicyclo[3.3.1]nonan-9-ones [1–3]. Wolff–Kishner reduction of the carbonyl group gave the corresponding amines which in turn were converted to hydroperchlorates in a general reaction as shown in Scheme 4. Both chair-chair (CC) and chair-boat (CB) systems were

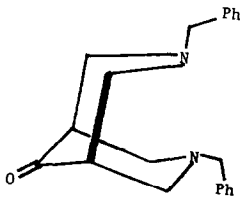


formed in certain condensations and these will be discussed in proper sequence. Due to the paucity of model systems, it became imperative to identify conformations in precursor ketones, amines, and salts in order to confirm the structures present in **6** and **7**.

In view of the strong antiarrhythmic action **1** [2] and the selenium analogue **2** [3, 7] in the dog models (note the absence of aryl groups alpha to the heteroatom), the thrust of the present work was to determine if changes in substituents at C(9), replacement of the S or Se atom by NCH_2Ph, and / or the introduction of aryl groups alpha to the heteroatom would enhance activity in terms of a size effect or difference in nature of the heteroatom involved. It had been noted that the alcohol **11** [2] was less active than **1** and the rationale for preparing **3–5** was based upon



11 12



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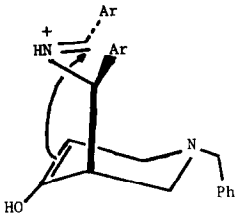
the above logic and that perhaps smaller and more polar groups than Ph would be beneficial for improved activity. Precursor ketone **12** [2] was treated with perchloric acid in methanol to yield **3.** Diol **4** was obtained by reaction of ketone **13** [8] in benzene with perchloric acid in isopropyl alcohol while ketal **5** was made in similar fashion but in methanol.

Diastereomeric compounds such as **6** and **7** are not common [4–6], but a mechanism has been delineated by which such isomers might be formed [4–6, 8]. In our examples, heterocyclic intermediates with dangling groups containing iminium ions, such as in **14** and **15,** are

reasonable and should lead to **16** and **17**, the ketone precursors of amines **18** and **19**, respectively. Conversion of **18** and **19** to hydroperchlorates **6** and **7** follows in a standard fashion. The actual isolation of diastereomeric salts **6** and **7** required meticulous operations which can be found in the *Experimental protocols*.



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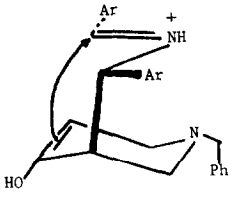

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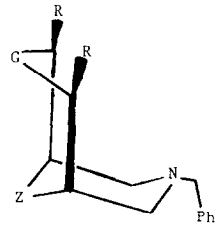
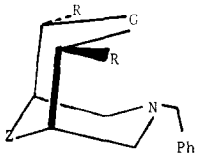


16 G = NH, R = o-ClC$_6$H$_4$
Z = C=O

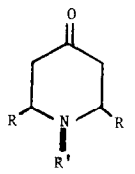
18 G = NH, R = o-ClC$_6$H$_4$
Z = CH$_2$



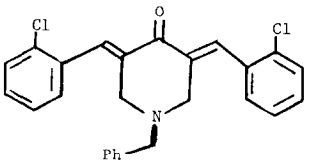
17 G = NH, R = o-ClC$_6$H$_4$
Z = C=O

19 G = NH, R = o-ClC$_6$H$_4$
Z = CH$_2$

The formation of **16** and **17** occurred in the reaction of *N*-benzyl-4-piperidinone **(20a)** with *o*-ClC$_6$H$_4$CHO (2 equivalents) in ethanol and in the presence of ammonium acetate. The chair-boat isomeric ketone **16** precipitated directly from the reaction mixture upon



20 a. R = H, R' = PhCH$_2$
b. R = Ph, R' = H



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cooling while ketone **17** could be extracted from the residual mother liquor after the solvent had been removed and the oil had been treated with dry ether. Recrystallization from 2-propanol:chloroform (3:1) in both examples gave melting points of 184.0–184.5°C **(16)** and 207–208°C **(17)**, respectively. The yield of **16** appeared to be maximum if the reaction was carried out at room temperature for 5 days while the yield of **17** was low. In contrast, the yield of **17** was maximum, with a concurrently low yield of **16,** when the reaction was done at the boiling point of ethanol for less than 2 h. Some 1-benzyl-3,5-*bis*(2-chlorophenylidene)piperidin-4-one **(21)** was always formed in the reaction mixture and this increased with longer reaction times at reflux. The ^{1}H and ^{13}C NMR signal patterns were not cleanly discernable in terms of diagnosing the stereochemistry of the systems described. However, analysis of the ^{15}N NMR signals was informative. In Table I the ^{15}N data have been recorded and some conclusions can be made. In view of the lack of any model compounds in the literature*, these data establish a profile for future work and confirm structures **3**–**7**, the test salts [9–11]. In systems **3**–**5**, $\overset{+}{N}$ has similar ^{15}N shifts regardless of whether or not the proton is shared (H-bonded) by the 2 nitrogen atoms, as in **4** and **5,** or with a S atom as in **3.** The values are similar to that (54.16 ppm) for 7-benzyl-3-thia-7-azabicyclo[3.3.1]nonanehydroperchlorate **(1)** [2], the latter structure being confirmed by X-ray diffraction of a crystal.

In the isomeric salts **6** and **7,** there is a discrepancy in terms of what is found by X-ray diffraction for solid **6** and what is defensible for the form present in solution analyzed by ^{15}N NMR spectroscopy. The diffraction work will be discussed latter, but the solid has the proton on the tertiary nitrogen in a chair. However, the ^{15}N NMR signal for N(3) at 54.6 ppm is only reasonable if the proton is attached to the secondary nitrogen in solution with the signal at 38.3 ppm being for the tertiary nitrogen in **6.** We tentative-

Table I. ^{15}N NMR analysis of 3,7-diheterabicyclo[3.3.1]nonanes and relatives.

