bronchospasm and salivation generally varied within a range of 10–20%.

Registry No. **3** (R_1 = MeO; R_2 = H), 54504-36-8; **3** (R_1 = Et; R_2 = H), 86371-00-8; **3** (R_1 = $(Me)_2CH$; R_2 = H), 118514-03-7; **3a**, 59456-03-0; **4a**, 41806-52-4; **4b**, 118513-80-7; **4b**·2HCl, 61709-32-8; **4c**, 118513-81-8; **4c**·2HCl, 118514-08-2; **4d**, 118513-82-9; **4e**, 118513-83-0; **4e**·2HCl, 118514-09-3; **4f**, 118513-84-1; **4f**·2HCl, 118514-10-6; **4g**, 118513-85-2; **4h**, 118513-86-3; **4h**·2HCl, 118514-11-7; **4i**, 118513-87-4; **4i**·2HCl, 118514-12-8; **4j**, 59456-04-1; **4j**·2HCl, 54504-40-4; **4k**, 62124-26-9; **4l**, 118537-26-1; **4m**, 87942-30-1; **4n**, 118513-88-5; **4n**·2HCl, 87942-25-4; **4o**, 87942-54-9; **4o**·2HCl, 87942-31-2; **4p**, 118513-89-6; **4q**, 87942-53-8; **4r**, 87942-43-6; **4s**, 87942-35-6; **4t**, 87942-45-8; **4u**, 87942-46-9; **4v**, 87942-50-5; **4w**, 87942-51-6; **5** (R_1 = R_2 = H), 86371-21-3; **5** (R_1 = Me; R_2 = H), 86371-16-6; **5** (R_1 = R_2 = Me), 86371-12-2; **5** (R_1 = R_2 = MeO), 60629-83-6; **6a**, 118513-90-9; **6a**·2HCl, 118514-13-9; **6aa**, 118514-01-5; **6b**, 118575-11-4; **6b**·2HCl, 118514-14-0; **6bb**, 86371-52-0; **6c**, 118513-91-0; **6cc**, 86371-77-9; **6d**, 60629-85-8; **6dd**, 86371-64-4; **6e**, 118513-92-1; **6f**, 118513-93-2; **6g**, 118513-94-3; **6h**, 95571-28-1; **6i**, 60629-86-9; **6j**, 118513-95-4; **6k**, 118513-96-5; **6l**, 60629-84-7; **6m**, 86371-74-6; **6n**, 86371-76-8; **6o**, 118513-97-6; **6o**·2HCl, 86371-61-1; **6p**, 86371-73-5; **6q**, 86503-95-9; **6q**·2HCl, 86371-48-4; **6r**, 118513-98-7; **6r**·2HCl, 86371-54-2; **6s**, 86371-75-7; **6t**, 118513-99-8; **6t**·2HCl, 86371-59-7; **6u**, 118514-00-4; **6v**, 86371-51-9; **6w**, 86371-53-1; **6x**, 86371-49-5; **6y**, 86371-50-8; **6z**, 86371-71-3; **7** (R_1 = R_2 = H; R_4 = Et), 86371-40-6; **7** (R_1 = R = Me; R_2 = H), 86371-44-0; **7** (R_1 = Me; R_2 = H; R_4 = Et), 86371-43-9; **7** (R_1 = MeO; R_2 = H; R_4 = Me), 86371-46-2; **7** (R_1 = MeO; R_2 = H; R_4 = Et), 86371-45-1; **7** (R_1 = R_2 = MeO; R_4 = Me), 86371-47-3; **7a**, 86371-40-6; **7b**, 86371-43-9; **7c**, 86371-45-1; **7d**, 118514-02-6; **8e**, 118514-04-8; **8j**, 118514-05-9; **8r**, 87942-41-4; **9**, 50461-27-3; **12**·HCl, 118514-06-0; **12**·2HCl, 118514-07-1; $(\overline{CH_2})_6$NH, 111-49-9; butanoic acid, 107-92-6; propionic acid, 79-09-4; 1-(2-chloroethyl)piperidine, 1932-03-2; *N*-(2-chloroethyl)-hexamethylimine, 2205-31-4; 2-chloro-*N*,*N*-dimethylethanamine, 107-99-3; 2-chloro-*N*,*N*-diethylethanamine, 100-35-6; 2-chloro-*N*,*N*-dipropylethanamine, 36716-60-6; 1-(2-chloroethyl)pyrrolidine, 5050-41-9; *N*-(2-chloroethyl)morpholine, 3240-94-6; 1-(2-chloroethyl)-2,2,6,6-tetramethylpiperidine, 773-50-2; 3-(2-chloroethyl)-3-azabicyclo[3.2.2]nonane, 54777-55-8; 3-(2-chloroethyl)-3-azabicyclo[3.3.1]nonane, 87942-52-7; 2-(2-chloroethyl)-2-azabicyclo[2.2.2]octane, 59882-35-8; 1-(3-chloropropyl)piperidine, 1458-63-5; pyrrolidine, 123-75-1; piperidine, 110-89-4; morpholine, 110-91-8.