Compd	Conformation	^{15}N shift (ppm)	Solvent
1 [2]	CC (salt)	54.2 [$\overset{+}{N}$(7)]-C	DMSO-d_6
2 [3]	CC (salt)	51.6 [$\overset{+}{N}$(7)]-C	DMSO-d_6
3	CC (salt)	53.5 [$\overset{+}{N}$(7)]-C	DMSO-d_6
4	CC (salt)	52.9 [$\overset{+}{N}$(3,7)]	DMSO-d_6
5	CC (salt)	52.9 [$\overset{+}{N}$(3,7)]	DMSO-d_6
6'	CB (salt) [*o*-ClC$_6$H$_4$]	54.6 [$\overset{+}{N}$(3)]-B	DMSO-d_6
		38.3 [$\overset{+}{N}$(7)]-C	
7	CC (salt) [*o*-ClC$_6$H$_4$]	52.6[$\overset{+}{N}$(3)]-C	DMSO-d_6
		50.0 [N(7)]-C	
8	CB (amine) [*p*-H$_3$CC$_6$H$_4$]	42.7 [N(3)]-C (H$_3$C-N)	H_2CCl_2
		44.5 [N(7)]-B (H$_3$C-N)	
9	CB (amine) [*p*-H$_3$CC$_6$H$_4$]	49.8 [N(3)]-C (H-N)	H_2CCl_2
		44.5 [N(7)]-B (H$_3$C-N)	
12 [2]	CB (ketone)	37.3 [N(7)]-C	$DCCl_3$
13 [5]	CC (ketone)	39.2 [N(3,7)]-C.C	$DCCl_3$
16	CB (ketone) [*o*-ClC$_6$H$_4$]	58.2 [N(3)]-B	$DCCl_3$
		38.3 [N(7)]-C	
17	CC (ketone) [*o*-ClC$_6$H$_4$]	54.3 [N(3)]-C	$DCCl_3$
		46.9 [N(7)]-C	
18	CB (amine) [*o*-ClC$_6$H$_4$]	50.5 [N(3)]-B	$DCCl_3$
		38.2 [N(7)]-C	
19	CC (amine) [*o*-ClC$_6$H$_4$]	53.8 [N(3)]-C	$DCCl_3$
		47.4 [N(7)]-C	
20a [2]	C (ketone)	49.1 -C	$DCCl_3$
20b [2]	C (ketone)	66.4 -C	$DCCl_3$

*During our investigation, one set of such isomers was recorded, namely rel. (2*R*,4*S*,6*S*,8*R*)-2,4,6,8-tetraphenyl-3-azabicyclo[3.3.1]nonane and rel. (2*S*,4*S*,6*R*,8*S*)-2,4,6,8-tetraphenyl-3-azabicyclo[3.3.1]nonane but the ^{15}N NMR spectra were not reported (see [5]).

ly suggest that an equilibrium exists between the two protonated forms and, for energy conservation in the lattice, the form with the proton on the tertiary nitrogen is preferred in solid **6**. Thus, **6'** is considered the major form in DMSO–d_6 as shown, presumably due to solvation preferences. In the chair-chair (CC) form for **7**, X-ray analysis shows the proton on tertiary nitrogen again, but in view of the situation for **6**, the ^{15}N assignments appear quite reasonable for **7** but must be assumed tentative.

The remaining ^{15}N data in Table I are for the precursor amines and the starting ketones along with model systems (**1, 2** [2], **8** [4], **12** [2], **13** [5], and **20a, b** [2]). Model systems *N*-benzyl-4-piperidone **(20a)** [2] *cis*-2,6-diphenyl-4-piperidinone **(20b)** [2] show the deshielding effect by the phenyl groups on the ^{15}N atom. Isomeric amines **18** and **19** show ^{15}N signals for secondary nitrogen at 50.5 and 53.8 ppm, respectively, while the tertiary nitrogen in **18** has a value of 38.2 ppm, reminiscent of that found for the tertiary nitrogen in **6'** in solution. This upfield shift for N(7) is undoubtedly due to an axial γ-shielding effect in these cases [9–11]. It is noteworthy that the chemical shift is unchanged for the methyl group attached to nitrogen in a boat in models **8** [4–6] and **9** [4–6]. This is consistent for increased shielding of ^{15}N in a boat as is true for N(3) in isomeric **18** [boat, N(3)] compared to that in amine **19** [chair, N(3)].

The ^{15}N NMR signals for the isomeric ketones **16** and **17** show interesting characteristics. The chair-boat (CB) for **16** has a shift for the secondary N(3) at 58.2 ppm which is more upfield from the signal (66.4 ppm) for biased chair model *cis*-2,6-diphenyl-4-piperidinone **(20b)** [2]. The (CC) system **17** with ^{15}N signals at 54.3 ppm (secondary N) and 46.9 ppm (tertiary N) can be related to those for model *N*-benzyl-4-piperidone **(20a)** (49.1 ppm) [2] and **13** [5] (39.2 ppm); the latter 2-compounds have presumably flattened (CC) conformers. The increased shielding of the nitrogen atoms in the chair forms of **17** by the γ-axial bonds is known [2, 3, 10–12, 14] and is also reflected in the ^{15}N signals for **12** [2] and **13** [8] as well as in **17** for N(7).

In summary of the ^{15}N NMR analysis, it appears that the (CB) and (CC) conformations are preserved starting with the ketones **16** and **17** and continuing through the amines **18** and **19** and finally to the salts **5** and **6**. To the best of our knowledge, such observations have not been examined in a rigourous manner for such diastereomers with different antiarrhythmic activity in this family of heterocycles. The X-ray analyses of salts **5, 6** and **7** and ketone **16** provide a basis for the stereochemical integrity of these systems, along with the NMR work. All X-ray data are available upon request and only a brief summary will be given here.

Salts **6** and **7** are isomeric structures which exhibit some difference in antiarrhythmic activity (Table II) and are the first cases so examined in this family. Crystal data revealed that **6** (CB) and **7** (CC) are isomeric perchlorates with *o*-ClC_6H_4 groups at C(2) and C(4). The bonds to the latter are pseudo equatorial as are the N(3)-H and N(7)-$CH_2C_6H_5$ bonds. The proton at N(7) is axial in both isomers while an intramolecular H-bond exists between the unshared pair on N(3) and N(7).

Table II. Antiarrhythmic properties of compounds **1–7** compared to those of lidocaine **(10)**[a].