Heterocyclic Analogues of Benzamide Antiarrhythmic Agents[1]

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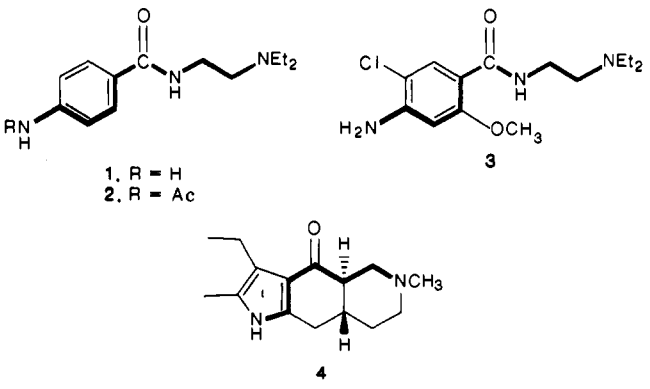
A series of heterocyclic *N*-[(diethylamino)alkyl]arenamides related to acecainide was prepared and examined for antiarrhythmic activity. The compounds were synthesized from the corresponding known heterocyclic carboxylic acids or esters by using standard amide formation methods. The effects of the compounds on the electrophysiological properties of canine Purkinje fibers and ventricular muscle strips were determined. Most of the compounds showed effects consistent with weak class I activity. Two compounds, *N*-[2-(diethylamino)ethyl]-3,4,5-trimethyl-1*H*-pyrrole-2-carboxamide and *N*-[2-(diethylamino)ethyl]-1*H*-indole-2-carboxamide, displayed prolongation of the action potential duration and functional refractory period indicative of modest class III electrophysiological activity. Representative compounds were examined by using molecular modeling techniques. Compounds of differing activity classes displayed qualitatively different electrostatic potential maps.

In the course of our studies aimed at the preparation of novel antiarrhythmic agents,[2] we noted structural similarities (highlighted below) between the known antiarrhythmic compounds procainamide, **1**, and acecainide, **2**, and the dopamine antagonists metoclopramide, **3**, and piquindone, **4**.[3] We noted that for the dopamine antagonists, certain heterocycles such as the pyrrole subunit found in **4** can substitute for the aniline seen in compounds such as **3**. In both **3** and **4** a hydrogen-bearing nitrogen is positioned so as to be in conjugation with a carbonyl group. Given the structural similarities between antiarrhythmic compounds such as **1** and **2** and the dopamine antagonist **3**, we reasoned that substitution of certain heterocycles for aniline might also be applicable to the preparation of analogues of benzamide antiarrhythmic agents.

There is some suggestion in the literature that this substitution might yield antiarrhythmic activity. In a study of the antiarrhythmic activity of a series of (dialkylamino)ethylamides, Giannini and co-workers[4] prepared compound **5**; they reported however that it displayed



less than half the activity of quinidine against aconitine-induced arrhythmias in the isolated guinea pig heart. To

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(1) Presented in part at the 192nd National Meeting of the American Chemical Society, Anaheim, CA, Sept 7–12, 1986.
(2) (a) Morgan, T. K., Jr.; Wohl, R. A.; Lumma, W. C., Jr.; Wan, C.-N.; Davey, D. D.; Gomez, R. P.; Marisca, A. J.; Briggs, M.; Sullivan, M. E.; Wong, S. S. *J. Med. Chem.* **1986**, *29*, 1398. (b) Lis, R.; Morgan, T. K., Jr.; DeVita, R. J.; Davey, D. D.; Lumma, W. C., Jr.; Wohl, R. A.; Diamond, J.; Wong, S. S.; Sullivan, M. E. *J. Med. Chem.* **1987**, *30*, 696. (c) Lumma, W. C., Jr.; Wohl, R. A.; Davey, D. D.; Argenteri, T. M.; DeVita, R. J.; Gomez, R. P.; Jain, V. K.; Marisca, A. J.; Morgan, T. K., Jr.; Reiser, H. J.; Sullivan, M. E.; Wiggins, J.; Wong, S. S. *J. Med. Chem.* **1987**, *30*, 755.

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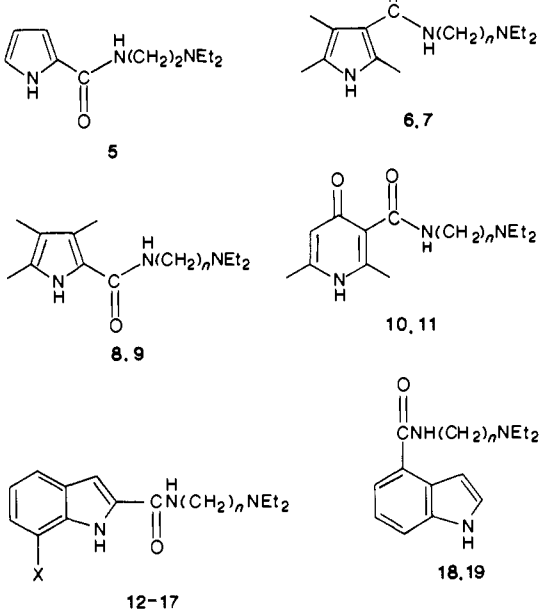
Table I. Physical Properties of Compounds 6–19

compd	n	X	method[a]	yield,[b] %	mp, °C	recrystn[c] solvent	formula[d]
6	2		A	29	60–62	A	$C_{14}H_{25}N_3O$
7	3		B	25	117–119	A	$C_{15}H_{27}N_3O$
8	2		B	39	125–126	B	$C_{14}H_{25}N_3O$
9	3		A	26	78–80	A	$C_{15}H_{27}N_3O$
10	2		B	22	243–245	C	$C_{14}H_{23}N_3O_2 \cdot 2HCl$[e]
11	3		B	41	225–227	C	$C_{15}H_{25}N_3O_2 \cdot 2HCl$
12	2	H	B	27	129–131	D	$C_{15}H_{21}N_3O$
13	3	H	B	15	142–144	A	$C_{16}H_{23}N_3O$
14	2	OBn	B	12	121–123	E	$C_{22}H_{27}N_3O_2$
15	3	OBn	B	6	105–107	A	$C_{23}H_{29}N_3O_2$
16	2	OH	C	49	157–159	F	$C_{15}H_{21}N_3O_2 \cdot HCl \cdot 0.25 \cdot H_2O$[e]
17	3	OH	C	35	192–194	F	$C_{16}H_{23}N_3O_2 \cdot HCl \cdot 0.50 \cdot H_2O$[e]
18	2		B	46	oil		$C_{15}H_{21}N_3O$
19	3		B	28	oil		$C_{16}H_{23}N_3O$[f]

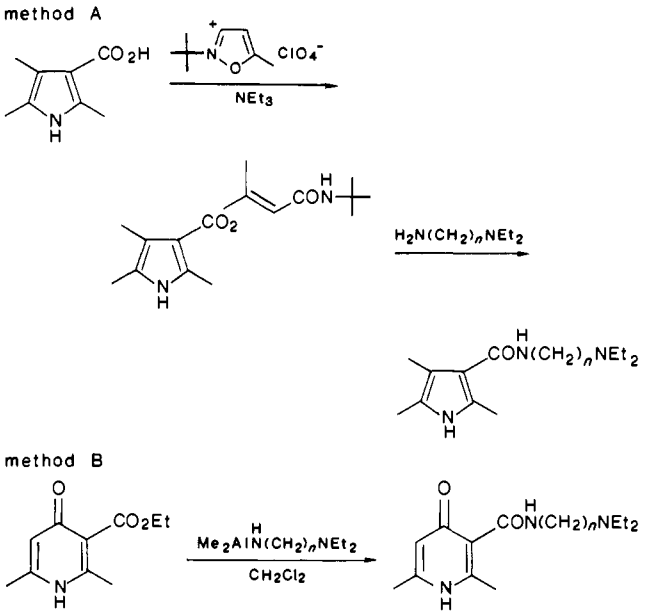
[a] Method of preparation. See text for description. [b] Yields are for analytically pure products and are not optimized. [c] A, ethyl acetate–hexanes; B, acetonitrile; C, ethyl acetate–ethanol; D, ethyl acetate; E, toluene, F, methanol. [d] The analyses for C, H, and N were within ±0.4% of the calculated values unless otherwise stated. [e] Cl analysis was within ±0.4% of the calculated value. [f] Calcd: C, 70.30. Found: C, 69.85.

further test this relationship, we prepared the series of heterocyclic amides **6–19**.

We were particularly interested in examining these structures because of the possibility that they would display differing electrophysiological profiles. In compounds such as **1** and **2**, the nature of the aniline nitrogen plays an important role in determining the compound's electrophysiological profile. Acetylation changes **1**, a class Ia antiarrhythmic agent, into **2**, which is a relatively selective, albeit weak, class III agent.[5] We expected that the heterocyclic structures **6–19** would be more closely related to compound **2** in terms of the character of their nitrogen atoms, and thus would display a greater propensity for class III antiarrhythmic activity.



Scheme I



Chemistry

The compounds for this study were prepared by one of two routes. Amides **6–9** could be prepared from the corresponding known pyrrole carboxylic acids[6] as shown in Scheme I, method A. Activation of the acids by the method of Woodman and Davidson[7] gave both the 2- and 3-substituted activated esters in fair yields after isolation and purification. Reaction of the activated esters with the appropriate diamines gave the pyrrole amides in modest yields. This method failed, however, when applied to targets **10** and **11**. No activated ester was formed, and only starting acid could be isolated from the activation reaction. After several unsuccessful attempts to prepare amides from the pyridonecarboxylic acid, Weinreb's amide synthesis[8]

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(7) Woodman, D. J.; Davidson, A. I. *J. Org. Chem.* **1973**, *38*, 4228.
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was found to give satisfactory results. Thus, as shown in method B, reaction of the pyridone ester with the necessary dimethylaluminum amides afforded the corresponding pyridone amides in fair yield.

Since method B thus proved to be a generally more useful route, it was adopted for the syntheses of the remaining compounds in this study. Hydroxyindole targets were prepared by hydrogenolysis of the corresponding benzyloxy compounds (method C). Table I lists the compounds prepared and provides a summary of physical data and the methods used to synthesize each of the amides.