	Control		3 mg/kg				6 mg/kg			
Compound	SVT[g]	BP[h]	SVT[g]	% ΔSVT[i]	BP[h]	% ΔBP[j]	SVT[g]	% ΔSVT[i]	BP[h]	% ΔBP[j]
1[b]	390	120	390	9	129	+7	330	-15	132	+10
10			330	-15	-		330	-15k	-	-
1[c]	270	70	n	-	75	+7	n	-	82	+17
10			270	-	-	-	240	-11	-	-
1[d]	360	77	220	-8	85	+10	300	-17	89	+16
10			330	-8	-	-	270	-25	-	-
1[e]	390	90	300	-23	97	+8	270	-31	103	+14
10			300	-23	-	-	270	-31	-	-
3[b]	390	120	n	-	133	11	n	-	130	+8
10			330	-15	-	-	330	-15	-	-
3[c]	370	70	n	-	90	+29	240	-11	95	+36
10			270	-	-	-	240	-11	-	-
3[d]	360	77	330	-8	99	+29	390	+8l	101	+31
10			330	-8	-	-	270	-25	-	-
3[e]	390	90	n	-	99	+10	n	-	99	+10
10			300	-23	-	-	270	-31	-	-
4	390	108	9	0	99	-8	300	-23	90	-17
10			300	-23	-	-	210	-46	-	-
4	390	102	330	-15	95	-7	300	-23	90	-12
10			330	-15	-	-	300	-23	-	-
5	330	116	300	-9	120	+3	n	-	111	-4
5[d]	360	77	240	-33	92	+19	210	-46	85	+10
10			330	-8	-	-	270	-25	-	-
5	330	107	270	-18	120	+12	240	-27	125	+17
5	390	90	210	-46	92	+2	n	-	95	+6
10			300	-23	-	-	270	-31	-	-
6	390-420m	70	340	-15	83	+19	390	9	82	+18
10			390	-7	-	-	360	-14	-	-
6	330	90	330	9	98	+9	330	0	101	+12
6			330	9	103	+14	300	-9	104	+15
10			n	-	-	-	300	-23	-	-
6	330	130	290	-12	133	+2	270	-18	129	-1
10			300	-9	-	-	360	+9	-	-
6	360	102	n	-	112	+10	n	-	101	-1
10			330	-8	90	-12	300	-17	86	-16
6[f]	390	75	n	-	85	+13	n	-	104	+39
10			n	-	-	-	9	0	-	-
7	360		300	-17	-	-	300	-17	-	-
10			300	-17	-	-	330	-8	-	-
7	330	-	330	9	-	-	330	9	-	-
10			360	l	-	-	330	k	-	-
7[f]	390	75	390	k	108	+44	420	l	104	+39
10			n	-	-	-	390	k	-	-
7	330	80	330	-	90	+12	330	k	86	+7
10			360	+8	-	-	330	k	-	-

[a]Each division represents experiments in one dog. [b]Dog 1. [c]Dog 2. [d]Dog 3. [e]Dog 4. [f]Dog 5. [g]Rate of sustained ventricular tachycardia (SVT in bpm). [h]Mean blood pressure during VT episode. [i]Percent change in rate of SVT relative to control experiment. [j]Percent change in mean blood pressure during VT episode. k: No effect. l: Proarrhythmic effect, *i.e.* induction of new or faster VT. m: multiple VT forms. n: Nonsustained VT.

Salt **5** exists in a chair-chair (CC) form possessing an axial N–H bond. Additional hydrogen bonding occurs between this hydrogen and the lone electron pair on N(7) [N(3)–H(100), 1.02 Å, N(7)...H(100), 1.82 Å, N(4)–H(100)...N(7), 138.8°]. The ring system displays no internal crystallographic symmetry elements. The data for **5** bear resemblance to that found for **1** [2] (which exhibited good antiarrhythmic ability) in that a (CC) form exists in both and the C-N average distance in **1** is 1.509 Å with internal H-bonding.

Ketone **16** was a key synthon leading to **6** and crystallized (2-propanol:$HCCl_3$, 3:1) and was determined to be a (CB). The piperidine ring with the *o*-chlorophenyl groups at C(2,4) was a boat form while the piperidine ring with the *N*-benzyl group was a chair form. All substituents, other than protons on carbon, were in equatorial or pseudo equatorial positions including the one proton on nitrogen which is not involved in hydrogen bonding. The bicyclic system in **16** resembles that of 2,4,6,8-tetraphenylbicyclo[3.3.1]nonan-9-one [12] in that the protonated nitrogen atom is at the prow of a boat. Both structures show a lack of non-bonded interactions between N(3) (the unshared electron pair) and the carbonyl group C(9)=O as reflected in the N(3)...C(9) distance of 2.474(6) Å in **16** and 2.516(2) Å in the previous ketone [12]. That strain is present in the molecule is evidenced by the C(1)-C(9)-C(5) angle (112.4(3)°; compared to that calculated for a bicyclo[3.3.1]nonan-9-one system [14]) and the elongation of the C(1)-C(2) and C(4)-C(5) bonds (av. 1.562(5) Å) relative to the C(1)-C(8) and C(5)-C(6) distances (av. 1.539(6) Å).

Conclusions

The techniques for determining the antiarrhythmic activity properties of **3**–**7**, compared to those of lidocaine **(10)**, have been previously described [2, 3]. Mongrel dogs were examined 24 h after ligation of the descending coronary artery, and the results are given in Table II. Ketals **3** and **5** exhibit superior antiarrhythmic activity compared to lidocaine **(10)** in the dog models in terms of not allowing sustained VT at both the 3 and 6 mg/kg dosages. Moreover, a small increase in mean blood pressure is an added quality. In both **3** and **5**, and with two separate dogs in each case, the VT was abolished completely at the 6 mg/kg level. Lidocaine **(10)** rarely suppressed the induced VT totally, but did reduce the rate of the VT by a maximum of 46%. Thus, the small polar groups [H_3CO] at C(9) appear extremely beneficial for enhancing antiarrhythmic abilities of members of the 3,7-diheterabicyclo[3.3.1]-nonane family. In addition, the presence of sulfur or the NCH_2Ph group does not markedly effect the activity when a second NCH_2Ph group is present at the 3- or 7-position.

A major difference in antiarrhythmic activity was observed when C(9) was bonded to hydroxyl groups as a diol **4**. Both a small reduction (≈ 15%) in the rate of the VT was noted along with a slight drop (–8%) in mean blood pressure at 3 mg/kg dosage. In fact, there were only small variations in activity between **4** and lidocaine **(10)** as noted in Table II. It is conceivable that the diol **4** is converted *in vivo* to the ketone precursor **13** [8] and ketone members of this family have not shown significant activity in previous examples [2, 3]. Whatever the reason, these data indicate the diol system is much less effective than ketals such as **3** and **5**.

Several very interesting observations were made in the analysis of the diastereomeric salts **6** (CB) and **7** (CC). The aryl groups at C(2,3) appear to limit the ability of the compounds to reduce or abolish the VT. In **6** (CB), there was a consistent ability to inhibit or suppress sustained VT. Mean blood pressure was also consistent at both dose levels. In contrast, **7** showed a variable suppression of sustained VT and a proarrhythmia action comparable to that of lidocaine. However, the ability to enhance mean blood pressure persisted with **7** at both 3 and 6 mg/kg dosages. A tentative conclusion is that aryl groups at C(2,4) reduce the antiarrhythmic activity of the system regardless of whether or not the ring is a chair or boat conformer. Although relatives of **6** and **7** devoid of only the aryl groups have not been reported, several close analogs like **1** [2], **2** [3], and **5** (this work) do exhibit good antiarrhythmic action in dog models. The implication is that steric hindrance around the heteroatom obviates the antiarrhythmic properties of certain members of his family of heterocycles. To the best of our knowledge, no previous study of diastereoisomers in this group of heterocycles has been evaluated for this type of activity in dog models or by any other screening mechanism. The results discussed herein support the candidacy of select members of the family of 3,7-diheterabicyclo[3.3.1] nonane salts as viable and potentially useful antiarrhythmic agents to control VT.