Pharmacology

The electrophysiological effects for each compound were determined in vitro in isolated canine Purkinje fibers by using standard microelectrode techniques.[9] The effects of the compounds on the action potential duration at 95% repolarization (APD_{95}) and the rate of rise of phase 0 of the action potential ($\dot{V}_{max}$) were recorded simultaneously. The results are presented in Table II as the percent change in APD_{95} ($\Delta\%APD_{95}$) at 10 μM, the maximum percent change observed in APD_{95} ($max\Delta\%APD_{95}$) along with the concentration at which the maximum occurred, the percent change in $\dot{V}_{max}$ ($\Delta\%\dot{V}_{max}$) at 10 μM, and the maximum percent change in $\dot{V}_{max}$ ($max\Delta\%\dot{V}_{max}$) with the concentration at which this maximum was observed. Increases in APD_{95} are taken as indications of class III activity; increases in $\dot{V}_{max}$ are taken as indications of class I activity.

Compounds were also studied in vitro in canine ventricular muscle strips by using an adaptation of the in vivo method of Carson and Dresel.[10] The effects of the compounds on the functional refractory period (FRP) and conduction time (CT) of the muscle strips were determined. In Table II we show the percent change in FRP ($\Delta\%$FRP) at 10 μM, the maximum percent change observed in FRP ($max\Delta\%$FRP) along with the concentration at which the maximum occurred, the percent change in CT ($\Delta\%$CT) at 10 μM, and the maximum percent change in CT ($max\Delta\%$CT) with the concentration at which this maximum was observed. Changes in CT of <10% from control values were considered minimal (marked "M" in the table). Increases in FRP are taken as indications of class I or class III activity, whereas increases in CT are taken as indications of class I activity.

In order to assess potential cardiodepressant properties of the compounds, inotropic effects of the compounds were determined in vitro in guinea pig papillary muscle. The concentrations of compounds leading to a 20% decrease in the force of contraction (EC_{-20}) are given in Table II.

The electrophysiology screens revealed modest class I activity in most of the compounds tested. The compounds showed minimal effects on action potential duration and functional refractory period and varying degrees of depression of $\dot{V}_{max}$. Two compounds, **14** and **15**, were more potent in this regard, showing an EC_{-20} for $\dot{V}_{max} \leq 5$ μM. The negative inotropic effects evoked by many of the compounds tested support this general picture of local anesthetic activity. Two compounds, **8** and **12**, showed combined effects on Purkinje fiber and ventricular muscle comparable to those of acecainide, **2**, suggesting some modest class III activity in these compounds.

The pyrrole- and indole-2-carboxamides with two carbon side chains (**8**, **12**) were the most potent class III agents in the series, as judged from their effects on APD_{95} and FRP; in contrast, pyrrole-3-carboxamides (**6**, **7**) were among the more potent class I agents, as judged from their effects on $\dot{V}_{max}$. Substitution of the indole nucleus with alkoxy groups abolished class III activity (**12** compared to **14**, **16**), while increases in lipophilicity tended to increase class I activity (**14** compared to **12**). The pyridone- and indole-4-carboxamide compounds were only weakly active.

Compound **8** and its close analgoue **9** were examined in vivo in the pentobarbital-anesthetized dog by using the method of Carson and Dresel.[10] These compounds showed only minimal effects on conduction time, functional refractory period, heart rate, and blood pressure when given in doses up to 3 mg/kg iv. Thus, the class III activity seen with these compounds in vitro did not translate into in vivo activity.

The dopamine receptor affinities for compounds **6** and **7** were determined in vitro by measuring their ability to displace specifically bound [^{3}H]ADTN from pig brain striatal membrane preparation.[11] The affinities for these compounds were found to be quite low; affinities for **6** and **7**, expressed relative to unlabeled ADTN as the ratio of the concentrations producing a 50% inhibition of binding, were 500 and 1800, respectively.

Molecular Modeling

In an effort to understand better the differing activities of the compounds prepared in this study, we have compared representative compounds by using molecular modeling techniques. Compounds **1** and **2** were studied as standard class I and class III agents, respectively; from among the new compounds reported here, compounds **6** and **12** were chosen as representative compounds with class I and class III electrophysiological properties, respectively. Structures for the four compounds were optimized by using molecular mechanics calculations.[12] A large number of conformations of approximately equal energy were found for each compound; conformations chosen for further study do not necessarily represent global minima, but are of energies such that they should be easily accessible to the molecules. Rather, structures were chosen in which the side chains were in approximately the same conformation for all compounds studied. Net atomic charges were determined for these conformations via a single-point calculation by using the MNDO method,[13] as implemented in AMPAC.[14] Electrostatic potential maps were then generated in the plane of the aromatic systems, as well as 1.5 and 3.0 Å above and below the plane, using the point charge approximation.[15] The potential maps taken at +1.5 Å proved to be most informative and are shown in Figure 1.