Experimental protocols

Chemistry

Melting points were obtained on a Thomas–Hoover capillary melting point apparatus and were uncorrected. All ^1H and ^{13}C NMR spectra were recorded on an XL-300 (operating at 299.99 MHz and 75.4 MHz, respectively) or on an XL-100(15) MHz (operating at 100 MHz and 25.2 MHz, respectively) spectrometer. The ^{15}N NMR spectra were recorded on the Varian XL-300 unit at 30.41 MHz. Chemical shifts were measured in either δ values (^1H) or in ppm (all other nuclei) downfield from a standard. Specifically, TMS was used with ^1H and ^{13}C while ^{15}N signals were measured from external references $^{15}NH_4NO_3$ and then referenced to $NH_3(l)$. IR spectra were recorded on a Perkin–Elmer 681 spectrometer as KBr pellets or as films. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN, and those indicated by the symbols of the elements were within ±0.47 of the theoretical values. Ketones **12** [2], **13** [8], **20a** [2] (Aldrich) and **20b** [2] (Frinton Labs) were obtained through literature routes or purchased. Data for **8** [4–6], **9** [4–6], and **11** [2] are published.

*7-Benzyl-9,9-dimethoxy-3-thia-7-azabicyclo[3.3.1]nonane hydroperchlorate **(3)** and oxime **22**. Caution*

The use of shields, protective goggles and gloves is very strongly recommended when performing this experiment. The formation of explosive methyl perchlorate is a likely side reaction in this experiment. No difficulty was noted when the reaction was performed as described, but this may have been fortuitous. The salt **3** was prepared after the reported [14] procedure from ketone **12** [2]. The mp of the salt **3** was 193–194°C (d). Since derivatives of 3,7-diheterabicyclo[3.3.1]nonan-9-ones are very rare [1], we report herein the preparation of the oxime of ketone **12.**

A flask was charged with ketone **12** (1.05 g, 4.26 mmol), $NH_2OH{\cdot}HCl$ (0.62 g, 8.57 mmol), $NaOAc{\cdot}H_2O$ (1.47 g, 10.8 mmol) and ethanol

(25 ml). The apparatus was flushed with N_2, and the mixture was heated at reflux for 4 h. The reaction mixture was cooled to RT and the unreacted NaOAc was filtered off. Evaporation of the filtrate left a white solid which was suspended in water (50 ml). Extraction with ether (3 × 50 ml), followed by drying (K_2CO_3, overnight), filtration, and evaporation afforded a new white solid. Recrystallization (95% ethanol, 30 ml) yielded the oxime **22** (0.71 g, 64%): mp: 128.4–129.2°C; IR (KBr) cm^{-1} 3275 (O–H), 2926 ,2790, 752, 697; (^1H NMR ($CDCl_3$) δ 2.26 (dd, J = 11.5, 4.2 Hz, 1H, H(8)ax), 2.32 (dd, J = 11.0, 4.3 Hz, 1H, H(6)ax), 2.83 (br s, 1H, H(1)), 2.89 (br t, J = ~11 Hz, 2H, H(6,8)eq), 3.04 (m, 4H, H(2,4)), 3.52 (s, 2H, PhCH_2), 3.88 (br s, 1H, H(5)), 7.24–7.30 (m, 5H, ArH), 9.28 (br s, 1H, OH); ^{13}C NMR ($DCCl_3$) ppm 29.9 (d, C(1)), 32.5 (t, C(2)), 34.1 (t, C(4)), 36.7 (d, C(5)), 57.2 (t, C(8)), 58.5 (t, C(6)), 61.7 (t, PhCH_2), 126.9 (d, p–ArC), 128.1 (d, o–ArC or m–ArC), 128.6 (d, m–ArC or o–ArC), 138.2 (i-ArC), 160.9 (s, C(9)); ^{15}N NMR ($DCCl_3$) ppm 336.3 (N(7), oxime N not observed). Mass spectral m/e calcd. for $C_{14}H_{18}N_2O$: 262.1136 (M^+). Found: 262.1140. Anal. ($C_{14}H_{18}N_2OS$) C, H, N, S.

3,7-Dibenzyl-3,7-diazabicyclo[3.3.1]nonan-9,9-diol hydroperchlorate ***(4)***
In a 50-ml Erlenmeyer flask, a vigorously stirred (magnetic) solution of ketone **13** [8] (1.00 g, 3.12 mmol) in C_6H_6 (20 ml) was treated dropwise with a solution of $HClO_4$ (60%, 1.56 g, 9.32 mmol) in 2-propanol (5 ml) over 15 min, thus precipitating the salt as a white powder. The mixture was stirred for an additional 1 h. The solid was filtered and recrystallized (2-propanol / H_2O, 11:1) to afford, after drying (Abderhalden, 82°C, 0.2 mmHg, P_2O_5, 24 h), diol **4** (0.51 g, 37%): mp 209.5–210.8°C; ^1H NMR (DMSO–d_6) δ 1.96 (2.2H, H(1,5))), 3.05 (s, 8H, H(2,4,6,7)), 3.89 (s, 4H, PhCH_2), 6.22 (s, 2H, O–H), 7.36–7.56 (m, 10H, ArH), 9.88 (s, 1H, $\overset{+}{N}$–H); ^{13}C NMR (DMSO–d_6) ppm 38.54 (d, C(1,5)), 54.3 (t, C(2,4,6,8)), 59.7 (t, PhCH_2), 89.2 (s, C(9)), 128.1 , 128.1, 128.4, 130.0, (ArC); ^{15}N NMR (DMSO–d_6) ppm 52.9 (N(3,7)). Anal. ($C_{21}H_{27}N_2Cl$) N, Cl.

N,N′-*Dibenzyl-9,9-dimethoxy-3,7-diazabicyclo[3.3.1]nonane hydroperchlorate* ***(5)***. *Caution*
The use of shields, protective goggles and gloves is very strongly recommended when performing this reaction. The salt was prepared by the reported [15] route. The sample of **5** melted at 223.6–224.0°C (d).

*(2-*endo*,3-*exo*,4-*endo*)-2,4-*Bis*(2-chlorophenyl)-7-benzyl-7*H*-3,7-diazabicyclo[3.3.1]nonane hydroperchlorate* ***(6)***
In a 100 ml flask, a solution of amine **18** (0.80 g, 1.83 mmol) in C_6H_6 (30 ml) was treated dropwise a solution of $HClO_4$ (60%, 1.50 g, 8.96 mmol) in 2-propanol (5 ml) resulting in the formation of a white powdery precipitate. The flask was fitted with a condenser and the mixture was warmed on a steam bath for 15 min. After cooling to RT, the precipitate was filtered and recrystallized in a minimum amount of 70% acetone to afford the monohydroperchlorate **6** (0.80 g, 81%) as fine white crystals: mp 246–247°C (dec); IR (KBr) cm^{-1} 3330 (N–H), 2900–2600 ($\overset{+}{N}$–H), 1110 (Cl–O); ^1H NMR (DMSO–d_6) (Recall that **6′** appears to be the dominant form in solution) δ 1.70 (d, J = 14 Hz, 1H, H(9)*endo*), 2.33 (d, J = 11 Hz, 2H, H(6,8)ax), 2.38 (br s, 2H, H(1,5)), 2.51 (overlapping d, J = 14 Hz, H(9)*exo* and br s, DMSO–d_6), 2.85 (d, J = 11 Hz, 2H, H(6,8)eq), 3.70 (s, 2H, PhCH_2), 5.00 (d, J = 8 Hz, H(2,4)), 7.32–7.94 (m, 13H, ArH), 8.10 (br s, 1H, N–H), 9.84 (br s, 1H, $\overset{+}{N}$–H); ^{13}C NMR (DMSO–d_6) ppm 24.5 (t, C(9)), 33.7 (d, C(1,5)), 55.9 (t, C(6,8)), 56.9 (d, C(2,4)), 60.9 (t, C(10)), 127.6–130.9 (ArC), 132.6, 135.5, 137.1 (ArC); ^{15}N NMR (DMSO–d_6) ppm 38.3 (N(7)), 54.6 (N(3)). Anal. ($C_{26}H_{27}Cl_3N_2O_4$) C, H, Cl, N.

*(2-*endo*,3-*endo*,4-*endo*)-2,4-*Bis*(2-chlorophenyl)-7-benzyl-7*H*-3,7-diazabicyclo[3.3.1]nonane hydroperchlorate* ***(7)***
In a 100-ml flask, a solution of amine **19** (0.4957 g, 1.14 mmol) in C_6H_6 (20 ml) was treated dropwise over 15 min with $HClO_4$ (60%, 0.5 ml) with vigorous stirring. This resulted in the precipitation of a white solid. The flask was fitted with a condenser and heated on a steam bath for an additional 5 min, followed by cooling to RT. The solution was filtered and the cloudy filtrate set aside. Recrystallization of this solid (CH_3OH, 30 ml) afforded the monoperchlorate **7** (0.1050 g) as white crystals, mp: 264.0–264.5°C (dec). The cloudy benzene filtrate was evaporated to about 2 ml and the resulting oil was dissolved in hot CH_3OH (30 ml). Upon cooling to RT, additional product precipitated as a white powder. This was filtered and recrystallized (CH_3OH, 65 ml) to afford additional **7** (0.3575 g, 74% total) again as white crystals, mp: 260–262°C (dec). The spectroscopic data were as follows: IR (KBr) cm^{-1} 3300 (N–H), 2850–2700 ($\overset{+}{N}$–H), 1090 (Cl–O); ^1H NMR (DMSO–d_6) δ 2.19 (d, J = 12 Hz, 1H, H(9)), 2.35 (d, J = 12 Hz, 1H, H(9)), 2.38 (br s, 2H, H(1,5)), 3.02 (br s, 4H, H(6,8)ax and eq), 4.08 (br s, 2H, PhCH_2), 4.88 (br s, 2H, H(2,4)), 5.63 (br s, 1H, N–H), 7.36–7.36 (m, 13H, ArH), 10.13 (br s, 1H, $\overset{+}{N}$–H); ^{13}C NMR (DMSO–d_6) ppm 29.8 (d, C(1,5)), 31.4 (t, C(9)), 53.0 (t, C(6,8)), 60.3 (t, PhCH_2), 60.8 (d, C(2,4)), 127.3, 127.4, 128.9, 129.3, 129.9, 130.8, 131.2, 131.3, 131.3, 142.0 (ArC); ^{15}N NMR (DMSO–d_6) ppm 50.0 (N(7)), 52.6 (N(3)). Anal. ($C_{26}H_{27}Cl_3N_2O_4$) C, H, Cl, N.

N,N′-*Dibenzyl-3,7-diazabicyclo[3.3.1]nonan-9-one* ***(13)***

Method A. Following a modified procedure to that reported [8] for this compound, a 50-ml flask was fitted with a dropping funnel, a condenser and a heating mantle, and charged with benzylamine (2.68 g, 25.0 mmol), glacial acetic acid (1.54 g, 25.8 mmol) and methanol (25 ml). Paraformaldehyde (1.58 g, 52.5 mmol) was added, the apparatus was flushed with N_2, and the mixture was brought to reflux with stirring. After 15 min, a solution of *N*-benzyl-4-piperidinone **(20a)**, (4.73 g, 25.0 mmol) and glacial acetic acid (1.50 g, 25.0 mmol) in methanol (19 ml) was added dropwise over 0.5 h. The resulting orange solution was then heated at reflux for an additional 9.5 h. Upon cooling to RT, the solvent was evaporated from the reaction mixture to leave an orange oil. Water (50 ml) and KOH pellets (85%, 3.30 g, 50.0 mmol) were added and the resulting oily, orange suspension was extracted (CH_2Cl_2, 3 × 50 ml). The organic extracts were combined and dried ($MgSO_4$, overnight). Filtration of the drying agent, followed by removal of the solvent, afforded another another orange oil (6.41 g) which was vacuum distilled (8 × 10^{-4} mmHg, diffusion pump). At 106–108°C, a colorless oil (0.36 g) was collected, the ^{13}C NMR of which was identical to that of the starting material **20a**. A second fraction (bp 180–205°C) was collected as a yellow oil but with substantial decomposition of the residue. Redistillation (180–185°C, 1.0 × 10^{-4} mmHg) of this second fraction again afforded a yellow oil; however, no significant decomposition was noted in this second distillation. The distillate from the second distillation was dissolved in hot Skelly B (80 ml). Upon cooling to −10°C, ketone **13** (2.53 g, 31.6%) precipitated as a white solid, mp: 61–63°C (lit. [8] 70–71°C). The compound was used in the next step without further purification since all spectra supported a highly purified compound. Spectroscopic data for this compound were: IR (KBr) cm^{-1} 2963, 2822, 1738, 1721, 748, 703; ^1H NMR ($DCCl_3$) δ 2.52 (br s, 2H, H(1,5)), 2.76, 2.78 (dd, J = 10.5, J = 10.7 Hz, 4H, H(2,4,6,8)ax), 3.00 (br d, J = 10.7 Hz, 4H, H(2.4.6.8)eq), 3.53 (s, 4H, PhCH_2), 7.23–7.30 (m, 10H, ArH); ^{13}C NMR ($DCCl_3$) ppm 46.7 (d, C(1,5)), 58.0 (t, C(2.4.6.8)), 61.1 (t, PhCH_2), 126.9 (d, p–ArC), 128.0 (d, o– or m–ArC), 128.5 (d, m– or o–ArC), 138.0 (s, i–ArC), 214.0 (s, C(9)); ^{15}N NMR ($DCCl_3$) ppm 39.2 (N(3,7)).