The class I active compounds **1** and **6** show very similar maps, which are characterized by a region of attractive potential centered about the carbonyl oxygen and side-chain nitrogen and by a region of repulsive potential near the aniline or ring nitrogen, approximately 7–8 Å away from the carbonyl oxygen. The class III active compounds **2** and **12** are differentiated from **1** and **6** in that they both show a significantly larger area of attractive potential that extends out over the aromatic system and that contains an additional local minimum in potential. One measure of the increase in area of attractive potential is the greatest distance from the carbonyl oxygen to the −10 kcal contour in the direction of the aromatic ring; this distance is increased by 2–4 Å in **2** and **12** over that measured in **1** and **6**. The distances between the minimum at the benzamide carbonyl oxygen and the minimum in the vicinity

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Table II. In Vitro Pharmacological Data[a]

		Purkinje fiber					ventricular muscle fiber				papillary muscle	
compd	*N*	Δ%APD$_{95}$ at 10 μM[b]	maxΔ%APD$_{95}$ (concn)[c]	Δ%$\dot{V}_{max}$ at 10 μM[d]	maxΔ%$\dot{V}_{max}$ (concn)[e]	*N*	Δ%FRP at 10 μM[f]	maxΔ%FRP (concn)[g]	Δ%CT at 10 μM[h]	maxΔ%CT (concn)[i]	*N*	EC$_{-20}$, μM[j]
1	4	−1 (−4 to 1)	1 (10); −8, −7, 3 (100)	−1.5 (−8 to 4)	4 (10); −14, −14, −10 (100)	3	8.7 (2–17)	14.3 (7–26) (100)	−3 (−12 to 2)	4 (100), −17, 5 (1)	2	NR
2	4	3 (−3 to 7)	16.3 (14–20) (100)	1 (0–2)[k]	6 (0.1), 2 (1), 5 (100)	4	16.8 (11–23)	13, 23 (10); 19, 31 (100)	−9.7 (−11 to 0)	−11 (0.1); −9, −9 (1); 6 (100)	3	NR
3	1	1	−17 (100)	−3	−25 (100)	1	17	33 (100)	M	17 (100)	1	10
6	1	2	−5 (100)	−18	−45 (100)	1	1	6 (30)	M	−8 (10)	1	30
7	3	3.7 (3–4)	5 (0.1), 6 (1), 4(10)	−13 (−36 to 1)	−14, −16 (30); −37 (100)	1	4	16 (100)	M	−3 (1)	2	72, NR
8	4	19.7 (−1 to 49)	7.49 (10), 12 (30), −9 (100)	−6.3 (−17 to 2)[k]	−3 (0.1), −17 (10), −42 (100)	2	22, 24	22, 24 (10)	M	7 (0.1), −5 (1)	1	NR
9	4	8.3 (0–25)	7 (10); 26 (30); −5, −28 (100)	−14.3 (−32 to −3)[k]	−50, −15, −20 (100)	3	5.7 (−4 to 17)	4 (0.1); 2, 28 (100)	M	−6 (1), −9 (10), 8 (100)	1	50
10	3	3 (1–4)	5 (0.1), 4 (10), 4 (100)	0.3 (−2 to 4)	−5 (1), −12 (30), −7 (100)	2	3, 21	11, 26 (100)	−5, −13	−5 (1), −16 (100)	1	NR
11	3	5 (3–7)	5 (0.1), 4 (1), 15 (30)	4.6 (1–7)	−1, −2 (30); 7 (100)	1	13	13 (10)	M	−7 (100)	1	NR
12	3	14.3 (9–18)	16, 18 (10); −24 (100)	−2.3 (−10 to 5)	5 (10), −6 (30), −35 (100)	1	15	24 (100)	M	15 (100)	2	14, 16
13	3	9.6 (5–16)	5, 16 (10); −14 (100)	−7, −13[k]	−13 (10), −13 (30)	1	5	5 (1)	M	−11 (100)	2	23, 26
14	3	−7 (−23 to 17)	−15, 17 (10); −25 (30)	−37.7 (−22 to −61)	−30 (10), −66 (30), CB (30)[e]	1	2	10 (100)	−13	4 (100)	1	6
15	3	−16.3 (−11 to −25)	−11 (10), −38 (30), 18 (100)	−30.3 (−21 to −37)	−33 (10), −56 (30), −79 (100)	3	8 (−1 to 20)	5, 20 (10); 7 (100)	−4 (−12 to −5)	−4 (−12 to 5) (10)	2	6, 8
16	3	0.7 (−5 to 5)	5 (10), −9 (30), −28 (100)	−7 (−13 to −2)	−23, −19 (30); −35 (100)	3	−1 (−5 to 3)	10 (5–18) (100)	−3.3 (−14 to 6)	−3 (1), −14 (10), 16 (100)	1	30
17	3	−10 (−19 to 1)	−14, −22 (30); −53 (100)	−11 (−17 to −7)	−20, −26 (30); −45 (100)	2	−5, 9	8 (1), 19 (100)	−3, −23	−8 (0.1), −23 (10)	2	7, 36
18	4	−3 (−6 to 2)	−6 (1); −20, 5 (30); −25 (100)	−10.5 (−18 to −4)	−14 (1); −22, −26 (30); −19 (100)	3	6.3 (−1 to 16)	10.7 (−3 to 26) (100)	M	14.7 (6–27) (100)	NT[l]	
19	3	−7.7 (−13 to −3)	−3 (10), −22 (30), −26 (100)	−11.3 (−20 to −3)	−15, −39 (30); −31 (100)	4	10 (−9 to 28)	−9, 11 (10); 10, 36 (100)	−8.8 (−20 to 2)	−7, −10 (10); 5, 12 (100)	NT[l]	