Method B. In a modification of the previous procedure, a solution of *N*-benzyl-4-piperidinone **(20a)**, (4,73 g, 25.0 mmol) and glacial acetic acid (1.50 g, 25.0 mmol) in methanol (25 ml) was added as before to a boiling mixture of paraformaldehyde (6.00 g, 200 mmol), glacial acetic acid (1.62 g, 27.0 mmol), benzylamine (2.68 g, 25.0 mmol), and methanol (100 ml). The mixture was permitted to heat at reflux for 25 h and the aqueous workup was as outlined above *(Method A)*. Instead of the distillation described, the crude oil from the workup was digested in Skelly B (300 ml) on a steam bath for 0.5 h. The hot supernatant was decanted from the yellow residue and evaporated (aspirator followed by vacuum pump, RT, 0.02 mmHg, 20 min). This afforded ketone **13** (6.84 g, 85.4%) as a white oil that did not solidify after 3 days at −10°C. The ^1H and ^{13}C NMR spectra of this oil were virtually identical to that described above and the material proved to be satisfactory for use in the next step.

*(2-*endo*,3-*exo*,4-*endo*)-2,4-*Bis*(2-chlorophenyl)-7-benzyl-7*H*-3,7-diazobicyclo[3.3.1]nonan-9-one* ***(16)*** *and isomer* ***17***
Method A. A 50-ml flask fitted with a condenser, addition funnel, thermometer, and heating mantle was charged with ammonium acetate (2.31 g, 30.0 mmol) and ethanol (10 ml), and the flask was flushed with N_2. The slurry was warmed to 40°C with stirring until all NH_4OAc dissolved; the solution was then cooled to RT. A solution of *o*-chlorobenzaldehyde (5.67 g, 40.3 mmol), ketone **20a** (3.78 g, 20.0 mmol), and ethanol (15 ml) was added in one portion. The resulting solution was slowly warmed to 70°C over 30 min. Upon cooling to RT, a white preci-

pitate (solid A) formed which was filtered and washed with anhydrous ethyl ether (20 ml). These washings were combined with the original filtrate, and this solution was cooled at −10°C for 1 h giving a second precipitate (solid B) which was also filtered and set aside. Evaporation of the filtrate afforded an oily organic solid which was dissolved in ether (10 ml). Upon standing for 1 h at −10°C, a third white solid (solid C) precipitated. This too was filtered and set aside. Upon standing for 24 h, a fourth white solid (solid D) precipitated which was also filtered and set aside. Upon standing for 22 days at −10°C, a small amount of a fifth solid (solid E) precipitated.

Solid A was recrystallized (2-propanol / $HCCl_3$, 3:1, 40 ml) to afford pure ketone **16** (1.06 g) as long white needles: mp: 184−185°C; IR (KBr) cm^{-1} 3340 (N−H), 1733 (C=O); ^1H NMR ($DCCl_3$) δ 1.61 (s, 1H, N−*H*), 2.54, 2.56 (overlappingd, J = 12 Hz, and br s, 4H, H(1,5) and H(6,8)ax), 3.49 (d, J = 12 Hz, 2H, H(6,8)eq), 3.73 (s, 2H, PhCH_2), 5.50 (br s, 2H, H(2,4)), 7.14−7.80 (m, 13H, Ar*H*); ^{13}C NMR ($DCCl_3$) ppm 55.2 (d, C(1,5)), 58.8 (t, C(6,8)), 59.0 (d, C(2,4)), 61.0 (t, PhCH_2), 127.4, 127.5, 128.3, 128.4, 128.6, 129.1, 129.2, 132.2, 138.4, 142.6 (Ar*C*), 212.0 (s, C(9)); ^{15}N NMR ($DCCl_3$) ppm 38.3 (N(7)), 58.2 (N(3)). Anal. for **16** ($C_{26}H_{24}Cl_2N_2O$) C, H, Cl, N.

Solid B, C and E were combined and recrystallized (2-propanol / $HCCl_3$, 3:1, 15 ml) to afford additional ketone **16** (0.50 g, 17.3% total), mp: 184−185°C. Solid D was also recrystallized from an identical solvent system (15 ml) to afford ketone **17** (0.36 g, 4.0%) as short white needles: mp: 207−208°C; IR (KBr) cm^{-1} 3270 (N−H), 1717 (C=O); ^1H NMR ($DCCl_3$) δ 2.54 (d, J = 12 Hz, 2H, H(6,8)ax), 2.76 (br s, 2H, H(1,5)), 3.12 (d, J = 12 Hz, 2H, H(6,8)eq), 3.32 (s, 2H, PhCH_2), 4.70 (br s, 1H, N−*H*), 4.80 (br s, 2H, H(2,4)), 7.15−7.60 (m, Ar*H*); ^{13}C NMR ($DCCl_3$) ppm 50.9 (d, C(1,5)), 55.5 (t, C(6,8)), 62.1 (d, C(2,4)), 62.5 (t, PhCH_2), 126.6, 127.4, 128.4, 128.6, 129.8, 129.9, 132.3, 136.6, 137.2 (Ar*C*), 212.2 (s, C(9)); ^{15}N NMR ($DCCl_3$) ppm 46.9 (N(7)), 54.4 (N(3)). Anal. for **17** ($C_{26}H_{24}Cl_2N_2O$) C, H, Cl, N.

Method B: reaction performed at RT. A 50-ml flask was fitted with a condenser and charged with 95% ethanol (50 ml); the apparatus flushed was with N_2. Ketone **20a** (4.73 g, 25.0 mmol), *o*-chlorobenzyladehyde (7.03 g, 50.0 mmol), and ammonium acetate (5.78 g, 75.0 mmol) were added to the flask. The apparatus was flushed with N_2 and the mixture was allowed to stir at RT. The NH_4OAc slowly dissolved over 1 h and the formation of a small amount of white precipitate was noted shortly thereafter. Continued stirring at RT for 5 days gave additional white precipitate while the supernatant slowly developed a bright red-orange color. The precipitate (solid A) was filtered and washed with ethyl ether (50 ml); the washings were combined with the original filtrate. This solution was cooled at −10°C for 2 d, thus precipitating additional white solid (solid B) which was filtered and washed with ether. The filtrate was evaporated (aspirator) to give an orange gum. Ethyl ether (100 ml) was added and the was mixture heated on a steam bath until a third, almost white solid separated from the orange supernatant. This was filtered, washed with ether and recrystallized (2-propanol / $HCCl_3$, 3:1, 10 ml) to afford **17** (0.1983 g, 1.8%) as tiny needles, mp: 207−209°C.

Solid A was recrystallized (2-propanol / $HCCl_3$, 3:1, 110 ml) to afford **16** (3.14 g) as long white needles, mp: 184.0−184.5°C. Solid B was recrystallized in the same solvent system (15 ml) to give additional **16** (0.40 g, 31.3% total), mp: 184−185°C. The IR, ^1H and ^{13}C NMR spectra for these products were identical to that given previously.

Method C: reaction performed in boiling ethanol. A 25-ml flask, fitted with a condenser, addition funnel, and heating mantle, was charged with ammonium acetate (1.16 g, 150.0 mmol) and ethanol (10 ml) and the flask flushed with N_2. The slurry was heated to reflux and the NH_4OAc was seen to dissolve. The resulting solution was cooled to RT and then treated in one portion with a solution of 1-benzyl-4-piperidinone (**20a**, 1.89 g, 10.0 mmol), *o*-chlorobenzaldehyde (2.81 g, 20.0 mmol) and ethanol (10 ml). This solution was heated at reflux for 1.3 h. Upon cooling to RT, a yellow white solid precipitated from the reaction mixture. This solid was filtered, washed with ether, and recrystallized (2-propanol / $HCCl_3$, 3:1, 10 ml) to afford **16** (0.1781 g, 4.1%) mp: 184−185°C.

The filtrate of the original reaction mixture was diluted with ether (20 ml) and allowed to stand at −10°C for 3 h. No additional solid was observed to precipitate. The solvent was evaporated, and ether (20 ml) was added to the resulting orange oil. Warming on a steam bath for a few minutes resulted in the precipitation of a white solid. Filtration of this solid, washing with cyclohexane, and recrystallization (2-propanol / $HCCl_3$, 3:1, 30 ml) afforded **17** (0.7300 g, 16.2%) mp: 209.5−210°C.

The remaining portion or the original reaction mixture was evaporated and partitioned between ether (30 ml) and water (30 ml). The red-orange ether layer was dried (Na_2SO_4), filtered, and evaporated to afford an orange-red oil that solidified. Addition of cyclohexane (30 ml) followed by heating on a steam bath, resulted in the dissolution of a red impurity from the now yellow solid. This solid was filtered and recrystallized (2-propanol / $HCCl_3$, 3:1, 10 ml) to afford 1-benzyl-3,4-*bis*(chlorobenzyliden)piperidin-4-one **(21)** (88.3 mg, 2.0%), mp: 171−172°C, IR (KBr) cm^{-1} 1665 (C=O); ^1H NMR ($DCCl_3$) = 3.63 (s, 2H, PhCH_2), 3.71 (s, 4H, ring CH_2), 7.06−7.50 (m, 12H), 8.10 (2, 1H); ^{13}C NMR ($DCCl_3$) 53.5 (t, ring CH_2), 60.0 (t, PhCH_2), 126.3, 127.2, 128.2, 128.9, 129.8, 129.9, 130.2, 133.5, 134.4, 135.0, 137.2, 187.2 (s, *C*=O). Mass spectral *m / e* calcd. for $C_{26}H_{21}Cl_2NO$: (M^+) 433.0994. Found: 433.1003. Anal. ($C_{26}H_{21}Cl_2NO$) C, H, N, Cl. The spectral properties of the bicyclic products **16** and **17** were identical to those given previously.

*(2-endo,3-exo,4-endo)-2,4-*Bis*(2-chlorophenyl)-7-benzyl-3,7-diazabicyclo[3.3.1]nonane* ***(18)***

A two-necked, jacketed flask, fitted with a thermometer, a lower take-off condenser, a heating mantle, and a condenser on the jacket, was charged with ketone **16** (90.80 g, 1.8 mmol) and triethylene glycol (50 ml), and the jacket charged with tetralin (bp 207°C). The apparatus was flushed with N_2 and warmed to 110°C with stirring to dissolve the ketone. To this solution was added in one portion hydrazine hydrate (85%, 0.52 g, 10.4 mmol), and the resulting solution was stirred at 110°C for 1 h. Potassium hydroxyde pellets (85%, 5.00 g) were then added and the mixture was heated to 195°C over 4.5 h with the continuous distillation of volatiles and until N_2 evolution ceased. Upon cooling to RT, the tan solution was poured into H_2O (50 ml), and the resulting suspension was extracted with ethyl ether (5 × 30 ml). The combined ether extracts were washed with NaOH solution (10%, 50 ml) and dried (Na_2SO_4, overnight). Filtration followed by evaporation (aspirator) of the filtrate afforded a yellow oil which was dissolved in hot ethanol (25 ml). Upon cooling, the product precipitated as white plates which were filtered and dried to afford amine **18** (0.54 g, 69%); mp: 136.4−137.0°C; IR (KBr) cm^{-1} 3300 (N−H); ^1H NMR ($DCCl_3$) δ 1.07 (dt, J = 12.3, 2.7 Hz, 1H, H(9)*endo*), 1.18 (br s, 1H, N−*H*), 1.83 (br s, 2H, H(1,5)), 2.09 (d, J = 10. Hz, 2H, H(6,8)ax), 2.35 (d, J = 12.3 Hz, 1H, H(9)*exo*), 3.08 (d, J = 10 Hz, 2H, H(6,8)ax), 3.50 (s, 2H, PhCH_2), 4.77 (d, J = 2.5 Hz, 2H, H(2,4)), 7.09−7.92 (m, 13H, Ar); ^{13}C NMR ($DCCl_3$) ppm 24.6 (t, C(9)), 36.1 (d, C(1,5)), 56.1 (d, C(2,4)), 58.8 (t, C(6,8)), 62.8 (t, PhCH_2), 126.8, 127.0, 127.5, 128.0, 128.1, 129.1, 129.3, 132.4, 139.2, 145.7 (Ar*C*); ^{15}N NMR ($DCCl_3$) ppm 32.8 (N(7)), 50.5 (N(3)). Anal ($C_{26}H_{26}N_2Cl_2$) C, H, N, Cl.

*(2-endo,3-endo,4-endo)-2,4-*Bis*(2-chlorophenyl)-7-benzyl-3,7-diazabicyclo[3.3.1]nonane* ***(19)***