[a] All concentrations are in μM. Results from individual experiments are shown; for $N \geq 3$, data are presented as the mean value, followed by the range of values in parentheses. [b] Percent change from control in the action potential duration at 95% repolarization (APD$_{95}$) at 10 μM concentration of the test compound. [c] Maximum percent change in APD$_{95}$ and the concentration at which it was observed (in parentheses). [d] Percent change from control in $\dot{V}_{max}$ at 10 μM concentration of the test compound. [e] Maximum percent change in $\dot{V}_{max}$ and the concentration at which it was observed (in parentheses). CB = conduction block. [f] Percent change from control in the functional refractory period (FRP) at 10 μM concentration of the test compound. [g] Maximum percent change in FRP and the concentration at which it was observed (in parentheses). [h] Percent change from control in conduction time (CT) at 10 μM concentration of the test compound. M = minimal (<10% change in CT). [i] Maximum percent change in CT and the concentration at which it was observed (in parentheses). [j] Concentration of test compound which gives a 20% decrease in contractile force. NR = not reached. [k] $\dot{V}_{max}$ data are not available for one of these experiments. [l] Not tested.

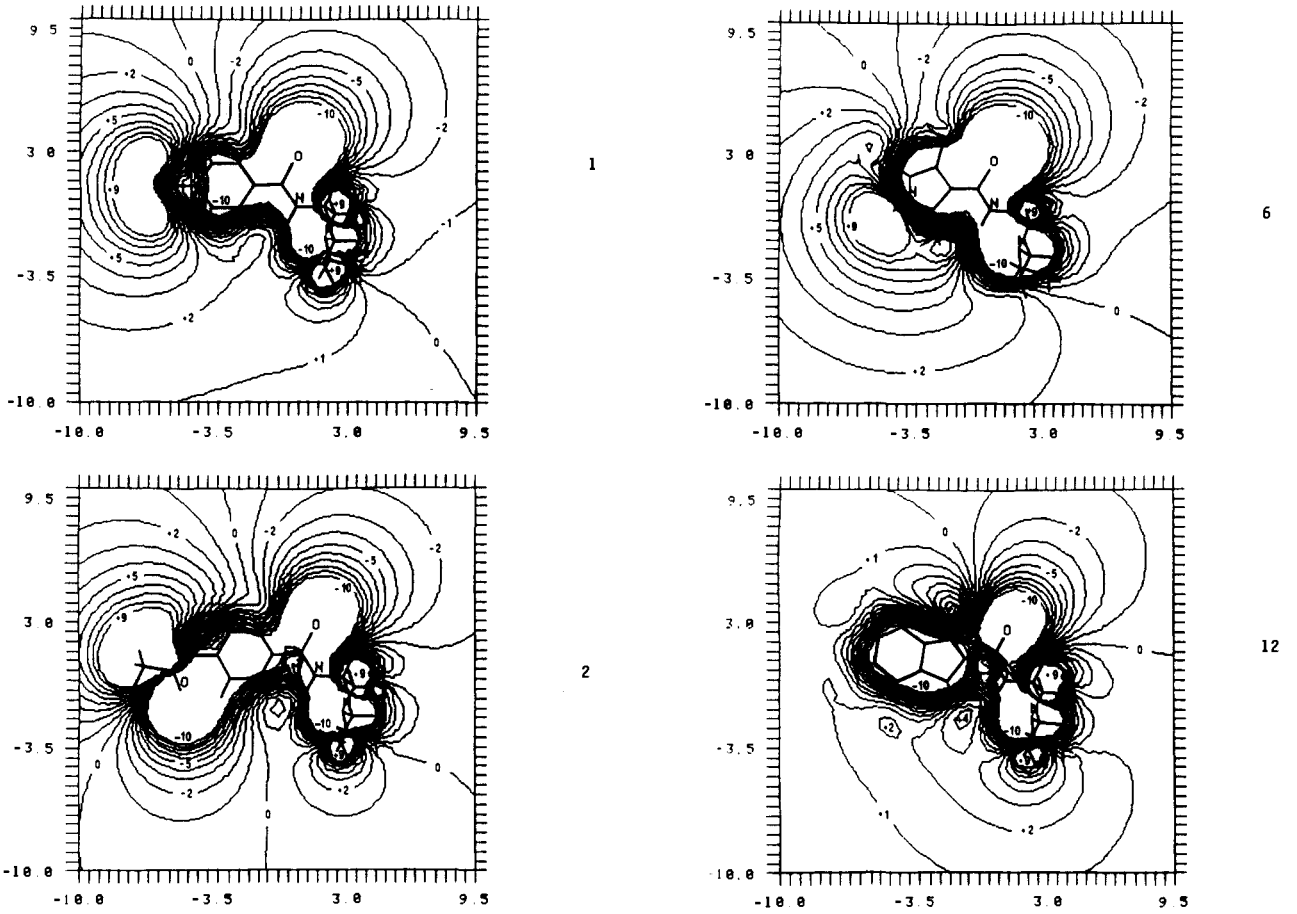

Figure 1. Electrostatic potential maps of **1**, **2**, **6**, and **12**. Contour interval is 1 kcal.

of the aromatic ring for **2** and **12** are approximately 8 and 5 Å, respectively. These features in the potential maps are indicative of differences in electronic structure in these molecules that may play a role in determining their behavior at their sites of biological action, and as such may be responsible for their differing activities.