A two-necked, 200-ml jacketed flask, fitted with a thermometer, a lower take-off condenser with receiving flask, a heating mantle, and a condenser on the jacket, was charged with ketone **17** (1.87 g, 4.15 mmol) and triethylene glycol (75 ml) while the jacket was charged with tetralin. The apparatus was flushed with N_2 and the mixture was heated to 110°C with stirring to dissolve the ketone. Hydrazine hydrate (85%, 1.22 g, 20.7 mmol) was added in one portion and the resulting solution was heated at 110−120°C for 1 h. Potassium hydroxide pellets (85%, 8.8 g) were then added, and the resulting mixture was heated to 195°C over 4 h with the distillation of volatiles and the evolution of N_2. After cooling to RT, the solution was poured into H_2O (50 ml), and the resulting suspension was extracted with ether (7 × 50 ml). The combined ether extracts were washed with NaOH solution (10%, 100 ml) and dried (K_2CO_3, overnight). Filtration followed by evaporation (aspirator) of the filtrate gave a yellow oil which was dissolved in warm ethanol (50 ml). Trituration with ethyl ether afforded, upon cooling, while cubic crystals which were filtered, washed with ether, and dried to give amine **19** (1.11 g, 61%), mp: 149−151°C; IR (KBr) cm^{-1} 3250 (N−H); ^1H NMR ($DCCl_3$) δ 2.04 (br s, 2H, H(1,5)), 2.06 (d, J = 10 Hz, 1H, H(9)), 2.17 (d, J = 10 Hz, 2H, H(6,8)ax), 2.29 (d, J = 10 Hz, 1H, H(9)), 2.82 (d, J = 10 Hz, 2H, H(6,8))eq), 3.10 (s, 2H, PhCH_2), 4.44 (br s, 1H, N−*H*), 4.68 (br s, 2H, H(2,4)), 7.08−7.44 (m, 13H, Ar*H*); ^{13}C NMR ($DCCl_3$) ppm 31.5 (d, C(1,5)), 35.9 (t, C(9)), 54.9 (t, C(6,8)), 61.6 (d, C(2,4)), 64.3 (t, PhCH_2), 126.5, 127.3, 127.5, 128.2, 129.3, 129.8, 132.3, 138.0, 140.2 (Ar*C*); ^{15}N NMR ($DCCl_3$) ppm 47.4 (N(7)), 53.8 (N(3)). Anal. ($C_{26}H_{26}Cl_2N_2$) C, H, Cl, N.

Crystal data
Crystals of **5** ((CC)-monoclinic from methanol; 0.3 × 0.3 × 0.4 mm), **6** ((CB)-orthorhombic), **7** ((CC)-monoclinic), and **16** ((CB)-triclinic) were sealed in individual capillary tubes and then mounted on a Syntex P3 automated diffractometer. Unit cell dimensions were determined by least squares refinement of the best angular positions for fifteen independent reflections ($2\theta > 15^o$) during normal alignment procedures using molybdenum radiation ($\lambda = 0.71069$ Å). Data points (4.719 for **5**, 5450 for **6**, 6441 for **7**, and 6277 for **16**) were collected at room temperature using a variable scan rate a $\theta-2\theta$ scan mode, and a scan width of 1.2° below $K\alpha_1$ and 1.2° above $K\alpha_2$ to a maximum 2θ value of 116° (for **5** and **16**) or 50.0° (for 6 and 7). Backgrounds were measured at each side of the scan for a combined time equal to the total scan time. The intensities of three standard reflections were remeasured after every 97 reflections, and, since the intensities of these reflections showed less than 6% variation (for **6** and **7**) or 8% variation (for **5** and **16**), corrections for decomposition were deemed unnecessary. Data were corrected for Lorentz, polarization, and background effects. After removal of the redundand and space group forbidden data, the following reflections were considered observed for **5** (2,123), **6** (1,544), **7** (1,383), and **16** (3,036) ($I.3.0\sigma(I)$). The structures were solved by direct methods using MULTAN 80 [15] in all cases. Refinement of scale factor, positional, and anisotropic thermal parameters for all nonhydrogens were carried to convergence. Hydrogen positional parameters were determined from a difference Fourier synthesis. Hydrogen on C(8) and on C(13) were calculated assuming normal geometry and a C−H bond distance of 0.97 Å in **5**. These hydrogen positional parameters with isotropic thermal parameters for $U = 0.03$ were included in the final cycles of refinement, but all parameters associated with hydrogen atoms were considered invariant as was true also for **6, 7** and **16**. The final cycle of refinement [16] - [function minimized $\sum(|F_o|-|F_c|)^2$ led to final agreement factors of R = 7.6% **(5)**, 6,8% **(6)**, 8.8% **(7)**, and 4.7% **(16)** [$\mathbf{R} = (\sum||F_o|-|F_c||/\sum|F_o|) \times 100$]. Anomalous dispersion corrections were made for chlorine in **5**. Unit weights were used throughout in **5** and **16.** Unit weights were equal to $1/\sigma F$ were introduced in **6** and **7**; $R_w = 8.3\%$ **(6)** and 11.0% **(7)**. Scattering factors were taken from Cromer and Mann [17]. Additional data can be obtained from the senior author.

Pharmacology

Methods and Results

Mongrel dogs. Mongrel dogs, weighing 12−28 kg, were anesthetized with sodium-phenobarbital, 30 mg/kg, after which a full 12 lead electrocardiogram (ECG) was recorded for baseline purposes [2, 3]. Lead II and V_2 were monitored continuously during the experimental procedures. Under positive pressure ventilation, a left thoracotomy was performed at the 4th intercostal space, and the heart was exposed through an opening in the pericardium. The left anterior descending coronary artery was dissected 508 mm from its origin and a silk ligature was used to interrupt flow partially; then after 20 min, the vessel was completely ligated in order to produce an anterior-septal myocardial infarction [18]. After repair of the thoracotomy the animal was allowed to recover for 24 h.

The next day, after induction of anesthesia with sodium-pentobarbital, the standard ECG leads V_2-V_6 revealed QS patterns indicative of an anterior wall myocardial infarction. The left heart was exposed through the original thoracotomy incision. Specially constructed composite electrodes [19, 20] were secured to the area overlying the infarct zone (anterior wall) and a normal zone (posterior wall) in order to obtain local electrical recordings during induced ventricular arrythhmias (see below). A His bundle electrogram from the aortic root [3] and central aortic pressures were continuously monitored by standard techniques.

Induction of ventricular arrhythmias. Ventricular pacing was achieved by delivering pacing pulses from an electrical stimulator (S-88 Grass Stimulator) to the right ventricle *via* a plunge wire electrode placed into the outflow tract area. Three-beat bursts, at rates between 240−390/min, were used to provoke ventricular arrhythmias. Sustained ventricular tachycardia was defined as a run of ventricular ectopic beats lasting at least 30 seconds or more than 100 consecutive ectopic beats, usually of uniform morphology, at a rate of 250/min or more. Non-sustained ventricular tachycardia were defined as a run of ventricular ectopic beats, usually of uniform morphology, lasting for less than 30 seconds or consisting of fewer than 100 beats at a rate of at least 250/minute.

Drugs. Both lidocaine **(10)** and agents **3−7** were administered intravenously in doses of 3 and 6 mg/kg. Each drug was given in order to achieve a higher cumulative dose over a period of 3−5 min and the testing procedures were completed within that period. Twenty to 40 min after each drug administration, control testing, *i.e.*, provocative ventricular pacing, was used to determine the dissipation of the drug's effect. Agents **3−7** were dissolved in equal parts of water and ethyl alcohol. In previous studies appropriate volumes of the solvent were tested alone. These tests found no significant effects of the injected ethyl alcohol on various electrophysiological properties nor on blood pressure [2].

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Supplementary material
Crystal data, bond distances, bond angles, dihedral angles, projection views, final atomic positions parameters, anisotropic thermal parameters, and complete bond angles and distances for **5, 6, 7** and **16** (40 pages). Ordering information is given on any current masthead.

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