Discussion

Although two of the compounds in this study displayed a class III electrophysiological profile comparable to that of acecainide, **2**, the predominant electrophysiological effect of most of the compounds was a weak class I action. This is consistent with the work of Giannini and coworkers.[4] These workers found optimum activity with lipophilic bicyclic aromatic amides derived from naphthalenes and quinolines. Similarly, our lipophilic indole-derived targets **14** and **15** were among the most potent within our series in their class I activity, as measured by effects on $\dot{V}_{max}$ in Purkinje fibers. Compound **8**, our closest analogue of compound **5**, was one of the more active of our compounds from the standpoint of class III activity measured in vitro. This in vitro class III activity demonstrates in principle our basic premise that the substitution of heterocyclic systems for aniline could be a viable route for the modification of benzamide antiarrhythmic agents to give class III compounds.

Experimental Section

Melting points were recorded on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Sargent-Welch 3-300 or a Beckman Acculab 2 infrared spectrophotometer. NMR spectra were recorded at 60 MHz on a Varian EM-360 or at 300 MHz on a Varian XL-300 spectrometer. Chemical shifts are reported in parts per million (δ) downfield from an internal standard of tetramethylsilane for all solvents except D_2O, where sodium 3-(trimethylsilyl)propionate was used as standard. Elemental analyses were performed by Galbraith Laboratories, Microlit Laboratories, or the Berlex Analytical Section; results are within ±0.4% of the calculated values unless otherwise stated. Solid products were routinely dried at 60 °C under reduced pressure for a minimum of 12 h. Reactions were monitored by thin-layer chromatography on silica gel (Merck) and alumina (Merck) plates and visualized by UV and Dragendorff reagent.

General Synthetic Methods. The following procedures are representative of the general methods that are described in the text.

Method A. 2,4,5-Trimethyl-1*H*-pyrrole-3-carboxylic Acid [[(1,1-Dimethylethyl)amino]carbonyl]-1-methylethenyl Ester. To a solution of 2-*tert*-butyl-5-methylisoxazolium perchlorate (6.80 g, 28.4 mmol) in dry CH_3CN (50 mL) under nitrogen was added a solution of 2,4,5-trimethyl-1*H*-pyrrole-3-carboxylic acid (4.36 g, 28.4 mmol) and triethylamine (3.01 g, 29.8 mmol) in CH_3CN (50 mL) and DMF (10 mL). The reaction solution was stirred at room temperature for 72 h. A precipitate formed and was collected by filtration. Recrystallization from CH_3CN afforded the title compound as light brown needles (4.0 g, 48%): mp 185 °C (partial melt at 167–169 °C); ^{1}H NMR ($CDCl_3$) δ 1.20 (s, 9 H), 1.36 (s, 9 H), 2.03 (s, 3 H), 2.16 (s, 6 H), 2.40 (s, 3 H), 2.50 (s, 3 H), 5.50 (s, 1 H), 5.66 (s, 1 H), 5.60–6.50 (br m, 1 H), 7.90–8.60 (br m, 1 H). Anal. ($C_{16}H_{24}N_2O_3$) C, H, N.

***N*-[2-(Diethylamino)ethyl]-2,4,5-trimethyl-1*H*-pyrrole-3-carboxamide (6).** To a suspension of 2,4,5-trimethyl-1*H*-pyrrole-3-carboxylic acid [[(1,1-dimethylethyl)amino]-carbonyl]-1-methylethenyl ester (5.60 g, 233 mmol) in CH_3CN (200 mL) was added *N*,*N*-diethylethylenediamine (2.98 g, 25.7 mmol) followed by triethylamine (2.60 g, 25.7 mmol). The reaction mixture was heated at reflux overnight under nitrogen after which it was cooled to room temperature. The resulting precipitate was removed by filtration, and the filtrate was concentrated in vacuo to an oil. Chromatography of the oil over silica gel, eluting first with CH_3CN and then with CH_3CN–NH_4OH (95:5) followed by trituration of the product with ethyl acetate–hexanes afforded **6** as a cream-colored solid (1.70 g, 29%): mp 60–62 °C; ^{1}H NMR ($CDCl_3$) δ 1.00 (t, 6 H), 2.16 (s, 6 H), 2.46 (s, 3 H), 2.56 (q, 6 H),

3.50 (q, 2 H), 6.00–6.70 (br m, 1 H), 7.50–8.00 (br m, 1 H). Anal. ($C_{14}H_{25}N_3O$) C, H, N.

Method B. *N*-[2-(Diethylamino)ethyl]-1*H*-indole-2-carboxamide (12). To a solution of *N*,*N*-diethylethylenediamine (5.40 g, 465 mmol) in CH_2Cl_2 (50 mL) under nitrogen was added trimethylaluminum (2 M in toluene, 23.4 mL, 46.5 mmol) dropwise via syringe. The reaction solution was stirred for 0.5 h, after which a solution of ethyl 2-indolecarboxylate (8.0 g, 42.2 mmol) in CH_2Cl_2 (50 mL) was added dropwise via syringe. The reaction solution was then heated at reflux for 24 h, cooled to room temperature, and concentrated in vacuo to an oil. The oil was partitioned between water and ethyl acetate. The aqueous layer was made slightly acidic (pH 6.5) and extracted with ethyl acetate, and the layers were separated. The aqueous layer was then made basic and extracted with ethyl acetate. The organic washes were combined, dried over $MgSO_4$, and concentrated in vacuo to a solid (10 g). Recrystallization from ethyl acetate afforded **12** as off-white crystals (2.92 g, 27%): mp 129–131 °C; ^{1}H NMR ($CDCl_3$) δ 1.07 (t, 6 H), 2.61 (q, 4 H), 2.69 (t, 2 H), 3.55 (q, 2 H), 6.84 (s, 1 H), 7.67 (d, 1 H), 9.78 (br m, 1 H). Anal. ($C_{15}H_{21}N_3O$) C, H, N.

Method C. *N*-[2-(Diethylamino)ethyl]-7-hydroxy-1*H*-indole-2-carboxamide Hydrochloride (16). To a solution of *N*-[2-(diethylamino)ethyl]-7-(phenylmethoxy)-1*H*-indole-2-carboxamide (9.27 g, 25 mmol) in methanol (100 mL) were added concentrated HCl (2.11 mL, 25 mmol) and 10% Pd/C (4.0 g). The reaction mixture was placed in a Parr apparatus under an atmosphere of hydrogen for 2 h at 45 psi, after which the solids were removed by filtration through Celite. The filtrate was concentrated in vacuo to a solid. Recrystallization from methanol afforded **16** as an off-white solid (3.75 g, 45%): mp 157–159 °C dec; ^{1}H NMR (D_2O) δ 1.33 (t, 6 H), 3.29 (m, 6 H), 3.66 (q, 2 H), 4.85 (s, 4 H), 6.85 (d, 2 H), 7.10 (t, 2 H), 7.33 (d, 1 H). Anal. ($C_{15}H_{21}N_3O_2 \cdot HCl \cdot 0.25H_2O$) C, H, N, Cl.

Pharmacology. Papillary muscle studies,[16] in vivo studies in anesthetized dogs,[10] and dopamine receptor binding studies[11] were carried out by using reported methods.

Intracellular Electrophysiological Profile.[2b] Canine cardiac Purkinje fibers (free running false tendons) were anchored in a tissue bath and perfused at a rate of 6 mL/min with modified Tyrode's solution containing the following ions in mmol/L: Na^+, 149.8; K^+, 4.0; Mg^{2+}, 0.5; Ca^{2+}, 2.5; Cl^-, 134.0; $H_2PO_4^-$, 1.8; HCO_3^-, 24.0; and glucose, 5.5. The solution was gassed with a mixture of 95% oxygen–5% carbon dioxide (pH 7.35–7.40) and maintained at 36 ± 0.5 °C. The tissues were stimulated at a control rate rate of 1.0 Hz through bipolar Teflon-coated platinum electrodes with square wave pulses of 2-ms duration and twice the diastolic threshold current. Intracellular action potentials were recorded with glass microelectrodes (3 M KCl) by using standard recording techniques.[9] Parameters measured were resting membrane potential, threshold current, action potential amplitude, maximum upstroke velocity, and action potential duration at 50% and 95% repolarization. Fibers were stabilized for up to 1 h before control measurements were taken. Test compounds were screened in the range of 10^{-8} to 10^{-3} M concentrations. Data were collected for each compound after 30 min of exposure to a given concentration. Only one compound was tested per Purkinje fiber preparation, and the appropriate vehicle controls were conducted in every experiment.

Extracellular Electrophysiological Profile.[2b] Canine ventricular muscle strips taken from the right ventricle papillary muscle near the base (5–6 mm long × 1–2 mm wide) were mounted on a silicone washer and placed in a 3.5-mL tissue bath. The preparation was continuously superfused with warmed (36 ± 0.5 °C), physiological saline equilibrated with a gas mixture of 95% oxygen–5% carbon dioxide. The preparation was stimulated at one end through bipolar, stainless steel, Teflon-coated electrodes (0.005 in.) impaled into the muscle. A bipolar electrogram was recorded at the opposite end of the muscle strip with the same type of bipolar electrodes described above. The output of the electrical signal was amplified and displayed on an oscilloscope. The diastolic threshold (DT) of the muscle preparation was determined with bipolar stimuli 2 ms in duration at a cycle length of 4000 ms. The muscle tissue was then stimulated at 4 times the diastolic threshold for an initial equilibration period of 60 min. The functional refractory period was determined at a cycle length of 1000 ms by applying a premature stimulus (S2) of the same duration and strength after every tenth basic stimulus (S1) at decreasing S1–S2 intervals until refractoriness occurred. Conduction time (CT), measured as the time interval from the stimulus to the peak of the electrogram, was determined for each S1–S2 interval that produced a propagated response. The relationship between the degree of prematurity (S1–S2 interval) and conduction time of the premature stimulus (S2) was constructed as a conduction–interval curve. The tissue was then superfused with various concentrations of test compound. Only one compound was tested per ventricular muscle strip preparation, and the appropriate vehicle controls were conducted in every experiment.

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Supplementary Material Available: ^{1}H NMR spectral data for compounds **7–11**, **13–15**, and **17–19** (2 pages). Ordering information is given on any current masthead page.

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